THE EFFECT OF DIMETHYL SULFOXIDE AND DIMETHYL SULFOXIDE WITH FLUOCINONIDE ON EDEMA IN SPRAINED ANKLES

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CHAPTER I

INTRODUCTION

Dimethyl sulfoxide (DMSO) has gained increasing notoriety as a quick acting remedy for sprains, strains, contusions, and other injury related disorders (Clark and Hager, 1981; Reed, 1981). This publicity has increased the unsupervised use of DMSO by laymen and athletes who hope to find a miracle cure for their injuries. Research on the effectiveness of dimethyl sulfoxide has had varying results.

Reduction of edema is a primary objective in treating athletic injuries, especially ankle sprains. Edema increases healing time by irritating the tissues of the injured area and by congesting normal blood flow. Any modality that can be found to speed the reduction of edema will help decrease healing time and be very beneficial to an injured athlete. A review of literature has indicated that the use of DMSO may have an effect on the reduction of edema. Brown (1971) demonstrated that, in the treatment of bursitis, 80% DMSO was effective in reducing inflammation while 10% DMSO was not. Oerud (1982) cited dimethyl sulfoxide as being a hydroxyl radical scavenger which causes DMSO to move fluid from the edemic area into the blood. DMSO also has been shown to perform as a fast acting carrier of cortisone into the stratum corneum. This penetration has been demonstrated to take place in less than five minutes (Oerud, 1982). Maiback and Feldman (1967) demonstrated a threefold increase in skin penetration when cortisone was dissolved in DMSO and applied to the skin.

In the past, injections of corticosteroids around injured tendons and ligaments have been used to treat inflammation in these structures. Follow-up studies have indicated that if the corticosteroid was inadvertently injected into a tendon or ligament, it had a tendency to weaken the connective tissue (Ryan, 1978). Since DMSO may carry a corticosteroid into the tissue, this may be a noninvasive way to introduce a corticosteroid into the injured area.

Statement of Problem

Dimethyl sulfoxide has been shown to reduce edema and to possess carrying and penetrating properties. Maibach and Feldman (1967) demonstrated that DMSO carried substances into the stratum corneum. The problem this study addressed was whether the DMSO could carry a corticosteroid (fluocinonide) into the underlying tissues and be more effective in reducing edema in sprained ankles than could DMSO alone.

Importance of Study

This study provides valuable information to sports medicine practitioners concerning the effectiveness of dimethyl sulfoxide used in combination with a corticosteroid on sprained ankles. Previous studies have shown DMSO to have varying degrees of success. However, these prior studies used primary observation rather than direct measurement to obtain their data. As a result of this research, physicians will have the information necessary to make educated decisions on the use of dimethyl sulfoxide in combination with a corticosteroid.

Hypothesis

The following hypothesis was tested at the .05 level of

significance:

There is no significant difference in the effect of dimethyl sulfoxide and dimethyl sulfoxide with .05% fluocinonide on edema in sprained ankles over the testing period.

Limitations

The research was limited by the following factors:

1. The physical effects of DMSO may be different in individuals with varying chemical makeups and skin types.

2. The measurement of the foot/ankle may have been affected by the length of time the subjects were on their feet during the day or by the amount of water retention at the time of measurement.

3. Edema may have been affected by the subjects practicing or not practicing football during the testing period.

Delimitations

The research was delimited by the following factor:

The subjects were male, collegiate football players at Oklahoma State University who were between the ages of 18 and 22, and who had sustained sprained ankles.

Definition of Terms

Dimethyl Sulfoxide (DMSO). A solvent derived from woody plants which is used medically for the treatment of sprains, strains, contusions, and many other physical disorders. (A description of 90% DMSO is listed in Appendix A.) The chemical formula for DMSO is: $CH_3-\overset{\overset{O}{\parallel}}{S}-CH_3$.

Fluocinonide .05%. Topical corticosteroid used for the relief of inflammatory and pruritic conditions that have a vasoconstrictive action. (A complete description of fluocinonide is listed in Appendix B.) The chemical formula for fluocinonide is $CH_2\ OCCH_3$ with $C{=}O$.

Volumeter. A commercially available device that measures the volume of feet and ankles by submerging the area to be measured in water and weighing the amount of water displaced (Archimedes' principle).

Obturator. A commercially available device used in conjunction with a volumeter to reduce the surface area of the water.

Archimedes' Principle. This principle states that a body immersed in a fluid is buoyed up by a force equal to the weight of the displaced fluid. (The amount of fluid displaced by an object is equal to the volume of the object.)

Edema (Swelling). A local or generalized condition in which the body tissues contain an excessive amount of tissue fluid.

High Frequency Galvanic Current. A form of electrotherapy using approximately a 300 kHz frequency to treat inflammatory disorders, circulatory problems, and post-traumatic states following athletic injuries (sprains, contusions, dislocations, and hematomas).

Whirlpool. A form of hydrotherapy using jets of water to give the injured area an underwater massage.

CHAPTER II

REVIEW OF LITERATURE

Dimethyl sulfoxide (DMSO) is a highly controversial, experimental drug which has been approved by the Federal Drug Administration (FDA) for human use in limited clinical situations. This review of literature discusses the history of DMSO, its chemical properties, clinical effectiveness, side effects, and the previous clinical investigations pertaining to this study.

Dimethyl sulfoxide is a simple, naturally occurring organic compound. It is an inexpensive, colorless solvent which is derived from lignin as an industrial byproduct. Lignin is the organic cement that combines with cellulose to form the major portion of woody plants. DMSO is synthesized by oxidizing dimethyl sulfoxide with nitrogen oxide. It is used as an industrial solvent in the manufacture of rayon and orlon synthetic fibers, as an antifreeze or hydraulic fluid mixed with water, as a paint or varnish remover, as a carrier solvent for insecticides, as a topical dressing for trauma in horses, and as a treatment for incurable bladder disorders in humans.

Dimethyl sulfoxide was first synthesized by Saytzeff (cited in Oerud, 1982) in 1866. It was not patented, however, until the 1940's, when Crown Zellerback used it as an industrial solvent (Albrechsten and Harvey, 1982). DMSO was introduced to medicine by Jacob (cited in Oerud, 1982) in 1963 for use in the reduction of arthritic swelling. Jacob promoted DMSO as having certain beneficial pharmacological properties for patients.

The following are Jacob's (cited in Harter, 1983) assumptions:

1. DMSO penetrated the intact skin rapidly and carried a number of chemicals with it; thus, some injections would not be necessary.

2. Various inflammatory diseases could be controlled because DMSO inhibited a number of prostaglandins.

3. DMSO's logal analgesic properties could reduce pain from swelling.

4. Science could harness DMSO's ability to dissolve amyloid and collagen compounds.

5. DMSO reduced intracranial pressure in head injuries, thus reducing mortality from head injuries (p. 1).

At the present time, the FDA has approved DMSO for human studies. During the period of 1963 to 1965, over 100,000 persons received the drug in experimental studies. In 1965, the FDA rescinded permission for DMSO to be used in human clinical studies. This decision came following the development of lenticular myopia in small, nonprimate animals treated with large doses of DMSO in several experimental studies. Further clinical data failed to show the same change in human lens refraction. Harter (1983) stated:

> Our toxicologists have reviewed studies on DMSO in seven species, all of which, after some dose for some duration, show incompletely reversible changes in the lens. It would be a biological quirk for human lenses not to behave similarly (p. 5).

Rubin (1983, p. 8) found that DMSO did not accumulate in the eye lens. In the DMSO-affected lens, there was a ". . . decreased concentration of urea, uric acid, glutalhioxe and amino acids, with an increase in albuminoids. The lens change is not caused by either hydration or dehydration nor does DMSO bind to lens protein."

The FDA approved DMSO again in 1966 for clinical studies concerning such untreatable diseases as scleroderma (thickening of skin and some internal organs) and persistent herpes zoster (shingles). The approval

for clinical use of DMSO in less serious conditions (such as bursitis and sprains) came in 1968. Fifty percent DMSO gained FDA approval in 1973 for incurable bladder conditions such as interstitial cystitis. The only product currently approved by the FDA for use in humans is a 50% DMSO solution marketed as "Rimso-50" by the Research Industries Corporation ("Topical DMSO as therapy in patients," 1980) of Salt Lake City, Utah.

In 1980, the FDA lifted restrictions on human studies, but still considered DMSO as an investigational new drug. The FDA gave approval for the Research Industries Corporation to study extensively the effect of DMSO on athletic injuries. Mr. Marv Robertson, the athletic trainer at Brigham Young University, has been working with research specializing in sprains and strains.

> After almost three years of work, I have concluded that DMSO is effective on soft-tissue injuries. . . . It's erratic, but it has no side effects except an occasional rash and bad breath. It reduces recovery time by 50%, on the average. It's amazing stuff. I think it should be legalized as a controlled substance. If aspirin were submitted to the FDA today for approval, it would take 10 years for approval and it would be a prescription drug. And, unlike aspirin, DMSO hasn't been proven responsible for one death yet (cited in Reed, 1981, p. 75).

However, DMSO has not been approved for general use by the FDA. This would include approval for use on soft tissue injuries.

The Journal of the American Medical Association ("Dimethyl sulfoxide: Controversy and current status," 1982) stated that DMSO is reported to be clinically effective in the following: (1) acute musculoskeletal injuries and inflammations; (2) diseases of connective tissues (rheumatoid arthritis, cutaneous manifestations of scleroderma, ankylosing spondylitis and gout); (3) burns; (4) post-operative pain; (5) viral, fungal, bacterial, and parasitic skin infections; (6) wound healing; (7) interstitial cystitis; and (8) mental conditions.

Dimethyl sulfoxide is a controversial drug which is sometimes illegally used. It has been increasingly hailed by a large number of professional and amateur athletes who look at it as a panacea for all types of ills from sprains to torn muscles. Even members of the medical profession hold differing opinions about DMSO. According to Dr. Frank Jobe (cited in Reed, 1981), orthopaedist for the Los Angeles Dodgers (a professional baseball club) and a founder of the National Athletic Health Institute (NAHI), "It's quite spectacular on soft-tissue injuries like sprains, contusions, bursitis, tendonitis. It could revolutionize sports medicine" (p. 72). Dr. Robert Kerlan (cited in Reed, 1981), sports orthopaedist and a founder of NAHI, said: "DMSO has some medical benefits, but curing routine sports injuries isn't one of them. It's almost useless for athletes" (p. 72). Athletic trainer Dick D'Olivia (cited in Reed, 1981, p. 75) said: "When a trainer uses DMSO, he uses ice, ultrasound, acupuncture, anything--all at the same time. He doesn't have time to sort out his treatments." D'Olivia continued by explaining that no one knows how much of a patient's rehabilitation is locked up in his head. Dr. Stan James (cited in Reed, 1981) and Oregon orthopaedist, has a more reasonable view of DMSO:

> DMSO is no miracle. . . . It's effective, yes. But when you withhold something from the public, whether it's laetrile, marijuana, liquor or Playboy, an artificial madness is created. DMSO is not dangerous. Legalize it, and it will take it's place in the pharmacology of sports medicine. People won't believe it, but miracles are few and far between. Penicillin was the last one, and DMSO is not penicillin (p. 75).

Pierre Pilote, a professional hockey player with the Chicago Black Hawks, might disagree with Dr. James' opinion that DMSO is not a miracle drug (Reed, 1981). In 1965, Pilote treated his dislocated shoulder with DMSO and started skating immediately. Sandy Koufax, a professional baseball player, used DMSO on a nagging elbow and was able to pitch brilliantly in

the 1965 World Series (Reed, 1981). Daryle Lamonica of the Oakland Raiders (a professional football team) used DMSO in 1968 on his jammed thumb and the swelling decreased in 15 minutes (Reed, 1981). However, DMSO did not work on his torn ligament. Lamonica stated that a number of professional football players used DMSO and ". . . the only side effect we ever noticed was body odor and incredibly bad breath" (Reed, 1981, p. 74). Because of DMSO's popularity in the sports arena, especially professional sports, several states have legalized its manufacture, prescription, and use under specified conditions. Florida now warns physicians and licensed health care practitioners against prescribing veterinary or industrial grade DMSO for their patients. There could be harmful contaminants in the industrial solution which may prove hazardous to the individual using DMSO. The veterinary product is usually a 90% solution which produces greater cutaneous toxicity.

The chemical properties of DMSO are the following: chemical empirical formula--$C_2H_6O_5$, structural formula--CH_3-S-CH_3, specific gravity--1.1014, molecular weight--78.15, melting point--18.4^{o}C, boiling point--189^{o}C, flashpoint--95^{o}C (Jacob and Wood, 1971).

DMSO is available in either gel or solution form. The highly polar dimethyl sulfoxide is miscible in water, ethanel, acetone, ether, benzene, and chloroform in the same manner in which alcohol goes into solution with water. It is exothermic, giving up 60 calories per gram when it is mixed with water. DMSO binds readily with moisture in the air (hygroscopic); however, when it is mixed 50-50 with water, it does not freeze, even at -270^{o}C. For this reason, it can be used as an antifreeze and as a cryogenics solution.

Dimethyl sulfoxide penetrates the skin rapidly. It crosses most body membranes without harming them. When radioactively labeled DMSO has

been rubbed on human skin, it has been detected in the blood in less than five minutes (Oerud, 1982). The peak level of concentration in the blood occurs between four and six hours. DMSO appears to remain at a constant level in the blood for 36 to 72 hours. It does not penetrate the nails or the tooth enamel (Maibach and Feldman, 1967). Maibach and Feldman's (1967) study on the percutaneous penetration of hydrocortisone in DMSO in humans showed that the maximum excretion occurred within 36 hours. They concluded that there was a threefold increase in penetration when cortisone was dissolved in DMSO and applied to the skin. When DMSO had a tracer added (i.e., methylene blue) but no cortisone, biopsies showed the stratum corneum was completely stained. Little or no staining occurred below this level (Maiback and Feldman, 1967).

Stoughton and Fritsch (1964, p. 516) reported that "In the case of transient exposure, DMSO was superior to water in promoting penetration of hydrocortisone by a factor of about seven." Klingman (1965) demonstrated that when there were steroids dissolved in solutions of 70% DMSO or greater, there was an enhanced skin penetration. Sulzberger (cited in McDermot, Murray, and Heggie, 1965) concluded from his experiments that since DMSO carries substances rapidly into the horny layer of the skin, it must be useful as a therapy vehicle for agents used on inflammatory dermatoses and superficial skin infections. DMSO carries hydrocortisone into the deeper layers of the skin (stratum corneum), ". . . producing a reservoir which remains for 16 days and resists depletion by washing the skin surface with soap, water and alcohol" (Jacob and Wood, 1971, p. 3).

Serum levels of DMSO are lower after dermal administration than after oral administration (Maiback and Feldman, 1967). Dermal absorption appears less complete than does gastrointestinal absorption.

The distribution of DMSO in the body is widespread. Traces of DMSO have been found in all body tissues, since it binds to protein in the blood. The highest concentration of DMSO appears to be found in the stomach, spleen, lungs, and skin. The lowest concentration of DMSO has been found in the cartilage, joint fluid, bone, eye lens, and adrenal glands (Oerud, 1982).

Dimethyl sulfoxide is metabolized by the body into DMS, DMSO2, and DMSO. DMS is excreted by the lungs. One-and-one-half to three percent of the total dosage given is excreted during the first 24 hours. DMSO2 and DMSO are given off by the kidneys, which is the main elimination route in humans (Oerud, 1982). Fifteen percent of the total dosage is excreted during the first 24 hours, and 50% during a 10-day period. Only a small amount of DMSO is excreted in the stool. The only site of DMSO accumulation is the skin (John and Laudahn, 1967).

DMSO is an anti-inflammatory agent. This is due to the fact that dimethyl sulfoxide is a hydroxyl radical scavenger, which is a response initiated by white blood cells (Oerud, 1982). There is a decreased antibody response and decreased antibody reproduction. The thirst DMSO produces is its key to relieving edema and pain. When DMSO moves fluid into the blood, it makes the body's work of healing quicker, easier, and less painful by relieving pressure and swelling (Reed, 1981). DMSO does not heal tissues by itself.

Weismann, Sessa, and Bevans (1967) documented that lysosomes can be stablized by cortisone. When cortisone was dissolved in DMSO, the amount of cortisone necessary to stabilize the lysosomes was reduced from tens to thousands. They suggested the possibility that DMSO rendered the steroids more available to target tissues.

Percy and Carson (1981), in a study of 80 patients using 70% DMSO, showed that DMSO was not effective in tennis elbow and rotator cuff tendonitis. The double-blind study of 70% DMSO and 5% DMSO assessed pain tenderness, but did not measure swelling, include X-rays of the injured areas, or characterize the injury or its duration. The application of DMSO was unsupervised. Twenty-two percent of the original subjects dropped out of the study.

Brown (1971) showed that in the treatment of bursitis, 80% DMSO was effective in reducing inflammation, while 10% DMSO was only fair to poor in reducing inflammation. The result obtained from standard therapy was comparable to the result obtained with 80% DMSO.

McDermott, Murray, and Heggie (1965) applied 6% DMSO to patients' skin. They found that it reduced the nerve conduction velocity by 40% for the first two weeks. This activity diminished and disappeared soon after the two-week period ended.

When the skin was swabbed once or twice a day with DMSO, a mild site erythematous scaling dermatitis appeared at the site. This rash regressed as the treatment progressed. "Skin erythema, edema, and pruritus are frequent occurrences in humans when concentrations of DMSO greater than 70% are used, but such side reactions also occur at concentrations of 10%" (Rubin, 1983, p. 7). A study using 80% DMSO prescribed for the patient at a ratio of one gram per kilogram per day was conducted on male prison volunteers. There were 78 subjects and 33 controls. No significant laboratory systemic side effects were noted, and all subjects had normal eye lens examinations. There were, however, several minor side effects. These included the following: sedation (52%), headache (42%), nausea (32%), and skin irritation and increased eosinophile count (18%) (Paul, 1967). The volunteer subjects also complained of generalized

dermatitis, diarrhea, burning irritation, and allergic reactions. Mild ointments help skin scaling and irritation, but the irritation decreases with continued usage.

The eye lens refraction change in most species of animals appears to be dose-related. Eye lens refraction has not been reported in human beings. When DMSO was given orally to dogs, rabbits, and pigs, it resulted in ". . . alterations of the refractive index of the lens with a progressive myopia. Lenses from treated animals do not become opaque" (Jacob and Wood, 1971, p. 2). Not all species appeared to be affected equally. Rabbits were the most sensitive animals, while rhesus monkeys were the least sensitive to lens change brought about by DMSO. Kutschera (cited in John and Laudahn, 1967) treated 84 patients for an average of 2-1/2 months with average doses of 18.4 milliliters of 90% DMSO. No toxicity to the eyes was noted.

Scherbel, McCormack, and Poppo's (1965) observations on 47 patients who had scleroderma, and who were given several ophthalmologic examinations, showed no toxicity after taking DMSO. The highest dosage was 30 milliliters of 90% DMSO; the longest treatment period was 2.5 years. Gordon and Kleberger (1968) stated:

> If any single fact has emerged from animal and human studies with DMSO to date, it is that the lens toxicity findings originally reported in dogs and later confirmed in certain other species have no equivalent or counterpart in human therapy utilizing DMSO in generally accepted regimens (p. 423).

There appears to be a marked increase in urine production when DMSO is used. The probable cause of the increase is an osmotic duresis, along with increased amounts of both sodium and potassium excretions (Oerud, 1982). DMSO, when applied as a pretreatment, has the tendency to make some resistant bacteria sensitive to antibiotics. This activity is helpful in treating skin infections.

Albrechtsen and Harvey (1982, p. 179) found that "The topical application of dimethyl sulfoxide was associated with periods of decreased mean separation forces in tendons." They strongly suggested that vigorous exercise and muscular activity be avoided during DMSO therapy, due to the tendons' increased susceptibility to injury. Sports Medicine Digest ("DMSO weakens tendons [in mice]," 1983) concurred with this suggestion.

Brown (1967), in a clinically controlled, double-blind study of 75 patients with acute sprains and tendonitis, used 10% and 80% DMSO gel. He proved that the 80% DMSO gave greater relief from tenderness and pain for longer periods of time and allowed greater range of motion than did the 10% solution of DMSO. The results of the 80% DMSO were comparable to results expected from normal treatment.

Myrer, Hickmann, and Francis (1986) investigated the use of topically applied DMSO to traumatized muscles of 80 rats. The rats were traumatized, treated, and sacrificed to discover the number of histologic healing cells. The rats were assigned to either a healing or inflammation group, and then were further divided into a control group (100% distilled water) and an experimental group (70% DMSO and 30% distilled water). During each treatment, the rats received one milliliter of either DMSO or water, while the inflammation group received an additional 15 treatments during a five-day period. Myrer, Hickmann, and Francis (1986) found that

> Significantly fewer healing cells were present in the experimental group than in the control group during the period inflammation was examined and no significant difference existed between the experimental and control groups during the period healing was examined (p. 165).

The drug DMSO has great potential in the treatment of various traumas. The most noticeable side effects are bad breath (amicably referred to as "death breath") and a distinguishable body odor. The

intensity of the odor varies from individual to individual. "Death breath" appears within five minutes after application of DMSO. A 10% aqueous solution of DMSO, although ineffective, produces the revealing "oyster" breath. In the lungs, the body releases dimethyl sulfoxide in the gas exchange, causing the odor. Only withdrawing the drug will alleviate breath odor. Because of this distinguishing odor, taste, and bad breath, there is some difficulty in setting up a double-blind study.

The University of Oregon Medical School has monitored patients who have been using dimethyl sulfoxide for as long as two years with hemalogic and chemical tests (Jacob and Wood, 1971). No significant abnormalities were found. Treating patients topically with DMSO produced potent histamine liberation at the application site.

The Drug Education Committee of the National Athletic Trainers Association has recognized 99 injuries/conditions that they considered worthy of further investigation of DMSO treatment (Weismann, Sessa, and Bevans, 1967). (A list of these injuries/conditions may be found in Appendix C).

There is an extensive amount of literature to warrant the investigative uses of DMSO as a therapeutic modality. It has not been proven to be a single, miracle cure for athletic injuries. DMSO is best used as an adjunct to conventional therapy, not as a replacement. It requires continuous study by qualified sports medicine professionals in order to determine optimum dosage and application techniques.

Summary

Dimethyl sulfoxide was released in 1980 by the FDA as an investigational new drug. Research Industries Corporation of Salt Lake City, Utah, markets a 50% DMSO solution called "Rimso-50," the only product currently approved for human use by the FDA.

DMSO has proven to be effective in the treatment of acute musculoskeletal injuries, connective tissue disease, burns, post-operative pain, skin infections, wound healing, interstitial cystitis, and various mental conditions. A large number of amateur and professional athletes view DMSO as a panacea for the treatment of numerous types of injuries. However, experimental and clinical studies over the last two decades have not proven conclusively that DMSO is more effective in the treatment of athletic injuries than are conventional methods.

Maibach and Feldman's (1967) study concluded that there was a threefold increase in skin penetration when cortisone was dissolved in DMSO and applied. Stoughton and Fritsch (1964) showed that DMSO was superior to water in promoting penetration of hydrocortisone by a factor of seven.

Weismann, Sessa, and Bevans (1967) documented that cortisone can stabilize lysosomes. When cortisone was dissolved in DMSO, the amount of cortisone necessary to stabilize the lysosomes was reduced from tens to thousands.

Brown (1971) showed that 80% DMSO was effective in reducing bursitis inflammation; however, the conclusions were comparable to results obtained solely with standard treatment. Albrechtsen and Harvey (1982) demonstrated that topically applied DMSO produced periods of decreased tendon mean separation. Thus, Albrechtsen and Harvey suggested that vigorous muscular activity be curtailed during DMSO treatment. Sports Medicine Digest ("DMSO weakens tendons [in mice]," 1983) concurred with this study.

Myrer, Hickmann, and Francis (1986) experimented with applying 80% DMSO, 30% DMSO, and 100% distilled water on traumatized rat muscles. After sacrificing the rats, they discovered that fewer healing cells were present in the DMSO group than were present in the distilled water group.

Also, there was no significant difference between the two groups during the healing period.

The literature has shown that DMSO is not a miracle cure for athletic injuries to be used in place of conventional therapeutic modalities; rather, it should be used as part of a total rehabilitative program after research determines the optimum DMSO dosage and application techniques.

CHAPTER III

METHODS AND PROCEDURES

This research was designed to test the hypothesis that, over time, there was no significant difference in the effect of dimethyl sulfoxide and dimethyl sulfoxide with .05% fluocinonide on edema in sprained ankles. The edema volume in the injured ankle and the volume of the uninjured ankle was measured using the basics of the Archimedes' Principle. The post-injury measurements were subtracted from the pre-injury measurement to determine the volume difference. The volume difference represented the volume of edema changes in the injured ankle and the volume changes in the uninjured ankle.

Selection of Subjects

The population for this study consisted of collegiate football players at Oklahoma State University who were between the ages of 18 and 22. The subjects were selected from a pool of 123 members of the Fall, 1987, Oklahoma State University football team. The 14 participants were randomly selected by the athletes' acquisition of sprained ankles and their willingness to participate in the research. All members of the football team were pre-measured with the prospect of possible ankle sprains, thereby becoming candidates for participation in the study.

All subjects treated with dimethyl sulfoxide or dimethyl sulfoxide with fluocinonide were required to sign an informed consent form, demonstrating their willingness to participate in the research (Appendix D).

In the state of Oklahoma, dimethyl sulfoxide is recognized as a prescription drug. The Oklahoma State Board of Health requires an alternative mode of treatment release to be signed by the patient and the prescribing physician (Appendix E). All participants were asked to read both releases and were invited to ask any questions before they were included in the study. The participants were under close scrutiny by the supervising physician and sports medicine personnel. In the event that any abnormalities had arisen, the subjects had available prompt and appropriate medical attention.

Instrumentation

The devices used to measure prospective subjects and participants were two commercially available foot and ankle volumeters with obturators. Figure 1 shows the measuring instruments used to collect the data.

Figure 1. Photograph of Measuring Instruments

The weight of the water displaced by the subjects'foot/ankle/lower leg was the measurement used to determine the size of each of the subjects' ankles pre- and post-injury. By utilizing the Archimedes Principle, the edema changes as demonstrated by the amount of water displaced could be accurately measured. The water was weighed on a commercially available Detecto scale used in blood banks and laboratories to make measurements in one gram increments. The volumeters and obturators were labeled "right" and "left," so that the same devices were used to measure the same ankle each time.

A protocol was determined by using the manufacturer's guidelines, in order to insure consistency of procedure for each measurement. The following procedures were precisely adhered to each time measurements were taken. The directions given to the subjects were the same for the initial measurement and for all additional measurements:

1. Before daily testing, the accuracy of the Detecto digital scale with the Ohaus exact weights was checked. The 10-gram weight was weighed first and then the next higher weight was added, up to the total of 12,100 grams. It was ascertained that the scale read the exact weight each time a weight was added. The two receivers (mixing pitchers) were weighed to assure a weight of 165 grams each. The scale zeroed out with one of the receivers on the scale. The receiver was removed and checked to see if the scale read 165 grams.

2. Before each measurement was taken, the position of the chair and the volumeters were checked. Caution was taken to insure that the chair and the volumeters were on the appropriate line marked on the floor. The volumeters (right and left) were situated in the correct position in front of the chair, with the overflow spouts pointing away from the subject. The receivers were placed under the overflow spouts.

3. The right and left obturators were filled with water from the holding tank (20 gallon plastic trash container) to within 1/2" of the top. The obturators were placed into their corresponding volumeters with water from the holding tank until water came out of the overflow spout. The water sat for three minutes; a stop watch was used. Although the water generally stopped coming out of the overflow in about two minutes, the full three minutes were used to confirm that the water had leveled off. The receivers were emptied, dried with a towel, and then were re-weighed to ascertain that they were zeroed out on the scales.

4. The subject sat on the chair with his back against the chair back and his arms on the arm rests. The right obturator was lifted and the subject immersed his right foot slowly into the volumeter. The lower leg was perpendicular to the floor, with the heel and ball of the foot sitting on the bottom of the volumeter. The back of the heel was touching the back of the volumeter. The obturator was replaced into the top of the volumeter. The procedure was then repeated with the left foot. The subject was asked to relax; the only pressure on the feet was the weight of the subjects' legs. After the subject was correctly positioned and relaxed, he was instructed to remain relatively motionless for three minutes (a stop watch was used).

5. After two minutes, the water had stopped coming out of the overflow spout. However, the full three minutes was used to insure that the water had leveled off. The right receiver was removed and placed on the Detecto scale, the weight was recorded on the record sheet, and this process was repeated with the left receiver.

6. The subject waited to remove his feet until both receivers were weighed, in order to avoid the splashing of water into either receiver.

After the weighing was completed, the obturators were removed and the subject withdrew his feet from the volumeters.

7. Step #3 was repeated so that the volumeters were ready to measure the next subject.

8. At the end of the day, the volumeters, obturators, and receivers were cleaned and dried. The holding tank was filled with fresh water so that the water would be room temperature for the following day's testing.

A reliability test of the volumeters and obturators was completed before the actual investigation measurements began. A uniformity trial was used to check reliability. This trial was analyzed using an analysis of variance. Twelve football players were selected at random and both ankles were measured once a day for five days (Monday through Friday) at approximately the same time each day. This produced a 12 x 2 x 5 factorial experiment. The testing procedures used were identical to those used in the present study. An analysis of variance was used to determine reliability. Results of the reliability test are shown in Table VI (Appendix H). The results of the reliability test indicated a difference ($P < .01$) among ankle volumes. This was expected, due to the different heights and weights of the football players tested. There were no other significant differences ($P = .05$) in the changes in ankle volume over the five-day testing period. Figure 7 (Appendix H) shows the relationship between the left and right ankle over the reliability testing period.

The dimethyl sulfoxide and fluocinonide used in this research were purchased from a pharmacy located in Stillwater, Oklahoma. The solution of 90 milliliters of 70% DMSO and 90 milliliters of 70% DMSO with a .01% concentration of fluocinonide was calculated and prepared by a registered pharmacist using the formula stated in Appendix F. The DMSO solutions were mixed in individual, 90 milliliter, airtight, light resistant, amber

glass, graduate bottles with child-resistant caps. The bottles were grouped in blocks of two--one bottle for each of the two treatments--because only a small number of subjects were expected to participate. This insured treatment groups of the same size. The bottles were labeled with the pharmacy label and the identifying bottle code numbers (i.e., BLOCK 1, BOTTLE 1). As each bottle was assigned to a subject, the pharmacist was notified as to which bottle and block was being used on each particular subject. The pharmacist then wrote the subject's name on the corresponding prescription. The pharmacist was the only person routinely notified during the study as to which solution was used on any subject. The supervising physician could obtain this information at any time in the event of an adverse reaction to the treatments.

Data Collection

Immediately after sustaining an ankle sprain, each candidate received the standard treatment consisting of 15 minutes of ice, compression, and elevation. During this initial treatment, the subject was asked to participate in the study. If the subject agreed to take part in the research and signed both release forms, his ankles were measured. Measurements were then recorded on the ankle injury record sheet (Appendix G). The subject's skin was washed thoroughly and 30 milliliters of one of the two DMSO solutions was applied, using four 3 x 3 gauze pads. The DMSO bottles were assigned in the order of the participants entering the study. The DMSO was rubbed into the skin and was covered with a plastic-backed, cellulose compress material. An elastic wrap was loosely applied, and each subject was instructed to leave the wrap and the DMSO on for 12 hours. The subject was told to return the following morning for another measurement and treatment.

The treatment regimen consisted of a cold (65^{o} - 55^{o}) whirlpool for 15 minutes, 10 minutes of high frequency galvanic current with the ankle elevated, and 10 minutes of cold whirlpool three times daily. An elastic wrap was reapplied after each treatment. Before football practice, the subject's ankles were measured again. If the subject could practice, the ankle was taped; if not, he stayed in the training room and received the standard treatment. After practice, both of the subject's ankles were again measured and a second treatment of DMSO was applied to the injured ankle. This process continued until three applications of DMSO were given and three consecutive days of measurements were taken. Additional measurements were taken on the fourth and seventh days after the injury occurred.

Analysis of Data

The data were compiled on the 14 subjects and analyzed using an analysis of variance. The analysis was done on a computer using the SAS Corporation Software. This was a 7 x 2 x 2 x 12 split-split plot experimental design (7 blocks, 2 treatments, 2 ankles, 12 measurements on each ankle). The mean volumes that were used for the computations were the pre-injury measurements minus the post-injury measurements (volume difference).

Summary

To compare the two dimethyl sulfoxide treatments as to their effectiveness, commercially available foot and ankle volumeters were used to pre- and post-test ankle volume to measure changes in the amount of edema in the injured ankle. By accurately measuring the volume of the ankles before an injury occurred, the investigator established a pre-test

measurement for the injured ankle. For the purposes of this study, the effectiveness of the two DMSO treatments was based on the amount of edema reduced over the one-week testing period, as measured by changes in the volume of the ankles.

CHAPTER IV

RESULTS

The purpose of this study was to test the hypothesis that, over the 168-hour testing period, there would be no difference in the effect of dimethyl sulfoxide and dimethyl sulfoxide with .05% fluocinonide on the reduction of edema in sprained ankles. All Oklahoma State University football players' ankles were premeasured using commercially available volumeters. Those players who acquired sprained ankles participated in the study. All post-injury measurements were subtracted from the pre-injury measurement to derive a volume difference value. From the 123 football players pretested, 14 subsequently became subjects in the study. Seven subjects received 70% DMSO and seven subjects received 70% DMSO with fluocinonide. A total of 12 measurements were taken after the injury on both ankles of the subjects over a seven-day period. The data compiled on the 14 subjects over the treatment and measurement period appear in Table VII (Appendix H), and a summary of the time, treatment, and ankle means is shown in Table VIII (Appendix H). The results of the analysis of variance on the sprained ankles are shown in Table I.

In comparing the results of the effect of dimethyl sulfoxide and dimethyl sulfoxide with fluocinonide it was found that, over time, the linear slopes were negative and identical ($P < .05$). This is demonstrated in Figure 2. The quadratic curvature of the DMSO curve was different from the DMSO with fluocinonide curve ($P < .01$). The cubic (curve

downward and back upward) over time were identical (P = .05). The average cubic curvature was significant (P < .01). The uninjured ankle was measured throughout the study and the resulting data is shown in Table II.

TABLE I

VOLUMETER RELIABILITY TEST DATA

SOURCE	DF	SUM SQUARES	M.S.	F
TOTAL	167	692,508.99		
Blk	6	159,381.04	26,563.51	0.74 NS
Trt (Chk vs Trt)	1	100,891.01	100,891.01	2.82 NS
Blk*Trt (Error A)	6	215,039.87	35,839.98	
Time	11	50,856.64		
Time Linear (T1)	1	8,424.34	8,424.34	6.39 *
Time Quad (T2)	1	7,548.59	7,548.59	5.72 *
Time Cubic (T3)	1	24,234.32	24,234.32	18.37 **
Time Residual	8	10,649.39	1,331.17	1.01 NS
Blk*Time (Error B)	66	87,062.82	1,319.13	
Trt*Time	11	21,028.78		
Trt*T1	1	400.70	400.70	0.45 NS
Trt*T2	1	18,336.29	18,336.29	20.78 **
Trt*T3	1	65.52	65.52	0.07 NS
Trt*Time Residual	8	1,726.26	215.78	0.24 NS
Blk*Trt*Time (Error C)	66	58,248.85	882.56	

** Significant at a =.01
* Significant at a =.05
NS Not Significant at a = .05

Figure 3 shows the mean volume difference for the DMSO uninjured ankle and the DMSO with fluocinonide uninjured ankle. The linear slopes were equal and were not significantly different from zero (P > .05). The quadratic curvatures were not the same (P < .01), and the cubic curvatures were not different (P = .05). The average cubic curvature was

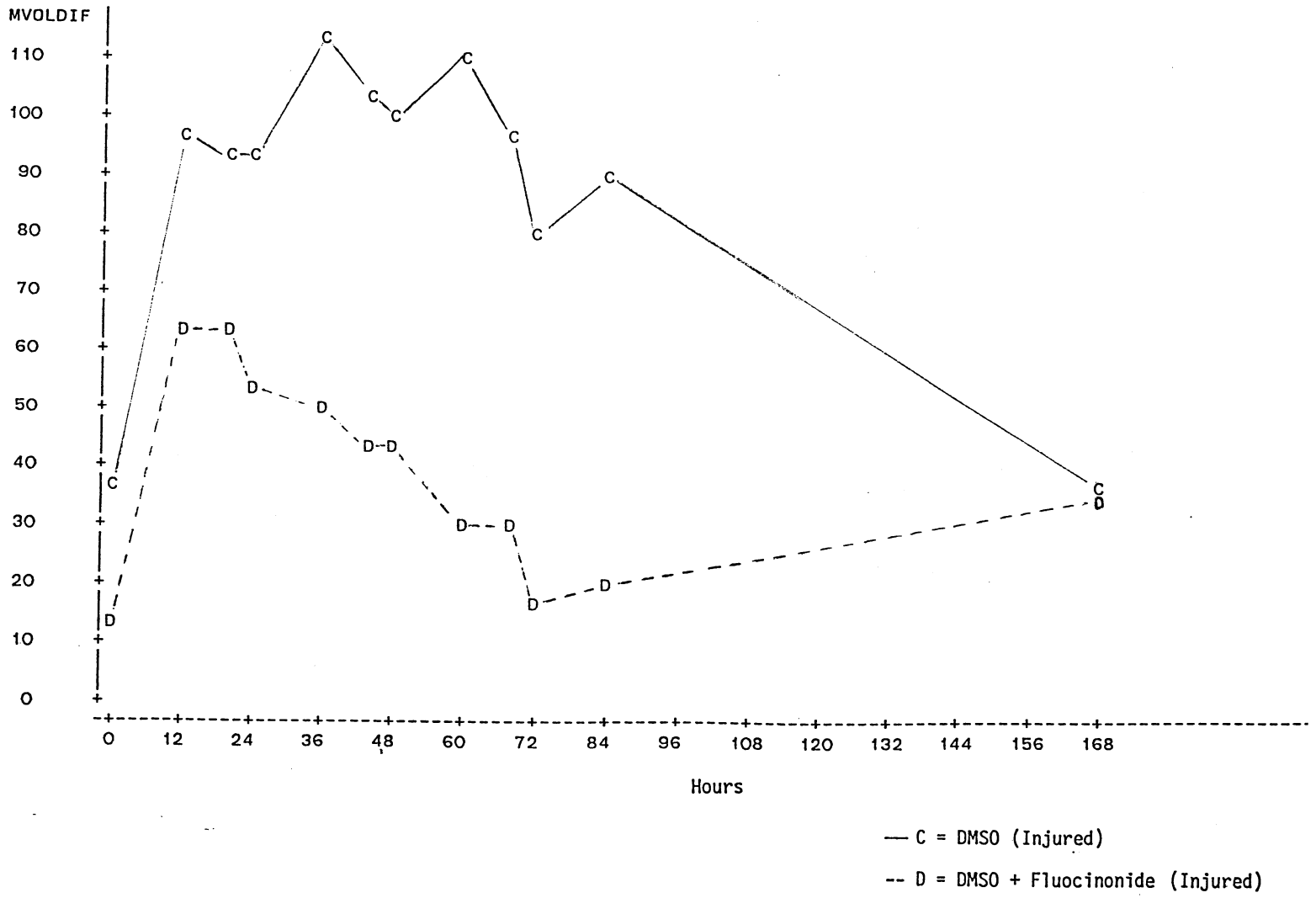

Figure 2. Comparison of Mean Volume Difference for DMSO Injured and DMSO With Fluocinonide Injured Ankles

significant ($P < .01$); both curved downwards and back upwards. The DMSO with fluocininode ankle rose slightly higher than did the DMSO curve.

TABLE II

ANALYSIS OF VARIANCE FOR VOLUMETER RELIABILITY

SOURCE	DF	SUM SQUARES	M.S.	F
TOTAL	167	200,707.40		
Blk	6	69,249.24	11,541.54	4.22 NS
Trt (Chk vs Trt)	1	2.38	2.38	0.00 NS
Blk*Trt (Error A)	6	16,396.45	2,732.74	
Time	11	15,394.69		
Time Linear (T1)	1	653.93	653.93	1.17 NS
Time Quad (T2)	1	1,635.00	1,635.00	2.93 NS
Time Cubic (T3)	1	6,125.76	6,125.76	10.97 **
Time Residual	8	6,980.01	872.50	1.56 NS
Blk*Time (Error B)	66	36,860.48	558.49	
Trt*Time	11	15,202.33		
Trt*T1	1	2,106.50	2,106.50	2.92 NS
Trt*T2	1	9,185.09	9,185.09	12.74 **
Trt*T3	1	120.29	120.29	0.17 NS
Trt*Time Residual	8	3,790.45	473.81	0.66 NS
Blk*Trt*Time (Error C)	66	47,601.83	721.24	

** Significant at a =.01
* Signicicant at a =.05
NS Not Significant at a = .05

Table III exhibits the combined analysis of variance for the two treatments, both ankles and the 12-time measurement periods. Table IV shows the mean responses for each ankle and treatment combination. The mean volume difference was 62.76 for the injured ankle and 18.94 for the uninjured ankle. This difference was significant ($P < .01$), and was expected since the injured ankle would be edemic. The mean volume difference was 53.16 for the DMSO treatment and 28.54 for the DMSO with

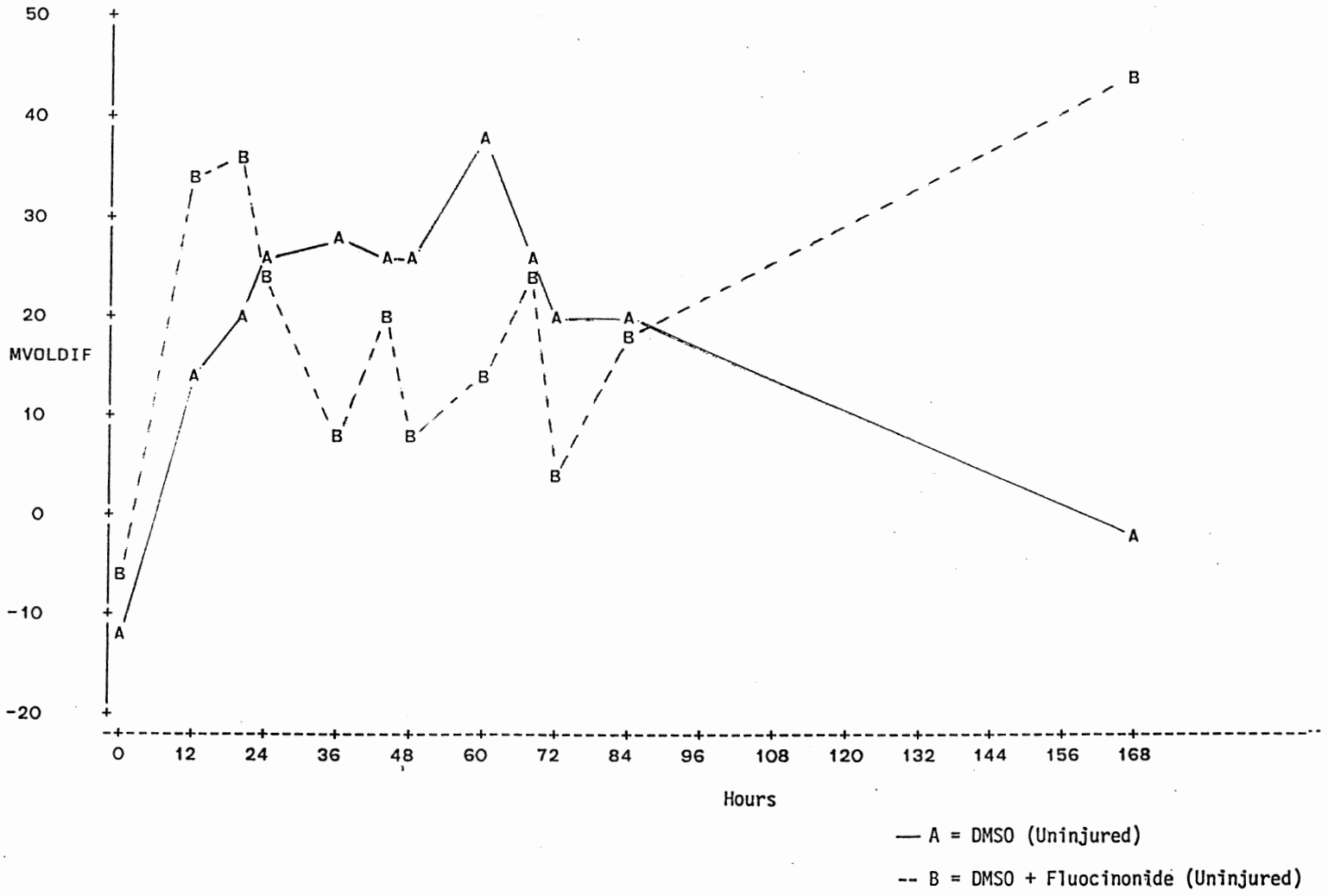

Figure 3. Comparison of Mean Volume Difference for DMSO Uninjured and DMSO With Fluocinonide Uninjured Ankles

TABLE III

EDEMA RESPONSES TO TWO TREATMENTS ON BOTH ANKLES FROM 0 TO 168 HOURS

SOURCE	DF	SUM SQUARES	M.S.	F	
TOTAL	335	1,054,479.26			
Blk	6	199,867.49	33,311.25	2.61	NS
Trt (Chk vs Trt)	1	50,936.81	50,936.81	4.00	NS
Blk*Trt (Error A)	6	76,482.83	12,747.14		
Leg (Sprain vs Good)	1	161,262.86	161,262.86	33.64	**
Blk*Leg (Error B)	6	28,762.79	28,762.79		
Trt*Leg	1	49,956.57	49,956.57	1.93	NS
Blk*trt*Leg (Error C)	6	154,953.49	25,825.58		
Time	11	53,565.29			
Time Linear (T1)	1	2,192.03	2,192.03	1.52	NS
Time Quad (T2)	1	8,104.90	8,104.90	5.61	*
Time Cubic (T3)	1	27,364.19	27,364.19	18.93	**
Time Residual	8	15,904.18	1,988.02	1.38	NS
Blk*Time (Error D)	66	95,411.73	1,445.63		
Trt*Time	11	33,670.65			
Trt*T1	1	2,172.34	2,172.34	1.85	NS
Trt*T2	1	27,164.13	27,164.13	23.19	**
Trt*T3	1	4.13	4.13	0.01	NS
Trt*Time Residual	8	4,330.06	541.26	0.46	NS
Blk*Trt*Time (Error E)	66	77,310.95	1,171.38		
Leg*Time	11	12,686.03	1,153.28		
Leg*T1	1	6,886.24	6,886.24	15.94	**
Leg*T2	1	1,078.69	1,078.69	2.50	NS
Leg*T3	1	2,995.89	2,995.89	6.93	**
Leg*Time Residual	8	1,725.22	1,725.22	3.99	**
Blk*Leg*Time (Error F)	66	28,511.57	431.99		
Trt*Leg*Time	11	2,560.46			
Trt*Leg*T1	1	334.86	334.86	0.77	NS
Trt*Leg*T21	1	857.25	857.25	1.98	NS
Trt*Leg*T3	1	181.69	181.69	0.42	NS
Trt*Leg*Time Residual	8	1,186.66	1,186.66	2.74	**
Blk*Trt*Leg*Time (Err G)	66	28539.73	432.42		

** Significant at a =.01
* Signicicant at a =.05
NS Not Significant at a = .05

fluocinonide treatment. Although this difference was 24.62, it was not significant (P = .05).

TABLE IV

EDEMA RESPONSES FOR TREATMENT AND ANKLE COMBINATIONS

Ankle	Treatment		Mean
	DMSO	DMSO and Fluocinonide	
Uninjured	19.06	18.82	18.94
Injured	87.26	38.25	62.76
Mean	53.16	28.54	40.85

Figure 4 shows the overall average edemic response, beginning at the time of injury and continuing for 168 hours. The linear slope of this line was not significant (P = .05). The quadratic effect was significant (P < .05), as was the cubic effect (P < .01). This was shown by the curve, which increased to a maximum of 52.96 at 20 hours, then decreased to a low value of 28.32 at 168 hours. The curve tended to flatten after 84 hours.

Figure 5 shows the DMSO and DMSO with fluocinonide responses from the time of injury to 168 hours. The linear effects were the same for both treatments, with no significant slope (P = .05). The quadratic curvature for both treatments did not follow the same pattern (p < .01). The cubic curvature was essentially identical (P = .05). The two plots

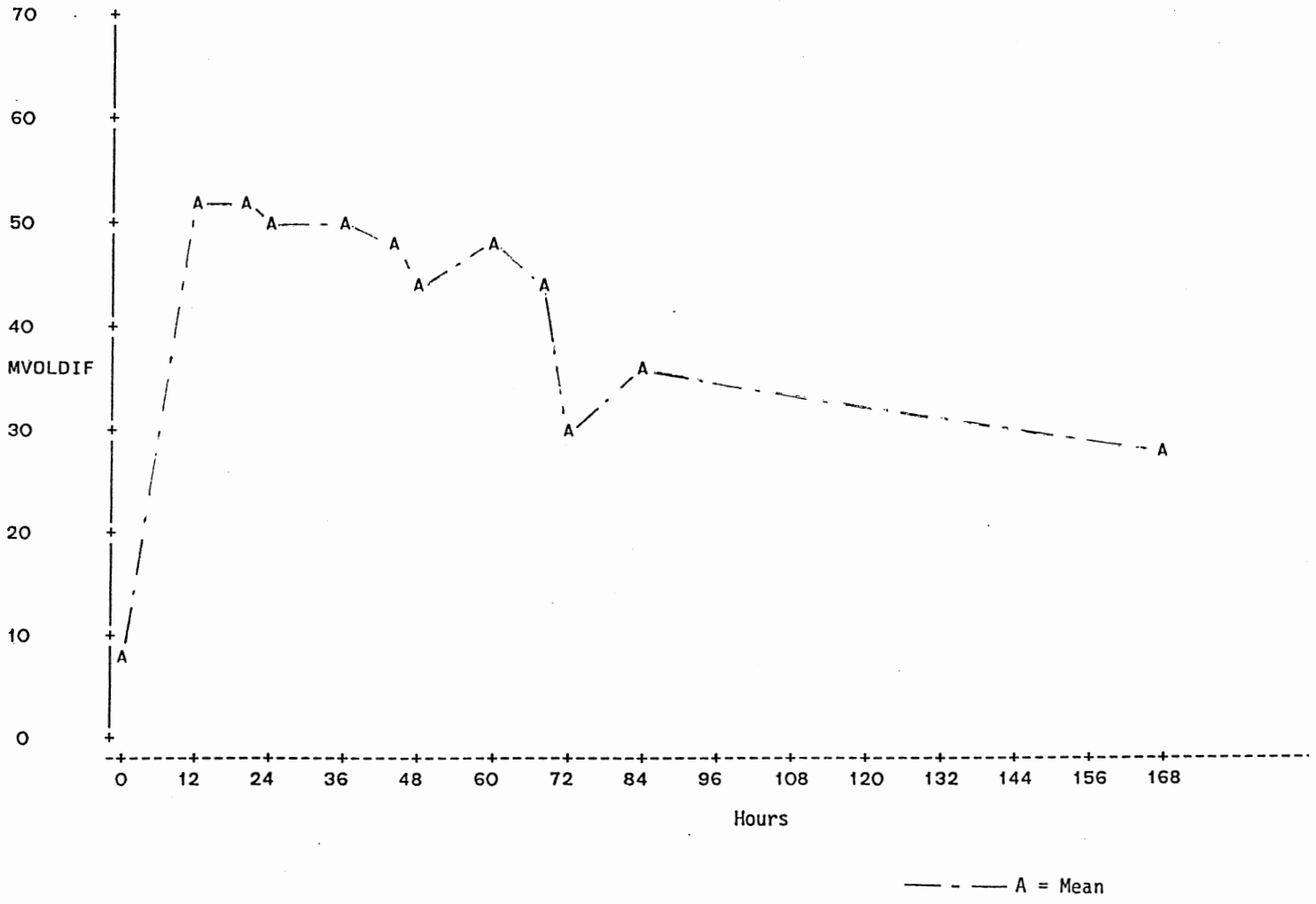

Figure 4. Overall Average Edemic Response

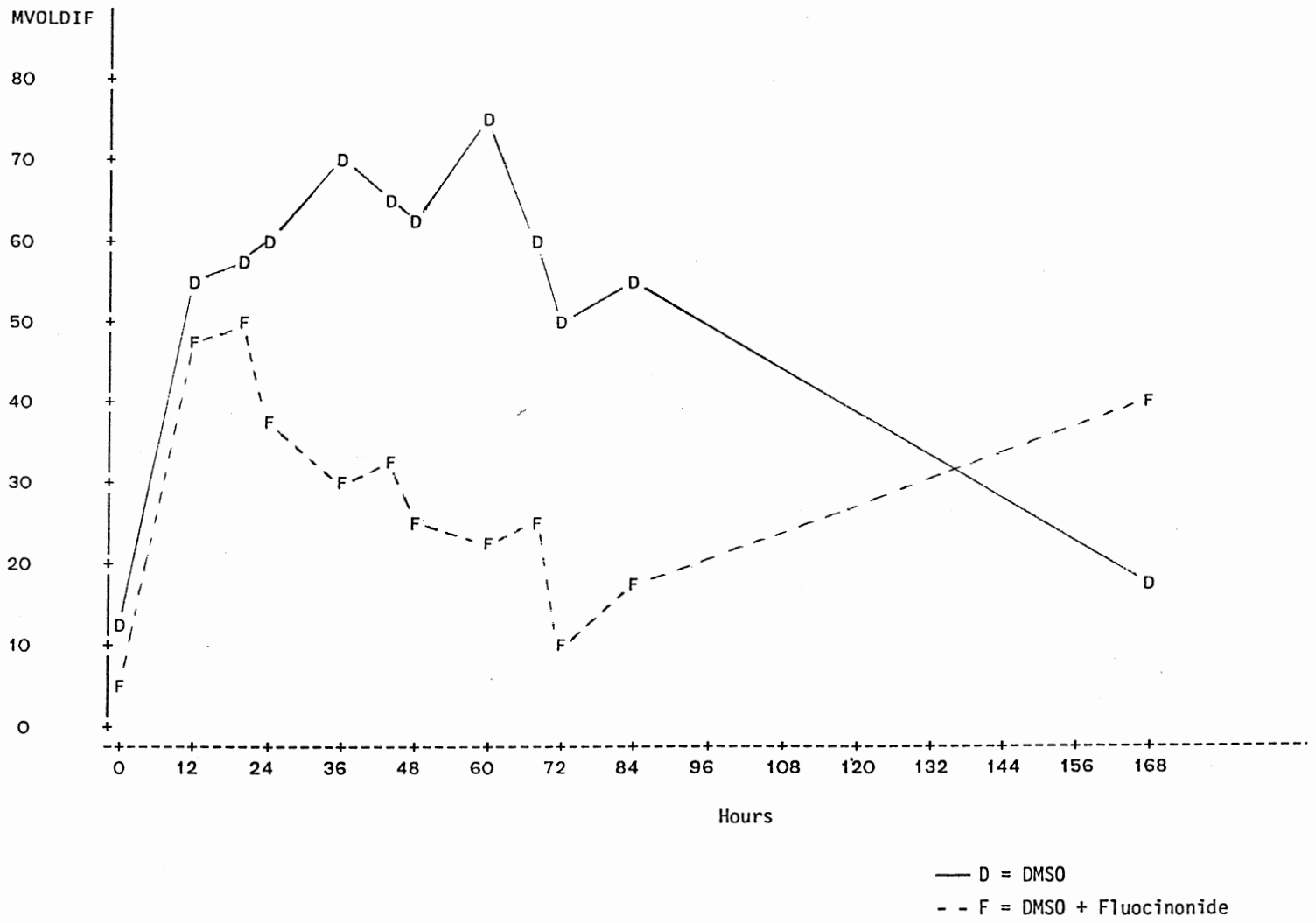

Figure 5. Comparison of DMSO and DMSO With Fluocinonide Over 168 Hours

showed that the edema for the DMSO curve was higher than the DMSO with fluocinonide curve. The DMSO edema curve remained higher from the time of injury until approximately 136 hours. The DMSO curve decreased to a mean volume difference of 17.21 at 168 hours, while the DMSO with fluocinonide curve reached a minimum mean volume difference of 9.71 at 72 hours, then tended to rise until 168 hours.

Figure 6 compares the injured ankles to the uninjured ankles without regard to the treatments. The linear slope for the injured ankle was different from the uninjured ankle ($P < .01$). The quadratic effects were identical and significant at the .01 level. The cubic curvatures were different ($P < .01$).

Discussion

Dimethyl sulfoxide and dimethyl sulfoxide with fluocinonide statistically demonstrated that they had significantly similar effects on edema during the 168 hour testing period. The difference between the two treatments appeared in the quadratic curvature. The DMSO with fluocinonide reduced mean volume difference faster during the 24 hour through 72 hour measurement period ($P < .01$). These findings concurred with the observation by Maiback and Feldman (1967) on the carrying properties of DMSO. The corticosteroid fluocinonide appeared to have been carried into the tissues and reduced more edema faster than did the DMSO alone. Since the DMSO with fluocinonide combination appeared to reduce edema faster, it may help the injured ankle heal more quickly.

A review of the comments on the study's data record sheets indicated that the common side effects of DMSO (skin wrinkling and dryness, burning, rash, itching) were less severe with the DMSO with fluocinonide. Bad breath and body odor were reported with both treatments. Apart from

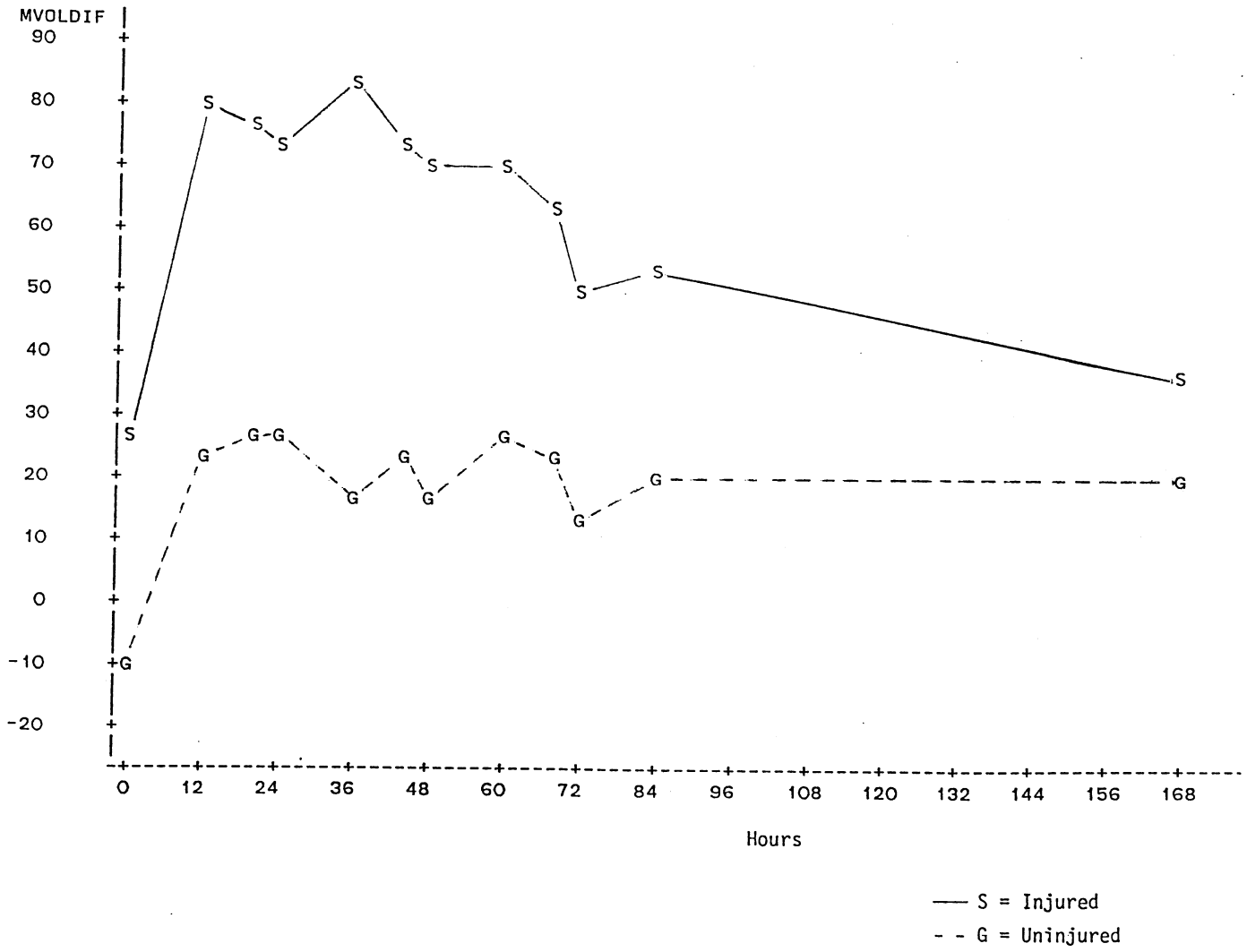

Figure 6. Comparison of Injured Ankles to Uninjured Ankles
Without Without Regard to Treatment

the benefits of faster edema reduction, the DMSO with fluocinonide combination may reduce some of the undesirable side effects. With this information, a physician prescribing dimethyl sulfoxide may want to add .05% fluocinonide, not only to reduce edema, but also to reduce some of the side effects. The cubic curvature seen in the data may be the result of a practice effect. All of the subjects had returned to football practice the last four days of the measurement period. Therefore, the ankles were stressed during practice, causing some of the edema to return. The addition of another DMSO treatment after the 48-hour post-injury period may have helped to reduce this effect.

The effect on the uninjured ankle appeared to be related to the edema in the sprained ankle. It is unknown if this sympathetic effect is caused by the DMSO treatments, additional stress put on the uninjured ankle from putting less weight on the injured ankle, or a purely physiological response on a paired limb.

CHAPTER V

SUMMARY, FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

Summary

This research tested the effect of 70% dimethyl sulfoxide and 70% dimethyl sulfoxide with .05% fluocinonide on edema in sprained ankles. The question this study addressed was whether DMSO with fluocinonide would carry the corticosteroid into underlying edemic tissues and thus reduce edema. The subjects were the 1987 Oklahoma State University football team members who sustained a sprained ankle. The entire team (123 members) was premeasured using commercially available volumeters and obturators. With the acquisition of a sprained ankle, the athlete was included in the study. Fourteen players participated; seven received 70% DMSO and seven received 70% DMSO with fluocinonide. Three one milliliter applications of one of the two treatments were administered. The first application was applied at the time of injury, with the second and third treatments being given 24 and 48 hours after the injury. The one milliliter DMSO or DMSO with fluocinonide was rubbed on the skin, covered with a cellulose compress material, wrapped with an elastic bandage, and left on overnight. All of the participants received a standard treatment of cold whirlpool and high frequency galvanic current with elevation three times a day. The measuring period consisted of seven days, with measurements taken three times a day for the first three days, and once on the

fourth and seventh days. This research was a double-blind study in that only the pharmacist knew which bottle contained DMSO or DMSO with fluocinonide. The data gathered were analyzed using an analysis of variance. It was found that both dimethyl sulfoxide and dimethyl sulfoxide with fluocinonide were effective in reducing edema over the testing period. A difference in the two treatments' quadratic curves indicated that DMSO with fluocinonide was more effective in reducing edema during the 24 to 72 hour period. Observed side effects of the two treatments differed in that the subjects treated with DMSO in combination with fluocinonide had less skin wrinkling and dryness, burning, rash, and itching.

Findings

On the basis of the results of this study, the following findings were drawn:

1. Dimethyl sulfoxide and dimethyl sulfoxide with fluocinonide statistically demonstrated that they have significantly similar effects on reduction of edema in sprained ankles over the 168 hour testing period. The differences between the DMSO and the DMSO with fluocinonide treatments were in the quadratic curvatures. The rate of edema reduction was faster for the DMSO with fluocinonide during the 24 hour through 72 hour period after the injury.

2. The cubic curvatures observed in the results indicated a recurrence of some of the edema during the last 96 hours of the measuring period.

3. After injury to one of the ankles, the uninjured ankle increased in mean volume difference and followed quadratic and cubic curvatures.

4. Through observation, the side effects (skin wrinkling and dryness, burning, rash, itching) appeared to be less severe with the DMSO

and fluocinonide treatment. All of the subjects reported similar problems with bad breath and body odor as a result of both treatments.

Conclusions

On the basis of the findings of this study, the following conclusions were drawn:

1. The findings demonstrated that dimethyl sulfoxide with fluocinonide was more effective during the first 24-72 hours at reducing edema than was dimethyl sulfoxide alone. For sprained ankles, physicians may want to consider using DMSO with fluocinonide as an additional treatment to decrease edema and healing time.

2. Since some edema returned to the sprained ankles during the last 96 hours, it may be appropriate to use one or two additional treatments at 72 and 96 hours after injury. The additional treatments and holding the players out of practice may help keep the edema from returning.

3. It is unknown why the uninjured ankle increased in size during the test period. It can be speculated that: (a) the DMSO and DMSO with fluocinonide had an effect on the uninjured ankle, (b) additional stress was applied to the uninjured ankle while the football player walked or practiced, or (c) it may have been a purely physiological response on a paired limb.

4. Dimethyl sulfoxide with fluocinonide had less severe side effects than did DMSO alone. Reduction of side effects of DMSO would provide another reason for physicians to prescribe DMSO with fluocinonide.

Recommendations

The following recommendations for future research are presented as a result of this study:

1. Another study should be conducted with an increased number of subjects.

2. Replication of the study with the addition of a third treatment group is needed. The third treatment group would receive standard treatment for sprained ankles with no dimethyl sulfoxide.

3. Different strengths of DMSO and variations of different concentrations of fluocinonide need to be tested to find the optimal mixture.

4. There is a need for additional scientific studies done on the uses and effectiveness of dimethyl sulfoxide. Because DMSO cannot be patented, future studies will have to be carried out by independent researchers. Large pharmaceutical companies tend not to do research unless they can control the market and the price of the drug.

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APPENDIXES

APPENDIX A

DESCRIPTION OF DIMETHYL SULFOXIDE

Package Insert Information

Domoso®

(dimethyl sulfoxide) Solution

90% Dimethyl Sulfoxide

Medical Grade

GENERAL

Dimethyl sulfoxide (DMSO), an oxidation product of dimethyl sulfide, is an exceptional solvent possessing a number of commercial uses.

DMSO is the lowest member of the group of alkyl sulfoxides with a general formula of RSOR. Its structural formula is:

It freely mixes with water with the evolution of heat and lowers the freezing point of aqueous solutions. It is soluble in many other compounds including ethanol, acetone, diethyl ether, glycerin, toluene, benzene and chloroform. DMSO is a solvent for many aromatic and unsaturated hydrocarbons as well as inorganic salts and nitrogen-containing compounds. DMSO has a high dielectric constant due to the polarity of the sulphur-oxygen bond. Its basicity is slightly greater than water due to enhanced electron density at the oxygen atom. It forms crystalline salts with strong protic acids and coordinates with Lewis acids. It modifies hydrogen bonding.

DMSO is a hygroscopic stable organic liquid essentially odorless and water white in color. Other physical characteristics include:

Molecular weight	78.13
Melting point	18.45°C
Boiling point	189°C

Each ml of Domoso® Solution Veterinary contains 90.0% dimethyl sulfoxide and 10.0% water.

METABOLISM

Dimethyl sulfoxide when administered topically or orally is rapidly absorbed and distributed in living material.

Using S^{35}-labeled DMSO (1) the maximal blood concentration after cutaneous application was achieved in approximately 10 minutes in rats and less than 1 hour in dogs. In rats and dogs the substance did not accumulate in the organs but the concentration in the treated skin and underlying muscle was increased. The main route of excretion is via the urine partially dependent on the species and route of application. In rats there was no significant difference in the elimination half time of 6 to 8 hours after intravenous or cutaneous administration; in the dog, the elimination half time was 1.5 to 2 days after intravenous or oral administration. In the dog, however, after cutaneous application about 55% of the administered material was eliminated within 14 days. The radioactivity eliminated via the lungs, and identified as dimethyl sulfide, was about 3% of the administered dose.

In another S^{35}-labeled study (2) with DMSO, following intravenous or cutaneous administration, the only metabolite detectable in the urine of humans and rats, was dimethyl sulfone ($DMSO_2$).

In another S^{35}-labeled rat study (3), DMSO was administered by the oral, intraperitoneal and dermal routes at a level of 500 mg/kg body weight. Plasma radioactivity after an intraperitoneal dose was highest at 0.5 hours, the half-time being 5 to 6 hours. When applied dermally, levels remained constant for 6 hours. Radioactivity in the urine collected for 22 hours represented 60% to 85% of the intraperitoneal and oral doses and 36% to 50% of the dermal dose. The skin contained 3% to 7% of the labeled dosage in all cases.

A peculiar sweetish odor was noted in the exhaled breath of cats treated with dimethyl sulfoxide (4). The compound responsible for this was identified as dimethyl sulfide. The same odor has been noted in all species treated with the compound.

In rabbits, dimethyl sulfone was detected in the urine following treatment of DMSO (5).

It has been shown that dimethyl sulfone is a constituent of normal cow's milk (6).

PHARMACOLOGY

The original biological applications of DMSO were primarily confined to its use in preserving various tissues and cellular elements including blood (7), blood cells and bone marrow (8), leukocytes (9), lymphocytes (10), platelets (11), spermatozoa (12, 13, 14), corneal grafts (15, 16), skin (17), tissue culture cells (18, 19, 20, 21) and trypanosomes (22), by freezing techniques. DMSO has also been investigated as a radioprotective agent (23, 24).

In early studies with plants it was claimed that DMSO exerted a profound effect on the biologic membrane, altering their natural selectivity and enhancing the penetration of antibiotics and fungicides (25).

In one of the first studies reported in animals, various drugs were added to 15% solution of DMSO instilled into the urinary bladder of intact, anesthetized dogs through which an enhancement of absorption was demonstrated (25). Utilizing a similar technique the transport of physiologically active insulin across the intact bladder mucosa was demonstrated. Results were judged on a decrease in blood sugar levels over that of controls (26).

In vivo and in vitro methods demonstrated that DMSO enhanced human percutaneous absorption of various compounds including steroids, vasoconstrictors, antiperspirants and dyes, as well as an anthelmintic (thiabendazole) and a skin antiseptic (hexachlorophene) (27, 28, 29, 60, 61, 62). Enhancement was not due to irreversible damage to the stratum corneum (28).

DMSO has been stated to increase the penetration of low molecular weight allergens such as penicillin G but not large molecular weight allergens such as house dust (30).

The rate of passage of tritiated water in the presence of DMSO on the epidermis of the hairless mouse was measured in vitro. DMSO did not appear to promote the passage of water by its presence, but when concentrated solutions (60% to 100%) were used, permanent changes were produced in the rate of passage of water. It was concluded that the concentration of DMSO used seemed more significant than the time of exposure in establishing the effect on the water barrier (31).

When the tails of mice were immersed in a 5% solution of various psychoactive drugs in DMSO, the drugs appeared to exert their usual pharmacological effects, indicating drug penetration as judged by the behavioral effects observed in the experimental subjects. Other solvents, including water, also appeared to permit some drug penetration in this study (32).

Using ten quaternary ammonium salts as test compounds and either water or DMSO as solvents, the oral LD_{50} values were determined in rats and mice. Toxicity changes were obtained in some instances by 50% DMSO and more changes were observed in rats than mice although the results in the two species were not always parallel. When toxicity was altered by DMSO it increased in all instances except one (33).

When administered systemically in another study, however, various drugs dissolved in DMSO did not differ significantly in their lethality or cellular penetration as compared to the same drug administered in saline (34).

When evaluated as a solvent for biologic screening tests, low doses of hormones in DMSO stimulated a response similar to that of the hormone in the control vehicle. Higher doses of hormone, however, failed to give the expected response, suggesting a partition coefficient in favor of the solvent (35). DMSO was also shown to carry physostigmine and phenylbutazone through the skin of the rat (36).

The absorption of phenylbutazone dissolved in an aqueous solution of DMSO was impaired when administered orally to the rabbit. Absorption of the same drug was not improved using the subcutaneous route simultaneously with DMSO.

However, phenylbutazone could be detected in rabbit's blood for several hours when an ointment containing DMSO and 5% phenylbutazone was applied to the skin. When the DMSO content of the ointment was increased, the phenylbutazone levels increased. An increase of phenylbutazone in the muscle tissues underlying the site of application over a control ointment containing phenylbutazone without DMSO could be demonstrated in rats (37).

When 1% fluorescein was injected intradermally at several different concentrations of DMSO in man, the dermal clearance of this substance was considerably decreased as compared to saline control solutions. This was believed due to reduced diffusion through the dermis (29).

The addition of 50% DMSO to solutions containing 1% old tuberculin (OT) abolished positive patch test reactions in tuberculin sensitive human subjects, and 50% DMSO also prevented the dermatitis produced by 1% trypsin. A possible explanation of these phenomena is the formation of complexes with proteins causing their denaturation (28). DMSO has also been reported to alter the Schwartzman reaction (30). It is believed that, similar to chelating agents, DMSO can form complexes with certain metallic salts (25, 38).

Based on the above evidence as well as gas chromatographic and radio-isotope studies it is established that DMSO can effectively penetrate the stratum corneum of the epidermis and enter the systemic circulation. DMSO also has the ability to allow some substances ordinarily unable to penetrate the skin barrier to be carried through it. The mechanism of penetrant action is not yet understood although some theories have been advanced as explanations (25, 38).

DMSO has been claimed to show anti-inflammatory activity against the baker's yeast granuloma in guinea pigs, and when administered orally, against the carrageenin granuloma in rats. The dose needed to achieve these effects is quite high, requiring 1 to 5 g/kg body weight (39).

In a number of other studies in experimental animals (32, 36, 40) where DMSO has been chiefly administered orally or by injection, no anti-inflammatory or analgesic activity could be established.

Following experimental hypersensitization to human gamma globulin in the horse, antigen challenge resulted in massive erythema, necrosis and slough. This reaction could be markedly reduced by the hourly application of undiluted DMSO to the reaction site, after challenge (30).

In the human, DMSO did not exert any beneficial effects on experimentally induced thermal burns, contact dermatitis or ultraviolet burns. It was noted in this study that the burns were of a non-infected nature (28, 29).

In experimentally induced thermal edema of the legs of rabbits, the leg volume was the same for DMSO treated and untreated groups at 3 and 24 hours, but less at 6 hours for the treated group. The DMSO in this experiment was applied at a site distant to the injury (30).

Sedative effects have been noted in dogs when 90% DMSO was administered at 10 mg/kg dosage levels and mild reserpine-like actions of the drug have also been described in mice (30).

DMSO, by itself, at concentrations of 100%, 66%, and 33%, has been shown to produce neurolysis following perineural injection in the rat's sciatic nerve (41).

The conflicting reports cited above for the anti-inflammatory and analgesic properties of DMSO are partially dependent upon the experimental models and methods used to measure these parameters. DMSO fails to show analgesic or anti-inflammatory activity in certain of these situations, particularly when used by the systemic route or when administered topically preceded by an irritant substance. In clinical studies in the horse, it was noted that when iodine, liniments or other strong irritants were present on the skin from previous therapy and DMSO applied, a temporary but marked local reaction would occur. This was due to the ability of DMSO to carry these substances into the underlying skin tissues where their irritant actions could be displayed. When DMSO was used clinically, it was applied topically to the involved area, while in the experimental situation this procedure was seldom used. In clinical situations, a marked reduction of pain and edema has often been noted following topical application. The mechanism of action, although not understood, may be partially related to the heat of dissolution of DMSO. It has been demonstrated that following cutaneous application of DMSO in dogs, the skin, dermis and underlying muscle tissues show a local rise in temperature (30).

The analgesic and anti-inflammatory activity of DMSO, as observed clinically and the differences noted by classical pharmacological methods, may be partially due to the ability of the compound to alter the underlying pathology of the disease state under treatment (42).

Using the isolated guinea pig heart it was found that DMSO did not influence the amplitude of cardiac contractions, heart rate, or coronary flow, although high intravenous doses in the rat and cat resulted in a transient lowering of blood pressure (36).

Isolated, innervated guinea pig preparations were also used to study the effects of DMSO on skeletal, smooth and cardiac muscles. The compound depressed diaphragm response to both muscle and nerve stimulation and also caused spontaneous skeletal muscle fasciculations. Actual contraction amplitude was augmented although contraction rate appeared unaffected. Vagal threshold was lowered almost 50% by a bath concentration of 6% DMSO. The fasciculations and increased tone of skeletal muscle, and lowering of the vagal threshold by DMSO could be due to cholinesterase inhibition (43). Intravenous doses of 50% DMSO in doses as high as 1 g/kg failed to alter the EKG of anesthetized dogs and monkeys (26).

With single intravenous doses of 200 mg/kg of DMSO to anesthetized cats, apnea and a transient fall in blood pressure were produced. Subsequent doses caused only a transient hypotension and apnea was no longer observed. Vagotomy failed to influence the course of DMSO-induced hypotension and bradycardia but atropine (1 mg/kg) significantly attenuated these effects. Repeated intravenous administration of DMSO where each succeeding dose was doubled, led to a gradually lowered blood pressure until death ensued at about 4 g/kg. Myoneural transmission, ganglionic transmission and force of cardia contraction also deteriorated gradually with repeated doses until death. The transient fall in blood pressure occurred only rarely after intraperitoneal administration. One cat exhibited hypotension following a 1 g/kg dose of DMSO but the remainder received dosages of 4 g/kg without showing this effect (44).

The in vitro oxygen consumption of liver, brain and hemidiaphragm tissues of rats is not affected by the intravenous administration of 75 mg DMSO/100 g body weight during the 7 subsequent days. Urease, trypsin and chymotrypsin are inhibited by DMSO, dependent upon its concentration. The in vitro metabolism of corticosterone by rat liver slices is not affected by the intravenous administration of 100 mg DMSO/100 g body weight during 3 subsequent days (2).

DMSO treatment administered intraperitoneally to rats for 35 days decreased experimentally induced intestinal adhesions by 80% over controls as compared to saline, cortisone acetate or a combination of cortisone and DMSO administered separately (45).

In rabbits, the application of 70% DMSO, adjacent to but not on the wound incision site, appeared to increase the development of wound tensile strength over controls (46).

Increasing the concentration of DMSO resulted in an increasing inhibition of fibroblast proliferation in vitro, which was reversible (30).

There is an increase in urinary production following the dermal or systemic administration of DMSO, and a transient doubling of urine volume after the intravenous administration of the drug (48).

Some studies have indicated that DMSO may potentiate the action of certain compounds including insulin (39), endogenous steroids and others. It was suggested that in the case of steroids it might be due to improved penetration at their sites of action on lysosomal membranes (30).

The minimal inhibitory concentration (MIC) of DMSO to the nearest 10% was determined for two isolates each of Staphylococcus aureus, Staphylococcus aureus var. albus, β-hemolytic Streptococci, Corynebacterium acnes, Corynebacterium species, Alcaligenes faecalis, Escherichia coli and Proteus species. Twenty percent DMSO was found to be bacteriostatic. For Staphylococcus aureus, the bactericidal concentration of 50% was 2.5 times that of the MIC; for the remainder, it ranged from 30% to 40% with the gram negative bacteria being somewhat more susceptible (29).

No growth of Staphylococci, Pseudomonas or Escherichia coli occurred in the presence of 36%, 25%, 33% or greater concentrations, respectively, of DMSO (49).

The minimal inhibitory concentration of DMSO in Sabouraud's broth to the nearest 10% was determined for three dermatophytes: Trichophyton mentagrophytes, Microsporum gypseum, and Microsporum canis. Ten percent DMSO was inhibitory to all three species. The fungicidal concen-

trations were 30% for the Microsporum species, while T. mentagrophytes survived the highest test concentrations of 50% (29).

TOXICOLOGY

Absorption of topically applied DMSO results in degranulation of the mast cells at the site of application and a release of histamine followed by characteristic histamine whealing of the overlying skin. Following repeated applications of the compound to the same skin area, the mast cells are eventually depleted and the wheal no longer occurs (28).

The erythema of the skin following topical application of DMSO is considered to be partially due to the release of histamine. In addition, DMSO has the typical action of most solvents in causing drying and defatting of the skin.

In a study designed to evaluate the effects of Domoso® (dimethyl sulfoxide) Solution Veterinary at a total daily dose of 100-300 ml, administered for a total period of 90 days, no essential or clinically meaningful ophthalmological effects were seen in the horse. There were no significant variations in glucose, sodium, potassium, SGOT, or SGPT measurements. There were a few fluctuations in hematologic values but no changes appear to be drug-related or of significance.

Another study was conducted in the dog to determine the effects of Domoso Solution Veterinary at a total daily dose of 20–60 ml administered topically for 21 consecutive days. No clinically meaningful ophthalmological effects were noted. No significant variations were observed in blood measurements, including glucose, BUN, SGOT and plasma electrophoresis. Hematologic values were similar to control animals used in this study.

Long-term topical applications of the drug to guinea pigs resulted in histopathologic changes similar to those observed in allergic contact dermatitis. The observed clinical changes were compatible with either an allergic contact dermatitis or a primary irritant effect (50). DMSO was shown to cause erythema and blistering of human and rat skin resulting in increased permeability of venules and capillaries (51).

In most cases the local irritation of the skin characterized by erythema, vesicle or blister formation and scurfing abates even with continued treatment. This phenomenon has been described as "accommodation" or "hardening" of the skin, and has been noted with other solvents.

The undiluted compound has low systemic toxicity but a marked local necrotizing and inflammatory effect when it is injected subcutaneously. In rats the subcutaneous injection of 10 g/kg or the intravenous injection of 2.5 g/kg of undiluted DMSO for 2 weeks showed no definite indication of systemic toxicity. The local necrotizing effects produced at these dose levels, however, prevented a longer period of treatment. No significant hematologic or biochemical changes were noted in 3 dogs receiving 0.4 g/kg for 33 days (35).

Four dogs were administered topical DMSO at 1 g/kg body weight, 5 days weekly for 18 months. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time, alkaline phosphatase, bilrubin, total protein and albumin globulin (AG) ratio, and blood urea nitrogen (BUN) were determined at the beginning of treatment and at monthly intervals. Significant abnormalities did not occur (39).

Upon injection of DMSO into the rat pleura, there is an accumulation of fluid, initially appearing as a transudate, but later as a protein-rich exudate. Exudate formation is thought to be due to increased vascular permeability, predominantly in venules, brought about by a delayed release of histamine together with activation of a vaso-active slow contracting substance (51).

Rats are orally dosed 5 days a week for 2 weeks at levels of 1, 3.5, 5 and 10 mg/kg of DMSO. The only deaths in this group were due to dosing injuries. No signs of dermal sensitization were noted following a course of intradermal injection of a 10% V/V aqueous solution of DMSO in guinea pigs, nor did the same species show signs of injury following 28 daily applications of the undiluted drug to the clipped skin of the back (52).

A compilation of the results for a number of acute toxicity (LD_{50}) determinations derived from several published reports (35, 52, 53, 54, 55) in several experimental animal species are as follows:

Species		Rt. of Administr.	LD_{50} g/kg
Mouse	–	SQ	– 13.9 - 20.5
Mouse	–	IV	– 3.82 - 10.73
Mouse	–	Oral	– 15.0 - 22
Mouse	–	IP	– 20.06
Rat	–	IV	– 5.25 - 5.36
Rat	–	Oral	– 16.0 - 28.3
Rat	–	IP	– 5.5 - 13.621
Dog	–	IV	– 2.5
Guinea Pig	–	IP	– 5.5
Chicken	–	Oral	– 12.5

Hemolysis resulting in hemoglobinuria and methemoglobinuria was noted in anesthetized cats following single intravenous doses of 200 mg/kg DMSO. The intraperitoneal administration of DMSO or the dilution of DMSO with isotonic saline prior to intravenous administration reduced its hemolytic activity. (44).

Tests in vitro showed that washed rabbit erythrocytes are hemolyzed in a short time with 40% to 60% DMSO solution. Higher concentrations caused, without hemolysis, an agglutination of the erythrocytes (55).

Teratology

The intraperitoneal administration of 5.5 g/kg of DMSO as a single dose to pregnant hamsters induced developmental malformation of their embryos (56). Both dimethyl sulfoxide and diethyl sulfoxide are teratogenic when injected into the chick embryo, the classification of malformations being dependent upon the stage of embryonic development at the time of treatment. The same drugs when administered by various techniques to mice, rats and rabbits in which fertility had been established did not cause any embryonic malformations (57).

Ocular Effects

In a variety of experimental animals including rats, dogs, swine, rabbits and primates, following oral or topical administration of DMSO, certain eye changes have been noted. These consist mainly of a change in the refractive index of the lens described as a "lens within a lens." The lens changes are characterized by a decrease in the normal relucency of the lens cortex, causing the normal central zone of the lens to act as a biconvex lens. When viewing the fundus of affected animals, it is necessary to interpose biconcave lenses in order to see the retinal vessels clearly. The functional effect would be a tendency toward myopia (58).

The lens changes were first observed in dogs receiving 5 g/kg after 9 weeks of administration. At lower dose levels the change was observed later. In rabbits these changes were seen after 90 days of dermal application, (8 mg 50% DMSO/kg/day and 4 mg 100% DMSO/kg/day and higher). In swine, dermal application of 4.5 g 90% DMSO/kg twice daily caused similar lens changes by 90 days of treatment (59).

The lens changes appear earlier with oral administration, and also bear a relation to the dosage employed; the higher the dose the more rapid their appearance.

The eye changes are slowly reversible but with a definite species difference, the dog being the slowest to exhibit improvement.

No effects were seen following direct application of aqueous solutions varying from 10% to full strength into the eyes of albino rabbits for a total dosage of DMSO between 0.1 and 0.2 g/kg body weight per day for six months. Rabbits which received daily doses as high as 10 g/kg orally or topically showed lines of discontinuity in their lenses. No cataract was seen after ten weeks of such daily treatment, although discontinuous lens lines could be detected in about two weeks by slit lamp examination. Chemical studies on these lenses revealed reduction in the usual concentration of urea, glutathione, uric and amino acids (30).

INDICATIONS
CANINE AND EQUINE

Domoso® (dimethyl sulfoxide) Solution Veterinary, is recommended as a topical application to reduce acute swelling due to trauma.

DOSAGE AND ADMINISTRATION

Domoso® (dimethyl sulfoxide) Solution Veterinary, is to be administered topically to the skin over the affected area. The spray pump should be initially held approximately 6 inches from the animal and the distance adjusted to provide a uniform coverage of the area. The volume delivered by depressing the spray pump is approximately ½ ml. Refer to user precautions below under "PRECAUTIONS AND CONTRAINDICATIONS."

Dogs

Liberal application should be administered three to four times daily. Total daily dosage should not exceed 20 ml. Total duration of therapy should not exceed 14 days.

Horses

Liberal application should be administered two to three times daily. Total daily dosage should not exceed 100 ml. Total duration of therapy should not exceed 30 days.

SIDE EFFECTS

In general, adverse reactions are local, and while they may prove to be annoying to some patients, they are usually not of a serious nature. Upon topical application, an occasional animal may develop transient erythema, associated with local "burning" or "smarting." Even when erythema or vesiculation occur, they are self-limiting reversible states, and not necessarily an indication to discontinue medication. Dryness of the skin and an oyster-like breath odor have been reported. These effects are temporary and are not considered to be of serious consequence. Changes in the refractive index of the lens of the eye and nuclear cataracts have been observed in animals, with the use of this drug. This appears to be related to dosage and duration of therapy.

PRECAUTIONS AND CONTRAINDICATIONS

Contact between Domoso Solution and the skin should be avoided. Rubber gloves should be worn while applying this drug. Forceps and swabs may be used to facilitate application. If absorbed through the skin, Domoso Solution will cause odorous breath and unpleasant mouth taste. Mild sedation or drowsiness, sensations of warmth, burning, irritation, itching and mild erythematous localized or generalized dermatitis have been reported in some persons following exposure to Domoso Solution. Treatment of such side effects is symptomatic. Consult a physician immediately if adverse effects appear.

Domoso Solution Veterinary may mask certain disease signs such as are seen in fractures etc.; this does not obviate the need for specific therapy in such conditions. Domoso should not be used directly prior to racing or other physical stress wherein the drug might mask existing pathology, such as a fracture.

Since Domoso Solution Veterinary effectively alter the biologic membrane, it will in some cases facilitate the systemic absorption of other topically applied drugs and may have a potentiating effect on drugs administered systemically. Therefore, great care should be exercised in use of other drugs at the Domoso application site because of the demonstrated—if variable—ability of DMSO to carry other chemicals through the dermis into the general circulation. If other topical medications are indicated they should not be applied until Domoso Solution Veterinary is thoroughly dry. Frequently, due to the heat of resolution, a "smoking" effect following application is noted due to vaporization of the drug.

Domoso Solution Veterinary should also be judiciously used when administered in conjunction with other pharmaceutical preparations, especially those affecting the cardiovascular and center nervous system. DMSO may potentiate the activity of atropine, insulin, endogenous sterioids, and certain other drugs.

Lowering of the vagal threshold, spontaneous skeletal muscle fasciculation, and increased smooth muscle tone in the stomach following DMSO exposure may be due to cholinesterase inhibition. Therefore, Domoso should not be used on dogs, or horses, simultaneously or within a few days before or after treatment with, or exposure to, cholinesterase-inhibiting presticides or drugs.

APPENDIX B

DESCRIPTION OF FLUOCINONIDE

Package Insert Information

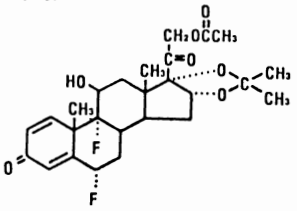
LIDEX®

(fluocinonide)

Topical Solution 0.05%

description

LIDEX solution 0.05% is intended for topical administration. The active component is the corticosteroid fluocinonide, which is the 21-acetate ester of fluocinolone acetonide and has the chemical name pregna-1, 4-diene-3,20-dione,21-(acetyloxy)-6,9-difluoro-11-hydroxy-16, 17-[(1-methylethylidene)bis(oxy)]-,(6α, 11β, 16α)-. It has the following chemical structure:



LIDEX topical solution contains fluocinonide 0.5 mg/ml in a solution of alcohol (35%), diisopropyl adipate, citric acid and propylene glycol. In this formulation, the active ingredient is totally in solution.

clinical pharmacology

Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and / or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. A significantly greater amount of fluocinonide is absorbed from the solution than from the cream or gel formulations.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See *DOSAGE AND ADMINISTRATION).*

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are

then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Indications and usage

LIDEX® (fluocinonide) topical solution 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

contraindications

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

precautions

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestation of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, the addition of occlusive dressings, and dosage form.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See *PRECAUTIONS—Pediatric Use).*

Not for ophthalmic use. Severe irritation is possible if fluocinonide solution contacts the eye. If that should occur, immediate flushing of the eye with a large volume of water is recommended.

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes. If there is contact with the eyes and severe irritation occurs, immediately flush with a large volume of water.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating HPA axis suppression:
Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids. Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

adverse reactions

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence.

Burning
Itching
Irritation
Dryness

Folliculitis
Hypertrichosis
Acneiform eruptions
Hypopigmentation
Perioral dermatitis
Allergic contact dermatitis
Maceration of the skin
Secondary infection
Skin atrophy
Striae
Miliaria

overdosage

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (See *PRECAUTIONS).*

dosage and administration

LIDEX® (fluocinonide) topical solution 0.05% should be applied to the affected area as a thin film from two to four times daily depending on the severity of the condition.
Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.
If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

how supplied

LIDEX® (fluocinonide) topical solution 0.05%.
Plastic squeeze bottles
20 cc. NDC 0033-2517-44
60 cc. NDC 0033-2517-46
Store at room temperature. Avoid excessive heat above 40°C (104°F).

CAUTION: Federal law prohibits dispensing without a prescription.

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02-2517-44-2

APPENDIX C

NATIONAL ATHLETIC TRAINER ASSOCIATION'S LIST OF 99 INJURIES OR CONDITIONS THAT MAY BENEFIT FROM DMSO TREATMENT

1. Abrasions
2. Abscesses
3. Achilles Tendon Strain
4. Achilles Tendon Tenosynovitis
5. Achillobursitis
6. Acne
7. Acromioclavicular Sprains
8. Adductor Longus Strains
9. Adductor Magnus Strains
10. Ankle Dislocation
11. Ankle Exostoses
12. Ankle Sprain
13. Ankle Subluxation
14. Anterior Tibial Compartment Syndrome
15. Anterior Tibial Tenosynovitis
16. Arch Strain
17. Arthritis
18. Baseball Finger-interphalangeal contusions
19. Bicipital Tenosynovitis
20. Blisters
21. Brachial Pleus Traction Injury
22. Bunion
23. Burns
24. Bursitis
25. Calcaneocuboid Ligament Strain
26. Carbuncle
27. Carpometacarpal Dislocation
28. Carpometacarpal Subluxation
29. Cellulitis
30. Contusions
31. Coccygodynia
32. Costochondral Sprain
33. Costochondral Strain
34. Contact Dermatitis
35. Seborrheic Dermatitis
36. Hematoma Aurus
37. Elbow Dislocation
38. Elbow Subluxation
39. Epicondylitis
40. Epidermatophytosis
41. Extensor Digitorum Longus Tenosynovitis
42. Extensor Hallucis Longus Tenosynovitis
43. Fat Pad Contusion
44. Felon
45. Fibular Collateral Ligament Bursitis
46. Finger Dislocation
47. Frostbite
48. Furunculosis
49. Gastrocnemius Strain

50. Glenohumeral Dislocation
51. Glenohumeral Subluxation
52. Gluteus Medius Strain
53. Gracilis Strain
54. Granuloma
55. Hamstring Strain
56. Hamstring Tenosynovitis
57. Heat Rash
58. Hemorrhoids
59. Herpes Simplex
60. Hip Dislocation
61. Hip Sprain
62. Hip Strain
63. Hives
64. Hiopectineal Bursitis
65. Hiopsoas Strain
66. Impetigo
67. Infrapatellar Bursitis
68. Ischiogluteal Bursitis
69. Knee Contusion
70. Knee Dislocation
71. Knee Sprain
72. Larynx Injury (Contusion)
73. Lumbosacral Sprain
74. Lumbosacral Strain
75. Lunate Dislocation
76. Metacarpalphalangeal Dislocation
77. Myositis Ossificans
78. Nail, Subungual Hematoma
79. Nail, Ingrown
80. Nerve Contusion
81. Neuritis
82. Osgood-Schlatter's Syndrome
83. Osteochondritis
84. Osteochondritis Desicans
85. Patellar Dislocation
86. Patellar Tendon Strain
87. Periostitis
88. Peroneal Nerve Contusion
89. Peroneal Tenosynovitis
90. Plantar Wart
91. Plantaris Strain
92. Tenosynovitis
93. Muscle Strains
94. Sprains
95. Insect Bites
96. Stye
97. Tarsal Tunnel Syndrome
98. Carpal Tunnel Syndrome
99. Tendonitis

APPENDIX D

INFORMED CONSENT FORM

INFORMED CONSENT FORM

By signing this document you are agreeing to participate in a double-blind research study dealing with alternative treatments for sprained ankles. This study is set up so that no one actively involved in the investigation knows which of the two possible treatments you will receive. The two possibilities are: 70% DMSO or 70% DMSO with a corticosteroid (a topical anti-inflammatory medication). The rest of your therapy will be the standard treatment for a sprained ankle.

Immediately after injury you will receive fifteen minutes of ice and elevation. Your ankles will be measured in a volumeter and then one of the two treatments will be applied to the injured ankle. The DMSO is to be left on for twelve hours. The next morning your ankles will be measured and your injured ankle will receive a cold whirlpool for fifteen minutes, ten minutes of high voltage galvanic current with elevation and ten minutes of cold whirlpool. Finally, an elastic wrap will be placed on your injured ankle that is to remain on until practice. If you are able to practice, your ankle will be taped and you will receive another treatment after practice. If you cannot practice you will receive treatment during practice of cold whirlpool and high frequency galvanic current. Before returning home after practice/treatment, your ankles will be measured and you will receive another DMSO treatment which is to be left on for twelve

hours. In total you will receive three, thirty cc treatments of DMSO/or DMSO with the corticosteroid. Your ankles will be measured three times a day for three days. Additional measurements will be taken on the fourth and seventh days after the injury. The standard treatment, cold whirlpool and high frequency galvanic current, will continue until your ankle is healed.

This research study will be supervised by Cary Couch, MD. Any adverse reactions from the DMSO or DMSO with corticosteroid will be referred to him for evaluation and treatment. Possible adverse reactions to DMSO have been reported to be: bad breath and taste, skin rash, headache, nausea, diarrhea and sedation. Possible adverse reactions to the topical corticosteroid have been reported to be: skin burning, itching, irritation and dryness.

It is understood that your participation is voluntary and confidential. You may withdraw from this experimental study at any time. In addition to this consent form it is required that you read and sign the State Board of Health informed consent form consenting the medical use of DMSO.

If you have any questions feel free to ask Jeff Fair (the investigator, phone number 624-5837) or Dr. Couch, (the supervising physician, phone number 624-1575) at any time during the extent of the study.

_____ SUBJECT DATE

_____ INVESTIGATOR DATE

_____ WITNESS DATE

APPENDIX E

OKLAHOMA STATE BOARD OF HEALTH

RELEASE FORM

WRITTEN INFORMED REQUEST FOR PRESCRIPTION OF DIMETHYL SULFOXIDE (DMSO) FOR MEDICAL TREATMENT
OKLAHOMA STATE BOARD OF HEALTH

Patient's Name _____ Age ____ Sex ___

Address _____

Disease, illness or physical condition supervised for medical treatment by Cary Couch, MD and administered by Jeff Fair, AT with dimethyl sulfoxide (DMSO): sprained ankle .

My Physician has explained to me:

(a) That the Federal Food and Drug Administration has determined dimethyl sulfoxide (DMSO) to be an "unapproved new drug" and that federal law prohibits the interstate distribution of an "unapproved new drug".

(b) That neither the American Cancer Society, The American Medical Association, nor the Oklahoma State Medical Association, recommends the use of dimethyl sulfoxide (DMSO) in the treatment of any disease, illness or physical condition.

(c) That there are alternative recognized treatments for the disease, illness or physical condition from which I suffer which he has offered to provide for me including: (Here described)
Use of standard therapeutic modalities (rest, ice, compression and elevation) for the treatment of a sprained ankle .

Possible side effects:

(a) Skin rash (erythematous scaling dermatitis)
(b) Bad breath and taste
(c) Headache, nausea, diarrhea and sedation

Notwithstanding the foregoing, I hereby request prescription and use of dimethyl sulfoxide (DMSO) in the medical treatment of the disease, illness or physical condition for which I suffer.

ATTEST:

_____ _____
PRESCRIBING PHYSICIAN DATE SIGNATURE OF PATIENT DATE

_____ _____
WITNESS DATE LICENSED ATHLETIC TRAINER DATE

APPENDIX F

DMSO MIXING FORMULAS

-DMSO MIXING FORMULAS-

A) 70% DMSO FROM 90% DMSO

70 ml of 90% DMSO plus 20ml of distilled water =

90ml of 70% DMSO

B) 70% DMSO COMBINED WITH FLUOCINONIDE

70ml of 90% DMSO plus 20ml of .05% Fluocinonide =

90ml of 70% DMSO with __?__ % concentration of Fluocinonide

$$20\text{ml} \times \frac{.05\text{gm}}{100\text{ml}} = .01\text{gm}$$

$$\frac{.01\text{gm} \times 100\text{ml}}{90\text{ml}} = .01\% \text{ concentration of}$$

Fluocinonide in the 70% DMSO

APPENDIX G

ANKLE INJURY RECORD SHEET

ANKLE INJURY RECORD

NAME _____ SPORT _____

INJURY DEGREE _____ (1,2,3) BLOCK _____ BOTTLE _____ Prescription #_____

INJURY: YEAR _____ MONTH _____ DAY _____ TIME _____

RIGHT _____ LEFT _____

				READINGS			
HOUR	DATE	WHEN	P/T**	RIGHT	LEFT	BY	COMMENTS
Pre-Test							
Injury *							
12		morn					
20		pre					
24 *		post					
36		morn					
44		pre					
48 *		post					
60		morn					
68		pre					
72		post					
84		morn					
168		morn					(1 week post-injury)

* DMSO Application

** P = Practice T = Treatment Only

APPENDIX H

ADDITIONAL STATISTICAL DATA

TABLE V

ANALYSIS OF VARIANCE ON INJURED ANKLE OVER TIME

SUBJECT	DATE					ANKLE
	6/1	6/2	6/3	6/4	6/5	
1.	1652	1624	1628	1639	1643	R
	1542	1560	1549	1562	1572	L
2.	1555	1566	1568	1549	1544	R
	1525	1543	1543	1525	1530	L
3.	1490	1518	1478	1518	1480	R
	1471	1494	1469	1472	1454	L
4.	1671	1679	1669	1676	1680	R
	1662	1666	1687	1672	1673	L
5.	1503	1515	1497	1486	1499	R
	1492	1489	1500	1482	1490	L
6.	1478	1501	1462	1491	1476	R
	1521	1538	1515	1527	1541	L
7.	1105	1118	1109	1098	1101	R
	1098	1106	1112	1108	1105	L
8.	1708	1696	1712	1694	1712	R
	1693	1681	1702	1683	1713	L
9.	1455	1448	1444	1445	1454	R
	1438	1426	1434	1450	1437	L
10.	1689	1701	1712	1703	1707	R
	1648	1655	1660	1663	1659	L
11.	1232	1242	1251	1241	1253	R
	1229	1243	1266	1246	1235	L
12.	1747	1747	1744	1736	1745	R
	1690	1681	1682	1686	1679	L

TABLE VI

ANALYSIS OF VARIANCE ON UNINJURED ANKLE OVER TIME

SOURCE	DF	SUM SQUARES		
Total	119	3,857,475.97		
Subj	11	3,807,835.37	346,166.85	130.18 **
Leg	1	10,267.50	10,267.50	3.86 NS
Subj*Leg (Error A)	11	29,250.30	2,659.12	
Days	4	468.72		
Days Linear (D1)	1	34.50	34.50	0.22 NS
Days Quad (D2)	1	148.00	148.00	0.95 NS
Days Cubic (D3)	1	277.35	277.35	1.78 NS
Days Quartic (D4)	1	8.86	8.86	0.06 NS
Subj*Days (Error B)	44	6,869.88	156.13	
Leg*Days	11	447.75		
Leg*D1	1	189.04	189.04	3.56 NS
Leg*D2	1	97.50	97.50	1.84 NS
Leg*D3	1	24.07	24.07	0.45 NS
Leg*D4	1	137.14	137.14	2.58 NS
Subj*Leg*Days (Error C)	44	2,336.45	53.10	

* Significant at a = .05
** Significant at a = .01
NS Not Significant at a=.05

TABLE VII

ANALYSIS OF VARIANCE ON BOTH ANKLES AND BOTH TREATMENTS OVER TIME

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
1	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	INJ	0	1521	1488	-32
2	1	11	2	LYDX	1527	1520	LEFT	GOOD	INJ	0	1521	1488	-6
3	1	11	2	LYDX	1527	1528	LEFT	SPRAIN	012	12	1517	1526	-2
4	1	11	2	LYDX	1527	1528	LEFT	GOOD	012	12	1517	1526	-10
5	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	020	20	1535	1540	20
6	1	11	2	LYDX	1527	1520	LEFT	GOOD	020	20	1535	1540	8
7	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	024	24	1529	1513	-7
8	1	11	2	LYDX	1527	1520	LEFT	GOOD	024	24	1529	1513	2
9	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	036	36	1498	1544	24
10	1	11	2	LYDX	1527	1520	LEFT	GOOD	036	36	1498	1544	-29
11	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	044	44	1523	1530	10
12	1	11	2	LYDX	1527	1520	LEFT	GOOD	044	44	1523	1530	-4
13	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	048	48	1492	1545	25
14	1	11	2	LYDX	1527	1520	LEFT	GOOD	048	48	1492	1545	-35
15	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	060	60	1516	1560	40
16	1	11	2	LYDX	1527	1520	LEFT	GOOD	060	60	1516	1560	-11
17	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	068	68	1556	1540	20
18	1	11	2	LYDX	1527	1520	LEFT	GOOD	068	68	1556	1540	29
19	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	072	72	1518	1554	34
20	1	11	2	LYDX	1527	1520	LEFT	GOOD	072	72	1518	1554	-9
21	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	084	84	1541	1598	78
22	1	11	2	LYDX	1527	1520	LEFT	GOOD	084	84	1541	1598	14
23	1	11	2	LYDX	1527	1520	LEFT	SPRAIN	168	168	1545	1599	79
24	1	11	2	LYDX	1527	1520	LEFT	GOOD	168	168	1545	1599	18
25	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	INJ	0	1719	1728	-48
26	2	11	1	DMSO	1767	1773	RGHT	GOOD	INJ	0	1719	1728	-45
27	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	012	12	1778	1766	11
28	2	11	1	DMSO	1767	1773	RGHT	GOOD	012	12	1778	1766	-7
29	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	020	20	1749	1745	-18
30	2	11	1	DMSO	1767	1773	RGHT	GOOD	020	20	1749	1745	-28
31	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	024	24	1724	1766	-43
32	2	11	1	DMSO	1767	1773	RGHT	GOOD	024	24	1724	1766	-7
33	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	036	36	1792	1770	25
34	2	11	1	DMSO	1767	1773	RGHT	GOOD	036	36	1792	1770	-3
35	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	044	44	1757	1762	-10
36	2	11	1	DMSO	1767	1773	RGHT	GOOD	044	44	1757	1762	-11
37	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	048	48	1774	1780	7
38	2	11	1	DMSO	1767	1773	RGHT	GOOD	048	48	1774	1780	7
39	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	060	60	1775	1768	8
40	2	11	1	DMSO	1767	1773	RGHT	GOOD	060	60	1775	1768	-5
41	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	068	68	1772	1766	5
42	2	11	1	DMSO	1767	1773	RGHT	GOOD	068	68	1772	1766	-7

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
43	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	072	72	1772	1768	5
44	2	11	1	DMSO	1767	1773	RGHT	GOOD	072	72	1772	1768	-5
45	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	084	84	1735	1755	-32
46	2	11	1	DMSO	1767	1773	RGHT	GOOD	084	84	1735	1755	-18
47	2	11	1	DMSO	1767	1773	RGHT	SPRAIN	168	168	1754	1769	-13
48	2	11	1	DMSO	1767	1773	RGHT	GOOD	168	168	1754	1769	-4
49	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	INJ	0	1678	1693	-58
50	3	21	1	LYDX	1686	1751	LEFT	GOOD	INJ	0	1678	1693	-8
51	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	012	12	1722	1699	-52
52	3	21	1	LYDX	1686	1751	LEFT	GOOD	012	12	1722	1699	36
53	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	020	20	1749	1704	-47
54	3	21	1	LYDX	1686	1751	LEFT	GOOD	020	20	1749	1704	63
55	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	024	24	1808	1735	-16
56	3	21	1	LYDX	1686	1751	LEFT	GOOD	024	24	1808	1735	122
57	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	036	36	1794	1775	24
58	3	21	1	LYDX	1686	1751	LEFT	GOOD	036	36	1794	1775	108
59	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	044	44	1772	1753	2
60	3	21	1	LYDX	1686	1751	LEFT	GOOD	044	44	1772	1753	86
61	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	048	48	1746	1734	-17
62	3	21	1	LYDX	1686	1751	LEFT	GOOD	048	48	1746	1734	60
63	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	060	60	1758	1766	15
64	3	21	1	LYDX	1686	1751	LEFT	GOOD	060	60	1758	1766	72
65	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	068	68	1766	1778	27
66	3	21	1	LYDX	1686	1751	LEFT	GOOD	068	68	1766	1778	80
67	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	072	72	1695	1716	-35
68	3	21	1	LYDX	1686	1751	LEFT	GOOD	072	72	1695	1716	9
69	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	084	84	1752	1729	-22
70	3	21	1	LYDX	1686	1751	LEFT	GOOD	084	84	1752	1729	66
71	3	21	1	LYDX	1686	1751	LEFT	SPRAIN	168	168	1930	1842	91
72	3	21	1	LYDX	1686	1751	LEFT	GOOD	168	168	1930	1842	244
73	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	INJ	0	1759	1757	73
74	4	21	2	DMSO	1686	1751	RGHT	GOOD	INJ	0	1759	1757	6
75	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	012	12	1811	1747	125
76	4	21	2	DMSO	1686	1751	RGHT	GOOD	012	12	1811	1747	-4
77	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	020	20	1842	1780	156
78	4	21	2	DMSO	1686	1751	RGHT	GOOD	020	20	1842	1780	29
79	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	024	24	1843	1781	157
80	4	21	2	DMSO	1686	1751	RGHT	GOOD	024	24	1843	1781	30
81	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	036	36	1892	1797	206
82	4	21	2	DMSO	1686	1751	RGHT	GOOD	036	36	1892	1797	46
83	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	044	44	1919	1814	233
84	4	21	2	DMSO	1686	1751	RGHT	GOOD	044	44	1919	1814	63

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
85	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	048	48	1924	1820	238
86	4	21	2	DMSO	1686	1751	RGHT	GOOD	048	48	1924	1820	69
87	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	060	60	1930	1842	244
88	4	21	2	DMSO	1686	1751	RGHT	GOOD	060	60	1930	1842	91
89	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	068	68	1908	1838	222
90	4	21	2	DMSO	1686	1751	RGHT	GOOD	068	68	1908	1838	87
91	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	072	72	1900	1814	214
92	4	21	2	DMSO	1686	1751	RGHT	GOOD	072	72	1900	1814	63
93	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	084	84	1937	1777	251
94	4	21	2	DMSO	1686	1751	RGHT	GOOD	084	84	1937	1777	26
95	4	21	2	DMSO	1686	1751	RGHT	SPRAIN	168	168	1812	1727	126
96	4	21	2	DMSO	1686	1751	RGHT	GOOD	168	168	1812	1727	-24
97	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	INJ	0	1287	1253	28
98	5	22	1	DMSO	1259	1247	RGHT	GOOD	INJ	0	1287	1253	6
99	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	012	12	1329	1251	70
100	5	22	1	DMSO	1259	1247	RGHT	GOOD	012	12	1329	1251	4
101	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	020	20	1318	1258	59
102	5	22	1	DMSO	1259	1247	RGHT	GOOD	020	20	1318	1258	11
103	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	024	24	1378	1278	119
104	5	22	1	DMSO	1259	1247	RGHT	GOOD	024	24	1378	1278	31
105	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	036	36	1368	1263	109
106	5	22	1	DMSO	1259	1247	RGHT	GOOD	036	36	1368	1263	16
107	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	044	44	1323	1259	64
108	5	22	1	DMSO	1259	1247	RGHT	GOOD	044	44	1323	1259	12
109	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	048	48	1306	1253	47
110	5	22	1	DMSO	1259	1247	RGHT	GOOD	048	48	1306	1253	6
111	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	060	60	1325	1269	66
112	5	22	1	DMSO	1259	1247	RGHT	GOOD	060	60	1325	1269	22
113	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	068	68	1293	1165	34
114	5	22	1	DMSO	1259	1247	RGHT	GOOD	068	68	1293	1165	-82
115	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	072	72	1318	1254	59
116	5	22	1	DMSO	1259	1247	RGHT	GOOD	072	72	1318	1254	7
117	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	084	84	1360	1290	101
118	5	22	1	DMSO	1259	1247	RGHT	GOOD	084	84	1360	1290	43
119	5	22	1	DMSO	1259	1247	RGHT	SPRAIN	168	168	1283	1240	24
120	5	22	1	DMSO	1259	1247	RGHT	GOOD	168	168	1283	1240	-7
121	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	INJ	0	1344	1291	39
122	6	22	2	LYDX	1305	1287	RGHT	GOOD	INJ	0	1344	1291	4
123	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	012	12	1345	1349	40
124	6	22	2	LYDX	1305	1287	RGHT	GOOD	012	12	1345	1349	62
125	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	020	20	1354	1324	49
126	6	22	2	LYDX	1305	1287	RGHT	GOOD	020	20	1354	1324	37

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
127	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	024	24	1342	1261	37
128	6	22	2	LYDX	1305	1287	RGHT	GOOD	024	24	1342	1261	-26
129	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	036	36	1338	1239	33
130	6	22	2	LYDX	1305	1287	RGHT	GOOD	036	36	1338	1239	-48
131	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	044	44	1344	1310	39
132	6	22	2	LYDX	1305	1287	RGHT	GOOD	044	44	1344	1310	23
133	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	048	48	1320	1316	15
134	6	22	2	LYDX	1305	1287	RGHT	GOOD	048	48	1320	1316	29
135	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	060	60	1336	1306	31
136	6	22	2	LYDX	1305	1287	RGHT	GOOD	060	60	1336	1306	19
137	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	068	68	1334	1298	29
138	6	22	2	LYDX	1305	1287	RGHT	GOOD	068	68	1334	1298	11
139	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	072	72	1321	1293	16
140	6	22	2	LYDX	1305	1287	RGHT	GOOD	072	72	1321	1293	6
141	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	084	84	1332	1311	27
142	6	22	2	LYDX	1305	1287	RGHT	GOOD	084	84	1332	1311	24
143	6	22	2	LYDX	1305	1287	RGHT	SPRAIN	168	168	1325	1319	20
144	6	22	2	LYDX	1305	1287	RGHT	GOOD	168	168	1325	1319	32
145	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	INJ	0	1673	1684	15
146	7	23	1	DMSO	1690	1669	LEFT	GOOD	INJ	0	1673	1684	-17
147	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	012	12	1702	1737	68
148	7	23	1	DMSO	1690	1669	LEFT	GOOD	012	12	1702	1737	12
149	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	020	20	1722	1745	76
150	7	23	1	DMSO	1690	1669	LEFT	GOOD	020	20	1722	1745	32
151	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	024	24	1714	1753	84
152	7	23	1	DMSO	1690	1669	LEFT	GOOD	024	24	1714	1753	24
153	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	036	36	1745	1766	97
154	7	23	1	DMSO	1690	1669	LEFT	GOOD	036	36	1745	1766	55
155	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	044	44	1709	1704	35
156	7	23	1	DMSO	1690	1669	LEFT	GOOD	044	44	1709	1704	19
157	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	048	48	1714	1719	50
158	7	23	1	DMSO	1690	1669	LEFT	GOOD	048	48	1714	1719	24
159	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	060	60	1763	1780	111
160	7	23	1	DMSO	1690	1669	LEFT	GOOD	060	60	1763	1780	73
161	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	068	68	1738	1773	104
162	7	23	1	DMSO	1690	1669	LEFT	GOOD	068	68	1738	1773	48
163	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	072	72	1723	1747	78
164	7	23	1	DMSO	1690	1669	LEFT	GOOD	072	72	1723	1747	33
165	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	084	84	1734	1756	87
166	7	23	1	DMSO	1690	1669	LEFT	GOOD	084	84	1734	1756	44
167	7	23	1	DMSO	1690	1669	LEFT	SPRAIN	168	168	1707	1713	44
168	7	23	1	DMSO	1690	1669	LEFT	GOOD	168	168	1707	1713	17

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
169	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	INJ	0	1592	1514	45
170	8	23	2	LYDX	1547	1529	RGHT	GOOD	INJ	0	1592	1514	-15
171	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	012	12	1725	1571	178
172	8	23	2	LYDX	1547	1529	RGHT	GOOD	012	12	1725	1571	42
173	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	020	20	1712	1560	165
174	8	23	2	LYDX	1547	1529	RGHT	GOOD	020	20	1712	1560	31
175	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	024	24	1705	1545	158
176	8	23	2	LYDX	1547	1529	RGHT	GOOD	024	24	1705	1545	16
177	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	036	36	1675	1512	128
178	8	23	2	LYDX	1547	1529	RGHT	GOOD	036	36	1675	1512	-17
179	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	044	44	1670	1539	123
180	8	23	2	LYDX	1547	1529	RGHT	GOOD	044	44	1670	1539	10
181	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	048	48	1700	1526	153
182	8	23	2	LYDX	1547	1529	RGHT	GOOD	048	48	1700	1526	-3
183	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	060	60	1615	1532	68
184	8	23	2	LYDX	1547	1529	RGHT	GOOD	060	60	1615	1532	3
185	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	068	68	1628	1541	81
186	8	23	2	LYDX	1547	1529	RGHT	GOOD	068	68	1628	1541	12
187	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	072	72	1617	1530	70
188	8	23	2	LYDX	1547	1529	RGHT	GOOD	072	72	1617	1530	1
189	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	084	84	1584	1535	37
190	8	23	2	LYDX	1547	1529	RGHT	GOOD	084	84	1584	1535	6
191	8	23	2	LYDX	1547	1529	RGHT	SPRAIN	168	168	1597	1538	50
192	8	23	2	LYDX	1547	1529	RGHT	GOOD	168	168	1597	1538	9
193	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	INJ	0	1548	1521	22
194	9	24	1	LYDX	1526	1524	RGHT	GOOD	INJ	0	1548	1521	-3
195	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	012	12	1586	1542	60
196	9	24	1	LYDX	1526	1524	RGHT	GOOD	012	12	1586	1542	18
197	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	020	20	1572	1536	46
198	9	24	1	LYDX	1526	1524	RGHT	GOOD	020	20	1572	1536	12
199	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	024	24	1556	1534	30
200	9	24	1	LYDX	1526	1524	RGHT	GOOD	024	24	1556	1534	10
201	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	036	36	1542	1531	16
202	9	24	1	LYDX	1526	1524	RGHT	GOOD	036	36	1542	1531	7
203	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	044	44	1530	1526	4
204	9	24	1	LYDX	1526	1524	RGHT	GOOD	044	44	1530	1526	2
205	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	048	48	1530	1522	4
206	9	24	1	LYDX	1526	1524	RGHT	GOOD	048	48	1530	1522	-2
207	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	060	60	1541	1520	15
208	9	24	1	LYDX	1526	1524	RGHT	GOOD	060	60	1541	1520	-4
209	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	068	68	1530	1524	4
210	9	24	1	LYDX	1526	1524	RGHT	GOOD	068	68	1530	1524	0

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
211	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	072	72	1532	1520	6
212	9	24	1	LYDX	1526	1524	RGHT	GOOD	072	72	1532	1520	-4
213	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	084	84	1527	1526	1
214	9	24	1	LYDX	1526	1524	RGHT	GOOD	084	84	1527	1526	2
215	9	24	1	LYDX	1526	1524	RGHT	SPRAIN	168	168	1524	1520	-2
216	9	24	1	LYDX	1526	1524	RGHT	GOOD	168	168	1524	1520	-4
217	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	INJ	0	1686	1794	52
218	10	24	2	DMSO	1699	1742	LEFT	GOOD	INJ	0	1686	1794	-13
219	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	012	12	1717	1883	141
220	10	24	2	DMSO	1699	1742	LEFT	GOOD	012	12	1717	1883	18
221	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	020	20	1722	1871	129
222	10	24	2	DMSO	1699	1742	LEFT	GOOD	020	20	1722	1871	23
223	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	024	24	1738	1878	136
224	10	24	2	DMSO	1699	1742	LEFT	GOOD	024	24	1738	1878	39
225	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	036	36	1706	1862	120
226	10	24	2	DMSO	1699	1742	LEFT	GOOD	036	36	1706	1862	7
227	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	044	44	1714	1866	124
228	10	24	2	DMSO	1699	1742	LEFT	GOOD	044	44	1714	1866	15
229	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	048	48	1692	1858	116
230	10	24	2	DMSO	1699	1742	LEFT	GOOD	048	48	1692	1858	-7
231	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	060	60	1709	1829	87
232	10	24	2	DMSO	1699	1742	LEFT	GOOD	060	60	1709	1829	10
233	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	068	68	1715	1812	70
234	10	24	2	DMSO	1699	1742	LEFT	GOOD	068	68	1715	1812	16
235	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	072	72	1698	1792	50
236	10	24	2	DMSO	1699	1742	LEFT	GOOD	072	72	1698	1792	-1
237	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	084	84	1690	1779	37
238	10	24	2	DMSO	1699	1742	LEFT	GOOD	084	84	1690	1779	-9
239	10	24	2	DMSO	1699	1742	LEFT	SPRAIN	168	168	1678	1751	9
240	10	24	2	DMSO	1699	1742	LEFT	GOOD	168	168	1678	1751	-21
241	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	INJ	0	1567	1482	72
242	11	25	1	LYDX	1495	1495	RGHT	GOOD	INJ	0	1567	1482	-13
243	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	012	12	1658	1545	163
244	11	25	1	LYDX	1495	1495	RGHT	GOOD	012	12	1658	1545	50
245	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	020	20	1661	1556	166
246	11	25	1	LYDX	1495	1495	RGHT	GOOD	020	20	1661	1556	61
247	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	024	24	1624	1532	129
248	11	25	1	LYDX	1495	1495	RGHT	GOOD	024	24	1624	1532	37
249	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	036	36	1616	1519	121
250	11	25	1	LYDX	1495	1495	RGHT	GOOD	036	36	1616	1519	24
251	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	044	44	1620	1519	125
252	11	25	1	LYDX	1495	1495	RGHT	GOOD	044	44	1620	1519	24

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
253	11	25	1	LYDX	1495	1495	RGHT	SPRAIN	048	48	1612	1504	117
254	11	25	1	LYDX	1495	1495	RGHT	GOOD	048	48	1612	1504	9
255	11	25	2	LYDX	1495	1495	RGHT	SPRAIN	060	60	1525	1508	30
256	11	25	2	LYDX	1495	1495	RGHT	GOOD	060	60	1525	1508	13
257	11	25	2	LYDX	1495	1495	RGHT	SPRAIN	068	68	1532	1519	37
258	11	25	2	LYDX	1495	1495	RGHT	GOOD	068	68	1532	1519	24
259	11	25	2	LYDX	1495	1495	RGHT	SPRAIN	072	72	1512	1516	17
260	11	25	2	LYDX	1495	1495	RGHT	GOOD	072	72	1512	1516	21
261	11	25	2	LYDX	1495	1495	RGHT	SPRAIN	084	84	1506	1513	11
262	11	25	2	LYDX	1495	1495	RGHT	GOOD	084	84	1506	1513	18
263	11	25	2	LYDX	1495	1495	RGHT	SPRAIN	168	168	1508	1502	13
264	11	25	2	LYDX	1495	1495	RGHT	GOOD	168	168	1508	1502	7
265	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	INJ	0	1589	1674	112
266	12	25	2	DMSO	1600	1562	LEFT	GOOD	INJ	0	1589	1674	-11
267	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	012	12	1668	1706	144
268	12	25	2	DMSO	1600	1562	LEFT	GOOD	012	12	1668	1706	68
269	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	020	20	1665	1707	145
270	12	25	2	DMSO	1600	1562	LEFT	GOOD	020	20	1665	1707	65
271	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	024	24	1659	1681	119
272	12	25	2	DMSO	1600	1562	LEFT	GOOD	024	24	1659	1681	59
273	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	036	36	1666	1711	149
274	12	25	2	DMSO	1600	1562	LEFT	GOOD	036	36	1666	1711	66
275	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	044	44	1681	1714	152
276	12	25	2	DMSO	1600	1562	LEFT	GOOD	044	44	1681	1714	81
277	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	048	48	1653	1695	133
278	12	25	2	DMSO	1600	1562	LEFT	GOOD	048	48	1653	1695	53
279	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	060	60	1642	1714	152
280	12	25	2	DMSO	1600	1562	LEFT	GOOD	060	60	1642	1714	42
281	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	068	68	1658	1706	144
282	12	25	2	DMSO	1600	1562	LEFT	GOOD	068	68	1658	1706	58
283	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	072	72	1643	1681	119
284	12	25	2	DMSO	1600	1562	LEFT	GOOD	072	72	1643	1681	43
285	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	084	84	1630	1675	113
286	12	25	2	DMSO	1600	1562	LEFT	GOOD	084	84	1630	1675	30
287	12	25	2	DMSO	1600	1562	LEFT	SPRAIN	168	168	1612	1586	24
288	12	25	2	DMSO	1600	1562	LEFT	GOOD	168	168	1612	1586	12
289	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	INJ	0	1591	1562	27
290	13	26	1	DMSO	1564	1576	RGHT	GOOD	INJ	0	1591	1562	-14
291	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	012	12	1683	1581	119
292	13	26	1	DMSO	1564	1576	RGHT	GOOD	012	12	1683	1581	5
293	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	020	20	1668	1584	104
294	13	26	1	DMSO	1564	1576	RGHT	GOOD	020	20	1668	1584	8

TABLE VII (Continued)

OBS	SUBJ	BLK	BOTL	TRT	RGHTI	LEFTI	LGINJ	LEG	HOUR	TIME	RGHT	LEFT	VOLDIF
295	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	024	24	1653	1586	89
296	13	26	1	DMSO	1564	1576	RGHT	GOOD	024	24	1653	1586	10
297	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	036	36	1650	1591	86
298	13	26	1	DMSO	1564	1576	RGHT	GOOD	036	36	1650	1591	15
299	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	044	44	1678	1585	114
300	13	26	1	DMSO	1564	1576	RGHT	GOOD	044	44	1678	1585	9
301	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	048	48	1662	1604	98
302	13	26	1	DMSO	1564	1576	RGHT	GOOD	048	48	1662	1604	28
303	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	060	60	1672	1607	108
304	13	26	1	DMSO	1564	1576	RGHT	GOOD	060	60	1672	1607	31
305	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	068	68	1652	1632	88
306	13	26	1	DMSO	1564	1576	RGHT	GOOD	068	68	1652	1632	56
307	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	072	72	1609	1573	45
308	13	26	1	DMSO	1564	1576	RGHT	GOOD	072	72	1609	1573	-3
309	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	084	84	1628	1593	64
310	13	26	1	DMSO	1564	1576	RGHT	GOOD	084	84	1628	1593	17
311	13	26	1	DMSO	1564	1576	RGHT	SPRAIN	168	168	1604	1590	40
312	13	26	1	DMSO	1564	1576	RGHT	GOOD	168	168	1604	1590	14
313	14	26	.	LYDX	1475	1464	RGHT	SPRAIN	INJ	0	1486	1461	11
314	14	26	.	LYDX	1475	1464	RGHT	GOOD	INJ	0	1486	1461	-3
315	14	26	.	LYDX	1475	1464	RGHT	SPRAIN	012	12	1522	1500	47
316	14	26	.	LYDX	1475	1464	RGHT	GOOD	012	12	1522	1500	36
317	14	26	.	LYDX	1475	1464	RGHT	SPRAIN	020	20	1518	1502	43
318	14	26	.	LYDX	1475	1464	RGHT	GOOD	020	20	1518	1502	38
319	14	26	.	LYDX	1475	1464	RGHT	SPRAIN	024	24	1516	1471	41
320	14	26	.	LYDX	1475	1464	RGHT	GOOD	024	24	1516	1471	7
321	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	036	36	1488	1472	13
322	14	26	2	LYDX	1475	1464	RGHT	GOOD	036	36	1488	1472	8
323	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	044	44	1485	1466	10
324	14	26	2	LYDX	1475	1464	RGHT	GOOD	044	44	1485	1466	2
325	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	048	48	1480	1465	5
326	14	26	2	LYDX	1475	1464	RGHT	GOOD	048	48	1480	1465	1
327	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	060	60	1479	1468	4
328	14	26	2	LYDX	1475	1464	RGHT	GOOD	060	60	1479	1468	4
329	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	068	68	1479	1471	4
330	14	26	2	LYDX	1475	1464	RGHT	GOOD	068	68	1479	1471	7
331	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	072	72	1474	1469	-1
332	14	26	2	LYDX	1475	1464	RGHT	GOOD	072	72	1474	1469	5
333	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	084	84	1475	1460	0
334	14	26	2	LYDX	1475	1464	RGHT	GOOD	084	84	1475	1460	-4
335	14	26	2	LYDX	1475	1464	RGHT	SPRAIN	168	168	1472	1462	-3
336	14	26	2	LYDX	1475	1464	RGHT	GOOD	168	168	1472	1462	-2

TABLE VIII

MEAN EDEMIC RESPONSES FOR EACH ANKLE AND TREATMENT COMBINATION

OBS	TRT	LEG	TIME	_TYPE_	_FREQ_	MVOLDIF
1			.	0	336	40.8482
2			0	1	28	8.0714
3			12	1	28	51.5000
4			20	1	28	52.9643
5			24	1	28	49.5357
6			36	1	28	50.2143
7			44	1	28	48.4286
8			48	1	28	43.9286
9			60	1	28	47.8214
10			68	1	28	43.1429
11			72	1	28	30.1071
12			84	1	28	36.1429
13			168	1	28	28.3214
14		GOOD	.	2	168	18.9405
15		SPRAIN	.	2	168	62.7560
16		GOOD	0	3	14	-9.4286
17		GOOD	12	3	14	23.5714
18		GOOD	20	3	14	27.8571
19		GOOD	24	3	14	25.2857
20		GOOD	36	3	14	18.2143
21		GOOD	44	3	14	23.6429
22		GOOD	48	3	14	17.0714
23		GOOD	60	3	14	25.7143
24		GOOD	68	3	14	24.2143
25		GOOD	72	3	14	11.8571
26		GOOD	84	3	14	18.5000
27		GOOD	168	3	14	20.7857
28		SPRAIN	0	3	14	25.5714
29		SPRAIN	12	3	14	79.4286
30		SPRAIN	20	3	14	78.0714
31		SPRAIN	24	3	14	73.7857
32		SPRAIN	36	3	14	82.2143
33		SPRAIN	44	3	14	73.2143
34		SPRAIN	48	3	14	70.7857
35		SPRAIN	60	3	14	69.9286
36		SPRAIN	68	3	14	62.0714
37		SPRAIN	72	3	14	48.3571
38		SPRAIN	84	3	14	53.7857
39		SPRAIN	168	3	14	35.8571
40	DMSO		.	4	168	53.1607
41	LYDX		.	4	168	28.5357
42	DMSO		0	5	14	12.2143
43	DMSO		12	5	14	55.2857
44	DMSO		20	5	14	56.5000
45	DMSO		24	5	14	60.5000
46	DMSO		36	5	14	71.0000
47	DMSO		44	5	14	64.2857
48	DMSO		48	5	14	62.0714
49	DMSO		60	5	14	74.2857

TABLE VIII (Continued)

OBS	TRT	LEG	TIME	_TYPE_	_FREQ_	MVOLDIF
50	DMSO		68	5	14	60.2143
51	DMSO		72	5	14	50.5000
52	DMSO		84	5	14	53.8571
53	DMSO		168	5	14	17.2143
54	LYDX		0	5	14	3.9286
55	LYDX		12	5	14	47.7143
56	LYDX		20	5	14	49.429
57	LYDX		24	5	14	38.571
58	LYDX		36	5	14	29.429
59	LYDX		44	5	14	32.571
60	LYDX		48	5	14	25.786
61	LYDX		60	5	14	21.357
62	LYDX		68	5	14	26.071
63	LYDX		72	5	14	9.714
64	LYDX		84	5	14	18.429
65	LYDX		168	5	14	39.429
66	DMSO	GOOD	.	6	84	19.060
67	DMSO	SPRAIN	.	6	84	87.262
68	LYDX	GOOD	.	6	84	18.821
69	LYDX	SPRAIN	.	6	84	38.250
70	DMSO	GOOD	0	7	7	-12.571
71	DMSO	GOOD	12	7	7	13.714
72	DMSO	GOOD	20	7	7	20.000
73	DMSO	GOOD	24	7	7	26.571
74	DMSO	GOOD	36	7	7	28.857
75	DMSO	GOOD	44	7	7	26.857
76	DMSO	GOOD	48	7	7	25.714
77	DMSO	GOOD	60	7	7	37.714
78	DMSO	GOOD	68	7	7	25.143
79	DMSO	GOOD	72	7	7	19.571
80	DMSO	GOOD	84	7	7	19.000
81	DMSO	GOOD	168	7	7	-1.857
82	DMSO	SPRAIN	0	7	7	37.000
83	DMSO	SPRAIN	12	7	7	96.857
84	DMSO	SPRAIN	20	7	7	93.000
85	DMSO	SPRAIN	24	7	7	94.429
86	DMSO	SPRAIN	36	7	7	113.143
87	DMSO	SPRAIN	44	7	7	101.714
88	DMSO	SPRAIN	48	7	7	98.429
89	DMSO	SPRAIN	60	7	7	110.857
90	DMSO	SPRAIN	68	7	7	95.286
91	DMSO	SPRAIN	72	7	7	81.429
92	DMSO	SPRAIN	84	7	7	88.714
93	DMSO	SPRAIN	168	7	7	36.286
94	LYDX	GOOD	0	7	7	-6.286
95	LYDX	GOOD	12	7	7	33.429
96	LYDX	GOOD	20	7	7	35.714

TABLE VIII (Continued)

OBS	TRT	LEG	TIME	_TYPE_	_FREQ_	MVOLDIF
97	LYDX	GOOD	24	7	7	24.000
98	LYDX	GOOD	36	7	7	7.571
99	LYDX	GOOD	44	7	7	20.429
100	LYDX	GOOD	48	7	7	8.429
101	LYDX	GOOD	60	7	7	13.714
102	LYDX	GOOD	68	7	7	23.286
103	LYDX	GOOD	72	7	7	4.143
104	LYDX	GOOD	84	7	7	18.000
105	LYDX	GOOD	168	7	7	43.429
106	LYDX	SPRAIN	0	7	7	14.143
107	LYDX	SPRAIN	12	7	7	62.000
108	LYDX	SPRAIN	20	7	7	63.143
109	LYDX	SPRAIN	24	7	7	53.143
110	LYDX	SPRAIN	36	7	7	51.286
111	LYDX	SPRAIN	44	7	7	44.7143
112	LYDX	SPRAIN	48	7	7	43.1429
113	LYDX	SPRAIN	60	7	7	29.0000
114	LYDX	SPRAIN	68	7	7	28.8571
115	LYDX	SPRAIN	72	7	7	15.2857
116	LYDX	SPRAIN	84	7	7	18.8571
117	LYDX	SPRAIN	168	7	7	35.4286

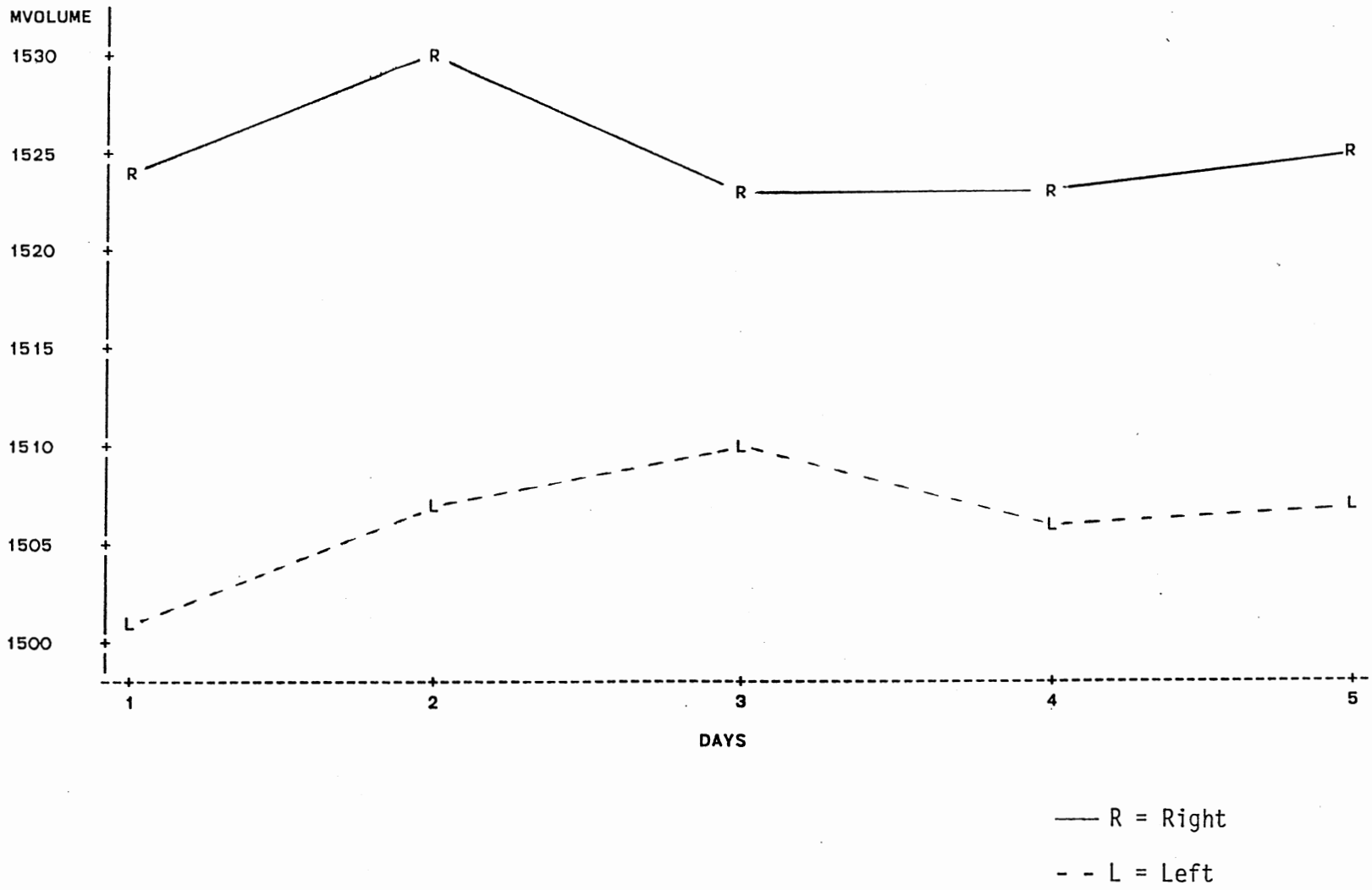

Figure 7. Reliability Measurements of Ankles Over Time