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Clinical Considerations of Dimethyl Sulfoxide

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INTRODUCTION

Dimethyl sulfoxide (DMSO) has been heralded as a "miracle" drug capable of a wide range of therapeutic capabilities. While its biological actions are indeed diverse, one must reserve judgement on the attributes of DMSO until further clinical studies involving the specific actions of DMSO are conducted. It is clear that DMSO has amazing properties that certainly could be useful in the treatment of many medical disorders.

DMSO is a naturally occurring organic compound. All plant matter of marine origin contain trace quantities of DMSO.¹ The phytoplankton growing near the ocean surface constantly expell volatile dimethyl sulfide (DMS) which evaporates to the ozone layer of the atmosphere and is oxidized to dimethyl sulfoxide. DMSO then reaches the earth in the form of rain. In 1963, studies of DMSO indicated that this by-product of paper manufacturing had remarkable properties, including: rapid penetration of skin, transport of other drugs across biological membranes, local anesthetic properties, reduction of swelling and promotion of healing.⁴

The first Investigational New Drug exemption (IND) for the study of DMSO in humans was filed with the Food and Drug Administration in 1963.⁴ Unfortunately, the lack of controlled studies and widespread use of DMSO up to 1965 led to many unorthodox treatment regimes which included DMSO. In November of 1965 the FDA terminated all clinical studies of DMSO because toxicological studies indicated that DMSO caused changes in the refractive index in the lens of the eye in

experimental animals. In 1966 and 1968 the FDA revised its policy on DMSO to allow clinical evaluation of DMSO in certain specific medical conditions, and in 1980 the FDA revoked the regulation establishing specific requirements for the clinical testing of DMSO in humans.⁴ Although the restrictions regarding clinical research of DMSO have been relaxed, the initial enthusiasm of the clinical use of DMSO has not resurfaced. This is unfortunate in light of the many potentially beneficial uses of DMSO in the medical field.

CHEMISTRY OF DMSO

Dimethyl sulfoxide, $(\text{CH}_3)_2\text{SO}$, is a dipolar, organic compound, with a molecular weight of 78.13.² DMSO is a stable, colorless, nonvolatile, hygroscopic, highly associated liquid with a sulfur-like smell and a slightly bitter taste.⁵

DMSO is completely miscible with water in any proportion and acts as the acceptor of hydrogen bonds. DMSO can complex with a multitude of compounds including: metal cations, various drugs, and components of tissue, blood, plasma, spinal fluid, etc.

DMSO can act as both an oxidizing and a reducing agent. When acting as an oxidant, DMSO is reduced to dimethyl sulfide (DMS) and when acting as a reducing agent, DMSO is oxidized to dimethyl sulfone (DMSO_2).

METABOLISM OF DMSO

Regardless of the route of administration of DMSO, a remarkable amount of radioactive DMSO is found in the plasma after only 30 minutes. Cutaneous administration of DMSO generally results in lower serum levels than when DMSO is administered per os or intravenously.⁷ Maximal blood concentrations of DMSO applied cutaneously are reached in 2 hours.

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An oral dose of 1g/kg-body weight results in peak plasma concentrations in 4–6 hours, and detectable levels persisted for 400 hours. DMSO administered intravenously at the same dosage achieves higher plasma levels and is rapidly distributed throughout all tissues.⁷

DMSO is metabolized in animals and man to form dimethyl sulfide (DMS) and dimethyl sulfone (DMSO₂). DMSO and DMSO₂ are present in all examined tissues including both hard (i.e. lens and bone) and soft tissues.³ Unaltered DMSO is by far the most prevalent in tissues, blood, feces and urine, with DMSO₂ also present but in much smaller concentrations. A small percentage of the original dose of DMSO is reduced to DMS and exhaled.

It appears that the primary route of excretion of DMSO is through the urine.⁸ One and one-half to two hours after cutaneous administration of DMSO, the highest concentration is found in the kidneys, indicating that the kidney is the organ of excretion. In dogs, studies indicate that approximately 50% of a total dose of DMSO-35S is collected in urine after 36 hours whether given by oral or intravenous administration.⁸ When DMSO-35S is applied cutaneously, only 12–25% of the total dose is found in the urine collected over a 24 hour period. Only a small fraction of an original dose of DMSO is excreted in the feces, regardless of the route of administration.

The biliary system also appears to play a role in the excretion of DMSO. In rats administered DMSO intravenously, 8% of the total dose is recovered in a 24 hour period. This suggests that a large portion of the DMSO dose is reabsorbed in the enterohepatic circulation.

The odoriferous breath associated with administration of DMSO led researchers to investigate the possibility of pulmonary excretion. It was found that a small amount of DMSO is reduced to DMS and exhaled in the breath. Approximately 3–6% of a total DMSO dose is exhaled in the breath, regardless of the route of administration.³

BIOLOGICAL ACTIONS OF DMSO AND THEIR CLINICAL SIGNIFICANCE

Dimethyl sulfoxide has a multitude of biological actions which have been demonstrated

in the laboratory and also under clinical situations. Many of the pharmacological properties of DMSO are still under laboratory investigation and have not yet been extended to use in the field of veterinary medicine. However, with additional research into the potential uses of DMSO it may prove to have an amazing diversity of applications in the medical field.

Membrane Penetration

DMSO readily crosses most tissues of animals and man with the exception of tooth enamel and keratinized structures. The exact mechanism involved in the membrane-penetrant action of DMSO has yet to be elucidated. It has been hypothesized that DMSO substitutes for water in the skin causing a reversible configurational change of the skin protein, thus accounting for the rapid passage of DMSO through the skin.¹¹ The ability to penetrate body membranes and to become widely distributed throughout the body is advantageous, especially the ability of DMSO to transport other pharmacological agents through the skin and other biological membranes.

Membrane Transport

DMSO can serve as a vehicle for topical drugs and facilitate their transport through the skin. DMSO carries substances rapidly and deeply into the horny layer of the skin.¹² Non-ionized molecules of low molecular weight are transported through the skin with DMSO, but substances of high molecular weight do not pass through the skin with DMSO to any significant extent.¹¹ This ability to enhance percutaneous penetration of topical medications lends itself well to use in dermatological disorders because the primary limitation to topical therapy is the skin's protective characteristics. DMSO has been found to enhance the penetration of the following therapeutic agents: Antibacterials,¹¹ antivirals,⁵ estrogens,¹¹ corticosteroids, anti-parasitics, and local anesthetics. In one human case, DMSO was used to maintain nourishment by percutaneous absorption of nutrients dissolved in DMSO.¹⁴ Most evidence indicates that DMSO itself, does not have healing properties in the majority of dermatological disorders, but its ability to serve as a vehicle for the transfer of drugs through the intact

skin and for deposition of these drugs into the skin is its beneficial effect.^{2,12,14}

Anti-Inflammation

DMSO apparently has significant anti-inflammatory properties. Researchers indicate that the anti-inflammatory effect of DMSO may be due to its ability to scavenge inflammation-triggering free radicals⁵ and/or its ability to inhibit the influx of polymorphonuclear cells and monocytes into the sites of inflammation.¹⁵ One of the most popular uses of DMSO is for treatment of acute swelling associated with traumatic injuries. Another use of DMSO which utilizes its anti-inflammatory properties is in the treatment of toxic snake bites.¹⁶ It is thought that use of DMSO decreases the swelling resulting from the snake bite, and it also potentiates the action of the administered corticosteroids. DMSO also decreases the inflammation associated with perivascular injections of thiace-tarsamide sodium.¹⁷ DMSO decreases the swelling and dissipates this irritating antiparasitic, and thus prevents sloughing of surrounding tissues. DMSO is also used in the treatment regime for otitis externa to reduce irritation. Treatment of ulcers and wounds is also augmented by DMSO therapy, in part due to its anti-inflammatory properties.¹⁸ Topical application of DMSO to canine mammary glands reduces swelling and engorgement.¹⁹ DMSO has also been used to relieve post-operative pain and swelling following joint and tendon repair procedures.²⁰

Analgesia

DMSO alone has analgesic properties, and when used in conjunction with topical anesthetics appears to potentiate their effects. DMSO reversibly decreases the conduction velocity of nerves and produces analgesia by acting on both the peripheral nervous system and the central nervous system.²¹ Subcutaneous injection of 10% DMSO can result in a total loss of central recognition of pain.¹¹ DMSO produces an analgesic effect comparable to morphine, but it is longer lasting and is not reversible by administration of naloxone.²⁰ Since it is not reversed by naloxone, this indicates that opiate receptors are not involved in DMSO-induced analgesia. DMSO can also induce total anesthesia of an animal when injected into the cerebral spinal fluid

without apparent adverse reactions.¹¹ However, clinical application of this method of anesthesia is impractical.

Effects on Connective Tissue

DMSO decreases the concentration of collagen and its metabolites and also reduces the pathogenic deposition of collagen in response to injury. Experimentally, DMSO injected intraperitoneally will decrease the incidence of intestinal adhesions.¹¹ This may prove useful for post-operative treatment of gastrointestinal surgery. Studies involving the use of DMSO for treatment of collagen-related arthritis resulted in conflicting results^{11,23,24} and requires further studies to determine the efficacy of DMSO in treating this disorder.

Effect on Bacteria, Fungi, and Viruses

DMSO exhibits a remarkable inhibitory effect on a wide range of bacteria, fungi, and both RNA and DNA viruses.¹¹ The bacteriostatic effect of DMSO may occur due to a loss of RNA conformational structure required for protein synthesis.¹¹ Pre-treatment with DMSO restored and increased the sensitivity of antibiotic-resistant strains of bacteria and increased the sensitivity of bacteria in general to antibiotic treatment.¹¹ This characteristic of DMSO may prove to be valuable.

Diuresis

DMSO has been shown to be an effective diuretic due to an increase in the urinary excretion of sodium and potassium. This diuretic effect may prove valuable in treating cases of central nervous system trauma because the diuretic effect of DMSO is effective in decreasing intracranial pressure.²⁵ In man, intravenous DMSO is more effective than mannitol, urea, cortisone, or barbiturates for reducing intracranial pressure associated with severe head injuries.²⁶

Vasodilation

DMSO has potent histamine-releasing properties which result in significant vasodilation.¹¹ This vasodilatory effect may be useful in decreasing edema, improving circulation in localized areas, and increasing the absorption of other drugs. DMSO vasodilation increases the cortical and spinal blood flow, thus reducing the edema resulting from acute cranial

and spinal cord trauma.^{25,27} Experimentally, DMSO has been used to treat intestinal,²⁸ renal,²⁹ and cerebral ischemia.^{30,31}

Action on Free-Radicals

DMSO has the ability to scavenge free-radicals, especially hydroxyl radicals and hydrogen atoms.⁵ The carcinogenic effect of many organic compounds is related to the formation of free-radical intermediates. It has been shown that DMSO causes a significant inhibition of promoters of neoplasia, with reduction of both tumor rate and yield.⁵ DMSO has also been shown to protect tissues and cells against radiation damage. This protective effect is due to inhibition of hydroxy radicals by DMSO. The scavenging of free-radicals also aids in reduction of pain induced by inflammation.² DMSO has been shown to increase the effectiveness of griseofulvin and potentiate the action of digitoxin.¹¹ This is clinically important when using DMSO concomitantly with other therapeutic agents.

TOXICITY OF DMSO

The potentially toxic effects of DMSO is the subject which virtually brought clinical investigations of DMSO to a standstill, but it is interesting to note that DMSO is of such low toxicity that grams per kilogram are used to measure toxicity instead of milligrams per kilogram as in the case of most other drugs. The toxic effects of DMSO vary with concentration, dosage, and route of administration.

Common complaints associated with the use of DMSO are the garlic-like breath odor, erythema, dryness, occasional pruritus associated with cutaneous administration, and diarrhea. In humans, headache,³² nausea, sedation, and less frequently, dizziness^{25,26} are reported and it is assumed that animals may experience similar phenomena. Urea-modified DMSO moderates some of these side effects. Urea-modified DMSO consists of 60-parts DMSO, 20-parts urea, and 20-parts water.⁶ This formula decreases the garlic or sulfur odor in the breath and the cutaneous irritation, pruritus and dryness.

Since the potential for systemic toxicity is the greatest with intravenous administration of DMSO, the LD50 has been determined for several species and are in the range of 2.5–8.9g/kg body weight.³³ Symptoms at near le-

thal doses were similar in all species investigated and include spontaneous motor activity, tremors, muscular weakness, prostration, transient convulsions, dyspnea, pulmonary edema, and hemorrhage.³³ The oral LD50 of DMSO is higher than the intravenous LD50 and is approximately 10g/kg body weight.³⁴

With intravenous administration of DMSO it was found that there is no increased toxicity with repeated daily dosing, assuming that the repeated daily does not exceed the single maximum tolerated dose.³⁵ Damage to blood vessels due to DMSO is directly proportional to the concentration of DMSO and the number of repeated injections. The concentration of DMSO administered intravenously should not exceed 50% or the injected vessel may be subject to intimal damage, fibrosis, perivascular inflammation, and/or intravascular thrombi.³⁵ However, no necrosis or sloughing of the blood vessel occurs. At or above the maximum tolerated dose there is a transient increase in respiratory rate, an increase in diuresis, and evidence of hemoglobinuria and bilirubinuria which are a direct result of erythrocyte damage and subsequent release of hemoglobin.³⁵

Rapid intravenous administration of DMSO can induce seizures.²¹ Local tissue reactions to subcutaneous or intramuscular injections are directly related to the concentration and total amount of DMSO injected. Reported responses to these injections include inflammatory, hemorrhagic, gelatinous, and edematous tissue reactions, but there is no abscess formation, necrosis, or sloughing.³⁵ Intradermal injections of undiluted DMSO cause an intense local vasoconstriction followed by hemorrhage and necrosis,³⁵ and therefore, should be avoided.

Most biochemical changes associated with the administration of DMSO are related to the damage incurred by the red blood cells.^{35,36} This direct hemolytic effect is dose-related and is seen with intravenous DMSO in high concentration or high dosage rate. Very high doses of oral DMSO cause hemorrhagic gastroenteropathy. Hemolysis results in a reversible anemia with a reduction in hemoglobin in the circulating blood, hemoglobinuria, hematuria, and bilirubinuria. As a result of red blood cell damage, reticulocytosis and increased erythroid activity in the spleen and bone marrow are often observed.

In spite of the dose-related hemolysis and subsequent hemoglobinuria associated with high concentrations of intravenous DMSO, there is no decrease in renal function and in general, no evidence of renal structural changes.³⁶ Some reports indicate the presence of a mild tubular nephrosis,³³ but there are no reports of nephrotoxic tubular damage. Also, there are no urine sediment abnormalities, and no increases in urine protein or glucose.

Liver damage with high doses of DMSO consists of fatty degeneration, cloudy swelling, granulation of parenchymal cytoplasm, and inflammation in the portal spaces.^{33,35} Other changes include hemolyzed red blood cells in the hepatic sinusoids, cytoplasmic fragmentation of the Kupffer cells, and hemosiderin granules in the interstitium.

Pulmonary changes associated with the conventional administration of DMSO are not common but with near-lethal doses of DMSO, development of pulmonary edema can occur.³⁵ The pathogenesis of pulmonary edema is related to a decreased heart rate and blood pressure, vascular distention, and stasis of blood.

Teratogenic effects of DMSO appear to be minimal unless extraordinarily high doses of DMSO are administered. The most definite teratogenic effects are seen in the hamster and the chicken.³⁵ In the hamster, the teratogenicity of DMSO is directly related to the stage of development of the embryo when DMSO is administered. Direct injection of DMSO into the chick embryo results in fetal abnormalities, but injection of DMSO into the yolk sac does not produce any teratogenic effect. Rabbits treated with very high doses of DMSO demonstrate a reduction in embryo viability.³⁵ Administration of DMSO in high doses, to both male and female rats prior to mating, does not cause any reduction in fertility nor is it associated with any teratogenic effects.³³ The major concern associated with administration of DMSO to gravid animals is the dosage given, but it is unlikely in a clinical situation that such high doses would be dispensed.

The topical route of application of DMSO appears to be the least toxic. The most important aspect of the cutaneous toxicity of DMSO involves local tissue reactions. DMSO passes through the skin fairly rapidly and causes vasodilation and erythema proportional to the concentration of DMSO applied. Cutaneous

application of high concentrations of DMSO solutions exaggerate the hygroscopic effects of DMSO, depriving the tissues of water.³³ Dogs and monkeys treated with 90% DMSO over an extended period exhibit a slight hyperkeratosis of the skin with no other significant histological changes in the skin.³⁵ In humans, 80% DMSO applied topically results in a significant incidence of eosinophilia, attributed to the cutaneous histamine-releasing effect of DMSO.³³

Cutaneous administration of DMSO with occlusive bandages may cause a papillovesicular reaction which leads to inflammation and epidermal death.³⁷ Although these are not permanent changes, occlusive bandaging should be avoided when using topical DMSO.

The transport and penetrant properties of DMSO impose a hazard to the cutaneous administration of DMSO. DMSO has the capability to enhance the absorption of topical medications and other materials into the skin, and therefore, any other medication or compound present on the skin should be removed prior to cutaneous application of DMSO.

DMSO and its metabolites will not accumulate in the tissues, and no delayed toxicity to DMSO has been reported.³⁵ In animals treated with intradermal DMSO for 3 weeks, no signs of sensitization were noted when challenged with an intradermal dose of DMSO.³⁵ Therefore, any toxic effects of DMSO will most likely be observed during or immediately following DMSO therapy.

Administration of DMSO causes the cortical fibers of the lens of the eye to become less reluctant than normal and this change results in the production of a refractive error and myopia.³⁴ The severity of this change is directly related to the length of administration of DMSO and the concentration of DMSO used. Clinically, severely affected animals have an opalescence in the center of the lens although the lens remains optically clear. The pathogenesis of the DMSO-induced lenticular change is not known. DMSO does not accumulate in the lens but following chronic administration, DMSO can be found in the cornea, aqueous humor, and vitreous body.³³ These lenticular changes, once established, persist for long periods of time.

In summary it is apparent that the toxicity of DMSO is minimal when used in clinically normal doses and concentrations. The toxic

effects are most frequently seen in abnormally high experimental doses and concentrations. In view of the toxicological evidence, certain precautions should be exercised when using DMSO, including proper and safe doses, concentrations, and routes of administration of DMSO and proper patient selection. Patients with a history of blood disorders, renal disease, seizures, pregnancy, dermal disorders, hepatic disease, pulmonary disease or ocular disease should be screened carefully, and it should be ascertained that the beneficial effects of DMSO outweigh the possible detrimental effects.

CURRENT STATUS

Since 1972 there have only been two New Drug Applications (NDA) for DMSO.⁴ In 1978 an NDA for the use of 50% DMSO intravesicularly for interstitial cystitis was approved. The NDA for the use of DMSO in the treatment of scleroderma was rejected because the data did not demonstrate conclusively the efficacy of DMSO in treating this disorder. Thus, the only FDA approved use of DMSO in humans is for treatment of interstitial cystitis. Currently, there are no NDA's pending for DMSO.

For use in veterinary medicine, DMSO is labeled for use in dogs and horses for treatment of acute swelling caused by trauma. It is recommended for topical use only. The label includes the restriction that DMSO is not to be used in horses to be slaughtered for food. Veterinarians may use DMSO for treatment of other disease processes but must inform the client that this is not an approved use of DMSO, and the individual practitioner is liable for any untoward consequences.

CONCLUSION

While DMSO is certainly not a "miracle" drug, its potential for beneficial use in the medical field is probably underrated. Due to restrictions imposed by the FDA almost twenty years ago, progress in the use of DMSO in clinical situations has been slow. Although the chemical structure of DMSO is relatively simple, it is capable of a diverse range of chemical reactions which probably attribute to its wide variety of biological actions. The ability of DMSO to penetrate most biological membranes and disperse itself widely throughout the body and its ability to transport other drugs in a similar manner cer-

tainly has important therapeutic implications. The anti-inflammatory properties of DMSO are currently the most frequently utilized clinically. The numerous biological actions of DMSO require further laboratory and clinical investigations if these properties are to be utilized to their maximum potential. The biological actions of the metabolites of DMSO also require further research to determine their specificity of action. The use of DMSO metabolites may be the answer to decreasing the adverse side effects of DMSO therapy. The toxicity of DMSO appears to be minimal, and while the FDA is concerned with the ocular effects of DMSO, the importance of this adverse side effect in domestic animals may be questionable when compared to the potential beneficial effects of DMSO treatment. It appears that DMSO has important implications in treatment of a wide range of medical disorders, but these biological effects require much more extensive investigations. Therefore, indiscriminate use of DMSO is contraindicated.

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