Preliminary Communication

Dimethyl Sulfoxide in Musculoskeletal Disorders

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Recent discovery that dimethyl sulfoxide (DMSO), a versatile commercial solvent, possesses unique medicinal properties opens up a new and rewarding field of pharmacotherapeutics. Dimethyl sulfoxide was first synthesized in 1867. Today, it is available in crude form as a by-product of the paper pulp industry, and during the past five years it has found extensive use as an industrial solvent. Its value in protecting biologic specimens against freezing damage is well known.

Several years ago one of the authors (S.J.) of this paper consulted another (R.H.) relative to obtaining dimethyl sulfoxide for protecting surgically removed kidneys and hearts against freezing damage prior to transplantation. On this occasion one author mentioned that he had observed that DMSO enhanced the penetration of dyes into human skin and possessed the property of rapid absorption through the bark or roots of trees and plants. It had been noted that DMSO enhanced the penetration of antibiotics and fungicidal agents into the circulatory system of the plant or tree, resulting in better growth with a decrease in fungus or blight infestation. The suggestion was advanced that topical application in humans might improve skin penetration of various medicinal agents.

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On the basis of these suggestive findings, it was decided to undertake an experiment employing DMSO as a vehicle to aid penetration of antibiotics into burn eschars in rats to reduce infection and allow healing. In the initial study, DMSO alone was used. Not only did it prolong animal survival following third degree burns, but it appeared also to enhance healing. Following this it was observed that application of dimethyl sulfoxide to a chemical burn in a patient relieved pain and promoted rapid healing of the injured tissue. Similarly, it was noted that the topical application of 100% DMSO for treating laboratory personnel who had complaints such as ecchymoses, bruises, muscle strains, and ligamentous sprains resulted in prompt pain relief, reduced the swelling, and appeared to hasten recovery.

The significance of these empirical observations was obvious: DMSO was rapidly absorbed through the intact skin, possessed local analgesic activity, lessened swelling, and appeared to promote healing of injured tissue. Laboratory and clinical studies were then undertaken to further explore these and other possible therapeutic uses.[1,2] Several of the primary pharmacological properties of dimethyl sulfoxide were delineated in the laboratory and the effects of DMSO on the permeability of biologic membranes studied. Two preliminary reports encompassing the use of DMSO in some of these patients with acute bursitis and chronic arthritis have appeared.[3,4]

The present publication covers our experience with the use of dimethyl sulfoxide in the treatment of patients with acute musculoskeletal injuries, acute and chronic bursitis, osteoarthritis, rheumatoid arthritis, gouty arthritis, scleroderma, and Dupuytren's contracture.

Chemistry

Dimethyl sulfoxide is a clear, colorless liquid which is practically odorless in its purified state. It is the lowest member of the group of alkyl sulfoxides having the formula of

$$CH_3\overset{O}{\overset{\|}{S}}CH_3$$

and a molecular weight of 78.13. As a highly polar organic liquid which is hygroscopic and miscible with water, it acts as a powerful solvent, dissolving most aromatic and unsaturated hydrocarbons, organic nitrogen compounds, and many other substances. When the 100% solution of DMSO is mixed with water, some heat of solution is evolved

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(60 calories per gram at 20 C). One of the many commercial uses of DMSO is as a solvent in the manufacture of synthetic fibers; consequently, contact of clothing with DMSO may destroy the fabric. The following fibers are readily destroyed by DMSO solutions: rayon, polyurethane, and acrylic.

Pharmacology and Toxicity

Animal Toxicity.—Earlier studies to determine whether or not DMSO presented any occupational disease hazard indicated that this compound was relatively nontoxic.[5] Since toxicity is of prime concern when any new therapeutic agent is introduced, a composite table is offered to show the comparative toxicity of DMSO given by various routes of administration to small animals (Table 1).

Recently in our laboratory, four dogs receiving dermal applications of 1 gm (1 ml of 100%/kg of body weight of DMSO to the shaved area of the back five days weekly over a period of 15 months, showed no significant abnormalities in liver function tests, renal function tests, hemogram, or urinalyses when performed at monthly intervals. Similarly, when Rhesus monkeys were given from 0.4 to 4 gm/kg of body weight of DMSO intravenously five days weekly for a total of 69 such injections (two animals), no consistent biochemical or hematologic alterations occurred, and no significant pathology was noted when they were killed.[6]

Absorption of DMSO in Man.—DMSO is rapidly absorbed when applied to the intact skin. This may be demonstrated by the simple experiment of placing a drop of DMSO on a glass slide or watch crystal and another drop on the skin of the forearm. The drop on the skin is completely absorbed within 30 minutes while that on the glass remains. When liberal amounts of DMSO are applied to the skin for several applications, a garlic-like odor may be noted on the breath. The odor is apparently due to dimethyl sulfide resulting from the breakdown of DMSO in the body.[7]

Clinical Use

Technique of Application.—Most patients will tolerate applications of 60% to 90% dimethyl sulfoxide to the skin of the dorsal area of the wrist, elbow, shoulder, knee, and hip joint. While the use of 60% to 90% dimethyl sulfoxide is currently recommended in acute musculoskeletal injuries, lower concentrations are advised in sensitive patients.

The prescribed dosage is measured into a graduated container. In these patients it was applied with a cotton-tipped applicator to the involved area and the surrounding region. As an example, the technique of application of DMSO in the treatment of gout of the great toe would be to apply about 6 ml of the material to the great toe and the entire forefoot. Usually it requires several minutes of application and reapplication before an adequate dosage is achieved with amounts of 6 to 8 ml applied over a knee joint, 8 to 15 ml over the shoulder, and 10 to 15 ml over the skin of the hip joint.

Table 1.—Toxicity of Dimethyl Sulfoxide by Various Routes of Administration in Animals*

Animal	Route	Median Lethal Dose (Mg/Kg)
Mouse	Intravenous	3,800
Mouse	Intravenous	5,750
Rat	Intravenous	8,000
Rat	Intravenous	5,360
Dog	Intravenous	2,500
Mouse	Oral	21,400
Mouse	Oral	20,000
Mouse	Oral	15,000
Rat	Oral	28,300
Rat	Oral	20,000
Rat	Oral	17,800
Chicken	Oral	10,000
Guinea pig	Oral	10,000
Rat	Intraperitoneal	5,000
Rat	Intraperitoneal	10,000
Guinea pig	Intraperitoneal	5,000

*Compiled from data offered in references 5,8-11.

Treatment must be individualized. The most frequently employed daily dosage among this group of 548 patients was 30 ml of dimethyl sulfoxide. Chronic conditions are treated twice daily and acute conditions as frequently as every four hours. The treated area is allowed to remain uncovered for a period of 30 to 40 minutes; any remaining solution should be wiped off with an absorbent material to prevent injury to the patient's clothing.

When 60% to 90% DMSO is applied to the skin, the patient may experience warmth, erythema, itching, and sometimes local urticaria. In most cases this local irritation disappears within two to three hours. The volar skin surfaces of the knee and elbow joints and skin of the face, neck, and axillae are sensitive to strong concentrations of DMSO. When 60% to 90% DMSO is applied to the palm of the hand, a wrinkling appearance of the skin can occur which may last for several days.

Clinical Results

Table 2 summarizes results noted with topical applications in the treatment of various types of musculoskeletal disorders in 548 patients. In the evaluation of these results, the number of patients listed as "improved" in the table denotes unequivocal benefit; in all other patients the results were considered to be unsatisfactory. A more detailed description of these results in the various types of musculoskeletal disorders treated with DMSO follows:

Acute Musculoskeletal Injuries.—Application of DMSO in acute injuries of this type usually provides prompt relief of pain and swelling. The earlier DMSO is applied following injury, the more dramatic the result. For example, a 14-year-old boy was struck in the right cheek by a fist. Examination 15 minutes later revealed a one inch laceration with edema extending over the bridge of the nose to the region of the eye. After application of 6 ml of DMSO to this area, some mild skin irritation was observed within 30 minutes and an hour later the pain, edema, and skin irritation had disappeared. Four hours later, minimal swelling returned which

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Table 2.—Clinical Effectiveness of Dimethyl Sulfoxide When Used Topically in Musculoskeletal Disorders

Diagnosis	Patients: No. Treated	Patients: No. Improved	Usual Daily Dosage of DMSO (Ml)	Maximum Period of Treatment	Results and Comments
Acute musculoskeletal injuries	210	195	30	7 days	Relief of pain and muscle spasm within 30 min; duration of benefit 2-12 hr
Bursitis					
subacromial acute	25	22	30	7 days	Rapid increase in range of motion and diminution of rest pain within 30 min
subacromial chronic	40	32	30	3 months	Continued treatment for 3 months required before patient symptom free; reduction of calcium by x-ray in 25% of patients exhibiting initial calcification
Arthritis					
osteoarthritis	110	88	30	10 months	Diminished pain, lessened muscular spasm; increased range of motion
rheumatoid					
grades 1, 2	80	60	30	10 months	Diminished pain, lessened muscular spasm; increased range of motion
grades 3, 4	70	30	30	10 months	Objective evidence of diminution of swelling; subjective relief of pain. Six of 10 patients followed for 8-10 months are improved
gouty	5	3	30	3 days	Diminution of swelling and redness, relief of rest pain in 30 min; some discomfort persists on walking
Scleroderma	5	4	30	3 months	Improved range of motion at joint with softening of skin
Dupuytren's contracture	3	3	30	3 months	Reduction of plaque size in palmar fascia with increased range of finger motion
Total	**548**	**437**			

was controlled by a second application of 6 ml of DMSO.

Acute Subacromial Bursitis.—When DMSO is employed in the treatment of acute subacromial bursitis, dramatic relief of pain and muscle spasm occurs within 30 minutes. Following relief of rest pain, there is an increased range of motion. The solution should be applied liberally to the involved shoulder, the upper arm, and the skin over the muscles of the lower neck. During the first day of treatment, three or four applications of DMSO given at three or four hour intervals may be required to maintain the benefit. After this, one or two applications daily usually suffice until recovery is complete.

Chronic Subacromial Bursitis.—In our experience the benefits derived from topical application of DMSO in this disorder are definite and predictable. If the patient has rest pain with limitation of motion, application of DMSO results in pain relief within 20 to 30 minutes. If, however, pain occurs only with certain movements of the arm, DMSO is less likely to be of benefit.

A typical patient was a 52-year-old college professor who came to the office with subacromial bursitis of the right shoulder. He had severe pain with limitation of motion in this shoulder for the previous six months and was treated with intra-articular hydrocortisone acetate and oral cortisone acetate without benefit. A month following the onset of this disorder, similar involvement was noted in the left shoulder, and it was not relieved by standard methods of therapy. Two months following the onset of his illness, it was necessary to remove the calcium from his left shoulder by operation. Following surgery limitation of motion with pain in both shoulders continued, and when first seen by us, the patient had been taking injections of 100 mg of meperidine hydrochloride four times daily for several weeks. Topical application of DMSO to both shoulders was started and continued twice daily. Forty-eight hours later, the patient was able to discontinue the meperidine. At this time marked improvement was observed in the range of motion of both arms. Applications of DMSO twice daily were continued for three months until the patient was entirely pain free and showed a complete recovery of range of motion in both upper extremities.

Twenty-five percent of the patients in this series with chronic bursitis who showed calcification on x-ray films prior to treatment demonstrated objective evidence of diminution in calcification at the end of one month of therapy.

Osteoarthritis.—Usually the administration of dimethyl sulfoxide is associated with improvement in patients with osteoarthritis involving the joints of the hand, the knee, and the ankle. Less dramatic results are achieved with DMSO in treating osteoarthritis of the hip. In this affliction, at least 10 to 15 ml should be applied to the back and buttocks twice daily and therapy continued for six to eight weeks before benefit can be expected. The frequency of application of DMSO may be decreased as the disorder improves. It has been possible for some patients with osteoarthritis of the hip to forego the use of DMSO for as long as 48 hours, although no patient has been able to discontinue therapy completely.

Rheumatoid Arthritis.—The response to DMSO in rheumatoid arthritis is less dramatic. We have found DMSO to be most effective in patients with rheumatoid arthritis who show minimal systemic manifestations and in whom the disease is limited to one or two joints.

In the severe rheumatoid arthritic with marked systemic involvement, application of up to 30 ml of DMSO per day for only two months to the involved joints is followed by minimal therapeutic benefit. On the other hand, in this group of patients with grades 3 and 4 rheumatoid arthritics, six out of ten patients treated for eight to ten months are considered as unequivocally improved. As we learn more and more about the usefulness of dimethyl

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sulfoxide, the axiom that the older pathological process, the longer it takes to see improvement appears to be the common denominator.

Dimethyl sulfoxide serves as a useful adjunct in some severe rheumatoid patients who are being treated with gold, chloroquine, phenylbutazone, or cortisone. Thus far, patients receiving DMSO have not shown any consistent changes in the usual anemia accompanying this disease or in the sedimentation rate. The major benefit derived from DMSO in the rheumatoid patient is a reduction of edema and pain, thus permitting increased use of the limb.

Gouty Arthritis.—Dimethyl sulfoxide applied liberally to an inflamed joint and surrounding region provides relief of edema and swelling in 30 minutes lasting for from one to four hours. Repeated applications up to four times daily adequately control the pain.

Scleroderma.—In four of the five patients, it has been noted that application of DMSO permits an increased range of motion and softening of the involved skin areas within a two-week period.

Dupuytren's Contracture.—When DMSO was applied in amounts of 15 to 30 ml daily to the involved hand and continued over a two to three week period, softening of the palmar fascia, diminution in the size of the plaques, and increased range of motion in the involved fingers occurred. After three months of DMSO therapy in three patients, the plaques have not completely disappeared nor has there been complete recovery despite improvement in this condition.

Toxicity and Untoward Effects

No serious toxicity has been encountered to date clinically in the topical use of dimethyl sulfoxide. The usual local dermal reaction from application of DMSO is a sensation of warmth and sometimes erythema and itching. In 70 of the 548 patients reported in this paper, itching at the site of application persisted for from one to 24 hours. In three of the 70 patients, the itching persisted for three days. In 28 (5%) of the patients, an increase in skin pigmentation at the area of application similar to that caused by sunburn appeared after two weeks of therapy. After discontinuing the medication, skin color returned to normal. A moderately severe local dermatitis requiring discontinuance of the therapy was noted in 11 (2%) of the patients. In another 11 patients, a generalized dermatitis, either urticarial or maculopapular, followed the local application of DMSO and cleared without additional treatment in from three to seven days when DMSO was discontinued. Seventeen patients complained of increased fatigue and lethargy during DMSO therapy. This disappeared within one to seven days after discontinuing the medication. Also, it seems that the complaints of fatigue and lethargy were dosage and time related, since these symptoms were noted when 30 ml daily of DMSO was used for periods of from one to two months. The only adverse reactions requiring discontinuance of DMSO were in 39 or 7% of the patients who showed local dermatitis, generalized dermatitis, or extreme lethargy.

Twelve of these 548 patients have been followed for over a ten-month period while receiving daily topical applications of from 8 to 24 ml of DMSO. We have arbitrarily insisted that patients on long-term treatment with DMSO discontinue this medication for one week every three months. In the 12 patients referred to, as well as in others who have been followed for shorter periods, so far no significant alterations have been observed in serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, prothrombin time, alkaline phosphatase, bilirubin, total protein and albumin-globulin ratio, blood urea nitrogen, or hemogram. Following ten months of chronic administration, the epidermis showed some exfoliation and desquamation but was otherwise normal to gross evaluation. DMSO has not been used on women known to be pregnant.

Comments

The criticism sometimes made that clinical trials reported here for dimethyl sulfoxide lack comparison with control studies can be answered. Except for a few instances, all patients had received or tried other remedial measures such as heat, salicylates, methyl salicylate, liniments, ointments, and in a number of patients, oral phenylbutazone and corticosteroids, or injections of corticosteroids without significant benefit before trial with DMSO. At the beginning of this study ten patients with acute subacromial bursitis first had their shoulders painted with a solution of glycerol and were observed for 30 minutes; in none was there any relief of pain or increase in motion noted from the placebo. The area was then wiped dry and DMSO applied with, in most cases, noticeable benefit reported by the patient.

While 60% to 90% DMSO often elicits burning and stinging when applied to the skin, this irritation seems to be of little consequence and is usually of short duration. Obviously, the pain relief and decrease of muscle spasm with increased mobility of the joint is not a counterirritant effect, since the skin reaction disappears while the beneficial effects last for several hours. In some patients, also, we have observed that the application of DMSO to one affected joint or area often leads to pain relief in some other location suggesting that DMSO has systemic effects. Supporting the possibility that DMSO has a central nervous system depressant action is the fact that 17 patients in this series who received 30 ml of DMSO daily over a period of from one to two months complained of fatigue and lethargy.

Dimethyl sulfoxide has the ability to carry some compounds through the human skin. This can be shown by placing 2% iodine by weight in alcohol on the back of one hand and 2% iodine by weight

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in 100% DMSO on the back of the other hand. The iodine in alcohol mixes with skin protein producing the brown color while the DMSO-iodine color (red brown) disappears in two hours. If one sets aside a test tube of each of these solutions, no change in color occurs.

That DMSO has a definite and rapid anti-inflammatory effect can be demonstrated by applying from 6 to 8 ml of the 90% solution over an acutely inflamed, reddened joint. Within an hour there is a noticeable reduction in redness and swelling.

Some of the interesting therapeutic possibilities for DMSO mentioned in previous reports[1,2] now undergoing further study at the University of Oregon Medical School are (1) as a "penetrant carrier" based on the observation that 15% solution of DMSO mixed with heparin, insulin, sodium salicylate, Evans Blue Dye, sulfadiazine, aminophylline, and thio-tepa (triethylenethiophosphoramide) enhances absorption through the urinary bladder in dogs; (2) as a local analgesic agent as demonstrated by reversible blockade of conduction in isolated nerves; (3) as an anti-inflammatory agent as shown by the effect on a baker's yeast granuloma in guinea pigs; (4) as a bacteriostatic agent in vitro against *Pseudomonas*, *Staphylococcus*, *Escherichia coli*, and *Mycobacterium Tuberculosis;* (5) as a diuretic in dogs; (6) as a tranquilizer in rats; and (7) as a potentiator of the action of other compounds such as insulin when DMSO-insulin combinations are given intravenously to dogs. Stoughton and Fritsch[12] have evaluated the influence of DMSO on human percutaneous absorption concluding that they were "unaware of any agent other than water which will influence percutaneous absorption to the extent of DMSO and not cause any obvious or prolonged damage to the skin other than transient erythema."

Summary

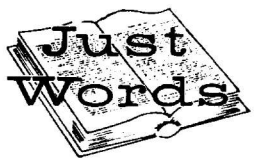
Dimethyl sulfoxide (DMSO) has been used clinically by topical application to 548 patients with acute and chronic musculoskeletal injuries and inflammations, including acute musculoskeletal trauma, acute subacromial bursitis, chronic subacromial bursitis, osteoarthritis, rheumatoid arthritis, gouty arthritis, scleroderma, and Dupuytren's contracture. Of these patients, 437 were unequivocally improved. Dimethyl sulfoxide has been administered to patients for as long as ten months without evidence of serious toxicity.

Generic and Trade Names of Drugs

Hydrocortisone acetate—*Cortef Acetate, Cortril Acetate, Hydrocortone Acetate.*
Cortisone acetate—*Cortisone Acetate, Cortogen Acetate, Cortone Acetate.*
Chloroquine phosphate—*Aralen Phosphate.*
Phenylbutazone—*Butazolidin.*
Thio-Tepa—*Thio-Tepa.*

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There are people without a backbone. There are others who have lost their heads. There are people with no foot to stand on. There are people without brains. Some of my best friends have two left feet. Widespread too is the condition of not having a heart at all. This is worse than being halfhearted. I know of more than one case of a person who has no guts. The condition of having no stomach seems intermittent. A broken heart is often chronic. There are people who have no nerves, others who have nerves of steel, and then there are those who apparently have only one, which is quite bad when they lose it.

The number of ills besetting mankind is legion. There are people who have a white liver, a heavy hand, a sweet tooth, a green thumb, or even blue blood. And the medical profession keeps callously aloof, blithely convinced that all these remarkable conditions are for the linguist to worry about.

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