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Comparative use of dimethyl sulphoxide (DMSO) in different animal species

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ABSTRACT: Dimethyl sulphoxide has a variety of biological effects that have made it the subject of numerous pharmacological studies. The first dimethyl sulphoxide therapeutic indication approved by the United States Food and Drug Administration (FDA) in 1978 was for intravesical instillation in cases of interstitial cystitis. Since then, due to its distinctive properties, it has been the subject of studies in several areas. This review describes indications, adverse effects and contraindications, as takes a critical approach to the main articles addressing the clinical use of dimethyl sulphoxide.

Keywords: dimethyl sulfoxide; indications; adverse effects; contraindications; interstitial cystitis; therapeutic properties; cryopreservation; DMSO toxicity; experimental models

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1. Introduction

Dimethyl sulfoxide (DMSO) was first synthesised in the nineteenth century by the chemist Alexander Saytzeff (Brayton 1986). In 1940, the plastics industry started using the substance as a solvent, later employed in insecticides, fungicides, herbicides, as well as in a number of industrial applications (David 1972). Since the mid-1980s, owing to its pharmacological and therapeutic properties, DMSO has been used in medicine (Brayton 1986).

DMSO is an amphipathic molecule with a highly polar domain and two apolar groups (Brayton 1986). It is organic, with a molecular weight of 78 (Ferm 1966) and displays hydrophilic and hydrophobic

characteristics. Its freezing and boiling points are 18.5 °C and 189.0 °C, respectively (Brayton 1986).

DMSO's reported biological effects include induction and alteration of inflammatory tissue responses, modulation of collagen deposition, influence on neurotransmitters and on nerve conduction, as well as alteration of fibroblast and hepatocyte proliferation and induction of cell differentiation in hepatocytes (Melchior et al. 2003) and in cultured Friend leukaemia cells, which provides a model for studying factors that regulate differentiation of neoplastic cells (Preisler et al. 1978).

In non-uremic human patients, DMSO exhibits a distribution volume of 36 l, half-life of 16 h, and clearance rate of 14.1 ml/min (Egorin et al. 1998).

It can be administered directly to the target organ or site of therapy, as well as the intravitreal cavity (Garcia-Aguirre et al. 2008), skin, ears, articulations, urethra, bladder, peritoneum, cornea, vascular system (Brayton 1986), and oral cavity (Scheinberg et al. 1984).

Assessment of DMSO concentrations in plasma and other fluids can be done through gas chromatography (Paulin et al. 1966) or high-performance liquid chromatography, which enables measurement in complex solutions and tissue cultures (Carpenter and Dawson 1991).

DMSO has therapeutic properties which are antagonistic to the inflammatory cascade (Stone 1993). It also has a myorelaxant effect (Sum and Pablo 2003), and preserves the stability of lysosomal membranes (Scheinberg et al. 1984), promotes analgesia, not only due to anti-inflammatory properties, but also to a central action similar to morphine (Brayton 1986). Some of the other described effects are histamine release causing vasodilation (Stone 1993), inhibition of P450 cytochrome biotransformation activity (Lind and Gandolfi 1997), high affinity for free radicals (Jo et al. 2004), increase of cerebral blood flow without changing blood pressure, and rapid reduction of intracranial pressure. It is a potent diuretic that does not affect cardiac rate; it blocks Na⁺ channel activation, among others (Jacob and Torre 2009). Recently it has been used as a cryopreservative for tissues (Egorin et al. 1998), cells, and enzymes (Sum and Pablo 2003).

It is noteworthy that DMSO is able to cross any barrier, such as the placental barrier (Ferm 1966), blood-brain barrier (Santos et al. 2003), or even the intact bladder wall (David 1972); therefore, extra attention is required when it is used as vehicle for other drugs.

The major route of excretion is renal; however, the pulmonary route contributes with less than 3% and causes a characteristic halitosis that resembles garlic, which is undesirable to most human patients using it (Scheinberg et al. 1984).

2. Therapeutic applications of DMSO

DMSO has been used in several therapeutic modalities of different areas of medicine and veterinary medicine, such as in the genitourinary tract (Santos et al. 2003; Senior 2006; Jacob and Torre 2009; Crivellenti 2015), dermatology (David 1972;

Gurtovenko and Anwar 2007; Notman et al. 2007; Paes and Cortes 2008; Capriotti and Capriotti 2012), oncology (Chen et al. 2003; Wang et al. 2012), and for acute injuries (Lind and Gandolfi 1997; Jo et al. 2004; Garcia-Aguirre et al. 2008), neurology (Jacob and Torre 2009), and especially as a preservative for freezing organic tissues (Egorin et al. 1998; Sum and Pablo 2003). Most reports published to date have described studies conducted in humans. In veterinary medicine, there are only few reports, and most of these are experimental in nature. The main indications of DMSO reported in the literature will be described and discussed below.

2.1. Genitourinary tract

The first therapeutic indication approved by the United States Food and Drug Administration (FDA) was in 1978 for intravesical instillation in women with interstitial cystitis (Santos et al. 2003; Jacob and Torre 2009), and even though instillation of DMSO for feline lower urinary tract disease appears to yield good results (Senior 2006; Crivellenti 2015), no controlled study has been performed in this species.

Intravesical administration of DMSO was observed to reduce inflammatory parameters of the bladder on histopathology and the expression of various inflammatory factor mRNAs in a study performed in transgenic mice with autoimmune cystitis (Kim et al. 2010). A reduction in levels of hyaluronic acid in rats with cystitis induced by protamine sulphate was also observed, which suggests a possible restoration of the damaged glycosaminoglycan layer (Kim et al. 2010).

In contrast to those positive results, there are studies with rats that show evidence of irreversible damage to the muscular layer of the bladder as well as reduced bladder contractility (Melchior et al. 2003). Another study in humans in which DMSO was instilled as a cocktail with other drugs such as hydrocortisone, heparin, sodium bicarbonate, and local anaesthetic directly into the bladder yielded no satisfactory outcome; several factors could have interfered with the results, such as drug interaction or patient comorbidity (e.g. *diabetes mellitus*, decreased oestrogen levels; Stav et al. 2012).

Therefore, further studies are necessary to evaluate the real participation and importance of DMSO for the treatment of interstitial cystitis, especially in cats, interactions between drugs administered

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concurrently with DMSO, and comparison with other types of treatment.

DMSO has also been used for experimental model treatment of ischaemic renal injuries (Garcia-Aguirre et al. 2008), and as late administration for nephrotoxic lesions in rats (Lind and Gandolfi 1997; Jo et al. 2004). However, studies conducted in dogs (Crivellenti et al. 2013) and a report in humans (Zenhausern et al. 2000) with chronic renal insufficiency demonstrated greater adverse effects, likely owing to an overload associated with the use of DMSO.

DMSO has also been used for the treatment of renal amyloidosis in humans, which resulted in increased creatinine clearance and a significant reduction in proteinuria (Ravid et al. 1982), possibly due to the capacity of DMSO to dissolve amyloid fibrils, as observed in *in vitro* and *in vivo* studies with mice. Although its efficacy has not been fully proven (Ware 2006), rats with induced glomerulonephritis exhibited decreased proteinuria after receiving low doses of DMSO, which persisted for one month after cessation of treatment (Lotan et al. 1984).

DMSO has been used in association with zinc gluconate for chemical neutering of male dogs. This combination led to a reduction in libido, sperm motility and vigour, providing permanent sterilisation. Even though the association of zinc gluconate with DMSO was important for diffusion of the product into the testicular parenchyma, no statistical differences were observed when compared to animals that received zinc gluconate alone (Soto et al. 2009).

2.2. Skin and appendages

DMSO has been used as a vehicle for drugs, especially for transdermal formulations in which concentrations above 20 mol % are capable of reducing the stiffness of the phospholipid barrier and increasing the number of water pores in the cell membrane (Gurtovenko and Anwar 2007). Lower concentrations induce the lateral expansion of membranes (Gurtovenko and Anwar 2007), and increase blood flow to the skin (David 1972). Thus, although DMSO can favour the entrance of drugs into the cell, it may also facilitate the penetrance of microorganisms through intact skin (Paes and Cortes 2008). Several dermatological case reports showing satisfactory results with the use of DMSO have been published, among them a review about the benefits of DMSO use in dermatological formulations for humans

(Capriotti and Capriotti 2012). Topical application of DMSO for ischaemic ulcers several times per day over several weeks promoted increased skin flexibility and a decrease in pain, with a consequent increased range of motion. Another study showed that DMSO cream applied during the early stages of pressure ulcers led to a decrease in pressure ulcer occurrence among high-risk patients (Lishner et al. 1985). Duimel-Peeters et al. (2003) looked at the efficacy of topical DMSO on wound healing of decubitus ulcers and its use as an anti-inflammatory drug. The effects reported were beneficial, both for wound healing and analgesia (Duimel-Peeters et al. 2003). The most frequent positive outcomes were a reduction of erythema and rapid healing of ulcers, along with decreased signs of inflammation, such as redness, pain, heat, and swelling (Duimel-Peeters et al. 2003). In veterinary medicine, topical application of dimethyl sulfoxide in dogs and equines is used to reduce acute swelling due to trauma.

Chronic use of DMSO yielded encouraging results in human patients with scleroderma, keloids, and hypertrophic scars. It has also been used to treat skin necrosis as a result of accidental extravasation of chemotherapeutic agents (e.g. mitomycin C; Capriotti and Capriotti 2012).

Despite apparent satisfactory effects, it is important to highlight that most reports are anecdotal, without controls, placebo groups, or blinded outcome assessment; results have not even been compared to other treatments. Furthermore, some studies conducted more than three decades ago reported unsatisfactory or biased results. A study on second- and third-degree burns in laboratory rats reported no statistically significant difference between the effectiveness of 1% silver sulfadiazine in DMSO and 1% silver sulfadiazine in a hydrophilic base (Silvadene) when used topically as an antimicrobial agent on infected thermal burn wounds (Raskin et al. 1983). According to Sehtman (1975), DMSO probably does not possess any intrinsic healing properties for the majority of dermatological complaints; however, it acts as a vehicle for the transfer of drugs through intact skin.

2.3. Oncology

Cisplatin is a chemotherapeutic drug routinely used in veterinary oncology, and it has been used in association with DMSO to mitigate nephrotox-

icity. A reduction of hypoxia/reperfusion and in the formation of free radicals has been postulated (Baliga et al. 1998). A more recent study in humans showed that cisplatin combined with DMSO stimulates human liver DnaJ-like protein (HLJ1), which inhibits the proliferation of lung cancer cells such as adenocarcinoma (Wang et al. 2012). In that same study, DMSO at concentrations of 1–2% was compared to ethanol at 0.1–5%; the most effective dose for the upregulation of HLJ1 protein was found to be 2% (Wang et al. 2012).

DMSO has also been added to the chemotherapeutic drug paclitaxel in its formulation with Cremophor for the treatment of bladder tumours in order to prove that DMSO could reverse the undesirable entrapment of paclitaxel in cremophor micelles, reducing its free fraction (Chen et al. 2003). The rearrangement of Cremophor micelles and reversal of the entrapment of paclitaxel enhanced urine production rate and drug removal by perfusing capillaries, with an overall effect of increasing the bladder tissue delivery of paclitaxel formulated with Cremophor (Chen et al. 2003). Besides helping with the absorption of the product by the urothelium of the bladder, DMSO/paclitaxel/Cremophor also increased diuresis when compared to paclitaxel/water and paclitaxel/DMSO in rats (Chen et al. 2003). Although this experiment was performed in dogs as an experimental model, these dogs did not have bladder tumours; despite the potentially promising effects of the combination mentioned above, its satisfactory action on bladder cancer itself has not been investigated.

2.4. Cardiovascular system

DMSO has been used for the treatment of experimental cardiac ischaemic insults (Garcia-Aguirre et al. 2008) with promising results in disorders affecting both heart and brain, coronary thrombosis, myocardial infarction, central nervous system injury, cranial trauma, brain ischaemia, spinal cord injury, as well as memory dysfunction in humans, stroke (Jacob and Torre 2009) and immunologically mediated disorders, such as experimental myasthenia gravis (Lotan et al. 1984).

However, there are also studies showing deleterious effects, often antagonistic to those described above. Besides triggering apoptosis in lymphoid tissue *in vitro* and *in vivo*, a report has shown that

DMSO promotes apoptosis in the central nervous system, suggesting that DMSO-induced apoptosis might cause significant learning and memory deficits (Hanslick et al. 2009).

3. Adverse effects and contraindications

It should be taken into account that, as well as facilitating the absorption of other drugs, DMSO can also potentiate the effects of other agents (Paes and Cortes 2008). Therefore, drug interactions should always be evaluated prior to administration, particularly in view of the fact that medications that are unabsorbed or administered into sites of low absorption (e.g., bladder) may reach toxic levels and increase the risk to patients' lives. Patients medicated with high doses of some drugs, such as general anaesthetics, caustic revulsives (Brayton 1986), or anticholinesterase drugs (Stone 1993), on occasion experience undesirable effects. The literature reports nausea, vomiting, diarrhoea, severe haemolysis which can be compared to haemolytic reaction to blood transfusion, anaphylactic reactions such as rashes, redness, and in rare cases bronchospasm, kidney insufficiency, systolic and diastolic hypertension, bradycardia and pulmonary oedema or cardiac arrest (Brayton 1986; Stone 1993; Benekli et al. 2000; Zenhausern et al. 2000; Crivellenti et al. 2013).

Chronic oral administration of DMSO in dogs has been associated with unusual lens changes with unexplained pathogenesis. The lens alteration was characterised by a reduction in the refractive index of newly synthesised lens (Davidson and Nelms 2013).

Structural alterations of the blood-brain barrier have also been linked to the use of DMSO. Chaloupka et al. (1994) described the occurrence of subarachnoid haemorrhaging, severe vascular spasms, stroke, and death of swine that received a fast injection (≤ 15 s) of DMSO through the internal carotid artery. It is believed, however, that such effects were due to the speed of infusion, since a recent study showed that at slow administration (> 30 s), via the carotid artery, DMSO did not elicit angiotoxicity or neurotoxicity (Bakar et al. 2012). It has also been suggested that DMSO does not alter the blood-brain barrier's permeability when slowly infused via the intra-arterial route, since it is rapidly dissolved in the water content of the blood and taken away from the neural tissue by arterial circulation (Bakar et al. 2012). Further studies are

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necessary to better understand the consequences of different routes and speeds of infusion of DMSO.

Although intravascular administration of 0.1–4 g/kg of DMSO at 10% concentration is considered to be safe for dogs (Stone 1993), chronic use at high doses resulted in alterations of the transparency of the eye lens in dogs and rabbits (Brayton 1986; Davidson and Nelms 2013), even when administered through the transdermal route (Wood et al. 1971). Intravascular administration of formulations containing concentrations above 20% results in high risk of haemolysis (Stone 1993) and haemoglobinuria (Jacob and Torre 2009). Microscopic haematuria has been reported as an important alteration in humans receiving DMSO combined with other drugs through the intravesical route (Hung et al. 2012), which might be related to findings such as tissue degradation, lack of epithelial lining, changes in the colour of the muscular layer, smooth muscle cell vacuolisation, as well as a decrease in bladder contractility in rats (Melchior et al. 2003).

Young animals have also been the subject of DMSO research. Rats exhibited changes in weight gain and increased mortality (Lotan et al. 1984); in rabbits, animals that received low doses exhibited increased glomerular filtration rates and, at high doses, reduced kidney blood flow and urinary volume (Rijtema et al. 1999). This could potentially be explained by prostaglandin inhibition, which is important for modulation of renal vasodilation.

DMSO can still, in some cases, cause mast cell degranulation and consequent histamine release (Zenhausern et al. 2000). Following this line of reasoning, it is contraindicated in cases of mastocytoma.

The use of DMSO is contraindicated in pregnant animals, since it is capable of crossing the placental barrier and causing damage to the foetus, especially during foetus formation (Ferm 1966).

A recent study which evaluated renal function in dogs with chronic kidney disease receiving DMSO showed that the most severe adverse effects were mainly observed in stage IV of the disease, which is a contraindication factor for the use of the drug (Crivellenti et al. 2013).

4. Final considerations

Most studies on the effects of DMSO reviewed here were performed in experimental models and were focused on particular organs. Thus, to this

day we lack a complete picture of the effects of this drug and there remains considerable uncertainty about the use of DMSO. In veterinary medicine, it has often been used indiscriminately and without basis on previous scientific studies, which can result in drug interactions, higher toxicity, and adverse effects. Although it has been widely used as a cryopreservative agent, its real participation in adverse effects is unclear and should encourage future research, especially since cell and tissue transplantation are rapidly developing fields in veterinary medicine.

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