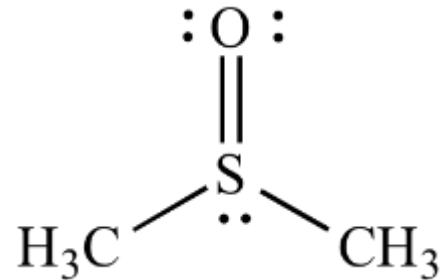




Dimethyl Sulfoxide (DMSO)

Background

Dimethyl Sulfoxide (DMSO) is a hygroscopic solvent and free radical scavenger that has multiple uses in humans and animals.ⁱ It is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. DMSO has been credited with over 30 pharmacological properties. It can be administered topically, intravenously, intra-articularly, and orally.ⁱⁱ It is most commonly used for primary reduction of inflammation and as a vehicle for percutaneous transport of other therapeutic agents into the body.ⁱⁱⁱ The only FDA-approved veterinary indication for DMSO is as a topical application to reduce acute swelling due to trauma.^{iv}



<http://web.chem.ucla.edu/~harding/IGOC/D/dms001.png>

DMSO has the unique ability to penetrate intact skin and mucous membranes without affecting their integrity. It penetrates cell membranes and micro-organisms and crosses the blood-brain barrier. This permeability allows it to be used to increase the absorption of other drugs through the skin (e.g. corticosteroids). DMSO increases the percutaneous absorption of corticosteroids at least three-fold.^v Additionally, DMSO is used for its anti-inflammatory, antibacterial, and antifungal properties. Other effects include provision of analgesia, reduction of platelet aggregation, and a mild cholinesterase-inhibiting effect.^{vi} DMSO has also been used in treating musculoskeletal conditions, neurologic diseases, colic, endotoxemia, reperfusion injury, certain reproductive issues, and most commonly open wounds.^{vii} However, many uses of DMSO lack corresponding well-controlled studies validating its efficacy.^{viii}

DMSO is commercially available as a gel and liquid formulation (Domoso™ and generics).^{ix} Both are formulated as 90% by volume and approved for external use only. Dosages range widely based upon condition, medication combination protocol, and practitioner preference.^x DMSO is absorbed rapidly after topical administration and extensively distributed throughout the body.

DMSO is a byproduct of the process of paper making. It also occurs naturally in trace levels in fresh, ocean and rainwater and may be found in feedstuffs, including lucerne (alfalfa) hay. Consequently, trace concentrations of DMSO may be present in the urine or plasma of horses not administered DMSO therapeutically.^{xi}

When administered appropriately, DMSO's toxicity in horses is low and associated with few side effects. Most commonly reported are local effects such as erythema, vesiculation, and dry skin, allergic reactions, and garlic/ oyster-smelling breath.^{xii} DMSO's potential for harm lies in its ability to potentiate the toxicity of other drugs by increasing their absorption. It should be used with caution when administering anesthetic agents and sedative drugs, heparin, insulin, aminophylline, and sulfadiazine. Additionally, two cases of fatal mercury poisoning have been reported in horses receiving topical DMSO with mercury-based blisters.^{xiii} It is important to note that rapid administration of intravenous DMSO, or administration of concentrated (inadequately diluted) DMSO has been known to cause hemolysis, hemoglobinuria, diarrhea, muscle tremors, and signs of colic.^{xiv}

DMSO Regulation

Historic Threshold

The threshold of 10 microgram/mL in plasam or serum, corresponding to a withdrawal time of 48 hours for topical use of up to two ounces, is a historic international threshold that predates the RMTC's existence.

Administration Study

Intravenous Administration Study

Following requests from practitioners for withdrawal guidelines for intravenous (IV) administration of DMSO at the existing threshold concentration, an IV administration study was performed. DMSO was administered to 30 Thoroughbred horse of racing age (mares, fillies, colts, geldings, and horses). The horses were clinical cases housed at racetracks in Kentucky, California, New York, and Florida and managed consistent with their individual trainers' feed and exercise programs.

Note: Controlled administration study design includes a washout period prior to commencing the project during which time the research horses receive no other medications, and no substances other than the one being investigated are administered during the study interval. Field studies, such as this IV DMSO administration, are conducted in a training and racing environment where other medications may be co-administered or administered at other time points during the study period. For this reason, field studies typically enroll a larger number of horses to mitigate the impact of variables than would be strictly controlled in a research facility.

In this field study, 19 of the 30 horses received additional medications, most commonly phenylbutazone and flunixin (14/19). Other horses received phenylbutazone alone (3/19) and

most were administered furosemide (11/19). Ponazuril, carbocaine, procaine penicillin G and gentamicin, dexamethasone, and methocarbamol were each administered to individual horses, alone or in combination with flunixin and/or phenylbutazone. This study did not have sufficient statistical power to determine the effect of individual medications or specific combinations of medications on DMSO elimination.

70 mL of medical grade 90% by volume DMSO was added to either 500 mL or 1.0 L of Lactated Ringers Solution (LRS) for a total of 63 grams DMSO administered as a single dose to each horse.

Blood samples were obtained via direct venipuncture immediately before dose administration and at 24, 48, and 72 hours post administration. An additional blood sample was collected at 4 hours post administration in 20 of the 30 horses.

Extraction and Analysis Procedures

Quantification of DMSO in plasma was performed at the Texas A & M Veterinary Medical Diagnostic Laboratory (College Station, TX) using validated methods^{xv}. DMSO concentrations were determined using LC-MS/MS methodology. A DMSO-d6 internal standard (Santa Cruz Biotechnology) was used to ensure accurate and reproducible quantitation.

Results

Plasma concentrations of DMSO are expressed in mean, median, and range for each time point (Table 1.0). There was a marked difference in the 48-hour sample concentration mean between the horses that received other medications during the study and those that did not. (Table 1.1)

Table 1.0 Mean (\pm S.D.), Median, and Range for Horses Sampled Prior to DMSO Administration and 4, 24, 48, and 72 hours post administration

Time	Mean (\pm SD) (mcg/mL)	Median (mcg/mL)	Range (mcg/mL)
Pre-Administration	0.36 \pm 0.36	0.31	0.02-1.43
4 Hour	175.58 \pm 38.69	181.05	81.41-219.71
24 Hour	40.63 \pm 18.88	32.42	15.58-77.40
48 Hour	0.32 \pm 0.21	0.32	0.03-1.02
72 Hour	0.36 \pm 0.28	0.32	0.03-1.06

Table 1.1 Mean (\pm S.D.), Median, and Range at 48 hours post-administration for horses receiving other medication and horses not having received other medications.

Time-48 hours	Mean (\pmSD) (mcg/mL)	Median (mcg/mL)	Range (mcg/mL)
Horses receiving other medications	0.25 (\pm 0.17) mcg/ml	0.28 mcg/ml	0.03-0.74 mcg/ml
Horses <u>not</u> receiving other medications	0.43 (\pm 0.22) mcg/ml	0.36 mcg/ml	0.09-1.02 mcg/ml

Discussion

DMSO is a naturally occurring substance in the environment and DMSO was detectable in all study samples — including those collected prior to administration. However, all pre-administration plasma DMSO concentrations were well below the 10 mcg/mL threshold, as were all of the study samples collected at 48 and 72 hours post administration. The IV administration, however, of 63 grams of DMSO in LRS **24 hours** prior to racing can be expected to result in DMSO concentrations in excess of the regulatory threshold as was observed in all samples collected at 24 hours in this study.

Scientific Advisory Committee (SAC) Recommendation

The current RMTc threshold concentration of 10 mcg/mL of plasma or serum for DMSO corresponds to withdrawal guidance of 48 hours for topical use of up to two ounces. Intravenous administration of DMSO is an extra-label use of the medication. However, due to the potential benefit of IV DMSO, the RMTc SAC determined that a field study examining compliance with a 48-hour withdrawal interval and the existing threshold concentration was warranted. Based on the findings of this study, the withdrawal guideline of 48 hours is also applicable for an intravenous administration of up to a 63 grams dose of DMSO.

A 2018 study examined IV, PO and topical doses and added further support for the 10 mcg/mL threshold with a recommended 48-hour withdrawal time.^{xvi} This study also demonstrated that exercise increased the absorption of DMSO applied topically to the distal limb. For all of the administration protocols in this study, the concentration of DMSO was below 10 mcg/mL in all plasma samples by 48 hours.

Practice Tips

Different formulations of DMSO, compounded versions, administration of higher doses, use of other injection or application sites, or combinations of DMSO with other substances represent

unknown risk for a concentration in excess of the threshold and therefore an extended withdrawal time is recommended. Veterinarians are advised to use caution when deviating from doses and routes that have been studied and to use an extended withdrawal time and/or submit a sample for analysis prior to competition.

The withdrawal guidance as it pertains to topical administration refers to a 90% by volume DMSO solution. It does not contemplate the addition of other medications to the DMSO and veterinarians are advised to consider withdrawal guidance relevant to other substances when added to DMSO.

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