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DMSO: an aid to combat pain and pruritus

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Abstract

Dimethyl sulfoxide (DMSO) is a highly reactive by-product of paper production in the form of an odorless, colorless liquid that has been studied since the 1860s. Initially it was utilized as a solvent, but more recently it is being investigated for therapeutic applications. Owing to its versatility, the use of DMSO has been proposed in many different medical fields for a variety of applications, with possibly the widest use being in the field of dermatology.

Keywords: chronic pain; dimethyl sulfoxide; DMSO; pharmacology; pruritus

Introduction

The clinical interest in the use of DMSO for dermatology conditions stems from this solution's efficacy as a vehicle to deliver pharmacological agents across the stratum corneum and its ability to penetrate biological membranes. Currently there is only one FDA approval for the use of DMSO, and it is not in the dermatologic field but rather for interstitial cystitis. Outside of the FDA scope of usage, DMSO is used frequently to treat osteoarthritis in humans and animals, as well as other chronic pain conditions. This suggests the possible utility of DMSO being applicable to other inflammatory conditions such as pruritus. Further research is necessary to explore the promising utilization opportunities of DMSO in dermatology.

Chronic pain and pruritus are two of the most common dermatologic complaints that effect

millions of American every year and often require chronic management because of their longitudinal life-altering nature [1]. The long-term management of conditions like chronic pain and pruritus has sparked expansive research into unique and non-conventional approaches to dermatologic treatment. Dimethyl sulfoxide or DMSO is a highly reactive by-product of paper production in the form of an odorless, colorless liquid. It is formed by converting sulfoxides to less toxic intermediates [2]. This solution has been studied since the 1860s, first as a chemical solvent and more recently for therapeutic applications [1]. DMSO is an easily accessible over-the-counter medication attainable from numerous suppliers such as Walmart, Kroger, and Amazon. It is often labeled as a topical gel and comes in a variety of concentrations ranging from 70-99% with personal selection depending on patient and prescribing physician preference. Dermatologists, in particular, have utilized this compound for a variety of reasons, with the two most prominent functions being its ability to deeply penetrate the skin and its anti-inflammatory properties [2]. Although there are many FDA approved DMSO uses for animals, alone and in combination with other drugs, the FDA has only approved the use of DMSO in humans for one condition, interstitial cystitis [2,3]. Although not supported by the FDA for human uses other than interstitial cystitis, DMSO is an over-the-counter topical product that provides an interesting new approach to the treatment of common chronic dermatologic conditions such as pain and pruritus.

Pharmacologic properties of DMSO

Dimethyl sulfoxide is a polar but non-hydrogen binding solvent that is readily miscible with water and is able to dissolve both polar and non-polar moieties [2,4]. These properties allow DMSO to be an efficient solvent/vehicle for the delivery of pharmacological agents, especially across the relatively lipophilic stratum corneum. Multiple mechanisms of transport contribute to the success of DMSO. Primary among these is the ability of DMSO to penetrate biological membranes [5,6]. He et al. studied the mechanism of biological membrane penetration and found that DMSO forms non-selective transient water pores in the membrane [6]. This allows DMSO, as well as any solute it is carrying, to easily cross cell membranes. It also enhances deposit formation in the subcutaneous tissue and transport of the solute it carries into blood vessels [7]. An additional mechanism proposed for DMSO's ability to effect substantial epidermal penetration is that as a non-protogenic entity it is able to enhance diffusion into cells, thereby increasing the concentration of the therapeutic solute to exert more potent effects [2,8].

Despite DMSO's advantageous uses, many studies have found contradicting evidence of adverse effects related to DMSO's ease of penetration through membranes. The side effects that have been noted are based on the mode of application, with dermal use causing a rash, pruritis, blisters, erythema, tingling, burning, and mild scaling [2,3,9]. Many studies have also found the non-appealing side effect of garlic-like breath odor with dermal application owing to its sulfoxide component [2,9–11]. More specifically, Olver *et al.* found that blisters occurred on the application site in 20% of the patients and 30% of the patients experienced the characteristic breath odor [9]. Swanson found adverse effects to be tolerable and very common and also acknowledged the relationship between the concentration of DMSO and the risk of experiencing adverse effects, which could be mitigated through diluting the solution [3]. In contrast, a study performed by Duimel-Peeters *et al.* reported that when the concentration of DMSO was below 50%, there were almost no adverse effects reported by the

patients [12]. One argument worthy of consideration is the potential variation in effects depending on the way DMSO is applied to the dermal surface, such as by topical or aerosolized spray.

Application to treat pain

Dimethyl sulfoxide has been studied most prominently as a treatment for pain. More specifically, DMSO has been found to be very helpful with the treatment of certain chronic pain conditions, such as osteoarthritis, scleroderma, and reflex sympathetic dystrophy (RSD). With chronic pain being such a prominent problem affecting 116 million Americans, many treatment modalities are being investigated in order to circumvent a need for oral opioid medications [1,13]. Numerous studies have found that DMSO provides a significant analgesic effect that may be promising for pain management in several chronic conditions [11,12,14].

The most widely discussed amongst human and animal patient uses of DMSO is in the treatment of osteoarthritis. Dimethyl sulfoxide is an easily accessible solution that can be purchased in a store over-the-counter or via the internet. When applied to the skin in a topical manner, DMSO has been found to provide rapid and short-lived pain relief for arthritis and connective tissue injuries [3]. There are two possible targets to this joint analgesia that have been proposed. One target ascribed to DMSO is its activity as an anti-inflammatory agent [12,15,16]. In a large meta-analysis performed by Duimel-Peeters *et al.*, DMSO was found to produce a trend showing a reduction in erythema, the healing of ulcers, and a positive effect on the classic signs of inflammation (calor, dolor, rubor, tumor) [12]. This anti-inflammatory activity appears to be mediated through DMSO's significant reduction of pro-inflammatory cytokines and prostaglandin E2 release into joints [17]. Although that may be the main anti-inflammatory activity, DMSO has also been speculated to reduce inflammation through several other mechanisms. These include ability of DMSO as an antioxidant to scavenge free radicals and stabilize damaged membranes to prevent the slow leakage from injured cells. Suppression of cytokine production in signaling pathways through its actions

on c-Jun N-terminal kinase (JNK) and Akt phosphorylation has been noted [17].

Dimethyl sulfoxide has also been shown to be utilized with other drugs to expand upon the anti-inflammatory nature of the liquid. Though not approved in the United States, Pennsaid is a combination drug of diclofenac solution and DMSO. The excellent penetration promotion of DMSO distributes the diclofenac anti-inflammatory solution deeper into the pain-provoking areas of an osteoarthritic joint and provides pain relief through decreased inflammation [18–21]. This combination medication is currently approved in Canada and some European countries. Topical application has been found to enhance patient compliance and serve as a viable option for long-term treatment of chronic conditions [22]. Additionally, this approach for osteoarthritis treatment entails less systemic absorption of non-steroidal anti-inflammatory drugs that are often associated with numerous side effects, especially with chronic use.

The second mechanism, which was proposed by Evans, Reid, and Sharp, is that DMSO may have some C nerve fiber blocking ability [23]. Pain has been found to be transmitted through unmyelinated, slow conducting C nerve fibers [1,24]. These nerves provide a vulnerable target for inhibiting pain transmission before it reaches the central nervous system. In Evans et al.'s study, the researchers utilized feline sural nerves to observe the nerve conduction properties while being treated with DMSO. They found that the blockade of conduction through the C-type nerve fibers was accomplished with 9% DMSO [23]. They also found that lower concentrations could slow the transduction of the nerve and not completely block the signal [23]. Though more research must be conducted on humans using this approach, these results present a viable clue that may explain the promising potential for DMSO in the treatment of chronic osteoarthritis.

Other than the prominent example of osteoarthritis, DMSO has been studied in some other chronic pain conditions for its utility. Dimethyl sulfoxide was found to not have any noteworthy effect on the clinical aspects of scleroderma. However, it was

found to relieve pain through its local analgesic mechanism [14]. Another chronic pain condition, RSD, was found to be effectively treated with DMSO. In a study by Geertzen et al., DMSO was utilized as a hydroxyl radical scavenger to combat the chronic pain (burning) sensation associated with RSD and was found to cause a statistically significant improvement [11]. Lastly, there was a study performed by Rosenbaum et al. that utilized DMSO for unyielding pain in an eclectic group of surgical patients being treated for postpartum phantom limb, trigeminal neuralgia, posttraumatic pain, and postoperative pain [25]. This study found that 32 out of 37 patients experienced note-worthy pain relief with no reported toxicity [25]. Overall, DMSO has been shown to provide countless avenues to treating chronic pain conditions, especially osteoarthritis. Though there has been some research proposed on the acceptable therapeutic doses and concentrations of DMSO for specific treatments of pain, there still needs to be additional clinical trials to study safe and effective concentrations for specific modalities of treatment.

Application to treat pruritus

Similar to DMSO's use for treatment of acute and chronic pain, DMSO may also be useful in the treatment of disorders that have the common presenting symptom of pruritus. Similar to pain, pruritus is carried on the same unmyelinated C nerve fibers [1,24]. Also, along similar lines as pain, pruritus has become a chronic condition that may be debilitating to patients through its impact on the quality of life and the difficulty of long-term management. The literature, however, appears relatively devoid of studies regarding the use of DMSO in the treatment of pruritus even though there is a common neuronal path. However, there are many studies utilizing DMSO as a penetrating agent in conjunction with other drugs for the treatment of pruritus-invoking disorders.

Many chronic disorders exhibit pruritus as a predominant complaint. One of the most prominent examples of this is atopic dermatitis (AD). The standard of treatment for mild/moderate AD is a combination of emollients to keep the skin moisturized and corticosteroids to decrease the

inflammation and associated pruritus. One proposed mechanism of utilizing DMSO for AD is as a vehicle for more effective corticosteroid penetration into the epidermis and formation of deposits in the subcutaneous tissue [7]. Although this seems like a promising possible use for DMSO, current research has only shown negative effects of DMSO in atopic patients. A study performed by Gyeong et al. found that the irritated skin of an atopic dermatitis patient was much more susceptible to DMSO irritation than the non-atopic skin of an AD patient or the control group [26]. This could pose a problem with utilizing DMSO as a vehicle to provide increased corticosteroid penetration on previously irritated skin. The efficacy of corticosteroids applied concomitantly with DMSO for pruritus prevention in atopic dermatitis patients does warrant further research.

The second prominent example of using DMSO to treat pruritus is when combating macular and papular amyloidosis. Macular (MA) and papular (PA) amyloidosis are characterized by therapy-resistant pruritus and a vicious cycle of the pruritus causing itching which exacerbates more amyloid deposition [27]. In a study performed by Özkaya-Bayazit et al., the use of DMSO daily provided significant relief for MA and PA patients; pruritus resolved in an average of 4.1 weeks [27]. The decrease in pruritus allowed the papules to heal and decreased the pigmentation in a large subset of individuals. There were some reservations with the use of DMSO in this study pertaining to the concentrations of the solution. The 50% and 100% DMSO solution did cause a significant number of transient local side effects such as contact urticaria, a burning sensation, and desquamation at the application site, but did not show any systemic adverse effects [27]. Another study of the use of DMSO to treat MA also found that DMSO decreased the pigmentation and significantly decreased the pruritus, even by the first follow up appointment [28]. Further studies need to be pursued using varying concentrations of DMSO to weigh the risks of local and possible systemic adverse effects versus the benefit of pruritus and pigment relief. Although pruritus is transmitted along the same unmyelinated C nerve fibers as pain, there needs to be further research conducted to target these fibers in

chronically pruritic skin regions in a similar manner to how DMSO is used to target localized pain in joints.

Conclusion

Dimethyl sulfoxide has shown to be a liquid with countless numbers of applications in the chemical, pharmaceutical, and medical fields. Its unique properties have allowed it to be utilized in many different ways, with its topical uses becoming prominent in the dermatologic community. In particular, anti-inflammatory agents such as DMSO and corticosteroids have numerous uses in dermatology. One can find sources suggesting the use of DMSO in managing burns, wounds, eczema, psoriasis, herpes, pain, pruritus, acne, morphea, and scleroderma. Also, DMSO's antioxidant capabilities have made the chemical interesting to consider for photoaging. It has been reported to rejuvenate skin, reduce wrinkling, help the skin to appear more even, and slow signs of skin aging. In truth, DMSO may ultimately provide benefit for many skin diseases, but it needs more in-depth exploration.

Although DMSO is studied for many unique conditions, the FDA has still not approved its use for more than interstitial cystitis treatment in humans. This highlights the need for physicians to educate their patients on potential benefits and adverse effects of over-the-counter topical DMSO use. Necessary education helps to maximize the benefit to the patient, as well as limit potential side effects. The extensive research conducted on this liquid has shown that it may have promising potential in the treatment of numerous conditions, especially chronic pain such as osteoarthritis. It has also provided a safe alternative to oral non-steroidal anti-inflammatory drugs and the long-lasting effects those can have on the body during long-term treatments of chronic disorders. The aspect of research that is glaringly lacking is the ability of DMSO to treat pruritus, a sensation carried on the same nerve fibers as pain.

Potential conflicts of interest

The authors declare no conflicts of interest.

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