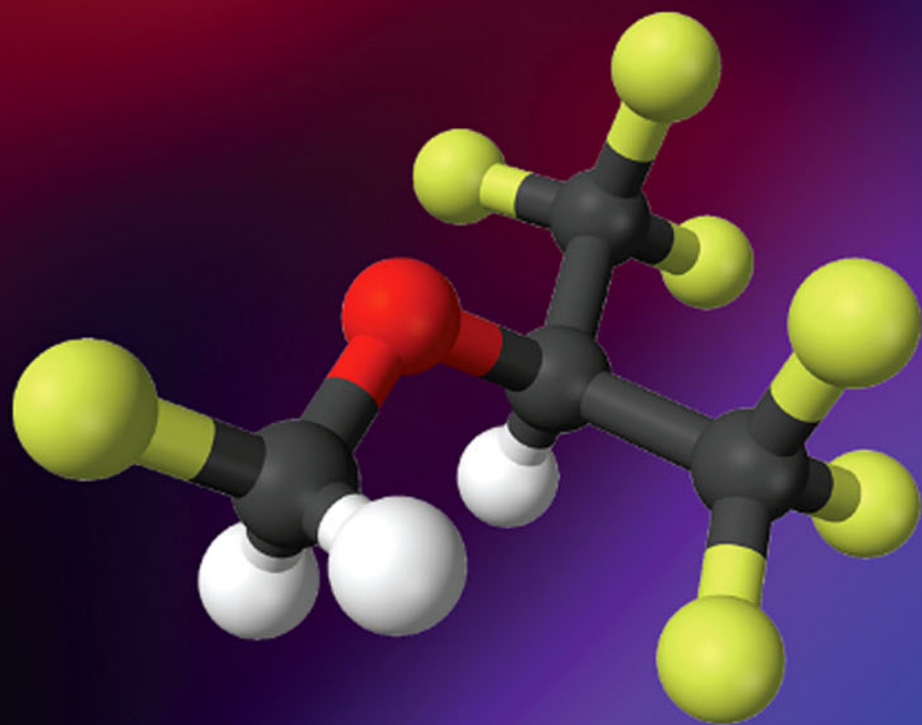


THIRD EDITION

LABORATORY ANIMAL ANAESTHESIA



PAUL FLECKNELL



Laboratory Animal Anaesthesia

Third Edition

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Laboratory Animal Anaesthesia

Third Edition

Paul Flecknell

Comparative Biology Centre
Medical School
Newcastle University
Newcastle-upon-Tyne, UK



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32 Jamestown Road, London NW1 7BY, UK
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA

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Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN: 978-0-12-369376-1

For information on all Academic Press publications
visit our website at www.elsevierdirect.com

Typeset by Macmillan Publishing Solutions
www.macmillansolutions.com

Printed and bound in the United States of America
09 10 11 12 13 10 9 8 7 6 5 4 3 2 1

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Preface

The additions and amendments to this new edition reflect developments in anaesthetic practice and changes in our attitudes towards laboratory animal welfare. Standards of anaesthesia for laboratory animals have increased greatly since the publication of the second edition, and the use of technically demanding procedures have become much more widespread. This new edition attempts to balance the need for additional information in these areas with the main goal of the first edition: the provision of an introductory text for new investigators.

With the continued move towards evidence-based medicine, the number of references has been increased. It has never been my intention to provide a comprehensive anaesthesia textbook, so references have been used primarily to support contentious statements, to indicate conflicting opinions and to provide a starting point for searching the more specialist scientific literature. Whenever possible, recent papers that contain a good discussion of the literature have been selected for citation at appropriate points in the text where older references represent original useful material they have been retained.

Paul Flecknell

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Preface to the Second Edition

Since writing the first edition of this book, there has been a welcome increase in concern for the welfare of laboratory animals. One result of this has been the introduction by a number of countries of formal training requirements for new research workers. This increased interest in animal welfare has also led to the improved dissemination of information regarding ‘best practice’ in many aspects of laboratory animal science. The second edition of *Laboratory Animal Anaesthesia* has benefited from this exchange of information, and the additions and revisions which have been included owe much to comments from my colleagues from around the world. A major addition to this new edition is the inclusion of illustrations of techniques and equipment. The format of the book remains relatively unchanged, except for Chapter 7, which now incorporates some of the information previously included in the appendices. This enables more of the information relating to a particular species to be accessed quickly and easily. Brief descriptions of anaesthetic techniques for fish, amphibia, reptiles and birds have also been included, to provide some basic guidance for dealing with these species.

Paul Flecknell

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Preface to the First Edition

The majority of laboratory animals are anaesthetized by staff who have not received specialist training in this field. Unfortunately, most currently available textbooks of human or veterinary anaesthesia assume that the reader has a basic knowledge of the subject. Because of this, a good deal of published information has remained relatively inaccessible, and this has limited the introduction of new techniques into the field of laboratory animal anaesthesia.

This handbook attempts to provide a basic guide to anaesthesia for research workers and animal technicians. It is not intended to be a comprehensive text on animal anaesthesia, but concentrates on those areas that are of greatest practical importance when anaesthetizing laboratory animals.

The first sections of the book deal with the general principles of pre-operative care, anaesthetic techniques and anaesthetic management. The most important properties of the anaesthetic and other agents used are outlined, but a detailed description of their pharmacology has been deliberately excluded. These sections also provide details of some of the equipment which the author has found useful when anaesthetizing laboratory animals.

These general sections of the book should be read before using any of the anaesthetic regimes described in the final sections. In particular, it is hoped that the reader will study the sections on post-operative care and the provision of effective pain relief before carrying out any operative procedures on animals.

In order to provide rapid, easily accessible guidelines, a list of recommended anaesthetic regimes for each of the common laboratory species is given in Appendix 1. For those research workers who require alternative techniques, a wider range of anaesthetic regimes is discussed together with an extensive list of dose rates for each species in Chapter 7.

In addition to providing guidance on basic anaesthetic techniques, an introduction to more specialist procedures such as long-term anaesthesia and the use of neuromuscular blocking agents has been included. These sections provide only initial guidance, and it is recommended that, whenever possible, an experienced veterinary anaesthetist should be consulted before attempting these techniques.

Paul Flecknell

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Glossary

Inevitably, a number of specialist terms are used throughout this book and these are defined below.

Anaesthesia a state of controllable, reversible insensibility in which sensory perception and motor responses are both markedly depressed

Analgesia the temporary abolition or diminution of pain perception

Analeptic drug which stimulates respiration

Anoxia complete deprivation of oxygen for tissue respiration

Apnoea temporary cessation of breathing

Arrhythmia (cardiac) alteration in the normal rhythm of the heart

Asystole lack of cardiac muscle contractions

Ataxia lack of co-ordination, 'wobbliness'

BMR basal metabolic rate

Bradycardia slowing of the heart rate

CNS central nervous system

CNS depressant any agent which modifies function by depressing sensory or motor responses in the CNS

Cyanosis blue or purple colouring of the skin or visible membranes due to the presence of an increased concentration of reduced haemoglobin in capillary blood, symptomatic of hypoxia

Dosages mg of drug per kg body weight (mg/kg) except for the neuroleptanalgesic combinations which are more conveniently expressed as ml of commercial or diluted premixed solution per kg body weight (ml/kg)

Dosage schedules u.i.d. – once daily

b.i.d. – twice daily

t.i.d. – three times daily

q.i.d. – four times daily

Dyspnoea laboured breathing

ECG electrocardiogram

Hypercapnia elevated blood carbon dioxide content

Hyperpnoea fast or deep breathing

Hypertension elevated (arterial) blood pressure

Hypnotic a drug which induces a state resembling deep sleep, but usually with little analgesic effect

Hypocapnia reduced blood carbon dioxide content

Hypopnoea slow or shallow breathing

Hypotension a fall in (arterial) blood pressure

Hypothermia a fall in body temperature

Hypovolaemia a fall in circulating blood volume

Hypoxia depressed levels of oxygen

Induction (of anaesthesia) the initial establishment of a state of anaesthesia

Injection routes iv – intravenous

im – intramuscular

ip – intraperitoneal

sc – subcutaneous

Laryngospasm spasm of the vocal cords, producing complete or partial obstruction of the airway

Minute volume the volume of gas breathed in 1 minute, that is, the product of tidal volume and respiratory rate

Narcosis a state of insensibility or stupor from which it is difficult to arouse the animal

Normovolaemic having a normal circulating blood volume

PCO₂ partial pressure of carbon dioxide

Per os by mouth

PO₂ partial pressure of oxygen

Polypnoea rapid, panting breathing

Pulmonary ventilation the mechanical expansion and contraction of the lungs in order to renew alveolar air with fresh atmospheric air

Tachycardia an increase in heart rate

Tachypnoea rapid respiration

Tidal volume the volume of gas expired with each breath



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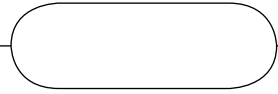
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Acknowledgements

This book has developed in scope and content as a result of the advice and helpful criticism by colleagues I have worked with during my career. I would like to thank those I worked with at the Clinical Research Centre, Harrow, Newcastle University, and those who I have joined on anaesthesia courses and workshops. Particular thanks are due to Dr. Ken Boschert, the instigator of 'COMPAMED', and to AALAS for continuing to support this resource. Without the benefit of this electronic conferencing system, the new edition of this book could not have benefited from the comments, contributions and requests for additional information from the many COMPAMEDDERS involved in anaesthetizing laboratory animals around the world.

Thanks are due to Jon Gledhill for providing many of the new illustrations for this edition, to Anne Al-Jumaili for help with preparation of the manuscript, to Margaret Canham for preparing the bibliography and to Eddie Clutton, Claire Richardson and Silke Corbach-Soehle for reading the text and providing many helpful comments.

I am particularly grateful to Ruth, my wife, for her constant assistance during all stages of the preparation of this book.

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Introduction

Providing the most appropriate and effective anaesthetic regimen is an essential part of good experimental design. Anaesthesia has profound effects on the physiological processes of animals, and this can have a marked effect on experimental data. These effects can arise as a direct result of the anaesthetic agents used, for example, hyperglycaemia caused by medetomidine. Other effects such as hypothermia may be secondary to the depression of various body systems. Some effects persist only during the period of anaesthesia, other effects may continue for hours or days. Most experiments that use living animals aim to produce a carefully defined abnormality, or to carry out a procedure such as catheter implantation. When such interventions have been completed, the goal is often to have no other significant effects on the animal's physiology. Achieving these goals can be frustrated by the use of inappropriate anaesthetics and a failure to provide high standards of peri-operative care. Sometimes, the effects of a poor choice of anaesthetic agent can be dramatic, for example, ileus (gut stasis) after administration of chloral hydrate. More usually, the effects are less obvious, but even subtle changes can result in an increase in the variability of study data. This increased variability can require an increased number of animals to be used to demonstrate treatment effects (Festing et al., 2002).

Aside from the requirements to carry out studies as efficiently as possible, it is generally accepted that when it is still necessary to use animals in experiments, research procedures should be refined to minimize pain and distress. A requirement to comply with the principles set out by Russell and Burch (1959), of Reduction, Refinement and Replacement, now forms part of the legislation controlling the use of animals in research in the UK and elsewhere. Reviewing our anaesthesia and peri-operative care so that they are the most appropriate for a particular study will contribute to both reduction and refinement of animal use. Achieving this is not always straightforward, and it is important that attention should be given not only to the anaesthetic agents used, but also to the measures adopted to minimize the unwanted side-effects of anaesthesia and surgery. The

use of effective analgesia following surgical procedures is particularly important, yet recent reviews of current practices in rodents suggest that analgesic use is still relatively low (Richardson and Flecknell, 2006; Coulter et al., 2009). This is somewhat ironic, in that almost all of the analgesic and anaesthetic techniques currently used in humans were developed and assessed in laboratory animals, before being accepted for clinical use in humans. We therefore have a very wide range of techniques and anaesthetic and analgesic agents available for use in laboratory animals. Careful consideration of the options available can lead to improvements both in the quality of scientific data obtained and in the welfare of the animals involved.

Preparing for Anaesthesia

Safe and effective anaesthesia requires careful preparation. Anaesthetic and monitoring equipment must be checked carefully to ensure they are in good working order and that any item that would come in contact with the animal has been cleaned and disinfected. It is also important to make sure that sufficient supplies of drugs and anaesthetic gases are available to meet both planned and emergency use. The animals to be anaesthetized should normally be allowed to acclimatize to the research facility. They should also have undergone a clinical examination to assess their state of health and their normal behaviour and response to humans.

To provide anaesthesia of the standard required in modern research laboratories, it is essential that adequate preparations be made before attempting to anaesthetize an animal. Good pre-operative care will reduce the incidence of many of the complications that can occur during anaesthesia, and thorough preparation of facilities and equipment contributes to the smooth running of a research protocol. It is important to consider preparation of not only the animals to be anaesthetized but also the equipment, drugs, facilities and personnel involved in the procedure.

ANAESTHETIC EQUIPMENT AND ANAESTHETIC DRUGS

The factors influencing the choice of a particular anaesthetic are discussed in more detail later, but irrespective of the agent or combination of agents selected, it is important to establish that all the items of equipment necessary are available and in good working order. Ensure that sufficient anaesthetic drugs and anaesthetic gases have been provided not just for the anticipated period of anaesthesia but also to cover unexpected additional requirements (see Appendix 2 for calculations of inhaled anaesthetics). Check the expiry date of all drugs, and ensure they have been properly stored. For clear drugs stored in uncoloured glass bottles, check for unexpected turbidity or colour changes. In addition to the anaesthetic agents, drugs needed for coping with emergencies must also be readily available (see Chapter 4).

If an anaesthetic trolley is to be used to deliver an volatile anaesthetics or oxygen, then it is essential to check them carefully before use. A simple pre-use checklist for anaesthetic machines is given in Table 1.1. Anaesthetic machines appear complex, but their underlying design and operation is very simple. Most machines comprise a compressed gas source that, after pressure reduction, is passed through a flow meter and an anaesthetic vaporizer, and delivers anaesthetic gases to the animal through a breathing system. If using an unfamiliar machine, ask a colleague who has used the apparatus or the equipment supplier to provide a demonstration. Very detailed descriptions of medical anaesthetic equipment are available (Davey and Diba, 2005). An excellent description of anaesthetic equipment together with animations to illustrate breathing circuits can be found at <http://www.asevet.com/resources/index.htm>

TABLE 1.1 Pre-anaesthetic Checks of Anaesthetic Equipment.

- Is only one oxygen cylinder marked as 'in use' and the other full?
- Check that the valve on the cylinder in use is opened fully to provide a free flow of gas (the reading on the pressure dial on an oxygen cylinder gives a reasonable indication as to how much oxygen it contains, Appendix 2).
- Check that the cylinders are full and properly attached to the anaesthetic machine; ensure the flow meters are functioning correctly by opening the cylinder valves and the needle valves that control the flow of gas through the flow meters. The bobbins should rotate when gas is flowing (most are marked with a small white dot to assist in assessing this). The gas flow rate is measured from the top of the bobbin. Turn off the gas flow using the needle valve and check that the bobbin sinks smoothly back to zero and is not sticking and giving a false high gas flow rate.
- Check that the emergency oxygen button is functioning correctly.
- If a volatile anaesthetic is to be used, check that the vaporizer has been filled and that the control dial moves smoothly over the entire range of possible settings. If using a machine with several vaporizers, check that the correct one has been selected.
- If the anaesthetic machine has a built-in circle-type absorber, ensure that this is switched out of circuit (usually marked 'open') if the absorber is not to be used. Check that soda lime is not exhausted (indicated by a colour change from pink to white or white to violet).
- Attach the circuit which will be used to the anaesthetic machine, turn on the oxygen supply and check the circuit for leaks by occluding the patient end of the tubing and fully closing any valves. Open the valves to check they are not sticking.
- If a mechanical ventilator is to be used, switch it on and observe it for a few respiratory cycles. If possible, check the tidal volume that is being delivered with a respirometer.
- Run through the manufacturer's recommended pre-use check on any monitoring equipment.

These checks should be routine procedures since they will minimise the occurrence of anaesthetic accidents which could result in the death of the animal.

Compressed Gas Source

Gas is either supplied from cylinders on the anaesthetic machine or piped using hoses from larger cylinders. If using hoses, the pressure reducing valve (see below) should be fitted to the large cylinder so that gas at lower pressure is supplied through the hose. The mounts for the hoses or cylinders have small pins located in corresponding holes in the cylinders to ensure that the correct gas (e.g. oxygen or nitrous oxide) is attached (Fig. 1.1). Cylinders are also colour coded (oxygen cylinders are green in the USA and black with a white shoulder in the UK; nitrous oxide cylinders are blue). A small metal and neoprene seal (Bodok seal) ensures a gas-tight fit between the cylinder and the mount block (Fig. 1.1). Under no circumstances should oil or grease be used around the seal because the pressurized gases give off heat as they are released from the cylinder and may cause explosions if oil is used. A pressure gauge (Fig. 1.2) indicates that gas is available. Oxygen cylinders contain oxygen under pressure, and the pressure gauge gradually falls as the cylinder is depleted. A full-size E cylinder (the size fitted to most anaesthetic machines) contains approximately 680 litres of gas. Manufacturers label the cylinders to confirm this. Nitrous oxide cylinders contain liquid nitrous oxide, so, unlike an oxygen cylinder, the pressure reading will not fall until the cylinder is almost empty. Cylinders are either opened using a spanner or fitted with a hand-operated valve (Fig. 1.3). It is best to use a machine with two oxygen cylinders so that the supply can be switched from one



FIGURE 1.1 Pin index system – the pins in the mounting block (left) fit into the holes in the gas cylinder (see Fig. 1.3).



FIGURE 1.2 Pressure gauges for nitrous oxide (left) and oxygen (right) cylinders.



FIGURE 1.3 Cylinders are opened and closed either using a ratchet spanner (left), cylinder key (centre) or hand-operated valve (right).

cylinder to the other, if needed, during an anaesthetic. Most machines have check valves located in the hanger yolk so that the empty cylinder does not need to be turned off before turning on the full cylinder. Cylinders should be labelled 'full', 'in use' or 'empty' (and if empty, changed as soon as the anaesthetic induction is completed). When changing cylinders, handle them carefully, particularly full ones. If these are dropped, their 'neck' can fracture, leading to explosive decompression and injury to personnel. For this reason, cylinders should always be secured to a wall or placed on special carts when not mounted on an anaesthetic machine.

Pressure-Reducing Valve

The pressure-reducing valve is sited between the cylinder and the rest of the anaesthetic machine. This reduces the pressure from approximately 134 bar (in a full-size E cylinder) to the 4 bar required in the anaesthetic machine. The valve also acts as a regulator to provide a constant pressure of gas.

Flow Meter

Separate flow meters are provided for each gas. A flow control valve controls the flow of gas. As the valve is opened, a bobbin moves up the flow meter. The flow of

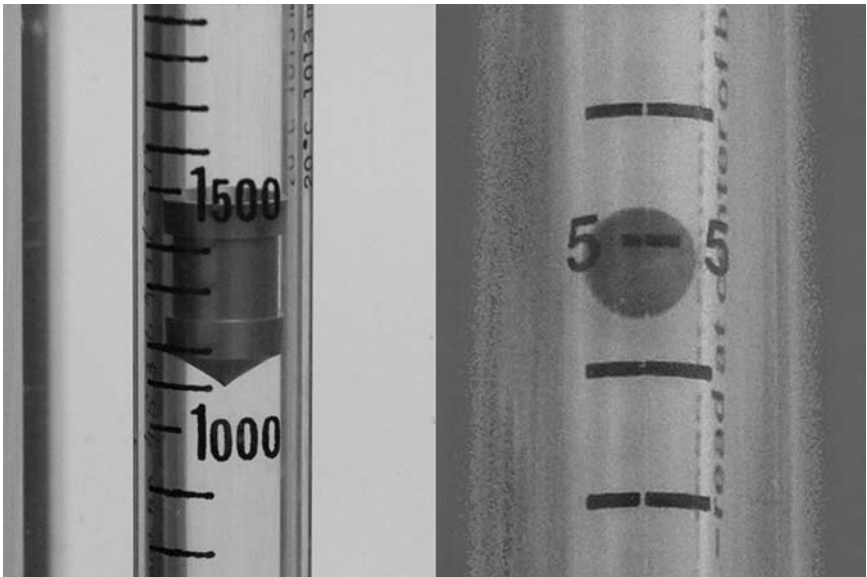


FIGURE 1.4 The gas flow rate is read from the position of the top of the bobbin of the flow meter. In flow meters with a ball, rather than a bobbin (right), the reading is taken from the centre of the ball.

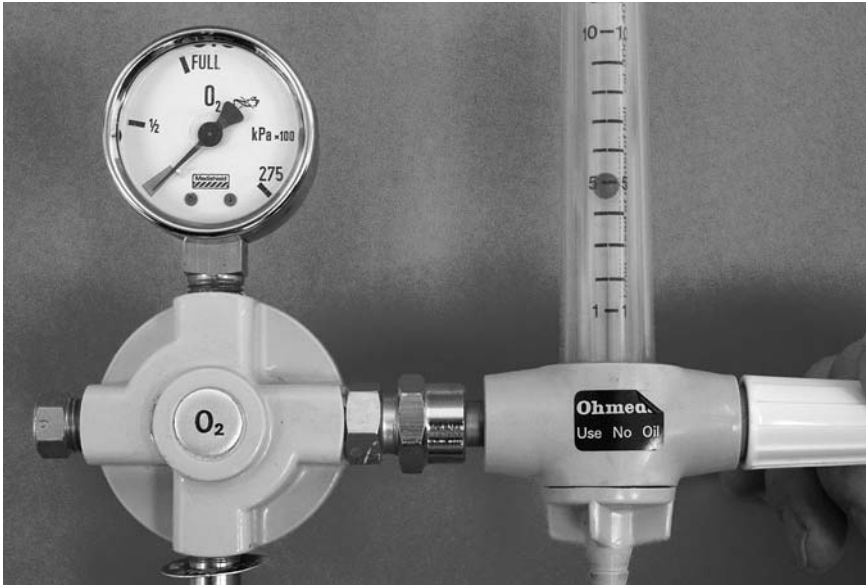


FIGURE 1.5 Turret-type flow meters can be used as a simple means of providing a controlled source of oxygen, during both anaesthesia and recovery.

gas is read from the position of the top of the bobbin (Fig. 1.4). The flow control valves are delicate, and should only be opened and closed by hand. Some basic anaesthetic machines use turret-type flow meters (Fig. 1.5) in which the gas leaves the flow meter from the bottom of the unit. These can also be purchased combined with a pressure-reducing valve and regulator and used on a compressed gas cylinder as a simple and inexpensive means of supplying oxygen.

Vaporizers

Volatile anaesthetics are supplied as liquids that are vaporized (evaporated into a gas) before being mixed with anaesthetic gases and delivered to the animal. Vaporizers are designed for use with a specific agent, and many have a filling system that prevents them from being filled inadvertently with the wrong anaesthetic (Fig. 1.6). An agent-specific filler tube is used, one end of which slots into a fitting on the vaporizer and the other end slots into a collar on the bottle of anaesthetic. The fitting on the vaporizer and the collar on the bottle are specific to each agent, making it impossible to fill the vaporizer with the wrong agent. Modern vaporizers are usually fitted to the 'back bar' of the anaesthetic (Fig. 1.7). This may be via a special mounting system such as the 'Selectatec' mechanism that allows vaporizers to be exchanged quickly and easily between machines. Although more than one vaporizer may be fitted to the machine, most back bar systems prevent more than one vaporizer from being used at any one

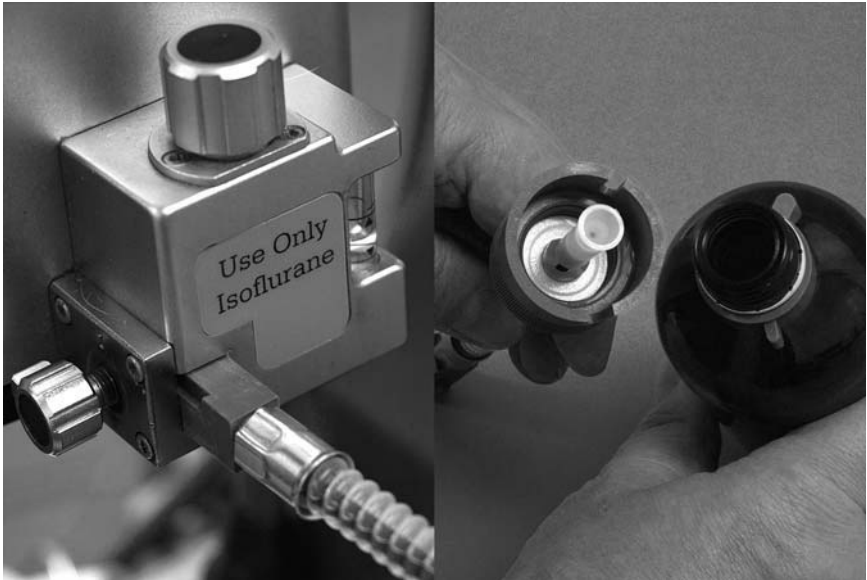


FIGURE 1.6 An example of a system designed to prevent filling of a vaporizer with the incorrect anaesthetic agent. The end of the filling tube fits into a slot in the vaporizer (left), and the other end of the tube fits onto a collar on the bottle (right).



FIGURE 1.7 Vaporizer mounting system (Selectatec) that allows vaporizers to be exchanged quickly and easily between machines.

time. Modern vaporizers are designed to deliver the designated concentration of anaesthetic and to compensate for changes in gas flow and the temperature drop that occurs as the agent is vaporized.

Modern vaporizers operate by splitting off a small proportion of the fresh gas flow and completely saturating it with anaesthetic. This is then remixed with the main gas flow. This requires that a pressurised gas is supplied, the vaporizer is correctly attached and any locking mechanism is fully engaged to avoid leaks. Vaporizers must be serviced regularly to function correctly.

Pressure Relief Valve

Some anaesthetic machines have a pressure relief valve, usually situated on the back bar, to protect the flow meters and vaporizer from inadvertent over-pressurisation, which can occur, for example, if the gas outflow is occluded. The valve usually operates at about 35kPA.

Emergency Oxygen Flow

The emergency oxygen supply is operated by a spring-loaded button, usually located next to the gas supply to the animal. It provides a supply of oxygen at high flow (35l/min) and bypasses the flow meters and vaporizers.

Oxygen Failure Alarm

Oxygen failure warning devices are now fitted to all anaesthetic machines designed for medical or veterinary clinical use. These are usually powered only by the oxygen pressure. When the oxygen pressure falls, they emit a loud whistle. They can only be reset by the return of the correct oxygen pressure.

OTHER EQUIPMENT

Anaesthetic gases or oxygen are delivered from the anaesthetic machine to the animal using a breathing system. Irrespective of the anaesthetic breathing system selected, a face mask, nasal tube (see Chapter 2) or an endotracheal tube will be required to connect it to the animal. Alternatively, an anaesthetic chamber can be connected to the anaesthetic machine.

Anaesthetic Chambers

When anaesthetising small animals, it is often most convenient to use an anaesthetic chamber. Volatile anaesthetics are delivered from a precision vaporizer to the chamber and waste anaesthetic is removed safely using a gas-scavenging system. Since all anaesthetics cause some degree of respiratory depression, oxygen, either alone or in combination with nitrous oxide, should be used as the carrier gas, rather

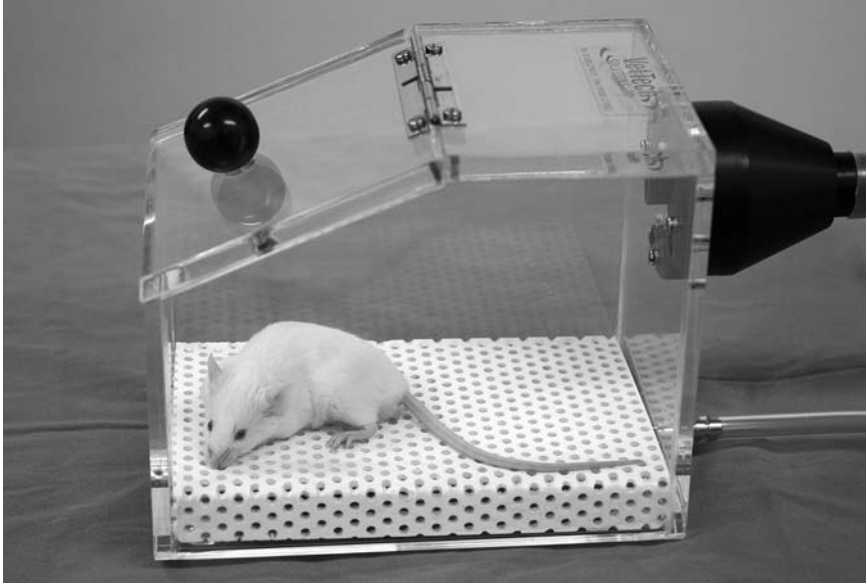


FIGURE 1.8 Anaesthetic chamber for use with small mammals (VetTech Solutions) – the anaesthetic agent is piped in at the bottom of the chamber, and an exhaust port at the top is connected to a gas-scavenging device.

than air. A suitably sized clear perspex box should be used (e.g. $30 \times 20 \times 20 \text{ cm}^3$ for rats) so that the animal can be observed during induction. Chambers can either be purchased commercially (Fig. 1.8) or constructed 'in house'. Some chambers are provided with a metal grid in the base to separate the animal from any urine that it produces. Alternatively, a pad of towelling or dry bed (William Daniels, United Kingdom) or some paper towels should be placed on the floor of the chamber. The apparatus should be cleaned thoroughly after use.

The waste anaesthetic gas should be removed in a controlled way and either ducted out of the room or adsorbed using activated charcoal. A particularly effective scavenging technique has been devised using a double-box system (VetTech Solutions) (Fig. 1.9).

Face Masks

The face masks manufactured for veterinary use are cone shaped and will be found suitable for sheep, pigs, dogs, cats and rabbits, provided the appropriate size is used. Face masks should fit snugly around the muzzle and must not obstruct the mouth or nose. If too large a mask is used, then the space around the animal's nose and mouth (the equipment dead space) may trap exhaled gas, high in carbon dioxide, and this may be rebreathed unless very high gas flows are used to remove it. However, since even the lowest flow rates that can be provided

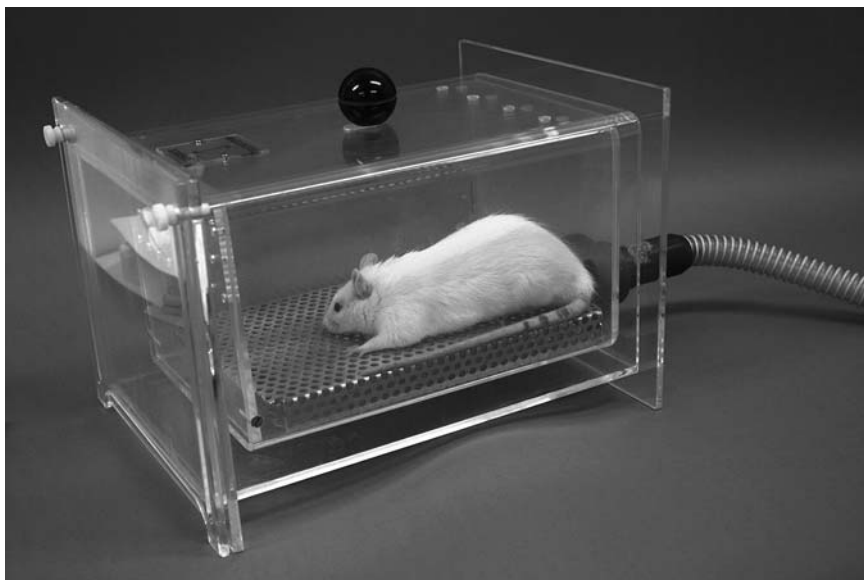


FIGURE 1.9 A double-chamber system that is designed to minimize exposure of personnel to waste anaesthetic gases (VetTech Solutions).

accurately by many anaesthetic machines are higher than those actually required by small rodents, most systems that use a face mask act as open systems and the dead space in the face mask becomes relatively unimportant.

A set of small, transparent masks fitted with flexible rubber diaphragms are useful for a range of animals and birds (Fig. 1.10). A mask design that incorporates a removal of waste anaesthetic gas to prevent exposure of the operator has been described (Hunter et al., 1984), and is available commercially (VetTech Solutions, Harvard Apparatus) (Fig. 1.11). A number of alternative systems that combines gas scavenging with anaesthetic delivery are also available. Face masks should be cleaned after use by washing in warm soapy water, followed by drying. Most cannot be autoclaved, but some may be sterilized using ethylene oxide.

Endotracheal Tubes

Endotracheal tubes are used to maintain a clear airway so that breathing can be assisted if necessary. They also protect the airway when the swallowing and coughing reflexes are suppressed, so that material such as saliva does not enter the trachea. Endotracheal tubes are available from many manufacturers and are provided either as plain tubes or with an inflatable cuff that seals the gap between the wall of the tube and the trachea (Fig. 1.12). The cuff can be inflated either with a syringe (2–5 ml) or with a specially designed inflator. The cuff is prevented from deflating either by means of a non-return valve (present on



FIGURE 1.10 Face masks for use with a range of laboratory species. The rubber diaphragm helps provide a better seal around the animals nose (F-042).



FIGURE 1.11 Concentric mask system for rodents and rabbits that combine delivery of an anaesthetic gases with removal of waste gas through an outer tube. An extraction fan and activated charcoal absorber are used to remove the anaesthetic gases and prevent exposure of personnel (Harvard Instruments).

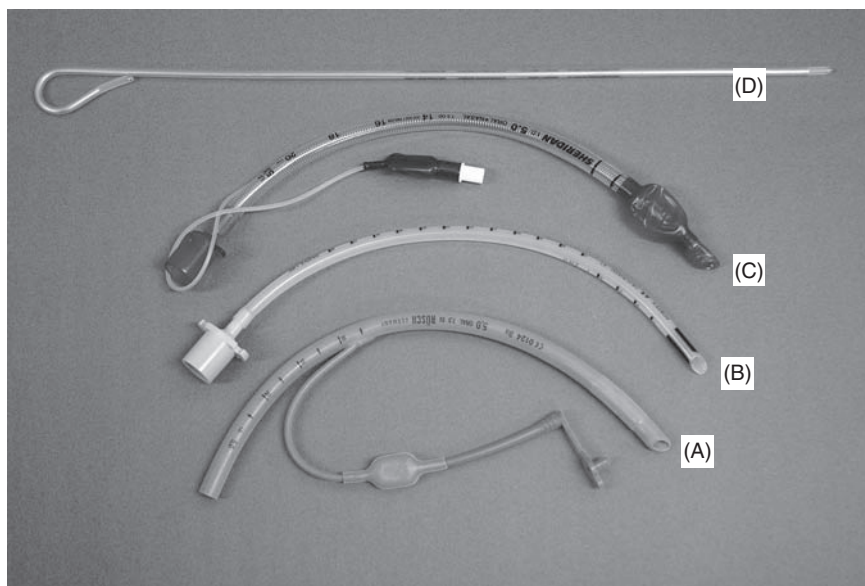


FIGURE 1.12 Endotracheal tubes of different sizes and designs. (A) Cuffed tube, (B) uncuffed tube, (C) armoured, cuffed, tube and (D) introducer.

most disposable tubes) or by clamping with a pair of haemostats. Tubes may be reusable or be intended only for single use. Reusable tubes are generally constructed of rubber and are opaque. They deteriorate gradually, becoming brittle and easily kinked. The cuff often becomes distorted and may leak, so it is preferable to purchase single-use tubes and allow a limited amount of reuse. Clear polyethylene tubes have the advantage in that condensation appearing in the tube with each breath provides an immediate indication that the tube is correctly positioned in the airway. Most commercially available tubes are excessively long for animal use and their length should be shortened to reduce unnecessary dead space (see Chapter 2). When animals are intubated and the head and neck are flexed excessively (e.g. when placed in some positions in a stereotaxic frame), there is a greater risk of the tube kinking. This can be prevented by using an armoured tube which is reinforced with a wire coil (Fig. 1.12C). Note that these types of tubes should not be used in an MRI.

Tubes should be inspected carefully before use to ensure they have not begun to deteriorate. The cuff should be inflated to make sure there are no tears and that it inflates evenly. They should be cleaned after use by washing in hot soapy water, then thoroughly rinsed and dried. If apparatus for pasteurization is available, tubes can be pasteurized. Many types do not withstand autoclaving, although some may be autoclaved a limited number of times at lower temperatures (121 °C for 15 minutes), or sterilized using ethylene oxide. If ethylene oxide is used it is

TABLE 1.2 Endotracheal Intubation, Equipment Required.

Species	Body weight	Endotracheal tube diameter	Laryngoscope
Cat	0.5–1.5 kg > 1.5 kg	2.0–3 mm O/D* 3–4.5 mm O/D	MacIntosh size 1
Dog	0.5–5 kg > 5 kg	2–5 mm O/D 4.0–15 mm O/D	MacIntosh size 1–4
Guinea pig	400–1000 g	16–12 gauge plastic cannula	Purpose-made laryngoscope [†] Otoscope
Hamster	120 g	1.5 mm	Purpose-made laryngoscope [†]
Mouse	25–35 g	1.0 mm	Purpose-made laryngoscope [†]
Primate	0.35–20 kg	2–8 mm O/D (or purpose-made tube for smallest animals)	MacIntosh or Wisconsin size 1–3
Pig	1–10 kg 10–200 kg	2–6 mm O/D 6–15 mm O/D	Soper or Wisconsin size 1–4
Rabbit	1–3 kg 3–7 kg	2–3 mm O/D 3–6 mm O/D	Wisconsin size 0–1 or Flecknell size 1
Rat	200–400 g	18–12 gauge plastic cannula	Purpose-made laryngoscope [†] Otoscope
Sheep	10–90 kg	5–15 mm O/D	MacIntosh size 2–4

* O/D, Outside diameter

† Costa et al. (1986)

critically important that all traces of the gas are eliminated before subsequent use of the tube. Since disposable tubes are readily available at low cost, if there are concerns relating to infection, it is better to simply dispose of the tube.

Laryngoscopes

Laryngoscopes are used to obtain a clear view of the larynx so that an endotracheal tube may be passed easily and atraumatically. A variety of designs is available commercially, and a list of recommended blades is given in Table 1.2 and illustrated in Figure 1.13. The handle, besides usually containing the batteries, acts as a counterbalance to the blade. For this reason it will be found most convenient to purchase handles of the appropriate size for each range of blade sizes. Replacement bulbs should also be purchased so that they are always readily available. Details of the use of a laryngoscope are given in Chapter 2. After use,

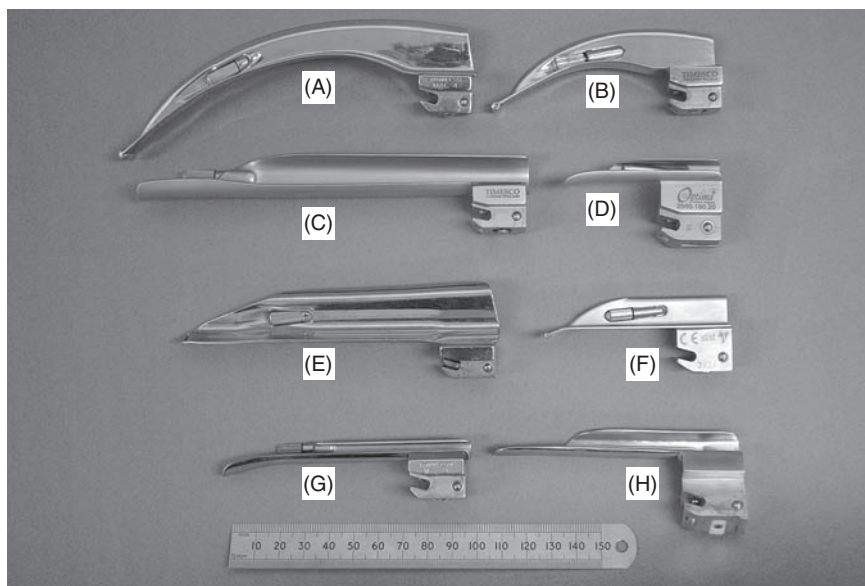


FIGURE 1.13 Laryngoscope blades of various designs. Macintosh (A, B), Wisconsin (C, D), Soper (E, F) and Miller (G, H).

the handle should be separated from the blade and wiped clean. The blade should be washed in hot soapy water and dried thoroughly.

Monitoring Equipment

Monitoring equipment should be switched on and allowed a period to stabilize if necessary; also its functions should be checked. Alarm limits should be reset from the default settings (which are often values appropriate for human patients) and then fine-tuned when the individual animal is connected. Heating pads and blankets should be switched on approximately 30–60 minutes before they are needed, to allow them to attain the desired operating temperature.

Incubators and Recovery Pens

Finally, if the animal is to recover from anaesthesia, check that a suitable area for post-operative recovery has been provided (see Chapter 6) and any incubator or heat pad needed in the recovery period is switched on well in advance.

PERSONNEL

If personnel are allocated to assist with anaesthesia, check that they have been properly briefed about the research protocol and are familiar with the equipment and techniques to be used. Ensure that they are aware of the time for which they

are required, including attendance for post-operative observation and care, which may be outside the normal working day.

THE ANIMAL

The single most important factor that can reduce the risks associated with anaesthesia is the use of animals of high health status. It is most important to ensure that any animal that is to be anaesthetized is at least in overt good health and free from clinical disease. Whenever possible, animals of defined health status should be obtained so that the occurrence of respiratory and other diseases can be eliminated. Anaesthetizing animals that have spontaneous disease, even if it causes no overt clinical signs, usually results in increased mortality and morbidity. Aside from the wasted resources and animal welfare implications, spontaneous disease increases variability in research data and so requires use of a larger number of animals.

Acclimatization

Animals should be obtained at least 7 and preferably 14 days before their intended use, so that an appropriate period is allowed for acclimatization to their new environment. Requirements vary in different establishments, and research workers should check on local practices. During this period the metabolic and hormonal changes caused by the stress of transportation will return to normal, and the animal can be monitored for any signs of ill health. Animal care staff and research workers will have the opportunity to familiarize themselves with the behaviour and characteristics of the particular group of animals, and body weight, growth rate and food and water consumption can be recorded. This information is invaluable if animals are intended to recover from anaesthesia after undergoing a surgical procedure. Many of the pain assessment schemes that are under development rely on knowledge of these variables, and it is important that such information is obtained and recorded (see Chapter 6). Even when planning non-recovery procedures, an assessment of food and water intake or growth rate will provide some reassurance that the animal is in a normal physiological state.

Acclimatization of species that can rapidly develop a relationship with their handler (e.g. dogs, cats and pigs) has the advantage of reducing unnecessary distress during induction and recovery from anaesthesia. Regular handling of most species, including small rodents, will habituate the animals to the procedure. Consequently, the animals will be easier to restrain and more co-operative, and induction of anaesthesia will be safer for both the animal and the staff involved.

If animals are to be housed singly after a surgical procedure, it is preferable to acclimatize them to this environment beforehand. This will allow them to adapt to the stress of social isolation and therefore be better able to cope with the stress of anaesthesia and surgery. It will also allow assessment of their normal behaviour when housed singly.

Clinical Examination

Whatever the health status of the animal, it is useful to carry out some form of clinical examination before induction of anaesthesia. Although many investigators may not be familiar with signs of disease or ill health in animals, they are often very familiar with normal animal behaviour and appearance. If there is any deviation from the normal, further advice can be sought from experienced animal technicians and veterinarians. The presence of discharges from the eyes or nose, matting of the fur around these regions or soiling of the perianal region with faeces requires further investigation. If the overall appearance of the animal is abnormal or any of the clinical signs mentioned is present, induction of anaesthesia should be delayed until expert advice is obtained. As mentioned above, it is helpful to monitor food and water intake and body weight for a few days pre-operatively. This will allow to assess whether the intake is normal and will be of use in monitoring the post-operative recovery of the animal.

Pre-Anaesthetic Fasting

Cats, dogs, ferrets, primates and pigs should receive no food during the 8–12 hours before anaesthesia to minimise the risk of vomiting during induction of anaesthesia or during recovery. Withholding food from ruminants has virtually no effect on the volume of ingesta that remain in the rumen, unless excessive periods of starvation are employed (3–4 days), but a short period of starvation (12–24 hours) may help reduce the incidence of rumenal tympany or bloat (the accumulation of gas in the stomach).

Pre-anaesthetic fasting of rabbits and small rodents is unnecessary since vomiting during induction does not occur in these species. Problems may occasionally be seen with guinea pigs since they may retain food in their pharynx after being anaesthetized. If this occurs in a significant number of animals then a short period of pre-anaesthetic fasting (3–4 hours) should be introduced. It has been claimed that fasting helps in accurate anaesthetic dosing in rabbits and guinea pigs. This might have been relevant when anaesthetics with a narrow therapeutic margin (i.e. the anaesthetic dose was close to the lethal dose, e.g. pentobarbital) were in use, but is probably less important when more modern agents are used. It is also important to note that rabbits and guinea pigs are particularly susceptible to gastrointestinal disturbances following surgery. This can lead to serious consequences as it can predispose to the development of enterotoxaemia. For this reason the author almost never withholds food from these species. An exception is if gastrointestinal tract surgery is to be undertaken and a reduction in the volume of gut contents is required. In these circumstances, fasting may be required in all species, but it is important to note that rodents and rabbits are coprophagic, so measures to prevent them ingesting their faeces may be necessary to provide a completely empty stomach. An additional complication arises because of the diurnal rhythms of some species. Although food may be provided immediately

post-operatively, it may not be eaten until the onset of the dark phase of the animal's photoperiod. In addition, if the animal's appetite is depressed because of pain, surgical stress or delayed recovery from anaesthesia, food and water intake may be severely depressed for at least 24 hours post-operatively. The metabolic consequences of this, especially when coupled with pre-operative fasting, can be severe and can compromise both the research data obtained and animal welfare. It is therefore preferable to withhold food only when required by a particular research protocol. If a short period of fasting is needed, this can be achieved by providing a limited amount of food in the food hopper. Rodents don't plan ahead and will eat normally until the food is exhausted, so food can be withdrawn for part of the night, without the need for attendance by animal care staff.

Withholding food from pregnant animals of all species, but in particular ruminants and guinea pigs, can produce severe metabolic disturbances that may prove fatal.

Large or medium-sized birds (e.g. ducks, chickens, pigeons) may be fasted for 6–12 hours to reduce the risk of regurgitation of the contents of the crop. Smaller birds should not be fasted for longer than 2 hours to avoid the risk of inducing hypoglycaemia. Fasting of reptiles and amphibians is generally unnecessary. Fish should be fasted for 24–48 hours prior to anaesthesia.

All animals should be provided with drinking water until approximately 60 minutes prior to induction of anaesthesia. If the animal has a reduced fluid intake, or if vomiting, diarrhoea or haemorrhage has occurred, then some pre-operative fluid therapy will be necessary. The basic principles are outlined in Chapter 5, but whenever possible veterinary advice should be obtained.

Whenever practicable, animals should be weighed before anaesthesia, both to allow accurate calculation of drug dosages and to enable assessment of any post-operative weight loss.

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Anaesthesia

Providing optimal anaesthesia for a wide range of research procedures that may need to be undertaken requires careful consideration of the numerous different anaesthetic agents that are available. Some procedures may require only loss of consciousness to provide restraint of the animal, and others may require deep surgical anaesthesia. In addition to selecting appropriate agents to produce and maintain anaesthesia, it may also be useful to use pre-anaesthetic agents to provide sedation or analgesia. Choices of anaesthetic regimens may include volatile anaesthetics, injectable agents or combinations of these. Depending on the duration of anaesthesia, and the species involved, techniques such as endotracheal intubation may be necessary, and anaesthetic breathing systems may be needed to deliver oxygen and anaesthetic gases.

Selecting the most appropriate techniques requires consideration of the welfare of the animals involved, the efficacy of the specific anaesthetic agents, their particular effects on body systems and the potential interactions of these agents with individual research protocols.

To carry out surgical procedures on animals, pain perception must be completely suppressed. If anaesthesia is being induced simply to provide humane restraint while non-painful procedures are carried out, then only light anaesthesia, with little pain suppression, will be required. These different levels of anaesthesia can be produced in various ways, using either a single agent, or combinations of agents and techniques. Local or regional anaesthetics block all sensation, including pain, in a specific area; general anaesthetics produce loss of consciousness and varying degrees of suppression of pain perception, depending on the dose given. Different general anaesthetic agents can appear to provide similar levels of hypnosis (sleep), but the degree of analgesia provided can vary widely.

The classification of agents as ‘hypnotics’ or ‘anaesthetics’ causes some confusion, since at high doses, hypnotics such as tribromoethanol produce anaesthesia. Different anaesthetics and hypnotics act in different ways to produce their effects (Antkowiak, 2001; Franks, 2006). Surgical planes of general anaesthesia require both loss of consciousness and loss of pain sensation, and this can

be produced by agents that have both analgesic and hypnotic properties. Even if an agent only produces sleep and has no specific analgesic effects, if a high enough dose is given, even intense pain will not be perceived, because of the very marked depression of all brain activity. However, if no specific analgesic component is provided, this may result in increased post-operative pain (see Chapter 5) because of the effects of the surgical stimuli on the nervous system. For this reason, anaesthetic techniques using hypnotics often also include use of analgesic agents.

GENERAL ANAESTHESIA

General anaesthesia can be induced by using a variety of drugs and techniques. Often a single drug can be given to produce all the required features of general anaesthesia: loss of consciousness, analgesia, suppression of reflex activity and muscle relaxation. Alternatively, a combination of agents can be given, each making a contribution to the overall effect. The advantage of such an approach is that the undesirable side-effects of anaesthetic agents can often be minimized. The side-effects of anaesthetics are usually dose dependent. Giving several drugs in combination, at relatively low dose rates, can often result in less effect on major body systems than that following induction of anaesthesia using a single anaesthetic agent. These combinations of agents are often administered as a single injection in small rodents, but in larger species, sedatives and analgesics are often given first, as 'pre-anaesthetic medication', followed by other drugs to produce anaesthesia. Alternatively, anaesthesia may be induced using an injectable anaesthetic, and then the depth or duration of anaesthesia prolonged using inhalational agents.

A brief review of some of the major effects of the more widely used pre-anaesthetic and anaesthetic agents is given below. More detailed reviews are available (e.g. Tranquilli et al., 2006) and further discussion on factors influencing the selection of a particular method of anaesthesia is included later.

Pre-anaesthetic Medication

It may be helpful to include pre-anaesthetic medication as part of the anaesthetic technique. The advantages of this are:

- Administering sedatives or tranquillizers can reduce aggression and fear or apprehension and aid stress-free induction of anaesthesia.
- Use of analgesics can reduce pain, especially in the immediate post-operative period, and may provide more effective pain relief through 'pre-emptive analgesia' (see Chapter 5).
- Atropine or glycopyrrolate can be given to reduce bronchial and salivary secretions and to protect the heart from vagal inhibition caused by some procedures (e.g. endotracheal intubation, manipulation of the viscera during surgery). It is advisable to use glycopyrrolate in rabbits, as atropine is often relatively ineffective in this species (Harrison et al., 2006).

- Use of sedatives, tranquillizers and analgesics can reduce the amount of anaesthetic needed to produce the desired level of anaesthesia. These agents also provide smoother induction of anaesthesia and a smoother recovery.

Although the advantages listed above apply to all animal species, pre-anaesthetic medication is used most often in larger animals, where sedation and tranquilization are required to aid humane restraint and minimize the risk of injury to the animal and its handler. Pre-anaesthetic medication should be used in a wider range of species, since even when restraint is not a problem, the use of sedatives and tranquillizers may be advantageous. In humans, many of the drugs used have been shown to reduce fear and allay anxiety, and similar effects occur in animals. In addition to the use of drugs, careful and expert handling of laboratory animals is an essential part of their management before and after anaesthesia.

Consideration of the techniques used and their possible stressful effects upon the animal should enable modification of anaesthetic protocols to minimize pain or distress. For example, administration of a sedative/analgesic to an animal still housed in its pen or cage, followed by removal to the operating theatre or research laboratory only after the drug has taken effect, can considerably reduce the stress that might otherwise be caused.

If an intravenous induction agent is to be used, then it is helpful to apply a local anaesthetic cream (e.g. EMLA, Astra) to the skin overlying the vein, about 45–60 minutes before intravenous injection. This eliminates the pain or discomfort of venepuncture, and has the added advantage of eliminating any movement in response to the procedure, since the skin is completely anaesthetized (Flecknell et al., 1990b).

The selection of a pre-anaesthetic drug regime will depend on the animal species to be anaesthetized; the anaesthetic agents to be used; the particular requirements of the research protocol; and the personal preferences of the anaesthetist. The characteristics of the major groups of drugs available are listed below, and detailed recommendations for each species are given in Chapter 6.

Antimuscarinics (or Anticholinergics)

Atropine

Desirable Effects These include reduction of bronchial and salivary secretions that might partially occlude the airways. Atropine protects the heart from vagal inhibition, which can occur during endotracheal intubation or during surgical procedures, particularly if the viscera are handled. Atropine may also be used to correct any slowing of the heart caused by opioids such as fentanyl.

Undesirable Effects These include increased heart rate. In ruminants, atropine does not completely block salivary secretions, which become more viscous.

Special Comments Avoid the use of atropine if the heart rate is already elevated; also avoid if tachycardias are likely to be produced (e.g. during cardiac

surgery). Atropine is rapidly metabolized in some strains of rabbits and so its effects may be unpredictable in this species (Harrison et al., 2006).

Glycopyrrolate

Desirable Effects These include reduction of salivary and bronchial secretions, protection of the heart from vagal inhibition.

Undesirable Effects These include increased heart rate, although less pronounced than atropine in some species.

Special Comments Glycopyrrolate has a longer duration of action than atropine and has been reported to be the more effective agent in rodents and rabbits (Olson et al., 1993). It is the antimuscarinic agent of choice in rabbits since its duration of action is less affected by the high levels of atropinase that may be present in this species. Glycopyrrolate does not cross the blood–brain barrier, and in man produces less visual disturbances than atropine. This may be advantageous in some animal species.

Tranquillizers and Sedatives

Tranquillizers produce a calming effect without causing sedation. At high doses, they produce ataxia (lack of co-ordination), and animals become much less alert, but are readily roused, particularly in response to painful stimuli, since these drugs have no analgesic properties. Sedatives produce drowsiness and appear to reduce fear and apprehension in animals. There is considerable overlap in the action of many agents and a good deal of species variation in their effects, making definitive classification of drugs as either sedatives or tranquillizers difficult.

Phenothiazines: Chlorpromazine, Acepromazine, Promazine

Desirable Effects These agents produce sedation; potentiate the action of anaesthetics, hypnotics (agents that produce sleep), opiates (morphine and morphine-like) analgesics; and so reduce the dose of these drugs required to produce surgical anaesthesia. Sedation may extend into the post-operative period, so that recovery from anaesthesia is smooth.

Undesirable Effects Moderate hypotension (reduction in blood pressure) may occur because of dilation of peripheral blood vessels. Temperature regulation is depressed and moderate falls in body temperature may occur.

Special Comments The undesirable effects noted above are well tolerated by normal animals, but the drugs should not be used in animals with any form of fluid deficit, for example, dehydration or haemorrhage. This group of drugs has no analgesic action, but they potentiate the action of opiates.

Butyrophenones: Droperidol, Fluanisone, Azaperone

Desirable Effects These drugs have effects similar to those of phenothiazines (above), but are more potent.

Undesirable Effects The hypotensive effects of these drugs are generally less severe than those caused by phenothiazines.

Special Comments Butyrophenones such as droperidol and fluanisone are most widely used as components of neuroleptanalgesic combinations (see below).

Benzodiazepines: Diazepam, Midazolam

Desirable Effects These include sedation, but there is considerable species variation in effect: sedation is very variable in dogs, but marked in rabbits, rodents, sheep and pigs. Benzodiazepines potentiate the action of most anaesthetics and opioid (morphine-like) analgesics. They produce good skeletal muscle relaxation (NB: not muscle paralysis). A specific antagonist, flumazenil, is available, so that sedation can be reversed if necessary (Pieri, 1981; Amrein, 1990).

Undesirable Effects In some species (dog and cat), benzodiazepines may cause mild excitement and disorientation rather than sedation. Injection of some preparations of diazepam into small blood vessels can cause irritation and damage to the vessel.

Special Comments Benzodiazepines (e.g. diazepam, midazolam) have both potent tranquillizing and sedative actions. Diazepam is the agent most frequently used, although some injectable formulations in organic solvents cannot be mixed with other water-soluble agents. An emulsion formulation of diazepam (Diazemuls, Pharmacia and Upjohn) is not irritant to blood vessels and so avoids the problem mentioned above. Midazolam has effects similar to those of diazepam but has a shorter duration of action. Unlike diazepam, it is water soluble and so can be mixed with other agents (see below). The hypnotic (sleep-inducing) effects of these agents in animals, unlike humans, are generally minimal. When administered alone, benzodiazepines have a hyperalgesic effect in humans in some circumstances (i.e. they increase the degree of pain which is perceived). This may also occur in animals, so they should not be used for post-operative sedation unless effective analgesia is also provided, for example, by administration of opioids.

Alpha-2-adrenergic Agonist Tranquillizers: Xylazine, Medetomidine and Dexmedetomidine

Desirable Effects Xylazine and medetomidine are potent sedatives, and are hypnotics in some species. Their analgesic effects vary in different species, but in most animals, mild to moderate analgesia is produced. Xylazine and medetomidine markedly potentiate the action of most anaesthetic drugs. Their action can be reversed by administration of specific antagonists such as yohimbine and atipamezole. Medetomidine is an equal mixture of two optical enantiomers, dexmedetomidine and levomedetomidine. Dexmedetomidine, the active component in this mixture, is now available as a veterinary product. The majority of studies utilizing this single enantiomer has so far been undertaken in companion and farm animals (Murrell and Hellebrekers, 2005; Kastner, 2008), but data are

becoming available in laboratory species (Franken et al., 2008). These studies indicate that, as would be predicted, it has double the potency of an equal dose of medetomidine. This suggests that it can be used at 50% of the medetomidine doses listed in Tables 6.3–6.26 in laboratory species.

Undesirable Effects These drugs produce cardiovascular and respiratory depression, and when high doses are given, these side-effects can be significant. Cardiac arrhythmias may occur following administration of xylazine in some species. Xylazine may cause severe respiratory depression if administered in combination with barbiturates or alphaxalone/alphadolone. In species that vomit, medetomidine and xylazine often trigger this reflex.

Special Comments Xylazine is a useful sedative in cattle, sheep, goats, horses, cats and primates. It may also be a valuable (but relatively short acting) analgesic in sheep and goats (Grant and Upton, 2004). Xylazine, medetomidine and dexmedetomidine should be used with caution in sheep, since they can produce severe hypoxia (Kastner et al., 2008). The major use of xylazine in laboratory animal anaesthesia is in combination with ketamine to produce surgical anaesthesia (see below). Xylazine has been reported to cause pronounced hyperglycaemia (Saha et al., 2005) and a marked diuresis (Greene and Thurmon, 1988). A similar diuresis has been observed by the author during ketamine/xylazine anaesthesia in rats and mice. Medetomidine has similar effects to xylazine, but it is a much more specific alpha-2 agonist and is therefore claimed to have a lower incidence of side-effects (Virtanen, 1989). It can be used to provide deep sedation with complete immobilization in many species, avoiding the need for general anaesthesia, and can be rapidly and completely reversed using the specific antagonist, atipamezole. Atipamezole is preferable for use as a reversing agent for medetomidine, xylazine and other related agents, as it has fewer side-effects than older antagonists such as yohimbine. It can be given by the subcutaneous, intraperitoneal, intramuscular or intravenous routes. Absorption following subcutaneous injection is rapid, generally acting within 5–10 minutes. Dose rates of 0.5–1.0 mg/kg are required in small laboratory animal species, although less is required in larger species, for example, 25 µg/kg in sheep. Dose also depends upon the dose of medetomidine that has been administered. Other drugs of this group, for example, detomidine, are available for use in horses and ruminants, but there is only limited information available concerning their effects in small mammals (Virtanen and Nyman, 1985; Cox et al., 1994).

Morphine and Morphine-Like Analgesics (Opioids)

Morphine, Pethidine (Meperidine), Buprenorphine, Butorphanol, Nalbuphine, Pentazocine, Methadone, Fentanyl, Etorphine, Oxymorphone, Hydromorphone

Desirable Effects These compounds can produce moderate sedation and profound analgesia, but in some species, pre-operative administration will cause hyperactivity and excitement. Further details of the effects of each agent are given in Chapter 5.

Undesirable Effects These drugs may produce respiratory depression [generally only at high-dose rates and in combination with other central nervous system (CNS) depressants] and vomiting in some species (dog, primates). A more detailed discussion of side-effects can be found in Chapter 5.

Special Comments These analgesics can be used both to provide analgesia and to reduce the dose of anaesthetic agents necessary to produce surgical anaesthesia. It is also probable that pre-operative administration of analgesics may reduce the degree of post-operative pain (McQuay et al., 1988; Breivik, 1994), although this concept has been revised recently (Grape and Tramer, 2007; see Chapter 5). Opioids are also widely used as components of neuroleptanalgesic combinations (see below). A number of commercial preparations that combine a potent opioid with a sedative or tranquillizer are available, such as 'Hypnorm' (Vetapharma, UK) (fentanyl and fluanisone) in Europe and 'Innovar-Vet' (fentanyl and droperidol) in the USA. It is also possible to produce other combinations. For example, a mixture of acepromazine and butorphanol is useful when blood sampling in rabbits, as it provides some sedation, analgesia, and dilates the ear veins. Buprenorphine combined with acepromazine provides excellent restraint for procedures such as radiography in dogs. Dose rates for these combinations are included in Tables 6.3–6.19. A more detailed description of the individual agents is given in Chapter 5.

Dissociative Agents

Ketamine and Tiletamine

Desirable Effects Ketamine produces immobility in most species and can be administered by the intramuscular, intraperitoneal and intravenous routes. It causes only moderate respiratory depression in most species and increases blood pressure.

Undesirable Effects Skeletal muscle tone is increased. The degree of analgesia produced is very variable. Recovery can be prolonged and may be associated with hallucinations and mood alterations (Wright, 1982).

Special Comments Ketamine produces a state of cataleptic sedation with apparent lack of awareness of the surroundings (White et al., 1982). In those species in which profound analgesia appears to be produced (e.g. old-world primates), spontaneous movements often occur, but these are usually unrelated to painful stimuli. In some species, the corneal blink reflex is lost for prolonged periods, and drying of the cornea may occur unless the eyes are filled with a bland ophthalmic ointment as a preventive measure. Laryngeal and pharyngeal reflexes are maintained at all, except very high, dose rates, although salivary secretions are increased and airway obstruction remains a significant hazard. Ketamine is the drug of choice for immobilization of large primates; it is an effective chemical restraining agent in cats and pigs and, to a lesser extent, in rabbits. Its effects in rodents are variable, and high dose rates may be necessary to produce immobilization (Green et al., 1981a). It is extremely useful when administered in combination

with medetomidine, xylazine or diazepam for the production of surgical anaesthesia in sheep, primates, cats, dogs, pigs, rabbits and small rodents (see below and Chapter 6). In all species, it may be necessary to use atropine or glycopyrrolate together with ketamine to reduce the otherwise excessive bronchial and salivary secretions that are produced. The chronic administration of ketamine results in hepatic enzyme induction, and this may decrease the efficacy of the agent on subsequent administrations (Marietta et al., 1975).

Ketamine is widely used in old-world primates and produces immobility and some analgesia. It has the advantage that even at light levels of sedation, the bite reflex is lost. It is usually administered intramuscularly, but it can also be given by mouth if intramuscular injection is not possible. It is most effective if applied to the mucous membranes of the mouth, once in the stomach it undergoes some first-pass liver metabolism, and both the onset of action and the peak effect are markedly reduced compared to administration by injection (4–10 times the intramuscular dose is required). It can, however, be injected into foods such as bananas, to sedate animals that have escaped from their cages. Tiletamine is rarely used alone, and is available commercially combined with zolazepam (a benzodiazepine). More details of the use of dissociative agents are given below.

Anaesthetic Agents

Administration of Anaesthetics by Inhalation

Details of the equipment needed and its maintenance are given in Chapter 1. Controlled administration of an inhaled anaesthetic requires the use of an anaesthetic machine and a vaporizer, coupled to some form of delivery system – for example, a face mask and breathing system or anaesthetic chamber. For several reasons (see Chapter 3), it is desirable to supply oxygen even when volatile and gaseous anaesthetics are not used, that is, in animals anaesthetized with injectable agents.

Anaesthetic Chambers

Anaesthetic gases are denser than air, so it should be appreciated that anaesthetic chambers only fill gradually. To avoid gas-scavenging systems removing anaesthetic as rapidly as it is added, waste gas should be removed from the top of the chamber, and fresh anaesthetic gas should flow in at the base. To provide rapid induction, the entire chamber should be filled quickly. An appropriate gas flow can be estimated by measuring the chamber volume. The approximate time to completely fill the chamber can then be determined from the flow of anaesthetic:

$$\frac{\text{Chamber volume}}{\text{flow}} = \text{time to fill}$$

A chamber measuring 20 × 20 × 30 cm will have a volume of 12 litres, so with a flow rate of 4 l/min, the filling time would be 3–4 minutes. Filling times

for larger chambers (e.g. those designed for use in rabbits and cats), with volumes exceeding 50 litres, can be considerable, since most flow meters have a maximum flow of 10–12 l/min. Occasionally, it may be necessary to induce anaesthesia using a volatile anaesthetic in a larger animal, and in these circumstances, the entire cage may be enclosed in a polythene bag and anaesthetic vapour piped in. This can result in very slow induction. An alternative is to use a vapour wand (Hodgson, 2007) that provides much more rapid delivery of anaesthetic vapour, and consequently more rapid induction of anaesthesia.

‘Ether Jars’

In the past, it was common practice to anaesthetize small rodents by placing them in a glass receptacle containing a pad of gauze or cotton wool soaked in liquid anaesthetic. Direct contact with the liquid anaesthetic is extremely unpleasant for the animal, as it is irritant to mucous membranes. Even if the gauze is separated from the animal by a metal grid, liquid anaesthetic is often spilt onto areas that are in contact with the animal. The concentration of anaesthetic that can be achieved in such containers is unpredictable and is invariably dangerously high if potent, easily vaporized anaesthetics such as halothane are used. For example, the concentration of halothane produced at 20°C is 32%, more than six times the safe induction concentration (Table 2.1). If ether is used, there will be a significant risk of fire or explosion. Whichever volatile anaesthetic is used, it is frequently impossible to prevent contamination of the environment with anaesthetic vapour, and this may present a hazard to the anaesthetist. The use of such an anachronistic technique has no advantage other than the low cost of the apparatus. However, it may still be necessary to use if no alternative is available, or when anaesthetizing wild animals under field conditions. In these circumstances, attempts can be made to reduce the concentration of anaesthetic vapour produced by mixing the anaesthetic with propylene glycol (Itah et al., 2004). If ‘field’ anaesthesia is being undertaken regularly, it may be worthwhile investing in a mobile anaesthetic system, as described by Mathews et al. (2002).

Anaesthetic Breathing Systems

Anaesthetic chambers are useful for inducing anaesthesia in small animals that may be difficult to restrain, but the animals must be removed from the chamber to enable surgical manipulations to be carried out. Unless the operative procedure is of extremely short duration, some method of maintaining anaesthesia must be provided.

The first impression of anaesthetic breathing systems is that they are complex and difficult to use. This apparent complexity, coupled with a reluctance to develop the expertise necessary to carry out endotracheal intubation, has led to an over-reliance on open-mask systems. Other breathing systems can be used successfully, but care must be taken to avoid assembling them incorrectly, or choosing a system that is inappropriate for use in small animals. Several advances in breathing system

TABLE 2.1 Physical Characteristics and Relative Potency (MAC₅₀) of Different Volatile Anaesthetics.

	Desflurane	Enflurane	Halothane	Isoflurane	Methoxyflurane	Nitrous oxide	Sevoflurane
Molecular weight	168	184.5	197.4	184.5	163.9	44.0	200.1
Vapour pressure (mmHg at 20 °C)	669	172	240	240	23	Gas at room temperature	
Vapour concentration (% saturated at 20 °C)	89.6	23	32	32	3	100	22.4
MAC (in dog)	7.2	2.2	0.87	1.28	0.23	188–222	2.1–2.36
Stability in soda lime	Stable	Stable	Slight decomposition	Stable	Slight decomposition	Stable	Decomposition to compound A
Solubility							
• Blood–gas partition coefficient	0.42	1.9	2.3	1.4	15	0.47	0.69
• Rubber–gas partition coefficient	19	74	120	62	630	1.2	14
• Percentage of anaesthetic recovered as metabolite (in humans)	0–0.02	0–2	15–40	0–0.2	50	0.004	5–8

Data adapted from Steffey et al. (1974) and Preckel and Bolten (2005).

design have been introduced into human anaesthetic practice, and these developments can often usefully be transferred to laboratory animal anaesthesia.

General Considerations All anaesthetic breathing systems aim to deliver sufficient anaesthetic gases to meet the animal's requirements and to remove exhaled gases, which contain carbon dioxide. It is an advantage if these exhaled gases can be removed from the operating area, as trace concentrations of anaesthetic gases may have adverse effects on operating theatre personnel. An additional consideration when selecting a breathing system is the ease and efficiency with which assisted ventilation can be carried out.

Different types of breathing systems produce different degrees of resistance to breathing, and have different volumes of dead space. The dead space of a breathing system is the part of the system that remains filled with expired gas at the end of expiration. This carbon dioxide-rich gas is then re-inhaled by the animal. If a significant amount of expired gas is rebreathed, the blood carbon dioxide concentration will rise and produce a range of adverse effects (see Chapter 3). The resistance of an anaesthetic breathing system influences the effort that must be made by the animal to move gas in and out of, or around, the breathing system. Breathing systems with narrow or sharply angled components and those with valves will provide a greater resistance to gas flow and so will require a greater respiratory effort by the animal. This is important since excessive effort to breath can cause fatigue of the respiratory muscles, and depress respiration. It also increases the oxygen needs of the animal.

Tidal Volume and Minute Volume Two measures of an animal's respiratory function also influence the choice of breathing system – the 'tidal volume' and the 'minute volume'. The tidal volume is the volume of gas drawn into the respiratory tract with each breath. The minute volume is the volume of gas drawn into the respiratory tract in 1 minute and so is calculated by multiplying the tidal volume by the respiratory rate. The minute volume is not always equivalent to the flow of gas that needs to be delivered to the animal by the breathing system. During each respiratory cycle, gas is only drawn into the lungs for approximately one-third of the time, during inspiration and obviously not during expiration or during the pauses between expiration and inspiration. This means that the animal's minute volume is inhaled in approximately 20 seconds, so using a simple face mask system, a fresh gas flow of three times this volume per minute is required. Occasionally, an even greater flow, to meet the most rapid rate at which gas is drawn into the lungs, the peak inspiratory flow rate, may be needed. Using this type of breathing system is clearly very uneconomical, so various breathing systems have been designed to reduce the fresh gas flows required, by providing a reservoir for the unused gas delivered by the anaesthetic machine.

Open Breathing Systems As mentioned earlier, the most widely used breathing system is an open face mask (Fig. 2.1), which is a simple and convenient way of delivering anaesthetic gases to an animal. Expired gases pass around the edges

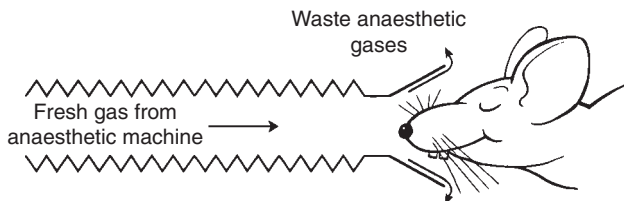


FIGURE 2.1 Open-mask breathing circuit.

TABLE 2.2 Recommended Fresh Gas Flow Rates for Different Anaesthetic Circuits.

Body weight (kg)	Estimated tidal volume (ml)	Minute volume (litre)	Flow rate (l/min)			
			Open system	T-piece or Bain's circuit	Magill	Closed circuit*
500	5–7.5	0.4–0.6	1–2	1–1.5	–	–
1	10–15	0.5–1	1.5–3	1.5–2.5	–	–
3	30–45	1–1.5	3–4.5	2.5–3.5	–	–
6	60–90	1.5–3	4.5–9	3.5–7.5	–	0.2
10	100–150	3–6	9–18	6–12	3–6	0.3
20	200–300	5–9	15–27	10–18	5–9	0.5

*See text.

of the mask. Provided the gas flow is sufficiently high, rebreathing of exhaled gases will be small and the dilution of the anaesthetic gases by breathing room air will be avoided. If the gas flow is too low, the animal will breathe in room air from around the edges of the mask. This will result in a reduction in the depth of anaesthesia if volatile anaesthetics are being used. As mentioned above, to meet inspiratory flow requirements, the gas flows must be three times the animal's minute volume. Typical flows are shown in Table 2.2.

This simple method of delivery has several drawbacks. The gas flow must be high, although when small rodents are anaesthetized; this is relatively unimportant as total flows will often be less than 500 ml/min. Removing waste anaesthetic gases is difficult, since gas escapes all around the mask. To avoid this, a concentric mask system can be used (see Chapter 1, Fig. 1.11). The concentric mask system appears to resemble the Bain coaxial breathing system described below, but it must be stressed that the outer tube does not act as a gas reservoir, so gas flows appropriate to an open system must be used (Table 2.2).

One problem with currently available concentric systems of this type is that the gas extraction rate is often too high, which results in dilution of the fresh gas

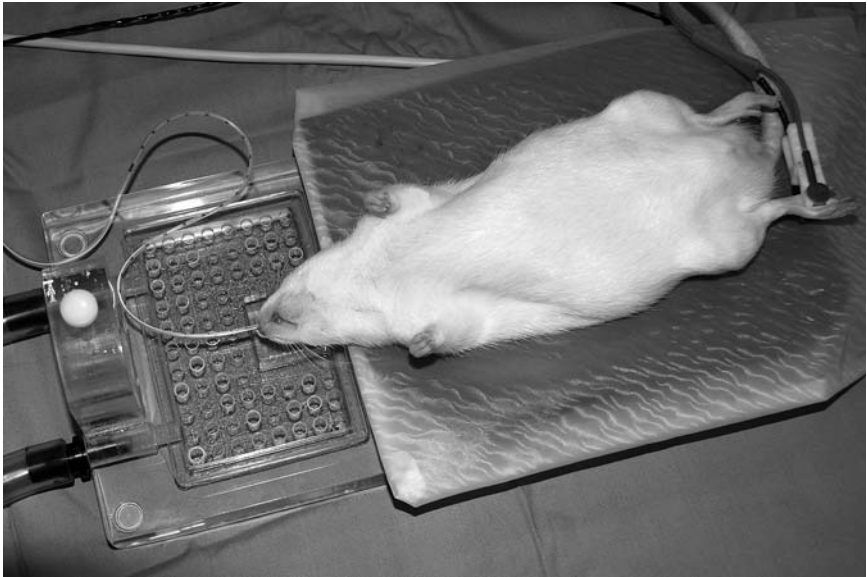


FIGURE 2.2 Down-draft operating table – a heating blanket has been added to maintain the animal's body temperature.

intended to supply the animal. As a result, when flows calculated on the basis of minute volume are employed, the animal may be inadequately anaesthetized. To avoid this, minimum flows of 500–1000 ml/min may be required. It is hoped that modified designs will become available that incorporate some means of varying the degree of suction applied for gas scavenging.

An alternative means of removing waste anaesthetic gas is to use a down-draft operating table. A number of systems are available commercially, including systems that incorporate heating systems to help maintain the animal's body temperature during anaesthesia (Fig. 2.2).

Perhaps the most serious disadvantage in using a simple open breathing system is that it is not possible to assist ventilation artificially should this be required.

Semi-closed Breathing Systems Semi-closed breathing systems are systems in which some rebreathing of expired gases may occur and in which no carbon dioxide absorption is used.

The T-Piece System. The T-piece breathing system was first described by Ayre (1937, 1956), to provide a low-resistance, low-dead space breathing system for use in infants and young children. The breathing system consists of a tube into which the anaesthetic gas mixture is introduced through a small inlet tube at right angles to the main limb (Figs. 2.3 and 2.4). One end of the T-piece is connected to the animal, while the other is left open to the air. A length of tubing is

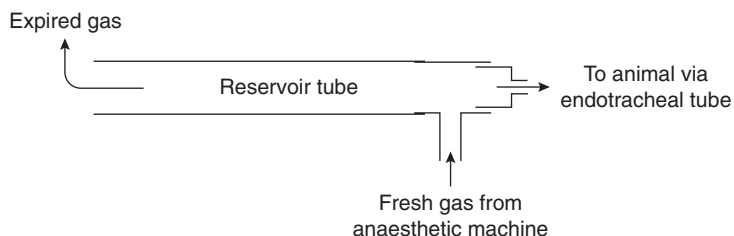


FIGURE 2.3 Ayre's T-piece to show gas flow pattern.

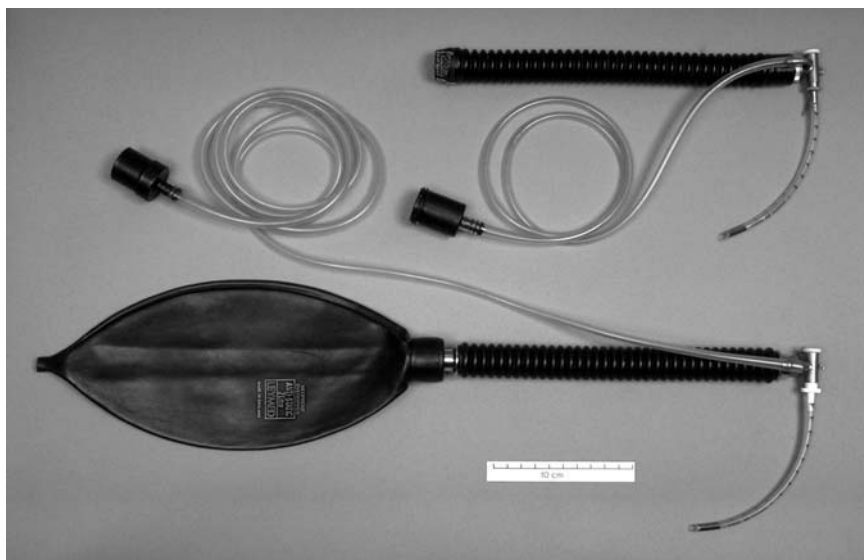


FIGURE 2.4 T-pieces with low-dead space connectors. Above, standard T-piece; below, Jackson Rees modified T-piece.

attached to this open end, providing a small reservoir for anaesthetic gases that would otherwise escape into the outside air. The presence of this reservoir enables the fresh gas flow to be reduced to about twice the animal's minute volume, without rebreathing (see Table 2.2).

During inspiration, fresh gas is drawn in both from the sidearm and from the reservoir. During expiration, exhaled gas fills the reservoir limb, and during the pause before the next inspiration, this is washed out by the fresh gas from the sidearm. The volume of the reservoir limb is unimportant so long as it exceeds one-third of the animal's tidal volume and does not impose any appreciable resistance to expiration. Ventilation can be controlled simply by intermittently occluding the end of the reservoir limb, but if carried out manually, the



FIGURE 2.5 Standard (left) and low-dead space (right) endotracheal tube connectors and T-pieces.

anaesthetist has very little idea of the pressure being delivered to the animal's lungs. It is preferable to attach an open-ended reservoir bag to the expiratory limb: the Jackson Rees modification. Squeezing the bag with the end occluded inflates the lungs, and exhalation occurs through the open end of the bag (Fig. 2.4). No increase in fresh gas flow is required when assisting ventilation in this way. It is easy to attach a mechanical ventilator to the reservoir limb and ventilate the limb with air. Provided the reservoir is of sufficient volume, little or no mixing of the anaesthetic gases and the ventilating gas occurs.

To use the T-piece effectively, it should be connected directly to an endotracheal tube or to a close-fitting face mask. The volume of the patient side of the T-piece should be low to reduce equipment dead space. Similarly, the volume of endotracheal tube connectors should be minimized. This is best achieved by using Oxford paediatric connectors and a Bethune T-piece (Penlon Limited, Appendix 4) or other, disposable, paediatric connectors. These connectors contribute a dead space of approximately 0.2ml compared to 1.5ml when using a conventional type of connector (Fig. 2.5). The dead space of a paediatric T-piece is approximately 1ml. If a face mask is used, it is essential that this fits closely around the animal's muzzle. If it does not, gas will be drawn in around the edges of the mask and the anaesthetic gas mixture will be diluted with room air. If ventilation is assisted, gas will escape around the mask, and the degree of lung inflation

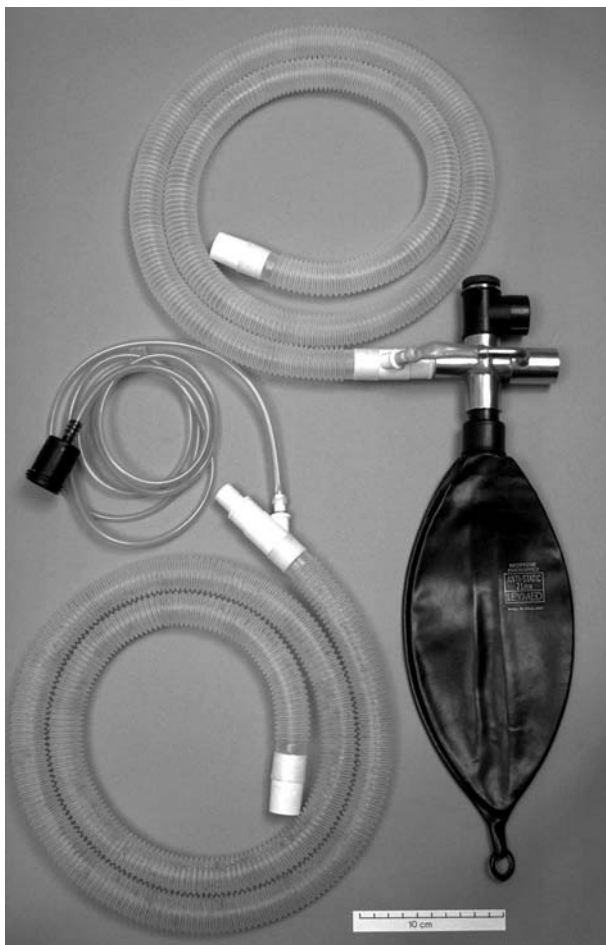


FIGURE 2.6 Bain's circuit (a) and modified Bain circuit (b).

produced will be inadequate. For these reasons, it is preferable to intubate the animal's trachea whenever possible.

The T-piece is an ideal breathing system for small laboratory animals since it offers low resistance to breathing and has a small dead space. It is not always necessary to purchase commercially produced T-pieces, as the apparatus can be constructed easily from plastic 'T' connectors (Portex Ltd., Appendix 4) and rubber tubing.

The Bain Coaxial Breathing System. The Bain breathing system is a coaxial version of a T-piece, in which the fresh gas inflow tubing runs inside the reservoir limb (Figs. 2.6 and 2.7). The breathing system was designed to provide a light-weight breathing system in which any valves or breathing bags were situated

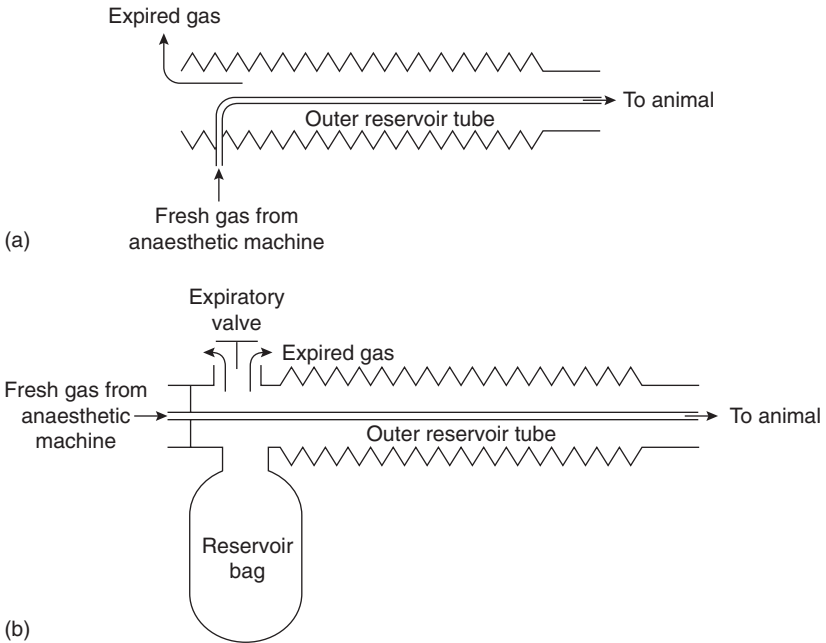


FIGURE 2.7 Bain's circuit (a) and modified Bain circuit (b).

some distance from the patient and close to the anaesthetic machine (Bain and Spoerel, 1972). The light-weight construction reduces the tendency for the breathing system to pull on the endotracheal tube and so reduces the risk of accidental extubation. Positioning the expiratory port well away from the patient allows ventilation to be assisted easily without interfering with sterile drapes or the activities of the surgeon. In addition, anaesthetic gases can be scavenged easily and do not accumulate at the surgical site. The breathing system has a low dead space ($<2\text{ ml}$) and so is suitable for use in small animals. The Bain breathing system functions similarly to a T-piece. During inspiration, gas is drawn in from the central fresh gas supply and also from the outer reservoir tube. During expiration, exhaled gas fills the reservoir tube, and during the pause before the next inspiration, this is replaced with fresh gas, provided the fresh gas flow is adequate.

Two modifications of the basic breathing system have been described. The expiratory limb may terminate with a 'pop-off' valve and a reservoir bag (Fig. 2.6), or an open-ended reservoir bag may be mounted at the end of the expiratory limb. Adding a 'pop-off' valve is unsuitable for small animals ($<10\text{ kg}$ body weight), since the presence of the valve increases breathing system resistance. When used in larger animals, the valve and the reservoir bag allow ventilation to be assisted easily by partially closing the valve and intermittently squeezing the reservoir bag.

The open-ended reservoir bag is equivalent to the Jackson Rees modified T-piece and serves a similar function by allowing easy control of ventilation. Mechanical ventilators can be connected to the reservoir limb, as with a T-piece.

The gas flows required to prevent rebreathing have been quoted as ranging from 100 ml/kg body weight/min (Manley and McDonell, 1979b) to 200–300 ml/kg body weight/min (Ungerer, 1978). The use of the lower flows can be explained by the animal responding to changes in blood carbon dioxide concentration by altering its rate and depth of respiration. When the fresh gas flow is low, some rebreathing of exhaled carbon dioxide from the reservoir limb will occur. This will result in an increase in the blood carbon dioxide concentration which stimulates respiration. This moderate hyperventilation results in blood carbon dioxide tensions being maintained at acceptable levels. It is not certain whether the additional respiratory effort produced is deleterious to the patient, but the conventional view has always been that rebreathing should be minimal during spontaneous respiration. For this reason, it is recommended that fresh gas flow rates of 2–2.2 times minute volume should be used (see Table 2.2). During mechanical ventilation, some degree of rebreathing of carbon dioxide is advantageous, since it helps to avoid the production of hypocapnia. Fresh gas flow rates of 70–100 ml/kg/min allow the maintenance of normal carbon dioxide concentrations (normocapnia) during mechanical ventilation (Manley and McDonell, 1979a), but inaccuracies in flow meter settings limit the usefulness of this technique in small animals (Hird and Carlucci, 1977).

Magill Breathing System. The Magill breathing system is widely used in human anaesthesia, and this probably accounts for the frequency with which it is used in animal anaesthesia. While the advantages that have assured its popularity in human anaesthesia are applicable to similar-sized animals, it is generally unsuitable for use in animals with a body mass below 10 kg.

The breathing system consists of a reservoir bag connected by a length of corrugated tubing to the animal (Figs. 2.8 and 2.9). An expiratory 'pop-off' valve is situated as close to the patient as possible, to reduce equipment dead space. During expiration, the first portion of expired gas is from the animal's anatomical dead space (the trachea and the bronchi), and since no gas exchange occurs in this region, it contains no carbon dioxide. The expired gas travels up the corrugated tubing towards the reservoir bag that fills; then, as the pressure in the breathing system rises, the expiratory valve lifts and the remaining expired gas passes out of the breathing system. The continuous flow of fresh gas down the breathing system flushes out any remaining carbon dioxide-rich alveolar gas during the pause before the next inspiration. Because of the preferential elimination of carbon dioxide-rich alveolar gas, significant rebreathing does not occur in humans until the fresh gas flow falls below 70% of the minute volume (Kain and Nunn, 1968). The breathing system is therefore extremely economical in its fresh gas requirements. It is important to realize that during controlled ventilation achieved by manual compression of the reservoir bag, this preferential



FIGURE 2.8 Magill circuit.

elimination of alveolar gas is lost. Under these conditions, fresh gas flows of three times minute volume may be required to prevent rebreathing.

The major problem in using the breathing system in small animals is that it imposes a significant resistance to expiration. In addition, the dead space of a typical breathing system is 8–10 ml, which is likely to represent a significant proportion of the tidal volume of a small animal. If it is to function effectively, the Magill breathing system must be attached to the animal by an endotracheal tube or a close-fitting face mask. It is common practice to connect this system to small animals with a badly fitting mask. Under these circumstances, the breathing system functions as an open system so that fresh gas flows in excess of three times minute volume are required to prevent either rebreathing or the dilution of the

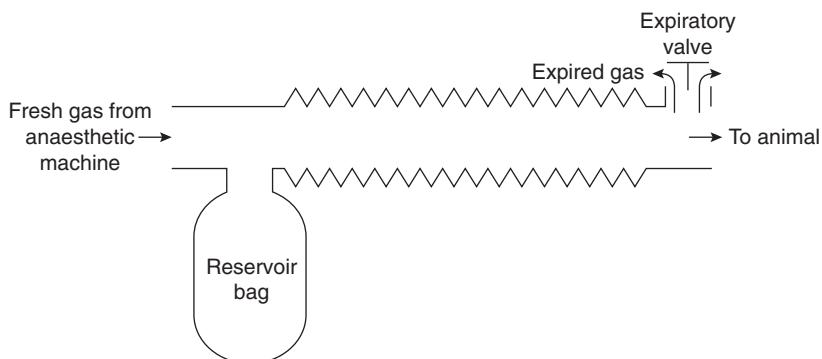


FIGURE 2.9 Magill circuit.

inspired gas mixture by room air, which will be drawn in around the face mask. When used correctly, waste anaesthetic gases can be scavenged by means of a suitable attachment on the expiratory valve. If used with a badly fitting face mask, the same problems of pollution arise as occur with open breathing systems.

Closed Breathing Systems. Closed breathing systems are systems in which the expired carbon dioxide is absorbed, usually by means of a soda lime canister. Because of the considerably lower fresh gas flows required, closed breathing systems are often used when anaesthetizing larger animals (body weight > 20–30 kg). The use of such breathing systems poses considerable problems for the inexperienced anaesthetist, and expert advice and assistance should be obtained before attempting to employ these techniques. The most widely used closed breathing system is the circle system (Figs. 2.10 and 2.11). In a circle system, the flow of gas is controlled by two unidirectional valves. These cause expired gases to pass through a soda lime canister, where carbon dioxide is absorbed, before the gases pass around the circuit, to be breathed in again by the animal.

When using a closed breathing system, it would be possible to supply only the animal's metabolic oxygen requirements (approximately $10 \times \text{body weight}^{0.75}$, i.e. 6–9 ml/kg/min for a 3-kg animal) (Brody, 1945), but for practical reasons, it is more usual to operate the circle system as a low flow rather than completely closed system. Typically, fresh gas flows of 100 ml/kg/min are used for small animals (<10 kg) and 20–30 ml/kg/min for larger animals. This represents a major advantage of circle systems in comparison with other breathing systems in controlling anaesthetic costs. The newer anaesthetic agents such as sevoflurane are expensive, and in larger animals, the use of a closed system, where appropriate, can reduce costs very significantly (Appendix 2).

Although circle systems have been more frequently used for larger animals, the introduction of light-weight disposable systems with low-resistance valves has increased their use in smaller animals. Despite advances in breathing system



FIGURE 2.10 Circle system.

construction, the system still offers more resistance to breathing than a T-piece or Bain breathing system, and it is advisable not to use these breathing systems on small (<5 kg) animals unless mechanical ventilation is used. As mentioned earlier, inexperienced users are strongly advised to seek assistance before using closed breathing systems. Two important points should be noted. If nitrous oxide is used, the concentration of this gas can build up in the breathing system, resulting in a dangerously low concentration of oxygen. Either nitrous oxide should not be used, or an oxygen content monitor should be included in the breathing system. When using a closed breathing system, the concentration of volatile anaesthetic in the breathing system will not be the same as that shown by the vaporizer setting. This can result in a failure to maintain adequate depths of

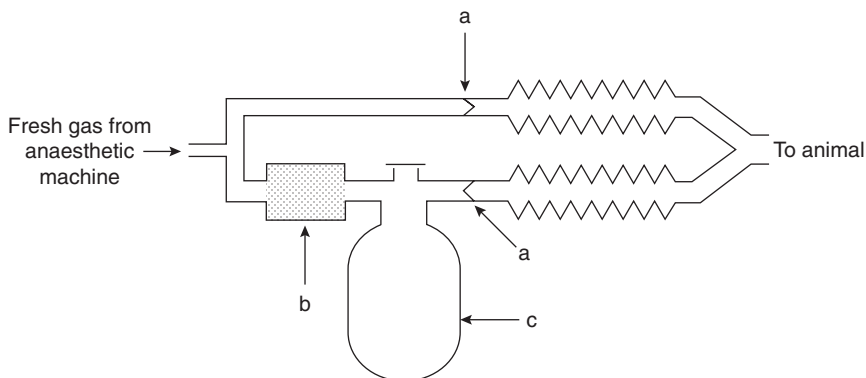


FIGURE 2.11 Circle system.

anaesthesia. As experience is gained, the vaporizer setting can be increased to compensate for the dilution of anaesthetic in the breathing system, and uptake by the animal. A more reliable technique is to purchase an anaesthetic gas analyzer. The cost of these monitors has fallen considerably, and if a calculation is carried out on the basis of the savings on volatile agent that would result, then they represent a worthwhile investment.

Besides economic considerations, another advantage of closed or low-flow breathing systems is that heat and moisture are conserved. A detailed comparison of the advantages and disadvantages of rebreathing and non-rebreathing systems has been given by Brouwer and Snowden (1987).

The diagram of the circle system in Figure 2.11 has the vaporizer placed outside the main breathing system. In-circle vaporizers can also be used, but a full discussion of the relative merits of each arrangement is outside the scope of this book. A full description of these breathing systems can be found in standard veterinary anaesthesia texts (e.g. Hall et al., 2001; Tranquilli et al., 2007).

Recommendations

Although open-mask techniques are best used only for short procedures in large animals, they may often be the most convenient system for small rodents, when the higher fresh gas flows required by these breathing systems ($<1.5\text{ l/min}$) will be of little significance. If nitrous oxide or volatile anaesthetic agents are used, the provision of effective gas scavenging must be considered essential. For larger animals such as the cat, rabbit and non-human primate, the advantage of lower fresh gas flow requirements, ease of gas scavenging and ability to assist ventilation favour the selection of a more sophisticated breathing system. If an Ayre's T-piece is used, it is strongly recommended that either a human paediatric model with a low dead space is obtained or one with similar features is constructed. The Bain breathing system offers several advantages for use in small animals, particularly

in respect of its low weight and small dead space. The ease with which controlled ventilation can be carried out from a point remote from the surgical field is a further distinct advantage. In addition, it is suitable for use both in small animals such as guinea pigs and rabbits and in larger species such as dogs. The Magill breathing system is not suitable for use in animals with a body weight of less than 10kg, but it may be used as an alternative to the Bain breathing system in larger animals such as dogs, sheep and pigs. Prolonged anaesthesia of larger animals (>10kg), particularly when using relatively expensive agents such as sevoflurane, is best provided using a circle system. Rather than attempt to use a fully closed system, a moderate fresh gas flow of 500–1000ml/min should be used, as this will simplify the use of the breathing system (see above).

All of the commonly used anaesthetic breathing systems are now available as light-weight single-use items for human anaesthesia (Appendix 4). Many of these disposable systems can be re-used on numerous occasions without difficulty, but it is essential that a careful check is made of the condition of the system each time it is used. In particular, ensure that any pressure-relief valves are functioning correctly and, when using a Bain breathing system, that the inner, fresh gas tube has not become disconnected at the anaesthetic machine end of the breathing system. Anaesthetic breathing systems and reservoir bags should be washed in hot soapy water and either pasteurized or rinsed with a chlorine disinfectant. Metal components can be autoclaved after washing.

Face Masks, Intranasal Catheters, Laryngeal Masks and Endotracheal Tubes

Whichever anaesthetic breathing system is selected (see above), a face mask, nasal tube, laryngeal mask or an endotracheal tube will be required to connect it to the animal. Selection of a suitable mask is described in Chapter 1, but delivering anaesthetic gases or oxygen using a face mask can cause practical difficulties, especially when anaesthetizing small rodents or birds. Masks can easily become displaced, and may interfere with access to the animal, for example, when carrying out head and neck surgery. A number of techniques to prevent masks becoming displaced have been described. Figure 2.12 illustrates one approach using an elastic band and the plastic mounts from a protective face mask. If an animal is placed in a stereotaxic frame, it becomes impossible to use a standard face mask, and a specialized mask must be purchased or constructed. These problems can be resolved by intubating the animal's trachea (see below), but this can be technically difficult. As an alternative, a catheter can be passed up one nostril and used to deliver anaesthetic gases (see below).

Endotracheal Intubation

Endotracheal intubation of large animals such as dogs, sheep, pigs, old-world primates and large birds (>1kg) is relatively straightforward, provided a suitable size and shape of the laryngoscope is available (Chapter 1, Fig. 1.13). A range of



FIGURE 2.12 Elastic band used to help maintain the position of a rat or mouse in a face mask. The attachment is made from the components of a protective face mask (Segre, Sweden). (Concentric mask supplied by VetTech Solutions.)

MacIntosh or Soper laryngoscope blades can be used for cats (size 1) and dogs (sizes 1–4) and a MacIntosh blade (sizes 2–4) for sheep. When anaesthetizing pigs, Soper (sizes 1–3) or Wisconsin (sizes 1–4) blades are preferable, although large pigs may require the use of a purpose-made laryngoscope blade. Rabbits can be successfully intubated using a Wisconsin blade (size 1 or 0) (Chapter 1, Table 1.2).

If intubation of a particular species is planned, a careful examination of the pharynx and the larynx should first be carried out on a post-mortem specimen. This will enable an appreciation of the anatomical relationships within this area, particularly that of the soft palate and the epiglottis. Once the normal anatomy of the region has been reviewed, a suitable-sized endotracheal tube should be prepared. Most commercially available tubes are excessively long; therefore, their length should be reduced so that it approximates to the distance from the external nares to just anterior to the thoracic inlet. If a small (<4 mm outside diameter) tube is to be used, an uncuffed tube is preferable, as this enables the largest possible diameter tube to be passed. It is advisable to lubricate the tube with a small quantity of lidocaine gel.

The animal should be anaesthetized to a sufficient depth to abolish the cough and swallowing reflexes. It is possible to intubate lightly anaesthetized animals, but while this may be desirable under some circumstances, it is advisable to gain some proficiency in the technique of intubation before attempting this. Before intubating any animal, oxygen should be administered for 2 minutes. If the larynx

is inadvertently obstructed during attempted intubation, it will usually take over 60 seconds for hypoxia to develop if the animal has been breathing oxygen. If the animal has been breathing air, hypoxia will develop more rapidly.

Dog, Cat and Sheep

The animal is placed in sternal recumbency, keeping its jaws opened as widely as possible by an assistant. The tongue is drawn forwards and the laryngoscope advanced over the tongue towards the pharynx. The larynx is usually masked by the epiglottis. Gentle upward pressure on the soft palate with the end of the endotracheal tube will disengage the epiglottis, allowing it to fall forwards, and so providing an unobstructed view of the larynx. In the cat and the sheep, the larynx should be sprayed with a local anaesthetic, to prevent laryngospasm. In the UK, the most recent formulation of lidocaine (Astra) has been associated with laryngeal oedema (Taylor, 1992), and it is advisable to check the suitability of any locally available product before use. An alternative is to use lidocaine (2%) without adrenaline (epinephrine) (0.25–0.5 ml/cat, equivalent to 5–10 mg total dose), delivered using a small nebulizer or syringe and a fine gauge needle. Disposable ‘insulin’ syringes with a pre-attached 25-SWG (Standard Wire Gauge) needle, with the needle bevel cut off, are ideal. The endotracheal tube can then be advanced through the larynx into the trachea. Then the tube should be connected to the anaesthetic breathing system, the cuff (if present) inflated and the tube tied in place to the animal’s jaw, using a 1-cm-wide cotton tape. It is preferable at this stage to assist ventilation (as described earlier) and observe that there is movement of both sides of the thorax. This ensures that the tube has not been inadvertently positioned in one of the two mainstem bronchi. In addition, manual inflation of the chest will enable an appreciation of the degree of resistance to gas flow. Increased resistance may indicate twisting or kinking of the tube, or its partial obstruction due to positioning close to the bifurcation of the trachea. If any uncertainty exists about tube placement, use a stethoscope to check that breath sounds can be heard on both sides of the thorax.

Pig

Intubation in the pig is complicated by the difficulty of obtaining an unobstructed view of the larynx. The animal is best positioned on its back, enabling the head and the neck to be fully extended. As with other species, care must be taken when the tongue is extended to avoid damaging its surface on the teeth, particularly the canines in boars. Intubation is easier if an introducer is used (Chapter 1, Fig. 1.12). This is a blunt stilette that is placed inside the tube to straighten it and make it easier to direct into the larynx. Introducers can be purchased commercially (Portex, Smiths Medical International, Appendix 4), and this ensures that the tip is soft and atraumatic.

The laryngoscope is advanced over the tongue and the epiglottis disengaged from the soft palate, if necessary, by pushing downwards on the soft palate using



FIGURE 2.13 Intubation of the rabbit by using a laryngoscope ('Flecknell' blade, Alstoe).

the tip of the introducer. Once the larynx has been located, it should be sprayed with lidocaine. The introducer and the endotracheal tube can then be gently advanced into the larynx and the introducer withdrawn. The tube should then be gently advanced; at this stage, its progress is usually arrested by the laryngeal wall. If this occurs, the tube should be withdrawn very slightly, rotated through 90 degrees and reinserted. This should be repeated as necessary until no resistance is experienced. Under no circumstances should attempts be made to pass the tube forcibly through the larynx, as this is likely to result in severe trauma, oedema, haemorrhage and consequent asphyxiation.

Rabbit

Visualization of the larynx in the rabbit is difficult, and it is necessary to use a purpose-designed laryngoscope blade (Flecknell blade), a Wisconsin laryngoscope blade (2- to 5-kg animal, size 1; 1- to 2-kg animal, size 0) or an otoscope if intubation is to be carried out under direct vision.

Intubation Using an Otoscope or Laryngoscope The rabbit is positioned on its back as shown (Fig. 2.13). To view the larynx, the tongue is gently grasped and pulled forwards and to one side, taking care to avoid the sharp edges of the incisor teeth. The otoscope or laryngoscope is introduced into the mouth and advanced until the larynx is visible. It is possible to advance the instrument into the oesophagus if the tip of the epiglottis is positioned on the nasal aspect of the soft palate. To avoid this, the soft palate can be pushed with the

otoscope or laryngoscope tip, or the introducer can be passed down the otoscope and pushed against the soft palate to reposition it and provide a clear view of the larynx.

As the speculum is advanced, the paler triangle of the epiglottis can often be seen through the end of the soft palate, alerting the anaesthetist to the need to manipulate the structure. In many cases, the larynx is immediately clearly visible. At this point, the larynx can be sprayed with lidocaine, although this is often unnecessary. An introducer can now be passed through the otoscope into the larynx and on into the trachea. If a purpose-made introducer is not available, then a bitch or cat urinary catheter can be used, depending upon the size of the rabbit. If a catheter is used, then the Luer fitting should be removed before use, since this will not pass through the tip of the otoscope. After placing the introducer, the otoscope or laryngoscope is removed, taking care not to change the position of the introducer. An endotracheal tube (2.5–3 mm for 2- to 3-kg rabbits) is then threaded onto the end of the introducer and advanced into the trachea. When the endotracheal tube reaches the larynx, some resistance is often felt. Gently rotating the tube as it is advanced may ease its passage into the trachea. Prior application of lubricating gel (e.g. lidocaine gel) can also aid the passage of the tube. Take care at this stage not to remove the introducer until the tube is in the trachea, or intubation will be unsuccessful. As the tube is advanced further into the trachea, the introducer is removed and the tube tied in place.

'Blind' Intubation An alternative technique for intubation does not require visualization of the larynx. The rabbit is placed in sternal recumbency, and the head gripped firmly and extended and the animal lifted so that its forelegs are just touching the operating table (Fig. 2.14). The endotracheal tube is advanced through the gap between the incisors and the premolars, over the tongue and towards the larynx. The operator listens for breath sounds at the end of the tube or alternatively, if a clear polyethylene tube is used, looks for the presence of condensation. A loud breath sound or condensation indicates that the tube tip is close to the larynx. As the rabbit breathes in, the tube is gently advanced. If it fails to enter the larynx, as indicated by cessation of breath sounds and loss of condensation, then the tube is withdrawn, the head repositioned either by tilting it further backwards or slightly forwards and another attempt made. Giving a quarter turn to the endotracheal tube as it enters the larynx can help its passage.

In some instances, intubation can be eased by the use of a local anaesthetic spray. This can be delivered onto the larynx by positioning the endotracheal tube at the point of maximal breath sounds, and then spraying lidocaine into the end of the tube, or injecting a small (0.1 ml) quantity of lidocaine into the end of the tube. The local anaesthetic is drawn down the tube as the rabbit inhales, and some reaches the larynx. After waiting a minute or two to allow the drug to act, another attempt at intubation can be made. If problems arise, oxygen should be administered every 2–3 minutes to ensure the animal does not become hypoxic.



FIGURE 2.14 Blind intubation of a rabbit.

Although this technique sounds challenging, it is relatively easy to become proficient and has the advantage of requiring no additional equipment. In small rabbits (<1 kg), it is not always possible to hear breath sounds or observe condensation in the small endotracheal tube (2–2.5 mm) that is needed. For this reason, it is best to intubate larger rabbits when first attempting this technique.

With both techniques, the confirmation of successful placement is based on observing condensation of breath on a cold surface (e.g. the end of the otoscope handle), or movement of a piece of tissue paper placed at the end of the tube. Alternatively, as in other species, a capnograph can be attached to confirm the tube is in the trachea.

Rat

Intubation of the rat is possible using a number of different purpose-made intubation devices (e.g. Costa et al., 1986), or using an otoscope. The rat is positioned on its back, and the tongue pulled gently forward and to one side. The laryngoscope or otoscope is then inserted until the larynx can be visualized. The animal can then be intubated using a suitably sized (12- to 16-gauge) arterial cannula (e.g. Abbotath, Abbott Laboratories, Appendix 4). Some modification of the Luer fitting is needed to provide connections to an appropriate anaesthetic breathing system, and care must be taken to ensure that these connectors introduce only a minimum of dead



FIGURE 2.15 Apparatus for intubation of rats and mice, available from Hallowell instruments.

space into the breathing system. To avoid inadvertent intubation of one bronchus, and to provide a seal around the larynx, a small piece of rubber tubing can be positioned around the catheter, about 0.75–1 cm from the tip. Alternatively, some ‘Micropore’ tape (3M) can be applied to make a similar cuff. This will reduce the leakage of gas around the tube, making ventilation more effective, and will also improve the efficacy of positive end expiratory pressure (PEEP) if this is required. A final modification that can be helpful is to superglue a silk ligature onto the base of the Luer mount of the catheter, to enable it to be anchored to the rat’s jaw.

When using an otoscope, it is necessary to use an introducer, since the cannula will not pass through the lumen of the otoscope. A guide wire from a Seldinger catheter makes an ideal introducer since its tip is soft and flexible. The wire is passed through the larynx under direct vision, the otoscope carefully removed and the endotracheal tube threaded over the wire into the trachea. These wires can be purchased separately, and a 0.7-mm-diameter wire will fit through both 16- and 18-gauge catheters. Alternatively, the neck may be transilluminated using a powerful light source and the mouth opened using a small gag (Remie et al., 1990). The tongue is pulled forwards and a bright spot of light seen, which flashes as the rat breathes; this indicates the opening of the larynx.

One of the simplest techniques to master is to purchase one of the commercially available systems that usually combine a small table for positioning the animal with a system for visualizing the larynx. The apparatus shown (Figs. 2.15 and 2.16) can be used for intubation of both rats and mice. An alternative



FIGURE 2.16 Rat positioned for intubation. (Tilting table from Hallowell instruments.)

approach using a fibre optic system has also been described (Rivera et al., 2005), and a commercially produced instrument is also available.

Guinea Pig, Mouse, Gerbil and Hamster

Intubation of the mouse, gerbil and hamster is difficult and requires especial skill and purpose-made apparatus (Hamacher et al., 2008). A suitable set of laryngoscope blades has been described by Costa et al. (1986). The guinea pig can also be intubated using a purpose-designed laryngoscope blade, or the technique employing an otoscope, described above for the rat, can be used. As with the rat, the use of an otoscope in combination with transillumination of the neck provides optimal conditions for intubation. Positioning of the otoscope is more difficult in the guinea pig than in the rat, and a narrow speculum is needed to pass between the cheek teeth. The pharynx narrows markedly at the junction with the larynx and the oesophagus, and considerable care must be taken to avoid inserting the speculum too far and occluding the larynx. As with the rat, intubation is achieved by passing a Seldinger guide wire through the larynx, removing the otoscope and then passing a 12- to 16-gauge catheter over the wire into the trachea.

Birds

Intubation of birds is relatively simple, since the opening to the airway is positioned much further forwards, compared to mammals. Opening the beak enables the opening to be seen at the base of the tongue. Intubation is assisted by pulling



FIGURE 2.17 Laryngeal mask.

the tongue forwards. Larger birds (poultry) can be intubated using standard paediatric tubes (2.5 mm upwards), but small birds require the use of either intravenous or urinary catheters cut to a suitable length as necessary. Uncuffed endotracheal tubes should always be used, since it has been suggested that the use of cuffed tubes can cause pressure necrosis of the tracheal mucosa because of the presence of complete tracheal cartilage rings in these species (Briscoe and Syring, 2004).

Laryngeal Masks

As an alternative to endotracheal intubation, a laryngeal mask (Fig. 2.17) can be used to maintain a patent airway and assist ventilation if required. These masks are designed to slide into the mouth and to be positioned over the larynx. The large cuff is then inflated to seal them in place. Laryngeal masks are produced to fit a human larynx, but the anatomy of some species is sufficiently similar to allow them to be used successfully (Wemyss-Holden et al., 1999). In rabbits and pigs, the use of a laryngeal mask has been reported to be more easily mastered by inexperienced anaesthetists than intubation, and to provide effective control of the rabbit's airway (Smith et al., 2004; Ludders, 2005; Fulkerston and Gustafson, 2007; Kazakos et al., 2007).

Intranasal Intubation

Placement of a catheter in one nostril allows delivery of oxygen or anaesthetic gases, and can be a useful alternative to a face mask, for example, when using a stereotaxic frame. A variety of catheters can be used, including vascular catheters,



FIGURE 2.18 Intranasal catheters used for delivery of anaesthetic agents or oxygen (guinea pig, left, with cat urinary catheter; rat, right, with paediatric nasogastric tube).

nasogastric feeding tubes, flexible oral-dosing catheters and urinary bladder catheters (Fig. 2.18). The catheter should be lubricated before insertion and, in most species, should be directed medially and ventrally. The nostrils of most small animals are surrounded by muscle, and this restricts the diameter of the nasal opening, but gentle pressure from the catheter tip will usually dilate the nostril slightly, allowing passage of the catheter. Slight rotation of the catheter can aid insertion. The diameter of the passage through the nasal chamber is often significantly larger than the external nasal opening. Occasionally, there may be slight trauma to the nasal mucosa, resulting in a small amount of haemorrhage, but this is usually minor and stops rapidly.

The fresh gas flows needed are similar to those when using a face mask, approximately three times the animals' minute volume. Some air will be drawn in through the other nostril, and this will dilute the supplied gas. However, increasing the vaporizer setting (e.g. by 0.5–1% when using isoflurane) will compensate for this. Gas scavenging can be accomplished using a down-draft table. The catheter can be connected to the anaesthetic machine using a Luer adapter and oxygen bubble tubing (Fig. 2.19). This tubing is extremely useful for adapting anaesthetic breathing systems, as its internal diameter varies along its length from 3 to 8 mm, allowing it to be cut at a convenient point to connect different-sized connectors.

Inhalational Agents Available

Information concerning the range of concentrations of the different inhalation anaesthetics which are required for induction and maintenance of anaesthesia is



FIGURE 2.19 Oxygen bubble tubing used for connecting a nasal catheter to an anaesthetic trolley, for delivery of oxygen or anaesthetic agents.

listed in Table 2.3. Several factors influence the apparent potency and efficacy of the different inhalation anaesthetics. The potency of each drug is indicated by its minimum alveolar concentration (MAC)₅₀ value. MAC ₅₀, most commonly referred to simply as MAC , is the alveolar concentration of an anaesthetic required to block the response to a specified painful stimulus, for example, clamping a haemostat onto a digit, in 50% of a group of animals. The lower the MAC value, the lower the concentration required to maintain anaesthesia (Table 2.1).

The concentration of anaesthetic that can be delivered to the animal is influenced by the drug's boiling point. The lower the boiling point of an anaesthetic, the easier it is to vaporize, and so the higher the concentration that can be delivered. This is of considerable practical importance when selecting an anaesthetic agent and deciding how to vaporize it. A very potent drug, that is, one with a low MAC value and low boiling point, which makes it easy to vaporize, must be used with great care. There will be a considerable risk of over-dosing the patient unless vaporization is carried out in a controlled way, using a calibrated vaporizer. Less potent anaesthetics, that is, ones with higher MAC values and higher boiling points, can be used with greater confidence in simple apparatus, since dangerously high concentrations will not usually be produced.

The speed of induction of anaesthesia and the rate of recovery are affected by the concentration of anaesthetic delivered, the anaesthetic potency (MAC value) and the blood-gas partition coefficient. The partition coefficient influences the

TABLE 2.3 Induction and Maintenance Concentrations of Inhalation Anaesthetic Agents.

Anaesthetic	Concentration for induction of anaesthesia (%)	Concentration for maintenance (%)	Minimum alveolar concentration (indicates relative potency of different agents) (in rat)
Desflurane	18	11	6.5–8
Enflurane	3–5	3	2.2
Ether	10–20	4–5	3.2
Halothane	4	1–2	0.95
Isoflurane	4	1.5–3	1.38
Methoxyflurane	3	0.4–1	0.22
Nitrous oxide	–	–	250
Sevoflurane	8	3.5–4.0	2.7

Data shown for rat; some species variation occurs; data from Mazze et al. (1985), Steffey et al. (1974), Kashimoto et al. (1997), Gong et al. (1998) and Brosnan et al. (2007).

rate at which the concentration of anaesthetic in the brain approaches that necessary for anaesthesia to be produced. The higher the partition coefficient, the slower the rate of induction of anaesthesia and the slower the recovery rate. These properties are summarized in Table 2.1. The MAC values of anaesthetics are relatively constant between species (Table 2.4), with the exception of nitrous oxide (see Chapter 5).

Of particular concern to some research workers is the fate of inhalation anaesthetics once absorbed into the animal. A common misconception is that all of the agent that is inhaled is exhaled from the body. Many inhalation anaesthetics undergo significant metabolism, and this can result in induction of liver enzyme systems, as may occur following the use of injectable anaesthetics. This can be of significance if the animal is to be used subsequently in a study which involves assessing the *in vivo* effects of a novel pharmaceutical or another compound. Although information is available concerning long-term exposure to inhalation anaesthetics (Linde and Berman, 1971; Brown and Sagalyn, 1974), there is little information concerning the effects on liver enzyme systems of brief periods of exposure. One means of avoiding the effects is to use isoflurane, an anaesthetic which undergoes virtually no metabolism (Eger, 1981). If other agents are used, it seems reasonable to suggest that brief (<5 minutes) periods of anaesthesia are unlikely to cause significant effects, but more prolonged exposure to anaesthetizing concentrations may result in induction of enzyme systems.

TABLE 2.4 Minimum Alveolar Concentration (MAC₅₀) Values (%) for Inhalation Anaesthetics in Different Species.

	Ether	Desflurane	Halothane	Enflurane	Isoflurane	Nitrous oxide	Sevoflurane
Human	1.92	6.6	0.75	1.63	1.17	104	1.8
Primate	–	–	1.15	1.84	1.28	200	–
Dog	3.04	7.2	0.87	2.20	1.28	188–222	2.1–2.36
Pig	–	8.3	1.25	–	1.45	277	3.5
Sheep	–	9.5	–	–	1.58	–	3.3
Cat	2.10	10.3	0.82	1.20	1.63	255	3.4
Rat	3.20	5.7	1.10	2.21	1.38	150	2.7
Mouse	3.20	6.5–8.8	0.95	1.95	1.41	275	2.5
Rabbit	–	8.9	1.39	2.86	2.05	–	3.7

Data from Barter et al. (2004), Conzen et al. (1992), Drummond (1985), Eger and Johnson (1987), Lukasik et al. (1998a, b), Maze et al. (1985), Martin-Cancho et al. (2006), Nickalls and Mapleson (2003), Moeser et al. (2008), Pirou et al. (2002), Puig et al. (2002), Scheller et al. (1988), Steffey et al. (1974) and Sonner et al. (2000).

Operator Safety

A variety of hazards is reportedly associated with pollution of the operating room environment with anaesthetic gases (NIOSH, 2007). The risk of explosion or fire associated with some older anaesthetic agents such as ether and cyclopropane is well recognized, and appropriate precautions must be taken to avoid these dangers. The risks to personnel which may arise from chronic exposure to low levels of certain inhalational anaesthetics are much more difficult to assess. The results of the many studies designed to determine these associated risks vary considerably, but at present, it would seem sensible to take appropriate steps to minimize operating theatre pollution. Measurements of trace anaesthetic concentrations in typical rodent operating areas have confirmed the need for modifying practices to reduce exposure of personnel.

A variety of gas-scavenging systems are available, and it should be possible to obtain equipment suitable for most applications. A scavenging system suitable for small laboratory animals was described by Hunter et al. (1984), and many such systems are now available commercially. Note that systems which use activated charcoal are not effective in removing nitrous oxide. Even with an effective scavenging system, spillage of waste gas will occur when the lid of an anaesthetic chamber is removed to gain access to the anaesthetized animal. If this is considered a significant problem, then either the whole procedure can be carried out in a fume hood, or specially designed chambers can be used, which completely remove the anaesthetic gases before the chamber is opened (Chapter 1, Fig. 1.9).

Specific Agents

Isoflurane

Desirable Effects

Isoflurane produces very rapid induction and recovery from anaesthesia, and the depth of anaesthesia can be altered easily and rapidly. It is non-irritant, non-explosive and non-flammable.

Undesirable effects

Isoflurane produces moderate respiratory and cardiovascular system depression. Its pungent odour has been reported to cause breath holding during induction in children, but this does not seem a significant problem in most species, with the exception of the rabbit and the guinea pig (see Chapter 6).

Special Comments

The main advantage of using isoflurane in experimental animals is that it undergoes even less biotransformation than any other agent and is almost completely eliminated in exhaled air. This suggests that there will be little effect on liver microsomal enzymes and, hence, minimal interference in drug metabolism or toxicology studies

(Eger, 1981). This characteristic, together with the rapid induction and recovery from anaesthesia, has led to the widespread adoption of isoflurane in many research establishments.

Sevoflurane

Desirable Effects

Sevoflurane produces even more rapid induction and recovery from anaesthesia than does isoflurane, and the depth of anaesthesia can be altered very easily and rapidly (Keefe and Healy, 1999; Preckel and Bolton, 2005). It is non-explosive and non-flammable. Sevoflurane is much less pungent than other agents, and mask induction is well tolerated in many species (with the exception of rabbits and guinea pigs).

Undesirable Effects

Sevoflurane is relatively expensive, and is unstable in the presence of soda lime, the carbon dioxide absorber used most commonly in closed-breathing system anaesthesia. The breakdown products can cause renal injury, but the concentrations produced are very low in normal circumstances (O’Keeffe and Healey, 1999). It is highly unlikely that significant toxicity will be encountered during use in laboratory animals.

Special Comments

The main advantage of sevoflurane is the even greater ease of matching the depth of anaesthesia to the degree of surgical stimulation, coupled with very rapid and smooth recovery. If undisturbed, many animals recover from sevoflurane without a period of involuntary excitement. In the author’s institute, it has been used with great success for very prolonged procedures, and also for very brief procedures when rapid induction and recovery are needed.

Desflurane

Desirable Effects

Induction of and recovery from anaesthesia with desflurane is the most rapid of any of the volatile anaesthetics (Eger, 1992). Desflurane undergoes the least degree of metabolism (Koblin, 1992). It is relatively non-irritant.

Undesirable Effects

Desflurane is relatively expensive and requires a pressurized, temperature-controlled vaporizer because of its very low boiling point.

Special Comments

Desflurane has not been widely used in either veterinary clinical practice or laboratory species.

Halothane

Desirable Effects

Halothane is easy to vaporize, and induction and recovery are rapid (1–3 minutes). It is a potent anaesthetic, is non-irritant and is neither flammable nor explosive.

Undesirable Effects

Halothane has a depressant effect on the cardiovascular system. Moderate hypotension is produced at surgical levels of anaesthesia because of a reduction in cardiac output and peripheral vasodilatation. A dose-dependent depression of respiration also occurs. Some hepatic metabolism of halothane occurs, and marked liver microsomal enzyme induction may follow anaesthesia (Wood and Wood, 1984).

Special Comments

The desirable effects listed above have made halothane a popular agent for maintaining anaesthesia in most species. However, it is now rarely used in medical anaesthetic practice in Europe and North America, and as a result, the manufacture of this agent is being discontinued. However, it will still be available from specialist sources and will continue to have an important role, particularly as an anaesthetic for neurophysiological studies (Murrell et al, 2007).

Enflurane

Desirable Effects

Induction of and recovery from anaesthesia are rapid, so the depth of anaesthesia can be altered easily and rapidly. Enflurane is non-flammable, non-explosive and non-irritant.

Undesirable Effects

Enflurane produces cardiovascular and respiratory depression, comparable to that which occurs during halothane anaesthesia.

Special Comments

Enflurane is largely eliminated via the lungs, and unlike halothane, very little drug is metabolized in the liver. This may offer advantages in certain experimental situations, although there is otherwise little to choose between halothane and enflurane in terms of efficacy as anaesthetic agents. The agent is rarely used in laboratory animal or veterinary clinical anaesthesia.

Methoxyflurane

Desirable Effects

Methoxyflurane is non-irritant, non-flammable and non-explosive in air or oxygen. It has a potent analgesic effect and has some post-operative analgesic action.

Undesirable Effects

Methoxyflurane produces some respiratory and cardiovascular system depression, but generally less than halothane at comparable depths of anaesthesia. The metabolism of methoxyflurane results in fluoride ion release, which may cause renal damage. The significance of this hazard in animals is small, except following very prolonged periods of anaesthesia (Murray and Fleming, 1972).

Special Comments

Methoxyflurane is now difficult to obtain in North America and Europe, although it is still available in Australia. In small animals, it can safely be used in anaesthetic chambers, using simple vaporizers, where its slow induction and the low vapour concentration produced can be an advantage in reducing the risk of inadvertent overdose. It is an excellent agent for inducing and maintaining anaesthesia in neonatal animals.

Ether (Diethyl Ether)

Desirable Effects

Ether is easy to vaporize in simple apparatus. It is difficult to kill an animal with an overdose of ether, so it is a relatively safe agent for inexperienced anaesthetists.

Undesirable Effects

Induction is unpleasant for the animal, and the irritant properties of ether can cause coughing, profuse bronchial and salivary secretions and occasional laryngospasm. Ether can cause pre-existing chronic respiratory disease to develop into an acute severe infection, following recovery from anaesthesia, and this may be particularly important in rodents and rabbits. Ether is flammable and forms explosive mixtures with both oxygen and air.

Special Comments

Anaesthetic ether is now difficult to obtain, although the agent can still be purchased from specialist suppliers. Induction of and recovery from anaesthesia are relatively slow. This is advantageous for inexperienced anaesthetists, as it makes accidental overdose less likely. Conversely, a prolonged induction period can present problems in restraining the animal, particularly as most animals strongly resent inhaling the vapour.

Administration of ether stimulates catecholamine release (Carruba et al., 1987), which counteracts the depressant effect that this anaesthetic exerts on the heart, so that blood pressure is maintained at near-normal levels at all except deep levels of anaesthesia. The catecholamine release also results in a moderate rise in blood glucose concentrations, and in a wide range of other metabolic changes, which may interfere with particular research protocols. Ether is not, as

commonly believed, an inert compound. It undergoes extensive metabolism and exposure to ether, which results in induction of liver enzyme activity (Linde and Berman, 1971).

Although ether has been a popular anaesthetic, its use for induction is unpleasant for the animal and hazardous in several species, particularly guinea pigs. Its explosive properties make it a significant safety hazard: animals should not be killed with ether, as the carcasses may be stored in refrigerators which are not spark-proof and an explosion may result.

Nitrous Oxide

Desirable Effects

Nitrous oxide causes minimal cardiovascular and respiratory system depression.

Undesirable Effects

Nitrous oxide has very low anaesthetic potency and cannot be used alone to produce anaesthesia, or even unconsciousness, in most species (e.g. Mahmoudi et al., 1989). It reacts with vitamin B12, producing vitamin depletion after prolonged (>6 hour) anaesthesia and can cause bone marrow depression.

Special Comments

Nitrous oxide is extensively used for anaesthesia in animals and humans, although the mechanisms of its anaesthetic and analgesic effects are still not fully characterized (Maze and Fujinaga, 2001). Since nitrous oxide has minimal effects on the respiratory and cardiovascular systems, it can be used to reduce the required concentration of other agents and so to reduce the overall degree of depression of blood pressure or respiration at a particular depth of anaesthesia. It is usually administered as a 50:50 or a 60:40 mixture with oxygen. Following the cessation of prolonged nitrous oxide administration, 100% oxygen should be administered to prevent so-called diffusion hypoxia. This phenomenon causes lowered alveolar oxygen tension due to the rapid diffusion of nitrous oxide from the blood to the alveoli. Because of its low analgesic potency, nitrous oxide must never be used as the sole anaesthetic agent in association with neuromuscular blocking (NMB) agents such as pancuronium. Its main value lies in reducing the required concentration of other more potent agents which have more marked side-effects. It is important to note that nitrous oxide is not absorbed by the activated charcoal canisters used in some gas-scavenging systems. If nitrous oxide is used, then an active scavenging system that ducts expired gases directly to the room ventilation extract must be used.

A common misconception is that it is necessary to administer nitrous oxide in order to administer other inhalation anaesthetics. This is not the case, and all of the other agents mentioned above can safely be administered in 100% oxygen. It is only necessary to avoid this if prolonged periods of anaesthesia are planned (>16–24 hours), when the inspired oxygen concentration should be reduced

(to approximately 40%) to avoid the possible development of oxygen toxicity. This can be achieved without the use of nitrous oxide by using an air/oxygen or nitrogen/oxygen mixture, the other gas being supplied from an appropriate compressed gas cylinder. If the gases are mixed at the outlet from the anaesthetic machine, then the delivered concentration of anaesthetic vapour will be reduced, and the vaporizer setting should be increased accordingly.

Older Agents

A number of other anaesthetics have been developed, but they are primarily only of historical interest. Chloroform vapour has numerous side-effects which resulted in it being discarded from human and veterinary clinical practice, and which make it unsuitable for laboratory use. Trichlorethylene vapour produces good analgesia, and is inexpensive, non-inflammatory and non-explosive. It also causes only minimal cardiovascular system depression, but it has poor muscle relaxant properties, low anaesthetic potency, and decomposes in the presence of soda lime to form toxic and explosive products, so that it must never be used in closed breathing systems. Trichlorethylene undergoes extensive hepatic metabolism and has been established as a hepatic carcinogen in some species (Green, 2000). It is rarely used for animal anaesthesia. The gas cyclopropane can be used to produce rapid induction of anaesthesia, and the depth of anaesthesia can be altered smoothly and rapidly. Recovery from anaesthesia is also rapid. Unfortunately, cyclopropane is flammable and explosive in air and oxygen, and this hazard limits the use of this anaesthetic in most laboratories.

Administration of Anaesthetics by Injection

Equipment

Although the equipment required for injection of anaesthetics consists basically of a syringe and a needle, some attention should be given to the range of syringe and needle sizes available and also to the use of indwelling catheters, cannulae, extension tubing and infusion devices.

Syringes

Plastic disposable syringes are almost universally used for delivering anaesthetics. These single-use syringes should not be resterilized for further use. Ensure that an appropriate-volume syringe is used so that the required dose of anaesthetic can be administered accurately. The syringes designed for insulin administration to human patients are particularly useful for administering small doses of drugs to rodents (Fig. 2.20). Select a syringe design that is comfortable to hold and that enables a firm grip to be maintained even when the barrel is wet. Avoid using syringes which have been stored for a length of time which exceeds the period recommended by the manufacturers, as the plastic may have become brittle and can fracture during use.

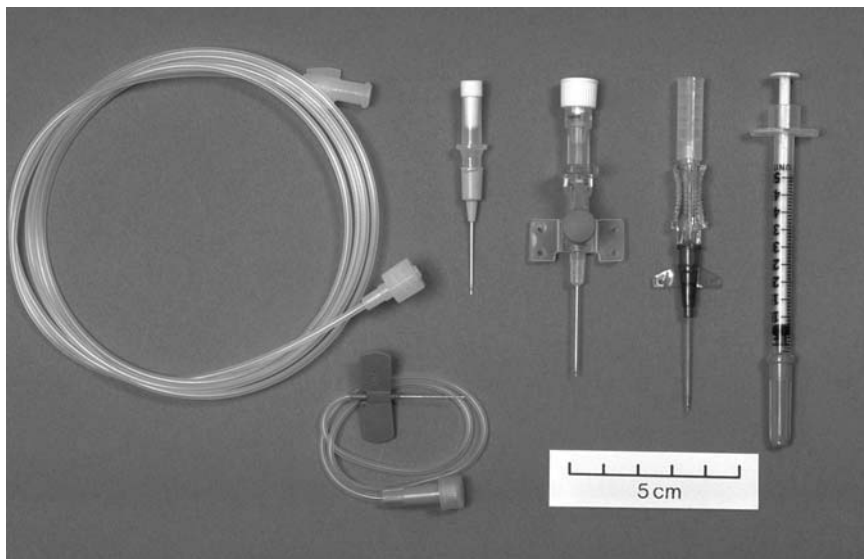


FIGURE 2.20 Insulin syringe, ‘butterfly’ infusion set, catheters and anaesthetic extension line.

Needles and Cannulae

Disposable hypodermic needles should be used and an appropriate gauge selected for each purpose. Needles should never be resterilized, as they rapidly become blunt when used and injection with a blunt needle can cause considerable discomfort. Successful venepuncture of small vessels is particularly difficult to achieve if the needle has been blunted. For this reason, it is advisable to replace the needle after drawing up liquid from a rubber-capped vial.

Often it is preferable to use a butterfly-type infusion set, rather than a simple hypodermic needle. These infusion devices provide a short length of flexible catheter between the needle and the syringe so that movements of the animal during injection are less likely to result in the needle becoming dislodged from the vein (Fig. 2.20). This is particularly important when inducing anaesthesia with short-acting anaesthetic agents since the administration of an inadequate dose of drug may produce involuntary excitement. If the ensuing limb movements result in displacement of the needle from the vein, its replacement may be virtually impossible.

Even more useful for intravenous induction are indwelling catheters, since these enable successive intravenous injections of anaesthetics and other drugs to be made easily and reliably. A flexible catheter will not pierce the vessel wall should movements of the animal occur, so accidental extravascular injection will be avoided. Several types of catheters are available, but they can be broadly grouped as ‘over-the-needle’ designs in which the flexible catheter is placed on the outside

of a needle which acts as an introducer and ‘through-the-needle’ designs in which the catheter runs through the needle. A further variation that is often used for placing catheters in deeper vessels, or for placing larger catheters, is ‘over-the-wire’ designs. A needle is placed into the blood vessel, and a flexible wire passed down the needle into the vessel. The needle is then withdrawn, and the catheter threaded along the wire and into the vessel. The wire is then withdrawn.

In most circumstances, ‘over-the-needle’ catheters are preferable for use in small animals since they allow the largest possible catheter to be inserted into the vessel (Fig. 2.20). In large animals, the skin may offer significant resistance to passage of the catheter and may damage an ‘over-the-needle’ type, but this does not occur when using a ‘through-the-needle’ design. An alternative solution is to make a very small skin incision with a scalpel blade to allow easy passage of an ‘over-the-needle’ catheter.

Simple ‘over-the-needle’ catheters are relatively inexpensive, and the advantages of maintaining a secure route for intravenous drug administration can be considerable. In addition to the administration of anaesthetics, other drugs and intravenous fluids can be administered rapidly, even by relatively unskilled assistants. It is important that the catheter is securely anchored in place. This can be achieved as illustrated in Figure 2.21. When anchoring catheters in the marginal ear vein in species such as the rabbit or sheep, it is helpful to cut off one wing to reduce the risk of dislodging the catheter (Fig. 2.21).

Extension Lines

It is often inconvenient to require access to the catheter site for repeated drug administration, and this can be avoided by the use of a plastic tubing of suitable length (Fig. 2.20). Extension lines that are equipped with a Luer-locking fitting are preferable, as they are less likely to become disconnected. A problem with many of the extension lines produced for human use is their large volume, which can cause problems if different drugs are to be administered successively to a small animal. It is often undesirable to administer a bolus of 4–5 ml of saline to a small animal to flush an infusion line. Small-volume extension lines (<1 ml) are available from Vygon Ltd. (Appendix 4). A useful compromise is to select an indwelling catheter with a side-injection port (Fig. 2.20). Routine infusion of anaesthetic can be carried out through an extension line and administration of other drugs through the side-injection port. Extension lines are also useful when administering large volumes of drugs by the intramuscular route to larger animals such as pigs. Use of an extension between the needle and the syringe enables placement of the needle, followed by controlled injection without the need to restrain the animal.

Infusion Pumps

It is often convenient to administer intravenous anaesthetics by continuous infusion. A range of infusion pumps is available commercially, and the cost of sophisticated microprocessor-controlled models has fallen rapidly. Pumps

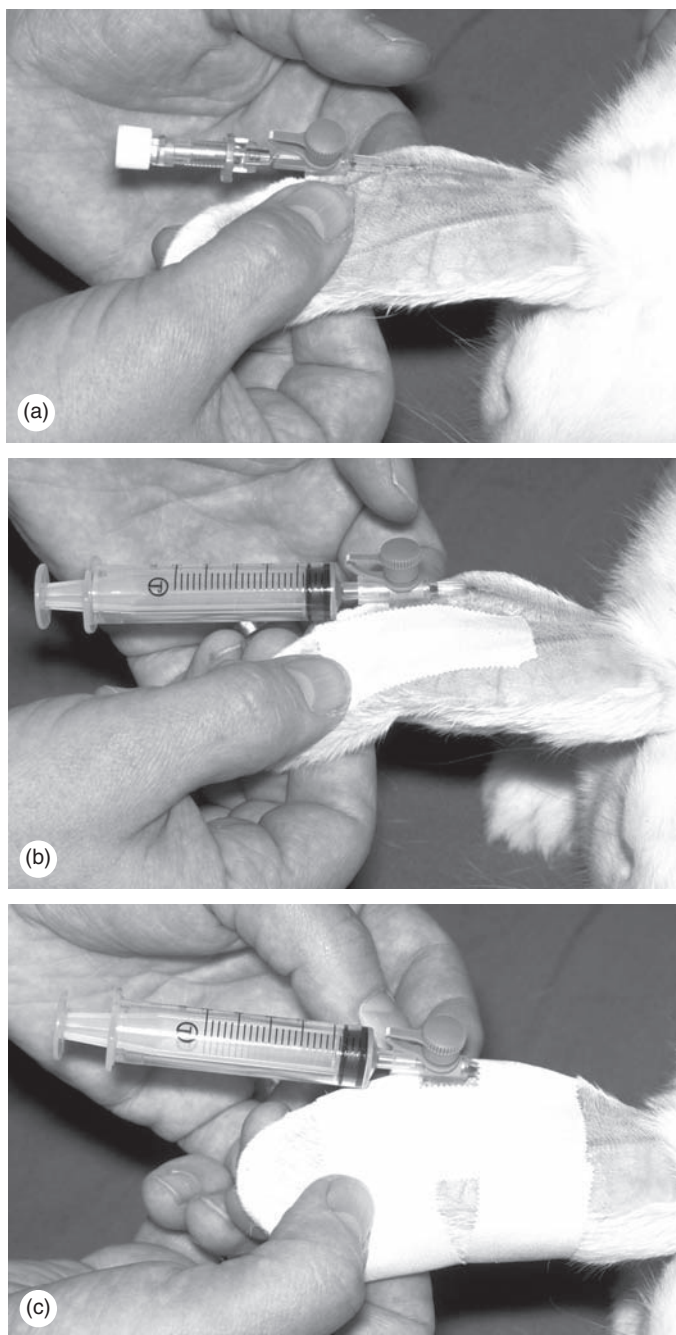


FIGURE 2.21 Method of anchoring intravenous catheters on a rabbit ear. One wing of the catheter is removed (a), a piece of tape is laid along the ear across the remaining wing (b) and two further pieces of tape are wrapped around the ear (c).

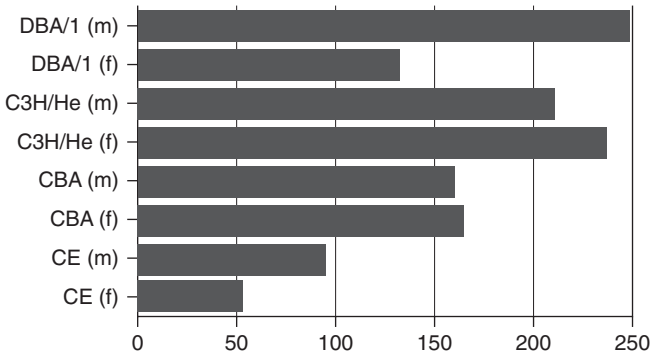


FIGURE 2.22 Sleep time in different strains of mice given pentobarbital. Data redrawn from Lovell (1986a,b,c).

designed for clinical use in humans generally operate using a 50-ml syringe. Although this syringe size is somewhat excessive for use in small animals, the rate at which drugs can be delivered can be as little as 0.1 ml/h.

Smaller volume pumps, particularly those designed for insulin infusion, are suitable for use in small animals. Purpose-designed infusion pumps that allow the use of different syringe sizes are more versatile and are a worthwhile investment if total intravenous anaesthesia is to be employed.

If an infusion pump is not available, drugs can be administered using an intravenous infusion set and a burette to allow better control over the volumes administered. The use of such gravity-feed devices has the obvious disadvantage that changes in the position of the cannula, or movements of the limb, can greatly affect the infusion rate. Nevertheless, such simple devices can be used successfully, particularly if a central venous cannula, which is less susceptible to occlusion, is used. The apparatus available for the infusion of anaesthetics has been reviewed by Glen (1988). Further details of infusion techniques and equipment are given in Chapter 5.

Routes of Administration

Injectable anaesthetics can be administered by a variety of routes. Intravenous administration is usually preferable, since this produces the most predictable and rapid onset of action. This enables the drug to be administered 'to effect' to provide the desired depth of anaesthesia. Practical considerations, such as the absence of suitable superficial veins or difficulty in providing adequate restraint of the animal, may limit the use of this route in some laboratory species. Administration by intramuscular, intraperitoneal or subcutaneous injection is relatively straightforward in most species, but the rate of drug absorption and hence its anaesthetic effects may vary considerably. A relatively high failure rate has been reported with intraperitoneal dosing (Das and North, 2007), with injection of some of the anaesthetic into the viscera, fat or the subcutaneous tissues. There is also a very great

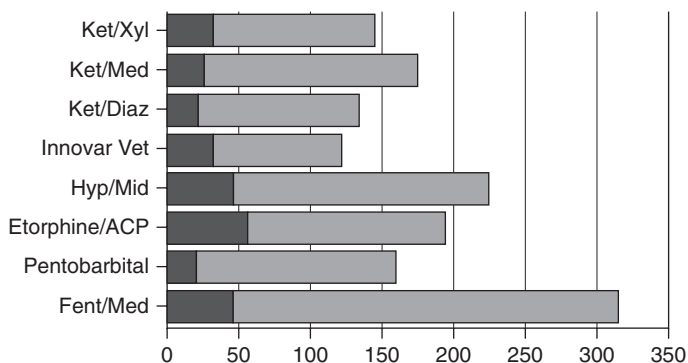


FIGURE 2.23 Duration of anaesthesia and sleep times in rats with different anaesthetics (data from various studies). Ket/Xyl – ketamine and xylazine; Ket/Med – ketamine and medetomidine; Ket/Diaz – ketamine and diazepam; Innovar-Vet – fentanyl and droperidol; Hyp/Mid – hypnorm and midazolam; Etorphine/ACP – etorphine and acepromazine; pentobarbital; Fent/Med – fentanyl and medetomidine.

variation in response to anaesthetics between different strains, ages and sex of animals. The magnitude of these effects is illustrated with pentobarbital in mice in Figure 2.22, but this variation must be anticipated in all species and with all anaesthetics. Similar major differences in response were noted with ketamine/medetomidine in response between male and female animals (Cruz et al., 1998), and similar effects have been observed with other anaesthetics in other species, including humans (Ciccone and Holdcroft, 1999). When using an anaesthetic technique for the first time, it is essential to assess its effects on one animal, before beginning to anaesthetize the remainder of the group. This will enable the recommended doses to be adjusted to suit the responses of the particular animals being used. As mentioned above, this variability in response can be a particular problem in small rodents, since most injectable anaesthetics are administered to these species by the intraperitoneal route as a single dose. When administering anaesthetics in this way, it is impossible to adjust the dose according to the individual animal's response, so accidental over- and under-dosing will frequently occur, until experience is gained with a particular strain, age and sex of the animal. Variation in response to anaesthetics, administered by any route, also occurs with changes in environmental factors. Standardization of all of these variables will not only simplify anaesthetic dose calculations but also constitute good experimental designs. When selecting anaesthetics for intramuscular, intraperitoneal or subcutaneous administration, it is also advisable to select those which have a wide safety margin.

A further disadvantage of the intraperitoneal, subcutaneous or intramuscular routes is that relatively large doses of anaesthetic must be given to produce the required effect. Absorption is slow relative to intravenous administration, residual drug effects can persist for prolonged periods and so full recovery can be very prolonged (Fig. 2.23).

An additional consideration with intramuscular or subcutaneous injection is that administration of an irritant compound can cause unnecessary pain or discomfort to the animal. This is a particular concern with intramuscular injection in small rodents. The problem often arises because commercial formulations of anaesthetics (e.g. ketamine) are designed to provide a convenient volume for injection into a particular species (e.g. cats). Small rodents require very much higher dose rates of some anaesthetics per unit of body mass than do larger species, for example, 75 mg/kg ketamine in rats compared to 10 mg/kg in a non-human primate. Since the concentration of the agent is fixed, this results in a major increase in the volume given – 0.75 ml/kg in rats compared to 0.1 ml/kg in a primate in the example given. Not surprisingly, there are a number of reports of tissue reactions and myositis following anaesthetic administration in small mammals (Gaertner et al., 1987; Smiler et al., 1990; Beyers et al., 1991). For this reason, it is recommended that the intramuscular route is avoided in small rodents.

Intravenous administration avoids the problems discussed above, and the technical problems associated with intravenous injection in small mammals are often more imagined than real. Research workers may avoid intravenous anaesthesia and yet administer other compounds by the intravenous route as part of their research protocol. Before discounting intravenous administration, consider whether the necessary expertise is already available, or if developing this expertise would be worthwhile. In rats, for example, placement of an ‘over-the-needle’ catheter allows both intravenous anaesthesia and administration of other drugs and fluids as necessary. A number of short-acting anaesthetics can be used to provide 5- to 10-minute periods of anaesthesia (see below and Chapter 4), and some are suitable for continuous infusion to provide long-term anaesthesia. When carrying out venepuncture in animals, consider using EMLA cream (Astra) to produce local anaesthesia of the skin (see above).

Drugs Available

Barbiturates

Pentobarbital

Desirable Effects. Pentobarbital can be administered either by intravenous or intraperitoneal injection and can be used in a wide range of animal species.

Undesirable Effects. Pentobarbital causes severe cardiovascular and respiratory system depression and has poor analgesic activity. Recovery can be prolonged, particularly after the administration of an additional dose to prolong anaesthesia.

Special Comments. Pentobarbital has been the most widely used laboratory animal anaesthetic. Surgical anaesthesia is attained in most small laboratory animals only when dosages close to those which cause respiratory failure have been administered. At these dose rates, severe cardiovascular depression and respiratory depression are produced. Slow intravenous administration of a dose sufficient to produce basal narcosis, followed by further incremental doses, usually achieves

surgical levels of anaesthesia reasonably safely. Intraperitoneal administration of the calculated amount of drug as a single bolus is often associated with high mortality not only because the anaesthetic dose is very close to the lethal dose, but because there is also considerable between-strain variation. Pentobarbital is probably best used to provide hypnosis rather than anaesthesia, and in most circumstances, safer and more effective agents are available.

Pentobarbital is no longer commercially available as an anaesthetic in a number of countries; however, the agent can be purchased from specialist suppliers (e.g. Sigma) if needed for specific research projects. It has relatively low solubility, and commercial preparations may include propylene glycol or other agents. Aqueous solutions of 50 mg/ml can be prepared from pentobarbital powder.

Like other barbiturates, pentobarbital solution has a very high pH, so intraperitoneal injection can cause pain (Svensden et al., 2007). When used as a euthanasia agent, the addition of a local anaesthetic can prevent pain on intraperitoneal injection.

Thiopental

Desirable Effects. Thiopental produces smooth and rapid induction of anaesthesia following intravenous injection and can be used in virtually all species.

Undesirable Effects. Thiopental has poor analgesic activity and causes transient apnoea after intravenous injection. It is irritant if injected perivascularly. Repeated administration results in very prolonged recovery time (see Chapter 4).

Special Comments. Thiopental is a short-acting barbiturate which is useful for rapid induction of anaesthesia when administered intravenously. It is unstable in aqueous solution, so once reconstituted, it should be used within 7–10 days. Its duration of action depends upon both the amount of drug injected and the rate of injection. The doses quoted in Chapter 6 should be administered as follows: half the calculated dose should be given rapidly, followed by the remainder to effect over 1–2 minutes. This will result in 5–15 minutes of anaesthesia. Transient apnoea usually follows administration, but assisted ventilation is rarely required. Thiopental solution is extremely irritant if injected perivascularly and should be diluted as much as practicable (preferably to enable the use of a 1.25–2.5% solution). If extravascular administration occurs, then the area should be infiltrated with a solution of 1 ml of lidocaine 2% in 4 ml normal saline. Since thiopental is highly irritant, primarily because of its high pH, it should not be administered by the intraperitoneal, intramuscular or subcutaneous routes. The drug's major use is by intravenous injection to provide rapid induction of anaesthesia, followed by maintenance using inhalational agents.

Methohexital

Desirable Effects. Methohexital produces smooth and rapid induction of anaesthesia after intravenous administration and can be used in a wide range of species.

Undesirable Effects. Like other barbiturates, methohexital has poor analgesic activity, and transient apnoea often occurs after induction. Recovery is frequently

accompanied by muscular tremors unless suitable pre-anaesthetic medication has been administered.

Special Comments. This agent is now rarely used as an anaesthetic, and is unavailable as a commercial product in many countries. Methohexital has a shorter duration of action than thiopental and is about twice as potent. It should be administered as described above for thiopental. Anaesthesia lasts for 2–5 minutes, and several incremental doses can usually be given without unduly prolonging the rate of recovery. Methohexital is a valuable drug for the induction of anaesthesia, provided intravenous administration is possible. Although intraperitoneal administration has been reported, the use of this route of administration often has less predictable effects, with some animals failing to become anaesthetized.

Inactin

Desirable Effects. ‘Inactin’ (sodium thiobutobarbital) produces smooth induction of anaesthesia after intravenous administration and has a prolonged duration of action.

Undesirable Effects. It has variable analgesic activity.

Special Comments. Inactin is a thiobarbiturate which has been claimed to produce prolonged anaesthesia in rats following intraperitoneal (Buelke-Sam et al., 1978) or intravenous (Walker et al., 1983) administration. Whilst it appears to be a satisfactory induction agent when given intravenously (resembling thiopental in its effects), its effects when given by the intraperitoneal route may vary. In the author’s experience, some rats remain lightly anaesthetized for several hours, whereas others appear completely recovered within 60 minutes. Provided that an appropriate dose rate has been established in the particular strain of rat which is to be anaesthetized, inactin can be used to produce prolonged anaesthesia.

Steroid Anaesthetics

Alphaxalone/Alphadolone, Alphaxalone

Desirable Effects. Alphaxalone/alphadolone and alphaxalone produce smooth induction of anaesthesia following intravenous administration. Administration of repeated doses of the drug has little effect on recovery time. The solution is non-irritant, and the mixture of alphaxalone and alphadolone has a wide margin of safety in most species (Child et al., 1971, 1972b, c). The commercial formulation of these agents is becoming unavailable, however the newer formulation of alphaxalone is likely to have similar properties. For this reason, the information and dose rates of the older mixture of agents has been retained, since at the time of writing, only limited data on alphaxalone is available.

Undesirable Effects. The solubilizing agent present in the commercial preparation of alphaxalone/alphadolone promotes histamine release in dogs, and the drug should not be used in this species. Mild histamine release also occurs frequently in cats, causing oedema of the paws, muzzle and ears. A more recently introduced formulation of alphaxalone (‘Alfaxan’) avoids this problem, as it does not use this solubilizing method.

Special Comments. Two commercial preparations of this anaesthetic are available: one consists of a mixture of two steroids, alphaxalone and alphadolone, together with a solubilizing agent, Chremophor EL (polyoxyethylated castor oil), and the other alphaxalone alone. Alphaxalone and alphadolone differ slightly in their anaesthetic potency, but dose rates of the commercial combination preparations are conventionally reported as mg/kg of total steroid.

Administration of alphaxalone/alphadolone by the intramuscular or intraperitoneal routes has very variable effects. Occasionally, light surgical anaesthesia is produced; but in most species, the volume of drug required precludes intramuscular administration, and absorption following intraperitoneal injection is very unpredictable (Green et al., 1978). It is an effective agent for immobilizing small primates when administered intramuscularly, however. Following intravenous administration, it produces rapid-onset anaesthesia followed by rapid recovery. The agent is non-irritant, and accidental extravascular injection does not appear to be associated with any adverse effects.

As the drug is rapidly metabolized, it is an excellent agent for maintenance of long-term anaesthesia, although moderate hypotension may occur (Child et al., 1972a; Dyson et al., 1987). Continuous intravenous infusion can be used to provide safe and stable anaesthesia in sheep, pigs, primates, cats and rodents, although in larger species economic considerations may limit its usefulness. In rabbits, the degree of analgesia produced is insufficient for major surgery until high doses have been administered, and at these dosages, respiratory arrest often occurs.

Alphaxalone/alphadolone must not be used in conjunction with barbiturates. Although structurally related to the steroid hormones, alphaxalone and alphadolone have no significant endocrine effects (Child et al., 1972b). Less information is available concerning the newer single-steroid product; however, it is likely to have similar properties as the older product in all species (e.g. Keates, 2003).

Dissociative Anaesthetics

Ketamine

Desirable Effects. Ketamine produces immobility in most species and can be administered by the intramuscular, intraperitoneal and intravenous routes. It causes only moderate respiratory depression in most species (NB: rodents, see below) and increases blood pressure. Although the degree of analgesia produced may vary, ketamine is an NMDA (N-methyl-D-aspartate) antagonist and has been shown to prevent sensitization to noxious stimuli during surgery (see Chapter 5).

Undesirable Effects. Skeletal muscle tone is increased. The degree of analgesia produced is very variable, and in small rodents, severe respiratory depression is produced following administration of the high dose rates needed for surgical anaesthesia. Recovery can be prolonged and may be associated with hallucinations and mood alterations (Wright, 1982).

Special Comments. Ketamine produces a state of cataleptic sedation with apparent lack of awareness of the surroundings (White et al., 1982). In those species in which profound analgesia appears to be produced, spontaneous movements often

occur, but these are usually unrelated to surgical stimuli. In some species, the corneal blink reflex is lost for prolonged periods, and drying of the cornea may occur unless the eye is filled with a bland ophthalmic ointment as a preventive measure. Laryngeal and pharyngeal reflexes are maintained at all, except very high dose rates, although salivary secretions are increased and airway obstruction remains a significant hazard. In all species, it may be necessary to use atropine or glycopyrrolate together with ketamine to reduce these otherwise excessive bronchial and salivary secretions. Ketamine is the drug of choice for immobilization of large primates and is an effective chemical restraining agent in cats and pigs and, to a lesser extent, in rabbits. Its effects in rodents are variable, and high dose rates may be necessary to produce surgical anaesthesia (Green et al., 1981a).

It is extremely useful when administered in combination with medetomidine, xylazine or diazepam for the production of surgical anaesthesia in sheep, primates, cats, dogs, pigs, rabbits and small rodents (see Chapter 6). It is important to appreciate that the stimulatory effects of ketamine on the cardiovascular system do not offset the depressant effects of drugs such as xylazine, and the use of these combinations almost invariably results in significant hypotension (Middleton et al., 1982; Allen et al., 1986). Ketamine can be mixed with medetomidine, xylazine or acepromazine and the combination administered as a single injection. The chronic administration of ketamine results in hepatic enzyme induction, and this may decrease the efficacy of the agent on subsequent administrations (Marietta et al., 1975).

Neuroleptanalgesics

Fentanyl/Fluanisone, Fentanyl/Droperidol, Etorphine/Methotrimeprazine, Etorphine/Acepromazine

Desirable Effects. Neuroleptanalgesic combinations produce profound analgesia and can be administered by the intramuscular, intraperitoneal or intravenous routes to most species. The effects of these drug combinations can be reversed by administration of mu-opioid antagonists such as naloxone, nalbuphine or butorphanol (see below).

Undesirable Effects. Neuroleptanalgesic combinations produce moderate or severe respiratory depression and a poor degree of muscle relaxation (NB: see below). Hypotension and bradycardia may also be produced.

Special Comments. Neuroleptanalgesic combinations consist of a potent opioid analgesic, which can abolish the perception of pain, and a neuroleptic – a tranquillizer/sedative (e.g. acepromazine or fluanisone) – which suppresses some of the undesirable side-effects of the narcotic such as vomiting or excitement. The analgesics used in commercially available neuroleptanalgesic combinations are fentanyl and etorphine. When neuroleptanalgesic combinations are used alone, the adverse effects mentioned above can be marked, and the poor degree of muscle relaxation produced makes them unsuitable for anything other than superficial surgery. When given in combination with a benzodiazepine (e.g. midazolam or diazepam), the dose of the commercial neuroleptanalgesic mixtures can be reduced by 50–70%, and the benzodiazepine produces good skeletal muscle relaxation. Used in this way,

combinations such as fentanyl/fluanisone and midazolam are often the anaesthetic method of choice for rodents and rabbits (Flecknell et al., 1984). Although pharmacologically similar, fentanyl/fluanisone (Hypnorm) and fentanyl/droperidol (Innovar-Vet, Thalamanol) differ in their effects in animals. As mentioned above, fentanyl/fluanisone in combination with diazepam or midazolam produces good surgical anaesthesia. The effects of a comparable mixture of fentanyl/droperidol and midazolam are much less predictable, and this latter combination cannot be recommended (Flecknell, unpublished observations; Marini et al., 1993). Another commercially available combination, etorphine/methotrimeprazine (Immobilon SA), has been evaluated in combination with midazolam. Although surgical anaesthesia is produced, respiratory depression can be severe (Whelan and Flecknell, 1994, 1995).

An important advantage of these drug combinations is that their action is readily reversible by the administration of opioid antagonists such as naloxone or mixed agonist/antagonists such as butorphanol or partial agonists such as buprenorphine (Flecknell et al., 1989) (see Chapter 7). Fentanyl/fluanisone and fentanyl/droperidol are useful for providing restraint and analgesia for minor procedures, and the combination of fentanyl/fluanisone/midazolam is recommended for surgical anaesthesia in rodent and rabbits. The use of other neuroleptanalgesic combinations has been described (Green, 1975).

Other Opioid Combinations

Because of their potent analgesic action, short-acting opioids such as fentanyl and alfentanil can be used in combination with a variety of compounds to produce balanced anaesthesia. Mixtures of fentanyl or alfentanil and a benzodiazepine produce effective surgical anaesthesia in dogs (Flecknell et al., 1989) and pigs, and they can be added to anaesthetics in which analgesia would otherwise be inadequate (e.g. propofol) (Michalot et al., 1980; Flecknell et al., 1990). The use of opioids often enables the production of profound analgesia, without major effects on the cardiovascular system, although bradycardia can be produced if the drugs are given rapidly. Opioid-induced bradycardia can rapidly be reversed with atropine, without affecting the analgesia produced by these drugs. Severe respiratory depression can occur when using high doses of opioids, although this can be overcome by the use of intermittent positive pressure ventilation (IPPV).

Fentanyl/Medetomidine Fentanyl and medetomidine can be combined to produce anaesthesia in dogs, rabbits, guinea pigs and rats. The combination is most effective in dogs and rats. In the dog, the drugs are given by intravenous injection, and in the rat, the two compounds are combined and given as a single intraperitoneal injection. A number of other opioid combinations have been described, and these are discussed in more detail in Chapter 7.

Desirable Effects. The combination reliably produces surgical anaesthesia with good muscle relaxation in some species (see Chapter 7). Anaesthesia is completely reversible by administering specific antagonists (nalbuphine or butorphanol together with atipamezole).

Undesirable Effects. Mild to moderate respiratory depression is produced. In the rat, the relatively large volume for injection is inconvenient for the operator, but does not appear distressing to the animal. In the mouse, the combination causes urinary retention which may result in rupture of the bladder, and so should not be used in this species.

Special Comments. The rapid and complete reversal of anaesthesia avoids the problems that may be associated with managing animals during the prolonged recovery that can be associated with other injectable anaesthetic techniques. Reversal of the fentanyl component with a mixed opioid agonist/antagonist results in maintenance of post-operative analgesia.

Other Hypnotics

Etomidate and Metomidate

Desirable Effects. Etomidate and metomidate are short-acting hypnotics with minimal effects on the cardiovascular system.

Undesirable Effects. Etomidate and metomidate have little analgesic action when used alone and suppression of adrenocortical function following prolonged infusion of etomidate has been reported (Kruse-Elliott et al., 1987).

Special Comments. Etomidate has been shown to cause little cardiovascular depression in animals (Nagel et al., 1979; Kissin et al., 1983), and so may be useful as part of balanced anaesthetic regimens. Metomidate and etomidate are useful for providing unconsciousness (and therefore restraint) in many mammals, birds, reptiles and fish (Janssen et al., 1975). Metomidate in combination with fentanyl, administered as a subcutaneous injection, is an effective anaesthetic combination for small rodents (Chapter 7) (Green et al., 1981b).

Propofol

Desirable Effects. Propofol produces rapid induction of a short period of anaesthesia in a wide range of species. Recovery is smooth and rapid with little cumulative effect if additional doses are administered.

Undesirable Effects. Insufficient analgesia for major surgery in some species, a short period of apnoea, may occur after induction if propofol is administered rapidly, and respiratory depression can occur with high doses of propofol. Prolonged infusion causes lipaemia because of the formulation (see below).

Special Considerations. Propofol (2,6-di-isopropyl phenol) is an alkyl phenol (Glen, 1980; Glen and Hunter, 1984) which, because of its poor water solubility, is prepared as an emulsion formulation in soya bean oil and glycerol. Intravenous administration of this compound produces rapid-onset anaesthesia in a wide range of species, with a sleep time similar to thiopental (Glen, 1980). In contrast to thiopental, animals recover more rapidly following propofol administration, and sleep times are not greatly prolonged following repeated dosing (Glen, 1980).

Because of its rapid redistribution and metabolism, propofol is best given by intravenous injection to be effective; otherwise, the rapid redistribution to body

tissues that occurs will prevent anaesthetic concentrations being achieved in the brain. Propofol should be administered relatively slowly, as this avoids causing transient apnoea. Typically, the dose needed to produce unconsciousness and sufficient relaxation to allow intubation should be given over 1–2 minutes in small animals (1–10 kg). Propofol produces a moderate fall in systolic blood pressure, and a small fall in cardiac output (Sebel and Lowdon, 1989). Propofol causes significant respiratory depression in most species, manifested either as a reduction in respiratory rate (Glen, 1980), or as little change in rate but a fall in arterial oxygen tension, suggesting a fall in tidal volume (Watkins et al., 1987). It is therefore advisable to provide supplemental oxygen. Propofol is believed to have no significant effects on hepatic (Robinson and Patterson, 1985) or renal function (Stark et al., 1985), nor on platelet function or blood coagulation (Sear et al., 1985). In humans, propofol causes a fall in intraocular pressure (Vanacker et al., 1987), but no data are available for its effects on ocular pressure in animal species. The pain on injection of propofol which has been reported in humans does not appear to be a significant problem in animals (Brearley et al., 1988; Flecknell et al., 1990; Weaver and Raptopoulos, 1990). Propofol is non-irritant when injected perivascularly (Morgan and Legge, 1989).

Tribromoethanol

Desirable Effects. Tribromoethanol ('Avertin') produces surgical anaesthesia in rats and mice, with good skeletal muscle relaxation and only a moderate degree of respiratory depression.

Undesirable Effects. If incorrectly stored, or administered more than once, tribromoethanol is irritant to the peritoneum (see below). Even freshly prepared solutions can cause undesirable side-effects (see below).

Special Comments. Tribromoethanol is a popular anaesthetic for mice, and it produces 15–20 minutes of anaesthesia with rapid recovery (Papaioannou and Fox, 1993). It has been known for some time that decomposition of stored solutions can result in severe irritation and peritoneal adhesions following its use. Even if a freshly prepared solution is used, administration of a second anaesthetic at a later date is often associated with high mortality (Norris and Turner, 1983). More recently, it has been established that the use of freshly prepared solutions can be associated with post-anaesthetic mortality (Lieggi et al., 2005a), and that tribromoethanol causes low-grade peritonitis (Zeller et al., 1998). Analysis of different batches of tribromoethanol by using a range of analytical techniques indicated that it contains a number of impurities, and that the concentration and the identity of these may vary (Lieggi et al., 2005b). This may account for the varying incidences of side-effects. This study also established that monitoring of the pH of tribromoethanol stock solution, to try to detect breakdown products, was ineffective. Given the unpredictable adverse effects, tribromoethanol use should be avoided and alternative anaesthetics used.

Chloral Hydrate

Desirable Effects. Chloral hydrate produces medium-duration (1–2 hours), stable, light anaesthesia (Sisson and Siegel, 1989; Field et al., 1993). The drug has minimal effects on the cardiovascular system and on baroreceptor reflexes.

Undesirable Effects. Chloral hydrate has poor analgesic properties, and the high doses required for surgical anaesthesia can produce severe respiratory depression. Intraperitoneal administration to rats has been associated with a high incidence of post-anaesthetic ileus (dilation and stasis of the bowel) (Fleischman et al., 1977). Although the use of low concentrations of chloral hydrate (36 mg/ml) may reduce the incidence of this effect, it may not completely solve the problem.

Special Comments. Chloral hydrate can often be replaced by more effective anaesthetics if surgical procedures are to be undertaken. As with many other anaesthetics, there is considerable strain variation in the response to chloral hydrate in rodents, and it is important to evaluate the drug's efficacy and safety in the particular strain of animals that will be used. Chloral hydrate has also been used in combination with magnesium sulphate and pentobarbital ('Equithesin') (Bo et al., 2003) as an anaesthetic for a number of species. It has been particularly widely used in pharmacological studies, because of the limited effects on a number of receptor systems. Although the concentration of chloral hydrate in 'Equithesin' is low, it can still produce ileus in some strains of rat (Deacon and Rawlins, 1996).

Alpha-Chloralose

Desirable Effects. Alpha-chloralose produces stable, long-lasting (8–10 hours) but light anaesthesia. It produces minimal cardiovascular and respiratory system depression (Holzgreffe et al., 1987; Svendsen et al., 1990).

Undesirable Effects. Alpha-chloralose has poor analgesic properties, although this varies considerably between different species and strains of animals. Both induction and recovery can be very prolonged and associated with involuntary excitement.

Special Comments. Alpha-chloralose is useful for providing long-lasting light anaesthesia for procedures involving no painful surgical interference. A more potent but short-acting anaesthetic can be administered to produce a depth of anaesthesia sufficient to allow surgical procedures to be undertaken, following which unconsciousness can be maintained with alpha-chloralose. Recovery is prolonged and associated with involuntary excitement, so alpha-chloralose is best used for non-recovery studies. A more detailed discussion of this anaesthetic can be found in Chapter 4.

Urethane

Desirable Effects. Urethane produces long-lasting (6–10 hours) anaesthesia, with minimal cardiovascular and respiratory system depression (Buelke-Sam et al., 1978; Maggi and Meli 1986a, b, c; Field et al., 1993).

Undesirable Effects. Urethane is carcinogenic (Field and Lang, 1988), and produces peritoneal effusion (Severs et al., 1981) and haemolysis.

Special Comments. Urethane resembles chloralose in producing long-lasting, stable anaesthesia, but unlike chloralose, the degree of analgesia produced is sufficient to allow surgical procedures to be undertaken in small rodents. It is a useful agent for long-term anaesthesia (see Chapter 5), but it is also a carcinogen, so its use should be avoided whenever possible. If it is necessary to use urethane,

precautions appropriate to the handling of a known carcinogen should be adopted. Animals should not be allowed to recover after being anaesthetized with urethane. A more detailed discussion of this anaesthetic can be found in Chapter 5.

Local and Regional Anaesthesia

Local anaesthetics act directly on nervous tissue to block the conduction of nerve impulses. For example, they can be applied to the surface of the cornea and the conjunctiva to produce local anaesthesia of that part of the eye, or they can be used to anaesthetize mucus membranes to ease the passage of catheters or an endotracheal tube.

Local anaesthetics (e.g. Bupivacaine or lidocaine) can also be injected into tissues to provide a localized area of anaesthesia. Infiltration of the skin and underlying connective tissue will usually provide sufficient anaesthesia to suture minor wounds or to take a biopsy of skin. Infiltration of more extensive areas and the different tissue planes can be used to provide sufficient anaesthesia to carry out surgical procedures such as laparotomy. When injecting local anaesthetics for this purpose, a fine (<26 gauges), long needle should be used, to minimize the discomfort associated with the injection. The syringes used in human dentistry, which are loaded with a local anaesthetic cartridge, are ideal for this procedure. Discomfort on injection can also be reduced by warming the solution to body temperature and by buffering the solution with sodium bicarbonate (8.4% solution). A 1:10 ratio with 0.5–2% lidocaine, and a 1:30 ratio with 0.25% bupivacaine, buffers the solution without affecting the solubility of the local anaesthetic (Bigeleisen and Wempe, 2001; Burns et al., 2006). Although the toxicity of local anaesthetics is similar in different laboratory mammals, the small size of rodents makes inadvertent overdose more likely. To avoid this, calculate the appropriate safe dose (do not exceed 10 mg/kg lidocaine, 2 mg/kg bupivacaine) and prepare this volume for injection in advance.

Care must be taken to infiltrate all of the tissue planes that will be involved in the surgical procedure. If reinsertion of the needle is necessary, this should be done through a previously anaesthetized area, so that discomfort to the animal is minimized. Considerable experience is necessary to ensure that complete blockage of the nerve supply to the surgical field is achieved, and expert practical advice should be obtained before carrying out this technique.

If the nerve supply to the operative site is well defined, regional anaesthesia can be produced by infiltration of local anaesthetics around the major sensory nerves. This may involve a single nerve or blockade of several nerves, for example, in producing a paravertebral block by infiltration of the lumbar spinal nerves as they emerge from the vertebral column, and so desensitizing the abdomen.

More extensive effects of local anaesthetics can be produced by injection of the drug into the spinal canal. The site of injection may be into the fat-filled space between the dura mater and the wall of the vertebral canal (epidural anaesthesia), or directly into the cerebrospinal fluid (subarachnoid or spinal anaesthesia). The techniques for injection have been described in both large animals

such as the cow, sheep and dog (see Tranquilli et al., 2007, for a review) and laboratory species such as the rabbit (Kero et al., 1981; Hughes et al., 1993) and the guinea pig (Thomasson et al., 1974). In attempting to become proficient in the technique, it is advisable to first practice injecting a dye, such as Methylene Blue, into the spinal canal of a recently killed animal.

A major problem associated with the use of local anaesthetic techniques in laboratory species is that it is often difficult to provide humane, stress-free restraint of the animal during the surgical procedure. It is possible, however, to produce effective surgical anaesthesia, with these techniques and combine this with low doses of hypnotics or anaesthetics, to provide effective restraint. In some animals, the use of a tranquillizer or sedative, together with the careful attention of an expert handler, may provide sufficient restraint to enable local anaesthesia to be used safely and humanely. When contemplating using local anaesthetic techniques, the likely behaviour of the animal, the type of surgical procedure involved and the expertise of the operator and his or her assistants should be carefully considered.

Selection of Anaesthetic Agents – Scientific and Welfare Considerations

Selection of a particular anaesthetic agent or anaesthetic technique will depend upon a variety of factors. Some of these will relate directly to the anaesthetic agent and its potential interactions with the research protocol, and others to its ability to produce the required depth of anaesthesia. A further series of factors relate to the practicalities of cost, the availability of equipment and the expertise of personnel in the research unit. These various considerations are discussed in more detail below.

Whichever method is chosen, it is important to keep in mind that two primary aims of anaesthesia are to prevent pain and provide humane restraint. The anaesthetic method itself should therefore be one which causes minimum distress to the animal. For example, the use of inhalational agents may involve exposure to irritant vapour (e.g. ether, see above), and the restraint required for induction using a face mask may be stressful. Similarly, restraint for the administration of injectable agents can cause distress to the animal, as can the pain associated with injection of certain anaesthetics and the longer term consequences of myositis following intramuscular injection of irritant agents (Gaertner et al., 1987; Smiler et al., 1990; Beyers et al., 1991). Other potential problems associated with the use of chloral hydrate and tribromoethanol have been discussed earlier in this chapter. Intravenous administration usually results in smooth and rapid induction of anaesthesia, provided that the animal is restrained effectively and that the injection is carried out with the required degree of skill. Local adverse reactions can result from inadvertent perivascular administration (e.g. of thiopental). Consideration must be given to ways of minimizing any fear or distress associated with handling or physical restraint and movement of the animal from its holding room to the operating theatre or laboratory.

Selecting a method of anaesthesia that is least likely to interfere with a particular research protocol is perhaps the most difficult task. The major pharmacological and physiological effects of the various anaesthetic agents should be reviewed, and this can at least minimize the interactions between the technique and the research protocol. It is important to appreciate that a superficial consideration of the compound's effects may be insufficient. For example, if one concern is to maintain systemic blood pressure within the range found in conscious animals, then in the rat, pentobarbital might appear preferable to fentanyl/fluanisone/midazolam in some strains of the animal. However, the apparently normal blood pressure is maintained by peripheral vasoconstriction, and cardiac output is markedly depressed (Skolleborg et al., 1990). Animals anaesthetized with fentanyl/fluanisone/midazolam have lower systemic blood pressure, but elevated cardiac output. Consequently, it is important to decide which is more important to a particular study – blood pressure or cardiac output. Other anaesthetics, such as urethane, may sustain blood pressure, but only because of their stimulatory effects on the sympathetic nervous system, so animals may have elevated plasma catecholamine concentrations (Carruba et al., 1987). This information can only be gained by a careful search of the relevant literature. It is important not to assume that such an assessment has been carried out by other research workers whose publications include details of the anaesthetic technique used. *Simply adopting the method of anaesthesia described in publications dealing with the particular animal model of interest will not necessarily ensure that an appropriate technique is used.*

Having suggested that an assessment of anaesthetic–animal model interactions should be made, it is important to place such interactions in the context of the overall response to anaesthesia. There is little point in carefully selecting an anaesthetic, and then allowing the animal to become hypothermic, hypoxic and hypercapnic because of poor anaesthetic management. These common problems can have wide-ranging effects on the animal's body systems, so attention to good anaesthetic management, described in Chapter 3, is of considerable importance. A second area to consider is the animal's response to surgery. Surgical procedures produce a stress response whose magnitude is related to the severity of the operative procedure. In mammals, this response consists of a mobilization of energy reserves, such as glucose, to enable the animal to survive injury. Although this response has clear evolutionary advantages, it is considered by many to be undesirable in humans and animals which are receiving a high level of intra-operative and post-operative care (Hall, 1985; Salo, 1988; Kehlet, 2006). It is also often undesirable because of the potential effects on particular research protocols.

A number of related endocrine responses occur, with elevation in plasma catecholamines, corticosterone or cortisone, growth hormone, vasopressin, renin, aldosterone and prolactin, and a reduction in follicle-stimulating hormone, luteinizing hormone and testosterone. Initially, insulin concentrations decrease and those of glucagon increase, but later, insulin concentrations rise. These hormonal responses produce an increase in glycogenolysis and lipolysis, and result in

TABLE 2.5 Checklist of Criteria for Selection of an Anaesthetic Regimen for Laboratory Animals.

	Possible anaesthetic agents		
	Anaesthetic 1	Anaesthetic 2	Anaesthetic 3
Is the depth and duration of anaesthesia appropriate?			
Is an appropriate degree of analgesia produced?			
Is the quality of anaesthesia satisfactory?			
Is it easy to assess changes in depth of anaesthesia?			
Is the regimen suitable for the particular species/strain?			
Are there any specific interactions with the experiment?			
Are there any legal/regulatory requirements (e.g. control of narcotics)?			
Is the regimen easy to use?			
Is it reliable and reproducible?			
Is it reversible?			
Is the operator familiar with the regimen?			
What is the cost of the regimen?			
Are all the agents readily available?			

Adapted from Morris et al. (1995).

hyperglycaemia. The duration of the hyperglycaemic response varies, but following major surgery, the response may persist for 4–6 hours. More prolonged changes in protein metabolism occur, leading to negative nitrogen balance lasting several days (Hoover-Plow and Clifford, 1978). Even minor surgical procedures can produce relatively prolonged effects. For example, blood vessel cannulation in rats produced an elevation in corticosterone for several days (Fagin and Dallman, 1983), and more subtle disruptions of circadian rhythmicity of hormonal secretions can persist for similar periods (Desjardins, 1981).

Research are often reluctant to refine their anaesthetic methodology because it is thought that the anaesthetics used in the new technique may affect their animal model in the post-surgical period. In some instances, there will be a sound scientific basis for this opinion, based on a critical review of the relevant literature. In other circumstances, the effects of anaesthesia may be relatively unimportant when compared with the effects of surgical stress. Similar concerns are also expressed about the use of post-operative analgesics, and once again, the side-effects of any analgesics used should be considered alongside the other effects of surgery and anaesthesia. Clearly, it is logical to consider all of the factors that may interact with a particular study and to develop an anaesthetic and surgical procedure which is humane and provides minimum interference with the overall aims of the research project.

Many of the significant considerations involved in selecting an anaesthetic were reviewed by a small working group (Morris et al., 1995), and this group's suggestion of tabulating relevant factors to simplify the selection process may be helpful (Table 2.5).

Anaesthetic Management

Successfully producing and maintaining anaesthesia requires more than simply selecting the most appropriate anaesthetic regimen. Throughout the anaesthetic period the vital signs of the animal must be monitored, together with the depth of anaesthesia. Simple observation of the animal and assessment of its responses can help to maintain anaesthesia safely and effectively. The monitoring process is often greatly improved by the appropriate use of electronic devices. Selecting these, and using them effectively, requires a basic understanding of their functions and limitations. It is also important to be able to interpret the information gained from both clinical assessments and electronic monitoring devices, and use this to prevent or correct problems and emergencies. After completion of the period of anaesthesia, an appropriate level of monitoring and supportive care needs to be extended into the recovery period. Adopting this approach will benefit both the quality of research data obtained and the welfare of the animals involved.

PRE-OPERATIVE PREPARATIONS

Following induction of anaesthesia with one or more of the drugs described in Chapter 2, the animal should be placed in a suitable position to enable the required surgical or other procedures to be carried out. A compromise must usually be made between a position considered ideal by the research worker and one that avoids compromising the function of any of the animal's body systems. In particular, care must be taken to ensure that the head and neck remain extended, so that the tongue or soft palate does not obstruct the larynx. The limbs should not be tied out in such a way that this impedes thoracic respiratory movements, and care must be taken during surgery that undue pressure is not placed on the chest wall or abdomen. Over-enthusiastic use of retractors and the inadvertent use of the thorax as an armrest during surgery are commonly overlooked and must be discouraged! In smaller species, the use of elastic bands or ties to position the animal can lead to excessive extension of the limbs and consequent interference with respiratory movements. Similarly, elastic bands placed around

the abdomen interfere with both diaphragmatic movements and the venous return from the hindquarters and abdominal viscera. This and other techniques that aim to ensure the immobility of an animal are rarely necessary and should be discouraged.

If it becomes necessary to retract the limbs, these should not be pulled into full extension and the anchoring bandages should be tied loosely. This is particularly important during prolonged anaesthesia, when constricting ties around the limbs can lead to tissue damage and peripheral limb oedema, which is likely to cause considerable discomfort to the animal in the post-operative period. If an endotracheal tube is used, it should be tied firmly to the animal's jaw. It is often helpful to tape the anaesthetic breathing system to the operating table, so that it cannot drag on the endotracheal tube and dislodge it. The risk of inadvertent disconnection is reduced by using light-weight disposable breathing systems (see Chapter 2). Particular care must be taken if an animal requires repositioning during an operative procedure. Turning the animal may result in kinking of the endotracheal tube, and it is usually preferable temporarily to disconnect the animal from the breathing system while moving it.

During anaesthesia, the protective reflexes that prevent damage to the eye are usually lost, so the cornea is susceptible to desiccation and damage. To reduce this danger, the eyelids should be taped closed with a small piece of adhesive dressing, or filled with bland ophthalmic ointment (Fig. 3.1).



FIGURE 3.1 During anaesthesia the eyes should be filled with ophthalmic ointment or 'liquid tears' or taped shut to prevent damage to the cornea.

MONITORING ANAESTHESIA

Following the administration of an anaesthetic, it is essential to assess that the required depth of anaesthesia has been achieved. It is also important to monitor the vital signs of the animal and the function of any anaesthetic equipment that is in use.

Assessment of Depth of Anaesthesia

Ensuring that an animal is maintained at the correct depth of anaesthesia requires the development of some degree of clinical skill by the anaesthetist. With the wide range of anaesthetic drugs currently available, the simple classical approach of dividing anaesthesia into a series of levels and planes is now of limited use (Urban and Bleckwenn, 2002). This classification of anaesthetic depth relied heavily on the assessment of cardiovascular and respiratory function and was developed in humans to enable the safe use of a single volatile agent (ether) to produce deep surgical anaesthesia (Bendixen, 1984). The widespread variation in response to anaesthesia in different animal species and the use of several drugs in combination make such a scheme virtually unworkable in modern laboratory animal anaesthetic practice. Although there is little scope for a general classification, a range of clinical observations can be made to aid in the assessment of the depth of anaesthesia. Following administration of a volatile anaesthetic agent or the intraperitoneal injection of a drug such as pentobarbital, most animals become ataxic, lose their righting reflex and eventually remain immobile. At this depth of anaesthesia they can easily be roused by painful stimuli, so anaesthesia must be allowed to deepen until there are no such responses to pain. This sequence of events will not be seen if induction is carried out by the intravenous injection of anaesthetics such as propofol. More sophisticated techniques for assessment of depth of anaesthesia have been developed in human beings, for example measurement of the electroencephalogram (EEG) and of sensory or somatic evoked potentials. Although these techniques are not yet widely applied in animals (Whelan and Flecknell, 1992; Otto, 2008), they may be of value in some circumstances (see 'Long-Term Anaesthesia', Chapter 4).

Responses to Painful Stimuli

The reason for inducing anaesthesia is often to block the perception of pain. Consequently, the response to painful stimuli is an essential part of the assessment of the depth of anaesthesia. In most species, the pedal withdrawal reflex should be assessed. One limb should be extended and the web of skin between the toes pinched between the anaesthetist's fingernails. If the limb is withdrawn, or the animal vocalizes, it indicates that the depth of anaesthesia is insufficient to allow surgical procedures to be carried out. In small rodents, it may be difficult to pinch the toes; hence, pinching the tail provides a convenient alternative stimulus. In many species, the hindlimb withdrawal response is lost at lighter

planes of anaesthesia than the forelimb response. Besides using the limb withdrawal response, the reaction to pinching an ear can be observed in rabbits or guinea pigs. At light levels of anaesthesia, the animal responds to ear pinching by shaking its head and at very light levels by vocalizing. The loss of a response to painful stimuli does not occur uniformly in all body areas. On occasion, it may be possible to begin to perform a laparotomy without eliciting either any movements or any autonomic responses, such as an increase in heart rate, in an animal that still shows a limb withdrawal reflex. However, further surgical stimulation, such as cutting or clamping the abdominal muscles or handling the abdominal viscera, may produce reactions indicating an inadequate depth of anaesthesia.

Although use of withdrawal responses provides a simple means of assessing depth of anaesthesia, the degree of suppression of these responses does not necessarily parallel loss of consciousness. Use of movement responses to assess depth of anaesthesia may therefore result in animals being maintained at planes of anaesthesia deeper than those required for the production of loss of consciousness and amnesia (Antognini et al., 2005). Withdrawal responses are mediated primarily by spinal mechanisms, and the depth of anaesthesia required to suppress these responses is greater than that needed for loss of consciousness. In human beings, extensive use of neuromuscular blocking (NMB) drugs to prevent movement has enabled the use of lower doses of anaesthetics. In animals, NMB drugs are used much less frequently, so anaesthetics need to be relied upon not only to produce unconsciousness, but also to suppress movement. Therefore, it is often impracticable to use light planes of anaesthesia, since surgery cannot be carried out safely or reliably. Consequently, it is recommended that marked suppression of a limb withdrawal response be used as an indication of the onset of surgical anaesthesia.

Alterations in Eye Reflexes

Examination of eye reflexes and of the position of the eyeball is of limited use in small laboratory species. In larger species, such as the dog, cat, pig, sheep and primates, the palpebral reflex (blinking when the edge of the eyelid is lightly touched) is lost during the onset of light surgical anaesthesia with barbiturates, volatile anaesthetics and some other drugs. Use of ketamine causes the loss of this reflex at lighter levels of anaesthesia, and the use of neuroleptanalgesic combinations has unpredictable effects on the reflex. The palpebral reflex is difficult to assess in small rodents, and in rabbits, it may not be lost until dangerously deep levels of anaesthesia have been attained. The position of the eyeball can also be of use once experience has been gained with the species of animal and the particular anaesthetic technique that is to be used. For example, in dogs anaesthetized with a volatile anaesthetic such as isoflurane, or with propofol, the eye rotates downward as a surgical plane of anaesthesia is attained. At very deep planes of anaesthesia, the eye rotates back to a central position, but the palpebral

reflex is absent, which enables this stage to be distinguished from very light anaesthesia. Since the position of the eyeball, the degree of pupillary dilatation and the occurrence of side-to-side movement (nystagmus) vary both between species and with different anaesthetics, they cannot be relied upon as indicators of the depth of anaesthesia and should always be combined with observation of other clinical signs.

Alterations in Cardiovascular and Respiratory Functions

Most anaesthetics cause a dose-dependent depression of the cardiovascular and respiratory systems. The way in which this depression is manifested can vary considerably with different anaesthetics. Respiratory rate may decrease or increase in response to a fall in the depth of respiration. Conversely, the depth of respiration may increase and respiratory rate decrease. Cardiovascular system depression usually results in a fall in systemic blood pressure, but this may be associated with either a fall or a rise in heart rate.

Given these wide variations in response, it is dangerous to generalize about the effects of anaesthetics on these body systems. Once again, experience with a particular anaesthetic technique and particular animal species will be needed before these changes can be interpreted with confidence. Methods of monitoring the cardiovascular and respiratory system are discussed as follows.

Assessment of Patient Well-being

All anaesthetics produce a reversible depression of many CNS activities, and on occasion, the degree of depression is excessive and the animal dies. It is important that the occurrence of a certain percentage of anaesthetic deaths does not become accepted as an unavoidable consequence of anaesthesia. The death of an animal during anaesthesia should stimulate a review of the entire process of animal selection and pre- and intra-operative care. In human beings, anaesthetic mortality rates are approximately 1:185,000 (Buck et al., 1987). Mortality rates in veterinary clinical practice have been reported as 1:400 (in cats) and 1:600 (in dogs) (Brodbelt et al., 2008). When anaesthetizing healthy, young adult laboratory animals, it does not seem unreasonable to expect a mortality rate of <1:1000. Anaesthetic mortality rate can usually be reduced by observation of the precautions described in Chapter 1. In addition, careful assessment of the physiological state of the animal during the period of anaesthesia can result in a dramatic improvement in recovery rates.

Monitoring of an anaesthetized animal does not necessarily involve the use of complex electronic apparatus; although as will be discussed later, such equipment can prove extremely valuable. Even when using sophisticated devices, basic clinical observation, such as noting the colour of the mucous membranes, the pattern and rate of respiration and the rate and quality of the pulse are of fundamental importance. These simple clinical observations are easy to undertake and will often detect problems before they become irreversible.

Although simple clinical observation by the anaesthetist should never be neglected, when the roles of anaesthetist and surgeon or anaesthetist and theatre technician are combined, uninterrupted or even regular observation is often impossible. In addition, fatigue during prolonged procedures may lead to human error, so the use of electronic equipment to provide continuous monitoring of physiological variables can be invaluable. Certain variables can only be measured directly by using electronic equipment. When anaesthetizing animals for prolonged periods or during complex or high-risk procedures, the additional information provided by such apparatus can greatly assist in anaesthetic management. A further advantage of electronic monitoring equipment is that it usually enables acceptable limits for each monitored variable to be set at the start of the period of anaesthesia. An audible or visible alert is triggered when these preset limits are exceeded. As mentioned earlier, the degree of monitoring required will depend upon the nature and duration of the surgical procedure.

Whatever monitoring is to be undertaken, it is of fundamental importance to make some record of the information obtained. In almost every case, problems develop gradually, rather than occurring as sudden catastrophes. If the observations made are recorded, preferably as simple graphs, adverse trends are easily detected and appropriate corrective action is taken in time. A second advantage of such a record is that it enables a retrospective review of a series of anaesthetics, so that techniques can be evaluated critically and improved.

As discussed earlier, it is only through practical experience that the ability to assess the significance of changes of physiological variables during the administration of a particular anaesthetic can be developed. Although the production of written records may seem unduly time-consuming, these records provide an invaluable source of reference both for the current anaesthetist and for less experienced staff who may be required to undertake the procedure in the future.

Monitoring Body Systems: Respiratory System

Clinical Observations

A number of observations can be made that will assist in detecting the deterioration in respiratory function. The rate, depth and pattern of respiration can be assessed by observation of the animal's chest wall, or of the anaesthetic breathing system's reservoir bag if one is present. In larger animals, an oesophageal stethoscope can be used to monitor breath as well as heart sounds.

Respiratory Monitors

The respiratory rate can be conveniently monitored with electronic monitors. The most inexpensive of these use a thermistor, which is either mounted in the anaesthetic breathing system in the endotracheal tube or face-mask connector, or placed close to the animal's external nares. The response of some of these devices is sufficient to enable monitoring of respiration in animals weighing as little as 300 g.

An alternative technique for monitoring respiratory rate relies upon movements of the chest wall to trigger a pressure sensor (Fig. 3.2). These devices can be used with most animals weighing over 1000 g. When buying a respiratory monitor, check that its sensitivity is sufficient to function reliably with the target species and that an alarm can be set to detect apnoea. If buying a more sophisticated instrument that allows upper and lower limits for respiratory rate to be set, make sure these are wide enough for the full range of species that will be monitored.

Assessment of Lung Gas Exchange

Although measurements of the mechanical aspects of respiration usually provide a reasonable indication of respiratory function, some attempt must also be made to assess the adequacy of lung gas exchange. This can be judged clinically simply by observing the colour of the visible mucous membranes and the colour of any blood which is shed at the surgical site. Although such simple clinical monitoring will show the onset of severe hypoxia, it gives no indication of blood carbon dioxide content. A more sensitive measure of blood oxygen saturation can be obtained using a pulse oximeter.

Pulse Oximetry

Pulse oximeters measure the percentage saturation of arterial blood by detecting changes in the absorption of light across the tissues. A variety of probes of different shapes and sizes are available, the majority designed for human use. Both reusable

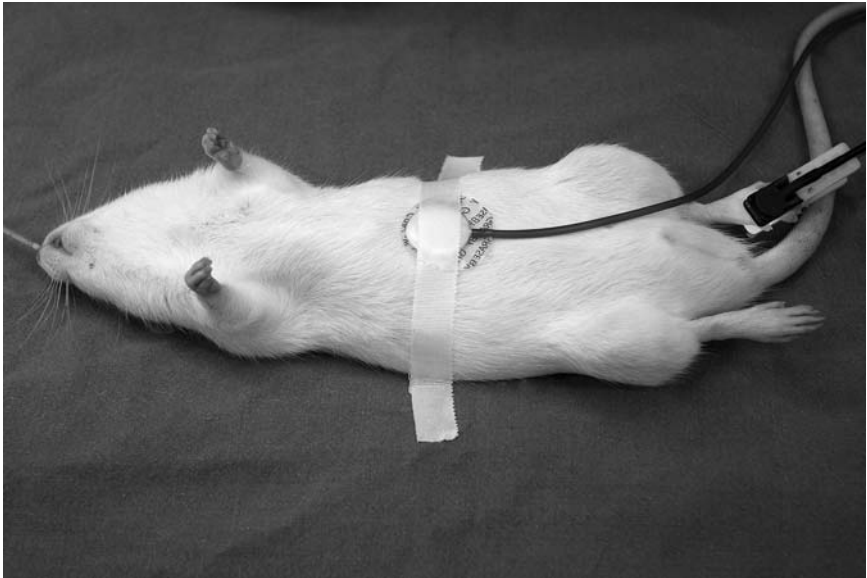


FIGURE 3.2 Respiratory monitor using a pressure sensor. The device shown is designed for use during MRI procedures.

and disposable probes can be obtained. Besides measuring the saturation of the haemoglobin with oxygen (SpO_2), the instrument measures the pulsatile nature of the signal and uses this to calculate the heart rate. Although the absorption spectra of haemoglobin vary between species, they are sufficiently similar to allow instruments designed for human use to be used successfully in most mammals (Decker et al., 1989; Erhardt et al., 1990; Vegfors et al., 1991; Allen, 1992; Jacobson et al., 1992).

Attaching a pulse oximeter gives three useful pieces of information:

- The degree of saturation of haemoglobin allows detection of hypoxia due to respiratory depression, airway obstruction or anaesthetic equipment failure.
- The heart rate reading is useful in detecting changes in rate associated with cardiovascular system depression, or tachycardia caused, for example, by carrying out surgical procedures at an inadequate anaesthetic depth.
- The strength of the pulsatile signal, usually displayed as a bar graph or as a waveform, provides some indication of the flow of blood through the tissues. This is often more informative than a simple indication of heart rate, since it reflects the mechanical action of the heart.

Pulse oximeters have been shown to be reasonably accurate at normal oxygen saturation levels (80–99%), but become increasingly inaccurate as saturation falls. They should therefore only be used to provide a general indication of the adequacy of tissue oxygenation, and cannot be relied upon to record low saturations accurately. Nevertheless, they are considerably more reliable than simple clinical assessment, and since development of low saturation requires immediate corrective action, their relative inaccuracy in this range is rarely of clinical importance.

Pulse oximeters are sensitive to movement artefacts, and this can cause difficulty if they are used in the later stages of recovery from anaesthesia. They will fail to provide a signal if the pulsatile blood flow through the tissues falls, as occurs during shock. In very small animals, the low volume of tissue available for monitoring limits the reliability of many currently available instruments. Several manufacturers' instruments can be used successfully in animals weighing more than 200 g, although the upper heart rates displayed, and the corresponding high heart rate alarm, is limited to 250 beats per minute. Instruments specifically designed for veterinary use are now widely available (Appendix 4), but only a few have upper rate limits above 250 beats per minute. Pulse oximeters sufficiently sensitive for use in mice have also become available (Fig. 3.3). One such model provides heart rate, oxygen saturation, respiratory rate and an indication of depth of respiration and respiratory effort.

Suitable sites for probe placement include the tongue, ears, tail, nail bed and across the footpad in rats and guinea pigs (Figs. 3.4 and 3.5).

End-tidal Carbon Dioxide

An indication of carbon dioxide exchange can be obtained by monitoring the concentration of carbon dioxide present in the exhaled gas using a capnograph.



FIGURE 3.3 The ‘Mouseox’ pulse oximeter in use. The system both provides pulse oximetry data and records respiratory rate by processing of the pulse pressure data. The instrument does not require positioning as closely to the animal as shown in this illustration (Y-27).



FIGURE 3.4 Placement of pulse oximeter probes in a guinea pig (left) and rabbit (right).



FIGURE 3.5 Placement of pulse oximeter probes in a rat (left) and a rabbit (using an angled probe in the mouth, shown being inserted over the tongue).

The maximum concentration detected, the end-tidal concentration, reflects the concentration of carbon dioxide present in alveolar gas. Considerable additional information can be obtained from the waveform that shows the changing concentration of carbon dioxide during the respiratory cycle (O'Flaherty, 1994). A capnograph can alert the anaesthetist to an abnormal build-up of carbon dioxide caused by respiratory failure and also to rebreathing of exhaled gas caused by inadequate fresh gas flows. It also indicates changes in respiratory rate and pattern. Sudden reductions in end-tidal carbon dioxide may indicate falls in cardiac output.

When used with larger species, a capnograph allows the fresh gas flow in a breathing system to be adjusted to prevent rebreathing in an individual animal. The flow required varies from that calculated, as described in Chapter 2, and is often lower. This can result in very significant savings in anaesthetic gases and volatile anaesthetic. When used with closed breathing systems, a capnograph also monitors the effectiveness of the absorption of carbon dioxide.

Capnographs are designed to either sample expired gases from a tube placed close to the endotracheal tube (side-stream systems) or have the carbon dioxide sensor placed directly in the anaesthetic breathing system (main-stream sampler). Although the latter design has some advantages in respect of sensitivity and speed of response, it has the disadvantage of introducing additional dead

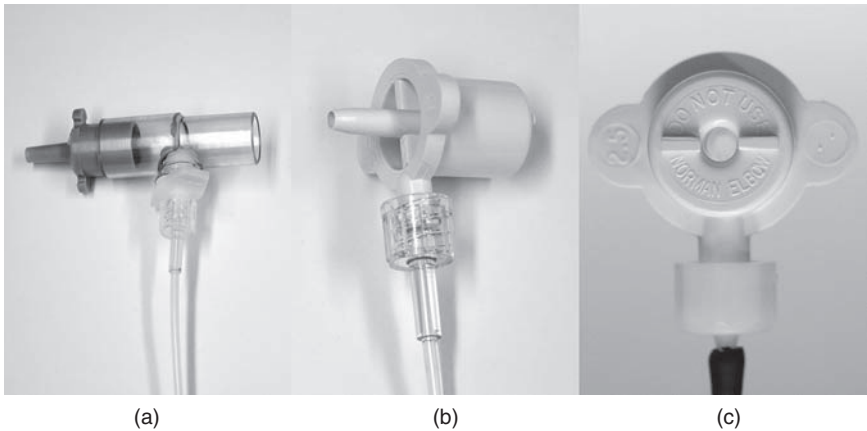


FIGURE 3.6 Standard side-stream capnograph adapter (a) and low dead space connector (side view: b; end-view: c).

space in the breathing system. This can be overcome to some extent by purchase of a paediatric airway adapter (most instruments were originally designed for use in humans) and by modification of the anaesthetic breathing system connectors. Side-stream samplers are generally satisfactory for most species, but low dead space adapters should be used for small animals (Fig. 3.6). It is also important to establish the instrument's gas sampling rate. Most capnographs sample 150–200 ml of gas per minute, but many have a paediatric setting of around 50 ml/min. Since the minute volume of a 200 g rat will be approximately 120–200 ml/min, even sampling at the lower rate of 50 ml/min can lead to dilution of the sample of gas that has been breathed out by the animal with fresh gas from the anaesthetic breathing system. This will result in underestimation of the end-tidal carbon dioxide concentration. However, provided the gas flow in the breathing system is not altered, capnograph readings will indicate trends during anaesthesia in these small animals, and so are useful, particularly in animals maintained using a mechanical ventilator. If blood gas analysis is carried out at the start and end of the procedure then the capnograph readings can be related to arterial PCO_2 values, and the constant readout from the capnograph provides reassurance that the carbon dioxide tension remained constant. An alternative is to purchase an instrument specifically designed for use in laboratory rodents that operates at very low gas sampling rates (C1240, Columbus Instruments, Capstar, Appendix 4). These instruments sample at 5–20 ml/min, and so can provide accurate readings in mice and rats (Thal and Plesnila, 2007).

Blood Gas Analysis

The most satisfactory method for measuring the adequacy of lung gas exchange is to obtain arterial blood samples and carry out blood gas analysis. Blood gas analysers will measure the partial pressure of oxygen, carbon dioxide and

pH of the blood and, in addition, will calculate the blood bicarbonate concentration and the base excess. Analysers designed for human paediatric use require sample volumes as low as 0.1 ml, so their use in monitoring blood gases in small animals becomes practicable. A major problem will often be the difficulty in obtaining arterial blood samples in smaller animals. It is also important to appreciate that the temperature of the patient must be recorded, since the instrument applies a correction to its measurements based on this. In view of the common occurrence of hypothermia in small animals, this can be a significant source of error. Instruments designed for human use carry out their calculations based on data from human haemoglobin. Results are generally applicable to animals, but for greater accuracy, instruments are available which allow data on animal haemoglobin to be used. Interpretation of blood gas data can be complex, but simply establishing that PCO_2 , PO_2 and pH are within acceptable limits is often of significant benefit. A full and easy-to-follow account of interpretation of blood gas data can be found in Martin (1999).

A reasonably close approximation of arterial carbon dioxide and oxygen concentration may be obtained non-invasively and continuously by using transcutaneous oxygen and carbon dioxide monitors (Rodriguez et al., 2006). These instruments have been less used in animal anaesthesia, but there have been reports of their accuracy in small rodents (Stout et al., 2001; Sahbaie et al., 2006) and limited experience suggests that they can be used successfully in sheep, lambs and rabbits.

Measurement of Tidal and Minute Volume

In some circumstances, it is also useful to assess the depth of respiration by measuring tidal volume. Both tidal and minute volumes (the volume of gas breathed in 1 minute) can be measured using a Wright's respirometer. The standard model of this instrument can measure tidal volumes down to 200 ml. A paediatric version is also available which has a range of 10–250 ml and is appropriate for use in animals ranging in size from large guinea pigs to medium-sized dogs. Respirometers are used primarily to perform intermittent measurements of tidal and minute volume, and are most widely used to assess that mechanical ventilators are delivering an appropriate volume of gas. The relatively large dead space of the instrument makes its permanent placement impracticable in the breathing system of a small animal, and in patients of all sizes, build-up of water vapour can cause the failure of the instrument.

Cardiovascular System

Clinical Observations

The rate, rhythm and quality of the peripheral pulse can be assessed in rabbits, cats and larger animal species. The femoral artery is easily palpable, but if the animal is covered with sterile surgical drapes, both this and other pulse points

may be inaccessible. In the dog and pig, the sublingual artery and the digital artery can be palpated, but some practice is needed before these pulse points can be used with confidence. The assessment of the quality of the pulse will give a rough indication of the adequacy of systemic arterial pressure. Some indication of the adequacy of tissue perfusion can be gained by observing the capillary refill time in the visible mucous membranes. The gums are usually the most accessible site, and the refill of the capillaries following blanching by digital pressure can be observed in most larger species. In normal animals, following blanching by pressing with a finger, the mucous membranes regain their normal colour in less than a second. If refill is significantly delayed (>1 second), it indicates poor peripheral tissue perfusion and possible circulatory failure.

The heart sounds and heart rate can be assessed by the use of a stethoscope positioned on the chest wall or, in dogs and larger animals, by means of an oesophageal stethoscope.

Electrocardiography

The electrical activity of the heart can be monitored by an electrocardiogram (ECG). Instruments designed for use in humans are normally acceptable for monitoring animals, but the maximum heart rate that can be displayed is usually 200 or 250 beats/min. Small rodents and rabbits frequently have heart rates in excess of 250 beats/min and this may limit the usefulness of some of these monitors. Purpose-designed instruments for animal use are now available (Appendix 4), which enable low-voltage ECG signals and rapid heart rates to be detected. ECG electrodes designed to stick on the skin can be used successfully in larger animals, provided any hair in the area of electrode placement is carefully removed. Human paediatric electrodes are suitable for cats, rabbits and small primates, but needle electrodes are usually required for small rodents. Electrode placement on the left and right thoracic limb and right pelvic limb will provide a standard ECG trace, but the signal amplitude from small animals may be insufficient to produce an adequate display on some monitors. Whenever possible, it is preferable to have a demonstration of an ECG on the species concerned before purchasing the instrument.

Some monitors simply extract and display the heart rate from the ECG waveform, but this is of limited value. Both the heart rate and the ECG trace should be displayed and constantly updated. Upper and lower rate limits can usually be set, although the restricted range of these settings in some instruments may limit their use in smaller animal species. It is important to appreciate that the ECG indicates only the electrical activity of the heart and not adequate circulatory function. It is possible to have a cardiac output of zero and a normal ECG!

A heart rate can also be obtained using a pulse oximeter (see above) or a Doppler flow probe positioned over a suitable artery. An ECG monitor is of most importance during procedures where cardiac arrhythmias or other disturbances in cardiac function may be anticipated, for example during thoracic surgery. It is

also particularly useful during long-term anaesthesia, when disturbances in acid-base and electrolyte balance can lead to arrhythmias.

Blood Pressure

Systemic Arterial Pressure

Direct or indirect recording of systemic arterial blood pressure can be carried out in most animal species (Van Vliet et al., 2000; Kurtz et al., 2005). Direct measurements are invasive, requiring arterial cannulation, but they can be applied easily to most larger species. Cannulation can be carried out either following surgical exposure of a suitable artery or by percutaneous puncture using a catheter and introducer. The femoral artery can be cannulated in this way in dogs, pigs, sheep and larger primates. Percutaneous cannulation of the femoral artery in the cat and rabbit requires considerable technical skill. In rabbits and sheep, the central ear artery provides a convenient vessel for percutaneous catheterization.

Invasive blood pressure monitoring has the advantage of providing a rapid indication of changes in pressure and recording accurately over a wide range of blood pressures. Blood pressure can also be monitored non-invasively using a sphygmomanometer. Instruments designed specifically for use in animals are now available, and these are preferable to those used in humans since an appropriate-sized cuff for occlusion of the artery must be used for accurate measurement (Kittleson and Olivier, 1983) (Appendix 4). The use of a Doppler probe to detect arterial blood flow, coupled with an inflatable cuff and a pressure sensor, can be used to measure arterial blood pressure in a range of animal species. These instruments are available commercially and can be used to measure arterial pressure in the caudal artery of rats (Harvard Apparatus Ltd., Appendix 4). Comparisons of direct and indirect blood pressure measurements have been made in a number of species including dogs (Gains et al., 1995), cats (Pedersen et al., 2002), pigs (Hodgkin et al., 1982), primates (McMahan et al., 1976; Chester et al., 1992), rabbits (Ypsilantis et al., 2005), guinea pigs (Kuwahara et al., 1996) and rats (Ikeda et al., 1991). In mice, a modified commercial non-invasive blood pressure device correlated well with direct measurements (Thal and Plesnila, 2007).

The main disadvantage of non-invasive monitoring is the intermittent nature of the information obtained. The most widely used automated instruments, which use an oscillometric technique to detect the arterial pressure changes, take readings at a minimum interval of a minute. During periods of cardiovascular instability, this interval may be considered unacceptable. A second problem is that when blood pressure falls, the instrument may fail to detect the reduced amplitude signals.

Pulse oximetry, which is described above, provides a measure of heart rate and gives a crude but effective indication of the pulsatile flow in the tissues.

Central Venous Pressure

Central venous pressure can be measured by inserting a catheter into the jugular vein and advancing it so that its tip lies in the cranial vena cava. The catheter

can be introduced percutaneously or following surgical exposure of the vein. The simplest method of recording central venous pressure is to connect the cannula to a water manometer that has had its baseline (zero) reading set at the estimated level of the animal's right atrium. Water manometer systems are generally unsatisfactory in smaller animals such as rodents and rabbits; hence in these species, it is preferable to use an electronic pressure transducer.

Pressure transducers for arterial and venous pressure are relatively expensive items of equipment, but a range of disposable transducers are available for human use (Gould Medical Ltd., Appendix 4). The initial purchase cost of these transducers is considerably less than that of non-disposable transducers, and provided absolute asepsis is not required, they can be reused successfully on numerous occasions.

Body Temperature

Body temperature is one of the easiest physiological variables to monitor during anaesthesia. Rectal temperature can be monitored simply by using a simple, glass clinical thermometer, but this requires repeated adjustment and replacement of the instrument in the rectum to record the changes in body temperature that may occur during anaesthesia. A second disadvantage is that the lowest temperature measurable by many instruments designed for clinical use is 35°C. The body temperature of small animals can rapidly fall below this value, and the onset of hypothermia may be overlooked. It is much more satisfactory to purchase one of the electronic thermometers that can provide continuous display of a wide range of body temperatures. The rectum is often the most convenient site for placing a temperature probe, but deep body or core temperature will often be underestimated. If the probe is positioned in the middle of a mass of faeces, its response time to the changes in temperature will be slow. For these reasons, it may be preferable to use a probe placed in the oesophagus, but it must be located in the lower part of the oesophagus to avoid the cooling effects of respiratory gases in the upper airway.

Measurement of skin surface temperature is also valuable and this can conveniently be carried out by taping a temperature probe between the animal's digits. In a healthy anaesthetized animal, the temperature differences between the core and the periphery rarely exceed 2–3°C. An increase in this temperature gradient indicates that peripheral vasoconstriction is occurring and the various possible causes of this should be investigated. It is also useful to place a temperature probe between the animal and any heating devices that are being used to maintain body temperature. This will detect any over-heating problems that might occur, and enable measures to be taken to correct these and prevent superficial burns.

If routine temperature monitoring of a range of different species is to be undertaken, it is worth purchasing a more sophisticated electronic thermometer that allows the simultaneous use of temperature probes of different designs. Suitable-sized probes for rectal or oesophageal placement in mice, rats, rabbits

and larger animals are available, together with skin surface temperature probes, needle probes and other special-purpose probes. Thermometers for measuring temperature at the tympanic membrane in human beings, which have an extremely rapid response time, may be used in animals (Hanneman et al., 2004) but their accuracy and reliability varies considerably when used in laboratory species. If use of one of these devices is contemplated, it should be carefully validated using a conventional electronic probe before reliance is placed on the data obtained.

Anaesthetic Equipment Function

Before administering an anaesthetic, it is important to check that all the equipment to be used is functioning properly (see Chapter 1). Even if the equipment is functioning correctly at the start of the anaesthetic, it is important to monitor its continued normal function.

Anaesthetic Breathing System Disconnection

The risk of inadvertent disconnection of the animal, the anaesthetic breathing system and the anaesthetic machine can be reduced by using safe-lock type connectors. The most frequent point of disconnection is at the junction of the breathing system and the endotracheal tube. It is possible to position a thermistor-type apnoea alarm in the breathing system and this can provide an alert if disconnection occurs. When anaesthetizing larger animals, pressure monitoring can be used in the breathing system that will detect both low pressure due to disconnection and high pressure caused, for example, by a malfunctioning expiratory valve. An oxygen analyser, positioned within the fresh gas flow of the breathing system, will detect disconnection of the breathing system from the anaesthetic machine and also any failure of the oxygen supply. Some machines are fitted with an audible alarm that is activated if the oxygen pressure falls below a lower limit.

Infusion Pumps

If anaesthesia is being administered by continuous intravenous infusion, it is useful to have a warning system that will detect if the pump fails or the infusion reservoir or syringe is emptied. This is particularly important if NMB agents are being employed, as these will prevent any spontaneous movements of the animal that might occur as anaesthesia becomes lighter. Older style infusion pumps generally have no warning devices, so it remains the anaesthetist's responsibility continuously to monitor their function. The more recently available microprocessor-controlled infusion pumps may be fitted with a variety of devices to alert the anaesthetist to a malfunction, but even these should be regularly inspected throughout the operative period. The main features to consider when purchasing such devices are listed in Chapter 4.

ANAESTHETIC PROBLEMS AND EMERGENCIES

Monitoring of the state of the animal during anaesthesia will enable early warning to be obtained of impending problems and emergencies, so that corrective action can be taken. There is little purpose in adopting the monitoring procedures described above unless the information obtained is of value and influences the course of action taken should problems arise. In clinical anaesthesia, the successful resuscitation of the patient is of paramount importance, but in a research setting, additional factors must be considered. An animal that has developed problems during anaesthesia, for example severe respiratory depression, may no longer be a suitable animal model for some studies. A second consideration is that extensive emergency therapy may result in some additional pain and distress to the animal concerned. These factors must be considered, preferably *before* starting a procedure, so that an appropriate course of action in the event of emergencies can be planned. Given these constraints, the following section outlines the major indications of impending problems and suggests appropriate corrective measures.

Respiratory System

Signs of Impending Failure

Respiratory Rate

Respiratory rate should be recorded before anaesthesia, so that any subsequent depression in rate can be assessed. If the animal is calm and relaxed then the assessment will be reasonably accurate, but many rodents and rabbits will have a marked increased respiratory rate in the immediate pre-anaesthetic period, caused by fear and apprehension. In these circumstances, all that can be done is to estimate the normal respiratory rate based on published data (Appendix 1). As a general guide, in rodents and rabbits, during anaesthesia, a fall in the respiratory rate to less than 40% of the pre-anaesthetic rate indicates impending respiratory failure. The pattern and depth of respiration may also change, and animals may show a gasping pattern of respiration, or respiratory movements may become very shallow.

Changes in respiratory pattern and rate with varying depths of anaesthesia differ depending upon the agent used, so considerable experience is needed to assess their significance across a wide range of techniques and species. Nevertheless, when using a single anaesthetic in one species, it is relatively easy to develop an appreciation of the effects of increased or decreased depth of anaesthesia. This learning process can be speeded by always taking the opportunity to observe animals which have been euthanased with an overdose of anaesthetic and, if possible, to use an overdose of the intended anaesthetic technique as the euthanasia agent.

Aside from a falling respiratory rate causing concern, a rise in rate may occur due to a lightening of the level of anaesthesia, and this also requires corrective action. The animal should be carefully assessed for other signs of a reduced depth

of anaesthesia (see below), since an increased respiratory rate and depth may also occur if carbon dioxide accumulates in the breathing system. This can occur during closed system anaesthesia if the soda-lime carbon dioxide absorber has become depleted, or if there is a failure of the fresh gas supply in any breathing system.

Tidal Volume

A progressive fall in tidal volume frequently indicates impending respiratory failure. As with most other monitored variables, it is important to record the trends that occur during the period of anaesthesia. An apparent sudden failure of respiration is nearly always preceded by a progressive deterioration in tidal and minute volumes.

Lung Gas Exchange

Mucous Membrane Colour Any noticeable blue coloration of the visible mucous membranes indicates the onset of severe hypoxia. In most species, oxygen saturation may fall below 50% before any evidence of cyanosis is detected. It is therefore important to regard development of cyanosis as an emergency requiring immediate corrective action. Assessment of the colour of the mucous membranes indicates only a lack of oxygen, and the mucous membranes may remain a normal pink colour despite an animal having grossly elevated blood carbon dioxide content.

Pulse Oximetry A more accurate assessment of the degree of oxygenation of the arterial blood can be obtained using a pulse oximeter. Oxygen saturation is normally 95–98% in animals that are breathing room air. Animals breathing oxygen will have a saturation of 100%. Falls of more than 5% should alert the anaesthetist to the onset of mild hypoxia, and a reduction of more than 10% requires immediate corrective action. Readings below 50% indicate severe, life-threatening hypoxia. It is important to note that one of the most common causes of an apparent sudden change in oxygen saturation is the pulse oximeter probe becoming displaced. Probe position should always be checked, and repositioned, while preparing to take action to correct hypoxia.

End-tidal Carbon Dioxide Animals that are breathing spontaneously have an end-tidal carbon dioxide concentration in the range of 4–8%. During artificial ventilation, a concentration of 4–5% should be maintained, so that arterial carbon dioxide tensions are maintained within the normal physiological range. A gradual rise in end-tidal carbon dioxide concentration indicates progressive hypercapnia and corrective action should be taken. Increased concentrations can also occur because of failure of the fresh gas supply, exhaustion of the soda lime during closed system anaesthesia or problems with the anaesthetic breathing system. If the capnograph trace fails to return to zero, this usually indicates that rebreathing of exhaled gas is occurring, and this can be prevented by increasing the fresh gas flow or reducing the breathing system dead space. A gradual fall

in carbon dioxide concentration can indicate increased ventilation, but may also occur during hypotension and decreased cardiac output. Sudden reductions in end-tidal carbon dioxide concentrations can indicate airway obstruction, disconnection of the animal from the breathing system or cardiac arrest. Assessment of the respiratory rate and tidal volume will help distinguish the likely cause. As experience is gained, considerable information can be obtained from the capnograph waveform (Cruz et al., 1994).

Blood Gases It is important to establish a baseline measurement of blood gas values as soon as possible following the induction of anaesthesia. This may be compared with normal values for the particular species, but these are broadly similar for most animals (Table 3.1). A progressive fall in blood oxygen concentration, or a rise in carbon dioxide concentration, usually accompanied by a fall in pH, indicates inadequate gas exchange. Animals breathing room air (20% oxygen) will normally have an arterial PO_2 of 11–12.5 kPa (82–95 mmHg); a fall below 10.5 kPa (80 mmHg) requires corrective action. It is important to note that animals receiving oxygen will normally have much higher arterial partial pressures of oxygen. Values in the range of 40–53 kPa (300–400 mmHg) can be anticipated. In these circumstances, a fall in PO_2 below 90–112 mmHg (12–15 kPa) in an animal breathing 40–60% oxygen should be considered serious. A rise in PCO_2 , from a typical baseline of 5 kPa (37.5 mmHg) to above 6.5 kPa (50 mmHg) indicates mild to moderate hypercapnia. Increases greater than 8 kPa (60 mmHg) indicate severe hypercapnia and consequent respiratory acidosis. Detailed interpretation of blood gases data is complex, but not difficult to master. An excellent source of reference is provided by Martin (1999).

Corrective Action

Impending respiratory failure requires immediate corrective action. The following list provides a quick guide to dealing with the most frequently encountered problems:

- If an anaesthetic breathing system and a source of oxygen are in use, quickly check that oxygen is still being supplied.
- Check that the breathing system is correctly assembled and still connected to the animal.

TABLE 3.1 Blood Gas Values for Animals Breathing Air.

	Arterial blood		Venous blood	
PCO_2	3.8–5.3 kPa	28–40 mmHg	3.8–5.6 kPa	28–42 mmHg
PO_2	11–12.5 kPa	82–94 mmHg	5.3–8 kPa	40–60 mmHg
pH	7.35–7.45 (units)		7.3–7.39 (units)	

- If volatile agents are in use, reduce the concentration to zero and remember to switch off any nitrous oxide and to increase the oxygen flow to compensate for the reduced total gas flow.
- If injectable agents are being administered, stop any continuous infusions and consider whether a reversal agent should be administered. For example, if a neuroleptanalgesic anaesthetic combination has been used, respiratory depression can be reversed using a specific antagonist such as naloxone or diprenorphine (Revivon: C-Vet) (Tables 6.1 and 6.2). Since this will reverse the anaesthetic and analgesic actions of the combination, it must not be administered if surgical procedures are still in progress.
- Fill the breathing system with oxygen using the emergency oxygen switch on the anaesthetic machine and assist ventilation as described in Chapter 3 for a few respiratory cycles. If the chest inflates easily, listen to both sides of the chest (in larger, >1 kg, animals) to assess whether they are being ventilated. If the endotracheal tube has moved down so that its tip is in one bronchus, this causes only one lung to be ventilated, and the tube must be repositioned.
- Observe the movement of the chest to ensure that gas is moving in and out of the lungs. If it is not, check the endotracheal tube – this may have become kinked, pushed too far down the airway or become blocked with secretions.
- If excessive secretions are present (indicated by bubbling noises during ventilation), disconnect the breathing system and clear the tube using gentle suction. Although a vacuum suction device is very useful, a simple technique is to use an appropriate-sized catheter attached to a 10–50 ml syringe.
- If an endotracheal tube is in place, but the chest cannot be inflated, and suction and repositioning the tube do not resolve the problem, then it may have become kinked or blocked. To replace a tube, pass an introducer down the tube, remove the tube and thread a new tube down over the introducer. If this is not possible then a laryngoscope will be needed to replace the tube.
- If the animal has not been intubated, check that the head and neck are extended, open the animal's mouth and pull its tongue forward to ensure that this is not obstructing the larynx.
- If oxygen is not being administered, but an oxygen supply is available, try to administer 100% oxygen as soon as possible. If an anaesthetic breathing system is in use, continue assisting ventilation. If a breathing system is not connected, assist ventilation by manual compression of the thorax. This can be carried out successfully even in small rodents, when compression with the thumb and forefinger can be used to produce some respiratory gas movements.
- Ventilation can also be assisted using a face mask in some species (dog, cat, primate), but in others (e.g. rabbit), this approach often only inflates the stomach. In small rodents, ventilation can be assisted by extending the head and neck, placing a syringe barrel over the nose and mouth, and gently blowing down the nozzle (Fig. 3.7).



FIGURE 3.7 Assisting ventilation with a syringe barrel placed over the mouth and nose of a rat.

- Consider other possible causes of depressed respiration. Check on the activities of the surgeon, for example whether movements of the animal's chest are being restricted, either by using the thorax as a support or by inappropriate positioning of retractors or packs.
- Respiration can be stimulated by the administration of an analeptic such as doxapram. This agent can be used in all species (Tables 6.1 and 6.2) but as its action is of relatively short duration repeated doses may be required every 15–20 minutes.
- If assisted respiration and administration of oxygen have improved respiratory function, observe the animal carefully to check whether any deterioration occurs when these measures are stopped. If respiration appears stable, recommence administering the anaesthetic drugs if these have been stopped and continue to observe the animal carefully. If respiratory function deteriorates, recommence assisted ventilation and preferably connect the animal to a mechanical ventilator. Try to reduce the depth of anaesthesia, but this may be limited by the continuance of any surgical procedures.

Cardiovascular System

Most anaesthetic drugs have a depressant effect on cardiovascular function, and overdose of anaesthetic is probably the most common cause of cardiac failure. Both the heart rate and the force of contraction can be depressed, and in addition,

cardiac arrhythmias may occur. These may also be caused by hypoxia and hypercapnia due to respiratory failure. If the circulation is severely depressed and insufficient oxygen is delivered to the body tissues, peripheral circulatory changes may occur which lead to the development of shock. Besides the adverse effects of anaesthesia or respiratory system failure, loss of blood and body fluids may result in a reduction in the circulating blood volume. If blood volume falls excessively, cardiovascular failure and cardiac arrest will occur. Severe hypothermia (body temperature approximately 25°C) will also result in cardiac arrest.

Clinical Signs of Cardiac Failure

Appearance of the Mucous Membranes

Progressive circulatory failure may be detected by deterioration in capillary refill time, assessed by blanching the peripheral mucous membranes by digital pressure. Any noticeable delay in refill indicates a reduction in tissue perfusion, which may also produce moderate cyanosis (bluish tinge) of the mucous membranes. Cyanosis is more frequently associated with respiratory failure and, if it is due to cardiovascular failure alone, it indicates severe circulatory disturbance. Severe circulatory failure due to hypovolaemia will produce a blanching of the visible mucous membranes.

Peripheral Temperature

Severe circulatory failure is also associated with a fall in peripheral temperature, and the animal's limbs will be noticeably cool to the touch. This can be detected more readily by using a temperature probe taped between the animal's digits and comparing the peripheral temperature with rectal temperature. This temperature change develops slowly, so it will not be of immediate value if rapid haemorrhage has occurred.

Blood Pressure

Systematic arterial pressure will fall during the development of cardiac failure. Usually the reduction is gradual and regular monitoring of blood pressure will allow corrective action to be taken before severe changes have occurred. If a pulse oximeter is in use, a fall in signal strength or complete loss of the signal may occur because of hypotension. As mentioned above, a fall in end-tidal carbon dioxide tensions can indicate hypotension. It is advisable to maintain mean arterial blood pressure above 60–70 mmHg, to avoid problems caused by poor tissue perfusion. A fall in mean arterial pressure below 45 mmHg can result in a failure of renal blood flow, severe metabolic disturbances and death.

Changes in Heart Rate or Rhythm

Circulatory disturbances may also be associated with changes in heart rate or rhythm. An increased heart rate that is not associated with increased surgical

stimulation can be due to blood loss. Severe slowing of the heart can be caused by vagal stimulation, for example when traction is applied to the viscera, when ocular surgery is carried out or when the vagus nerve is handled during surgical procedures in the neck. This can be sufficiently severe to cause marked hypotension and can even result in cardiac arrest.

Corrective Action

When attempting to correct signs of cardiovascular failure, it is helpful if there is some indication of the likely cause. However, whatever be the causative factor, the following measures should be undertaken:

- An immediate priority must be to ensure an unobstructed airway, preferably by endotracheal intubation. If intubation is possible, the animal's lungs should be ventilated with 100% oxygen, or at least this should be administered via a face mask. If assisted ventilation cannot be provided using an anaesthetic breathing system, intermittent compression of the chest wall should be commenced. In large animals, the air movements produced by this technique can be readily appreciated, but even in small rodents, gentle and rapid compression of the thorax between thumb and forefinger can result in effective ventilation.
- If complete cardiac arrest has occurred, external cardiac massage should be undertaken. In larger species, this is best achieved by placing the animal on its side and firmly compressing the chest over the region of the heart (just behind the point of the elbow). The compression should be applied smoothly and maintained for about half a second and at a rate of 60–70 compressions/min. With smaller animals, the chest should be held between thumb and forefinger and the area over the heart compressed regularly and rapidly, about 90 times/min. Even in small rodents, some circulatory support can be maintained whilst other corrective measures are being carried out. Combining assisted ventilation and external cardiac massage in small rodents requires practice and it is usually easier to compress all areas of the thorax simultaneously.
- After adequate ventilation has been established and cardiac massage attempted if it is necessary, an intravenous line should be inserted for drug and fluid therapy. To avoid the need to carry out emergency venepuncture, it is good practice it is good to tape a suitable catheter in a superficial vein (Briscoe and Syring, 2005), either during or shortly after induction of anaesthesia, in all except the smallest animals. If anaesthetic overdose is suspected, either a specific antagonist or an analeptic such as doxapram should be administered. The use of drugs to restore stable cardiac rhythm and output requires considerable care and presupposes that arterial pressure and the ECG are being monitored. However, as an emergency measure, adrenaline (6 ml/20 kg of 1:10,000) should be given if asystole is suspected, or lidocaine (2 mg/kg) administered if the heart is fibrillating. Arrhythmias will often

respond to lidocaine, or to other antiarrhythmic agents such as bretylium (5–10 mg/kg). Complete heart block or low cardiac output can be treated by atropine injection (0.02 mg/kg) and, if required, by the infusion of isoprenaline (isoproterenol) (5–20 µg/kg/min). If cardiac arrest has occurred, these drugs should be administered by intracardiac injection.

- After treatment of cardiac failure, sodium bicarbonate may be administered to correct the acidosis that is usually present. Although elaborate formulae are available for calculation of the dose required (see, e.g. Tranquilli et al., 2007), a useful guide for emergency use is 1 mmol/kg of body weight. If cardiovascular failure has arisen primarily from hypovolaemia, maintenance of adequate ventilation and effective fluid therapy will usually rapidly restore a normal acid–base balance without the administration of sodium bicarbonate.

The use of drugs to treat cardiac failure poses considerable problems for the inexperienced anaesthetist. Detailed descriptions of the techniques available are provided by Costello (2004). All of the more sophisticated means of correcting and treating cardiac failure, including measures such as defibrillation, which are used in humans, can be applied in animals, and if high-risk procedures such as cardiac surgery are planned then expert advice should be sought. A summary of emergency measures is given in Table 3.2.

Fluid Balance

It is of vital importance to support the circulation by correcting any fluid imbalances, and hypovolaemia should always be considered a possible primary cause of cardiovascular failure. Blood loss during surgery can be very gradual, and assessment of the volume lost is frequently highly inaccurate. One simple measure is to weigh the swabs used during surgery. This will provide a reasonable estimate of blood loss, but additional blood will have been lost by seepage into surgical wounds, body cavities and surgical drapes. Additional losses of plasma occur by exudation both into traumatized tissues and into the peritoneal cavity during prolonged abdominal surgery [approximately 100–200 ml/h in humans (Wiklund and Thoren, 1985)]. A further depletion of the extracellular fluid (ECF) occurs due to water loss by evaporation from the respiratory tract and from any surgical wounds and exposed viscera. As a routine, fluid should be replaced at a rate of 10 ml/kg of body weight per hour using either Hartmann's solution or 0.9% saline. It is common practice to warm fluids to body temperature before administration (Dix et al., 2006); however, the effect of infusing fluids at 20 °C rather than 38 °C will have minimal effects on the animal's body temperature compared to other sources of heat loss. The effect of infusing fluids at 40 °C would be greater, especially if administered rapidly, so it is recommended that fluids are warmed if practicable, but this should not usually delay or prevent their administration.

TABLE 3.2 Basic Guide for Coping with Cardiovascular Emergencies, and Infusion Rates of Some Drugs Commonly Used for Cardiovascular Support.

For all cardiovascular problems:

- Administer 100% oxygen and ventilate, and turn off anaesthetic vaporizer or anaesthetic infusion
- If blood loss, transfuse (in order of preference)
 - i. Whole blood
 - ii. Haemaccel or hespan (or equivalent products)
 - iii. Lactated Ringer's solution

If rapid blood loss has occurred replace estimated blood loss as quickly as possible, otherwise 10–15 ml/kg/h

- If low arterial pressure, administer:
 - i. Dopamine infused at 5–10 µg/kg/min, then 1–5 µg/kg/min after volume replacement
 Or
 - ii. Adrenaline 1 µg/kg (0.2 ml per 20 mg of 1:10,000), then infuse 0.05–0.5 µg/kg/min
- Cardiac arrest: start external cardiac massage
 - a. Fibrillating
 - i. Lidocaine 2 mg/kg iv (4 ml of 1% per 20 kg), if no response administer 5 mg/kg iv (10 ml of 1% per 20 kg) plus use defibrillation
 and/or
 - ii. Bretylium 5–10 mg/kg plus use defibrillation
 - iii. Adrenaline 30 µg/kg (6 ml per 20 kg of 1:10,000)
 - iv. Sodium bicarbonate 1 mmol/kg initially, reassess after blood gas analysis
 - b. Asystole
 - i. Adrenaline as above, repeat in 2 min if no response
 - c. Heart block, bradycardia
 - i. Atropine 0.02 mg/kg (0.6 ml per 20 kg)
 - ii. If continued treatment needed: isoprenaline 5–20 µg/kg/min

Drugs for cardiac support:

Bretylium	5–10 mg/kg	To prevent dysrhythmias
Dobutamine	2.5–10 µg/kg/min	To increase cardiac output
Dopamine	1–5 µg/kg/min	To increase renal and mesenteric blood flow
	5–20 µg/kg/min	To increase heart rate and cardiac output, decrease renal blood flow and increase peripheral vascular resistance at higher doses
Lignocaine	30–70 µg/kg/min	To prevent dysrhythmias

For detailed information, see Hensley and Martin (1990).

A healthy, unanaesthetized animal can withstand the rapid loss of 10% of its circulating volume. Once the loss exceeds 15–20% of circulating volume, signs of hypovolaemia and shock may develop. In an anaesthetized animal, many of the physiological mechanisms that act to maintain cardiovascular stability are depressed and hence less severe losses can still have serious effects. If blood loss exceeds 20–25% of the circulating volume, replacement with whole blood may be necessary. Smaller losses can be replaced by the infusion of crystalloid solutions or plasma volume expanders. Blood volume is approximately 70 ml/kg of body mass, so a 30 g mouse has a total blood volume of about 2.1 ml. It is easy to appreciate that any blood loss in these small species can rapidly become significant. A key measure in preventing problems is therefore to ensure careful surgical technique, with rapid and effective control of any haemorrhage.

Blood for transfusion can be obtained from a donor animal of the same species and collected in acid citrate dextrose solution (1 part ACD to 3.5 parts blood, using ACD from a human blood collection pack). It is preferable to use the blood within 4–6 hours as platelet function and red cell viability is likely to be well maintained during this period. More prolonged storage at 4°C is possible, but the storage characteristics of blood from many animal species have not been properly evaluated. Although cross matching will rarely be possible when dealing with laboratory animals, in the author's experience the incidence of adverse reaction to an initial transfusion appears to be low. Selection of donors of the same breed or strain as the recipient may help reduce the likelihood of transfusion reactions. Use of blood from a single individual, rather than pooled from a number of donors, will also help to reduce the risk of an adverse reaction. When using an inbred strain of rodents, there are obviously no problems of this nature.

Blood should be replaced at a rate of 10% of the calculated blood volume every 30–60 minutes. If severe and rapid haemorrhage has occurred, the estimated volume of blood lost should be transfused as rapidly as possible. If whole blood is unavailable, either previously stored plasma or a plasma volume expander such as Haemaccel (Hoechst) or Hespan (Du Pont) should be administered. Administration of dextrans can cause hypersensitivity reactions in some strains of rat (Cotran and Karnovsky, 1968), so it is preferable to use colloidal products such as 'Haemaccel' in this species. If stored plasma is to be used, it should be warmed to body temperature before infusion. If these fluids are unavailable, or if blood loss has been less severe, then Hartmann's solution or 0.9% saline should be administered, at the rate described for whole blood and at a volume of three to five times the estimated blood loss. Considerably greater volumes are needed because these crystalloids are distributed throughout the ECF, unlike blood, plasma and plasma volume expanders that remain in the circulatory system. Some controversy exists concerning the merits of crystalloids and plasma volume expanders for restoring the circulating volume following severe haemorrhage. Such controversy should not be a deterrent to the use of fluid therapy and it should be remembered that it is almost always better to give than to withhold fluids.

In small animals in which intravenous therapy is difficult, 0.9% sodium chloride or Hartmann's solution can be administered intraperitoneally to correct intra-operative fluid loss. It is often particularly convenient to replace intra-operative water losses and anticipated post-operative deficits by the administration of 0.18% sodium chloride with 4% dextrose by subcutaneous injection at a rate of 10–15 ml/kg. These routes of administration result in slow absorption and will be of no immediate value in treating cardiovascular failure.

Hypothermia

Hypothermia is a frequent cause of anaesthetic deaths. Hypothermia prolongs recovery time from anaesthesia (Fig. 3.8) and increases the potency of volatile anaesthetics (Regan and Eger, 1967). It is a particularly common problem in small rodents and birds, but also occurs in larger species, especially during prolonged anaesthesia. Small mammals and birds lose heat rapidly because of their high surface area to body weight ratio. The homeostatic mechanisms that control body temperature are depressed during anaesthesia and severe hypothermia can result. Hypothermia can develop rapidly in small animals; the author has recorded reductions in body temperature of 10 °C in as little as 15–20 minutes in anaesthetized mice.

The fall in body temperature can be exacerbated by the flow over the animal of cold, dry gases from an anaesthetic machine. In addition, shaving the animal before surgery will remove insulating hair and the use of cold skin disinfectants will cause further heat loss. During surgical procedures, exposure of the viscera

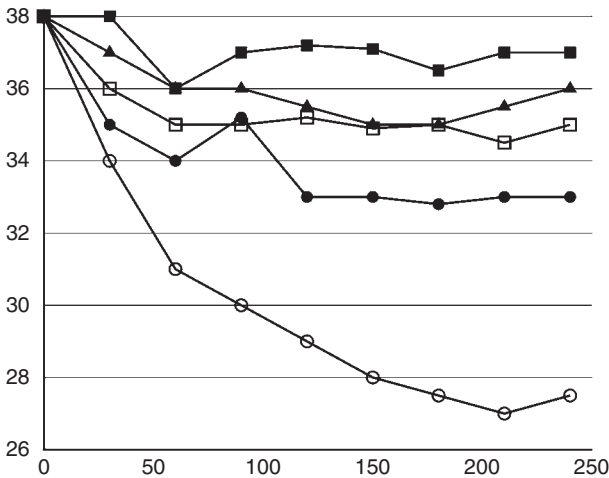


FIGURE 3.8 Body temperature (rectal probe, in °C) in rats when using different methods to maintain body temperature (data from studies in the author's laboratory). Solid squares, Harvard electric blanket; triangle, electric heat pad; open squares, space blanket; solid circles, bubble wrap; open circles, no insulation.

and use of swabs soaked in cold saline, or the administration of cold intravenous fluids, will cool the animal.

Hypothermia prolongs recovery from anaesthesia and, if severe, can result in death of the animal. It can also have direct and indirect effects on research data, by its effects on a range of biological processes. For example, it has been shown to influence implantation rates after embryo transfer (Bagis et al., 2004). It is therefore essential to take effective measures to prevent even mild hypothermia from developing.

Preventive Measures

Careful pre- and intra-operative management can reduce any fall in body temperature. Most animals will require some additional heating and insulation to minimize heat loss. Effective insulation can be provided either by wrapping the animal in cotton wool, followed by an outer wrapping of aluminium foil, or by using the bubble packing which frequently forms part of the packaging of laboratory equipment, or other insulating materials. After wrapping the animal in an insulating layer of material, a window can be cut to expose the operative field (Fig. 3.9). When insulating small rodents, ensure that the tail is included in the wrapping, since heat loss from this part can be considerable. These simple measures will help reduce heat loss, but supplemental heating should be considered essential, even for brief periods of anaesthesia in small animals.

Supplemental heating can be provided by heat lamps and heating blankets, but care must be taken not to burn the animal. A thermometer placed next to

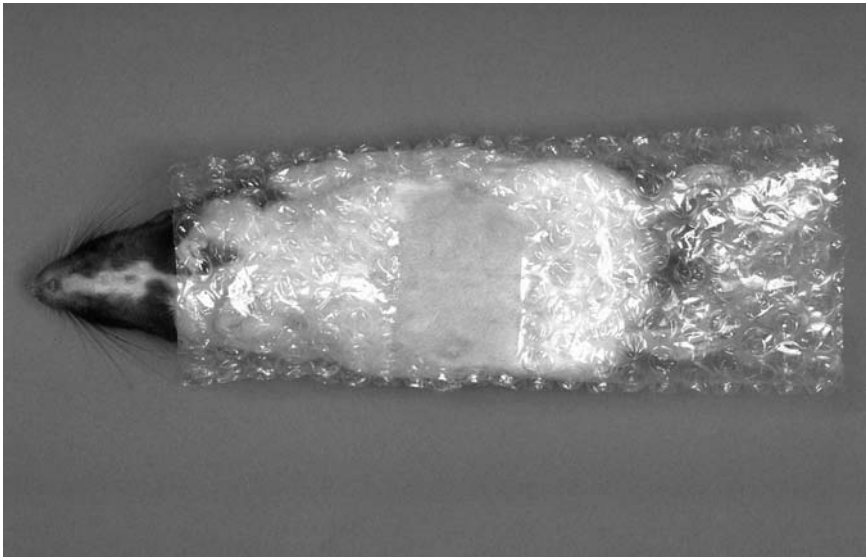


FIGURE 3.9 Maintaining body temperature in a rat using bubble packing. A window has been cut to expose the surgical site.

the animal, or between the animal and a heating pad, will show whether excessive heat is being applied. The probe temperature should not exceed 40°C. It is possible to cause hyperthermia by over-enthusiastic or uncontrolled heating, and this can result in superficial burns or even the death of the animal. To avoid such problems, and provide effective, well-controlled warming, it is preferable to use a thermostatically controlled heating blanket, regulated by the animal's body temperature using a rectal probe (Harvard Apparatus Ltd., IMS, Appendix 4). If such a unit is not available, a simple heating pad or lamp can be used which, provided the animal's rectal temperature is monitored, can be switched on and off manually as required (Fig. 3.10). It is important to switch on heating pads and lamps before they are required, to allow their temperature to stabilize and to prevent a period of inadequate heating when the pad or lamp is warming up. Thermostatically controlled pads can be set up with the probe in contact with the blanket, so that they reach body temperature before the animal is anaesthetized.

Heating blankets may use electrical elements, have circulating warm water, or employ warm air. Warm water heating systems may not provide sufficient warmth for small animals because of the fall in water temperature between the water reservoir and the blanket, but are effective in larger species (Sikoski et al., 2007). Forced air warming systems (Fig. 3.11), such as the Bair Hugger (Appendix 4), provide excellent maintenance of body temperature (Rembert et al., 2004), but the design of the blankets makes them best suited to use in larger (<3–4 kg) species.

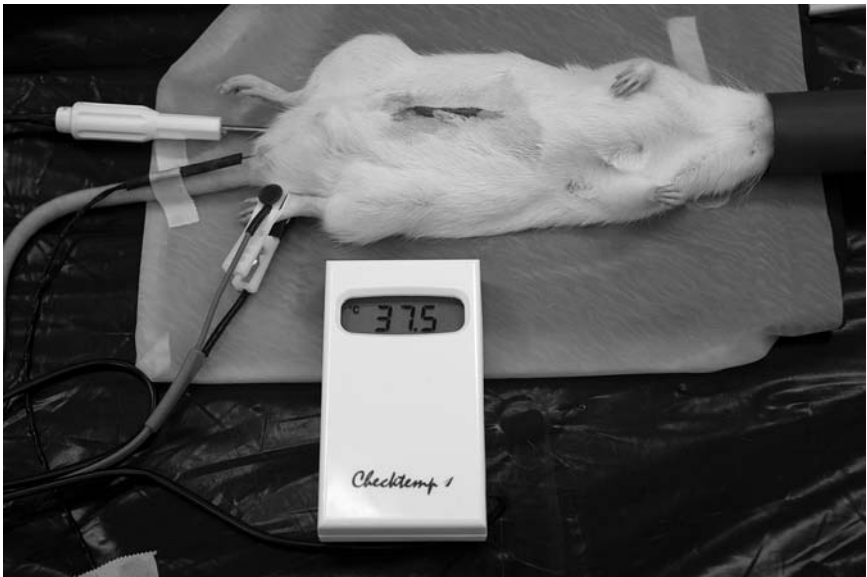


FIGURE 3.10 Heat pad and temperature monitoring (two thermometers – one to monitor the animal's temperature, and used to control the blanket temperature, and the other to monitor the heating pad temperature).



FIGURE 3.11 'Bair Hugger' warm air heating blanket in use.

Vomiting and Regurgitation

Vomiting or regurgitation of stomach contents may occur either during induction of anaesthesia or during the recovery period. It is a potentially serious problem and requires prompt treatment. Inhalation of gastric contents can produce immediate respiratory obstruction, asphyxiation and death, or lead to the development of aspiration pneumonia.

If vomiting occurs, the animal should immediately be placed in a head-down position and the vomit aspirated from the mouth and pharynx. If an effective suction apparatus is not available, one can be improvised from a large-diameter catheter and a 50 ml syringe. Since speed of reaction is of paramount importance, such apparatus should be available as standard equipment in the anaesthetic preparation room and recovery area.

If aspiration of vomit has occurred, oxygen should be administered and ventilation supported if respiratory distress develops. A broad-spectrum antibiotic should be administered, and corticosteroids given immediately by the intravenous route (30 mg/kg methyl prednisolone). If administration is delayed, steroids may be of little benefit.

It is obviously preferable to reduce the incidence of vomiting and its associated problems by withholding food pre-operatively when appropriate (see Chapter 1) and by rapid endotracheal intubation of all animals whenever this is practicable.

Special Techniques

Some research procedures require the use of more specialized anaesthetic techniques. The use of NMB drugs may be needed, particularly for cardiothoracic and neurophysiological procedures. Use of these agents is challenging, and requires careful monitoring of anaesthetic depth. Their use will also require use of controlled ventilation and an understanding of the function of mechanical ventilators and the various types of apparatus that are available. Mechanical ventilation may also be needed during long-term anaesthesia, another challenging technique. Maintaining anaesthesia for prolonged periods can be achieved using a variety of ways. The advantages and disadvantages of the different techniques in relation to the scientific aims of the procedure, the experience of the staff, the welfare and well-being of the animals involved must be carefully considered.

Some groups of animals also provide particular challenges, for example anaesthesia of pregnant animals, fetuses and neonates. Finally, this chapter briefly outlines some of the particular issues relating to anaesthesia for non-invasive imaging.

USE OF NEUROMUSCULAR BLOCKING AGENTS

NMB drugs produce paralysis of the skeletal muscles. They may be used either to aid stable mechanical ventilation by blocking spontaneous respiratory movements or, more frequently, to provide more suitable conditions for surgery. If skeletal muscle tone is eliminated by using a NMB agent, exposure of a surgical site can be achieved more easily and with less trauma to the surrounding tissues. NMB drugs are also used in neurophysiological and other studies, to enable very light planes of anaesthesia to be maintained. Under these conditions, if a relaxant had not been administered, spontaneous muscle movements could occur which would interfere with data collection.

The NMB drugs in common clinical use are classified as either depolarizing or non-depolarizing agents (Bowman, 2006). Depolarizing agents, such as suxamethonium and decamethonium, act similarly to the normal transmitter at the neuromuscular junction, acetylcholine. They bind to muscle receptors and trigger a muscle contraction but then produce a persistent depolarization, so preventing

further muscle contractions. When drugs that act in this way are administered to an animal, generalized disorganized muscle twitches (fasciculations) are produced before complete skeletal muscle paralysis.

Non-depolarizing, or competitive blocking agents do not cause a muscle contraction before producing paralysis. Drugs in this group include tubocurarine, gallamine, pancuronium, alcuronium and vecuronium (Table 4.1). Since these agents act by competing with acetylcholine for receptor sites at the neuromuscular junction, their action can be reversed by increasing the local concentration of acetylcholine. This can be achieved by administering drugs such as neostigmine that block the activity of the enzymes which normally break down acetylcholine.

NMB agents must be used with great care, since their administration prevents all movements in response to pain. It would be possible, but obviously inhumane, to carry out a surgical procedure on an animal which had been paralysed but was still fully conscious. It is for this reason that the use of NMB drugs in experimental animals is subjected to careful control in many countries, for example special permission is required to use these agents in the UK, and Institutional Animal Care and Use Committee review is required in the USA. NMB agents are nevertheless extremely useful adjuncts to anaesthesia and enable, for example the use of balanced anaesthetic regimens such as an opioid, an hypnotic and a muscle relaxant to provide stable surgical anaesthesia. Dose rates of a number of different NMB agents are given in Table 4.1.

If NMB drugs are used, other methods of assessing the depth of anaesthesia must be adopted. As a preliminary step, the proposed anaesthetic technique, excluding the NMB drug, should be administered to an animal of the same species and the proposed surgical procedure carried out. This will establish that the degree of analgesia and unconsciousness will be sufficient to allow surgery to be carried out humanely. Since considerable individual variation in response to anaesthesia occurs and some inadvertent alteration in the technique can arise, for example due to equipment malfunction, it is also necessary to provide an independent assessment of the depth of anaesthesia. Several indicators of anaesthetic depth are of use. Despite muscle paralysis, twitching of muscles may occur in response to a major surgical stimulus and this indicates that the depth of anaesthesia is inadequate. In humans, pupillary size may alter in response to surgical stimulation, but this sign is of little value in most animals, particularly if atropine has been included in the pre-anaesthetic medication.

Changes in blood pressure and heart rate are the most widely used indicators of adequacy of the depth of anaesthesia. Dramatic changes in heart rate or blood pressure are believed to indicate a depth of anaesthesia insufficient for the surgical procedures that are being undertaken. It has been suggested that increases in heart rate and blood pressure by 10–20% indicate the need for additional anaesthesia. However, many anaesthetics do not block these autonomic responses and 10–20% increases in heart rate can be seen in animals that have not received NMB drugs, and yet these animals show no movement in association with the stimulus. If inadequately anaesthetized, most animals respond to surgical stimuli

TABLE 4.1 Dose Rates for Neuromuscular Blocking Agents (mg/kg, by Intravenous Injection).

Muscle relaxant	Mouse	Rat	Guinea pig	Rabbit	Cat	Dog	Sheep	Goat	Pig	Non-human primate
Alcuronium	–	–	–	0.1–0.2	0.1	0.1	–	–	0.25	–
Atracurium	–	–	–	–	0.2	0.5	0.5	–	–	0.3–0.6
Gallamine	–	1	0.1–0.2	1	1	1	1	4	2	–
Pancuronium	–	2	0.06	0.1	0.06	0.06	0.06	0.06	0.06	0.08–0.1
Suxamethonium	–	–	–	0.5	0.2	0.4	0.02	–	2	–
Tubocurarine	1	0.4	0.1–0.2	0.4	0.4	0.4	0.4	0.3	–	–
Vecuronium	–	1	–	–	0.1	0.1	0.05	0.15	0.15	0.04–0.06

with a rise in blood pressure, but some animals may show a fall in pressure. So despite their widespread acceptance, these parameters may not always be reliable indicators of adequate anaesthesia (Whelan and Flecknell, 1992).

An alternative method of monitoring the depth of anaesthesia is to use the EEG. Although this requires specialist equipment and expert interpretation, these may be available, especially if neurosurgical or neurophysiological studies are being carried out. Simple changes in the unprocessed EEG, such as onset of burst suppression, can be useful when using some anaesthetic agents, for example halothane. Various derived measures, for example total power and spectral edge frequency have also been used to assess depth of anaesthesia (Murrell and Johnson, 2006; Otto, 2008); however, these measures generally cannot be used easily with balanced anaesthetic techniques which involve simultaneous use of hypnotics and analgesics. These same difficulties occur in human subjects, and great efforts have been made to develop monitoring devices that can measure loss of consciousness. The most recently developed have been bispectral index (BIS) monitors (Appadu and Vaidya, 2008), and these are now widely used in human patients, particularly in North America. Initial studies suggest that the instrument may also be of value in animals (Antognini et al., 2000; Lamont et al., 2004; Martin-Cancho et al., 2006). The attraction of this monitor is that it provides a single number as an index of consciousness, or depth of anaesthesia. The disadvantage is that, like the EEG from which it is derived, it is primarily intended to assess the degree of loss of consciousness, and is most predictive when a single anaesthetic agent is used. It is less reliable when using balanced anaesthesia. A further drawback is that it is designed for use in human beings, and the mathematical processing used to create the 'index' has been derived from measures made in large numbers of human subjects. Despite these problems, BIS monitors may be of use, particularly for long-term anaesthetic procedures with neuromuscular blockade, but extensive validation for each specific protocol will be needed before these monitors can be relied upon. It is also apparent that BIS values may vary between species at equivalent anaesthetic depths (Lamont et al., 2004).

Given the difficulties of monitoring the level of consciousness in paralysed animals, a more simple approach is to allow the action of the muscle relaxant to subside periodically. The animal will then be capable of responding to painful stimuli with voluntary movements. The degree of neuromuscular blockade can be monitored using a peripheral nerve stimulator. This device delivers a small electrical stimulus, either using skin electrodes or needle electrodes, to a peripheral nerve supplying muscle. In a non-paralysed animal the stimulation causes a muscle twitch. Allowing the actions of the muscle relaxant to subside will not always be practicable, especially during prolonged neurophysiological studies, however it is almost always feasible to delay administration of the relaxant until after the start of the surgical procedure. This allows an initial assessment of the adequacy of the depth of anaesthesia to be obtained. It also avoids difficulties in interpreting changes in heart rate and blood pressure that can occur as a side-effect of administration of some muscle relaxants (Rowlee, 1999; Appadu and Vaidya, 2008).

Decisions as to what constitutes an appropriate depth of anaesthesia, especially in paralysed animals, remains controversial. It has been suggested that very much lighter planes of anaesthesia should be used routinely (Antognini et al., 2005), but this approach does not take account of our current poor knowledge of indicators of consciousness in animals. A more conservative approach (e.g. Drummond et al., 1996) is recommended by most regulatory authorities, scientific journals and is adopted at the author's own institution.

CONTROLLED VENTILATION

Many anaesthetic agents depress respiration and this can lead to the production of hypercapnia, hypoxia and acidosis. To maintain blood carbon dioxide and oxygen concentrations within normal levels, it is often necessary to assist ventilation. If the thoracic cavity is opened, the normal mechanisms of lung inflation are disrupted and it is usually necessary to ventilate the animal's lungs artificially. It is not necessary to use a mechanical ventilator provided a suitable anaesthetic breathing system is in use (see Chapter 3), but using a ventilator will often be more convenient than manually assisting ventilation. A mechanical ventilator will often allow the precise control of the duration of inspiration and expiration, the volume of gas delivered to the lungs and the pressure reached in the airway during inspiration. It is not necessary to administer a NMB agent (muscle relaxant, curare-like drug) in order to carry out artificial ventilation but, unless the animal is deeply anaesthetized or is hyperventilated to produce hypocapnia, spontaneous respiratory movements may occur and these may interfere with ventilation and surgery.

Mechanical Ventilators

Ventilators for use with animals may have either been specifically designed for these species, or may be adapted from their original use as ventilators for human subjects (Table 4.2). Ventilators are designed to achieve controlled ventilation of the animal's lungs by means of the application of intermittent positive pressure to the airway. This may be achieved either by delivering gas directly to the anaesthetic breathing system or, indirectly, by compressing a rebreathing bag or bellows, which in turn delivers gas to the animal.

A variety of techniques have been devised to control the delivery of gas to the patient and to determine the patterns of gas flow and gas pressure that occur during ventilation. It might be thought that all that was required of a ventilator was to deliver the required volume of gas to the lungs at a predetermined rate. However, since the characteristics of the patient's lungs, changes in airway resistance and leaks in the anaesthetic breathing system can all influence the volume of gas delivered, different techniques for terminating inspiration have been devised.

There are basically only two ways in which gas can be delivered during inspiration. The ventilator may deliver gas at a set pressure pattern: the pressure is determined by the machine, but the patient's airway characteristics will influence

TABLE 4.2 Suggested Ventilation Rates for Laboratory Animals.

Species	Breaths/min
Pig, dog (<20 kg)	15–25
Pig (>20 kg), sheep (>20 kg), dog (>20 kg)	10–15
Primates (>5 kg)	20–30
Marmosets	40–50
Cat and rabbit (1–5 kg)	25–50
Guinea pig	50–80
Rat	60–100
Other small rodents	80–100

Tidal volumes of 10 ml/kg are normally required. Whenever possible the adequacy of ventilation should be assessed by monitoring the end-tidal carbon dioxide concentration or by arterial blood gas analysis.

the volume of gas which is delivered; this is because the pressure reached in the airway depends upon the resistance to flow provided by the patient's lungs. If the ventilator is set to achieve a predetermined pressure, it will be reached earlier, and less gas will be delivered, if the patient's lungs provide a higher resistance to flow.

In contrast, a ventilator may be set to produce a fixed flow pattern, which will be uninfluenced by the patient's lung characteristics. Under these circumstances, the flow of gas will be constant but the pressure that develops in the airway will vary depending upon the patient's lung characteristics.

It is important to understand how these two types of ventilators, termed 'pressure generators' and 'flow generators' respectively, are switched or cycled from inspiration to expiration. This can be achieved in several different ways, but the most frequently used method in animal ventilators is time cycling. Here, the change to expiration occurs after a preset time and is uninfluenced by changes in the patient's lungs. If a time-cycled ventilator is used, the pressure developed in the lungs, the gas flow and the volume delivered can all vary. The actual values of these variables will depend both upon the characteristics of the patient and upon whether the ventilator is a pressure or flow generator. If the power of the ventilator is very great relative to the resistance of the patient's lungs then, although time-cycled, the ventilator may in fact deliver a preset volume during inspiration.

An alternative to time cycling is to determine the volume of gas that should be delivered during inspiration based on the animal's estimated tidal volume and change from inspiration to expiration when this volume has been delivered. In contrast, the changeover may be triggered not when a fixed volume of gas has been delivered, but when a predetermined airway pressure has been reached.

Once the lungs have been inflated and expiration begins, some mechanism must be used to trigger inspiration. In practice, only two techniques are used: either



FIGURE 4.1 Merlin ventilator (Vetronic Services).

the changeover can occur after a fixed time or after airway pressure falls to a preset level.

The apparent complications introduced by the mechanics of ventilator design do have real effects on the patient. For example, if a fixed tidal volume is delivered, there will be no compensation for leaks in the anaesthetic breathing system so, if any leaks are present, there will be a fall in the volume of gas actually delivered to the lungs. A ventilator set to deliver gas until a preset pressure is achieved will compensate for leaks in the anaesthetic breathing system, but an increase in the animal's airway resistance will result in a fall in the tidal volume delivered to the lungs. Ventilators that deliver gas at a fixed flow with a high generating pressure and that are either time or volume cycled, are unaffected by changes in the patient's lungs, but they may produce excessive airway pressures.

In selecting a ventilator for use in laboratory animals, the most important factor to be considered is the ability to ventilate a wide range of animal species. It should be emphasized that the successful delivery of small tidal volumes (e.g. less than 50 ml) often requires a leak-proof anaesthetic breathing system and minimal compliance of breathing system components such as connecting tubing. Additional features that may be needed are the ability to apply PEEP and a facility for humidification of gases. It is also important to select a machine that is simple to use and is reliable and easy to maintain. The author's personal preference for a suitable multi-purpose ventilator is the Merlin ventilator (Vetronic Services, Appendix 4) (Fig. 4.1) which can deliver a wide range of tidal volumes ranging from 1 to 800 ml.

An important practical consideration is that some ventilators require a source of compressed gas to provide the driving power for the ventilator. If a piped gas supply is available, then this does not represent a particular problem. If small gas cylinders are used to drive the ventilator, then large numbers may be required during a prolonged anaesthetic, even when used on a relatively small animal. Since the driving gas does not reach the animal's lungs, a compressor delivering medical air is one possible solution. Alternatively a large cylinder of compressed air can be provided as the driving gas. If none of these solutions are thought practicable, then a mechanically driven ventilator is required. Most of these ventilators are designed to ventilate the animal either with room air or with gas provided from an anaesthetic machine. If gas is supplied from an anaesthetic machine, then it is important that a pressure relief valve is incorporated into the breathing system between the fresh gas inflow and the ventilator to prevent over-inflation of the animal's lungs. Most ventilators designed for clinical use incorporate this highly desirable feature.

Practical Considerations

To establish IPPV, calculate the required tidal volume (approximately 7–10 ml/kg body weight) and select a suitable respiratory rate. Generally, a rate slightly lower than the normal resting rate, when conscious, is adequate. Suggested initial ventilation rates are given in Table 4.2. This process may be more complex since some ventilators do not provide direct settings for these variables. If a setting for tidal volume is not provided, then the ventilator should have a setting for inspiratory time and inspiratory flow rate. Since

$$\text{Tidal volume} = \text{inspiratory time} \times \text{inspiratory flow rate}$$

The tidal volume needed can be calculated. Setting these may also influence the breathing rate, since

$$\text{Breathing rate (breaths per minute)} = \frac{60}{\text{inspiratory time} + \text{expiratory time}}$$

Separate controls for inspiratory and expiratory time may not be provided; some ventilators have only a control for the inspiratory time, and one for the inspiratory:expiratory (I:E) ratio. During IPPV, the heart and large veins in the thorax are compressed during inspiration, in contrast to the negative pressure that develops in the thorax during inspiration with spontaneous ventilation. The positive pressure produced during IPPV can reduce cardiac performance and cause a fall in blood pressure. To reduce this effect, inspiration should be completed in as short a period as possible, but must not be too rapid as this could result in high airway pressure. Conventionally, I:E ratios are set to be 1:2, but ratios of 1:3 and 1:4 will often cause less cardiac depression, while maintaining inflation pressures below 20 cm water.

TABLE 4.3 Suggested Regimens for Total Intravenous Anaesthesia for Long-Term Anaesthesia.

Species	Regimen
Cat	Propofol 7.5 mg/kg i.v., then 0.2–0.5 mg/kg/min Alphaxalone 5 mg/kg i.v., then 0.1–0.2 mg/kg/min i.v.
Dog	Propofol 5–7.5 mg/kg i.v., then 0.2–0.4 mg/kg/min; addition of alfentanil (2–3 µg/kg/min) enables propofol rate to be reduced to 0.14–0.18 mg/kg/min Midazolam 50–100 µg/kg i.v. and alfentanil 10–20 µg/kg, then midazolam 5 µg/kg/min and alfentanil 4–5 µg/kg/min Alphaxalone, 2 mg/kg then 0.1–0.2 mg/kg/min i.v.
Mouse	Propofol 26 mg/kg i.v. then 2–2.5 mg/kg/min i.v.
Non-human primate	Propofol 7–8 mg/kg i.v. (after ketamine (10 mg/kg i.m.) then 0.2–0.5 mg/kg/min i.v.; addition of alfentanil (1–10 µg/kg/min) enables propofol rate to be reduced to 0.1–0.2 mg/kg/min
Pig	Propofol 2–2.5 mg/kg i.v. after ketamine (10 mg/kg i.m.), then 0.1–0.2 mg/kg/min, addition of alfentanil (20–30 µg/kg i.v.), then 2–5 µg/kg/min enables the dose of propofol to be reduced to 0.05–0.1 mg/kg/min
Rabbit	Fentanyl/fluanisone 0.3 ml/kg i.m. and midazolam (1–2 mg/kg i.v.), then fentanyl 2–5 µg/kg/min
Rat	Propofol 10 mg/kg i.v., then 0.5–1.0 mg/kg/min i.v.
Sheep	Propofol 4–6 mg/kg i.v., then 0.3–0.5 mg/kg/min i.v.

Note that regimens using opioids often require IPPV to maintain adequate ventilation.

After setting the rate and tidal volumes, and I:E ratio (if possible), set the maximum inspiratory pressure – this should be less than 15 cm water for small animals and should not exceed 25 cm water in most circumstances.

To monitor inflation pressures, if the ventilator is not equipped with a pressure monitor, place a needle in the inspiratory side of the anaesthetic breathing system and attach it to a pressure transducer. Besides checking that excessive pressures do not develop, by setting appropriate limits on the pressure monitor, it can act as an alert should the animal become disconnected from the breathing system or the ventilator malfunction.

When the chest is open, the lungs collapse completely, and to prevent this many ventilators allow a positive pressure to be maintained at the end of expiration (PEEP). Only very low pressures, ranging 1–5 cm of water, are normally required for small animals. PEEP can be applied either via a specific feature on some ventilators, or by attaching a PEEP valve onto the ventilator. In some models of rodent ventilator (e.g. the Harvard volume cycled model, Fig. 4.2), PEEP

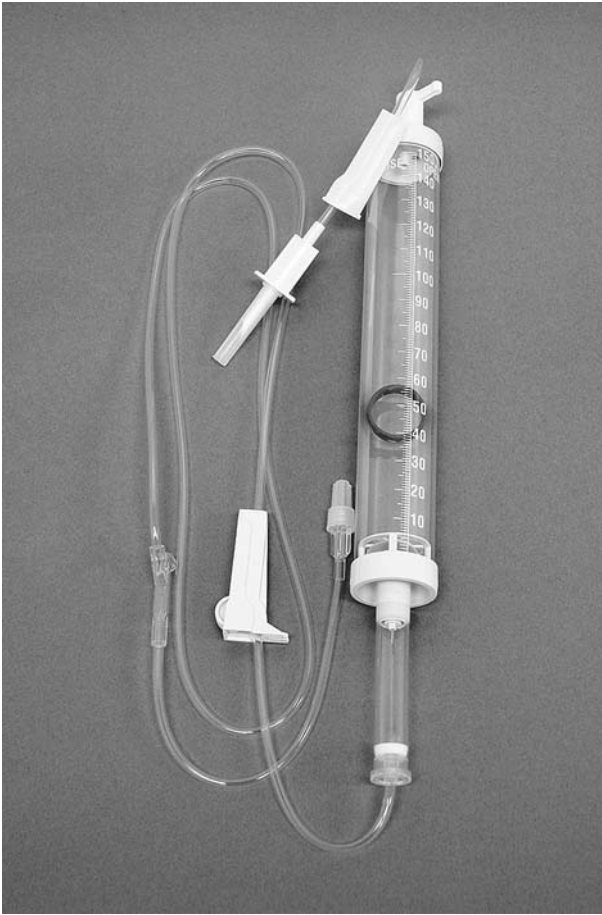


FIGURE 4.2 Paediatric burette.

can be achieved simply by immersing the end of the tubing from the expiratory gas port into a few centimetres of water.

If a muscle relaxant is not being used to prevent spontaneous respiratory movements, then these can occur and interfere with the breathing cycles produced by the ventilator. One technique that can often reduce or eliminate these spontaneous movements is to increase the respiratory rate by approximately 50%, and slightly over-ventilate the animal for a few minutes. The respiratory rate can then be reduced slowly, and in many animals any spontaneous movements will remain suppressed, or will be occurring in synchrony with the ventilator.

Setting up and managing IPPV can seem daunting, but it is particularly useful in long anaesthetics (>1 hour). Many veterinary or medically qualified anaesthetists should be able to provide expert advice. Once some simple protocols

have been established, IPPV should be a relatively easy technique to master. Two recommended articles that provide a straightforward account of IPPV for veterinary practice are Dugdale (2007a) and (2007b).

LONG-TERM ANAESTHESIA

When animals are anaesthetized for only a short period, their ability to withstand numerous disruptions to their normal physiology will often enable them to survive even very poor anaesthetic techniques. As the period of anaesthesia is extended, the adverse effects caused by poor technique become increasingly important. Similarly, the undesirable side-effects of many anaesthetic drugs become more apparent and a considerably higher standard of intra-operative care becomes necessary. Long-term anaesthesia is of course an arbitrary term, but here it is used to describe anaesthesia lasting longer than 60 minutes.

There is little practical difference between anaesthesia from which the animal will be allowed to recover and that in which the animal will be killed at the end of the procedure. Prolonged, non-recovery anaesthesia, often undertaken to enable the study of physiological mechanisms or drug metabolism, usually requires stable anaesthesia with minimal depression of the various body systems. However, since recovery is not required, cumulative effects of drugs become less important, provided physiological stability can be maintained.

Choice of Anaesthetic

Injectable Agents – Use of Short-acting Anaesthetics

It might be thought that the simplest method of prolonging anaesthesia would be to give repeated doses of an injectable anaesthetic. Two problems arise if this approach is adopted. Giving intermittent doses of the drug will cause the depth of anaesthesia to vary considerably, although this can be overcome by administering it as a continuous infusion so that steady plasma concentrations of the anaesthetic are maintained. A second problem arises because of the pharmacokinetics of the anaesthetic. Following an initial injection of, for example a barbiturate, the blood concentration of the drug rises rapidly and the concentration in tissues with high relative blood flows, such as the brain, also increases rapidly. Redistribution of the drug to other body tissues then follows, with equilibration with body fat occurring most slowly. As this redistribution occurs, the concentration of drug in the brain falls. Recovery from the anaesthetic effects of the drug is primarily due to this redistribution, rather than to drug metabolism or excretion. If a second dose of anaesthetic is given, redistribution occurs more slowly, since the body tissues already contain some of the drug, and the duration of anaesthesia is prolonged. Repeated doses will have progressively greater effects. In addition to extending the duration of surgical anaesthesia, the sleeping time following anaesthesia is also very prolonged. If the animal does eventually

wake up, the residual effects of the drug may persist for 24–48 hours. For this reason, repeated incremental doses of drugs such as the barbiturates are not an ideal way of prolonging anaesthesia. The cumulative effects of different types of anaesthetic do vary considerably and some, such as alphaxalone/alphadolone, alphaxalone and propofol, are rapidly metabolized following their administration. These drugs can be used to produce prolonged periods of anaesthesia without causing greatly extended recovery times (Coetzee, 2005).

Whichever injectable anaesthetic is used, it is preferable to administer incremental doses of the drug by the intravenous route, so that its effects on the depth of anaesthesia will be seen rapidly and be readily adjusted. Administration by other routes is possible with some drugs, but the depth of anaesthesia will vary less predictably.

Drugs Available

Barbiturates

Recovery following repeated doses of barbiturates is very prolonged, so the use of these drugs for procedures from which the animal is expected to recover consciousness is not recommended. Incremental doses of barbiturates can be used for non-recovery experiments, but the hypotension and respiratory depression that may result can cause serious problems. In addition, the depth of anaesthesia will vary considerably and may be insufficient to allow surgical procedures to be undertaken in rodents and rabbits. In larger species, continuous infusion of pentobarbital or repeated administration can be used successfully for long-term anaesthesia, but recovery is very prolonged and often associated with long periods of involuntary excitement and ataxia. The drug is therefore best reserved for use in non-recovery procedures.

Alphaxalone/Alphadolone, Alphaxalone

Even after several hours of continuous infusion of alphaxalone/alphadolone, recovery is rapid (Cookson and Mills, 1983) and it is useful for producing long-term anaesthesia in primates, cats, sheep, pigs, rats, mice and guinea pigs. In rabbit, the poor degree of analgesia and the respiratory depression that is produced at high dose rates limits the usefulness of this drug unless ventilation is assisted. Approximate infusion rates are given in Table 4.3.

Initially, an induction dose of the drug should be given, followed by a continuous infusion at the rate quoted. The animal should be monitored to ensure the depth of anaesthesia is appropriate and the infusion rate increased or decreased as required. Stable anaesthesia is usually achieved within 30–60 minutes and will be established more rapidly as experience is gained with a particular species and strain of animal.

It is likely that the related, recently marketed steroid anaesthetic, alphaxalone (Alfaxan) will have very similar features when used by continuous infusion (Ferre et al., 2006).

Propofol

Propofol has been shown to have little cumulative effect, and this drug has been used to provide prolonged anaesthesia in a number of species (Hall and Chambers, 1987; Blake et al., 1988; Flecknell et al., 1990a; Brammer et al., 1992; Robertson et al., 1992; Aeschbacher and Webb, 1993b; Fowler et al., 2001; Murayama et al., 2005). Maintenance of full surgical anaesthesia with propofol alone requires relatively high infusion rates, and this may result in more prolonged recovery times in some species. It is often preferable to supplement propofol anaesthesia with a potent opioid such as alfentanil. This allows lower infusion rates of propofol to be used, and since the opioid can be reversed using a partial agonist such as butorphanol, recovery is generally rapid (Flecknell et al., 1990a). When using higher doses of opioids with propofol, respiration may be depressed, and it is preferable to connect the animal to a ventilator. This does not represent a significant disadvantage since the physiological state of the animal during long-term anaesthesia is almost invariably improved by using IPPV.

Infusion with propofol will result in marked lipaemia, since the commercial preparation of the drug is as an emulsion in soya bean oil. This appears to have little clinical significance, but potentially could interfere with some experiments.

Ketamine

Ketamine is metabolized moderately rapidly and incremental doses can be given to extend the period of anaesthesia. The recovery rate is prolonged after repeated administration and severe respiratory depression can occur. If repeated doses or a continuous intravenous infusion are to be used, it is usually necessary to monitor respiration and to have facilities for mechanical ventilation available. It is a poor anaesthetic and analgesic in most rodents (see Chapters 3 and 6) so is almost always administered in combination with medetomidine or xylazine or a sedative such as diazepam to eliminate the muscle rigidity, which occurs when ketamine is used alone (see Chapter 3).

Ketamine can be used in combination with propofol to provide stable, long-term anaesthesia in rats (Welch, personal communication). After induction of anaesthesia with isoflurane, an intravenous catheter is placed in the tail vein and a loading dose of ketamine (50 mg/kg) and propofol (3 mg/kg) is administered. This is followed with an infusion of ketamine (50 mg/kg/h) and propofol (50 mg/kg/h) commenced. The infusion rates can then be varied to produce the required depth of anaesthesia.

Etomidate and Metomidate

Etomidate and metomidate are potentially useful drugs for the production of long-term anaesthesia. Rapid metabolism of these agents occurs and continuous infusion results in only a mild cumulative effect on recovery time. The drugs suppress adrenal cortical activity when used in this way (Fellows et al., 1983; Wagner and White, 1984) and this side-effect must be considered if they are to be administered to experimental animals. Neither drug produces sufficient analgesia to allow

surgical procedures to be carried out and an opioid such as fentanyl should be administered to produce full surgical anaesthesia. Metomidate and etomidate have relatively little depressant effect on the cardiovascular system (Nagel et al., 1979; Kissin et al., 1983; Fresno et al., 2008) and when used with an opioid they produce good surgical anaesthesia and maintain stable cardiac function.

Neuroleptanalgesic Combinations

These combinations, when administered with a benzodiazepine, produce excellent surgical anaesthesia in rodents and rabbits (Chapters 3 and 6), but several problems arise when they are used to produce long-term anaesthesia. Neuroleptanalgesic preparations consist of a mixture of an opiate analgesic and a potent tranquilizer. If repeated doses of a fixed-dose preparation are given, relative overdosage with the tranquillizer may occur since it usually has a longer duration of action than the analgesic component. In practice, this seems to have only a minor effect in prolonging recovery times when fentanyl/fluanisone (Hypnorm, Janssen) is administered to rats, mice and rabbits. The problem can be avoided by inducing anaesthesia with the neuroleptanalgesic combination and a benzodiazepine and then maintaining anaesthesia with an infusion of an analgesic alone (e.g. fentanyl). Repeated doses of the benzodiazepine are usually required only every 4–6 hours.

A more serious side-effect can be the respiratory depression that is frequently seen following the administration of neuroleptanalgesics. This is not usually so severe as to necessitate assisted ventilation, but a moderate hypercapnia and respiratory acidosis will develop. During prolonged anaesthesia it is preferable to assist ventilation by using a mechanical ventilator.

The neuroleptanalgesic combination that has been used most extensively in rodents and rabbits is fentanyl/fluanisone (Hypnorm), together with diazepam or midazolam. The combination of fentanyl and dropiderol (Innovar-vet) differs in its effects, and is generally unsuitable when used in this way. Repeated doses of Hypnorm can be given every 20–30 minutes to maintain anaesthesia in rats, mice, rabbits and guinea pigs, following an initial dose of Hypnorm together with a benzodiazepine, although the depth of anaesthesia will fluctuate markedly. It is preferable to administer a 1:10 dilution of the drug by intravenous infusion. In other species, such as the dog and pig, a combination of fentanyl or alfentanil and midazolam can be used to provide long-lasting surgical anaesthesia (Flecknell et al., 1989; Table 4.3).

Delivery Techniques

A number of different methods can be used, varying in cost and reliability.

Burette Infusion Sets and Drip-rate Controllers

Anaesthetic can be administered using a paediatric burette (Fig. 4.3), although often the drug will need to be diluted to allow better control of the infusion rate. Paediatric burettes deliver 60 drops per millilitres so allowing greater control over



FIGURE 4.3 Infusion pump (Imed).

the infusion rate than the standard adult type apparatus. It is important to remember that this method of delivery will be very sensitive to partial occlusion of the catheter caused, for example by changing the position of the animal or by the formation of thrombi in the catheter tip. In addition, gradual movements of the drip control device will result in changes in the infusion rate. For these reasons, if simple drip sets are used for infusion of anaesthetics they must be monitored carefully and frequently. The degree of control over the infusion rate can be improved by use of a drip-rate controller, which varies the infusion rate by changing the diameter of the drip tubing. The simplest and least expensive of these are disposable devices, but greater accuracy can be achieved using electronically controlled devices which measure the flow by counting the fluid drip rate. Electronic controllers also incorporate an alarm to alert the anaesthetist to cessation of flow caused for example, by occlusion of the catheter or exhaustion of the fluid reservoir. All of these devices will fail should occlusion of the catheter occur.

Infusion Pumps

Catheter occlusion is less likely to occur when using an infusion pump, since the driving pressure generated by the pump tends to maintain catheter patency. Infusion pumps are available from a number of different manufacturers and vary considerably in their suitability for laboratory animal anaesthesia. When selecting a pump, the most important considerations are as follows:

1. Can the pump deliver a wide range of different infusion rates? Ideally, the range should extend from microlitres per hour to millilitres per minute, and

be capable of being varied in small increments – pumps that can only double or halve the rates of infusion should be avoided.

2. Can the pump accept syringes of different sizes, from a variety of different manufacturers?
3. Is the pump fitted with an occlusion alarm, a ‘syringe empty’ alarm, a ‘bubble’ detector and a power failure or low-battery alarm?
4. Is a battery backup provided in case of failure of the electrical supply or inadvertent disconnection?
5. Is the pump small, light, portable, easily cleanable and robust?
6. Is it easy to set and vary the infusion rate and are any necessary calculations carried out by the pump’s own microprocessor?
7. Is an interface provided for microcomputer control of pump operation and is appropriate software provided to simplify this control process?

Pumps can broadly be divided into those designed for clinical use in human beings and those designed for laboratory or research use. Pumps designed for clinical use normally have a full range of alarms and alerts, but may require purchase of specific disposable items for each use of the apparatus. They may also be designed to operate with a limited range of drug and fluid reservoirs that are most suited for use with larger (i.e. human-sized) subjects (Fig. 4.4). Laboratory-style pumps are often general-purpose devices that may lack many of the features found on pumps designed for clinical use, but may be very versatile in the range of infusion rates and syringe types. A number of pumps specifically designed for drug infusion are now available, and these often combine many of the desirable features listed above (Fig. 5.1).

As with other anaesthetic apparatus, it is helpful to obtain potentially suitable infusion pumps on a trial basis, to ensure that they have all of the features required, and prove reliable during routine operation.

Whichever method of infusion is used, initial adjustments to the infusion rate will be required after induction of anaesthesia, but once experience has been gained with a particular anaesthetic technique, stable infusion rates and depth of anaesthesia can be established relatively rapidly. Initially the infusion rate should be based on the pharmacokinetics of the anaesthetics used, although it must be appreciated that even when full details of these have been published for a particular species, considerable between-animal variability will occur. Nevertheless, if the drug has been well-characterized, then the required infusion rate can be estimated from its volume of distribution (the theoretical space in the body available to contain the drug) and its rate constants (Mather, 1983).

A simple analogy may be helpful to those unfamiliar with pharmacokinetics. If a particular concentration of dye is needed in a sink filled with water, the concentration of dye needed to be added is equal to the volume of water in the sink multiplied by the target concentration. If the sink’s taps are turned on, and the plug is pulled out, then the situation becomes more complicated. In these circumstances, dye must be added continuously to maintain the desired concentration. If



FIGURE 4.4 Laboratory-style infusion pump.

dye is added at a constant rate, then eventually a situation will be reached where the rate at which it is removed is equal to the rate at which it is added, a situation known as ‘the steady state’. These same considerations apply to continuous intravenous infusion of anaesthetics. If anaesthetic is infused at a constant rate, eventually the rate of removal from the plasma will equal the rate of infusion. Under these circumstances:

$$\text{Maintenance infusion rate} = \text{Clearance} \times \text{Plasma concentration}$$

Unfortunately this is an oversimplification for many anaesthetics, as their kinetics are better described by more complex models than a single sink, or single compartment. Many intravenous anaesthetics are characterized by one compartment with rapid distribution and elimination, and one or more compartments with slower equilibration and elimination times. The rapid distribution compartment is often thought to represent the blood and other well-perfused tissues. Drugs with these characteristics will have a single rapid half-life, and one or more slower half-lives. These are calculated from the rate of fall of the plasma concentration after administration of a single intravenous dose of the compound. The half-life of a compound is the time taken for its plasma concentration to fall by 50%.

If the anaesthetic is infused at a constant rate, it will require 4–5 half-lives to achieve a steady state. The more usual alternative is to administer an initial loading dose to induce anaesthesia, followed by a constant infusion. The problem

with this latter technique is that if the drug's pharmacokinetics are best represented by a multicompartment system, then the plasma concentration will fall rapidly as redistribution to other compartments occurs. If additional anaesthetic is given rapidly to compensate, then dangerously high plasma levels can be attained. One method of estimating the loading dose required to achieve a steady plasma concentration rapidly has been described by Norwich (1977) as:

$$\text{Loading dose} = \text{Maintenance infusion rate} \times \frac{\text{Half-life}}{0.693}$$

The slow half-life is used with anaesthetics modelled using multicompartment systems. This method can result in high plasma concentrations, so if the required loading dose exceeds the recommended safe induction concentration, a safer approach is to multiply the maintenance rate by the half-life of the anaesthetic. This would prolong the time taken to reach a steady state, but would reduce the chance of overdose. An alternative approach is to use two infusions, an initial rapid rate followed by a slow maintenance rate, with the rates determined by the drug clearance and the half-life (Wagner, 1974; Musk et al., 2005).

If the half-life of the drug is not known, but practical experience has been gained by giving intermittent injections of the anaesthetic to maintain anaesthesia, then the total quantity of drug given in a specific time period can be used to estimate an infusion rate. It may also be possible to extrapolate half-lives of anaesthetics between species, as has been suggested for antibiotics, using the relationship of body weight 0.75 (Morris, 1995).

After establishing an infusion rate, it may be necessary to dilute the anaesthetic to provide a volume that can more easily be controlled using an infusion pump. In theory, many pumps are capable of delivering very low volumes, but the actual rates, especially when using plastic syringes, may vary, as the plunger in the syringe may not move smoothly and continuously in response to the pump. Increasing the volumes that are being infused may help provide more stable infusion rates. However, care must be taken not to infuse too much fluid, especially in smaller animals. As a general guide, infusion rates should not exceed 10–15% of the animal's blood volume each hour (i.e. <7–10 ml/kg/h).

Injectable Agents – Use of Long-acting Anaesthetics

An alternative to administering repeated doses or a continuous infusion of short-acting agents is to select an anaesthetic with a very prolonged duration of action.

Urethane

Urethane has been widely used for the production of long periods of anaesthesia in a range of laboratory species, although its mechanism of action remains uncertain (Hara and Harris, 2002). It is reported to cause minimal depression of the cardiovascular and respiratory systems (Buelke-Sam et al., 1978; Princi et al.,

2000; Janssen et al., 2004). It should be noted, however, that this cardiovascular stability is in part due to sustained sympathetic nervous system activity, associated with high circulating levels of adrenaline (epinephrine) and noradrenaline (norepinephrine) (Carruba et al., 1987). Although respiratory function is usually stable, problems of airway patency can arise, especially in small mammals and intubation and ventilation may be required (Moldestad et al., 2009). The properties and effects of urethane have been extensively reviewed elsewhere (Maggi and Meli, 1986a, b and c).

Urethane has been reported to be both mutagenic and carcinogenic (Field and Lang, 1988) and although the experimental studies on its potency are somewhat limited, it is now widely regarded as a potential hazard to staff. Before using urethane it is suggested that other anaesthetics are assessed and an alternative regime is used whenever possible. If it can be shown that the use of other anaesthetics would frustrate the purpose of the experiment and a decision is taken to use urethane, it is recommended that it be treated as a moderate carcinogen. In most institutes there will be guidelines for the safe handling of such materials and these will usually include the use of gloves and face masks when handling the substance and use of fume cupboards or similar cabinets for preparing solutions from the dry powdered drug.

If such precautions are adopted, urethane can be used in a reasonably safe manner and is a valuable anaesthetic for providing long-lasting, stable surgical anaesthesia. In view of its carcinogenic action in rodents, it seems inadvisable to allow animals to recover from urethane anaesthesia.

Although classed as a long-acting anaesthetic, urethane's duration of action can vary considerably, and it also causes peritoneal effusions when administered intraperitoneally. An alternative approach is to lightly anaesthetize the animal with a volatile anaesthetic, place an intravenous catheter and administer urethane by this route (Millar et al., 1989).

Chloralose

When prolonged anaesthesia is required and surgical interference is to be kept to a minimum, chloralose may be used. This drug is a hypnotic and has little analgesic action, although this varies considerably between different species and strains of animal and in some individuals surgical anaesthesia is produced (Luckl et al., 2008). It is usually necessary to administer a short-acting anaesthetic, such as propofol while carrying out any surgical procedures, following which chloralose can be administered to produce long-lasting, light anaesthesia. This drug is believed to be particularly valuable for studies of the cardiovascular system, since the various autonomic reflexes are well maintained (Holzgrefe et al., 1987).

Chloralose is prepared by heating the powdered drug in water at 60°C to form a 1% solution. Care must be taken to avoid boiling the drug and the solution must be cooled to 40°C before administration. Administration in propylene glycol improves solubility and is claimed to reduce problems of acidosis associated with administration of chloralose (Shukla and Shukla, 1983). A more stable

solution can also be produced using cyclodextrin (Storer et al., 1997). The onset of action following intravenous administration is about 15 minutes, so even if surgical procedures are not to be undertaken, it is preferable to administer a short-acting drug to induce anaesthesia, followed by the chloralose. The drug produces 8–10 hours of light anaesthesia in most species (see Tables 6.3–6.25 for dose rates). Chloralose is normally used only for non-recovery procedures, because of the prolonged recovery time. However, it has been used successfully for recovery procedures (Luckl et al., 2008).

In addition to the use of chloralose as the sole anaesthetic, various combinations with urethane have been described, which aim to reduce the quantity of urethane required, and provide improved analgesia in comparison to chloralose alone (Korner et al., 1968; Sharp and Hammel, 1972; Hughes et al., 1982). These combinations do not, of course, circumvent one of the main difficulties of using urethane, its classification as a carcinogen. An alternative approach is to provide additional analgesia using opioids in combination with chloralose (Rubal and Buchanan, 1986).

Inactin (Thiobutobarbital)

Inactin, a thiobarbiturate, has been widely used as a long-acting anaesthetic in rats. In this species it produces surgical anaesthesia in some strains of animal, with well-maintained systemic arterial pressure (Buelke-Sam et al., 1978). Despite near-normal arterial pressure, blood flow to specific organs may be significantly reduced, due to depressed cardiac output (Holstein-Rathlou et al., 1982; Walker et al., 1983; Rieg et al., 2004), and it should not be assumed that cardiovascular function is normal. Nevertheless, this agent can be extremely useful for producing 3–4 hours of general anaesthesia in some strains of rodents.

Use of Inhalational Agents

There is very little practical difference between administering an inhalational agent for half an hour, and for 8 hours. Once the animal has been anaesthetized, it will remain anaesthetized if supplied with an appropriate maintenance concentration of anaesthetic. After 1–2 hours, the maintenance concentration of anaesthetic can usually be reduced, and further reductions may be possible, particularly if no further surgical stimulus is given. Great care must be taken, however, if NMB agents are used, since signs of lightening of anaesthesia may be less obvious. Recovery times after prolonged periods of anaesthesia using inhalational agents may differ significantly between agents, and the predicted more rapid recovery from desflurane and sevoflurane, in comparison to isoflurane may be much more apparent (Bailey, 1997). The other advantages of sevoflurane and desflurane, of being able to rapidly alter the depth of anaesthesia, also become more significant during prolonged anaesthesia.

Although it is possible to use a volatile anaesthetic as the sole agent for prolonged anaesthesia, the undesirable side-effects of cardiovascular and respiratory

depression can be significant. The concentration of anaesthetic needed can be reduced markedly by infusion of a short-acting opioid (Criado and de Segura, 2003). Typically, reductions of 30–50% can easily be achieved. Alfentanil has been widely used for this purpose, but remifentanil is even more suitable, as it is rapidly eliminated (within a few minutes) even after several hours of continuous infusion. This characteristic makes it easy to both vary the depth of anaesthesia and produce rapid recovery. As with all opioids, some respiratory depression is produced, so the availability of assisted ventilation is recommended.

When using volatile anaesthetics for prolonged periods it is essential to select an anaesthetic breathing system with minimal dead space and resistance. It is also important to ensure that adequate supplies of compressed gas cylinders and anaesthetic agent are available (Appendix 2). It is not uncommon to exhaust four or five gas cylinders during a prolonged period of anaesthesia, particularly if the compressed gas source is also used to drive a mechanical ventilator.

Nitrous Oxide/Relaxant Anaesthesia

An alternative technique that has been claimed to produce prolonged, stable anaesthesia is the use of NMB agents in combination with nitrous oxide. This type of regime is totally unacceptable for use in animals, since it will not provide sufficient depth of anaesthesia to allow surgical procedures to be carried out humanely, or even produce loss of consciousness reliably. Confusion appears to have arisen because of the widespread use of relaxant/nitrous oxide techniques in human beings considered at high risk of anaesthetic complications. The potency of inhalational anaesthetics is commonly expressed as the MAC (see Chapter 2). In humans, the MAC value of nitrous oxide is 95% and when used alone it can produce loss of consciousness and moderate analgesia. In animals, the MAC value ranges from 150 to 220% (Steffey et al., 1974; Weiskopf and Bogetz, 1984; Tranquilli et al., 1985; Mahmoudi et al., 1989; Gonsowski and Eger, 1994) (Table 2.4). When used alone, it cannot produce sufficient analgesia for even the most superficial surgical procedure and does not even appear to produce loss of consciousness in most species. The occurrence of awareness during relaxant/nitrous oxide anaesthesia is a recognized problem in human beings (Breckenridge and Aitkenhead, 1983). In animals, the low potency of nitrous oxide will almost invariably result in awareness in animals paralysed by NMB agents. Even if surgical procedures are not carried out, this is likely to cause considerable distress to the animal.

There have been suggestions that following completion of surgery using conventional anaesthetic techniques involving NMB agents, the surgical wounds can be infiltrated with local anaesthetic, and anaesthesia continued using nitrous oxide alone. Besides the problem of awareness discussed above, the local anaesthetic agents used (lidocaine) have a short duration of action and movements at the sites of surgical incision could result in pain once the drug's effects had disappeared. For these reasons the technique is considered unacceptable by the author.

Management of Long-term Anaesthesia

As mentioned earlier, all the potential problems and adverse effects of anaesthesia assume greater importance during a prolonged period of unconsciousness. All the factors discussed in Chapter 4 should be considered, but some additional care will also be required.

Respiratory and Cardiovascular Function

Since all anaesthetics depress respiration to some extent, it is advisable to administer oxygen to all animals that are anaesthetized for prolonged periods. It is also preferable to intubate the animal's trachea and provide facilities for mechanical ventilation. Mechanical ventilation is essential if an attempt is to be made to provide stable blood gas levels during anaesthesia.

In a spontaneously breathing animal, the depression in respiration caused by anaesthesia produces a rise in PCO_2 . The rebreathing that occurs because of equipment dead space will also contribute to this rise. In most animals, this will be of relatively little clinical consequence for an hour or so, but after this period problems associated with hypercapnia and respiratory acidosis begin to develop.

One approach to control this problem is periodically to assist ventilation by manual compression of a reservoir bag or by intermittent occlusion of a T-piece. Since, during anaesthesia, respiratory drive is influenced strongly by blood oxygen tension, temporarily increasing oxygen tension by ventilating with 100% oxygen can produce a short period of apnoea. In addition, an elevation in blood carbon dioxide tension increases the release of catecholamines and these have a stimulating effect on the cardiovascular system. If carbon dioxide tensions are reduced by a short period of assisted ventilation, this can produce a fall in cardiac output. The previously elevated carbon dioxide tensions will also have produced a peripheral vasodilatation and this will persist during the period of assisted ventilation. The fall in cardiac output, coupled with the persistent vasodilatation may produce a period of hypotension. These problems are best avoided by ensuring that the animal's initial ventilation is adequate and if a minute volume is low, mechanical ventilation should be started early in the course of the anaesthetic and maintained throughout its duration.

A second problem occurring during long-term anaesthesia is caused by a buildup of bronchial secretions, which can block small airways (Moldestad et al., 2009). Use of atropine or glycopyrrolate can help to reduce the quantity of these secretions, but partial airway obstruction may still occur. A more free flow of bronchial mucus can be produced by humidifying the inspired gas mixture. Although purpose-made nebulizers are to be preferred, simply bubbling gases through a temperature-controlled water bath appears satisfactory during controlled ventilation of rats (Odom, personal communication). An alternative approach using a disposable nebulizer has been used successfully when anaesthetizing rats (Martenson et al., 2005). When anaesthetizing larger species, disposable humidifiers can be incorporated into the anaesthetic breathing system, however these

have a relatively large volume, and the increase equipment dead space precludes their use in smaller (<5 kg) animals.

During prolonged periods of anaesthesia, metabolic acidosis may gradually develop. This can only be detected by monitoring arterial blood gases and pH, and may be corrected by administration of sodium bicarbonate. Gradual fluid loss from surgical wounds, the respiratory tract and by urine formation should be replaced by continuous infusion of balanced electrolyte solutions (Hartmann's solution). During prolonged anaesthesia it is useful to monitor urine production, by catheterizing the bladder, to check on continued renal function.

Hypothermia and Fluid Balance

In addition to the problems of providing adequate ventilation, all the monitoring and management techniques described in Chapter 4 assume much greater importance. Particular attention should be given to the prevention of hypothermia, and fluid balance should be carefully monitored. Although fluid deficit is the major concern during prolonged surgery and anaesthesia, it is important to avoid fluid overload, caused by a combination of enthusiastic intravenous therapy and the infusion of large volumes of anaesthetic drugs. As a general guide, total fluid infusions of up to 10–15% of circulating volume per hour (7–10 ml/kg/h) are well tolerated by most animals.

Posture

A problem which is of considerable importance in human anaesthetic practice, but which receives little attention in laboratory animal anaesthesia is the damage that can be caused to muscles and nerves by the imposition of abnormal positions during anaesthesia. To avoid unnecessary post-operative discomfort, try to ensure that the animal is placed in as normal a posture as possible. Avoid 'tying out' the limbs and instead use positioning pads. Try to protect pressure points such as the elbow, hock and the wings of the pelvic bones. If possible, change the animal's position and massage these pressure points every 1–2 hours. The eyes should be protected, preferably by taping them shut, to avoid corneal desiccation. The addition of a bland ophthalmic ointment (e.g. 'Visco-Tears', Ciba Vision or 'Lacri-lube', Allergan) is also of use and this has the advantage of providing some protection during post-operative recovery. The mouth, nose and pharynx can become blocked with viscous secretions and these should be removed using gentle suction before the animal is allowed to recover.

ANAESTHESIA OF PREGNANT ANIMALS

Pregnant animals require special care when anaesthetized. Consideration must be given both to the adverse effects of anaesthesia on the mother and also its effects on the fetus(es). The increasing size of the fetuses in the last third of pregnancy leads to an increase in abdominal pressure and consequent interference with

respiratory movements. This may be of minimal importance under normal circumstances, but may be of considerable significance when the mother is placed in an abnormal posture during anaesthesia. The pressure of the uterine contents on the abdominal blood vessels may also interfere with venous return.

To minimize these problems, care should be taken to avoid maintaining the animal in dorsal recumbency. Wherever possible, position the animal so that it is lying on one side. It may be advisable to carry out endotracheal intubation and assist ventilation, particularly during the last third of pregnancy. Good anaesthetic practice, such as providing oxygen by face mask to the animal before induction assumes greater importance, but care must also be taken to reduce stress. Pregnant animals should not be fasted before inducing anaesthesia, as this can have adverse metabolic effects both on mother and fetus. The fetus is extremely sensitive to changes in maternal acid–base balance caused, for example by hypercapnia. Maternal hypotension can seriously reduce placental blood flow and cause the fetus to become hypoxic. The fetus in many species is very susceptible to hypothermia, and special care must be taken both to maintain maternal body temperature, and to keep the fetus warm if it is exteriorized.

Placental Transfer of Anaesthetics

Most commonly used anaesthetics cross the placenta. This may be advantageous in providing some degree of anaesthesia in the fetus to allow surgical procedures to be undertaken. Conversely, the drug may have serious acute or long-term effects on the fetus. If the fetus is to be delivered by Caesarean operation, residual effects of the anaesthetic drug may cause sedation, respiratory depression and cardiovascular system depression.

General Recommendations

The choice of a particular anaesthetic will depend upon the type of experimental procedures which are to be undertaken, but the following advice can be offered as a general strategy for anaesthetizing pregnant animals:

1. Use a balanced anaesthetic technique to reduce adverse effects such as hypotension in the mother and so minimize hazards to the fetus.
2. Use local and regional anaesthesia if possible, but this must be balanced against welfare considerations (see Chapter 3).
3. Carry out surgical and other techniques as rapidly as possible to reduce the duration of anaesthesia.
4. Whatever the anaesthetic technique, maintain good oxygenation of the mother and limit hypercapnia by assisting ventilation.
5. Maintain blood pressure with intravenous fluids and plasma volume expanders when necessary.
6. Monitor maternal blood glucose and correct any hypoglycaemia that may develop.

7. If the fetus is being delivered by Caesarean operation and opioid analgesics have been administered to the mother, administer naloxone to the neonate to reverse any respiratory depression caused by these agents. Irrespective of the anaesthetic used, administration of doxapram to stimulate respiration can be helpful.

Foetal Surgery

If surgical procedures are to be undertaken on the fetus, care must be taken to ensure that it is adequately anaesthetized. The stage of gestation at which the CNS is sufficiently well developed to respond to painful stimuli varies in different species and expert advice should be sought before commencing work as to the likely stage of development of the fetus.

If the fetus is sufficiently developed to respond to noxious stimuli, then these responses should be prevented by means of an appropriate anaesthetic. There has been extensive debate concerning the capacity of the fetus to experience pain (White and Woolf, 2004), and in medical anaesthetic practice much of the debate has focused on the effects of noxious stimulation of the development of the CNS, and the effects of this after birth. These considerations will often apply to foetal surgery in animal subjects. It has been suggested that awareness occurs only after the start of parturition (Mellor et al., 2005; Mellor and Diesch, 2006). Irrespective of whether this applies to all species, preventing movement responses to noxious stimuli makes surgical procedures simpler to undertake. It may also be important to reduce nociceptor activation and the foetal stress response in order to minimize the longer-term effects of such interventions (Smith et al., 2004).

The simplest approach is to anaesthetize the mother to a sufficiently deep level so that the fetus is also anaesthetized. This is most readily achieved by using a volatile general anaesthetic such as isoflurane. However, maintenance of this depth of anaesthesia may be undesirable because of possible adverse effects, such as cardiovascular system depression, on mother and fetus. A single dose of an anaesthetic administered by the intravenous route, although sufficient to produce anaesthesia in the mother, is very unlikely to produce anaesthesia in the fetus.

The most widely used alternative to deep general anaesthesia is to infiltrate the surgical site on the fetus with local anaesthetic. If carried out carefully, this technique appears suitable for procedures such as cannulation of superficial blood vessels. It is unlikely to be sufficiently effective for more major surgery such as laparotomy or thoracotomy.

If the mother and fetus are to recover from surgery, then post-operative analgesia should be provided for the mother. Providing effective pain relief can be essential in encouraging rapid return of food and water consumption and minimizing the endocrine stress response to surgery, all of which can have effects on the fetus. However, the positive effects of analgesia need to be balanced against the potential adverse effects of the analgesics on foetal development. Since many surgical procedures involving the fetus are undertaken to study normal or abnormal

development, interactions with analgesics could compromise some studies. It is important to note that the majority of studies of the interactions of analgesics (e.g. opioids or non-steroidal anti-inflammatory drugs, NSAIDs) have been undertaken to assess the likely effect of these agents in pregnant human subjects. To try to model these effects, analgesic agents are almost invariably administered at high dose rates for relatively prolonged periods (e.g. Shavit et al., 1998; Gokcimen et al., 2007; Cappon et al., 2003; Slamberova et al., 2005). As with other uses of analgesics, the potential interactions of pain, surgical stress, anaesthesia and analgesic drug administration must all be considered (see Chapter 5). In most circumstances, administration of analgesics for a limited period (12–36 hours) at normal therapeutic dose rates should have positive effects on studies on pregnant animals. This approach has been adopted by the author and colleagues with success.

If opioid analgesics are to be used, their pre-operative administration, as part of a balanced anaesthetic technique, enables reduction of the dose of anaesthetic agents. This can limit the acute adverse effects of anaesthesia, such as hypotension.

ANAESTHESIA OF NEONATES

Neonatal animals have an increased susceptibility to hypothermia and may also have poor pulmonary and circulatory function. They frequently have low energy reserves, which can lead to problems during the recovery period. In addition, any period of fasting, as a result of removal from their mother for the period of anaesthesia and recovery, can lead to rapid depletion of hepatic glycogen stores and result in hypoglycaemia. Depending on species, neonates have a reduced capacity to detoxify a wide range of drugs and hence their response to anaesthetics can differ considerably from adult animals.

When anaesthetizing neonates, it is essential to maintain body temperature using the techniques described in Chapter 4. Care must be taken to maintain good ventilation and to maintain fluid balance. In large species (dog, cat, sheep, pig) the umbilical vessels provide a convenient route for intravenous infusion.

It is preferable to use inhalational anaesthetics so that recovery is rapid and normal feeding is resumed as soon as possible. Methoxyflurane is particularly safe and effective in neonates, however this agent is now difficult to obtain, and isoflurane has been reported to be safe and effective (Danneman and Mandrell, 1997). Neonatal animals usually require higher concentrations of anaesthetic, for example young adult rats require a concentration of approximately 2% halothane for maintenance of surgical anaesthesia, whereas neonates require 2–3%.

Anaesthesia Using Hypothermia

Deliberate production of hypothermia has been used as a means of immobilizing neonatal rats and mice to enable surgical procedures to be undertaken. It is not

clear whether the technique produces anaesthesia or simply immobility although it seems likely that during the period of hypothermia the degree of depression of peripheral nervous system and CNS is sufficient to prevent the animal experiencing pain. It should be pointed out that there is considerable debate concerning the capacity of neonates to experience pain – both human and animal. In case of rodents, significant post-natal brain development occurs, and the pathways responsible for nociception and pain in adults are not fully developed (White and Wolf, 2004; Fitzgerald, 2005). Although there is disagreement about the nature of pain perception, both nociception and pain can be considered undesirable because of the effects on later development. It has been suggested that recovery from hypothermia and the return of sensation to the body may be associated with nociceptor activation and pain, based on analogy with human experiences. Recent studies in our laboratory have shown that hypothermia in neonatal rats is associated with *cfos* activation, which is presumably triggered by cooling or rewarming. It is uncertain whether the CNS is sufficiently well developed for pain perception, but since safe and effective alternatives are available, for example isoflurane (Dannemann and Mandrell, 1997), halothane, fentanyl/droperidol (Park et al., 1992) or fentanyl/fluanisone (Clowry and Flecknell, 2000), it seems advisable to avoid the use of hypothermia whenever possible until its efficacy has been established.

ANAESTHESIA FOR IMAGING

The increased use of medical imaging (functional magnetic resonance imaging, fMRI, MRI; positron emission tomography, PET) as research tools has introduced new requirements for anaesthesia. Animals need to be immobilized for image acquisition, however the anaesthetic methodology should not influence the data obtained. A further requirement is that imaging may need to be repeated at relatively frequent intervals, so that progression of physiological or pathophysiological processes can be monitored. This requires standardized anaesthetic protocols that will result in reproducible effects on the animal. An added complication is that often the animal is not easily observed during the process, access for monitoring devices may be limited and some imaging studies may require several hours of data collection from an individual animal. For some imaging modalities (e.g. MRI and fMRI), specialized monitoring equipment is required. It may also be necessary to synchronize data capture with respiratory movements, or at the very least, produce stable cardiorespiratory parameters. Finally, changes in body temperature can differentially affect brain temperature and it has been suggested that this could influence results of fMRI (Zhu et al., 2004).

Anaesthetic Techniques

A review of the literature indicates that a wide range of different agents are currently used to anaesthetize animals for imaging. In many instances these have

probably not been selected as the most appropriate for specific purposes, so it is important to review the main requirements of each study, and develop a protocol that is compatible with these (Austin et al., 2005; Steward et al., 2005).

Although mixtures of injectable agents can be used (see Chapter 6), the depth of anaesthesia produced will vary between individuals, and within individuals at successive anaesthetics. Use of continuous intravenous infusion (e.g. with propofol) or use of inhalant anaesthetics allows anaesthetic depth to be adjusted more precisely.

Intravenous agents can be delivered via an over-the-needle catheter securely fixed in a convenient vein. It may also be advisable to splint (using a plastic splint) the catheter site to avoid inadvertent kinking due to repositioning of the limbs, or the tail in rodents. Catheter extensions can be used to connect to an infusion pump, positioned a safe distance from the scanner. In some circumstances, only deep sedation may be required, and drugs such as medetomidine can be used to provide sufficient immobility for imaging (Weber et al., 2006). Medetomidine may have disadvantages, however, since it produces marked respiratory depression and has a range of metabolic effects. Its major advantage is that it is reversible with atipamezole (see Chapter 6).

Inhalational anaesthetics can be delivered either via an endotracheal tube, a nasal catheter or a specially designed face mask (Steward et al., 2005). Anaesthetic breathing systems can be extended to an anaesthetic trolley positioned a safe distance from the scanner. We have found oxygen bubble tubing ideal for providing fresh gas, and disposable paediatric ventilator tubing for the expiratory limbs of breathing systems for small animals (Fig. 5.2). When an open mask system or nasal catheter is used, gas scavenging may be necessary, but in small rodents the relatively low fresh gas flows used may be rapidly diluted and extracted by normal room ventilation. When intubated, mechanical ventilation can be carried out either using an MRI compatible ventilator positioned close to the scanner (Hedlund et al., 2000), or by extending the breathing system. It is not necessary to use NMB drugs in order to ventilate animals (see above), but they may be required to prevent small movements that could interfere with imaging. As with any use of NMBs, they should always be used in conjunction with adequate anaesthesia (e.g. Keilholz et al., 2004), and never used to immobilize conscious animals (Van Camp et al., 2003).

Monitoring Equipment and Management

Standard monitoring apparatus can be used for certain imaging modalities (e.g. PET), although there may be problems of access. Significant problems arise when undertaking MRI or fMRI. All sensors used must be compatible with high magnetic fields, and the instruments need to be positioned at a safe distance from the scanner. Pulse oximetry sensors suitable for use in high magnetic fields can be purchased (e.g. Nonin Medical, Inc., Appendix 4), and these function reliably during image acquisition. Other devices, such as some ECG leads, may be safe to use, but the signal quality degrades markedly during imaging. Extension lines

to allow invasive blood pressure monitoring and side-stream capnography can be used, but when long lines are used the signal may be damped or altered. For example, capnogram traces may fail to show a normal plateau if several metres of sample tubing are required. Nevertheless, the trends obtained from this monitoring remains of considerable value. An alternative approach is to position a compatible transducer close to the animal, although this then makes it difficult to obtain repeated arterial blood gas samples for blood gas analysis, to ensure stable conditions are being maintained. Transcutaneous gas monitoring may also be used to assess pulmonary function. This can be used to indicate trends in PaCO₂ (Stout et al., 2001; Ramos-Cabrer, 2005), and in some circumstances can correlate well with direct measures (Sahbaie et al., 2006). If the animal is not being ventilated, and capnography is not used, then respiratory movements can be monitored using simple pneumatic sensors that are compatible with the magnet.

Some specialized imaging procedures may require the animal to be placed in specific postures, for example sitting upright, which may increase the anaesthetic risk. In these circumstances careful monitoring becomes even more important.

Body temperature must be controlled, and most studies have used circulating warm water systems, although forced air warming is also suitable. MRI compatible temperature probes are available, and these should be used to monitor both the animal's core temperature, and also the skin temperature that is in contact with the heat source.

At the time of writing of this edition, the considerable increase in imaging, especially of rodents, is leading to the development of purpose-made, commercially available monitoring systems (e.g. SA Instruments Appendix 4).

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Analgesia and Post-operative Care

Successful anaesthesia requires careful attention to the entire peri-operative period. It is particularly important to provide effective post-anaesthetic care, as it is in this period that most anaesthetic-related problems occur. The recovery area environment must be appropriate for the species and the procedure involved. The continued provision of supplemental warmth, fluid and nutritional support and nursing care is often necessary. Of particular importance following surgical procedures is the continued maintenance of effective analgesia. This requires careful assessment of the animal, effort to determine if any signs of pain or discomfort are present and the selection of an appropriate analgesic regimen. The choice of analgesic regimen depends not only upon the species of animal involved and the nature, duration and intensity of the pain that might otherwise be experienced, but also upon the nature of the specific research procedure. Balancing these factors is complex. Although analgesic agents may interact with a range of physiological processes, pain itself can have numerous confounding effects on research procedures, in addition to being a major ethical and animal welfare concern.

Post-operative care must be considered a natural and essential extension of good anaesthetic practice. Failure to attend to the animal's needs during this critical period will inevitably complicate recovery from anaesthesia and is in any case inhumane. Poor post-operative care will exacerbate and prolong the metabolic disturbances caused by surgery, and if seriously neglected, the animal may die. The results of a recent survey of anaesthetic-related mortality in small animal veterinary practice has shown that the majority of deaths (> 50%) occurred in the post-operative period (Brodgelt et al., 2008). Although some risk factors will differ from those in a laboratory animal facility, these results highlight the critical importance of good post-operative care.

All animals will require some degree of additional attention in the post-operative period, and this is usually best achieved by providing a special recovery area. This will simplify the provision of the most appropriate environmental conditions, which will frequently differ from those present in a normal animal holding room. It will also highlight the special needs of animals placed in the recovery area and encourage extra attention from animal husbandry and nursing staff.

THE RECOVERY ROOM ENVIRONMENT

The recovery area for most laboratory mammals should be warm and quiet. Lighting should be subdued but adequate to allow easy observation of the animal. Higher intensity lighting must be readily available to enable more detailed examination and to allow procedures such as intravenous injection. In the immediate post-operative period, when homoeothermic responses are depressed and the animal is still recovering from anaesthesia, the ambient temperature should be 27–30 °C for adult animals and 35–37 °C for neonates. Once the animal has recovered from the major depressant effects of the anaesthetic, the temperature can be reduced to 25 °C for adults, but should be maintained at 35 °C for neonates. This gradation in temperature can be achieved by maintaining a general room temperature of 21–25 °C and providing supplemental heating using warming lamps or heating pads. Ideally, an animal incubator should be used: this will allow careful control of the ambient temperature and enable easy administration of oxygen. Unfortunately, many commercially available incubators do not maintain stable temperatures. This is less of a problem with larger animals (<2 kg) but can result in transient hypothermia in small rodents. If available, paediatric incubators designed for use in human neonates provide excellent conditions for small rodents. These incubators are often available when being replaced by hospitals with new models. One practical point to note is that most of these infant incubators have a gap around the inner tray to allow air circulation, so small rodents need to be confined in an inner cage. Stable temperatures can also be provided using forced air warming systems placed around a standard rodent cage (Rembert et al., 2004).

Although hypothermia is a potentially serious problem in the post-operative period, care must be taken not to overheat the animal, and both the animal's rectal temperature and the temperature of its immediate environment should be carefully monitored. In small experimental units, it may be impracticable to allocate space permanently for use as a recovery room. This should not lead to the concept being abandoned, as a temporary area within a laboratory can be set aside for this purpose. This can most easily be achieved by equipping a suitably sized trolley with an animal incubator and other necessary equipment. This can then be moved around the unit to wherever it is required.

Caging and Bedding

In most instances, small animals can be allowed to recover in their normal cages, placed either in a recovery room or inside an incubator. Small rodents and rabbits should not be allowed to recover from anaesthesia in cages that contain sawdust or wood shavings as bedding. This type of bedding will often stick to the animal's eyes, nose and mouth and so should be replaced by more suitable materials. A synthetic bedding with a texture similar to sheepskin (fleece) has proven particularly useful for all animal species and can be obtained from a number of different suppliers ('Vet-Bed', 'Dry-Bed'). It is washable, autoclavable and

extremely durable and appears to provide a comfortable surface for the animal. If such material is unavailable, towelling or a blanket should be used. Tissue paper is often provided as bedding for small rodents, but it is relatively ineffective as animals usually push it aside during recovery from anaesthesia and end up lying on the bottom of a plastic cage, soiled with urine and faeces. Shredded paper of a type that will not stick to the animals' orifices or wounds should be used, since it provides a warm and comfortable nesting material (e.g. 'paper shavings', RS Biotech, Appendix 4). Rabbits and guinea pigs should not be placed in grid-bottomed cages to recover from anaesthesia, but should be placed either directly in an incubator or in a temporary plastic or cardboard holding box.

Nursing Care

The response to human contact varies considerably among different animal species and is influenced by previous experiences. Excessive contact may have adverse, stressful effects in some small rodents and rabbits, but most animals will benefit from some degree of nursing care carried out in a calm and reassuring manner. The degree of alarm caused to the animal can be reduced if it has been gradually familiarized to regular handling in the pre-operative period. This process forms an important part of pre-operative acclimatization in all species (see Chapter 1) and should be considered essential when planning any series of experiments.

Most cats, dogs and many pigs will respond positively to stroking or scratching and to a reassuring, familiar voice. If the recovery period is prolonged and the normal grooming activity not resumed, some animals, particularly dogs and cats, may respond favourably to regular grooming by nursing staff. Time should be provided to encourage any dogs and cats that are reluctant to eat following surgery. Most can be tempted by hand feeding. Warming the food will often make it more appetizing. Very often, the presence of a familiar staff member to encourage eating will greatly affect the animal's appetite. Similar techniques can also be useful in pigs, provided they have been properly familiarized to human contact in the pre-operative period.

All species, including rodents and rabbits, should be checked at least once a day. In the immediate post-operative period, constant attention may be needed, followed by observation every 1–4 hours for the first 8–12 hours. Particular attention should be given to cleaning the eyes, nose and mouth, which can become clogged with dried mucus or other debris. Monitoring of body weight and checking of wounds and surgical implants are also an important part of post-operative care. Rodents may be offered food pellets softened with warm water in bowls placed on the cage bottom, as many may be reluctant to reach up to food hoppers at this time.

It is important that a daily routine is followed as far as possible. It will be an advantage if some staff are assigned to the care of post-surgical animals throughout the peri-operative period, as they are more likely to notice any slight changes that may take place on a day-to-day basis. Careful record keeping is essential, so that other staff attending the animal, for example, for out-of-hour emergencies,

will be aware of all treatments given and the animal's progress. It is important to record not only all active interventions, but also that the animal has been examined and found to be progressing satisfactorily.

PROBLEMS DURING THE RECOVERY PERIOD

Vomiting, Regurgitation and Hypostatic Pneumonia

The swallowing and cough reflexes are usually suppressed during anaesthesia, and these gradually return as the animal recovers consciousness. If an endotracheal tube is present, it should be removed when the animal begins to swallow spontaneously or attempts to cough. If the tube has been tied in position, the ties should be loosened in anticipation of the need to remove the tube. Care must be taken that the tube is not pulled out too soon, for example, when the animal is repositioned as surgical drapes are removed. The mouth should be inspected and any secretions removed using suction. Most anaesthetists deflate the endotracheal tube cuff before removal. During this initial recovery period, drapes and surgical equipment should be removed, together with any non-essential monitoring devices. This will allow the animal to be moved rapidly to a more comfortable environment if it regained consciousness more rapidly than expected.

Non-ruminant species should be placed on their sides, with head and neck extended, to try to minimize the risk of airway obstruction. If the animal is recumbent for more than 4 hours, then it should be repositioned to lie on its other side, to prevent passive congestion of the lungs and the development of hypostatic pneumonia. In large animals such as dogs and farm animals, it may be necessary to massage areas such as the elbow and hock, to prevent pressure sores developing. If prolonged recumbency is anticipated, it may be advisable to protect these areas with padded bandages.

If the animal begins to vomit, an attempt should be made to position it so that its head is below the level of the thorax and abdomen, to try to prevent aspiration of the vomit. If practicable, the mouth and pharynx should be cleared using a vacuum suction, or a piece of suitably sized tubing attached to a 50-ml syringe. Oxygen should be administered, and if inhalation of vomit is believed to have occurred, corticosteroids should be administered (30mg/kg iv of methyl prednisone), together with a broad-spectrum antibiotic.

Ruminants (sheep, goats and cattle) can present particular problems during recovery from anaesthesia. They should be propped up on their sternums to minimize the risk of over-distension of the rumen with gas (rumenal tympany) and the risk of inhalation of regurgitated rumen contents. If rumenal tympany develops, it should be relieved immediately either by passing a stomach tube or by puncturing the rumen through the left abdominal wall with a large-bore trochar. If a trochar is not available, the largest possible needle (preferably 12 SWG or larger) should be used. If the member of staff involved is not familiar with this technique, veterinary advice should be sought immediately.

Respiratory Depression

The respiratory depression produced by most anaesthetic agents frequently persists into the post-operative period. The degree of depression may also increase post-operatively, and this may go unnoticed until severe hypercapnia and hypoxia have developed. It is preferable to continue monitoring the respiratory system, and the use of a pulse oximeter is ideal for this purpose in larger species (see chapter 3). If not already in use, the probe can be attached to the animal in the operating theatre and a battery-operated instrument used to monitor the animal during movement to the recovery area. The probe can be left taped in place on the tail or on a digit until the animal has regained its righting reflex. If a pulse oximeter is unavailable, then other forms of respiratory monitor can be used, for example, positioning a sensor close to the animal's nose. At the very least, regular clinical observation of the animal should be made and the respiratory rate recorded. If respiratory depression is noted, it should be treated using a respiratory stimulant such as doxapram and by the administration of oxygen. Since doxapram has a relatively short duration of action (10–15 minutes), it may be necessary to administer repeated doses or to establish a continuous infusion of the drug.

Many animals appear to benefit if oxygen administration is continued into the immediate post-operative period. This is best achieved in small animals by piping the gas into an animal incubator, but in large animals, it is often more practicable to tape a small, soft-ended catheter at the external nares and use this to administer the gas. If oxygen is not to be provided, it is reassuring if oxygen saturation can be monitored for several minutes after the animal commences breathing room air, to ensure that saturations above 85–90% are maintained.

Fluid Therapy

The voluntary water intake of all animals should be recorded post-operatively, even if this consists simply of making a rough estimate based on the level in a water bottle. Fluid intake is frequently reduced post-operatively, and if dehydration is allowed to develop, it can seriously compromise the recovery of the animal. Fluid requirements of most species are approximately 40–80 ml/kg/24 h, but the presence of vomiting or diarrhoea or other abnormal losses will increase this requirement.

If the animal is fully conscious, supplemental fluid is best given by the oral route. If the animal is unable or unwilling to accept oral administration, then dextrose–saline (4% Dextrose, 0.18% Saline) or saline (0.9%) can be given quickly and easily by the subcutaneous or intraperitoneal routes (Fig. 5.1, Table 5.1). Severe dehydration causes loss of skin tone that causes it to tent and tend to remain elevated when a fold is twisted between the fingers. In larger animals, dehydration will result in the mucous membranes becoming dry to the touch. If this degree of dehydration has inadvertently been allowed to develop, fluids must be administered intravenously. If the animal is severely depressed, then it



FIGURE 5.1 Administration of subcutaneous fluids to a rat.

TABLE 5.1 Approximate Volumes for Fluid Replacement Therapy by Intraperitoneal or Subcutaneous Administration.

	Subcutaneous (ml)	Intraperitoneal (ml)
Cat (3 kg)	50	50–100
Gerbil (60 g)	1–2	2–3
Guinea pig (1 kg)	10–20	20
Hamster (100 g)	3	3
Marmoset (500 g)	5–10	10–15
Mouse (30 g)	1–2	2
Rabbit (3 kg)	30–50	50
Rat (200 g)	5	5

may not interfere with the intravenous line; however, as the beneficial effects of rehydration occur, it will become more active. Various bandaging and splinting techniques can be used (Fig. 5.2), and Elizabethan collars (Fig. 5.3) can be used in rats, rabbits, dogs and cats to prevent interference with catheter sites. These bandages and collars may interfere with the animals' normal activities, and may delay resumption of voluntary food and water intake. They also prevent coprophagy in rats and rabbits, and may cause significant distress to some

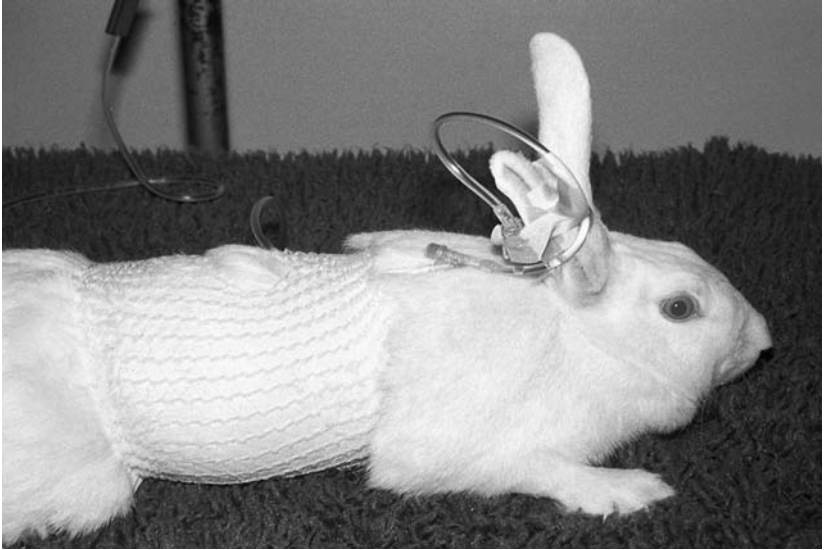


FIGURE 5.2 Stockinette bandage used to secure an intravenous line (placed in the peripheral ear vein).



FIGURE 5.3 Elizabethan collar placement in the rabbit.

individuals. It is therefore important to monitor the animals closely, to ensure the benefits outweigh possible problems.

If peripheral vessels are too constricted to catheterize, the intraosseous route can be used in small mammals. A hypodermic needle can be inserted into the proximal end of the femur or tibia, in the same manner as when taking a bone marrow biopsy or performing a marrow transplant (Zehnder, 2008). If the animal is severely depressed, this can be performed under local anaesthesia; otherwise, a light general anaesthetic using an agent such as isoflurane is required.

The monitoring of body weight in the pre- and post-operative periods can provide a good indication of the adequacy of fluid intake. Although a small fall in body weight will be recorded because of the almost inevitable reduction in food intake that occurs post-operatively, most weight loss represents a fluid deficit.

Besides assessing food and water intake, the urinary and faecal output of the animal should be recorded and any abnormalities investigated. As with most of these variables, a meaningful judgement can only be made if the animal has been observed in the pre-operative period. A reduction in urine output may be the result of dehydration, urinary tract injury, or the animal suffering pain. If the bladder is full, it may require catheterization to empty it. This is a relatively simple technique, but requires some degree of expertise, and it will usually be preferable to consult a veterinary surgeon or experienced animal technician. If catheterization is not possible, it may prove necessary to drain the bladder by direct puncture through the body wall. This procedure should only be attempted by individuals who have undergone training in the technique. Catheterization of most laboratory species requires induction of a brief period of general anaesthesia, or heavy sedation.

Food Intake and Bowel Function

If the animal fails to pass faeces, this may be due simply to an absence of faecal material because of pre-operative fasting. It may also be caused by a paralytic ileus (see below), or the animal may be constipated and require administration of an enema (e.g. Microlax, SmithKline Beecham). Defaecation may also be suppressed if the animal is in pain, particularly following a laparotomy.

Ileus (gut stasis) can be a serious post-operative complication, and can be life-threatening in rabbits and guinea pigs. Ileus is particularly common after laparotomy, but can also occur after any surgical procedure. The incidence of ileus following abdominal surgery can be reduced by reducing handling of the bowel to a minimum. When displacing and handling the viscera is unavoidable, ensure they are kept moist and handled gently. Pigs seem particularly sensitive to handling of the intestines, and we have found 'bowel bags' designed for use in humans to protect the intestines during surgery to be of great value.

If ileus is suspected, then motility stimulants (metaclopramide and cisapride) can be administered to stimulate gut function. In rabbits, ranitidine (2–5 mg/kg by mouth, daily) has been used for managing post-operative inappetence and gut stasis

as it promotes gut motility (Kounenis et al., 1992). Pain must be controlled, since this can increase the severity of ileus. The surgical notes should be reviewed to check that a swab was not inadvertently left in the abdomen.

In some species (e.g. rabbits and guinea pigs), inappetence due to other causes can lead to the development of ileus, since normal gut function appears to depend to some extent on regular intake of fibre. Supplemental feeding, using nasogastric tubes if necessary, may be beneficial. A range of specialist dietary preparations are now available for veterinary use in companion species, and these can be of considerable benefit in laboratory animals.

It is important that food and water intake and the other observations described above are recorded carefully. It is helpful to provide a standard record card for each animal, which will encourage nursing staff to complete the required observations. It will also allow easy and rapid reference by staff who may be called in to deal with any problems that might arise. It is always preferable to obtain measures of pre-operative body weight and, if possible, of food and water consumption, so that the progress of an animal can be assessed accurately in the post-operative period.

Prevention of Wound Infection

Provided careful aseptic surgical techniques have been employed, it may be considered unnecessary to administer antibiotics routinely to animals in the post-operative period. In addition, some species appear to show a remarkable resistance to the development of wound sepsis and appear to tolerate standards of cleanliness that would be totally unacceptable in human medical practice. This apparent resistance to infection must not be used as an excuse for poor surgical standards, and every effort should be made to adopt aseptic techniques for all animal surgical procedures. It has been demonstrated, for example, that rats are not only susceptible to infection but also show behavioural changes following the establishment of wound infections (Bradfield et al., 1992). It is therefore important that all animal species should be monitored carefully for any signs of infection (Morris, 1995).

Since animals will almost inevitably soil their wounds with faeces and urine, administration of prophylactic antibiotics may be useful in minimizing the risk of infection. One problem of providing peri-operative treatment with antibacterials is the risk of inducing enterotoxaemia in some species, particularly the guinea pig, hamster and rabbit. The use of antibacterial agents in rodents and rabbits has been reviewed by Morris (1995), and provided care is taken in the choice of agent, such problems can be avoided. Suggested dose rates of antibiotics for each species are given in Tables 5.2 and 5.3.

MANAGEMENT OF POST-OPERATIVE PAIN

Pain in laboratory animals is a major animal welfare problem that must be addressed if we are to apply Russell and Burch's principle of refinement (1959) – 'to reduce

TABLE 5.2 Antibiotic and Antibacterial Drug Doses for Laboratory Animals.

	Mouse	Rat	Hamster	Gerbil	Guinea pig	Rabbit
Cephalexin	15 mg/kg im b.i.d.	15 mg/kg sc b.i.d.	–	25 mg/kg sc u.i.d.	15 mg/kg sc b.i.d.	15 mg/kg sc b.i.d.
Chloramphenicol	50 mg/kg sc b.i.d.	10 mg/kg im b.i.d.	30 mg/kg sc b.i.d.	30 mg/kg sc b.i.d.	20 mg/kg im b.i.d.	15 mg/kg im b.i.d.
Enrofloxacin	10 mg/kg sc b.i.d.	10 mg/kg sc b.i.d.	10 mg/kg sc b.i.d.	10 mg/kg sc b.i.d.	5–10 mg/ kg sc b.i.d.	5–10 mg/kg sc b.i.d.
Neomycin	2 mg/ml in drinking water	2 mg/ ml in drinking water	250 mg/kg per os in divided doses	100 mg/kg per os in divided doses	5 mg/kg per os b.i.d.	0.2–0.8 mg/ ml in drinking water
Co-trimazine 40/200	30–50 mg/ kg sc b.i.d.	30–50 mg/ kg sc b.i.d.	30 mg/kg sc b.i.d.	30 mg/kg sc b.i.d.	30–50 mg/ kg sc b.i.d.	30–50 mg/ kg sc b.i.d.
Tylosin	–	10 mg/kg sc u.i.d.	10 mg/kg sc u.i.d.	10 mg/kg sc u.i.d.	–	–

Note that the majority of these doses are based solely on clinical experience, since only limited pharmacokinetic data are available for these species (with the exception of enrofloxacin). Before administering any of these compounds, research workers are strongly advised to consult their laboratory animal veterinarian for advice on drug selection and the duration of treatment. For a comprehensive review of the effects of antibiotics in laboratory species, see Morris (1995).

to an absolute minimum the pain and distress experienced by those animals that are used' (in research procedures). In order to provide effective analgesia, it is essential that we have a good knowledge and understanding of animal pain. We need to know when pain might occur and how long it might last, and assess how well it responds to therapy. We also need to consider the advantages and the disadvantages of the various methods of managing pain, and how we can best apply these in different situations. If we are to manage pain relief optimally, and monitor the effects of our therapy, then we will need to recognize the presence of pain and assess its severity. When developing our understanding of this area, we will also need some information about the basic mechanisms involved in pain perception. More fundamentally, we need to be certain that pain occurs in animals – that it can result in suffering, in a similar way to pain in humans – and so need to become convinced that its avoidance and alleviation need to be given a high priority.

Despite the emphasis given to humane treatment of laboratory animals in the national legislation of many countries, analgesics may still not be administered routinely in the post-operative period. This omission is particularly common when the animals concerned are small rodents (Richardson and Flecknell, 2005; Coulter et al., 2009). When analgesics are administered, assessment of their

TABLE 5.3 Antibiotic and Antibacterial Drug Doses for Laboratory Animals.

	Ferret	Cat	Dog	Pig	Sheep	Primate
Amoxycillin	7 mg/kg sc u.i.d.	7 mg/kg sc u.i.d.	7 mg/kg sc u.i.d.	7 mg/kg im u.i.d.	7 mg/kg im u.i.d.	7 mg/kg sc u.i.d.
Cephalexin	10 mg/kg sc u.i.d.	10 mg/kg sc u.i.d.	10 mg/kg sc u.i.d.	10 mg/kg im u.i.d.	10 mg/kg im u.i.d.	10 mg/kg im b.i.d.
Chloramphenicol	25 mg/kg sc u.i.d.	25 mg/kg sc u.i.d.	50 mg/kg sc u.i.d.	11 mg/kg im u.i.d.	–	20 mg/kg im b.i.d.
Enrofloxacin	5–10 mg/kg sc b.i.d.	5 mg/kg sc u.i.d.	5 mg/kg sc u.i.d.	2.5 mg/kg sc u.i.d.	–	5 mg/kg sc b.i.d.
Neomycin	10 mg/kg per os u.i.d. in divided doses	10 mg/ml per os u.i.d. in divided doses	10 mg/kg per os u.i.d. in divided doses	11 mg/kg per os b.i.d.	11 mg/kg per os b.i.d.	10 mg/kg per os b.i.d.
Trimethoprim/ sulphonamide	15–30 mg/ kg sc b.i.d.	30 mg/kg sc u.i.d.	30 mg/kg sc u.i.d.	15–24 mg/ kg im u.i.d.	15–24 mg/ kg im u.i.d.	30 mg/kg sc u.i.d.

Note that the majority of these doses are based solely on clinical experience, since pharmacokinetic data are not available for these species. Before administering any of these compounds, research workers are strongly advised to consult their laboratory animal veterinarian for advice on drug selection and the duration of treatment. For a comprehensive review of the effects of antibiotics in laboratory species, see Morris (1995).

efficacy is usually based on highly subjective criteria. The lack of an objective means of pain assessment may account in part for the relatively infrequent use of analgesics in animals, in comparison to their use in human beings. This is not meant to imply that research workers, veterinary surgeons and others involved in animal care are incapable of recognizing that an animal is in pain, but preconceptions about animal pain may limit the value of any assessment of its severity (see ‘Pain Assessment’ below).

Pain in humans is defined as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage’ (IASP, 1979)

So pain in humans is a sensory and psychological experience with several aspects:

- Sensory discriminative – where the pain is, how intense it is, what type it is and when it occurs.
- Affective and emotional – the ‘feeling’ of pain, which is unpleasant and distressing.
- Cognitive – people can think about what their pain means to them and what it could indicate (Am I having a heart attack? Do I have cancer?), and this can change the intensity of pain and their need for analgesics.

All of these aspects of pain can cause behavioural reactions.

The experience of pain is largely subjective, so different people will respond to similar sources of pain differently, have differing experiences and require different treatments. It seems likely that the subjective experience of pain in animals will differ from that in humans, and that different species of animals will experience pain in different ways. In order to accept that animals can experience pain, we have to accept that animals have a conscious awareness of their emotional states – in other words, that they have ‘feelings’ (Duncan, 1996).

This remains a controversial topic. We can demonstrate relatively easily that animals can experience the sensory components of pain – they have very similar mechanisms for detecting damaging or potentially damaging stimuli (with nociceptors), and this information is transmitted to spinal and higher brain centres in similar ways in animals and humans (Livingston and Chambers, 2000; Vinuela-Fernandez et al., 2007). However, the demonstration of equivalent anatomical structures and physiological processes does not provide conclusive evidence that both the sensory and emotional components of the experience of pain are similar in animals and humans. It is possible that the relative significance, magnitude and duration of pain in response to particular types of injury may all vary in animals. Whether animals possess the same, or a similar capacity as humans, to experience emotions such as pain has been extensively debated for centuries. The main reason for the continued debate is that it is impossible to investigate such emotional states directly – we can only draw inferences from other, indirect, measures, such as investigation of behavioural responses. Some philosophers and scientists have firmly asserted that animals cannot experience pain (Bermond, 1997, 2001) but only respond to noxious stimuli, without being consciously aware. Others argue in support of the presence of emotional states such as pain (see for example Duncan, 1996; Panksepp, 2005; Weary et al., 2006). This uncertainty regarding animal pain is similar to that relating to pain in human neonates, a debate that still generates controversy especially in relation to pre-term infants (Bowsher, 2006; Bartocci et al., 2006). The inferences drawn from neuroanatomy, neurophysiology and behaviour that have been used to argue for the capacity to experience pain in neonatal humans (Simons and Tibboel, 2006) have clear parallels in the debate relating to animal pain.

Since pain is a subjective experience, it is doubtful that we will ever be able to demonstrate its presence in animals conclusively, but the growing body of evidence supporting conscious emotional states suggests it is preferable to assume a capacity for pain in animals. Certainly, most members of the public have no hesitation in stating that animals experience pain. On reflection, many would agree that the experience might not be exactly the same as the pain they might experience themselves, but nevertheless would have no doubt that it was ‘pain’. This view is reflected in the legislation that controls our treatment of animals.

Irrespective of whether animals experience pain or simply respond to nociceptor activation, this process results in major physiological and pathophysiological changes. Consequently, pain or nociception will represent a source of uncontrolled variation in research and may introduce specific confounding factors in

some studies. We can therefore advocate the control or elimination of both pain and nociception on both scientific and welfare grounds (ILAR, 2009).

Although we would wish to alleviate pain either because of concerns for animal welfare or to reduce a potential confounding factor in a research project, a number of counter-arguments have been advanced to justify withholding analgesics.

- ‘Alleviation of post-operative pain will result in the animal injuring itself’

Pain has a protective function and is of value in warning of tissue damage in an individual. Pain arising from injured tissues often results in the animal or human immobilizing the affected area that helps to prevent further injury. Nevertheless, pain is also harmful since the immobility and muscle spasm it produces can cause muscle wasting and weakness. Thoracic and abdominal pain may reduce ventilation and cause hypoxia and hypercapnia. Pain may also cause a marked reduction in food and water consumption (Liles and Flecknell, 1993a, b). Pain in humans has been shown to prolong the metabolic response to surgery (Kehlet, 1978), to increase the requirement for hospital care following operative procedures (Alexander and Hill, 1987) and to have a range of other detrimental effects (Breivik, 1994).

Provided that surgery has been carried out competently, administration of analgesics, which allow resumption of normal activity, rarely results in problems associated with the removal of pain’s protective function. Claims that analgesic administration results in skin suture removal are unsubstantiated, and contrary to findings in our laboratory. In certain circumstances, for example, after major orthopaedic surgery, additional measures to protect and support the operative site may be required, but this is preferable to allowing an animal to experience unrelieved pain. All that is required in these circumstances is to temporarily reduce the animal’s cage or pen size, or to provide additional external fixation or support for the wound. It must be emphasized that these measures are very rarely necessary, and in our institute, administration of analgesics to laboratory animals after a wide variety of surgical procedures has not resulted in any adverse clinical effects.

- ‘Analgesic drugs have undesirable side-effects such as respiratory depression’

In human clinical practice, analgesic drugs were frequently withheld because of fears of their undesirable side-effects such as respiratory depression and addiction (Smith, 1984). This attitude has changed significantly (Bonnet and Marret, 2007). It is also important to note that the side-effects of opioids, such as respiratory depression in animals, are generally less marked than in humans and should rarely be a significant consideration when planning a post-operative care regimen. It is important to consider the potential interactions between analgesic therapy and research protocols, and this is discussed in more detail below.

- ‘We do not know the appropriate dose rates and dosage regimens’

Another factor that may limit the use of analgesic drugs is a lack of knowledge of appropriate dose rates and dosage regimens. This is primarily a problem of poor

dissemination of existing information. Virtually every available analgesic drug has undergone extensive testing in animals. Safe dose rates are therefore available for a range of drugs in several common laboratory species (Flecknell, 1984; Liles and Flecknell, 1992; Flecknell and Waterman-Pearson, 2000). The main problem that we currently face is extrapolating available dose rates from one species to another and translating dose rates that are effective in anti-nociceptive tests into those that are appropriate for clinical use. Nevertheless, in many instances, a reasonable guide as to a suitable, and safe, dose rate can be obtained.

- ‘Pain-relieving drugs might adversely affect the results of an experiment’

It is clear that some research scientists are reluctant to administer pain-relieving drugs because their use might adversely affect the results of an experiment. Although there will be occasions when the use of one or other type of analgesic is contra-indicated, it is extremely unlikely that there will be no suitable analgesic that could be administered. More usually, the reluctance to administer analgesics is based upon the misconceived idea that the use of any additional medication in an experimental animal is undesirable. The influence of analgesic administration in a research protocol should be considered in the context of the overall response of the animal to anaesthesia and surgery. As discussed in Chapter 2, the responses to surgical stress may overshadow any possible adverse interactions associated with analgesic administration. An additional consideration is that many arrangements for intra-operative care fail to control variables such as body temperature, respiratory function and blood pressure. It seems illogical to assume that changes in the function of the cardiovascular or respiratory systems are unimportant, but that administration of an analgesic will be of overriding significance. It should be considered an ethical responsibility of a research worker to provide a reasoned, scientific justification if analgesic drugs are to be withheld. It is also important to realize that the presence of pain can produce a range of undesirable physiological changes, which may radically alter the rate of recovery from surgical procedures (Keeri-Szanto, 1983). In animals, post-surgical pain can reduce food and water consumption, interfere with normal respiration (for example, after thoracotomy) and reduce a whole range of ‘self-maintenance’ behaviours. The immobility caused by pain can lead to muscle spasm, can cause atrophy of areas and can slow healing. Prolonged immobility can also cause pressure sores, urine scalding and faeces soiling and can greatly complicate animal care routines.

Finally, there may be legal constraints concerning analgesic use that can restrict their administration. In many countries, the use of the majority of opioids is controlled by legislation (e.g. the Misuse of Drugs Act in the UK). Complying with this legislation often requires careful record keeping of the purchase, storage and dispensing of opioids and may restrict the persons who are able to dispense and administer these substances. In some countries, the degree of record keeping required can act as a strong disincentive to the use of these analgesics in animals. Legislative control, together with genuine safety concerns, may also limit the dispensing of this class of analgesics for use by investigators or technicians. These issues can be addressed by the use of non-opioid analgesics when

these would be appropriate, and by evolving systems of prescribing and supply that make it easier to meet legislative requirements.

PAIN ASSESSMENT

The approach to animal pain based on comparative biology, outlined at the start of this section, leads naturally to the assumption that conditions which would cause pain in humans would also lead to the production of pain in animals. When examining such animals, we interpret certain clinical signs as suggesting the presence of pain. Following a surgical procedure, a dog might howl or whimper, perhaps guarding the surgical wound, and show signs of avoidance or aggression when the area is handled. These types of behaviour are easy to equate with the behaviour of humans in pain, so we readily diagnose animals showing these clinical signs as being in pain and may then give analgesics. Unfortunately, this anthropomorphic view of pain is flawed. Many animals do not respond to conditions and procedures that would cause pain in humans in a way that is immediately apparent as pain-related behaviour. For example, to an untrained observer, rats do not appear to show obvious signs of pain following routine laparotomy. This is an apparent contradiction of the previous hypothesis based on comparative biology – human patients do experience significant pain after abdominal surgery, most complain about their pain and most require opioids or other forms of analgesia. This discrepancy between the apparent behaviour of animals and the behaviour which would be predicted from human experience gives rise to the view that, although pain may occur in animals, it is less severe than that in humans. It also leads to the assumption that the more resilient nature of animals results in more rapid recovery with less experience of pain. The natural consequence of this is to assume that animals do not require analgesics as frequently as human beings, and perhaps may not even require them at all. The key to introducing effective pain control is therefore to improve our methods of pain recognition and assessment. For example, in the laparotomy example mentioned earlier, if the animal is observed closely and its behaviour analyzed carefully, then more subtle changes become apparent (Roughan and Flecknell, 2001). These changes may be normalized by administration of an analgesic, and this supports the view that they may be related to the presence of post-operative pain.

Pain assessment is important not simply because it would encourage greater use of analgesics, but because it would also encourage more appropriate use of these drugs. In many animal research units, national legislation requires that pain is assessed based on the assumption that procedures which are painful in humans will be equally painful in animals. Following a surgical procedure, it is therefore assumed that an analgesic will be required. The choice of analgesic should be determined in some part by the degree of pain that is present, since inappropriate use of potent analgesics may lead to the undesirable side-effects of these agents outweighing any benefits arising from alleviation of pain (Blaha and Leon, 2008). Similarly, the use of low-potency agents in circumstances in which

severe pain is present will result in insufficient pain relief. Simply assuming that after identical surgical procedures, the degree of pain present in all animal species and in humans will be identical is highly unlikely to be correct. Even if this broad comparison were possible, it would also be necessary to assume that the duration of pain, and hence requirement for pain relief, was identical in all animal species and humans in equivalent circumstances. It also fails to account for individual variation in response to analgesics. Following identical surgical procedures, different human patients can have markedly different analgesic requirements (Alexander and Hill, 1987). This has become clearly apparent with the introduction of patient-controlled analgesia, which removed some of the obstacles to analgesic administration (Skues et al., 1993). Although equivalent data in laboratory animals are limited, data from analgesiometry in research animals show similar variation among individuals (Cowan et al., 1977a, b), and both age and sex have been shown to influence the responses to analgesics (Frommel and Joye, 1964; Kest et al., 2000). Major variations in the behavioural and endocrine responses to surgery have been reported in mice (Wright-Williams et al., 2007), and similar changes in nociceptive thresholds occur (Mogil et al., 1999, 2006). Different strains of rats also differ in their responses to different analgesics (Morgan et al., 1999). Selection of an arbitrary dose of analgesic will therefore almost certainly lead to overdosage of some animals, and provision of inadequate analgesia for others. Development of reliable methods of pain assessment would enable analgesic treatment to be tailored to suit the needs of each individual animal.

Methods of Assessing Animal Pain

Assessment of Acute Pain Responses – Anti-nociceptive Tests

During drug development programs, an acute noxious stimulus is often used to determine the efficacy of different analgesics. The majority of these investigations have been carried out in rodents, and use mechanical, thermal or electrical stimuli to produce brief painful stimuli (reviewed by Le Bars et al., 2001). Most studies are designed in such a way that the animal can terminate the stimulus. These assessment methods enable determination of the analgesic potency of different drugs, but the neurological mechanisms involved do not fully reflect those involved in clinical pain. In addition, the dose rates required vary depending upon the test and the analgesic used (Flecknell, 1984; Liles and Flecknell, 1992). For example, NSAIDs are generally relatively ineffective in tests using thermal and electrical stimuli, and the test systems used require some modification when assessing this class of analgesics. This relative lack of efficacy in response to acute brief noxious stimuli, in comparison with opioids, is sometimes misinterpreted as showing that NSAIDs are therefore unlikely to be effective in controlling clinical pain. This is clearly not the case. It is also difficult to relate the dose rates that are effective in these test systems with those that are needed to control

clinical pain (Roughan and Flecknell, 2002). In all analgesics, both the potency and the duration of action vary depending on the test used and the strain and the sex of the animal. Results from these tests indicate a likely effective dose range, and data from studies of adverse effects indicate the likely dose ranges that could cause significant clinical problems. Taken together, these results allow initial suggestions of dose rates to be made, but objective scoring systems that can be applied to the assessment of post-operative pain are needed. These would enable assessment of an individual animal to confirm that an appropriate and effective dose of analgesic had been administered following a given surgical procedure. If appropriate pain scoring schemes cannot be used, then dose rates are probably best estimated from the results of tonic analgesiometric tests such as the late-phase formalin test (Roughan and Flecknell, 2002).

Assessment of Post-operative Pain

A number of different approaches to pain assessment in animals have been suggested, but progress in developing and validating scoring systems has been slow. Although suggestions for assessing pain were published over two decades ago (Flecknell, 1984), these were largely based on subjective clinical criteria that had not been subjected to any form of validation. A proposal to develop more robust scoring schemes was published by Morton and Griffiths (1985). This paper influenced a large number of other groups, who modified the original hypothesis, but retained the central notion of identifying pain-specific behaviours and rating them in some way (Association of Veterinary Teachers and Research Workers, 1986; LASA, 1990; Flecknell, 1991; ILAR, 1992; FELASA, 1994). However, attempts to apply this were largely unsuccessful (Beynen et al., 1987), primarily because the variables selected for inclusion were not fully identified and the scales used (0–3) not sufficiently well characterized. The scheme has proven much more successful when applied as a means of developing more humane endpoints for studies. These problems were identified by the original authors, but indiscriminate application of the system seems to have led to failure in identifying animals in pain, and most units in the UK do not use any pain scoring systems (Hawkins, 2002). This is to be regretted, since when applied carefully, the Morton and Griffiths scheme provides a structured method for assessing animals, and can be a useful aid for developing endpoints in a range of different situations.

Measurements of body weight and food and water intake have been proposed as potential indicators of post-operative pain and the efficacy of analgesic therapy (Flecknell and Liles, 1991; Liles and Flecknell, 1993b; Liles et al., 1998). These latter measures are objective, but they are retrospective measures and so could not be used to modify analgesic therapy for a particular animal. They can, however, be used as a simple measure of post-operative recovery, and as a means of adjusting future analgesic regimens for similar animals undergoing similar surgical procedures.

Behaviour-Based Pain Scoring Systems

More recently, behaviour-based schemes for assessing animal pain have been developed (Roughan and Flecknell, 2001). Further development of the system showed it could be used successfully by placing the rat in an observation cage for a brief period of time (5–10 minutes) (Roughan and Flecknell, 2003). Staff can learn to apply this scoring system after a short period of training (Roughan and Flecknell, 2006). A problem with applying behaviour-based systems is that it relies on animals recovering relatively rapidly from anaesthesia. When recovery is delayed, or is associated with prolonged sedation, then animals may fail to express pain behaviour. At present, it is not certain whether this is because the animals are not experiencing pain, or whether the heavy sedation prevents them showing signs of pain. The scoring system may also be influenced by other factors, such as fear and apprehension, and unexpected variations in behaviour between different strains of the animal may be encountered. Nevertheless, this approach offers a step forward in developing a practically useful scoring system for use after at least some types of surgery in rats. Initial studies in mice (Wright-Williams et al., 2007) and rabbits (Leach et al., 2009) suggest it may be possible to develop similar systems in other laboratory species.

Although well-validated, quantitative methods of post-operative pain assessment have yet to be developed for all species, virtually all studies of post-operative pain in animals have demonstrated a beneficial effect of analgesic therapy (Flecknell, 1994). It is not unreasonable, then, to suggest that most animals require some analgesics post-operatively. It is recommended that attempts are made to assess pain using a modification of the Morton and Griffiths technique, by selecting the variables used for scoring to suit the specific type of surgery and animal species concerned. The choice of variable is made after observing a small number of animals following surgery, and determining which variables are most affected by the procedure. The general types of changes that may be assessed are outlined below, and more specific descriptions of abnormal, pain-related behaviours for the rat, mouse and rabbit are listed in Table 5.4. Suggestions as to methods of evaluating pain in other species are also available (Harvey-Clarke et al., 2000; Hay et al., 2003; Ashley et al., 2005; Fitzpatrick et al., 2006; Weary et al., 2006; Hudson et al., 2008).

Activity

As mentioned above, the overall level of activity of an animal suffering pain is usually reduced, and most laboratory species will tend to remain motionless in a corner of their cage. Occasionally, an animal may show unusual restlessness and may seem unable to relax. When the animal moves, its posture or gait may be altered. This is most obviously seen when limb pain is present, but is often noted following laparotomy, when the back may be arched to reduce tension on the abdominal muscles. This altered posture, coupled with a tendency to shorten the length of each stride, can be seen both in rodents and rabbits, and also in dogs, cats and farm animals. Pain from an abdominal incision may also affect

TABLE 5.4 Pain-Related Behaviour Following Abdominal Surgery in Rats, Mice and Rabbits.

Species	Behaviours
Rat	Back arching (vertical stretch from crouched position as in felines upon waking); belly-press (muscular contraction where the ventral abdomen is pressed upon bedding – occurs immediately prior to or during ambulation); fall/stagger (stagger or fall during ambulation – a rapid transition to crouch from high or low rear. More often a partial loss of balance during grooming, resulting in lateral lying position from which recovery to balanced crouched posture occurs almost immediately); writhing (writhing involving lateral contortion of flank abdominal muscles, usually when crouching but also during transient break in walking or grooming); twitch (brief, seemingly spasmodic contraction, usually of the muscles of the back, travelling in an anterior–posterior direction)
Mouse	Writhing (slow contraction of abdominal muscles); rear-leg lift (momentary lifting of rear paw, often associated with writhe or press); belly-press (pressing of abdomen to cage floor, often associated with hindlimb extension); flinching (rapid contraction of muscles of back, as in twitching, but also involving other areas of the body)
Rabbit	Twitch (rapid movement of fur on back); wince (rapid movement backwards in a rocking motion, accompanied by eye closing and swallowing); stagger (partial loss of balance); flinch (body jerks upwards for no apparent reason); press (abdomen pushed towards floor, usually before walking); writhe (contraction of the abdominal muscles)

For further details, see Roughan and Flecknell (2003, 2004), Wright-Williams et al. (2007) and Leach et al. (2009).

the frequency of urination and defaecation in species in which this process requires marked abdominal muscle contraction. Particular behaviours such as climbing, rearing up onto the hindlimbs, stretching and scratching may also be affected, but careful observation by an experienced assessor may be necessary before such changes are noticed. A further complication in assessing behaviour is that the animal may change its responses in the presence of an unfamiliar observer. In addition, some species are nocturnal, and observation of normal behaviour will require attendance during the dark phase of its photoperiod. Both of these problems can be solved to some extent by using video cameras to monitor the animal's behaviour.

Appearance

Even when at rest, the animal's overall appearance may be altered. The animal may adopt a hunched-up posture and position itself in a corner of its cage or pen. Pain may result in a reduction in grooming activity, which leads to the development of an

unkempt appearance of the coat and soiling of the anus. Lack of grooming may also lead to the build-up of an encrusted discharge around the eyes, nose and mouth. Rats may develop dark encrustations around the eyes or nose. This material is porphyrin excreted from the Harderian glands, and if wiped with moist cotton wool, it has a red colour. The presence of porphyrin staining is a non-specific stress response, but should alert the observer to the possibility that the stress involved may be pain.

Temperament

Changes in temperament often occur in animals experiencing pain. Previously tractable animals may become uncharacteristically aggressive and may bite or scratch. Alternatively, a previously active animal which showed obvious interest in its handler may appear completely apathetic. The animal may cower away from the handler and attempt to avoid being restrained. The interpretation of any of these types of behaviour will require not only a knowledge of the normal predicted behaviour of an animal of that particular age, sex and species, but also prior knowledge of the normal behaviour of that particular individual. Clearly, close liaison with animal care staff is essential in attempting to assess the behaviour of an animal in the post-operative period.

Vocalizations

Acute pain can make an animal cry out, and handling an animal which is in pain may provoke such a response. The pitch of the cry may be abnormal and may be accompanied by attempts to bite the handler or to escape. Animals in pain rarely cry continuously, although on occasions dogs may howl or whimper for long periods and sheep and cattle may also make prolonged vocalization. When assessing pain in rodents, it is important to appreciate that many of their cries are at high sound frequencies which are inaudible to humans.

Feeding Behaviour

Food and water intake are often markedly reduced if an animal is in pain. Severe pain is often associated with a complete cessation of eating and drinking. These changes in feeding may go unnoticed if the animal is fed *ad libitum* from a hopper, or if other animals that are feeding normally are present in the cage or pen. A reduction in body weight as a consequence of this inappetance can usually be readily detected, but normal day-to-day variations in body weight must also be appreciated. To improve the detection of changes in food and water intake, weighed quantities of food and water should be dispensed and daily intake measured. Weighing the food hopper and the water bottle provides a satisfactory means of monitoring intake in larger rodents. Care must be taken that spillage of food by the animal does not result in intake being erroneously assessed as normal. In addition to recording food consumption, the animal should be weighed each day to determine any changes in body weight.

A reduction in food and water intake will also be reflected in a reduction in faecal and urine output, but the latter may be difficult to detect. The onset of dehydration will be reflected in the clinical appearance of the animal. Loss of skin tone will cause it to tent and tend to remain elevated when a fold is twisted between the fingers.

Alterations in Physiological Variables

Pain generally causes changes in the respiration pattern and rate. This can be dramatic following thoracic surgery, when the reduction in the depth of respiration can cause considerable concern. In other instances, the change may be less obvious and masked by the normal tendency of animals such as rodents or rabbits to respond to restraint or close observation with an increase in their respiratory rate. Pain may also affect the cardiovascular system. Frequently, the heart rate is increased, but the natural responses to handling may mask these changes. The other factors influencing these cardiorespiratory variables may render them of little use for routine assessment of post-operative pain (Conzemius, 1997).

Severe pain may cause the development of circulatory failure (shock), with blanching and chilling of the extremities and a decrease in the strength of the peripheral pulse.

All of the changes listed above are primarily indicators of ‘abnormality’ and are not necessarily indicative of pain – they could be caused by the general response to surgery or anaesthesia, or could be the result of dehydration, hypothermia or other factors. Noting a positive response to analgesic therapy helps indicate which measures can be useful, but remember that some analgesics (e.g. opioids) can alter behaviour.

Irrespective of whether a formal scoring system is used or not, pain assessment will be facilitated by:

- A good knowledge of the species-specific behaviours of the animal being assessed
- A knowledge and comparison of the individual animal’s behaviour before and after the onset of pain (e.g. pre- and post-operatively)
- The use of palpation or manipulation of the affected area and assessment of the responses obtained
- Examination of the level of function of the affected area, for example, leg use following injury or limb surgery, together with a knowledge of any mechanical interference with function
- The use of analgesic regimens or dose rates that have been shown to be effective in controlled clinical studies, and evaluation of the change in behaviour this brings about
- A knowledge of the non-specific effects of any analgesic, anaesthetic or other drugs that have been administered

PAIN RELIEF

Leaving aside the problems of pain assessment, empirical treatment of presumed painful conditions will continue, and it is not unreasonable to assume that analgesic therapies shown to be effective in human beings are also likely to be effective in animals. Although the assessment of clinical efficacy may not have been completed, studies of novel analgesic compounds and delivery systems in animals have established their safety and efficacy in analgesiometric tests. Analgesics can be broadly divided into two groups, the opioids or narcotic analgesics and the NSAIDs such as aspirin. Local anaesthetics can also be used to provide post-operative pain relief by blocking all sensation from the affected area. Suggested dose rates of analgesics are given in Tables 5.5–5.8.

TABLE 5.5 Suggested Dose Rates for Non-steroidal Anti-inflammatory Drugs in Laboratory Animals.

Drug	Mouse	Rat	Guinea pig	Rabbit	Ferret
Aspirin	120 mg/kg per os	100 mg/kg per os	87 mg/kg per os	100 mg/kg per os	200 mg/kg per os
Carprofen	5 mg/kg sc	5 mg/kg sc	4 mg/kg sc ? once daily	1.5 mg/kg per os u.i.d., 4 mg/ kg sc u.i.d.	4 mg/kg sc u.i.d.
Diclofenac	8 mg/kg per os	10 mg/kg per os	2.1 mg/kg per os	–	–
Flunixin	2.5 mg/kg sc or im ?12 hourly	2.5 mg/kg sc or im ?12 hourly	2.5 mg/kg sc or im ?12 hourly	1–2 mg/kg sc im ? 12 hourly	0.5–2 mg/ kg sc 12– 24 hourly
Ibuprofen	30 mg/kg per os	15 mg/kg per os	10 mg/kg im ?4 hourly	10 mg/kg iv ? 4 hourly	–
Indomethacin	1 mg/kg per os	2 mg/kg per os	8 mg/kg per os	12.5 mg/kg per os	–
Ketoprofen	5 mg/kg sc	5 mg/kg sc	–	3 mg/kg im	3 mg/kg im
Meloxicam	5 mg/kg sc or per os	1 mg/kg sc or per os	0.1–0.3 mg/ kg sc or per os every 24 h	0.6–1 mg/ kg sc or per os	0.1–0.2 mg/ kg sc or per os
Paracetamol (acetaminophen)	200 mg/kg per os	200 mg/kg per os	–	–	–

Note that considerable individual and strain variation in response may be encountered and that it is therefore essential to assess the analgesic effect in each individual animal

TABLE 5.6 Suggested Dose Rates for Non-steroidal Anti-inflammatory Drugs in Laboratory Animals.

Drug	Pig	Sheep	Primate	Dog	Cat
Aspirin	10–20 mg/kg per os, 4–6 hourly	50–100 mg/kg per os, 6–12 hourly	20 mg/kg per os, 6–8 hourly	10–25 mg/kg per os, 8 hourly	10–25 mg/kg per os, every 48 hours
Carprofen	2–4 mg/kg iv or sc, once daily	2–4 mg/kg sc or iv, once daily (? 2–3 days)	3–4 mg/kg sc u.i.d.	4 mg/kg iv or sc, once daily 1–2 mg/kg b.i.d. per os, for 7 days	4 mg/kg sc or iv
Flunixin	1–2 mg/kg iv or sc, once daily	2 mg/kg iv or sc, once daily	0.5–2 mg/kg sc or iv daily	1 mg/kg iv or im, 12 hourly 1 mg/kg per os, daily for up to 3 days	1 mg/kg sc, daily for up to 5 days
Ibuprofen	–	–	7 mg/kg per os	10 mg/kg per os, 24 hourly	–
Ketoprofen	1–3 mg/kg iv, im, sc, per os, 12 hourly	–	2 mg/kg sc daily	2 mg/kg sc, im or iv, once daily for up to 3 days 1 mg/kg per os, daily for 5 days	1 mg/kg sc, once daily for up to 3 days 1 mg/kg per os, once daily for up to 5 days
Meloxicam	0.4 mg/kg sc, once daily	0.5 mg/kg iv, sc up to b.i.d. for 1 day, then 0.5 mg/kg per os u.i.d. for 5 days	0.1–0.2 mg/kg u.i.d. sc or per os	0.2 mg/kg u.i.d. sc or per os, then 0.1 mg/kg sc or per os	0.2 mg/kg u.i.d. sc or 0.3 mg/kg per os, then 0.1 mg/kg sc or per os
Tolfenamic acid	–	–	–	4 mg/kg sc daily for 2 days	4 mg/kg sc daily for 2 days
Paracetamol (acetaminophen)	–	–	–	15 mg/kg per os, 6–8 hourly	Contra-indicated

Note that considerable individual and strain variation in response may be encountered, and that it is therefore essential to assess the analgesic effect in each individual animal.

TABLE 5.7 Suggested Dose Rates for Opioid Analgesics in Laboratory Animals.

Drug	Mouse	Rat	Guinea pig	Rabbit	Ferret
Buprenorphine	0.05–0.1 mg/kg sc 12 hourly	0.01–0.05 mg/kg sc or iv, 8–12 hourly 0.1–0.25 mg/kg per os, 8–12 hourly	0.05 mg/kg sc, 8–12 hourly	0.01–0.05 mg/kg sc or iv, 8–12 hourly	0.01–0.03 mg/ kg iv, im or sc, 8–12 hourly
Butorphanol	1–2 mg/kg sc, 4 hourly	1–2 mg/kg sc, 4 hourly	1–2 mg/kg sc, 4 hourly	0.1 – 0.5 mg/kg iv, 4 hourly	0.4 mg/kg im, 4–6 hourly
Hydromorphone	–	–	–	0.1–0.2 mg/kg ? 6–8 hourly	0.1–0.2 mg/kg ? 6–8 hourly
Morphine	2.5 mg/kg sc, 2–4 hourly	2.5 mg/kg sc, 2–4 hourly	2–5 mg/kg sc or im, 4 hourly	2–5 mg/kg sc or im, 2–4 hourly	0.5–2 mg/kg im or sc, 6 hourly
Nalbuphine	2–4 mg/kg im ? 4 hourly	1–2 mg/kg im, 3 hourly	1–2 mg/kg iv, ip or im	1–2 mg/kg iv, 4–5 hourly	–
Oxymorphone	0.2–0.5 mg/kg sc ? 4 hourly	0.2–0.5 mg/kg sc ? 4 hourly	0.2–0.5 mg/kg sc ? 4 hourly	0.05–0.2 mg/kg sc ? 6–8 hourly	0.05–0.2 mg/kg sc ? 6–8 hourly
Pentazocine	5–10 mg/kg sc 3–4 hourly	5–10 mg/kg sc, 3–4 hourly	–	5–10 mg/kg sc, im or iv, 4 hourly	–
Pethidine (Meperidine)	10–20 mg/kg sc or im, 2–3 hourly	10–20 mg/kg sc or im, 2–3 hourly	10–20 mg/kg sc or im, 2–3 hourly	5–10 mg/kg sc or im, 2–3 hourly	5–10 mg/kg im or sc, 2–4 hourly
Tramadol	5 mg/kg sc, ip ?	5 mg/kg sc, ip ?	–	–	–

*Note that considerable individual and strain variation in response may be encountered, and that it is therefore essential to assess the analgesic effect in each animal.
? = duration of action uncertain.*

TABLE 5.8 Suggested Dose Rates for Opioid Analgesics in Laboratory Animals.

Drug	Pig	Sheep	Primate	Dog	Cat
Buprenorphine	0.01–0.05 mg/kg im or iv, 6–12 hourly	0.005–0.01 mg/kg im or iv, 4 hourly	0.005–0.01 mg/kg im or iv, 6–12 hourly	0.005–0.02 mg/kg im, sc or iv, 6–12 hourly	0.005–0.01 mg/kg sc or iv, 8–12 hourly
Butorphanol	0.1–0.3 mg/kg im or iv, 4 hourly	0.5 mg/kg im or iv, 2–3 hourly	0.01 mg/kg iv, ?3–4 hourly	0.2–0.4 mg/kg sc or im, 3–4 hourly	0.4 mg/kg sc, 3–4 hourly
Hydromorphone	–	–	–	0.05–0.2 mg/kg im, sc 2–4 hourly	0.1 mg/kg im, sc 0.2 2–4 hourly
Morphine	0.2–1 mg/kg im , ?4 hourly	0.2–0.5 mg/kg im, ?4 hourly	1–2 mg/kg sc or im, 4 hourly	0.5–5 mg/kg sc or im, 4 hourly	0.3 mg/kg sc, 4 hourly
Nalbuphine	–	–	–	0.5–2.0 mg/kg sc or im, 3–4 hourly	1.5–3.0 mg/kg iv, 3 hourly
Oxymorphone	0.15 mg/kg im 4 hourly	–	0.15 mg/kg im 4–6 hourly	0.05–0.22 mg/kg im, sc or iv, 2–4 hourly	0.2 mg/kg sc or iv
Pentazocine	2 mg/kg im or iv, 4 hourly	–	2–5 mg/kg im or iv, 4 hourly	2 mg/kg im or iv, 4 hourly	–
Pethidine (meperidine)	2 mg/kg im or iv, 2–4 hourly	2 mg/kg im or iv, 2–4 hourly	2–4 mg/kg im or iv, 2–4 hourly	10 mg/kg im, 2–3 hourly	2–10 mg/kg sc or im, 2–3 hourly
Tramadol	–	–	? 1–2 mg/kg sc or iv, 2 mg/kg orally ? b.i.d.	2–5 mg/kg iv or sc, 2–5 mg/kg orally t.i.d.	2–4 mg/kg sc

Note that considerable individual and strain variation in response may be encountered, and that it is therefore essential to assess the analgesic effect in each animal. ? = duration of action uncertain.

Analgesic Agents

NSAIDs

Traditionally, NSAIDs have been considered low-potency analgesics, suitable for the control of mild pain, or as agents primarily for use in conditions such as arthritis, where the inflammatory component of the disease process was responsible for some or all of the pain. The perception of NSAIDs has changed with the introduction of a number of compounds that have been shown to have considerable analgesic potency (Cunningham and Lees, 1994). In laboratory species, data from a number of analgesiometric tests provide a basis for estimating appropriate dose rates for clinical use in these species (Liles and Flecknell, 1992). Estimating the frequency of administration is much more difficult, however, since there are very considerable variations in elimination times for NSAIDs in different species (Lees et al., 1991; Bishop, 2004). Despite these problems, there are now a range of NSAIDs with clear indications for use in alleviating pain in animals (Bishop, 2004).

NSAIDs exert their main effects by inhibiting the action of the enzyme cyclooxygenase (COX). COX is an enzyme that catalyses the conversion of arachidonic acid to prostaglandin H₂, the first step in the synthesis of prostanoids. The prostanoids are important mediators of inflammation, and both directly and indirectly influence the degree of pain associated with tissue injury and other inflammatory processes. COX exists in two isoforms: COX-1 and COX-2. A third isoform, COX-3, has now been described (Chandrasekharan et al., 2002). COX-1 mediates essential physiological responses in a wide range of body tissues; in contrast, COX-2 is expressed by cells that are involved in inflammation (e.g. macrophages), and it has emerged as the isoform primarily responsible for the synthesis of prostanoids involved in acute and chronic inflammatory states. It was initially thought that developing NSAIDs with effects only on COX-2 would avoid any undesirable side-effects; however, this relatively simple view of the functions of COX and the effects of COX-1 and COX-2 inhibition have become steadily more complex.

One of the problems that arises when trying to interpret information about new and older NSAIDs is the wide variation of assays used to determine COX-1 and COX-2 inhibitory effects. This is further compounded by the use of both EC₅₀ and EC₈₀ for comparison, and the failure in some studies to link these data to the tissue concentrations that are likely to be produced when the drug is used clinically. A further problem is that the drug concentration produced, the relative COX-1–COX-2 inhibition and the duration of action of the drug are likely to vary between species. It is therefore important to balance an enthusiasm to provide the most effective pain management, with the need for caution when using drugs in different species. It is clear, however, that the new generation of highly selective COX-2 NSAIDs, in particular the coxibs such as deracoxib and firocoxib, are likely to provide effective pain relief with a reduced risk of side-effects, particularly those involving the gastrointestinal tract (McCann et al.,

2004). Information is also becoming available on the use of these agents in less familiar species (e.g. birds; Baert and De Backer, 2003).

The most significant problems associated with NSAID administration are gastrointestinal disturbances, notably ulceration and haemorrhage, nephrotoxicity and interference with platelet function (Mathews, 2000; MacPherson, 2000). Other problems such as blood dyscrasias and liver toxicity can also occur (Lees et al., 1991; Liles and Flecknell, 1992). These side-effects are seen primarily following prolonged administration, and are rarely of significance when treatment is for 2 or 3 days post-operatively. It should be noted that some NSAIDs (e.g. aspirin) have been reported as causing fetal abnormalities, so their use should be avoided in pregnant animals. In the research environment, the non-specific effects of NSAIDs may preclude their administration in certain research protocols. However, they offer an alternative to opioids, which have different non-specific side-effects. Consideration of the nature of the research study and potential interactions with analgesics allows a logical choice of analgesic agent to be made.

Drugs Available

Aspirin

Aspirin can be used to alleviate mild pain. It is most effective in humans for musculoskeletal pain, and is less effective for visceral pain. Dispersible tablets and enteric-coated tablets are available. Injectable formulations are generally available only for research use. There are few reports of the use of aspirin for the control of post-operative pain in animals, although it appeared to have some positive effects in rats (Jablonski and Howden, 2002).

A wide range of preparations that combine aspirin with other analgesics [e.g. paracetamol (acetaminophen), codeine, dextropropoxyphene] are available for use in humans, but their efficacy in animals for use in post-operative pain has not been evaluated.

Paracetamol (Acetaminophen)

Paracetamol has similar analgesic efficacy as aspirin but has little anti-inflammatory activity. It causes less gastrointestinal irritation, but overdosage causes liver toxicity. These analgesics should not be administered to cats, because of problems of toxicity. Tablets and oral suspensions are available for human use, and these may be used in a wide range of laboratory species, although very little data concerning efficacy in post-operative pain in animals are available (Mburu et al., 1988). In acute pain models in mice and rats, paracetamol has clear analgesic effects (Miranda et al., 2008; Mickley et al., 2006), and its use for post-operative pain relief has been suggested (Bauer et al., 2003). Work in the author's laboratory, in mice, indicated that it had very limited effects after surgery (Dickenson personal communication).

Ibuprofen

Ibuprofen is effective against mild pain in human beings, but controlled clinical trials in animals have not been undertaken. Both tablets and suspensions are available for human use.

Phenylbutazone

Phenylbutazone has been widely used for controlling mild pain in larger species. Analgesiometric studies enable initial estimates of dose rates for small rodents, but no clinical trials have been carried out in these smaller laboratory species. Injectable (intravenous only) and oral preparations (tablets and powder) are available.

Flunixin

Flunixin has been reported as being effective in controlling post-operative pain in dogs (Reid and Nolan, 1991), and it has been widely used as an analgesic in larger species (cattle and horses). It also appears to be an effective analgesic in pigs, sheep and cats, but no controlled trials have been undertaken in these species. Both injectable and oral preparations are available. The most significant problem reported has been nephrotoxicity either when administered together with a known nephrotoxic agent (Mathews et al., 1990), or in circumstances when renal blood flow was likely to have been compromised (McNeil, 1992). The mechanism of action has been suggested to be inhibition of the normal prostaglandin regulation of renal blood flow, resulting in a failure of renal perfusion during periods of hypotension. Good anaesthetic practice, appropriate fluid therapy and administration of flunixin after the completion of surgery are likely to minimize this risk. Administration to conscious, healthy animals appears not to be associated with any significant risk, but more recently developed NSAIDs should be used when practicable.

Carprofen

Carprofen can provide effective post-surgical pain relief in the dog, cat and rat (Nolan and Reid, 1993; Liles and Flecknell, 1993a; Slingsby and Waterman-Pearson, 2000; Shih et al., 2008), and has also been used in a number of different species with apparent success (Allison et al., 2007; Paull et al., 2007). Both oral and injectable preparations are available.

Ketoprofen

Ketoprofen provides moderate pain relief in rats, dogs, cats and horses. Its efficacy in other species is uncertain, although likely effective dose rates can be suggested from analgesiometric data. Both oral and injectable formulations are available.

Ketorolac

Ketorolac is used in humans to control moderate to severe post-operative pain, and early clinical trials suggest it may be effective in the dog (Mathews et al., 1994).

Both injectable and oral formulations are available. As with other NSAIDs, ketorolac is best not administered to animals with pre-existing renal disease or fluid deficits.

Meloxicam

Meloxicam is available in the UK as an oral suspension and an injectable preparation for use in dogs, cats and cattle. It has been shown to be effective for alleviating post-operative pain in rats (Roughan and Flecknell, 2003), mice (Wright-Williams et al., 2007), dogs, cats and cattle. It is effective against mild to moderate pain, and the palatable oral preparation makes it particularly useful when additional doses of drugs are required.

Naproxen

Naproxen is unusual in having an exceptionally long half-life in the dog (35 hours) and has been used to alleviate moderate pain in this species, although, as with most analgesics, no controlled clinical trials have been undertaken. Naproxen is available as tablets and as an oral suspension.

Coxibs – Deracoxib, Eterocoxib, Firocoxib, Paracoxib, Roficoxib

The coxibs are a group of NSAIDs with high selectivity for COX-2 (Hinz et al., 2007). The degree of inhibition of COX-1 and COX-2 may vary in different species, but generally, when used at therapeutic dose rates, their effect is primarily on COX-2. Initially, these agents were only available as oral preparations, but injectable formulations are now becoming available. Since these agents have minimal effects on COX-1 in most species, there are no effects on platelet function. The coxibs still have adverse effects on the gastrointestinal system when administered for prolonged periods, but these effects are less than those produced by older NSAIDs.

Opioids (Narcotic Analgesics)

A wide range of different opioid analgesics are available for use in animals. The different drugs vary in their analgesic potency, duration of action and also effects on other body systems. Opioids are classified by their activity as specific opioid receptors. The most clinically important of these are the mu (μ) and kappa (κ) receptors. Morphine is a mu agonist (it binds to, and activates mu receptors). Mu antagonists (e.g. naloxone and naltrexone) bind to mu receptors but do not activate the receptor. Some analgesics are mu antagonists, and so will reverse the effects of mu agonists such as morphine, but also have agonist effects at kappa receptors. These agents are generally referred to as mixed agonist/antagonist analgesics (nalbuphine, butorphanol, pentazocine). Some opioid analgesics are classified as partial agonists that have both agonist (analgesic) effects at the mu receptor, and also antagonize pure mu agonists (buprenorphine).

Opioid agonists and partial agonists relieve pain without impairing other sensations. However, they can cause some undesirable side-effects. All opioid

agonists can produce some degree of respiratory depression, but when administered at clinically effective dose rates, this is rarely a serious problem in animals. Opioids may also cause sedation or excitement, their effects varying considerably in different animal species (Le Bars et al., 2001). The effects on behaviour also depend upon the dose of the drug which has been administered (Flecknell, 1984).

When administered at dose rates appropriate for providing post-operative analgesia, opioids have minimal effect upon the cardiovascular system (Pircio et al., 1976; Cowan et al., 1977a; Popio et al., 1978; Trim, 1983; O'Hair et al., 1988). Higher dose rates, such as those that might be administered when using opioids as part of a balanced anaesthetic regime, can cause bradycardia, although this can be prevented by administering atropine. In addition, morphine, pethidine and some other opioids can stimulate histamine release that can produce a peripheral vasodilatation in some species. Clinically significant hypotension is usually seen only after administration of high dose rates or after rapid intravenous administration.

Opioids can cause vomiting in some animal species, notably in non-human primates and dogs. This side-effect is seen primarily when opioids are administered to pain-free animals (e.g. as pre-anaesthetic medication), and is less frequent when administered post-operatively. Apart from causing vomiting, opioids may delay gastric emptying, increase intestinal peristalsis and cause spasm of the biliary tract. These effects may preclude the use of opioids in certain experimental procedures, but generally, the effects are of minimal clinical significance in animals. The detailed pharmacology of opioids has been extensively reviewed; general introductions to the field can be found in a number of sources (Camu and Vanlersberghe, 2002; Tranquilli et al., 2006).

Drugs Available

Opioid Agonists

Morphine Morphine is obtained from opium and has been used as an analgesic in humans for many years. It has been extensively studied in a range of experimental animals and is also used in veterinary clinical practice (Hall et al., 2001). Its duration of action in most animals is 2–4 hours, but a slow-release injectable preparation (Duromorph) and a slow-release oral preparation (MST, Napp; Oramorph SR, Boehringer Ingelheim; Appendix 4) are also available. Initial trials of oral slow-release morphine in rats indicated it had a prolonged duration of action in anti-nociceptive tests (Dickenson personal communication), and it may be of value for providing prolonged post-operative pain relief. Rapid intravenous injection in the dog can cause transient hypotension, because of histamine release, but this is not a problem if the drug is given by continuous intravenous infusion (see below). Although morphine remains one of the most useful and potent analgesics, it is relatively short acting in many species (<4 hours), and its administration after neuroleptanalgesic anaesthetic techniques in laboratory

species can, not surprisingly, result in severe respiratory depression. It is also a drug with significant abuse potential.

Pethidine (Meperidine) Pethidine (meperidine) has been widely used as an analgesic in veterinary practice in the UK, but it has a relatively short duration of action in many species (<2 hours). It has a spasmolytic action on smooth muscle in some species, and this has led to its recommendation for use in specific clinical situations such as colic in horses. Both oral and injectable formulations are available.

Methadone Methadone has been used clinically as an analgesic in the horse, dog (Hall et al., 2001) and cat (Dobromylskyj, 1993), and dose rates for use in other species can be extrapolated from the results of experimental analgesiometry (Flecknell, 1984). Both injectable and tablet formulations are available.

Oxymorphone Oxymorphone has actions similar to morphine and has been reported to be an effective analgesic in dogs and cats (Palminteri, 1963; Vesal et al., 1986). Its activity in anti-nociceptive tests has been evaluated in rats (Peckham and Traynor, 2006). Because of its relatively short duration of action, oxymorphone offers no particular advantages in comparison with morphine; however, slow-release preparations of this analgesic have been produced and evaluated in rodents (Clark et al., 2004). If these slow-release preparations become available commercially, then they may be of considerable value in providing prolonged post-operative pain relief.

Hydromorphone Hydromorphone, like oxymorphone, is a pure mu agonist, with greater potency than morphine but a similar duration of action. It is used for analgesia in dogs and cats in veterinary practice in the USA (Robertson and Taylor, 2004; Bateman et al., 2008). Slow-release injectable formulations have been produced for research purposes (Smith et al., 2006), and shown to be effective in rats. Oral slow-release capsule preparations of hydromorphone are available commercially, and these may be of value for providing prolonged pain relief in larger species.

d-Propoxyphene d-Propoxyphene is a derivative of methadone which is used in humans for the relief of mild to moderate pain. In human clinical practice, it is frequently administered in combination with aspirin or paracetamol, and these preparations have occasionally been used in dogs in veterinary clinical practice in the UK (Yoxall, 1978).

Codeine and Dihydrocodeine Codeine and dihydrocodeine are morphine derivatives of low and moderate potency, respectively. Codeine is used in combination with paracetamol for the relief of mild to moderate pain. Dihydrocodeine is also available as an oral preparation, and is an effective analgesic in human beings. To date, no information concerning its clinical efficacy in animals is available.

Fentanyl Fentanyl is a potent, relatively short acting synthetic opiate. Its main use in laboratory animal anaesthesia is in the neuroleptanalgesic combinations Hypnorm (fentanyl/fluanisone) and Innovar-Vet (fentanyl/droperidol). Because of its short duration of action (under 30 minutes in most species; Tranquilli et al., 2006) fentanyl is most widely used for providing analgesia during surgical procedures (Andrews and Prys-Roberts, 1983). If it is to be used to control post-operative pain, it should be administered as a continuous infusion or transdermally (see below).

Alfentanil Alfentanil is a synthetic opioid related to fentanyl. It has pharmacodynamic properties similar to fentanyl, but has a more rapid onset and shorter duration of action. Alfentanil can be administered by continuous infusion to provide analgesia during surgical procedures, and its short duration of action enables good moment-to-moment control of the intensity of the analgesic effect.

Sufentanil Sufentanil is a highly potent mu opioid (approximately 60 times more potent than fentanyl in humans) used primarily for the provision of analgesia as part of balanced anaesthetic regimens (Camu and Vanlersberghe, 2002).

Remifentanil Remifentanil is a very short acting mu agonist. Its short duration of action is primarily due to hydrolysis by non-specific blood and tissue esterases. This has led to its use to provide analgesia as part of balanced anaesthetic regimens in humans and animals (Murrell et al, 2005). Even after very prolonged periods of administration, its effects are absent within a few minutes of ceasing intravenous infusion. Administration by other routes are unpredictable and not recommended (Alves et al., 2007).

Opioid Mixed Agonists/Antagonists and Partial Agonists

Pentazocine Pentazocine has been reported to provide effective analgesia in a range of animal species (Lumb and Wynn Jones, 1973; Cooper and Organ, 1977; Taylor and Houlton, 1984). It has been reported to produce dysphoria in humans (Rosow, 1985), but it is uncertain whether similar effects occur in animals. Generally, the sedative effect of pentazocine is less than that of morphine. Both oral and injectable formulations are available.

Butorphanol Butorphanol has a veterinary product licence as an analgesic in several countries, and is believed to provide post-operative analgesia in a variety of species (Sawyer and Rech, 1987; Flecknell and Liles, 1990; Sawyer et al., 1991). It has marked mu opioid antagonist properties and can be used to reverse the action of fentanyl while maintaining some analgesic effects by its action at kappa receptors.

Buprenorphine Buprenorphine is a potent partial mu agonist that has the advantage of having a prolonged duration of action in many species (Cowan et al., 1977a, b; Dum and Herz, 1981; Nolan et al., 1987; Flecknell and Liles, 1990; Roughan and Flecknell, 2002; Christoph et al., 2005). The drug has been used

in veterinary clinical practice in dogs and horses (Hall et al., 1991), cats (Taylor, 1985) and a wide range of laboratory animal species (Roughan and Flecknell, 2002). It is available as an injectable formulation, and as tablets for sublingual administration in humans.

Buprenorphine has been reported to cause pica (eating of bedding) in rats (Clark et al., 1997; Bosgraf et al., 2004), a behaviour that may reflect nausea (Mitchell et al., 1977). This uncommon but undesirable side-effect may occur with other opioids and may be preventable with methylnaltrexone (Aung et al., 2003); however, it is best managed by avoiding the use of opioids in susceptible strains of rat.

Since buprenorphine is a partial agonist that has been shown to be effective in reversing the effects of full mu agonists (Flecknell et al., 1989), it has been suggested that mu agonists such as morphine cannot be given after buprenorphine has been administered. Paradoxically, this does not appear to be the case, and it has been demonstrated that within the analgesic dose range, a switch from buprenorphine to morphine is possible, without a loss of analgesic efficacy. There also appeared to be no refractory period between termination of buprenorphine analgesia and onset of the effects of morphine (Kogel et al., 2005).

Nalbuphine Nalbuphine has been reported to provide effective analgesia in dogs (Flecknell et al., 1991) and rats (Flecknell and Liles, 1991). It has a duration of action of 2–4 hours in most species. It rapidly and effectively antagonizes the effects of mu agonists such as fentanyl, while maintaining an analgesic effect at kappa receptors. It is therefore particularly suitable for reversal of opioid-based anaesthetic regimens.

Other Agents

Tramadol Tramadol is an opioid agonist that also has an analgesic action mediated via the inhibition of serotonin and noradrenaline reuptake in the spinal cord. Both oral and injectable formulations are available. Although it has been advocated for use in animals as an alternative to more potent opioids because of its second mode of action (Myers, 2005), it is rapidly metabolized in several species. The main metabolite has moderate opioid activity but no effects on serotonin and noradrenaline. It has been assessed in animal models relevant to post-surgical pain (Affaitati et al., 2002; Guneli et al., 2007), and its pharmacokinetics have been studied in dogs (Kukanich and Papich, 2004), rats (Garrido et al., 2003), mice (Beier et al., 2007), goats (de Sousa et al., 2007) and rabbits (Souza et al., 2008).

Local Anaesthetics As discussed in Chapter 3, local anaesthetics can be used both as adjuncts to general anaesthesia and to provide post-operative pain relief. This is likely to be more effective if a longer lasting local anaesthetic (e.g. bupivacaine) is used. These techniques are well established in larger species (Tranquilli et al., 2007), but only limited data are available in rodents. This

is presumably due to the practical difficulties associated with the use of the very small volumes of drug that can safely be administered (see Chapter 3). Nevertheless, this offers a potentially valuable means of providing analgesia when concerns related to drug interactions and a particular scientific protocol preclude the use of NSAIDs and opioids. The use of local anaesthetic can also be incorporated into a multimodal analgesic regimen.

Clinical Use of Analgesics When formulating an analgesic regimen for a particular animal, several factors need to be considered:

- What is the likely severity of pain, and what is its anticipated duration?
- Which drug or drugs should be administered, and at what dose rates?
- Are there any special factors that will influence the choice of analgesic, for example, the animal species, any pre-existing abnormalities and any particular features of the current project or the type of pain?
- What facilities are available for management of the animal? What level of post-operative care and monitoring of the animal is available? Can staff attend throughout a 24-hour period? Are there facilities for continuous infusion of analgesics?

Timing of Analgesic Administration One of the most important advances in the control of post-operative pain has been the realization that the timing of analgesic intervention may have a significant bearing on the intensity of post-operative pain. The concept was originally formulated early in the 20th century, by Crile (Crile, 1913), based on clinical observations. Crile suggested using regional blocks with local anaesthetics, in conjunction with general anaesthesia, to prevent post-operative pain in humans and the ‘formation of painful scars caused by alterations in the CNS as a result of the noxious stimulation caused during surgery’. The discovery that changes in the central processing of noxious stimuli occurred in response to peripheral injury (Coderre, 1993; Woolf and Chong, 1993) increased interest in this concept. After demonstration that the changes in the CNS were suppressed to a greater extent by administration of opioids before rather than after injury (Woolf and Wall, 1986; Kissin, 2000), the concept of ‘pre-emptive analgesia’ was developed. This advocated administration of analgesics before noxious stimulation began to prevent the adverse CNS changes that this stimulation induces. To be most effective, pre-emptive analgesia must prevent the noxious stimuli from reaching the CNS. It should also aim to reduce or eliminate peripheral inflammation, which in itself increases input into the CNS and so aggravates central hypersensitivity.

The clinical application of this approach in humans has had mixed results (Grape and Tramer, 2007), but it has been recognized that administering analgesics before the return of consciousness has significant advantages. As a result, the concept is now often referred to as ‘preventive analgesia’. This approach aims to ensure that post-operative pain treatment starts before surgery and lasts long enough after surgery to avoid pain-induced sensitization of nociceptive

processes (Pogatzki-Zahn et al., 2007). In animals, a positive effect of pre-emptive drug administration has been found experimentally (Woolf and Wall, 1986; Lascelles et al., 1995) and clinically in animals that are given opioids (Lascelles et al., 1997) and NSAIDs (Welsh et al., 1997; Lascelles et al., 1998). In addition, as in humans, ensuring pain relief has been provided before the animal recovers consciousness is clearly preferable to not administering analgesics until pain is experienced.

It is important to appreciate that a single dose of analgesic, administered prior to surgery, will not usually be all the analgesia that will be required. Additional analgesic medication will still be needed in the post-operative period, but this pain will be more easily controlled because pre-emptive analgesia has been used. A further practical advantage of pre-emptive analgesia is that it will often reduce the dose of anaesthetic drugs required, and by integrating analgesic therapy into a balanced anaesthetic technique, the potential adverse effects of anaesthesia can be improved, in addition to providing more effective pain relief.

Adopting pre-emptive analgesia does not necessarily imply administration of opioids or NSAIDs before surgery. Crile's original concept, of using local anaesthetics, should also be considered. In addition, the use of anaesthetic agents with analgesic properties will produce 'pre-emptive' analgesia. Of particular relevance to laboratory animals are the potential effects of ketamine. This drug has the potential to reverse central hypersensitivity because of its actions as an NMDA antagonist. Experimental studies have confirmed its efficacy, but clinical trials in humans have given mixed results (Visser and Schug, 2006). Its clinical benefit in animals is uncertain, but it is reasonable to suggest that the very high doses used in rodent anaesthesia may have beneficial effects.

Administration of NSAIDs pre-operatively could potentially increase the risk of adverse side-effects related to renal function. However, these concerns are most relevant to clinical veterinary practice when animals may have chronic renal disease (Lascelles et al., 2007). The adverse effects are also only of concern during periods of hypotension. Pre-operative administration in healthy human patients is not considered to be a significant risk (Cooper et al., 2007) and it seems likely that this will apply to healthy animals. NSAIDs with significant COX-1 activity decrease platelet function and so could increase bleeding times during surgery; however, this has not proven to be a significant problem when COX-2-preferential, or COX-2-selective, agents are used (Fresno et al., 2005).

In some circumstances, it may not be possible to administer analgesics pre-emptively; nevertheless, administering analgesics as soon as practicable is of significant benefit. The longer pain is established, the greater will be the degree of central hypersensitivity, and the more difficult pain management becomes.

'Multi-modal' Pain Therapy Post-operative pain arises from the activation of a multiplicity of pathways, mechanisms and transmitter systems. Administering a single class of analgesic often fails to suppress all of these mechanisms, even when high dose rates are used. The 'multi-modal' pain therapy advocates the use

of several different analgesics to provide more effective analgesia. In humans, this concept has been widely adopted, and has the advantage that lower doses of each different analgesic can often be used, when they are given in combination (Elia et al., 2005). There are good experimental data in animals to support this concept (e.g. Martin et al., 2004; Miranda et al., 2008), but no well-controlled trials involving post-operative pain. However, it is an easy technique to use, and the balance of evidence suggests it will be of benefit. For example, the use of an opioid such as buprenorphine can be combined with an NSAID such as carprofen. The opioid acts centrally to limit the input of nociceptive information into the CNS and so reduces central hypersensitivity. In contrast, the NSAID acts centrally to limit the central changes induced by the nociceptive information that does get through. In addition, the NSAID peripheral actions decrease inflammation during and after surgery and limit the nociceptive information entering the CNS, as a result of the inflammation. By acting on different points of the pain pathways, the combination should be more effective than either drug given alone. Adding a local anaesthetic to this regimen can provide additional analgesia by blocking specific nerve pathways and so further improve the degree of pain control.

Using combinations of different classes of analgesics can also overcome some of the problems associated with differences in the speed of onset of action of the various agents. In a study comparing the degree of post-operative analgesia provided by pethidine and carprofen in cats, animals which received pethidine had good analgesia immediately following recovery from anaesthesia, compared to animals which received carprofen (Lascelles et al., 1995). In contrast, dogs receiving carprofen had better analgesia later in the post-surgical period. Clearly, combining the two analgesics would produce a more effective approach for controlling post-operative pain – immediate pain relief due to the opioid, and more prolonged analgesia provided by the NSAID.

Pain Relief – Problems A number of clinical problems arise when analgesics are administered to control post-operative pain. The most important problem is the short duration of action of most of the opioid (narcotic) analgesics. Maintenance of effective analgesia with, for example, pethidine may require administration every 1–3 hours, depending upon the species. Continuation of such a regime overnight can cause practical problems. One method of avoiding this difficulty is to use buprenorphine as the analgesic, since there is good evidence in humans, rodents, rabbits and pigs that it has a duration of action of 6–12 hours (Cowan et al., 1977a; Heel et al., 1979; Dum and Herz, 1981; Hermansen et al., 1986; Flecknell and Liles, 1990). In clinical use in a wide range of animal species, it appears to provide effective pain relief for 6–12 hours. Its duration of action in the sheep appears to be considerably less, although of longer duration than pethidine and morphine (Nolan et al., 1987).

An alternative approach is to adopt the well-established human clinical technique of administering analgesics as a continuous infusion. Infusions of analgesics have the advantage of maintaining effective plasma levels of the analgesic,

and so providing continuous pain relief. This is in contrast to intermittent injections, where pain may return before the next dose of analgesic is administered. This technique obviously poses some methodological difficulties in animals, but if an indwelling catheter and harness and swivel apparatus are available, then this can be arranged quite simply. In larger species (> 3–4 kg body weight), a light-weight infusion pump (Smiths Medical, Appendix 4) can be bandaged directly to the animal and continuous infusion made simply by means of a butterfly-type needle anchored subcutaneously or intramuscularly. When analgesics are to be administered by continuous infusion, the infusion rate can be calculated from a knowledge of the pharmacokinetics of the analgesia to be used (Mather, 1983, Chapter 5). If these data are not readily available, an approximation that appears successful in clinical use is as follows: calculate the total dose required over the period of infusion, reduce this by half and set the pump infusion rate accordingly; administer a single, normal dose of the drug as an initial loading dose and start the infusion. The rate can then be adjusted depending upon the animal's responses.

Prolonged analgesia can also be provided by the use of slow-release patches that are placed on the animal's skin. Both fentanyl and buprenorphine patches are available, and they have been used with some success in a range of species (Harvey-Clarke et al., 2000; Shafford et al., 2004; Malavasi et al., 2005; Egger et al., 2007). The patches are manufactured for use in humans, so the rate of drug release varies in different animal species (Riviere and Papich, 2001; Mills and Cross, 2006). Measurement of plasma concentrations of drugs has shown that considerable individual variation occurs (Davidson et al., 2004). For this reason, it is best to consider these patches as providing basal analgesia, and to assess the animal regularly to ensure sufficient analgesia is being provided. Patches need to be placed on the skin for approximately 24 hours before adequate plasma concentrations of analgesic are attained.

Oral Administration The need for repeated injections of analgesics is time consuming and may be distressing to the animal, particularly smaller species that require firm physical restraint to enable an injection to be given safely and effectively. In addition, the need for repeated injections requires veterinary or other staff to attend the animal overnight. To circumvent this problem, the possibility of incorporating analgesics in food or water has been investigated (Kistler, 1988). Long-term analgesia can be produced by this route: Kistler (1988) reported that rats had demonstrable analgesia for a 2-week period when buprenorphine was administered continuously in drinking water. Unfortunately, several practical problems limit the use of this technique. Some animals eat and drink relatively infrequently, or may only do so in the dark phase of their photoperiod. In addition, food and water intake may be depressed following surgery, and this, coupled with wide individual variation in consumption, makes routine application of the technique difficult. If opioids are used, the high first-pass liver metabolism following oral administration requires that high dose rates are given, and this can represent a significant cost if all of the animals' drinking water or food

is medicated. Finally, there may be problems of palatability (Speth et al., 2001). Despite these problems, encouraging results have been obtained with paracetamol (acetaminophen) in rats (Mickley et al., 2006), and the approach deserves further evaluation in a range of different circumstances. If this approach is to be adopted, it is important to deliver an adequate dose, and this should be confirmed by measuring the animals' actual fluid consumption.

Medication of the feed has also been suggested as a means of providing repeated dosing with analgesic, and palatable preparations of a number of NSAIDs are available. Administration of small quantities of medicated food does not avoid the need for repeated attendance overnight, but does remove the need for repeated subcutaneous or intramuscular injections in small rodents. Provision of analgesia with buprenorphine in flavoured gelatin ('Buprenorphine Jello'; Pekow, 1992) has been recommended as a means of providing post-operative pain relief in rats; however, the efficacy of this approach has been questioned. Using thermal anti-nociceptive tests, the oral dose of buprenorphine required to produce analgesia equivalent to the recommended subcutaneous dose too high to be clinically useful (Martin et al., 2001; Thompson et al., 2004). In contrast, other studies have indicated oral administration is effective (Liles et al., 1998; Flecknell et al., 1999b; Roughan and Flecknell, 2004). It is clear that in some animals, this route of administration is likely to be ineffective, so it should only be used if a reliable pain assessment system is in place. With all medicated food-stuffs, rats are initially cautious of jelly pellets, but once a few pellets have been consumed, subsequent pellets are eaten as soon as they are offered. It is therefore advisable to commence administering pellets, which do not contain analgesic, 2–3 days before surgery. After surgery, analgesic-containing jelly can be given. The flavoured gelatin used is domestic fruit-flavoured jelly, reconstituted at double the recommended strength.

Techniques for administration of food pellets at intervals to experimental animals are well established, and it would be a relatively simple procedure to introduce an automated means of delivering pellets at appropriate time intervals. The technique could also be used with larger species, and need not be restricted to opioids, or indeed analgesics. Provided that the animal is eating or drinking, small quantities of highly palatable material could be provided at appropriate intervals. Simple timer devices to achieve this are already marketed for delayed feeding of pet dogs and cats.

Epidural and Intrathecal Opioids Epidural and intrathecal opioids have been shown to have a prolonged effect in humans, and to provide effective analgesia (Glynn, 1987). In animals, both clinical and experimental studies have indicated that the technique can be used in a number of species (Dodman et al., 1992; Duke et al., 1993; Pablo, 1993; Pascoe, 1993; Popilskis et al., 1993). Although used as a research tool in laboratory species (Yaksh et al., 1988), this route of administration has yet to be exploited as a means of controlling post-operative pain. The necessary techniques of epidural or intrathecal injection have been described in rabbits (Kero

et al., 1981; Hughes et al., 1993), guinea pigs (Thomasson et al, 1974) and small rodents (Fairbanks, 2003). In larger species such as the cat, dog, sheep and pig, descriptions of the injection technique can be found in most veterinary anaesthesia texts and a number of other publications (e.g. Klide and Soma, 1968; Hall et al., 2001; Tranquilli et al, 2006).

As mentioned above, the administration of opioids by any route can be associated with the development of respiratory depression. It must be emphasized that this is rarely of clinical significance in animals, unless high doses of pure mu agonists (e.g. fentanyl) are used. If respiratory depression occurs, it can be treated by the administration of the opiate antagonist drug naloxone. Administration of naloxone will also reverse the analgesic effects of the opioid, and it may be preferable to correct the respiratory depression by the use of doxapram. Alternatively, if a mu agonist opioid such as morphine or fentanyl has been used, the respiratory depression can be reversed using nalbuphine or butorphanol, and some analgesia maintained because of the action of these latter two agents at kappa receptors. Repeated administration of these agents may be required, and the animal should be observed carefully for several hours to ensure adequate respiratory function is maintained.

Slow-Release Formulations A number of slow-release preparations of analgesics have been marketed for use in humans (e.g. morphine, oxycodone, hydromorphone). These may be useful in larger species, but should be used with caution pending establishment of the pharmacokinetics of these agents in the particular species. In smaller animals, the tablets and the capsules would need to be divided into smaller doses, and in most instances, this results in a loss of the slow-release properties of the formulation. An exception appears to be an oral morphine preparation ('Oramorph SR', Boehringer Ingelheim) which has been shown to produce prolonged anti-nociception in rats (Dickinson Personal communication). A range of slow-release preparations have been developed specifically for use in laboratory animals; however, none of these are yet commercially available. Some of these formulations are simple to prepare and have proven effective in rodents (Page et al., 1998). An excellent review of these potential approaches to providing long-lasting analgesia is available (Krugner-Higby et al., 2008).

Additional Considerations in Pain Relief Although the use of analgesic drugs remains the most important technique for reducing post-operative pain, the use of these drugs must be integrated into a total scheme for peri-operative care (Carli and Asenjo, 2003; ACLAM, 2007). As discussed in Chapter 1, pain relief in the immediate recovery period can be provided by including an analgesic drug in any pre-anaesthetic medication. Alternatively, if a neuroleptanalgesic combination has been used to produce anaesthesia, it can be reversed by the use of buprenorphine, nalbuphine or butorphanol, rather than naloxone. These agents have been shown not only to reverse the respiratory depressant effects of opioids such as fentanyl but, in contrast to naloxone, to provide effective prolonged analgesia (Robertson and Laing, 1980; Latasch et al., 1984; Flecknell et al., 1989).

The expertise of the surgeon can also greatly influence the degree of post-operative pain. A good surgical technique which minimizes tissue trauma and the prevention of tension on suture lines can considerably reduce post-operative pain. The use of bandages to pad and protect traumatized tissue must not be overlooked and forms an essential adjunct to the use of analgesic drugs.

Aside from measures directed towards alleviating or preventing pain, it is important to consider the overall care of the animal and the prevention of distress. Distress is used in this context to describe conditions which are not in themselves painful, but which are unpleasant and which the animal would normally choose to avoid. For example, recovering from anaesthesia on wet, uncomfortable bedding in a cold, unfamiliar environment would be likely to cause distress to many animals. It is essential to consider the methods described for the control of pain, in conjunction with the techniques discussed earlier in this chapter, aimed at providing good post-operative care.

Recommendations It is difficult to make firm recommendations concerning which analgesics to use routinely, and how often to give them, because of the various factors outlined above. Nevertheless, as a general guide, the following techniques are used routinely in the author's research facility.

When carrying out any surgical procedure, buprenorphine is administered either pre-operatively or immediately following the induction of anaesthesia, if a volatile anaesthetic is used. If neuroleptanalgesic regimens are used, or mu opioids are given as part of a balanced anaesthetic technique, then administration of buprenorphine is delayed until completion of surgery. If the procedure is relatively minor, for example, jugular or carotid cannulation, then only a single dose of analgesic is administered. In some circumstances, a potent NSAID, such as meloxicam or carprofen, may be used as an alternative to buprenorphine.

Following more invasive surgical procedures, such as laparotomy, orthopaedic surgery or craniotomy, opioid administration is continued for 8–48 hours, depending upon the species and the expertise of the surgeon (since this has a major influence on the degree of tissue trauma). When undertaking major surgery, particularly in larger species when the degree of tissue trauma tends to be greater, analgesic administration may continue for 72 hours. In addition, local anaesthetics (e.g. bupivacaine) may be infiltrated into the wound margins, or used to provide a localized nerve block of the area. Frequently, the technique chosen consists of an opioid (buprenorphine) in combination with an NSAID for 8–24 hours, followed by NSAID alone for further 24–36 hours (see Tables 5.5–5.8 for suggested dose rates).

It is important to note that extended use of opioids can produce significant negative effects on animals (Cooper et al., 2005). In rats, the major signs of pain are present for only 6–8 hours following laparotomy (Roughan and Flecknell, 2003), although more subtle effects persist for longer in both rats and mice (Arras et al., 2007). This suggests that a single dose of a long-acting opioid such as buprenorphine, combined with a longer acting NSAID, may provide sufficient

pain relief after mild and moderate surgical procedures in some species. In all instances, it is important to establish the intensity and the duration of pain, and the efficacy of analgesic therapy by the use of pain assessment systems.

CONCLUSIONS

Attention to the suggestions made in this chapter concerning post-operative care can have a dramatic effect on the speed with which animals return to normality following surgical procedures. It has been repeatedly demonstrated in humans that the provision of effective analgesia reduces the time taken for post-operative recovery (Smith and Covino, 1985). The provision of good post-operative care should be considered essential both because of a concern for the animal's welfare and also because it is good scientific practice.

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Anaesthesia of Common Laboratory Species: Special Considerations

The earlier chapters in this book provide important general information needed to provide safe and effective anaesthesia. After having read these, and having considered the various aspects of the anaesthetic process, the final factor to consider is the species of animal involved. The small body size of rodents can make some procedures difficult or impracticable, the potential risk of physical injury to personnel may increase the need for chemical restraint in non-human primates and differences in anatomy and physiology influence the choice of anaesthetic agents for birds, reptiles, amphibians and fish.

This chapter provides suggested dose rates for a range of different anaesthetic agents for common laboratory species. It is important to recognize that individual responses to anaesthetic agents can vary considerably. In addition, different inbred strains also vary in their responses. Factors such as age, sex and environment can also influence responses. For this reason, dose rates and anaesthetic regimens often need adjusting to suit the particular animals being used in a research facility.

Careful consideration of these individual and species-specific factors, together with the general principles of anaesthesia and perioperative care, will help deliver anaesthetics that meet the scientific needs of specific projects, and ensure the maintenance of high standards of animal welfare.

Laboratory animals are anaesthetized either to provide humane restraint while relatively atraumatic procedures are carried out, or to eliminate the perception of pain during surgical operations. Two main factors influence the selection of a method of anaesthesia – concern for the welfare of the animal and the constraints imposed by specific types of research. An anaesthetic technique should therefore:

- Cause a minimum of distress
- Provide an appropriate degree of analgesia
- Result in an uneventful recovery, free from unpleasant side-effects.

Ideally, the technique should also be easy to implement, should have a high success rate and use anaesthetic agents that have a minimum influence on the experimental work that is being undertaken.

These factors have been considered carefully when selecting the methods recommended for each species in this chapter. The primary consideration has been the well-being of the animal, coupled with ease of use and safety of the drug or drug combination. For a more extensive discussion of selecting an anaesthetic agent, see Chapter 2.

Alternative anaesthetic regimes are included since some research protocols will preclude the use of the drugs recommended and, in addition, some drugs may not be readily available in certain laboratories. A comprehensive listing of anaesthetic drug dose rates for each species is also provided.

It is particularly important to read the general chapters on intra-operative care in conjunction with the notes below on anaesthetic techniques for different species.

The dose rates recommended in this chapter are those that have been found effective in the majority of individuals of the species concerned. The response to an anaesthetic drug can vary considerably and may be influenced by the strain of animal, sex, age and environmental conditions in which the animal is housed (Green, 1981; Lovell, 1986a, b, c; Mogil et al., 2005). Strain variations may also become apparent only during recovery from anaesthesia; for example, different inbred strains of mice have shown varying degree of respiratory depression immediately after isoflurane anaesthesia (Groeben et al., 2003). When using a drug or drug combination for the first time, or when anaesthetizing a different strain of animal, it is advisable to proceed cautiously. As experience is gained, a dose rate appropriate to the particular strain can be established.

In order to provide some guidance as to the predicted effect of the different anaesthetics and their duration of action, the dose rate tables for each species include an estimate of the likely depth of anaesthesia, its duration and the anticipated duration of loss of the animal's righting reflex. It is important to note that considerable variation in response is to be expected. With many agents, a range of dose rates is given with a corresponding range of anticipated effects (e.g. light–deep anaesthesia). The terminology used is as follows:

Sedation (light, medium or heavy): The animal will have reduced activity and may become completely immobile, but is easily aroused, particularly by painful stimuli.

- Analgesia: Some pain-alleviating effect is present.
- Immobilization: The animal is immobilized but still responds to painful stimuli.
- Light anaesthesia: The animal is immobile and unconscious, but still responsive to even minor surgical procedures.
- Medium anaesthesia: Most surgical procedures (e.g. laparotomy) may be carried out without causing any response, but the animal may still respond to major surgical stimuli (e.g. orthopaedic surgery).
- Deep anaesthesia: The animal is unresponsive to all surgical stimuli.

These terms are used to provide a general guide, but in all instances the depth of anaesthesia produced in a particular animal should be assessed before commencing surgery (see Chapter 4).

SMALL RODENTS

The problems that arise when anaesthetizing rodents are related primarily to the small body size of these species. Their high surface area to body weight ratio makes them particularly susceptible to the development of hypothermia; intravenous drug administration is limited by the size of the superficial veins, and the small and relatively inaccessible larynx makes endotracheal intubation difficult. A further consequence of the small size of these species is that the volumes of anaesthetic required may be very small. In many instances it might be convenient to mix together the required compounds and dilute them with saline or sterile water for injection. Suggested dilutions are given in Appendix 3. Given these practical constraints, it is often simplest to select an inhalational anaesthetic agent, as induction can be achieved smoothly and rapidly in an anaesthetic chamber, and anaesthesia maintained using a suitable breathing system.

Improvement in the health status of laboratory animals has greatly reduced the incidence of spontaneous disease; however, some rodent colonies still have endemic respiratory infections. The disease may not cause obvious clinical signs, but may cause respiratory failure during the period of anaesthesia or result in the development of severe clinical respiratory disease in the post-operative period.

It is unnecessary to withhold food and water before induction of anaesthesia since vomiting on induction or recovery does not occur in any of the small rodents. As mentioned earlier (Chapter 1), problems may be seen with some guinea pigs that retain food in their pharynx after being anaesthetized. If this occurs then a short period of pre-anaesthetic fasting (3–4 hours) may be introduced.

Rats

Pre-anaesthetic Medication

Most rats can easily be restrained humanely to enable the intraperitoneal or intramuscular injection of an anaesthetic agent, provided they have become accustomed to being handled. One simple way to achieve this is to weigh the animal daily during its acclimatization period (see Chapter 1). This also provides useful information on its normal growth pattern and ensures that it has recovered from the stress associated with transportation. In general, intraperitoneal and subcutaneous injections are tolerated better than intramuscular injections as they cause less pain to the animal. Pre-anaesthetic medication to sedate the animal is not usually required as many injectable anaesthetics are given as a single mixture of two or more agents. If an intravenous induction agent is to be used, initial sedation with a tranquillizer or sedative/analgesic is recommended.

The following drugs can be used to produce sedation and are listed in order of preference (see Table 6.1):

1. Hypnorm (fentanyl/fluanisone; Janssen) (0.2–0.5 ml/kg im; 0.3–0.6 ml/kg ip). At the lower dose rate, sedation and some analgesia is produced. The higher dose rate produces sufficient analgesia to enable procedures such as skin biopsy or cardiac puncture to be carried out (Green, 1975). Occasionally,

TABLE 6.1 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Rat.

Drug	Dose rate	Comments
Acepromazine	2.5 mg/kg im, ip	Light sedation
Atropine	0.05 mg/kg ip, sc	Anticholinergic
Diazepam	2.5–5.0 mg/kg ip, im	Light sedation
Fentanyl/dropiderol (Innovar-Vet)	0.3–0.5 ml/kg im	Immobilization/analgesia
Fentanyl/fluanisone (Hypnorm)	0.2–0.5 ml/kg im	Light/moderate sedation, moderate analgesia
	0.3–0.6 ml/kg ip	
Glycopyrrolate	0.5 mg/kg im	Anticholinergic
Ketamine	50–100 mg/kg im, ip	Deep sedation, immobilization, mild to moderate analgesia
Medetomidine	30–100 µg/kg sc, ip	Light to heavy sedation, mild to moderate analgesia
Midazolam	5 mg/kg ip	Light sedation
Xylazine	1–5 mg/kg im, ip	Light to heavy sedation, mild to moderate analgesia

Considerable variation in effect occurs between different strains.

marked respiratory depression is seen when the drug is administered at the higher dose rate. If this produces severe cyanosis, it can be reversed with nalbuphine, butorphanol or naloxone.

- Medetomidine (30–100 µg/kg sc) produces light to heavy sedation, and at the higher dose rate, many animals will lose their righting reflex. Some strains require significantly higher dose rates (300 µg/kg) before becoming sedated and losing their righting reflex. The degree of analgesia produced is insufficient for anything other than very minor procedures, but is suitable for non-painful manipulations such as radiography (Virtanen, 1989). Medetomidine markedly potentiates the effects of other anaesthetic agents. For example, the concentration of volatile agent needed to produce surgical anaesthesia may be reduced by more than 60%.
- Xylazine (1–3 mg/kg im or ip) produces mild to moderate sedation. Although the drug provides little analgesia when used alone, it markedly potentiates the effects of other anaesthetic agents.
- Ketamine (50–100 mg/kg im or ip) produces deep sedation. The degree of muscle relaxation is poor, and the level of analgesia is insufficient for even superficial surgery (Green et al., 1981a).
- Acepromazine (2.5 mg/kg im or ip) produces moderate sedation, but has no analgesic action.

6. Diazepam or midazolam (2.5–5 mg/kg im or ip) produces light sedation, but neither drug has any analgesic action.

Atropine (0.05 mg/kg ip or sc) or glycopyrrolate (0.5 mg/kg im) (Olson et al., 1993) can be administered to reduce salivary and bronchial secretions and protect the heart from vagal inhibition.

Appropriate pre-anaesthetic medication will reduce the stress caused by induction of anaesthesia and also ease handling and restraint. In addition, it will reduce the amount of other anaesthetic agents required to produce general anaesthesia. The dose rates of anaesthetic drugs quoted in Table 6.2 apply to rats that have received no pre-anaesthetic medication unless otherwise stated. Generally, these dosages can be reduced by at least 30–50% if one of the drugs listed above has been administered.

General Anaesthesia

Injectable Agents

The small body size of the rat makes intravenous injection difficult; hence, drugs are usually administered by the intraperitoneal or intramuscular route. If these routes are used, it is not possible to administer the drug gradually to effect and the anaesthetic must be given as a single, calculated dose. Because of the wide variation in drug response between different strains of rat, between male and female animals and between individuals, it is best to use a drug or drug combination that provides a wide margin of safety. Anaesthetic dose rates are summarized in Table 6.2.

The anaesthetic combination of choice for rats is fentanyl/fluanisone (Hypnorm, Janssen) together with diazepam or midazolam (0.6 ml/kg ip 'Hypnorm', and diazepam 2.5 mg/kg ip). When using midazolam the components are mixed together with water for injection (see Appendix 3). These combinations provide good surgical anaesthesia with excellent muscle relaxation lasting about 20–40 minutes (Green, 1975; Flecknell and Mitchell, 1984). Longer periods of anaesthesia can be achieved by the administration of additional doses of Hypnorm (about 0.1 ml/kg im every 30–40 minutes). Following the completion of surgery, the anaesthesia can be reversed using nalbuphine (0.1 mg/kg iv, 1.0 mg/kg ip or sc) or butorphanol (0.1 mg/kg iv, 2 mg/kg ip or sc).

A second effective alternative is to administer medetomidine (0.5 mg/kg ip) or xylazine (10 mg/kg ip) in combination with ketamine (75 mg/kg ip). The two compounds can be mixed in the same syringe to provide good surgical anaesthesia, although the depth of anaesthesia may be insufficient for major surgery in some animals (Van-Pelt, 1977; Green et al., 1981a; Hsu et al., 1986; Wixson et al., 1987; Nevalainen et al., 1989). This combination provides about 30 minutes of surgical anaesthesia. The combination can be partially reversed using atipamezole (1 mg/kg sc or ip), but early reversal (10–20 minutes after induction) may be associated with undesirable behavioural disturbances due to the effects of ketamine (Morris, personal communication). Ketamine/xylazine has been reported to

TABLE 6.2 Anaesthetic Dose Rates in the Rat.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	10–12 mg/kg iv	Surgical anaesthesia	5	10
Chloral hydrate	400 mg/kg ip	Light/surgical anaesthesia	60–120	120–180
Alpha-chloralose	55–65 mg/kg ip	Light anaesthesia	480–600	Non-recovery only
Etorphine/methotrimeprazine (Immobilon) + midazolam	0.5 ml/kg sc*	Surgical anaesthesia	60–70	120–240
Fentanyl/fluanisone + diazepam	0.6 ml/kg ip + 2.5 mg/kg ip	Surgical anaesthesia	20–40	120–240
Fentanyl/fluanisone/ midazolam	2.7 ml/kg ipt	Surgical anaesthesia	30–40	120–240
Fentanyl/medetomidine	300 µg/kg + 200 µg/kg ip	Surgical anaesthesia	60–70	240–360
Inactin (thiobutobarbital)	80 mg/kg ip	Surgical anaesthesia	60–240	120–300
Ketamine/acepromazine	75 mg/kg + 2.5 mg/kg ip	Light anaesthesia	20–30	120
Ketamine/diazepam	75 mg/kg + 5 mg/kg ip	Light anaesthesia	20–30	120

Ketamine/medetomidine	75 mg/kg + 0.5 mg/kg ip	Surgical anaesthesia	20–30	120–240
Ketamine/midazolam	75 mg/kg + 5 mg/kg ip	Light anaesthesia	20–30	120
Ketamine/xylazine	75–100 mg/kg + 10 mg/kg ip	Surgical anaesthesia	20–30	120–240
Ketamine/xylazine/ acepromazine	40–50 mg/kg + 2.5 mg/kg + 0.75 mg/kg im			
Methohexital	10–15 mg/kg iv	Surgical anaesthesia	5	10
Pentobarbital	40–50 mg/kg ip	Light anaesthesia	15–60	120–240
Propofol	10 mg/kg iv	Surgical anaesthesia	5	10
Thiopental	30 mg/kg iv	Surgical anaesthesia	10	15
Tiletamine/zolezepam	40 mg/kg ip	Light anaesthesia	15–25	60–120
Urethane	1000 mg/kg ip	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

**Dose in millilitres per kilogram of a mixture of one part 'Immobilon', one part midazolam (5 mg/ml initial concentration) and two parts water for injection.*

†Dose in millilitres per kilogram of a mixture of one part 'Hypnorm' plus two parts water for injection, and one part midazolam (5 mg/ml initial concentration).

cause an increased incidence of post-anaesthetic corneal ulceration, although the incidence can be reduced by reversal of xylazine (Turner and Albassam, 2005). Ketamine and xylazine can also be administered in combination with acepromazine, enabling the use of lower doses of the individual components (Welberg et al., 2006).

A third safe and effective anaesthetic regimen is fentanyl (300 µg/kg ip) and medetomidine (300 µg/kg ip). The two agents can be mixed and administered as a single injection. Fentanyl/medetomidine provides about 60 minutes of surgical anaesthesia (Hu et al., 1992). Sufentanyl (40 µg/kg) and medetomidine (150 µg/kg), mixed and administered subcutaneously as a single injection, may also be used (Hedenqvist et al., 2000). Both combinations produce respiratory depression and this can be severe, so administration of oxygen is strongly recommended. However, recovery is very rapid provided anaesthesia is reversed by administration of atipamezole (1 mg/kg sc or ip) (to reverse medetomidine) and either nalbuphine (0.1 mg/kg iv, 1.0 mg/kg ip or sc), butorphanol (0.1 mg/kg iv, 2 mg/kg ip or sc) or another mixed agonist/antagonist opioid analgesic (see Tables 5.5–5.8 and Table 6.3). Experience has shown that the quality of induction and recovery with this method of anaesthesia is greatly improved by allowing the rats to acclimatize for 1–2 hours after movement into the room in which the procedure is undertaken (Drage, personal communication).

If intravenous administration of drugs is feasible, then propofol (10 mg/kg iv) (Glen, 1980; Brammer et al., 1992; Cockshott et al., 1992) or alphaxalone/alphadolone (6–9 mg/kg iv) (Green et al., 1978) produces surgical anaesthesia, and both compounds are especially useful for administering by continuous infusion to provide stable, long-lasting anaesthesia. The maintenance dose of propofol can be markedly reduced if buprenorphine is administered as pre-anaesthetic medication (Penderis and Franklin, 2005). When administered by the intraperitoneal route the effects are less predictable and these drugs can only be relied upon to produce heavy sedation. It is likely that alphaxalone will have similar properties.

Tiletamine/zolezepam generally only produces light anaesthesia, but surgical planes of anaesthesia can be produced in some strains of rat. In these animals the degree of cardiovascular system depression seemed less than with other anaesthetic agents (Saha et al., 2007).

Pentobarbital should be diluted to provide a 30 mg/ml solution and up to 40–50 mg/kg administered intraperitoneally. Severe respiratory depression invariably accompanies the onset of surgical anaesthesia and this agent has a narrow safety margin. Until an appropriate dose rate is established, both inadequate and excessively deep anaesthesia may result, so this drug is best avoided in rats. Intraperitoneal administration of pentobarbital may also cause pain, as a result of the low pH of the solution (Svendsen et al., 2007).

Inhalational Agents

The most convenient method of inducing anaesthesia in the rat is to use an anaesthetic chamber. This should be constructed from perspex, so that the animal can

TABLE 6.3 Antagonists to Anaesthetic Regimens for Use in Rodents and Rabbits.

Compound	Anaesthetic regimen	Dose rate	Comments
Atipamezole	Any regimen using xylazine or medetomidine	0.1–1 mg/kg im, ip, sc or iv	Highly specific alpha ₂ adrenoreceptor antagonist; dose required varies depending on dose of xylazine or medetomidine administered
Buprenorphine	Any regimen using μ opioids (e.g. fentanyl)	See Table 14c	Slower onset than butorphanol and nalbuphine, but longer-acting analgesia
Doxapram	All anaesthetics	5–10 mg/kg im, iv or ip	General respiratory stimulant
Flumaznil	Benzodiazepine (e.g. midazolam)	0.1–10 mg/kg	Dose varies depending upon dose of benzodiazepine; resedation may occur
Butorphanol	Any regimen using μ opioids (e.g. fentanyl)	See Table 14c	Almost as rapid-acting as naloxone, maintains post-operative analgesia
Naloxone	Any regimen using μ opioids (e.g. fentanyl)	0.01–0.1 mg/kg iv, im or ip	Reverses analgesia as well as respiratory depression
Yohimbine	Any regimen using xylazine or medetomidine	0.2 mg/kg iv 0.5 mg/kg im	Relatively non-specific antagonist; not recommended

be observed during induction. Anaesthetic vapour should be supplied from an anaesthetic machine, and the chamber should be designed so that excess anaesthetic gas can be ducted to a gas-scavenging device or removed from the room via the ventilation system. Following induction of anaesthesia, the rat should be removed from the chamber and anaesthesia maintained using a small face mask connected to the anaesthetic machine (see Chapter 3).

Endotracheal Intubation

The major disadvantage of using a face mask for connection of the animal to the anaesthetic gas supply is that it is difficult to assist ventilation should this prove necessary. Endotracheal intubation, together with use of an appropriate anaesthetic circuit, allows easy control of ventilation. Intubation is not a difficult procedure to master, especially if specialized apparatus is purchased. Further details of the technique are given in Chapter 3.

Mechanical Ventilation

Several different ventilators are available for use in rats, with a variety of mechanisms of action. All aim to achieve controlled ventilation of the lungs by means of the application of intermittent positive pressure to the patient's airway. The ventilators manufactured by Harvard Apparatus Ltd. (Appendix 4) are the most widely used in the UK. A volume-cycled piston model and a pressure-cycled ventilator are available. Neither of these ventilators has facilities for humidification of anaesthetic gases, but this can be achieved quite readily by bubbling the gases through a water bath. An economic approach is to purchase a human infant feeding bottle warmer, fill it with water and pipe anaesthetic gases through a glass aerator placed in the unit.

Anaesthetic management is particularly important to prevent the development of hypothermia in rats. Ideally, the rat should be placed on a thermostatically controlled heating blanket (Harvard Apparatus Ltd.) or alternatively, heating lamps can be used. Both measures can be combined with the use of insulating material such as cotton wool, aluminium foil or bubble packing (Chapter 4). These measures must be continued in the post-operative recovery period.

Mice

Pre-anaesthetic Medication

Mice are easily restrained humanely and it will rarely be necessary to produce sedation before induction of anaesthesia. If sedation is required, the following drugs can be used (Table 6.4):

1. Hypnorm (Janssen; 0.1–0.3 ml/kg ip) provides sedation and sufficient analgesia for superficial procedures such as ear punching (Green, 1975). The drug is most conveniently administered as a 1:10 dilution of the commercial preparation. The effects of this mixture can be partially reversed using nalbuphine (4 mg/kg sc or ip) or butorphanol (2 mg/kg ip or sc).
2. Medetomidine (30–100 µg/kg ip) produces light to deep sedation. As with the rat, considerable strain variation may occur. Sedation can be completely reversed using atipamezole (1 mg/kg ip).
3. Xylazine (5–10 mg/kg ip) produces sedation but appears to have little analgesic action when used alone in mice.
4. Acepromazine (2–5 mg/kg ip) produces sedation but has no analgesic action.
5. Diazepam (5 mg/kg ip) or midazolam (5 mg/kg ip) produces sedation but no analgesia.

Atropine (0.04 mg/kg sc, im or ip) can be administered to reduce salivary gland bronchial secretions. Dose rates for general anaesthetics given below should be reduced by 30–50% if one of the sedative drugs listed above has been administered.

TABLE 6.4 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Mouse.

Drug	Dose rate	Comments
Acepromazine	2–5 mg/kg ip, sc	Light sedation
Atropine	0.04 mg/kg sc	Anticholinergic
Diazepam	5 mg/kg im, ip	Light sedation
Fentanyl/dropiderol (Innovar-Vet)	0.5 ml/kg im	Immobilization, analgesia
Fentanyl/fluanisone (Hypnorm)	0.1–0.3 ml/kg ip	Light sedation, moderate analgesia
Ketamine	100–200 mg/kg im	Deep sedation, mild to moderate analgesia
Medetomidine	30–100 µg/kg sc	Light to deep sedation, mild to moderate
Midazolam	5 mg/kg im, ip	Light to moderate sedation
Xylazine	5–10 mg/kg ip	Light sedation, mild to moderate analgesia

Considerable variation in effects occurs between different strains.

General Anaesthesia

Injectable Agents

As with rats, drugs are most conveniently administered by the intraperitoneal route. Dose rates of anaesthetic agents are summarized in Table 6.5.

The anaesthetic combination of choice is fentanyl/fluanisone (Hypnorm, Janssen) together with midazolam or diazepam (0.4 ml/kg ip 'Hypnorm', and diazepam 5 mg/kg ip). When using midazolam the components are mixed together with water for injection (see Appendix 3). These combinations provide good surgical anaesthesia lasting about 20–40 minutes (Green, 1975; Flecknell and Mitchell, 1984). Anaesthesia can be prolonged by the administration of additional doses of Hypnorm (0.3 every 30–40 minutes). Following the completion of surgery, anaesthesia can be partially reversed by the administration of nalbuphine (4 mg/kg ip or sc) or butorphanol (2.0 mg/kg sc or ip).

A combination of ketamine (75 mg/kg ip) and medetomidine (1.0 mg/kg ip) produces moderate surgical anaesthesia in most strains of mouse. In some strains, however, the degree of analgesia is insufficient for major surgery (e.g. laparotomy) (Voipio et al., 1990; Cruz et al., 1998). In contrast, this dose of medetomidine caused increased mortality; better results were obtained with a dose of 0.25 mg medetomidine and 100 mg/kg ketamine (Kilic et al., 2001). This illustrates the importance of assessing the effects of injectable anaesthetics in the particular strain, age and sex of mouse that is to be used.

TABLE 6.5 Anaesthetic Dose Rates in the Mouse.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphachoralose	100–120 mg/kg ip	Light anaesthesia	300–420	Non-recovery only
Alphaxalone/alphadolone	10–15 mg/kg iv	Surgical anaesthesia	5	10
Chloral hydrate	400 mg/kg ip	Light anaesthesia	30	60–90
Fentanyl/fluanisone (Hypnorm) + diazepam	0.4 ml/kg ip + 5 mg/kg ip	Surgical anaesthesia	30–40	120–240
Fentanyl/fluanisone (Hypnorm)/midazolam	10.0 ml/kg ip*	Surgical anaesthesia	30–40	120–240
Ketamine/acepromazine	100 mg/kg + 5 mg/kg ip	Immobilization/anaesthesia	20–30	40–120
Ketamine/diazepam	100 mg/kg + 5 mg/kg ip	Immobilization/anaesthesia	20–30	60–120
Ketamine/medetomidine	75 mg/kg + 1.0 mg/kg ip	Surgical anaesthesia	20–30	60–120
Ketamine/midazolam	100 mg/kg + 5 mg/kg ip	Immobilization/anaesthesia	20–30	60–120
Ketamine/xylazine	80–100 mg/kg + 10 mg/kg ip	Surgical anaesthesia	20–30	60–120
Ketamine/xylazine/acepromazine	80–100 mg/kg + 10 mg/kg ip + 3 mg/kg ip	Surgical anaesthesia	30–40	60–120
Methohexital	10 mg/kg iv	Surgical anaesthesia	5	10
Metomidate/fentanyl	60 mg/kg + 0.06 mg/kg sc	Surgical anaesthesia	40–60	90–120
Pentobarbital	40–50 mg/kg ip	Immobilization/anaesthesia	20–40	120–180
Propofol	26 mg/kg iv	Surgical anaesthesia	5–10	10–15
Thiopental	30–40 mg/kg iv	Surgical anaesthesia	5–10	10–15
Tiletamine/zolezepam	80 mg/kg ip	Immobilization		60–120
Tribromoethanol	240 mg/kg ip	Surgical anaesthesia	15–45	60–120

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

**Dose in millilitres per kilogram of a mixture of one part 'Hypnorm' plus two parts water for injection, and one part midazolam (5 mg/ml initial concentration).*

Ketamine and medetomidine can be mixed in the same syringe and given as a single injection. Anaesthesia can be partially reversed by administration of atipamezole (1 mg/kg sc).

An alternative combination is that of ketamine (80–100 mg/kg ip) and xylazine (10 mg/kg ip). This combination can also be pre-mixed in the correct proportions and administered as a single intraperitoneal injection. It provides 20–30 minutes of anaesthesia, but the depth of anaesthesia is often insufficient to enable major surgery to be carried out humanely (Mulder and Mulder, 1979; Green et al., 1981a; Erhardt et al., 1984). The depth and duration of anaesthesia can be increased by the addition of acepromazine (ketamine 100 mg/kg, xylazine 10 mg/kg, acepromazine 3 mg/kg, all administered ip) (Arras et al., 2001; Buitrago et al., 2008). Anaesthesia can be partially reversed by administration of atipamezole (1 mg/kg sc).

The combination of metomidate (60 mg/kg) and fentanyl (0.06 mg/kg) produces stable surgical anaesthesia in mice (Green et al., 1981b). The two drugs are combined and given as a single subcutaneous injection.

If the technique of intravenous injection can be mastered, then either propofol (26 mg/kg iv) (Glen, 1980) or alphaxalone/alphadolone (Child et al., 1971; Green et al., 1978) can be used to provide short periods (5–10 minutes) of anaesthesia. An advantage of these compounds is that repeated administration to prolong anaesthesia is not associated with prolongation of the recovery period (see section on Long-Term Anaesthesia in Chapter 5). It is likely that alphaxalone will have properties similar to those of alphaxalone/alphadolone. Intraperitoneal administration of propofol, either alone or together with opioid analgesics, has unpredictable effects and is not recommended in this species (Alves et al., 2007).

If pentobarbital is to be used, it should be diluted to provide a 6 mg/ml solution and administered at a dosage of 40–50 mg/kg ip. The variation of effect in different strains of mice is very considerable, sleep times ranging from 10 to 300 minutes (Lovell, 1986b) with identical doses of anaesthetic (45 mg/kg), so that over- or under-dosage with this drug frequently occurs.

Inhalational Agents

Induction of anaesthesia using an anaesthetic chamber is simple and convenient. Maintenance using a face mask is straightforward, but may require a suitably sized mask to be constructed, for example from the end of a disposable syringe barrel.

Endotracheal Intubation

Endotracheal intubation is technically difficult to carry out in mice and requires the use of a purpose-built laryngoscope (Costa et al., 1986) or purchase of specialist apparatus (see Chapter 3).

Mechanical Ventilation

Mechanical ventilation can be carried out using one of a number of purpose-designed ventilators (Schwarte et al., 2000) (Appendix 7, Chapter 5).

Anaesthetic Management

Mice are even more prone than rats to develop hypothermia, and it is essential to take measures to maintain body temperature (see Chapter 4).

Hamsters

Pre-anaesthetic Medication

Hamsters are easily restrained humanely and pre-anaesthetic sedation is rarely necessary. If restraint is a problem, an anaesthetic chamber should be used for induction of anaesthesia. If sedation is required, the following drugs can be used (see also Table 6.6):

1. Hypnorm (0.5 ml/kg ip) provides sufficient analgesia for superficial procedures.
2. Medetomidine (100 µg/kg sc) produces moderate sedation in hamsters, but animals do not lose their righting reflex even at high dose rates (Morris, 1991).
3. Diazepam (5 mg/kg ip) or midazolam (5 mg/kg ip) produces sedation but no analgesia.

TABLE 6.6 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Hamster.

Drug	Dose rate	Comments
Acepromazine	2.5 mg/kg ip	Light sedation
Atropine	0.04 mg/kg sc	Anticholinergic
Diazepam	5 mg/kg im, ip	Light to moderate sedation
Fentanyl/dropiderol (Innovar-Vet)	0.9 ml/kg im	Analgesia; unpredictable degree of sedation
Fentanyl/fluanisone (Hypnorm)	0.2–0.5 ml/kg im 0.3–0.6 ml/kg ip	Light/moderate sedation, moderate analgesia
Glycopyrrolate	0.5 mg/kg im	Anticholinergic
Ketamine	50–100 mg/kg ip	Deep sedation, immobilization, mild to moderate analgesia
Medetomidine	30–100 µg/kg sc, ip	Light to heavy sedation, mild to moderate analgesia
Midazolam	5 mg/kg ip	Light sedation
Xylazine	1–5 mg/kg im, ip	Light to heavy sedation, mild to moderate analgesia

Considerable variation in effects occurs between different strains.

Atropine (0.04 mg/kg sc, im or ip) can be administered to reduce salivary and bronchial secretions. Dose rates for general anaesthesia given below should be reduced by 30–50% if one of the sedative drugs listed above has been administered.

General Anaesthesia

Injectable Agents

As with other small rodents, drugs are most conveniently administered by intraperitoneal injection (see also Table 6.7).

The anaesthetic combination of choice for Syrian hamsters is fentanyl/fluanisone with midazolam or diazepam (1.0 ml/kg ip ‘Hypnorm’, and diazepam 5 mg/kg ip). When using midazolam the components are mixed together with water for injection (see Appendix 3). These combinations provide good surgical anaesthesia lasting about 20–40 minutes (Flecknell and Mitchell, 1984) and can be partially reversed with nalbuphine (2 mg/kg sc) or butorphanol (2.0 mg/kg sc).

An alternative, equally satisfactory combination in the Syrian hamster is ketamine (100–200 mg/kg ip) and xylazine (10 mg/kg ip), which in this species appears to reliably produce surgical anaesthesia (Curl and Peters, 1983). Ketamine (100 mg/kg) mixed with medetomidine (0.25 mg/kg) also appears to produce effective surgical anaesthesia (Erhardt et al., 2001). Anaesthesia can be partially reversed using atipamezole (1 mg/kg).

The use of pentobarbital (50–90 mg/kg ip) in hamsters is particularly hazardous and a high mortality often occurs. If pentobarbital is to be used in any small rodent, it is best to administer a dose sufficient to produce light anaesthesia (50 mg/kg ip) and then administer a volatile anaesthetic to produce full surgical anaesthesia.

Inhalational Agents

Induction of anaesthesia using an anaesthetic chamber is simple and convenient, and halothane, isoflurane and methoxyflurane provide effective and safe anaesthesia. A suitably sized mask may need to be constructed for anaesthetic maintenance, or a commercially available system purchased (e.g. IMS, Appendix 7).

Endotracheal Intubation

Endotracheal intubation is difficult to carry out in hamsters and requires the use of a purpose-built laryngoscope (Costa et al., 1986) (see Chapter 3).

Mechanical Ventilation

Mechanical ventilation can be carried out using a purpose-designed rodent (Appendix 7, Chapter 5).

Anaesthetic Management

As with other small rodents, prevention of hypothermia is of critical importance (see chapter).

TABLE 6.7 Anaesthetic Dose Rates in the Hamster.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alpha-chloralose	80–100 mg/kg ip	Immobilization		180–240
Alphaxalone/alphadolone	150 mg/kg ip	Immobilization/anaesthesia	20–60	120–150
Fentanyl/fluanisone (Hypnorm) + diazepam	1 ml/kg im or ip + 5 mg/kg ip	Surgical anaesthesia	20–40	60–90
Fentanyl/fluanisone (Hypnorm)/midazolam	4.0 ml/kg ip*	Surgical anaesthesia	20–40	60–90
Ketamine/acepromazine	150 mg/kg + 5 mg/kg ip	Immobilization/anaesthesia	45–120	75–180
Ketamine/diazepam	70 mg/kg + 2 mg/kg ip	Immobilization/anaesthesia	30–45	90–120
Ketamine/medetomidine	100 mg/kg + 250 µg/kg ip	Surgical anaesthesia	30–60	60–120
Ketamine/xylazine	200 mg/kg + 10 mg/kg ip	Surgical anaesthesia	30–60	90–150
Pentobarbitone	50–90 mg/kg ip	Immobilization/anaesthesia	30–60	120–180
Tiletamine/zolezepam	50–80 mg/kg ip	Immobilization/anaesthesia	20–30	30–60
Tiletamine/zolezepam/xylazine	30 mg/kg + 10 mg/kg ip	Surgical anaesthesia	30	40–60
Urethane	1000–2000 mg/kg ip	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

**Dose in millilitres per kilogram of a mixture of one part 'Hypnorm' plus two parts water for injection, and one part midazolam (5 mg/ml initial concentration).*

Gerbils

Pre-anaesthetic Medication

Initial restraint of gerbils for intraperitoneal administration of anaesthetics is reasonably simple, but young or particularly active individuals may be better anaesthetized using an anaesthetic chamber.

Information on the effects of sedative agents is limited in gerbils, but the following agents appear reasonably effective in this species (see also Table 6.8).

Hypnorm (0.5–1.0 ml/kg ip) provides sufficient analgesia for superficial procedures. Partial reversal is possible using nalbuphine (4 mg/kg ip or sc) or butorphanol (2 mg/kg ip or sc).

Diazepam (5 mg/kg ip) or midazolam (5 mg/kg ip) produces sedation but no analgesia.

Atropine (0.04 mg/kg sc, im or ip) can be administered to reduce salivary and bronchial secretions.

Dose rates for general anaesthesia given below should be reduced by 30–50% if one of the sedative drugs listed above has been administered.

General Anaesthesia

Injectable Agents

Drugs are most conveniently administered by intraperitoneal injection in gerbils (see also Table 6.9).

TABLE 6.8 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Gerbil.

Drug	Dose rate	Comments
Acepromazine	3 mg/kg im	Light sedation
Atropine	0.04 mg/kg sc	Anticholinergic
Diazepam	5 mg/kg im, ip	Light sedation
Fentanyl/fluanisone (Hypnorm)	0.5–1.0 ml/kg im, ip	Moderate sedation, moderate analgesia
Ketamine	100–200 mg/kg im	Heavy sedation, mild to moderate analgesia
Medetomidine	100–200 µg/kg ip	Light to heavy sedation, mild to moderate analgesia
Midazolam	5 mg/kg im, ip	Light/moderate sedation
Xylazine	2 mg/kg im	Light sedation, mild to moderate analgesia

Considerable variation in effect occurs between different strains.

TABLE 6.9 Anaesthetic Dose Rates in the Gerbil.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	80–120 mg/kg ip	Immobilization	–	60–90
Fentanyl/fluanisone (Hypnorm) + diazepam	0.3 ml/kg im or ip + 5 mg/kg ip	Surgical anaesthesia	20	60–90
Fentanyl/fluanisone (Hypnorm)/midazolam	8.0 ml/kg ip*	Surgical anaesthesia	20	60–90
Ketamine/acepromazine	75 mg/kg + 3 mg/kg ip	Immobilization	–	60–90
Ketamine/diazepam	50 mg/kg + 5 mg/kg ip	Immobilization	–	30–60
Ketamine/medetomidine	75 mg/kg + 0.5 mg/kg ip	Medium anaesthesia	20–30	90–120
Ketamine/xylazine	50 mg/kg + 2 mg/kg ip	Immobilization	–	20–60
Metomidate/fentanyl	50 mg/kg + 0.05 mg/kg sc	Surgical anaesthesia	45–90	180–240
Pentobarbital	60–80 mg/kg ip	Immobilization/anaesthesia	20	60–90
Tribromoethanol	250–300 mg/kg ip	Surgical anaesthesia	15–30	30–90

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs.

For recommended techniques, see text.

**Dose in millilitres per kilogram of a mixture of one part 'Hypnorm' plus two parts water for injection, and one part midazolam (5 mg/ml initial concentration).*

The combination of fentanyl (0.05 mg/kg sc) and metomidate (50 mg/kg sc) appears most reliable in producing general anaesthesia in gerbils (Flecknell, 1983).

Fentanyl/fluanisone with midazolam or diazepam (0.3 ml/kg ip 'Hypnorm', and diazepam 5 mg/kg ip) is less satisfactory in gerbils than in other rodents, and only light anaesthesia may be produced. When using midazolam the components are mixed together with water for injection (see Appendix 3).

Ketamine (75 mg/kg) and medetomidine (0.5 mg/kg), mixed together and administered by intraperitoneal injection, produce medium planes of anaesthesia in gerbils (Perez-Garcia et al., 2003). The medetomidine may be reversed using atipamezole (1 mg/kg sc or ip).

As in hamsters, the use of pentobarbital in gerbils is particularly hazardous and a high mortality often occurs if this drug is used to produce surgical anaesthesia (80 mg/kg ip). Lower dose rates (60 mg/kg ip) produce light anaesthesia which can be deepened using low concentrations of volatile anaesthetics (e.g. 0.5% halothane).

Inhalational Agents

Sevoflurane (Henke et al., 2004), halothane, isoflurane and methoxyflurane can be used to provide effective and safe anaesthesia. Induction using an anaesthetic chamber is simple and convenient, followed by maintenance if required using a face mask, as with other small rodents.

Endotracheal Intubation

Endotracheal intubation requires the use of a purpose-built laryngoscope (Costa et al., 1986).

Mechanical Ventilation

Mechanical ventilation can be carried out using a purpose-made ventilator (Appendix 7, Chapter 5).

Anaesthetic Management

Like other small rodents, gerbils are especially prone to develop hypothermia, and heating pads or lamps should be used to prevent this (see Chapter 4).

Guinea Pigs

Guinea pigs are among the most difficult rodents to achieve safe and effective anaesthesia. Their response to many injectable anaesthetics is highly variable, and post-anaesthetic complications such as respiratory infections, digestive disturbances and generalized depression and inappetence are frequently seen. Many of these problems can be avoided by careful selection of anaesthetic agents and a high standard of intra- and post-operative nursing care.

Pre-anaesthetic Medication

Guinea pigs are non-aggressive animals that are generally easy to handle and restrain. When frightened they run around their cage at high speed, making safe handling difficult. It is important to approach guinea pigs quietly and handle them gently but firmly. They should be picked up around the shoulders and thorax and the hindquarters supported as they are lifted clear of their cage. Intramuscular or intraperitoneal injection of anaesthetic agents can then be carried out. Pre-anaesthetic medication is therefore not usually required but, if an anaesthetic is to be administered by intravenous injection into an ear vein, cephalic vein or medial saphenous vein, initial sedation is advantageous.

The following drugs can be used to produce sedation and restraint (see also Table 6.10):

1. Fentanyl/fluanisone (Hypnorm, Janssen) (1.0 ml/kg im or ip) will produce restraint, sedation and sufficient analgesia for minor procedures such as skin biopsy.
2. Diazepam (5 mg/kg ip) or midazolam (5 mg/kg ip or im) produces heavy sedation and immobility, but no analgesia. The animal is easily roused by painful stimuli or other disturbances such as noise. This agent can be useful in providing sufficient sedation to allow local anaesthetic techniques to be used humanely.
3. Ketamine (100 mg/kg im) immobilizes guinea pigs but does not produce good analgesia.
4. Medetomidine and xylazine administered alone have very little sedative effect in guinea pigs, but do potentiate the effects of other anaesthetic agents (see below).

TABLE 6.10 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Guinea Pig.

Drug	Dose rate	Comments
Acepromazine	0.5–1.0 mg/kg im	Light to moderate sedation
Alphaxalone/ alphadolone	40 mg/kg im, ip	Heavy sedation, mild analgesia
Atropine	0.05 mg/kg sc	Anticholinergic
Diazepam	2.5 mg/kg ip, im	Heavy sedation
Fentanyl/dropiderol (Innovar-Vet)	0.44–0.8 ml/kg im	Sedation, analgesia
Fentanyl/fluanisone (Hypnorm)	1.0 ml/kg im, ip	Moderate sedation, moderate analgesia
Ketamine	100 mg/kg im, ip	Heavy sedation, light analgesia
Midazolam	5 mg/kg im, ip	Heavy sedation

Considerable variation in effects occurs between different strains.

Atropine (0.05 mg/kg sc) should be administered to minimize the volume of bronchial and salivary secretions. It is particularly useful in guinea pigs because of their relatively narrow airways, which are prone to obstruction.

The dose rates of drugs listed below apply to guinea pigs which have received no pre-anaesthetic medication unless otherwise stated. The dosages of general anaesthetics should be reduced by 30–50% if one of the drugs listed above has been administered.

General Anaesthesia

Injectable Agents

Intravenous administration of anaesthetics is difficult to achieve in guinea pigs, and drugs are usually administered by the intraperitoneal, subcutaneous or intramuscular route. The animals should be carefully weighed and dose rates calculated accurately. Anaesthetic dose rates are summarized in Table 6.11.

The anaesthetic combination of choice is fentanyl/fluanisone (Hypnorm, Janssen) together with midazolam or diazepam (1.0 ml/kg ip 'Hypnorm', and diazepam 2.5 mg/kg ip). When using midazolam the components are mixed together with water for injection (see Appendix 3). These combinations provide good surgical anaesthesia lasting about 45 minutes (Green, 1975; Flecknell and Mitchell, 1984). If a longer period of anaesthesia is required, further doses of Hypnorm can be given (approximately 0.5 ml/kg im every 20–30 minutes). Following the completion of surgery the anaesthesia can be partially reversed using nalbuphine (1 mg/kg ip or sc), butorphanol (1 mg/kg ip or sc) or buprenorphine (0.01 mg/kg iv or 0.05 mg/kg ip).

An effective alternative is to administer ketamine (40 mg/kg im) and xylazine (5 mg/kg sc). This combination provides about 30 minutes of surgical anaesthesia, although the degree of analgesia may be insufficient to carry out major surgery in some animals (D'Alleine and Mann, 1982; Hart et al., 1984; Barzago et al., 1994). Ketamine (40 mg/kg ip) and medetomidine (0.5 mg/kg ip) combination produces light surgical anaesthesia (Nevalainen et al., 1989). Anaesthesia can be partially reversed using atipamezole (1 mg/kg ip). A combination of fentanyl, climazolam and xylazine (0.05/2.0/2.0 mg/kg, im) has been reported to provide effective surgical anaesthesia. The effects of this combination can be completely reversed with naloxone, sarmazenil and yohimbine (0.03/0.3/2.0 mg/kg, iv) (Henke et al., 1996).

Alphaxalone/alphadolone produces only light surgical anaesthesia even when administered by the intravenous route. If additional anaesthetic is administered, severe respiratory depression frequently ensues.

If pentobarbital is to be used this is best administered at a dose of 25 mg/kg ip to sedate and immobilize the animal; anaesthesia should then be deepened using a volatile agent such as methoxyflurane. Use of higher dose rates of pentobarbital (37 mg/kg ip), which are needed to produce surgical anaesthesia, are frequently associated with an unacceptably high mortality.

TABLE 6.11 Injectable Anaesthetic Dose Rates in the Guinea Pig.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	40 mg/kg ip	Immobilization	–	90–120
Alpha-chloralose	70 mg/kg ip	Light to medium anaesthesia	180–600	Non-recovery only
Fentanyl/fluanisone (Hypnorm) + diazepam	1.0 ml/kg im or ip + 2.5 mg/kg ip	Surgical anaesthesia	45–60	120–180
Fentanyl/fluanisone (Hypnorm)/midazolam	8.0 ml kg ip*	Surgical anaesthesia	45–60	120–180
Ketamine/acepromazine	100 mg/kg + 5 mg/kg im	Immobilization/anaesthesia	45–120	90–180
Ketamine/diazepam	100 mg/kg + 5 mg/kg im	Immobilization/anaesthesia	30–45	90–120
Ketamine/medetomidine	40 mg/kg + 0.5 mg/kg ip	Moderate anaesthesia	30–40	90–120
Ketamine/xylazine	40 mg/kg + 5 mg/kg ip	Surgical anaesthesia	30	90–120
Methohexital	31 mg/kg ip	Immobilization	–	20
Pentobarbital	37 mg/kg ip	Surgical anaesthesia	60–90	240–300
Tiletamine/zolezepam	40–60 mg/kg im	Immobilization	–	70–160
Urethane	1500 mg/kg iv, ip	Surgical anaesthesia	300–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

**Dose in millilitres per kilogram of a mixture of one part 'Hypnorm' plus two parts water for injection, and one part midazolam (5 mg/ml initial concentration).*

Inhalational Agents

Anaesthesia can be induced either by use of an anaesthetic chamber or by administration via a small face mask. Following induction, it is usually most convenient to maintain anaesthesia using a face mask, since endotracheal intubation is an extremely difficult technique to carry out in guinea pigs. If it is necessary to intubate the animal, use can be made of a purpose-made laryngoscope (Costa et al., 1986; Blouin and Cormier, 1987). Alternatively, the larynx can be visualized by transilluminating the neck and placing an otoscope speculum in the oral cavity (see Chapter 3). A soft-tipped wire introducer is then used to insert a catheter into the larynx.

Methoxyflurane is an effective volatile anaesthetic in guinea pigs, is non-irritant, and has a wide margin of safety, although as with other species, induction is quite slow (4–5 minutes). Halothane can be used successfully and is non-irritant, but can produce profound hypotension even at normal maintenance concentrations. Prolonged halothane anaesthesia (4 hours) has been reported to cause liver toxicity (Lunam et al., 1985). Isoflurane and sevoflurane can also be used successfully, but hypotension may be produced. Both agents appear more irritant to guinea pigs than to other rodents; animals may rub their face and eyes, and lacrimate during induction of anaesthesia. It may therefore be preferable to administer a pre-anaesthetic agent to reduce any distress caused by the procedure.

Ether is unsuitable for use in guinea pigs since it is highly irritant to the respiratory tract, producing increased bronchial secretions that tend to occlude the narrow airways. In addition, bronchospasm may be produced during induction of anaesthesia with ether.

Local Anaesthetics

Intrathecal (spinal) anaesthesia using local anaesthetics has been described in guinea pigs (Thomasson et al., 1974), and this technique coupled with the use of sedatives or low doses of other anaesthetic agents for restraint may be a useful technique in some circumstances.

Anaesthetic Management

Care must be taken to prevent the development of hypothermia, using the methods described in Chapter 4. Although high standards of post-operative care are required for all species, this is particularly important in guinea pigs. Post-operative recovery is aided by administering 10–15 ml of warmed dextrose–saline (0.18% saline, 4% dextrose) subcutaneously to correct any fluid deficit. A warm (25–30 °C) recovery area should be provided and the animal must be given additional subcutaneous fluid for the next few days if its appetite is depressed. It may also be advisable to administer metaclopramide (0.2–1.0 mg/kg po, sc, im, iv q 6–12 hours) and/or cisapride (0.5–1 mg/kg po q 8–24 hours) to stimulate gut motility, particularly after abdominal surgery. Palatable foods should be provided to encourage an early return of appetite. For example, the animal can be provided with hay (autoclaved

if needed for disease control reasons) that can provide both insulation and security, and a source of food.

RABBITS

Rabbits are easily stressed by inexperienced pre-operative handling and induction with volatile anaesthetics. The combined effects of stress and anaesthesia can result in cardiac and respiratory arrest. In addition, some laboratory colonies may have endemic infection with *Pasteurella multocida*, and the consequent subclinical respiratory disease may result in respiratory failure during the period of anaesthesia. Recovery from anaesthesia is often slow, particularly following the use of barbiturates, and the prolonged inappetence that is a frequent post-operative complication can result in gastrointestinal disturbances.

The incidence of these potentially serious problems can be minimized by obtaining rabbits only from sources that are free from infectious diseases, by carefully selecting the anaesthetic regime, by avoiding stress both pre-operatively and post-operatively and by maintaining high standards of intra- and post-operative care. It is unnecessary to withhold food and water prior to induction of anaesthesia since vomiting during induction or recovery does not occur in this species. The large caecum in this species and the occurrence of coprophagy also make pre-operative fasting relatively ineffective in reducing the mass of abdominal viscera prior to abdominal surgery. Since normal gut motility is dependent on a continued supply of ingesta, fasting may exacerbate post-surgical ileus. Rabbits, like guinea pigs, are prone to develop enterotoxaemia following gut stasis (see below), so whenever possible, pre-operative withholding of food should be avoided.

Pre-anaesthetic Medication

As mentioned earlier, rabbits are easily stressed, so, whenever possible, a tranquillizer or sedative should be administered while the animal is still in its familiar surroundings. The rabbit can then be transported to the operating theatre when sedated, hence minimizing the stress caused by such manipulations. A wide variety of tranquillizers can be used successfully in rabbits, and these are listed in order of preference below (see also Table 6.12).

1. Hypnorm (fentanyl/fluanisone; Janssen) (0.2–0.5 ml/kg im). At the lower dose rate, sedation and some analgesia is produced (Green, 1975). The higher dose rate produces sufficient analgesia to enable procedures such as draining and cleaning of subcutaneous abscesses to be carried out. Occasionally marked respiratory depression is seen when the drug is administered at the higher dose rate. If this produces marked cyanosis, oxygen should be administered and the fentanyl component of the mixture reversed by the administration of nalbuphine (1 mg/kg sc or ip), butorphanol (1 mg sc or ip) or buprenorphine (0.05 mg/kg sc or ip) (Flecknell et al., 1989).

TABLE 6.12 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Rabbit.

Drug	Dose rate	Comments
Acepromazine	1 mg/kg im	Moderate sedation
Acepromazine + butorphanol	1 mg/kg + 1 mg/kg im	Moderate to heavy sedation, moderate analgesia
Alphaxalone/alphadolone	9–12 mg/kg im	Moderate to heavy sedation, little analgesia
Atropine	0.05 mg/kg im	Very short acting in some rabbits
Diazepam	0.5–2.0 mg/kg iv, im, ip	Light to moderate sedation
Fentanyl/dropiderol (Innovar-Vet)	0.22 ml/kg im	Immobilization, analgesia
Fentanyl/fluanisone (Hypnorm)	0.2–0.5 ml/kg im	Light to heavy sedation, light to deep analgesia
Glycopyrrolate	0.01 mg/kg iv, 0.1 mg/kg im sc	Anticholinergic
Ketamine	25–50 mg/kg im	Moderate to heavy sedation, mild to moderate analgesia
Medetomidine	0.1–0.5 mg/kg im, sc	Light to heavy sedation, mild to moderate analgesia
Midazolam	0.5–2 mg/kg iv, im, ip	Light to moderate sedation
Xylazine	2–5 mg/kg im	Light to moderate sedation, mild to moderate analgesia

Considerable variation in effects occurs between different strains.

- Medetomidine (0.25 mg/kg im) also produces safe and effective sedation. At higher doses (0.5 mg/kg im) animals lose their righting reflex. Only minimal analgesia is produced when medetomidine is administered alone. Sedation is completely reversed by administration of atipamezole (0.2 mg/kg iv, 1.0 mg/kg im).
- Xylazine (2–5 mg/kg im) produces light to heavy sedation but appears to have little analgesic action when used alone in rabbits. Sedation can be reversed using atipamezole (1.0 mg/kg im) or yohimbine (0.2 mg/kg iv) (Lipman et al., 1987).
- Acepromazine (1 mg/kg im) produces moderate sedation but has no analgesic action (Flecknell). Combining acepromazine (0.5 mg/kg) and butorphanol (0.5 mg/kg) produces good sedation combined with moderate analgesia (Flecknell).
- Diazepam or midazolam (0.5–2 mg/kg iv, 4 mg/kg im or ip) produces good sedation, but neither drug has any analgesic action. Sedation can be reversed using flumazenil (0.01–0.1 mg/kg iv), but the animal may become sedated again a few hours later.

6. Ketamine (25–50 mg/kg im) produces deep sedation. As with other species the degree of muscle relaxation is poor and the level of analgesia is insufficient for even superficial surgery.
7. Glycopyrrolate (0.01 mg/kg iv, 0.1 mg/kg sc or im) (Olson et al., 1993) may be administered to reduce salivary and bronchial secretions and protect the heart from vagal inhibition. Atropine is relatively ineffective in many strains of rabbits because of high levels of atropinase in the liver, and repeated doses are usually required if this drug is used.

In addition to reducing the stress caused by induction of anaesthesia and easing handling and restraint, the use of appropriate pre-anaesthetic medication reduces the amount of other anaesthetic agents required to produce general anaesthesia. The dose rates quoted in Tables 6.12 and 6.13 apply to rabbits that have received no pre-anaesthetic medication unless otherwise stated. The dose rates for intravenous induction agents can be reduced by 30–50% if one of the drugs listed above has been administered.

General Anaesthesia

Injectable Agents

Intravenous injection can be carried out relatively easily using the marginal ear vein, but use can also be made of the cephalic, saphenous or mammary vessels. In small rabbits, the jugular vein may be more accessible. Injection is made even easier if the ear is treated with EMLA cream to produce local anaesthesia 45 minutes prior to injection (see chapter). Anaesthetic dose rates are summarized in Table 6.13.

The anaesthetic combination of choice for routine anaesthesia of rabbits is fentanyl/fluanisone (Hypnorm) (0.3 ml/kg im) and midazolam or diazepam (2 mg/kg im, iv or ip) (Flecknell et al., 1983; Flecknell and Mitchell, 1984). This combination of drugs provides good surgical anaesthesia with excellent muscle relaxation for about 20–40 minutes. It is recommended that fentanyl/fluanisone be administered first and 10–15 minutes allowed so that the animal becomes sedated. The rabbit can then be transferred to the operating theatre or procedure room without causing any distress. Since marked analgesia is produced, the animal will be unresponsive to the pain of intravenous injection, and the vasodilation caused by ‘Hypnorm’ also aids placement of an intravenous needle or over-the-needle catheter. Midazolam or diazepam can then be administered to effect to produce loss of consciousness and relaxation. This usually requires a lower dose of the benzodiazepine (typically 0.5 mg/kg) and so recovery tends to be more rapid.

Longer periods of anaesthesia can be achieved by the administration of additional doses of Hypnorm (approximately 0.1 ml/kg im every 30–40 minutes). This is best achieved by diluting the commercial preparation 1:10 with water for injection. Use of saline results in precipitation of one of the components of ‘Hypnorm’. If anaesthesia of several hours duration is required, it is preferable to administer fentanyl (30–100 µg/kg/h) alone, to avoid undue accumulation of the fluanisone component of ‘Hypnorm’.

TABLE 6.13 Anaesthetic Dose Rates in the Rabbit.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	6–9 mg/kg iv	Light anaesthesia	5–10	10–20
Alpha-chloralose	80–100 mg/kg iv	Light to surgical anaesthesia	360–600	Non-recovery only
Etorphine/methotrimeprazine (Immobilon SA)	0.025–0.05 ml/kg im	Immobilization, analgesia	60 (analgesia)	120–240
Etorphine/methotrimeprazine (Immobilon SA) + midazolam	0.05 ml/kg im + 1 mg/kg iv	Surgical anaesthesia (severe respiratory depression, see text)	50–100	180–240
Fentanyl/fluanisone (Hypnorm) + diazepam	0.3 ml/kg im + 1–2 mg/kg iv, im or ip	Surgical anaesthesia	20–40	60–120
Fentanyl/fluanisone (Hypnorm) + midazolam	0.3 ml/kg im + 1–2 mg/kg iv or ip	Surgical anaesthesia	20–40	60–120
Fentanyl + medetomidine	8 µg/kg iv + 330 µg/kg iv		30–40	60–120
Ketamine/acepromazine	50 mg/kg im + 1 mg/kg im	Surgical anaesthesia	20–30	60–90
Ketamine/diazepam	25 mg/kg im + 5 mg/kg im	Surgical anaesthesia	20–30	60–90
Ketamine/medetomidine	15 mg/kg im + 0.25 mg/kg sc, im	Surgical anaesthesia	20–30	60–90

(Continued)

TABLE 6.13 (Continued)

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Ketamine/xylazine	35 mg/kg im + 5 mg/kg im	Surgical anaesthesia	25–40	60–120
	10 mg/kg iv + 3 mg/kg iv	Surgical anaesthesia	20–30	60–90
Ketamine/xylazine/ acepromazine	35 mg/kg im + 5 mg/kg im + 1.0 mg/kg im, sc	Surgical anaesthesia	45–75	100–150
Ketamine/xylazine/ butorphanol	35 mg/kg im + 5 mg/kg im + 0.1 mg/kg im	Surgical anaesthesia	60–90	120–180
Methohexital	10–15 mg/kg iv	Surgical anaesthesia	4–5	5–10
Pentobarbital	30–45 mg/kg iv	Light to medium anaesthesia	20–30	60–120
Propofol	10 mg/kg iv	Light anaesthesia	5–10	10–15
Thiopental	30 mg/kg iv	Surgical anaesthesia	5–10	10–15
Urethane	1000–2000 mg/kg iv	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

Following the completion of surgery the anaesthesia can be reversed using nalbuphine (0.1 mg/kg iv) or buprenorphine (0.01 mg/kg iv).

A useful alternative is to administer ketamine (25 mg/kg im) and medetomidine (0.5 mg/kg im) (Nevalainen et al., 1989), or ketamine (35 mg/kg im) and xylazine 5 mg/kg im) which both provide about 30 minutes of surgical anaesthesia (White and Holmes, 1976; Lipman et al., 1990). Stress can be reduced by initial administration of medetomidine (0.15–0.25 mg/kg sc) to sedate the animal. Five minutes later, oxygen can be given by mask to the animal, followed by ketamine (10–15 mg/kg sc or im). Alternatively, the two drugs can be mixed and administered as a single injection. Subcutaneous administration is better tolerated than the intramuscular injection of a relatively high volume of drug (0.4 ml/kg at the upper dose rate). Rabbits lose consciousness within 5–10 minutes of receiving both drugs after subcutaneous administration and 2–5 minutes after intramuscular administration (Orr and Flecknell, 2005). The upper dose rates can be used safely in healthy animals and will produce a sufficient depth of anaesthesia for surgical procedures such as laparotomy. The lower dose rates should be used for rabbits that are considered at higher risk. These lower dose rates are usually sufficient to allow endotracheal intubation, as laryngeal relaxation is usually good, but the degree of analgesia may be insufficient for major surgery. Adding a low concentration of a volatile anaesthetic, for example 0.5–1% isoflurane, enables the depth of anaesthesia to be deepened if this proves necessary.

Administration of medetomidine (or xylazine) produces moderate peripheral vasoconstriction, so placement of an over-the-needle catheter is more difficult than when other regimens are used. The peripheral vasoconstriction also produces a pale and bluish colouration of the mucous membranes, even when oxygen is being administered. If oxygen is not provided, severe hypoxia will contribute to the rabbit's appearance (Hedenqvist et al., 2001). Only moderate hypercapnia develops after anaesthesia with this technique and this is easily corrected by intubation and assisted ventilation if anaesthesia is to be prolonged.

In most animals, surgical anaesthesia is produced for 30–60 minutes. The duration of anaesthesia can be prolonged by the addition of butorphanol (0.1 mg/kg) or buprenorphine (0.03 mg/kg) to the ketamine/medetomidine regimen, resulting in approximately 80 minutes of surgical anaesthesia (Hedenqvist et al., 2002). If insufficient analgesia is produced, or an animal becomes too lightly anaesthetized during a prolonged procedure, it is possible to deepen anaesthesia by administration of additional ketamine and medetomidine, at approximately one-third of the original dose. However, this is not advisable. It is preferable to provide additional analgesia either by using 0.5–1% of sevoflurane or isoflurane, or by infiltrating the surgical site with local anaesthetic. If additional ketamine and medetomidine is to be used to prolong anaesthesia, then administer approximately one-tenth of the original dose, diluted 1:10 with water for injection, by slow intravenous injection until the desired effect is achieved.

This regimen has the particular advantage of being partially reversed when atipamezole is administered (0.5–1.0 mg/kg sc). Ketamine, at the dose rates used,

produces immobility and a mild degree of analgesia, and has a marked effect for only approximately 45 minutes, so recovery is rapid, especially if reversal occurs after 30 or 40 minutes. It is this feature that makes the combination so attractive, but since severe hypoxia is almost always produced, oxygen should always be administered to prevent this. It is worth noting that the agent's effects are clearly dose dependent, so the mixture can be used to provide light anaesthesia for radiography (medetomidine 0.2 mg/kg, ketamine 10 mg/kg sc), or initial sedation and immobilization followed by use of low concentrations of inhalant agents to produce full surgical anaesthesia.

Ketamine (35 mg/kg im) combined with xylazine (5 mg/kg im) can be used in much the same way, but the degree of analgesia produced is slightly less than when medetomidine is administered (White and Holmes, 1976; Lipman et al., 1990). The duration of anaesthesia can be prolonged by the addition of butorphanol (0.1 mg) to the ketamine/xylazine regimen, resulting in approximately 80 minutes of surgical anaesthesia (Marini et al., 1992). As with medetomidine, anaesthesia can be partially reversed using atipamezole (1 mg/kg sc or iv).

Ketamine (25 mg/kg) can also be combined with midazolam (5 mg/kg) to produce light to medium planes of anaesthesia (Dupras et al., 2001). Lower dose rates (15 mg/kg/3 mg/kg im) can be sufficient to allow intubation (Grint and Murison, 2008). Anaesthesia can then be deepened using an inhalational agent.

Propofol (10 mg/kg iv) is less effective in the rabbit than in other species, and only light anaesthesia is produced at this dose rate. Higher doses (15–20 mg/kg) cause respiratory arrest. Attempts to produce prolonged anaesthesia with propofol have been less successful in rabbits than in other species (Glen, 1980; Blake et al., 1988; Ko et al., 1992; Aeschbacher and Webb, 1993a, b). However, slow administration of propofol (60–90 seconds) does not result in apnoea and provides sufficient relaxation to allow intubation. Anaesthesia can then be deepened and prolonged using an inhalational agent. If sevoflurane is used, recovery is particularly smooth and rapid (Allweiler et al., in press).

Similar effects to propofol are seen with alphaxalone/alphadolone (6–9 mg/kg iv) which produces light general anaesthesia, but at the higher dose rates necessary to produce medium or deep surgical anaesthesia, it causes sudden apnoea (Green et al., 1978). Alphaxalone (2–3 mg/kg iv) administered after buprenorphine pre-medication (0.03 mg/kg) provides sufficient depth of anaesthesia to allow endotracheal intubation, and anaesthesia can then be prolonged using inhalational agents (Grint et al., 2008).

Fentanyl (8 µg/kg) and medetomidine (330 µg/kg) administered in combination by intravenous injection produces good surgical anaesthesia in rabbits, but some animals may make spontaneous movements in response to non-painful stimuli, and in general this combination is less satisfactory than it is in rats. An advantage of the combination is that it can be completely reversed using atipamezole (1 mg/kg iv) and nalbuphine (1 mg/kg iv). It is important that the rabbit is placed in a suitable recovery cage immediately once anaesthesia is reversed, as full recovery may occur in less than 1 minute.

Pentobarbital (30–45 mg/kg iv), if it must be used, should be diluted to provide a 30 mg/ml solution and administered slowly to effect. Considerable skill and extensive practical experience is required to use this drug effectively in the rabbit. Respiratory arrest frequently occurs before the onset of surgical anaesthesia, and because of the consequent high mortality, this drug is best avoided in this species (Flecknell et al., 1983; Peeters et al., 1988).

Inhalational Agents

It is possible to induce anaesthesia in rabbits using only inhalational agents, but this is usually stressful for both the patient and the anaesthetist. Induction is made more hazardous by a breath-holding response in the rabbit (Flecknell et al., 1996). Exposure to even low concentrations of halothane, isoflurane or sevoflurane, delivered either by face mask or via an anaesthetic chamber, caused apnoea for periods of up to 2 minutes (Flecknell et al., 1996, 1999). Administration of medetomidine, midazolam or acepromazine does not block this response (Flecknell and Liles, 1996). It is therefore generally preferable to induce anaesthesia with an injectable agent and maintain the rabbit on an inhalational anaesthetic. If induction with an inhalational agent is required, a sedative (e.g. acepromazine, midazolam, fentanyl/fluanisone or medetomidine) should be administered, and after 5–10 minutes, the animal should receive 100% oxygen for 2 minutes, followed by a gradually rising concentration of volatile anaesthetic. Use of the sedative allows induction to proceed with minimal physical restraint, so respiratory movements can be observed easily. Most rabbits will stop breathing during induction, and to avoid prolonged apnoea, the face mask should be removed temporarily. The rabbit will commence normal respiration, and the mask can then be replaced. This process may need to be repeated before the animal loses consciousness. The breath holding occurs in response to all of the commonly used volatile anaesthetics, but not to administration of oxygen. However, if the anaesthetic circuit has previously been used to deliver a volatile anaesthetic, significant concentrations of anaesthetic, sufficient to trigger breath holding, can be released for some time (e.g. 30 minutes) even after the vaporizer has been turned off.

Because anaesthesia lightens rapidly when the face mask is removed, endotracheal intubation needs to be carried out very rapidly; it is better to gain experience of this technique when using an injectable anaesthetic combination. Recovery from anaesthesia is rapid, and anaesthetic depth can be altered easily.

Ether is an unsuitable agent for use in rabbits; its irritant nature can result in laryngospasm if used for induction, and it frequently exacerbates pre-existing respiratory disease. Its irritant properties also result in profuse bronchial and salivary secretions. It is also explosive when mixed with oxygen or air, which makes it a serious safety hazard.

Endotracheal Intubation

Endotracheal intubation can be carried out by a number of different techniques, using a 3–4 mm endotracheal tube (see Chapter 3).

The most useful breathing circuits for rabbits are the Ayres T-piece and the Bain's coaxial circuit (Chapter 3).

Post-operative Care

Providing continued monitoring and support in the post-operative period can be of critical importance in rabbits. A suitable recovery area should be established as part of the pre-operative preparations, so that it can be stabilized at an appropriate temperature. Small rabbits will continue to be susceptible to hypothermia until they regain normal activity, so initially a temperature of approximately 35°C should be maintained. This can be lowered to 26–28°C as the animal recovers consciousness. Animals should be provided with warm, comfortable bedding. Once the animal has regained activity it can be transferred to a cage or pen containing good-quality hay or straw. This type of bedding allows the animal to surround itself with insulating material, which provides both warmth and a sense of security, and provides an immediate source of food.

Since many rabbits will have a reduced fluid intake post-operatively, even when good analgesia is provided, it is usually advisable to administer warmed (37°C) subcutaneous or intraperitoneal dextrose–saline at the end of surgery to provide some fluid supplementation in the immediate post-operative period.

Rabbits should be encouraged to eat as soon as possible after recovery from anaesthesia, as this reduces the incidence of digestive disturbances. Normal gastrointestinal function is more likely if effective post-operative analgesia is provided. Use of motility stimulants – metaclopramide (0.2–1.0 mg/kg p/o, sc, im every 6–12 hours), cisapride (0.5–1 mg/kg p/o every 12–24 hours) or ranitidine (2–5 mg/kg p/o every 12 hours) – may be advisable.

CATS

Pre-anaesthetic Medication

The majority of cats respond well to firm but gentle physical restraint, enabling intravenous administration of anaesthetics into the cephalic vein on the forelimb. Prior application of EMLA cream can prevent any struggling in response to intravenous injection (Flecknell et al., 1990) (see Chapter 1). If an experienced assistant is not available, it may be more convenient to administer drugs by the subcutaneous or intramuscular route. Some pre-anaesthetic agents such as medetomidine can produce complete relaxation and loss of consciousness at higher doses (see also Table 6.14).

Cats should be fasted for 12 hours prior to induction of anaesthesia to minimize the risk of vomiting during induction or the recovery period. In an emergency if fasting is possible, then medetomidine can be administered since this drug causes vomiting prior to sedation. The drugs listed below can all be used

TABLE 6.14 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for the Cat.

Drug	Dose rate	Comments
Acepromazine	0.05–0.2 mg/kg im	Light to moderate sedation
Acepromazine + buprenorphine	0.05 mg/kg im 0.01 mg/kg im	Heavy sedation immobilization
Acepromazine + morphine	0.05 mg/kg im 0.1 mg/kg im	Heavy sedation immobilization
Alphaxalone/ alphadolone	9 mg/kg im	Moderate to heavy sedation
Atropine	0.05 mg/kg im, sc	Anticholinergic
Dexmedetomidine	0.04 mg/kg sc	Light to heavy sedation, mild to moderate analgesia
Glycopyrrolate	0.01 mg/kg iv, 0.05 mg/kg im	Anticholinergic
Ketamine	5–30 mg/kg im, 10–20 mg/kg per os	Light to heavy sedation, mild to moderate analgesia
Medetomidine	30–100 µg/kg im or sc	Light to heavy sedation, mild to moderate analgesia
Pethidine	3–5 mg/kg im or sc	Light sedation, mild analgesia
Xylazine	1–2 mg/kg im, or sc	Light to moderate sedation, mild to moderate analgesia

to produce sedation and will ease handling and restraint. Some of the agents can produce a sufficient depth of anaesthesia to enable minor procedures to be carried out. An extensive review of feline anaesthesia is given in Hall and Taylor (1994).

1. Ketamine (5–20 mg/kg im) produces moderate analgesia and sedation, and the higher dose rate will immobilize a cat for about 30–45 minutes. Skeletal muscle tone is increased making minor manipulations difficult, but since pharyngeal and laryngeal reflexes are maintained, the drug is particularly useful if the animal has not been fasted.

The palpebral and corneal blink reflexes are lost, and if prolonged anaesthesia is anticipated, the eyes should be filled with a bland ophthalmic ointment to prevent damage to the cornea through desiccation. Although the volume of injection is small, the low pH of the solution makes intramuscular injection painful.

2. Medetomidine (0.05–0.15 mg/kg im or sc) or dexmedetomidine (0.04 mg/kg sc) (Granhölm et al., 2006) produces light to deep sedation, lasting 60–90 minutes.

Sedation can be completely and rapidly reversed with atipamezole (100–600 µg/kg sc, im or iv). Cats commonly vomit during the onset of sedation. The degree of analgesia is sufficient for minor procedures, such as percutaneous passage of a large-gauge over-the-needle catheter, but insufficient for surgical procedures.

3. Xylazine (1–2 mg/kg im or sc) produces good sedation lasting 30–40 minutes. Vomiting occurs commonly during the onset of sedation. The degree of sedation is sufficient to enable minor manipulation to be carried out, but the analgesic effects of the drug are variable. Reversal of sedation can be achieved by administration of atipamezole (100–600 µg/kg sc, im or iv).
4. Acepromazine (0.05–0.2 mg/kg im) tranquilizes cats prior to induction of anaesthesia and eliminates the excitement associated with recovery from barbiturate anaesthesia.
5. Alphaxalone/alphadolone (9 mg/kg im) produces heavy sedation sufficient to carry out minor, non-painful, manipulative procedures. To be effective, this agent must be administered into a muscle mass, rather than into intramuscular fascia. Full surgical anaesthesia can be produced by administering additional drug by the intravenous route.
6. Pethidine (3–5 mg/kg im or sc) will make some cats more tractable and provides some analgesia, although the sedative effects in certain individuals appear minimal.

Atropine (0.05 mg/kg im) or glycopyrrolate (0.01 mg/kg iv, 0.05 mg/kg im) can be administered prior to induction of anaesthesia to reduce salivation and protect the heart from vagally mediated bradycardia.

The dose rates of anaesthetic drugs listed below and in Table 6.15 can be reduced by 30–50% if one of the drugs (1–6) listed above has been administered.

General Anaesthesia

Injectable Agents

Propofol (5–8 mg/kg iv) will provide about 10 minutes of surgical anaesthesia. Induction and recovery are smooth and rapid. Incremental doses can be used to prolong anaesthesia without unduly prolonging recovery times (Glen, 1980; Brearley et al., 1988), although there are reports of more prolonged recovery after extended periods of anaesthesia (150 minutes, Pascoe et al., 2006).

Alphaxalone/alphadolone (9 mg/kg iv) provides about 10 minutes of surgical anaesthesia. Incremental injections of approximately 3 mg/kg can be given to prolong anaesthesia. Alternatively the drug can be given by continuous infusion at a rate of about 0.2 mg/kg/min. Alfaxan (2–5 mg/kg iv) has similar effects, although data on long-term infusions are not available at present. Recovery from these two agents can be associated with excitement and agitation, but this can be prevented by use of appropriate pre-medication, for example with acepromazine.

Ketamine (20–30 mg/kg im) can be used to provide sufficient analgesia and restraint for minor surgical procedures. Improved muscle relaxation can be achieved

TABLE 6.15 Anaesthetic Dose Rates in the Cat.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	9–12 mg/kg iv, 18 mg/kg im	Surgical anaesthesia	10–15	45–120
Alphaxalone	2–5 mg/kg iv	Surgical anaesthesia	10–15	45–120
Alpha-chloralose	70 mg/kg ip, 60 mg/kg iv	Light to medium anaesthesia	180–720	Non-recovery only
Fentanyl + medetomidine	0.02 mg/kg im + 20 mg/kg im	Surgical anaesthesia	–	300
Ketamine/acepromazine	20 mg/kg im + 0.11 mg/kg im	Surgical anaesthesia	20–30	180–240
Ketamine/medetomidine	7 mg/kg im + 80 µg/kg im	Surgical anaesthesia	30–40	180–240
Ketamine/medetomidine/ butorphanol	5 mg/kg im + 80 µg/kg im + 0.4/kg im	Surgical anaesthesia	30–40	180–240
Ketamine/midazolam	10 mg/kg im + 0.2 mg/kg im	Surgical anaesthesia	20–30	180–240
Ketamine/promazine	15 mg/kg im + 1.12 mg/kg im	Surgical anaesthesia	20–30	180–240
Ketamine/xylazine	22 mg/kg im + 1.1 mg/kg im	Surgical anaesthesia	20–30	180–240
Methohexital	4–8 mg/kg iv	Surgical anaesthesia	5–6	60–90
Pentobarbital	20–30 mg/kg iv	Surgical anaesthesia	60–90	240–480
Propanidid	8–16 mg/kg iv	Surgical anaesthesia	4–6	20–30
Propofol	5–8 mg/kg iv	Surgical anaesthesia	5–10	20
Thiamylal	12–18 mg/kg iv	Surgical anaesthesia	10–15	60–120
Thiopental	10–15 mg/kg iv	Surgical anaesthesia	5–10	60–120
Tiletamine/zolezepam	47.5 mg/kg im + 7.5 mg/kg im	Surgical anaesthesia	20–40	
Urethane	750 mg/kg iv, 1500 mg/kg ip	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

by the concurrent administration of medetomidine or xylazine. The dosage of ketamine required can be reduced to 7 mg/kg im ketamine and medetomidine (80 µg/kg im or sc), or 22 mg/kg im for ketamine and xylazine (1.1 mg/kg im or sc). Partial reversal of anaesthesia can be achieved by administration of atipamezole (mg/kg) (Verstegen et al., 1989, 1990, 1991a, b).

Ketamine (20 mg/kg) combined with acepromazine (0.11 mg/kg) provides light to moderate surgical anaesthesia (Colby and Sanford, 1981; Ingwersen et al., 1988). The degree of analgesia may be improved by pre-anaesthetic administration of an opioid such as butorphanol (0.4 mg/kg sc) to increase the degree of intra-operative analgesia (Tranquilli et al., 1988). As with other combinations, addition of a tranquillizer reduces the muscle rigidity associated with ketamine alone and appears to produce unconsciousness and a state more resembling conventional general anaesthesia, although the eyes remain open with a dilated pupil.

Pentobarbital (20–30 mg/kg iv) produces 30–90 minutes of light to moderate surgical anaesthesia. In order to avoid involuntary excitement during induction, half of the calculated dose should be administered rapidly, followed by the remainder more slowly, to effect. Pentobarbital has a relatively slow onset of action, so that administration of the remaining dose should generally take around 5–6 minutes. Too rapid injection is frequently associated with apnoea and severe cardiovascular depression. Alternative routes of administration (intraperitoneal, oral, intrathoracic and subcutaneous) have been described but these are generally unsatisfactory and therefore not recommended (Clifford and Soma, 1969). Pentobarbital has a narrow safety margin in the cat, as in other species, and dose rates of 72 mg/kg have been reported to be lethal (Clifford and Soma, 1969). Recovery can be very prolonged, especially if the animal is allowed to become hypothermic, and may be associated with excitement. Cats may remain ataxic and sedated for 8–24 hours.

Alphachloralose (70 mg/kg ip or 60 mg/kg iv) is suitable for prolonged, non-recovery procedures (see Chapter 5). In the cat, medium planes of surgical anaesthesia are produced in most animals. As in other species, induction is slow and may be associated with excitement, so it is best to administer a short-acting anaesthetic such as propofol before administration of chloralose.

Inhalational Agents

It is preferable to induce anaesthesia using an injectable agent and then maintain anaesthesia using an inhalational agent, since cats often resent the process of face mask induction. Prior administration of a sedative/tranquillizer coupled with expert handling may, however, enable smooth induction of anaesthesia by this method. Sevoflurane is better tolerated than the other inhalant agents, and the very rapid induction makes this a useful option when other agents are contraindicated, or when particularly rapid recovery is required (Tzannes et al., 2000). An alternative, which avoids the need for firm physical restraint, is to use an anaesthetic chamber.

Laryngospasm during induction with volatile anaesthetics may occur and the incidence of this problem may be reduced by increasing anaesthetic concentrations gradually.

Following induction of anaesthesia, with either an injectable or a volatile anaesthetic, the cat should be intubated using an uncuffed, 3–4 mm endotracheal tube. Endotracheal intubation in the cat can be carried out under direct vision using a paediatric laryngoscope blade. Care must be taken to spray the larynx with 2% lidocaine before attempting intubation, to help prevent the development of laryngospasm. In the UK, some formulations of lidocaine have been associated with the occurrence of laryngeal oedema; hence, it is advisable to check the suitability of any locally available product before use (see Chapter 3). In most instances, some spasm occurs immediately following spraying of the larynx, but this passes rapidly and intubation can then be successfully achieved. Alternatively suxamethonium (1.0 mg/kg iv) can be administered following induction of anaesthesia and the animal can be ventilated for a short period following intubation. Under these circumstances ventilation can be carried out using a face mask if difficulties are experienced during intubation.

Following intubation, it is preferable to attach the animal to an Ayre's T-piece or Bain's circuit, since expiratory resistance and equipment dead space are minimal when using these circuits.

Sevoflurane, isoflurane, halothane and enflurane can all be used for maintenance of anaesthesia, but ether is best avoided because of its irritant nature.

DOGS

Pre-anaesthetic Medication

Dogs respond positively to human contact, and if the animal's regular handler is present then restraint will rarely be a problem. It is often preferable, however, to administer pre-anaesthetic medication to dogs, to ease handling, to ensure a smooth and stress-free induction of anaesthesia and to provide a quiet and gradual recovery. Dogs should be fasted for 12 hours prior to induction of anaesthesia. Intravenous injection for induction of anaesthesia is easy to carry out, particularly if the skin has been anaesthetized by prior application of EMLA cream (see Chapter 2) and a sedative or tranquillizer has been administered.

The following drugs can be used for pre-anaesthetic medication and are listed in order of preference (see also Table 6.16).

Medetomidine (10–80 µg/kg im, sc or iv) produces light to deep sedation, and at higher dose rates, the dog is completely immobilized enabling minor procedures to be carried out. The degree of analgesia is insufficient for anything other than superficial surgical procedures. Sedation can be reversed completely and rapidly by administration of atipamezole (50–400 µg/kg im).

Buprenorphine (0.009 mg/kg im) and acepromazine (0.07 mg/kg im) produce moderate or deep sedation, enabling minor procedures such as radiography to be undertaken easily (Taylor and Houlton, 1986).

TABLE 6.16 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Dog.

Drug	Dose rate	Comments
Acepromazine	0.1–0.25 mg/kg im	Light to moderate sedation
Acepromazine/ buprenorphine	0.07 mg/kg im + 0.009 mg/kg im	Heavy sedation, immobilization, some analgesia
Atropine	0.05 mg/kg sc or im	Anticholinergic
Etorphine methotrime- pazine 'Immobilon SA'	0.5 ml/4 kg im	Immobilization/analgesia
Fentanyl/droperidol (Innovar-Vet)	0.1–0.15 ml/kg im	Immobilization/analgesia
Fentanyl/fluanisone (Hypnorm)	0.1–0.2 ml/kg im	Moderate to heavy sedation, moderate analgesia
Glycopyrrolate	0.01 mg/kg iv	Anticholinergic
Medetomidine	10–100 µg mg/kg im, sc or iv	Light to heavy sedation, mild to moderate analgesia
Xylazine	1–2 mg/kg im	Light to moderate sedation, mild to moderate analgesia

Acepromazine (0.2 mg/kg im) alone produces sedation, but has no analgesic action.

Fentanyl/fluanisone (Hypnorm, Janssen) (0.1–0.2 ml/kg) or fentanyl/droperidol (Innovar-Vet, Janssen) (0.1–0.15 ml/kg im) produces good analgesia, sufficient for minor surgical procedures and heavy sedation. A moderate bradycardia is often produced, but this can be prevented by administration of atropine (see below). Partial reversal of these agents is possible using nalbuphine or other mixed agonist/antagonist opioids (Tables 6.1 and 6.2).

Xylazine (2.0 mg/kg im) produces good sedation and mild analgesia. Vomiting often occurs after administration and animals may be easily roused by loud noises. Other side-effects include production of bradycardia, occasional heart-block and hyperglycaemia, although the cardiac effects can be prevented by pre-treatment with atropine.

Atropine (0.05 mg/kg sc) or glycopyrrolate (0.01 mg/kg) should be administered prior to the use of fentanyl/fluanisone, fentanyl/droperidol or xylazine. It may also be included as pre-medication prior to use of the anaesthetic regimens described below.

The dose rates of anaesthetic drugs listed below and in Table 6.17 can be reduced by 30–50% if one of the drugs (1–6) listed above has been administered.

TABLE 6.17 Anaesthetic Dose Rates in the Dog.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alpha-chloralose	80 mg/kg iv	Light anaesthesia	360–600	Non-recovery only
Alphaxalone	2 mg/kg iv	Surgical anaesthesia	10–15	15–20
Ketamine/medetomidine	2.5–7.5 mg/kg im + 40 µg/kg im	Light to medium anaesthesia	30–45	60–120
Ketamine/xylazine	5 mg/kg iv + 1–2 mg/kg iv or im	Light to medium anaesthesia	30–60	60–120
Methohexital	4–8 mg/kg iv	Surgical anaesthesia	4–5	10–20
Pentobarbital	20–30 mg/kg iv	Surgical anaesthesia	30–40	60–240
Propofol	5–7.5 mg/kg iv	Surgical anaesthesia	5–10	15–30
Thiamylal	10–15 mg/kg iv	Surgical anaesthesia	5–10	15–20
Thiopental	10–20 mg/kg iv	Surgical anaesthesia	5–10	20–30
Urethane	1000 mg/kg iv	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

General Anaesthesia

Injectable Agents

Intravenous administration is easily carried out using the cephalic vein on the anterior surface of the forelimb, provided adequate restraint can be provided.

Propofol (5–7.5 mg/kg iv) produces a short period (5–10 minutes) of general anaesthesia, which can be prolonged by administration of incremental injections of 1–2 mg/kg every 10–15 minutes. To avoid apnoea during induction of anaesthesia, propofol should be administered slowly, over 60–90 seconds. Recovery is smooth and rapid, even after prolonged anaesthesia (Glen and Hunter, 1984; Hall and Chambers, 1987; Watkins et al., 1987; Weaver and Raptopoulos, 1990).

Alfaxalone (Alfaxan CD) (mg/kg) produces smooth induction of anaesthesia, provided it is administered slowly (e.g. over 60–90 seconds) to avoid apnoea. Anaesthesia can be prolonged. Alphaxalone/alphadolone should not be used in dogs, as the solubilizing agent produces histamine release in this species.

The barbiturates thiopental (10–20 mg/kg of a 1.25 or 2.5% solution) or methohexital (4–8 mg/kg of a 1% solution) can be used to produce anaesthesia lasting 10–30 minutes, with recovery occurring within 15–20 minutes. Recovery can be associated with involuntary excitement and agitation unless a sedative or tranquillizer has been administered as pre-anaesthetic medication.

Pentobarbital is still used in research facilities, since it can provide 45–60 minutes of light anaesthesia following a single intravenous dose of the drug (20–30 mg/kg iv). It has the disadvantage of providing poor analgesia for major surgical procedures, unless high dosages are administered. At these higher doses, pentobarbital produces significant respiratory and cardiovascular system depression and it is preferable to ventilate the animal to maintain normal blood gas concentrations.

Ketamine is less widely used in the dog than in other species, primarily since it may cause behavioural disturbances. Despite these problems, ketamine (2.5–7.5 mg/kg im) and medetomidine (40 µg/kg im) can be used to produce surgical anaesthesia as can ketamine (5 mg/kg iv) and xylazine (12 mg/kg iv or im).

Inhalational Agents

Anaesthesia can be induced using a face mask in a co-operative animal, or following sedation with one of the drugs listed above in more apprehensive individuals. Even after sedation, some animals may resent this procedure. It is generally preferable to induce anaesthesia with an injectable anaesthetic agent (see above) followed by intubation and maintenance with a volatile anaesthetic. Intubation is a relatively straightforward procedure in the dog. The mouth can be opened widely to provide a clear view of the larynx, so that an endotracheal tube can be passed under direct vision. If difficulty is experienced in visualizing the larynx, a laryngoscope with a McGill or Soper blade can be used. Following intubation, the dog can be connected to an appropriate circuit, such as a Bain's or Magill circuit (see Chapter 3). Halothane (1–2%), methoxyflurane (1.0–1.5%), isoflurane (2–3%) or enflurane (1–2%) provide stable anaesthesia with good analgesia and muscle relaxation.

FERRETS

Pre-anaesthetic Medication

If a ferret has become accustomed to being handled it can be easily restrained to enable injection of an anaesthetic agent. Some animals may resent physical restraint, and administration of drugs to sedate the animal may be required before induction of anaesthesia with intravenous or inhalational anaesthetic agents. Ferrets should be fasted for 12 hours prior to induction of anaesthesia to minimize the risk of vomiting during induction of anaesthesia.

The following drugs can be used to produce sedation (see also Table 6.18):

1. Diazepam (2 mg/kg im) produces good sedation.
2. Acepromazine (0.2 mg/kg im) produces heavy sedation.
3. Ketamine (20–30 mg/kg im) produces deep sedation and light anaesthesia lasting about 30–40 minutes.
4. Fentanyl/fluanisone (Hypnorm, Janssen) (0.5 ml/kg im) or fentanyl/droperidol (Innovar-Vet) (0.15 ml/kg im) produces deep sedation and sufficient analgesia for minor surgical procedures.
5. Medetomidine (0.1–0.5 mg/kg sc) or xylazine (1–2 mg/kg im) produces light to heavy sedation in the ferret. Sedation can be reversed using atipamezole (1 mg/kg).

Atropine (0.05 mg/kg im) may be administered if necessary.

TABLE 6.18 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Ferret.

Drug	Dose rate	Comments
Acepromazine	0.2 mg/kg im	Moderate sedation
Atropine	0.05 mg/kg sc or im	Anticholinergic
Diazepam	2 mg/kg im	Light sedation
Fentanyl/fluanisone (Hypnorm)	0.5 ml/kg im	Immobilization, good analgesia
Ketamine	20–30 mg/kg	Immobilization, some analgesia
Medetomidine	10–80 µg/kg sc or im	Light to heavy sedation, mild to moderate analgesia
Medetomidine/ butorphanol	80 µg/kg + 0.2 mg/kg sc or im	Light to heavy sedation, mild to moderate analgesia
Xylazine	0.1–0.5 mg/kg sc or im	Light to heavy sedation, mild to moderate analgesia

General Anaesthesia

Injectable Agents

The cephalic vein on the anterior aspect of the foreleg can be used for intravenous injection, although firm restraint is necessary. Intramuscular injections can easily be made into the hindlimb muscles. Anaesthetic dose rates are summarized in Table 6.19.

Ketamine (25 mg/kg im) and xylazine (1–2 mg/kg im), or ketamine (4–8 mg/kg im) and medetomidine (50–100 µg/kg im) (Wolfensohn and Lloyd, 1994) produces good surgical anaesthesia lasting 30–60 minutes. As in other species, administration of atipamezole will accelerate recovery. Ketamine combined with diazepam (2 mg/kg im) or acepromazine (0.25 mg/kg im) has effects to those of ketamine/xylazine.

Alphaxalone/alphadolone (8–12 mg/kg iv) produces good surgical anaesthesia lasting 10–15 minutes. Additional doses of the drug can be administered to prolong the period of anaesthesia.

Pentobarbital (25–30 mg/kg iv, 36 mg/kg ip) can be used to provide 30–120 minutes of light to medium surgical anaesthesia.

Inhalational agents isoflurane, sevoflurane and halothane can all be used to produce or maintain surgical anaesthesia in ferrets. Animals can be induced in an anaesthetic chamber, following which anaesthesia can be maintained using a face mask. Alternatively, the animal may be intubated.

PIGS

Pre-anaesthetic Medication

Small pigs (<10 kg) are easily restrained humanely, but pigs of all sizes vocalize extremely loudly when restrained; hence, it may be useful to administer a sedative before induction of anaesthesia. Although it is possible to physically restrain larger pigs, use of pre-anaesthetic medication will considerably ease induction and reduce stress to the animal. Several of the pre-anaesthetic agents require administration of relatively large volumes of drug, and this appears to cause less distress if carried out slowly. A useful technique is to attach a 2 in. needle (or longer in animals >50 kg) to the syringe using an anaesthetic extension tube. The needle can be quickly placed in the pig's neck muscles, and the injection made slowly with the pig unrestrained.

Pigs are usually fasted for 12 hours prior to induction of anaesthesia, although vomiting on induction is rare.

The following drugs can be used for pre-anaesthetic medication (see also Table 6.20):

1. Diazepam (1–2.0 mg/kg im) provides rapid sedation, but is best followed by administration of ketamine (10–15 mg/kg im) to provide complete immobilization. Some preparations of diazepam can be mixed in the same syringe

TABLE 6.19 Anaesthetic Dose Rates in the Ferret.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	8–12 mg/kg iv	Surgical anaesthesia	10–15	20–30
	12–15 mg/kg im	Light anaesthesia	15–30	60–90
Ketamine/acepromazine	25 mg/kg im + 0.25 mg/kg im	Surgical anaesthesia	20–30	60–120
Ketamine/diazepam	25 mg/kg im + 2 mg/kg im	Surgical anaesthesia	20–30	60–120
Ketamine/medetomidine	4–8 mg/kg im + 50–100 µg/kg im	Light-Surgical anaesthesia	20–30	60–120
Ketamine/medetomidine/ butorphanol	8 mg/kg im + 80 µg/kg im + 0.2 mg/kg im	Surgical anaesthesia	20–30	60–120
Ketamine/xylazine	25 mg/kg im + 1–2 mg/kg im	Surgical anaesthesia	20–30	60–120
Pentobarbital	25–30 mg/kg iv, 36 mg/kg ip	Surgical anaesthesia	30–60	90–240
Urethane	1500 mg/kg ip	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

TABLE 6.20 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Pig.

Drug	Dose rate	Comments
Acepromazine	0.2 mg/kg im	Moderate sedation
Alphaxalone/alphadolone	6 mg/kg im	Sedation
Atropine	0.05 mg/kg sc or im	Anticholinergic
Azaperone	5 mg/kg im	Moderate to deep sedation
Diazepam	1–2 mg/kg im	Light to moderate sedation
Ketamine	10–15 mg/kg im	Sedation, immobilization
Ketamine/acepromazine	22 mg/kg im + 1 mg/kg im	Immobilization
Metomidate	2 mg/kg im	Moderate to deep sedation
Tiletamine/zolezepam	2–4 mg/kg im	Moderate to deep sedation

with ketamine; alternatively, midazolam (1–2 mg/kg) can be used. The large volume of injectate (6–8 ml) required for animals weighing over 15–20 kg limits the use of this combination for smaller pigs.

- Ketamine (10 mg/kg im) used alone in juvenile and adult pigs immobilizes the animal, but spontaneous movements occur. In young animals, this drug appears less effective and higher dose rates (20 mg/kg) may be required. Even at higher doses considerable spontaneous movements may occur. Although this drug is useful in older animals, it is an expensive means of producing sedation.
- Tiletamine and zolezepam (2–4 mg/kg of 'Zoetil', Virbac) combination produces heavy sedation and immobilization. An advantage of this combination is that the volume for injection can be reduced, making it particularly suitable for larger animals.
- Alphaxalone/alphadolone (6 mg/kg im) produces good sedation in pigs but the volume of injection (10 ml for a 20 kg pig) limits the use of this drug to smaller animals.
- Azaperone (5 mg/kg im) produces sedation but has no analgesic effect. It is best combined with the administration of metomidate (10 mg/kg im) to produce deep sedation and sufficient analgesia for minor surgical procedures.
- Acepromazine (0.2 mg/kg im) produces moderate sedation but has no analgesic action.
- Medetomidine and xylazine are relatively ineffective in many strains of pigs, and the degree of sedation produced is highly variable, although these agents may potentiate the effects of other anaesthetics.

Atropine (0.05 mg/kg im) can be administered to reduce salivary and bronchial secretions.

General Anaesthesia

Injectable Agents

Following physical or chemical restraint, a number of different anaesthetic agents can be administered by intravenous injection to produce surgical anaesthesia. The dose rates of anaesthetic drugs listed below and in Table 6.21 can be reduced by 30–50% if one of the drugs (1–6) listed above has been administered. The most convenient route is via the ear veins, and placement of an ‘over-the-needle’ catheter to ensure reliable venous access is strongly recommended.

1. Propofol (2.5–3.5 mg/kg iv) produces surgical anaesthesia lasting 10 minutes. As with other species a short period of apnoea often occurs immediately after injection. Anaesthesia can be prolonged by administration of incremental injections (1–2 mg/kg every 10–15 minutes) or by continuous infusion (8–9 mg/kg/h). If propofol is used as the sole anaesthetic agent for major surgical procedures, significant respiratory depression may occur, and ventilation may need to be assisted. An alternative approach is to administer propofol at a lower rate (5–6 mg/kg/h) together with alfentanil (20–30 µg/kg iv followed by 2–5 µg/kg/min) to provide supplemental analgesia, although use of alfentanil will require assisted ventilation. Recovery following propofol is smooth and rapid, as with other species, and if necessary the alfentanil can be reversed by administration of nalbuphine (0.5 mg/kg iv).
2. Alphaxalone/alphadolone (1–2.0 mg/kg iv, to effect, after immobilization or sedation with one of the agents listed above) will produce surgical anaesthesia and good muscle relaxation with minimal respiratory depression. Prolonged anaesthesia can be achieved by continuous infusion of this drug.
3. Methohexitone (5 mg/kg iv) or thiopentone (6–9 mg/kg iv) can be administered to produce 5–10 minutes of surgical anaesthesia. Recovery can be associated with excitement in some individuals unless a sedative or tranquillizer has been administered.
4. Pentobarbital (20–30 mg/kg iv) produces light surgical anaesthesia in pigs. The high dose rates (30 mg/kg) needed to produce deep surgical anaesthesia may cause severe cardiovascular system depression. The duration of anaesthesia in pigs is shorter than in other species, surgical anaesthesia persisting for only 20–30 minutes. Full recovery can take 3–4 hours, however.

Inhalational Agents

It is possible to produce anaesthesia with volatile anaesthetics administered by means of a face mask, but providing the necessary degree of physical restraint can be a problem, even in small pigs. Considerable pollution of the environment with anaesthetic gases will occur and this should be avoided if possible. As in other species, sevoflurane provides rapid induction and this makes it a suitable alternative in smaller pigs (<10 kg) (Moeser et al., 2008). In larger animals it is preferable to induce anaesthesia with an injectable anaesthetic, intubate the

TABLE 6.21 Anaesthetic Dose Rates in the Pig.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	6 mg/kg im then 2 mg/kg iv	Immobilization, surgical anaesthesia	– 5–10	10–20 15–20
Azaperone + metomidate	5 mg/kg im + 3.3 mg/kg iv	Light to medium anaesthesia	30–40	60–90
Ketamine	10–15 mg/kg im	Sedation, immobilization	20–30	60–120
Ketamine/acepromazine	22 mg/kg + 1.1 mg/kg im	Light anaesthesia	20–30	60–120
Ketamine/diazepam	10–15 mg/kg im + 0.5–2 mg/kg im	Immobilization/light anaesthesia	20–30	60–90
Ketamine/medetomidine	10 mg/kg im + 0.08 mg/kg im	Immobilization/light anaesthesia	40–90	120–240
Ketamine/midazolam	10–15 mg/kg im + 0.5–2 mg/kg im	Immobilization/light anaesthesia	20–30	60–90
Methohexital	5 mg/kg iv	Surgical anaesthesia	4–5	5–10
Pentobarbital	20–30 mg/kg iv	Light to surgical anaesthesia	15–60	60–120
Propofol	2.5–3.5 mg/kg iv	Surgical anaesthesia	5–10	10–20
Thiopental	6–9 mg/kg iv	Surgical anaesthesia	5–10	10–20
Tiletamine/zolezepam	2–4 mg/kg im 6–8 mg/kg im	Immobilization Light anaesthesia	20–30 20–30	60–120 90–180
Tiletamine/zolezepam + xylazine	2–7 mg/kg im + 0.2–1 mg/kg im	Light to medium anaesthesia	30–40	60–120

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

pig and maintain anaesthesia using an inhalational agent. Halothane, methoxyflurane, enflurane and isoflurane can all be used to maintain safe and effective anaesthesia. The potency of volatile anaesthetics appears lower in pigs than in other laboratory mammals, so slightly higher concentrations are required for induction and maintenance. A small number of pigs have been shown to develop malignant hyperthermia in response to halothane anaesthesia and, whenever possible, animals should be obtained from herds that have a low incidence of this problem.

Pigs should be maintained using a Bain's or Magill circuit, but large animals (>30 kg) may require closed-circuit anaesthesia in order to reduce the gas flow rates needed. As discussed in Chapter 3, closed-circuit anaesthesia requires considerable expertise and advice should be sought from a veterinary surgeon or medically qualified anaesthetist if this type of circuit is to be used.

Intubation of pigs is complicated by the difficulty of obtaining a clear view of the larynx and by the laryngeal anatomy which tends to obstruct passage of the tube. A brief description of the technique of intubation is given in Chapter 3. More detailed descriptions are given in Hall and Clarke (1991).

SHEEP AND GOATS

Pre-anaesthetic Medication

Opinion varies as to whether sheep and goats should be fasted before induction of general anaesthesia. Fasting has little effect on the volume of digesta present in the rumen, but may reduce the incidence of rumenal tympany (an accumulation of gas in the rumen caused by bacterial fermentation). This appears to be a greater problem in animals which are grazing. Unnecessary fasting should be avoided since it may cause distress to the animal, and the author has experienced few problems if food and water are provided up to an hour prior to induction of anaesthesia. If rumenal tympany develops it can be relieved by passage of a stomach tube (see Chapter 4). Should the condition occur repeatedly, pre-anaesthetic fasting may be introduced, although this may not resolve the problem.

Sheep and goats can generally be restrained easily for administration of anaesthetic agents. The stress associated with movement from its pen to the operating theatre can be reduced by use of sedatives and tranquillizers. High doses of sedatives and tranquillizers can also be used in conjunction with local anaesthetics to provide humane restraint and surgical anaesthesia. A useful review of anaesthetic techniques in sheep and goats is provided by Taylor (1991).

The following drugs may be used for pre-anaesthetic medication (see also Table 6.22):

1. Diazepam (2 mg/kg im or 1 mg/kg iv) and midazolam (0.5 mg/kg iv) are particularly effective tranquillizers in sheep and goats (Stegmann and Bester, 2001). When combined with ketamine (4 mg/kg iv) moderate surgical anaesthesia is produced.

TABLE 6.22 Sedatives, Tranquillizers and Other Pre-anaesthetic Medication for Use in the Sheep and Goat.

Drug	Dose rate	Comments
Acepromazine	0.05–0.1 mg/kg im	Moderate sedation
Diazepam	1–2 mg/kg im, 1 mg/kg iv	Light to moderate sedation
Ketamine	20 mg/kg im	Moderate to heavy sedation, immobilization, some analgesia
Medetomidine	25 µg/kg im	Light to heavy sedation, some analgesia
Midazolam	0.5 mg/kg iv	Moderate sedation
Xylazine	0.1 mg/kg im or iv (sheep) 0.05 mg/kg im (goat)	Light to moderate sedation, some analgesia

- Xylazine (0.1 mg/kg im) will provide heavy sedation and good analgesia in sheep, lasting 30–35 minutes. It can be combined with ketamine (4 mg/kg iv) to produce light surgical anaesthesia. Goats appear more sensitive to xylazine, and lower doses (0.05 mg/kg im) are usually adequate.
- Medetomidine (25 µg/kg im) is also effective in producing sedation and analgesia. As with xylazine, this agent can be combined with ketamine to produce surgical anaesthesia, but only a low dose of ketamine (1 mg/kg im) is required because of the potency of medetomidine in this species (Laitinen, 1990). Medetomidine, xylazine and dexmedetomidine can produce hypoxia in sheep due to pulmonary effects (Celly et al., 1994; Tulamo et al., 1995; Kastner et al., 2007). Sedation, and any undesirable side-effects, can be reversed using atipamezole (100–200 µg/kg iv or im).
- Acepromazine (0.05–0.1 mg/kg im) will sedate sheep but provides no analgesia.

The use of atropine in sheep is of limited value. Extremely high dose rates (0.5 mg/kg im) are needed to reduce salivary secretions and repeated doses of 0.2–0.3 mg/kg may be required every 15 minutes to maintain the effects.

General Anaesthesia

Injectable Agents

Intravenous injection is easily carried out using the marginal ear vein, anterior cephalic vein on the foreleg or jugular vein. Dose rates of injectable anaesthetics are summarized in Table 6.23.

TABLE 6.23 Anaesthetic Dose Rates in the Sheep and Goat.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	2–3 mg/kg iv (adult) 6 mg/kg iv (lamb or kid)	Surgical anaesthesia	5–10	10–20
Etorphine/acepromazine (Immobilon LA)	0.5 ml per 50 kg im (>30 kg)	Immobilization, analgesia	Analgesia 30–40	60–90
Etorphine/methotrimeprazine (Immobilon SA)	0.5 ml per 4 kg im (<30 kg)	Immobilization, analgesia	Analgesia 30–40	60–90
Ketamine/diazepam	10–15 mg/kg + 1–2 mg/kg im or 4 mg/kg iv + 0.5–1 mg/kg iv	Light to medium anaesthesia Surgical anaesthesia	20–30 20–30	60–90 45–90
Ketamine/medetomidine	1 mg/kg iv + 25 µg/kg iv	Surgical anaesthesia	30–60	60–90
Ketamine/xylazine	4 mg/kg + 0.2 mg/kg iv (sheep), 0.05 mg/kg iv (goat)	Surgical anaesthesia	15–20	30–90
Methohexital	4 mg/kg iv	Surgical anaesthesia	4–5	5–10
Pentobarbital	30 mg/kg iv	Immobilization, anaesthesia	15–30	30–60
Propofol	4–5 mg/kg iv	Light anaesthesia	5–10	10–15
Thiopental	10–15 mg/kg iv	Surgical anaesthesia	5–10	10–20
Urethane	1000 mg/kg iv	Surgical anaesthesia	360–480	Non-recovery only

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

1. Light to moderate surgical anaesthesia can be produced by use of ketamine (4 mg/kg iv) + xylazine (1 mg/kg iv) or ketamine (10–5 mg/kg im or 4 mg/kg iv) + diazepam or midazolam (2 mg/kg im or 1 mg/kg iv) (Coulson et al., 1991) as described above. The combination of ketamine and diazepam appears to cause less cardiovascular and respiratory system depression than does ketamine/xylazine.
2. Thiopentone (10–15 mg/kg iv) and methohexitone (4 mg/kg iv) both provide 5–10 minutes of anaesthesia.
3. Alphaxalone/alphadolone (2–3 mg/kg iv in adults, 6 mg/kg iv in lambs) provides excellent stable anaesthesia in sheep and lambs (Eales and Small, 1982) and can be administered by continuous infusion to maintain anaesthesia over prolonged periods.
4. Propofol can be used to induce anaesthesia in sheep (4–5 mg/kg iv) (Waterman, 1988) and goats (3 mg/kg iv, Prassinis et al., 2005).
5. Pentobarbital (30 mg/kg iv) produces anaesthesia lasting 15–30 minutes. The dose required varies considerably in different animals, and the drug generally produces marked respiratory depression.

Inhalational Agents

Sheep may be restrained and anaesthesia induced using a face mask, but considerable pollution of the environment with inhalational anaesthetics will occur because of the high fresh gas flows used when anaesthetizing these larger animals. It is generally preferable to induce anaesthesia with an injectable agent, intubate the animal and maintain anaesthesia with an inhalational agent if required.

It is essential to intubate sheep immediately following induction of general anaesthesia since regurgitation of rumen contents invariably occurs and these may be inhaled, resulting in an inhalational pneumonia. Intubation is relatively straightforward, provided that a suitable laryngoscope blade (Table 1.2 and Chapter 3) is available. The vocal cords should be sprayed with lignocaine prior to passage of an endotracheal tube to prevent laryngospasm.

Halothane, methoxyflurane, enflurane, isoflurane and sevoflurane can all be used to maintain effective anaesthesia in sheep. Animals should be maintained on a Bain's or Magill circuit. It may be advisable to use a circle system in large adult sheep to reduce the quantities of anaesthetic gases required.

Anaesthetic Management

Following intubation it is advisable to pass a stomach tube to try to minimize the risk or the development of rumenal tympany. Sheep should, if possible, be positioned on their sides as when positioned in dorsal recumbency, the pressure of the rumen and other viscera on the major abdominal blood vessels may interfere with venous return.

During the post-operative recovery period, sheep should be positioned on their sternum and observed carefully for signs of rumenal tympany.

PRIMATES

Pre-anaesthetic Medication

Small primates such as marmosets (*Callithrix jacchus*) can usually be restrained relatively easily to enable the intraperitoneal or intramuscular injection of an anaesthetic agent. Pre-anaesthetic medication to sedate these animals is generally only required prior to intravenous injection of induction agents, or to enable administration of inhalational agents by means of a face mask. Larger primates such as baboons (*Papio* sp.) and macaque monkeys (*Macaca* sp.) can cause physical injury to their handler if inexpertly restrained and it is strongly recommended that chemical agents be used to produce deep sedation.

The following drugs may be used for pre-anaesthetic medication (see also Table 6.24):

1. Ketamine (5–25 mg/kg im) is probably the drug of choice in larger primates. At the lower dose rate, heavy sedation is produced; higher doses of ketamine produce light surgical anaesthesia (Banknieder et al., 1978; White and Cunnings, 1979).
2. Alphaxalone/alphadolone (12–18 mg/kg im) is the agent of choice for sedating marmosets and small primates. Heavy sedation is produced and additional doses of the drug can be administered intravenously to produce surgical anaesthesia (Phillips and Grist, 1975; Whelan et al., 1999; Virley et al., 2003). It seems likely that alphaxalone (Alfaxan) can be used in a similar way.
3. Acepromazine (0.2 mg/kg im) produces sedation but will not immobilize the animal.

TABLE 6.24 Sedatives, Tranquillizers and Pre-anaesthetic Medication for Use in the Non-human Primate.

Drug	Dose rate	Comments
Acepromazine	0.2 mg/kg im	Moderate sedation
Alphaxalone/alphadolone	12–18 mg/kg im	Heavy sedation
Atropine	0.05 mg/kg sc or im	Anticholinergic
Diazepam	1 mg/kg im	Light to moderate sedation
Fentanyl/dropiderol (Innovar-Vet)	0.3 ml/kg im	Heavy sedation, good analgesia
Fentanyl/fluanisone (Hypnorm)	0.3 ml/kg im	Heavy sedation, good analgesia
Ketamine	5–25 mg/kg im	Moderate sedation, immobilization, some analgesia
Xylazine	0.5 mg/kg im	Light to moderate sedation, some analgesia

4. Diazepam (1 mg/kg im) sedates primates, but provides insufficient sedation for the safe handling of large primates.
5. Fentanyl/fluanisone (Hypnorm, Janssen) (0.3 ml/kg im) or fentanyl/droperidol (Innovar-Vet) (0.3 ml/kg im) produces heavy sedation and good analgesia (Field et al., 1966).
6. Medetomidine can be used to provide sedation, but animals may arouse in response to external stimuli (Miyabe et al., 2001) and this can present a significant hazard to the staff.

Atropine (0.05 mg/kg im) should be administered to minimize the bradycardia produced by neuroleptanalgesic combinations and to reduce the amount of salivary secretions.

Primates should be fasted for 12–16 hours prior to induction of anaesthesia.

General Anaesthesia

Injectable Agents

The cephalic vein on the anterior aspect of the forelimb of large primates or the lateral tail vein in marmosets can be used for intravenous injection. Dose rates of injectable anaesthetics are summarized in Table 6.25.

1. The combination of ketamine (10 mg/kg im) and xylazine (0.5 mg/kg im) or ketamine (5 mg/kg im) and medetomidine (0.05 mg/kg) produces surgical anaesthesia with good muscle relaxation, lasting 30–40 minutes. Ketamine (15 mg/kg im) and diazepam (1 mg/kg im) combination has similar effects.
2. Alphaxalone/alphadolone (10–12 mg/kg iv) produces good surgical anaesthesia in both Old and New World primates, and prolonged periods of anaesthesia can be provided by administration of additional doses (5 mg/kg iv) every 10–15 minutes or by continuous infusion (Cookson and Mills, 1983; Whelan et al., 1999; Virley et al., 2003).
3. Propofol (7–8 mg/kg iv) can be used to induce and maintain anaesthesia in both marmosets and larger primates. Good surgical anaesthesia is produced with rapid and smooth recoveries (Glen, 1980; Fowler et al., 2001).

Methohexital (10 mg/kg iv) or thiopental (15–20 mg/kg iv) can be administered to produce 5–10 minutes of surgical anaesthesia. The dosage of these agents can be reduced by at least 50% if the animal has received ketamine as pre-anaesthetic medication.

Pentobarbital (25–35 mg/kg iv) will provide 30–60 minutes of light surgical anaesthesia, but severe respiratory depression often occurs at higher dose rates and recovery can be prolonged, especially if incremental doses are administered. It is usually better replaced with other anaesthetic agents. If it is necessary to use pentobarbital, the dose should be reduced by at least 50% if ketamine or other sedatives have been administered as pre-anaesthetic medication.

TABLE 6.25 Anaesthetic Dose Rates in the Non-human Primate.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	10–12 mg/kg iv	Surgical anaesthesia	5–10	10–20
	12–18 mg/kg im	Immobilization, anaesthesia	10–20	30–50
Ketamine/diazepam	15 mg/kg im + 1 mg/kg im	Surgical anaesthesia	30–40	60–90
Ketamine/xylazine	10 mg/kg im + 0.5 mg/kg im	Surgical anaesthesia	30–40	60–120
Ketamine/medetomidine	5 mg/kg im + 0.0.5 mg/kg im	Surgical anaesthesia	30–40	60–120
Methohexital	10 mg/kg iv	Surgical anaesthesia	4–5	5–10
Pentobarbital	25–35 mg/kg iv	Surgical anaesthesia	30–60	60–120
Propofol	7–8 mg/kg iv	Surgical anaesthesia	5–10	10–15
Thiopental	15–20 mg/kg iv	Surgical anaesthesia	5–10	10–15

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable between-animal variation occurs. For recommended techniques, see text.

Inhalational Agents

All the commonly available inhalational anaesthetics can be administered to primates. It is usually most convenient to induce anaesthesia using injectable agents. Small primates can then be maintained using an inhalational agent delivered by means of a face mask, but with larger primates, it is preferable to intubate the animal. Endotracheal intubation is relatively straightforward in larger primates using a Magill laryngoscope blade. The larynx should be sprayed with lignocaine before attempting to pass an endotracheal tube. Following intubation, a T-piece or Bain's circuit should be used for administration of oxygen and the inhalational anaesthetic. As in other species, the concentration of inhalational agent can be reduced by administration of a continuous infusion of short-acting opioids (Table).

OTHER SPECIES

A full description of all of the available anaesthetic techniques for fish, reptiles, amphibia and birds is beyond the scope of this book, but the following section gives initial guidance on anaesthesia of these species. Further information is available in a number of reviews and textbooks (Green, 1981; Brown, 1993; Machin, 2004; Gunkel and Lafortune, 2005; Longley, 2008).

Birds

A number of unique aspects of avian physiology influence the selection of anaesthetic agents and the overall management of anaesthesia. Birds, particularly smaller species, have higher metabolic rates relative to mammals of comparable size and have higher body temperatures (39–42 °C). The higher body temperature results in an increased temperature gradient between core temperature and the external environmental temperature, and so cooling during anaesthesia is rapid. In small birds, as with mammals, the high surface area to body weight ratio also increases heat loss. It is therefore particularly important to adopt measures to minimize heat loss. In addition to those described in Chapter 4, avoid removing large numbers of feathers. Because of their high metabolic rate, small birds do not tolerate fasting and may develop hypoglycaemia, so only individuals weighing more than 1 kg should undergo pre-anaesthetic fasting.

The respiratory system in birds differs from that of mammals, having a series of air sacs that connect with the lungs. The presence of air sacs may allow a build-up of anaesthetic vapour in dependent areas of the respiratory system, and consequent overdose. Induction of anaesthesia with volatile agents is rapid in birds. This is not a problem provided that the anaesthetist appreciates the shorter time frame within which induction may occur.

When positioning the bird for surgery, avoid taping the wings and legs in full extension as this can inhibit both respiratory movements and venous return. Birds should be handled gently at all times, taking particular care to avoid obstructing

respiratory movements, since even short periods of apnoea can result in hypoxia. As with small mammals, care must be taken to avoid laying instruments across the chest or resting the operator's hands on the bird, since this can easily impede respiration in small species.

In the post-anaesthetic period, continued attention to maintaining body temperature is essential. Birds should recover in a heated incubator or cage (40°C for small birds, 35°C for larger, >250 g, species). The recovery area should be quiet, with subdued lighting. Prolonged recovery can be associated with episodes of wing flapping, and if not restrained, the bird may injure itself. Placing a temporary bandage or cloth around the wings can help to control this problem. Such difficulties can be largely avoided, however, by using isoflurane or sevoflurane for anaesthesia, since recovery from these agents is extremely rapid. Very little information is available concerning the use of analgesics for post-operative pain relief in birds. No clinical trials of their efficacy have been undertaken, and only very limited data are available from analgesiometry (Machin, 2005). Pharmacokinetic data are available for aspirin, flunixin and meloxicam (Baert and De Backer, 2002). Suggestions based on clinical impression include buprenorphine (0.05 mg/kg im), butorphanol (2–4 mg/kg im), or the NSAIDs flunixin (1–10 mg/kg) (Harrison and Harrison, 1986) or ketoprofen (2 mg/kg) (Wolfensohn and Lloyd, 1994). However, care should be taken when using NSAIDs in birds, since toxicity of this class of analgesic appears higher in some species (Cuthbert et al., 2006). Surveys of analgesic use by veterinarians suggest that meloxicam may be the NSAID of choice in terms of safety profile (Cuthbert et al., 2007). Dose rates of anaesthetics and analgesics are summarized in Table 6.26.

Pre-anaesthetic Medication

Ketamine

Ketamine can be administered to a wide range of avian species, but its effects can vary considerably. In the domestic fowl, 15–20 mg/kg im produces immobilization and some individuals may be lightly anaesthetized. Following initial chemical restraint with ketamine, anaesthesia can be deepened using isoflurane. When using ketamine in small birds (e.g. small finches, body weight, 20–49 g), the required dose (30–40 mg/kg) is best administered by diluting the commercial veterinary preparation with saline to provide a 10 mg/ml solution. A volume of 0.1 ml/bird im will then provide heavy sedation and 0.2 ml/bird will produce light anaesthesia (Green, 1981).

Metomidate

Metomidate (10–20 mg/kg im, 5% solution) sedates and immobilizes many species of birds. It is particularly effective in the domestic fowl. When anaesthetizing small birds (<100 g), a dilute solution (0.1%) should be used.

TABLE 6.26 Anaesthetic, Sedative and Analgesic Drugs for Use in Birds.

Drug	Dose rate	Effect	Duration of anaesthesia (minutes)	Sleep time (minutes)
Alphaxalone/alphadolone	10–14 mg/kg iv	Light anaesthesia	10–15	20–60
Buprenorphine	0.01–0.05 mg/kg im	Analgesia		
Butorphanol	2–4 mg/kg im	Analgesia		
Equithesin*	2.5 ml/kg im	Light to medium anaesthesia	20–30	60–120
Flunixin	1–10 mg/kg im	Analgesia		
Ketamine > 1 kg	15–20 mg/kg im	Immobilization, some analgesia	20–30	30–90
Ketamine < 1 kg	30–40 mg/kg im			
Ketamine/diazepam	20–40 mg/kg im + 1–1.5 mg/kg im	Medium surgical anaesthesia	20–30	30–90
Ketamine/midazolam	20–40 mg/kg im + 4 mg/kg im	Medium surgical anaesthesia	20–30	30–90
Ketamine/xylazine	5–30 mg/kg im + 0.2–5 mg/kg im	Light to medium surgical anaesthesia	10–30	30–60
Ketamine/medetomidine	5–10 mg/kg im + 0.05–0.1 mg/kg im	Light to medium surgical anaesthesia	10–30	30–60
Ketoprofen	2 mg/kg sc	Analgesia		
Metomidate	10–20 mg/kg im	Immobilization	10–30	30–60
Propofol	5–10 mg/kg iv	Medium surgical anaesthesia	10	20

Duration of anaesthesia and sleep time (loss of righting reflex) are provided only as a general guide, since considerable species variation occurs. For recommended techniques, see text.

**See Appendix 3.*

General Anaesthesia

Injectable Agents

Ketamine combinations Ketamine in combination with xylazine will produce light to moderate surgical anaesthesia in birds. As with ketamine alone, the effects vary between species, and it may be necessary to carry out a pilot study to assess the response of the species which are to be anaesthetized. Allometric scaling of ketamine/xylazine doses appears to provide a reasonable guide to an appropriate dose rate (Harrison and Harrison, 1986), with doses ranging from 10 to 30 mg/kg ketamine and 2 to 6 mg/kg xylazine, smaller birds requiring higher dose rates per kilogram.

Ketamine (20–40 mg/kg) and diazepam (1–1.5 mg/kg) or midazolam (4 mg/kg), given by intramuscular injection, produce light to medium surgical anaesthesia in birds, but as with other ketamine combinations, dose rates vary with the body weight and species involved.

Alphaxalone/Alphadolone Alphaxalone/alphadolone has unpredictable effects when given intramuscularly (Green, 1981), but it can be administered by the intravenous route (10–14 mg/kg) in larger species to produce light surgical anaesthesia.

Propofol Propofol produces smooth and rapid induction of anaesthesia if administered intravenously (up to 10 mg/kg). As in mammalian species, it should be administered slowly as rapid injection can cause apnoea (Machin, 2005). Further doses or a continuous infusion can be administered to prolong anaesthesia.

'Equithesin' (pentobarbital, chloral hydrate and magnesium sulphate, see Appendix 3) Equithesin (2.5 ml/kg im) produces medium planes of surgical anaesthesia in pigeons and domestic fowl. It provides effective anaesthesia in domestic fowl chicks (0.15 ml/40 g chick ip), although occasional post-anaesthetic mortality may occur.

Inhalational Agents

Inhalational agents can be administered via a face mask or endotracheal tube, but in birds use can also be made of the caudal air sac; this can be of particular value if birds are placed in a stereotaxic frame for surgical procedures (Nilson et al., 2005).

Isoflurane Isoflurane is widely regarded as the anaesthetic agent of choice for birds. It provides smooth and rapid induction of anaesthesia (4–5%), and anaesthesia may be maintained with concentrations of 2–3%. The depth of anaesthesia can be changed very rapidly by changing the inspired concentration, allowing birds to be maintained at an anaesthetic plane appropriate to the degree of surgical stimulus. This feature probably contributes to this agent's reputation for providing 'safe' anaesthesia, since unnecessarily deep planes of anaesthesia can be avoided. Induction can be achieved using a face mask or by placing the bird in an anaesthetic chamber. Recovery is rapid, and usually free from involuntary excitement.

Sevoflurane Sevoflurane appears non-irritant in many species of birds, and face mask induction is smooth and rapid. Recovery also seems smoother and more rapid than with other agents. Induction and maintenance concentrations are similar to those in mammals (7–8% and 3–4%).

Halothane Halothane can be used to provide surgical anaesthesia in birds, but the margin of safety appears to be considerably less than that provided by isoflurane. In addition, recovery is more prolonged, and birds may be inappetent (Harrison and Harrison, 1986). Provided the bird is observed carefully, however, induction with 3–4% halothane and maintenance with 1.5–2% provides reasonably safe and effective anaesthesia.

Reptiles

Anaesthesia of many species of reptiles can be complicated due to their ability to hold their breath for several minutes. This can slow the speed of induction when using volatile anaesthetics, or make their use impracticable, and can cause alarm when breath holding occurs after administration of injectable agents. Breath holding is commonly seen in snakes and chelonians and some species of lizards. Once anaesthesia has been induced, intubation is relatively simple as the larynx is easily visualized. This should be undertaken as a routine procedure, since in many reptiles the glottis may close as anaesthesia is deepened. Ventilation can be assisted if required, but only low inflation pressures are needed (usually less than 10 cm water; Longley, 2008).

Recovery from anaesthesia in these species is particularly influenced by environmental temperature; however, it is not advisable to try to accelerate recovery by placing the animals in a very warm environment. Animals are best recovered in their preferred optimum temperature range, and this varies with different species of reptiles. Small snakes should be fasted for 24 hours before anaesthesia, and larger species should be deprived of food for 7 days. Chelonians and lizards do not require pre-anaesthetic fasting.

General Anaesthesia

Injectable Agents

Ketamine Ketamine is the most widely used injectable anaesthetic for reptiles, producing light to moderate anaesthesia in most species. In snakes, doses of 50 mg/kg im produce sedation and 50–80 mg/kg im results in light to moderate anaesthesia (Cooper, 1974). The effects of ketamine may persist for 1–2 days. Chelonians are usually lightly anaesthetized at dose rates of 60 mg/kg im (Green, 1981), although once again recovery can take up to 24 hours. Lizards are generally lightly anaesthetized at dose rates of 25–50 mg/kg im (Cooper, 1984), and recovery may take up to 6 hours. In all species, anaesthesia may be deepened by administration of volatile anaesthetics.

Alphaxalone/Alphadolone and Propofol Alphaxalone/alphadolone (6–9 mg/kg iv) can be used to produce surgical anaesthesia, and is particularly effective in chelonians. Propofol is now considered the anaesthetic of choice in reptiles (Longley, 2008), provided that it can be administered by the intravenous or intraosseous route (12–15 mg/kg iv, chelonians; 5–10 mg/kg, other reptiles).

Inhalational Agents

Sevoflurane, isoflurane, halothane, and methoxyflurane can all be used to produce safe and effective anaesthesia. Use of an anaesthetic chamber is convenient for most smaller species of reptiles. Anaesthesia can then be maintained using a face mask or, preferably, the animal can be intubated and maintained on an appropriate anaesthetic circuit.

Amphibia

Anaesthesia of amphibia can be achieved either by injection of anaesthetic or administration by inhalation. Alternatively, the animal can be placed in water or a moist environment and liquid anaesthetic or anaesthetic vapour added. Absorption occurs through the skin, resulting in induction of anaesthesia. During anaesthesia and recovery, the skin must be kept moist in frogs and newts, but complete immersion in water must be avoided until the animal has regained consciousness, otherwise it might drown. Pre-anaesthetic fasting is not necessary.

Hypothermia has been suggested as a suitable means of immobilizing amphibia for surgery, but this technique is not considered humane since the degree of analgesia produced is unknown.

General Anaesthesia

Injectable Agents

Immersion in tricaine methanesulphonate (MS 222) rapidly induces anaesthesia. The concentration of agent required ranges from 0.2 to 0.5 g/l for larvae and newts, 1 to 2 g/l for adult frogs and salamanders, and is 3 g/l for toads. The animal can then be removed from the anaesthetic solution. Anaesthesia generally lasts for 18–30 minutes, and can be prolonged by applying anaesthetic solution to the skin. During anaesthesia and recovery, the skin should be kept moist. Recovery usually occurs within 30–90 minutes and this can be reduced by washing the animal with water to remove surplus anaesthetic. The solution should be buffered to a pH of 7–7.4 before use, and this is easily achieved by addition of sodium bicarbonate.

Inhalational Agents

Methoxyflurane can be used to provide safe and effective anaesthesia in amphibia, by exposure to the vapour in an anaesthetic chamber. During induction the base of the chamber should be lined with moist cotton wool to prevent drying of the skin.

Fish

Fish are most easily anaesthetized by immersion in anaesthetic solution. Since these animals may be sensitive to sudden changes in pH and temperature, it may be advisable to use some of the water from their normal tank to fill the anaesthetic chamber (Jolly et al., 1972). The induction tank should be aerated using a standard aquarium pump and airstone. Following induction of anaesthesia, the fish can be removed from the solution of anaesthetic and wrapped in moist gauze to prevent desiccation, and any procedure should be undertaken rapidly. For some procedures, it is possible to position the fish so that its gills remain submerged in anaesthetic solution. Alternatively, a more complex system, in which oxygenated anaesthetic solution is passed over the gills, can be constructed. A simpler recirculating system has been described (Brown, 1987; Longley, 2008). It is important to minimize handling of the fish during anaesthesia, since the skin is easily damaged, resulting in infections post-operatively. Fish should be fasted for 24–48 hours prior to anaesthesia, as they may vomit and this can interfere with gill function.

The signs of onset of anaesthesia in fish have been described in detail (Green, 1981), and differ significantly from mammals. Briefly, after loss of equilibrium and muscle tone, and onset of very shallow opercular movements, the response to pressure on the muscles at the tail base is reduced, but not abolished. At this stage the fish can be removed from the anaesthetic solution and surgery or other manipulations carried out. If surgical stimuli cause muscle spasms, then either the fish can be returned to the anaesthetic solution, or additional solution can be dripped or sprayed over the gills, for example by placing a drip in the buccal cavity. Overdosage is indicated by loss of regular opercular movements and occasional exaggerated respiratory movements. Cardiac arrest follows in 1–2 minutes unless the fish is resuscitated. This can be achieved either by flushing the mouth, and hence the gills, with fresh water, or by placing the fish in a tank of fresh water and moving it back and forth with its mouth open.

General Anaesthesia

Injectable Agents

Tricaine Methanesulphonate (MS222) Tricaine is used for induction and maintenance of anaesthesia of a wide range of fish species. It is administered as a 25–300 mg/l solution, by immersion; the concentration used determines the depth of anaesthesia. Most small to medium-sized fish (e.g. goldfish, trout) require 100 mg/l for surgical anaesthesia. Anaesthesia is induced in around 2 minutes, and recovery occurs about 5 minutes after removal from the anaesthetic solution. The anaesthetic solution should be buffered before use, using sodium bicarbonate. The effects of MS222 have been evaluated in zebra fish embryos for both short- and long-term (24 hours) immobilization (Rombough, 2006).

Benzocaine Benzocaine should be administered as a freshly prepared solution of 200 mg benzocaine in 5 ml acetone (Green, 1981), which when added to 8 litres of water provides a solution of 25 ppm (25 mg/l). This concentration is sedative, enabling minor manipulations to be undertaken. Higher concentrations (50 ppm, 50 mg/l) induce surgical anaesthesia. Some species (e.g. Tilapia) require higher concentrations (100 ppm, 100 mg/l) (Iwama, 1992).

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Appendix 1

Recommended Techniques and Physiological Data. When no Injectable Anaesthetic is Recommended, Inhalational Agents Should be Used.

	Rat	Mouse	Gerbil	Hamster	Guinea pig	Rabbit	Dog
Adult body weight	250–350 g	30–40 g			500–1000 g	3–6 kg	15–20 kg
Body temperature	38°C	37.4°C	39°C	37.4°C	38°C	38°C	38.3°C
Respiration rate	80 min ⁻¹	180 min ⁻¹	90 min ⁻¹	80 min ⁻¹	120 min ⁻¹	55 min ⁻¹	25 min ⁻¹
Resting heart rate	350 min ⁻¹	570 min ⁻¹	260–300 min ⁻¹	350 min ⁻¹	155 min ⁻¹	220 min ⁻¹	100 min ⁻¹
Sedation/ pre-medication	Fentanyl/ fluanisone (‘Hypnorm’) (0.5 ml/kg ip)	Fentanyl/ fluanisone (‘Hypnorm’) (0.4 ml/kg ip)	Fentanyl/ fluanisone (‘Hypnorm’)(0.5– 1.0 ml/kg ip)	Fentanyl/ fluanisone (‘Hypnorm’) (0.5 ml/kg ip)	Fentanyl/ fluanisone (‘Hypnorm’) (1.0 ml/kg ip)	Fentanyl/ fluanisone (‘Hypnorm’) (0.4 ml/kg ip)	Medetomidine (10–80 µg/kg im or sc) (reverse with atipamezole (50–400 µg/kg iv or im) if necessary)

Injectable anaesthesia

Short term (5–15 min)	Propofol (10–12 mg/kg iv)	Propofol (26 mg/ kg iv)				Methohexital (10–15 mg/kg iv, 1% solution)	Propofol (5–7.5 mg/kg iv)
Medium term (20–30 min)	Fentanyl/ fluanisone and midazolam (2.7 ml/kg ip of two parts water for injection, one part ‘Hypnorm’ and one part midazolam)	Fentanyl/ fluanisone and midazolam (10 ml/kg ip of two parts water for injection, one part ‘Hypnorm’ and one part midazolam)	Metomidate (50 mg/kg) plus fentanyl (0.05 mg/kg) sc	Fentanyl/ fluanisone and midazolam (4 ml/kg ip of two parts water for injection, one part ‘Hypnorm’ and one part midazolam)	Fentanyl/ fluanisone and midazolam (8 ml/kg ip of two parts water for injection, one part ‘Hypnorm’ and one part midazolam)	Fentanyl/ fluanisone and midazolam (0.3 ml/kg im and midazolam (0.5–2 mg/kg iv)	Continue propofol (0.2– 0.4 mg/kg/min)

Long term (1–12 hours)	Propofol (10–12 mg/kg iv) then 0.5–1.0 mg/kg/min. Alternatively continue medium-term regimen with fentanyl/fluanisone (0.15–0.3 ml/kg im every 20–30 min) and midazolam (2 mg/kg ip, every 4 hours)	Propofol (26 mg/kg iv) then 2–2.5 mg/kg/min		Use regimen for medium term, with additional fentanyl/fluanisone (0.5 ml/kg ip) every 20–40 min and midazolam (5 mg/kg ip) every 2–4 hours	Continue medium-term regimen with fentanyl/fluanisone (1.0 ml/kg/h ip) and midazolam (2 mg/kg ip, every 4 hours)	Continue medium-term regimen with fentanyl/fluanisone (0.1–0.3 ml/kg/h iv (preferably dilute 1:10 and infuse 1–3 ml/kg/h, or use fentanyl alone, µg/kg/min) and midazolam (1 mg/kg iv, every 4 hours)	Propofol (0.2–0.4 mg/kg/min)
Inhalational anaesthesia	Isoflurane using a face mask	Isoflurane using a face mask	Isoflurane using a face mask	Isoflurane using a face mask	Isoflurane using a face mask	Isoflurane using a Bain's circuit or Ayre's T-piece	Isoflurane using a Bain's or a Magill circuit.
Analgesia	Buprenorphine (0.01–0.05 mg/kg sc or ip, tid). Carprofen 5 mg/kg sc, uid or meloxicam, 1 mg/kg sc uid	Buprenorphine (0.05–0.1 mg/kg sc or ip, tid) Carprofen 5 mg/kg sc, uid or meloxicam, 5 mg/kg sc uid	Buprenorphine (0.01–0.05 mg/kg sc or ip, tid) Carprofen 5 mg/kg sc, uid or meloxicam, 1 mg/kg sc uid	Buprenorphine (0.01–0.05 mg/kg sc or ip, tid) Carprofen 5 mg/kg sc, uid or meloxicam, 1 mg/kg sc uid	Buprenorphine (0.01–0.05 mg/kg sc or ip, tid). Carprofen 4 mg/kg sc, uid	Buprenorphine (0.05–0.1 mg/kg sc or ip, tid). Carprofen 4 mg/kg uid.	Buprenorphine (0.005–0.02 mg/kg sc or ip, tid) or carprofen (4 mg/kg sc, uid or meloxicam 0.2 mg/kg sc)

(Continued)

Recommended Techniques and Physiological Data. When no Injectable Anaesthetic is Recommended, Inhalational Agents Should be Used.

	Cat	Ferret	Pig	Sheep	Goat	Primate (marmoset)	Primate (rhesus)
Adult body weight	3–5 kg	500–1000 g	40–200 kg	60–80 kg	40–100 kg	500 g	8–12 kg
Body temperature	38.6 °C	39 °C	39 °C	39.1 °C	39.4 °C	38.5–40 °C	39 °C
Respiration rate	26 min ⁻¹	33–36 min ⁻¹	12–18 min ⁻¹	20 min ⁻¹	20 min ⁻¹	min ⁻¹	35 min ⁻¹
Resting heart rate	150 min ⁻¹	250 min ⁻¹	220 min ⁻¹	75 min ⁻¹	80 min ⁻¹	225 min ⁻¹	150 min ⁻¹
Sedation/pre-medication	Ketamine (5–20 mg/kg im) Medetomidine (50–150 µg/kg sc or im (reverse with atipamezole (0.2 mg/kg iv, 1.0 mg/kg im) if necessary)	Ketamine (20–30 mg/kg im)	Ketamine (10–15 mg/kg im) plus diazepam or midazolam (1–2 mg/kg im)	Xylazine (0.1–0.2 mg/kg im)	Xylazine (0.05 mg/kg im)	Diazepam (1 mg/kg im)	Ketamine (5–25 mg/kg im)

Injectable anaesthesia

Short term (5–15 min)	Propofol (5–8 mg/kg iv)	Propofol (4–8 mg/kg iv)	Propofol (2.5–3.5 mg/kg iv)	Propofol (4–5 mg/kg iv)	Propofol (3 mg/kg iv)	Propofol (5–10 mg/kg iv)	Propofol (7–8 mg/kg iv)
Medium term (20–30 min)	Continue propofol (0.2–0.5 mg/kg/min) or ketamine (7 mg/kg im) plus medetomidine (80 µg/kg im or sc)	Ketamine (4–8 mg/kg im) and medetomidine (50–100 µg/kg im)	Propofol, as above, then 0.1–0.2 mg/kg/min (preferable to add alfentanil 2–5 µg/kg/min with IPPV)	Ketamine (10–15 mg/kg im or 4 mg/kg iv) and xylazine (0.1 mg/kg iv)	Ketamine (5–10 mg/kg iv) plus diazepam (0.5–1.0 mg/kg iv)	Propofol (5–10 mg/kg iv) then 0.3–0.6 mg/kg/min	Ketamine (5 mg/kg im) plus medetomidine (0.05 mg/kg im)

Long term (1–12 hours)	Propofol (0.2– 0.5 mg/kg/min)	Use inhalational agents	Continue medium-term regimen as above	–	–	Propofol (5–10 mg/kg iv) then 0.3–0.6 mg/ kg/min	Propofol (7–8 mg/kg iv) then 0.3–0.6 mg/ kg/min
Inhalational anaesthesia	Isoflurane using an Ayre’s T-piece or Bain’s circuit.	Isoflurane using a face mask	Isoflurane using a Bain’s or McGill circuit or Circle system	Isoflurane using a Bain’s or McGill circuit or Circle system	Isoflurane using a Bain’s or McGill circuit or Circle system	Isoflurane using a Bain’s circuit or Ayre’s T-piece	Isoflurane using a Bain’s circuit, Ayre’s T-piece (<10 kg) or Magill circuit (>10 kg)
Analgesia	Buprenorphine (0.005–0.01 mg/ kg sc or ip, tid) or carprofen (4 mg/kg sc, uid or meloxicam 0.2 mg/kg sc)	Buprenorphine (0.01–0.05 mg/kg sc or ip, tid). Carprofen 4 mg/ kg sc, uid	Buprenorphine (0.01–0.05 mg/kg sc or ip, tid). Carprofen 2–4 mg/kg uid	Buprenorphine (0.005–0.01 mg/kg im or iv, qid). Carprofen 2–4 mg/ kg sc, uid	Buprenorphine (0.005–0.01 mg/ kg im or iv, qid). Carprofen 2–4 mg/kg sc, uid	Buprenorphine (0.005–0.01 mg/ kg im or iv, qid). Carprofen 3–4 mg/kg sc, uid, meloxicam 0.1–0.2 mg/kg sc, uid	Buprenorphine (0.005–0.01 mg/kg im or iv, tid). Carprofen 3–4 mg/kg sc, uid, meloxicam 0.1–0.2 mg/kg sc, uid

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Estimation of Required Quantities of Volatile Anaesthetics and Anaesthetic Gases

Oxygen: Oxygen cylinders are coloured black, with a white top segment in the UK and green in the USA. A size E cylinder when full contains approximately 680 litres of oxygen, sufficient for 340 hours use at 2 l/min. The quantity of gas remaining (in litres) in a size E cylinder can be estimated from the pressure, in psi, multiplied by 0.3.

Nitrous oxide cylinders (coloured blue in the UK and in the USA) contain liquid N₂O, and the pressure reading on the pressure-reducing valve does not indicate whether the cylinder is full or almost empty. When the pressure does fall, it will do so very rapidly as the cylinder empties. A full size E cylinder of nitrous oxide can deliver approximately 1800 litres of gas (at room temperature), in other words, 900 hours use at 2 l/min.

Volatile anaesthetics: The quantity of volatile anaesthetic required can be calculated from the molecular weight (1 gram mole of anaesthetic produces 22.4 litres of vapour at standard temperature and pressure) and the density of the liquid anaesthetic. For the most commonly used anaesthetics, at a temperature of 21 °C:

Agent	Liquid density (g/ml)	Molecular weight	Volume from 1 ml (litres)	Concentration for maintenance	Quantity of agent (ml/min) for maintenance at 4 l/min fresh gas flow
Enflurane	1.52	184.5	0.198	2%	0.4
Halothane	1.87	197	0.228	1.5%	0.26
Isoflurane	1.5	184.5	0.195	2%	0.41
Methoxyflurane	1.43	146	0.235	0.4%	0.07
Sevoflurane	1.52	200	0.17	5.5%	1.3

From the above information, and a knowledge of the price/bottle, the relative costs of the anaesthetics can be calculated. At the time of publication, typical costs of the agents available in the UK were:

Agent	Cost	Cost/ml	Cost/min with 4l/min flow (see above table)
Enflurane	£45/250 ml	£0.18	£0.072
Isoflurane	£20/100 ml	£0.20	£0.082
Sevoflurane	£62/100 ml	£0.62	£0.80

Examples of Dilutions of Anaesthetic Mixtures for Small Rodents

- Look up the dose of each drug in mg/kg.
- Convert to ml/kg according to the concentration of stock solution.
- Convert to ml/100 g (rats), and ml/10 g (mice).
- Add diluent (water for injection, WFI) to make an appropriate volume per animal (e.g. 0.2 ml/100 g ip for rats, 0.1 ml/10 g ip for mice).
- Before making up these cocktails, check that the strengths of the stock solutions you are using are the same as those used here.

RAT

Except for fentanyl/medetomidine and fentanyl/fluanisone/midazolam and the reversal agents, the volumes listed below make up sufficient material for animals with a total body weight of 1 kg (i.e. 4–5 young adults). The dilutions are adjusted to provide a volume of injectate of 0.2 ml/100 g.

Ketamine/Xylazine

75 mg/kg ketamine + 10 mg/kg xylazine ip

0.75 ml (75 mg) ketamine + 0.5 ml (10 mg) xylazine + 0.75 ml WFI gives approximately 4–5 doses of 0.2 ml/100 g.

Ketamine/Medetomidine

75 mg/kg ketamine + 0.5 mg/kg medetomidine ip

0.75 ml (75 mg) ketamine + 0.5 ml (0.5 mg) medetomidine + 0.75 ml WFI gives approximately 4–5 doses of 0.2 ml 100 g.

Ketamine/Midazolam

75 mg/kg ketamine + 5 mg/kg midazolam ip

0.75 ml (75 mg) ketamine + 1 ml (5 mg) midazolam + 0.25 ml WFI gives approximately 4–5 doses of 0.2 ml/100 g

Ketamine/Acepromazine

75 mg/kg ketamine + 2.5 mg/kg acepromazine ip

0.75 ml (75 mg) ketamine + 0.25 ml (2.5 mg) acepromazine + 1 ml WFI gives approximately 4–5 doses of 0.2 ml/100 g.

Fentanyl/Fluanisone ('Hypnorm')/Midazolam

1 ml 'Hypnorm' (0.315 mg fentanyl/ml; 10 mg fluanisone/ml) + 1 ml midazolam (5 mg) + 2 ml WFI gives approximately 4–5 doses of 0.33 ml/100 g ip. (Add water for injection to 'Hypnorm' before adding midazolam.)

Fentanyl/medetomidine

300 µg/kg fentanyl + 300 µg/kg medetomidine ip

2 ml (100 µg) fentanyl + 0.1 ml (100 µg) medetomidine gives 1 dose of 0.63 ml/100 g.

Reversal for Fentanyl/Medetomidine

Nalbuphine

2 mg/kg s/c

0.2 ml (2 mg) + 0.8 ml WFI gives approximately 4–5 doses of 0.1 ml/100 g.

Atipamezole

1 mg/kg sc

0.2 ml (1 mg) + 0.8 ml WFI gives approximately 4–5 doses of 0.1 ml/100 g.

MOUSE

The quantities listed below make up sufficient material for animals with a total body weight of 500 g (i.e. 15–20 young adults). Except for 'Hypnorm'/midazolam, the dilution is adjusted to provide a volume of injectate of 0.1 ml/10 g.

Ketamine/Xylazine

100 mg/kg ketamine + 10 mg/kg xylazine ip

0.5 ml (75 mg) ketamine + 0.25 ml (5 mg) xylazine + 4.25 ml WFI gives approximately 17 doses of 0.1 ml/10 g.

Ketamine/Midazolam

100 mg/kg ketamine + 5 mg/kg midazolam ip

0.5 ml (50 mg) ketamine + 0.5 ml (2.5 mg) midazolam + 3.75 ml WFI gives approximately 17 doses of 0.1 ml/10 g.

Ketamine/Acepromazine

100 mg/kg ketamine + 5 mg/kg acepromazine ip

0.5 ml (50 mg) ketamine + 1.25 ml (2.5 mg) acepromazine + 3 ml WFI gives approximately 17 doses of 0.1 ml/10 g.

Fentanyl/Fluanisone ('Hypnorm')/Midazolam

1 ml 'Hypnorm' (0.315 mg fentanyl/ml; 10 mg fluanisone/ml) + 1 ml midazolam (5 mg) + 2 ml WFI gives approximately 4–5 doses of 0.1 ml/10 g ip.

Ketamine/Medetomidine

75 mg/kg ketamine + 1 mg/kg medetomidine

0.38 ml (38 mg) ketamine + 0.5 ml (0.5 mg) medetomidine + 4.22 ml gives approximately 17 doses of 0.1 ml/10 g.

GUINEA PIG

The quantities listed below make up sufficient material for animals with a total body weight of 1 kg (i.e. 2 young adults). Except for ketamine/acepromazine and 'Hypnorm'/midazolam, the dilution is adjusted to provide a volume of injectate of 2 ml/kg.

Ketamine/Xylazine

40 mg/kg ketamine + 5 mg/kg xylazine ip

0.4 ml (40 mg) ketamine + 0.25 ml (5 mg) xylazine + 1.35 ml WFI gives enough mixture for 1 kg at 2.0 ml/kg.

Ketamine/Acepromazine

125 mg/kg ketamine + 5 mg/kg acepromazine ip

1.25 ml (125 mg) ketamine + 2.5 ml (5 mg) acepromazine + 0.25 ml WFI gives enough mixture for 1 kg at 4.0 ml/kg.

Fentanyl/Fluanisone ('Hypnorm')/Midazolam

2 ml 'Hypnorm' (0.315 mg fentanyl/ml; 10 mg fluanisone/ml) + 2 ml midazolam (5 mg) + 4 ml WFI gives enough mixture for 1 kg at 8 ml/kg ip.

Ketamine/Medetomidine

40 mg/kg ketamine + 0.5 mg/kg medetomidine

0.4 ml (40 mg) ketamine + 0.5 ml medetomidine + 1.1 ml WFI gives enough mixture for 1 kg at 2.0 ml/kg.

BIRDS**Equithesin**

5.25 g chloral hydrate + 12.5 ml absolute alcohol

20.25 ml pentobarbital (60 mg/ml)

49.5 ml propylene glycol

2.65 g magnesium sulphate + 25 ml sterile water for injection

Mix all of the above and make up the total volume to 125 ml with sterile water for injection. The dose rate of the mixture is 2.5 ml/kg im.

Manufacturers of Equipment and Other Items Illustrated or Cited in the Text

Harvard Apparatus (www.harvardapparatus.com)
(Infusion pumps, heating blankets)
Fircroft Way, Edenbridge
Kent TN8 6HE
England
UK

Alstoe Animal Health (www.alstoe.co.uk)
(Flecknell laryngoscope blade)
Sheriff Hutton Industrial Park, Sheriff Hutton
York, YO60 6RZ
UK

VetTech Solutions (www.vet-tech.co.uk)
(Waste anaesthetic gas scavenging systems, ventilators, anaesthetic chambers)
Unit 17, Daneside Business Park
River Dane Road
Congleton
Cheshire CW12 1UN
UK

Arizant Inc. (www.arizant.com)
(Bair Hugger forced air warming blankets)
10393 West 70th Street Eden Prairie
MN 55344
USA

SA Instruments Inc. (www.i4sa.com)
(MRI compatible monitors)
PO Box 740
Stony Brook, NY 11790
USA

Starr Life Sciences Corporation (www.starrlifesciences.com)
(Mouseox pulse oximeter)
333 Alleheny Avenue
Suite 300
Oakmont, PA 15139
USA

Hallowell EMC (www.hallowell.com)
(Rodent intubation systems, ventilators)
63 Eagle Street
Pittsfield, MA 01201
413-445-4263 USA

Smiths Medical International (UK) (www.smiths-medical.com)
(Portex low-dead space connectors, endotracheal tubes)
Colonial Way, Watford
UK

Vetronic Services (www.vetronic.co.uk)
(Merlin ventilator, capnography)
4 Brunel Buildings
Brunel Road, Newton Abbot
Devon TQ12 4PB
UK

Petlife International Ltd. (www.petlifeonline.co.uk)
(Veterinary bedding)
Unit 2
Cavendish Road
Bury St Edmunds
Suffolk IP33 3TE
UK

Penlon Limited (www.penlon.com)
(Anaesthetic circuits, vaporizers)
Abingdon Science Park
Barton Lane
Abingdon, OX14 3PH
UK

Abbott Laboratories (www.abbott.com)
(Catheters)
Abbott Park, Illinois
USA

C.R. Bard Inc. (www.bardmedical.com)
(Feeding tubes)
Covington
GA 30014
USA

3M (www.3M.com)
(Micropore tape)
3M United Kingdom PLC
3M Centre
Cain Road
Bracknell
Berkshire RG12 8HT,
UK

VetaPharma
(‘Hypnorm’)
Sherburn Enterprise Park
Sherburn-in-Elmet
Leeds LS25 6NB
UK

Vygon Ltd. (www.vygon.com)
(Connectors, catheters)
Bridge Road
Cirencester
Gloucestershire, GL7 1PT
UK

Sigma-Aldrich Company Ltd. (www.sigmaaldrich.com)
(Anaesthetic drugs – e.g. inactin)
The Old Brickyard
New Road, Gillingham
Dorset SP8 4XT
UK

Columbus Instruments (www.colinst.com)
(Low sample volume capnograph)
950 N. Hague Ave

Columbus, OH 43204
USA

Nonin Medical, Inc. (www.nonin.com)
(Pulse oximeter)
13700 1st Avenue North
Plymouth, MN 55441-5443
USA

CIBA VISION Corporation
11460 Johns Creek Parkway
Duluth, GA 30097-1556

Allergan Inc.
P.O. Box 19534
Irvine, CA 92623-9534

Napp Pharmaceuticals Ltd
Cambridge Science Park
Milton Road
Cambridge
Cambridgeshire, CB4 0GW

Boehringer Ingelheim Limited,
Ellesfield Avenue,
Bracknell,
Berkshire, RG12 8YS
United Kingdom

Smiths Medical
1265 Grey Fox Road,
St Paul, Minnesota 55112,
USA

RS Biotech,
Tower Works,
Well Street, Finedon,
Northamptonshire NN9 5JP

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