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MODERN ASPECTS OF THE USE OF DIMETHYL SULFOXIDE (DMSO)

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Abstract

The invention of new drugs is quite labor-intensive and expensive process in our time, so the use of already known drugs for new indications is extremely important in modern science. Literature analysis of studies of dimethyl sulfoxide (DMSO) helps to find options for expanding the capabilities of this drug. DMSO is a drug with more than a century of history and during this time it has proven itself as a safe drug. The experience of using dimethyl sulfoxide (DMSO) described by scientists in their studies has shown that this drug can be used as a single drug and in combination with other drugs. Studies in dermatology, oncology, dentistry, surgery, traumatology, urology are unique and prove that different properties of DMSO can be used in different ways in the treatment of a wide range of diseases. The results of various studies prove once again that dimethyl sulfoxide is a promising drug, but requires research into new uses.

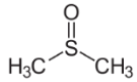
Key words: *dimethyl sulfoxide (DMSO), application, properties, safety, research, solvent, analgesic*

Introduction

Dimethyl sulfoxide (DMSO) is a substance with a long pharmaceutical history. DMSO was first discussed in the second half of the 19th century, at which time in 1866 the Russian chemist OM Zaitsev oxidized nitric sulfide of nitric acid and obtained the substance dimethyl sulfoxide. In the following years after the invention the chemists of that time positioned DMSO as a product of wood processing in the paper industry, therefore dimethyl sulfoxide did not represent great relevance. Actively DMSO began to be used in hospitals of the Russian army for treatment of wounds, injuries, fractures during the First World War. The Soviet Union in 1960 established industrial production of this drug. Having extensive experience in the use of DMSO in medicine, the Soviet Union in 1960 established industrial production of this drug.

In Europe and the United States until 1963, dimethyl sulfoxide was used in industry as a solvent, in medicine it was used only as a cryoconservative for tissues. In 1963, the US Food and Drug Administration (FDA) approved the first DMSO clinical trial, but in 1965, due to side effects in experimental animals (these studies were later refuted), all clinical trials were prohibited. In 1966, the FDA allowed the study of dimethyl sulfoxide in the treatment of rheumatoid arthritis, scleroderma, shingles. Later, in 1972, the US National Academy of Sciences analyzed all research data and information on DMSO. Thus, in 1978, the FDA allowed Rimso to produce the first commercial DMSO drug, and since 1980, the FDA no longer controls the study of dimethyl sulfoxide [1, 2 ,3].

Physico-chemical properties. Dimethyl sulfoxide (CH3) 3SO4 is a dipolar organic compound with a molecular weight of 78.13. The drug is a clear, hygroscopic, non-volatile liquid with a slightly bitter taste and sulfur-like odor. DMSO is quite easily mixed with H2O in any proportions, and therefore acts as an acceptor of



hydrogen bonds, it makes it possible to form complexes with many bonds such as: metal cations, drugs, blood components, plasma, cerebrospinal fluid, tissues. The drug can act as an oxidant and as a reducing agent [4, 5, 6].

New opportunities of DMSO. The first feature is the ability to dissolve a variety of origins and chemical structure of substances (vitamins, antibiotics, hormones, salts, cytostatics, alkaloids) [7]. DMSO is an important bipolar aprotonic solvent, it is less toxic than others of this group, such as dimethylformamide, dimethylacetamide. Due to its strong solubility, it is used as a solvent in chemical reactions involving inorganic salts, in particular in nucleophilic substitution reactions. The acidic properties of DMSO are weak, so it has become an important solvent in the chemistry of carbon anions [8, 9].

The second property for which dimethyl sulfocide is popular is transport. Delivery of any active substance from the surface to the deeper layers of the skin is regulated by the barrier function of the stratum corneum. There are four basic principles that affect the penetration of solute through any membrane:

1) the thickness of the membrane barrier,

2) the partition coefficient between the membrane and the carrier,

3) the concentration of the agent in the carrier,

4) diffusion coefficient across the membrane.

Penetrating agents are designed to affect one or more of these principles without causing permanent structural or chemical modification of the physiological barrier. Changing the thickness of the membrane is less practical for drug delivery (it is difficult to imagine non-toxic agents that could stop or reduce the thickness of the stratum corneum), so most penetration agents, including DMSO, try to stop or change principles 1-3 [10]. There is evidence that DMSO can increase diffusion through the stratum corneum by disrupting barrier function. This is likely due to aprotonic interactions with intercellular lipids and may also include a reversible change in major lipid groups that create a more permeable structure. DMSO can also play a role in the separation, forming a microenvironment of the solvent inside the tissue, which can effectively extract solutes from the carrier. Finally, DMSO can have a strong solubilizing effect on less soluble agents in various carriers, increasing penetration simply by delivering a higher concentration to the membrane barrier [11].

The third important effect is anti-inflammatory. DMSO exhibits anti-inflammatory properties by

reducing the activation of the universal transcription factor NF-κB, which controls the expression of immune response genes and apoptosis in combination with decreased secretion and expression of mRNA of proinflammatory mediators such as IL-1 [12]. The anti-inflammatory effect of dimethyl sulfocide is realized by inhibiting the activation of NLRP3-inflamosome and the expression of pro-inflammatory cytokines (interleukins 1, 6, 8, 12, TNF-α) [13, 14].

The analgesic effect is the fourth unique property of dimethyl sulfoxide. The substance reduces the speed of impulses through the nerves (blockade) and causes analgesia, affecting both the peripheral and central nervous systems. Opiate receptors are not involved in analgesia [15, 16].

It should be noted about the antibacterial properties of dimethyl sulfocide. In their work, P.A. Khernov and T.V. Chestnova studied the effect of different concentrations of DMSO on the virulence and adhesive properties of staphylococci. The results showed that higher concentrations of the drug have a more pronounced bacteriostatic effect. Such findings make it possible to use dimethyl sulfocide as an independent drug for the treatment of bacterial inflammation [17].

The sixth unique opportunity of DMSO is to improve the local blood supply to ischemic tissues. Such conclusions were reached by American surgeons in 1996 after observing patients who underwent radical mastectomy. A skin and muscle flap was used to reconstruct the breast, which was treated daily with a solution of dimethyl sulfocide for 10 days after surgery. L. RandLuby and co-authors found that in the group of patients treated with DMSO, ischemia and weak vascularization were less common than in patients who were not treated with DMSO ($p = 0.01$) [18].

In the literature there is information about immunosuppressive [19], antioxidant, antiexudative [20] and other properties of dimethyl sulfocide. Some of these properties have been identified in isolated studies, some have been observed more systematically [21, 22, 23].

Safety of use. Extensive data on the toxicity and side effects of dimethyl sulfoxide have been obtained from the FDASA High Volume Program [24]. It should be noted that for almost 50 years of production, no genotoxicity was recorded in workers, and genotoxicity was not detected after taking DMSO [25]. The drug did not show carcinogenic and mutagenic properties, so it is widely used as a solvent in mutagenicity tests [26]. The lack of embryotoxicity allows the drug to be used as a cryopreservative for sperm [27]. Transdermal administration has been shown to be mildly toxic, which may lead to local reactions such as itching, redness, burning, contact dermatitis, and dry skin. These reactions are usually minor and do not require discontinuation of the drug and additional treatment [28, 29].

Studies of the local effect of the drug on the eyes did not reveal signs of toxicity [30]. In the body, dimethyl sulfoxide is metabolized to dimethyl sulfone and dimethyl sulfide, which is excreted by the lungs, this process gives the breath the smell of garlic, with no other side effects [31, 32].

Application in dentistry. Inflammatory diseases of the oral tissues and destructive changes in the tissues of the prosthetic bed adversely affect the body as a whole, low oral hygiene leads to activation of pathogenic microflora of the oral cavity and increase its pathological effect on the severity and course of inflammation [oral tissues 33 34]. A study by Ignatiadi O.N. and co-authors showed that a 1% suspension of ibuprofen dissolved in a 10% solution of dimexid was highly effective in patients with generalized paradontitis complicated by abscess. As a result of treatment, the gums acquired a normal configuration, consistency and color; the gingival margin became tighter to the teeth, the resistance of the capillaries of the gums increased. [35].

Application in oncology. Christensen and co-authors studied the effectiveness of photodynamic therapy of 5-aminolevulinic acid (5-ALA), dimethyl sulfoxide and scraping in 60 patients with basal cell carcinoma. After 72 months of follow-up, 81% of patients noted a remission of the disease (confirmed histologically) with favorable cosmetic results. An additional similar study evaluated long-term follow-up of 19 cases of Bowen's disease and 15 cases of basal cell carcinoma using 5-ALA in combination with DMSO and ethylenediaminetetriacetic acid under a single exposure to a diode laser with a wavelength of 630 nm at different doses of energies. After 60 months, 57.7% of cases of Bowen's disease and 63.3% of basal

cell carcinoma remained histologically clear. DMSO with its unique solubility is used to transfer 5-ALA further into the dermis in the hope of effectively treating non-melanoma skin cancer with less invasive agents [36].

In surgery. Wound healing is another potential area for the use of DMSO. The use of DMSO cream in the early stages of bedsores leads to a decrease in the incidence of bedsores in high-risk patients [37]. A systematic review by Duimel-Peeters examined the effectiveness of topical DMSO in the healing of bedsores and its use as an anti-inflammatory agent [38]. The effects of its use were beneficial for both wound healing and analgesia. The most common indicators of the result were a reduction in erythema and rapid healing of ulcers, as well as a reduction in signs of inflammation. DMSO has also been found to be extremely effective in the treatment of severe skin necrosis caused by accidental extravasation of the antitumor drug mitomycin C during intravenous administration [39].

In virology. DMSO has also been shown to have some antiviral effects. A study of the effects of DMSO on several parameters of herpes simplex virus (HSV) replication revealed some unexpected results. DMSO reduces virion infectivity, inhibits viral deoxyribonucleic acid (DNA) replication, and reduces transcriptional levels of many HSV-1 genes. These data suggest that DMSO itself may play a role in antiherpetic activity, which differs from previous notions that it acts only as a penetrant for antiviral drugs [40]. Given the data, you can think about the use of the drug both alone and in combination with other drugs for the treatment of COVID-19.

In dermatovenereology. The most defining role of DMSO in dermatology is its ability to act as a means of improving percutaneous penetration when used in combination with other substances. DMSO promotes diffusion through the stratum corneum, causes the formation of deposits in the dermis and promotes transfer to local blood vessels, as evidenced by increased penetration of 5-fluorouracil (5-FU) in the treatment of superficial tumors and warts.

Topical application of DMSO with 5-FU showed excellent absorption compared to DMSO alone or only with 5-FU in cream bases. Patients with scleroderma have also reported increased skin flexibility and reduced pain, leading to a greater range of motion. Keloids and hypertrophic scars began to decrease after several months of use, which indicates clinical efficacy in diseases affecting the dermis. [41, 42, 43].

Use in the treatment of musculoskeletal system. The most popular form of using DMSO in the treatment of diseases of the musculoskeletal system are gels based on dimexid sulfide. Such drugs are used to relieve pain in the treatment of rheumatoid arthritis, ankylosing spondylitis, deforming osteoarthritis, arthropathy, radiculitis, for the treatment of bruises, ligament damage, traumatic infiltrates [44]. Thus, the advantages for the patient when using such gels are the increase of anti-inflammatory and analgesic effect due to synergism and acceleration of the result due to the "conductor function". DMSO reduces the speed of impulses through the nerves (blockade) and causes analgesia, affecting both the peripheral and central nervous systems. Opiate receptors do not participate in analgesia caused by DMSO [45, 46].

The double-blind placebo-controlled randomized study, described in Eberhardt et al., involved 112 patients with acute knee arthritis and divided into two equal groups (50% received 25% DMSO gel for 3 weeks; 50% placebo). All efficacy criteria in the DMSO group were significantly better than in placebo. Statistically and clinically significant reduction of pain during exercise, at rest, on palpation compared with placebo, no serious side effects were observed [47].

In a study of the effectiveness of a solution of diclofenac in the carrier DMSO (TDiclo), used topically to relieve the symptoms of osteoarthritis of the knee. The results of this combination were better than in the comparison groups on three main indicators of effectiveness: pain reduction, recovery of function and general health of the patient [48]. This is due to the increased absorption of diclofenac through human skin after repeated application in the form of DMSO, as described in the publication Hewitt et al. [49].

In the studies of E.S. Rogozhin and I.V. Boynova when using a gel based on DMSO was shown pronounced analgesic and anti-inflammatory effects, significantly different from placebo in patients with dorsalgia. The drug reduced the incidence of pain, relieved muscle spasm, which was

accompanied by improved quality of life - reducing disorders of daily functioning [50, 51].

Application in urology. Dimethyl sulfoxide has been used effectively for over 40 years in the treatment of inflammatory diseases of the bladder, which are not amenable to standard conservative therapy. With its properties, DMSO is able to relax the detrusor muscles, reduce inflammation, cause local analgesic and bacteriostatic effects, as well as increase the permeability of the urothelium, which contributes to the deeper layers of other drugs that were introduced during intravesical instillation [52, 53, 54].

The Perez-Marrero study in the distant 80's consisted of instilling 50 ml of 50% DMSO solution with bladder exposure for 15 minutes and an interval of 14 days. One month after treatment, 93% of patients in the main group reported a significant reduction in cystitis symptoms, while in the placebo group, only 35% reported improvement [55].

In another study, Peeker R. and co-authors treating patients with interstitial cystitis compared intravesical BCG instillations and DMSO intravesical instillations. Each patient underwent 1 instillation per week for 6 weeks. As a result, 47% administered dimethyl sulfoxide showed improvement, whereas in the BCG instillation group, none of the patients showed improvement [56].

In the clinical recommendations of the American Urological Association (AUA), dimethyl sulfoxide is indicated as a drug for the treatment of interstitial cystitis, cystalgic pain [57]. There are no such data in the clinical recommendations of the European Association of Urologists yet.

Prof. Shulyak in his study, which consisted of adding DMSO to chemotherapy to perform intravesical instillation in bladder cancer, proved that the effectiveness of adjuvant intravesical chemotherapy in combination with DMSO is better. In the group where dimethyl sulfoxide was added to the chemotherapeutic agent, recurrence was observed in 14.3%, in the group where only the chemotherapeutic agent was used, recurrence was observed in 22.5%, and in the group where no treatment was performed, recurrence was recorded in 52.8% of patients [58, 59].

Conclusions

Dimethyl sulfoxide is a drug with a long and multifaceted history. Throughout its use in industry and medicine, it has proven itself positively, but there are still issues that remain open and require further research. In modern medicine, it plays an important role, it can be used as a single drug, and in combination with many other drugs, the effect of which it can enhance, creating the conditions for their effectiveness. Taken into account the effects of DMSO such as the smell of garlic when breathing, local reaction - this drug is quite safe to use, and its versatility and ease of use makes it possible to treat many diseases. In the future, we would like to demonstrate its wider capabilities, which will be demonstrated in our research.

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