COMPLEMENTARY AND ALTERNATIVE THERAPIES
FOR RHEUMATIC DISEASES I

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TOPICAL AGENTS IN THE TREATMENT OF RHEUMATIC DISORDERS

Elliot D. Rosenstein, MD

In the late 1800s, if you were a Parisian who suffered from *le rheumatisme*, you might have consulted Dr. Bengue, the French practitioner who had developed various pills and ointments that had achieved great popularity. A century later, one of his preparations, *Baume Bengue*, a combination of methyl salicylate and menthol, remains quite popular for those same complaints, although the spelling has become anglicized (Ben-Gay, Pfizer Consumer Health Care Group, New York, NY).

RATIONALE FOR USING TOPICAL PREPARATIONS

When a topical anti-inflammatory formulation is applied to the skin, its effectiveness depends on the transcutaneous absorption of the active moiety and its penetration in sufficient quantities into underlying inflamed tissues such as muscle, tendon sheath, and the synovium and synovial fluid of superficial joints. The pharmacologic action of the topical medication would not be dependent on absorption into the circulation and subsequent redistribution to peripheral tissues. Ideally,

From the Arthritis and Rheumatic Disease Center and Division of Rheumatology, Saint Barnabas Medical Center, Livingston, New Jersey; and Department of Medicine, Mount Sinai School of Medicine, New York, New York

the concentration of drug in the tissues underlying the site of application would equal or exceed those achievable with oral medications.

The topical therapies used in the treatment of rheumatic and other inflammatory conditions include the following:

- Salicylates and nonsalicylate nonsteroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroids
- Capsaicin
- Dimethyl sulfoxide (DMSO)
- Immunosuppressives (methotrexate, cyclosporine, tacrolimus)

SALICYLATES AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The introduction of a transdermal formulation for salicylates and other NSAIDs in particular raises the possibility of achieving therapeutic benefit without the risks of gastrointestinal or other side effects suffered via the oral route. To establish the validity of this hypothesis requires proof that percutaneous absorption occurs in sufficient amounts to achieve therapeutic levels in the target tissues, that clinical efficacy is demonstrable in suitably controlled clinical trials, that the safety profile of topical NSAIDs and other agents is superior to that of oral NSAIDs (particularly with regard to gastrointestinal side effects), and that topical NSAIDs are cost-effective. As illustrated below, only some of these criteria have been adequately supported.

Absorption

The principal barrier to transdermal absorption of drugs is the stratum corneum, the outer-most layer of the skin.[68] Its structure has been depicted as that of brick in mortar, with anucleated keratinized cells embedded in a lipid matrix, which is arranged in multiple bilayers providing alternate hydrophobic and hydrophilic barriers.[36] Variation in transdermal diffusion is highly individual and is crucially dependent on various factors, including the hydration state of the epidermis and local blood flow in the corial vessels.[68] Aside from anatomic considerations, the mode of application (e.g., repetitive administration, occlusion) inclusion of penetration-enhancing substances, massage, temperature, and other factors that affect blood flow may potentially influence the amount of drug penetration. It remains unclear what concentration is required to exert a clinically meaningful analgesic and anti-inflammatory effect

in inflamed or painful tissues. The closest estimates can be derived from in vitro data relating to the inhibition of cyclooxygenase (COX) responsible for the synthesis of tissue prostaglandins. The concept of transdermal NSAID application has been controversial as a result of numerous early experimental reports indicating that drug concentrations required for COX inhibition cannot be achieved underlying the application site.[46, 57] Most of these studies were performed in animals, the epidermis of which may not have equivalent characteristics to those of human skin, or on human cadaveric skin. More recent studies suggest that penetration of 3 to 4 mm in depth is likely.[57] Other authors have demonstrated concentrations in deep tissues sufficient to inhibit inflammatory events, however.[12, 62] The findings of Rolf et al[48] suggest that direct penetration to 5 to 15 mm in depth below the stratum corneum can be achieved. After a single application, in vivo studies reveal that only a small proportion of the applied topical dose is absorbed.[48] Multiple-dose administration of NSAID preparations appears to offer more consistent penetration, however. Repeated daily applications have been documented to provide concentrations in skeletal muscle that are clearly within the potentially effective pharmacodynamic range.[39]

The pharmacologic potencies of NSAIDs differ considerably, with a range of cutaneous absorption almost 10^5-fold in magnitude noted.[11] Attempting to determine the rate and extent of absorption of topical salicylates, human subjects were treated with two different preparations, one containing 12.5% methyl salicylate and the other 10% trolamine salicylate, with 5 g applied twice daily. The total amount of salicylate recovered in the urine was used to calculate the bioavailability of the product. The rate of absorption increased significantly as treatment continued. Urinary recovery of total salicylate during the first 24 hours averaged 175.2 mg with methyl salicylate and only 6.9 mg with trolamine salicylate.[38]

Yano et al[75] compared the skin permeability of nine salicylates (aspirin, methyl salicylate, ethyl salicylate, N-butylsalicylate, N-propylsalicylate, ethylene glycol monosalicylate, salicylic acid, salicyluric acid, salicylamide) and nine NSAIDs (bufexamac, indomethacin, alclofenac, diclofenac, flufenamic acid, ibuprofen, flurbiprofen, ketoprofen, naproxen). Lipophilicity was an important factor influencing percutaneous absorption, with methyl salicylate and ethylene glycol monosalicylate among the salicylates and alclofenac and ketoprofen among the NSAIDs demonstrating the greatest absorption rates.

Rolf et al[48] examined the concentration of ketoprofen in various tissues after topical plaster application in patients undergoing surgery for Achilles or patellar tendon repair, comparing the use of topical plasters with that of oral administration for 5 days prior to surgery. Higher tissue concentrations up to 52-fold were observed in fat, tendon

sheath, and tendon after topical application, whereas plasma levels were 126-fold lower. The penetration of topically applied salicylates into joint fluids has been demonstrated using radioisotope techniques. In dogs, topical salicylate application resulted in higher salicylate concentrations than oral aspirin in a number of tissues, including cartilage, fascia, ligament, muscle and tendon, despite much lower blood levels.[45] Riess et al[47] demonstrated effective concentrations of diclofenac in synovial fluid and biopsied synovial tissue following multiple topical applications of 100.mg of diclofenac gel for 3 days.

In six patients with active knee synovitis, intra-articular salicylate levels 1 to 2 hours after topical administration of trolamine salicylate were 60% of the levels obtained after oral aspirin ingestion.[45]

The penetration and absorption of ibuprofen from a topical gel and oral tablets were tested in an open study of patients with knee osteoarthritis. Patients were administered 1125 mg of topical ibuprofen daily or 1200-mg oral preparation daily. At the time of arthroplasty, drug levels were determined in blood, synovial fluid, muscle, fascia, and subcutis using a validated high-performance liquid chromatography method. Oral administration led to higher concentrations in the plasma, synovial fluid, and fascia, although higher levels were observed in muscle and subcutis after topical administration. Potentially therapeutically effective levels of ibuprofen were still observed 15 hours and longer after topical or oral administration. These results would suggest that therapy of intra-articular processes requires oral (systemic) administration of NSAIDs, whereas topical therapy may be sufficient for soft-tissue rheumatic complaints, including periarticular (tendinous) inflammation.[15]

Penetration Enhancement

Some essential oils and their terpene constituents (e.g., eucalyptus [1,8-cineole] and peppermint [menthol]) as well as 10% ethanol have been used as vehicles to enhance or accelerate salicylate absorption.[5, 71] Independent of their use in combination with salicylates, essential oils such as peppermint and eucalyptus are present in many other preparations for external application, many of which have been used for the treatment of various pain conditions. Menthol has a subjective cooling effect lasting up to 70 minutes in most patients, a response lasting 14 times as long as that of topical alcohol application. The rationale for their use may simply be the inhibition of nociceptive impulses via afferent segmental stimulation in the region of the posterior horns (the gate-control theory of pain). In experimental models of headache, however, these agents have beneficial effects on pain perception that are

independent of their cooling effects. Applying different preparations to the forehead and temples of healthy volunteers, it was determined that peppermint oil (mixed with ethanol) had significant muscle-relaxing action and local analgesic effect, whereas the addition of eucalyptus retained the muscle-relaxing effect but had little influence on pain sensitivity.[20]

CLINICAL EFFICACY OF TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Topical NSAIDs are variously indicated for a wide range of clinical conditions, including sprains, strains, soft-tissue rheumatism, sports injuries, periarthritis, and tendinitis. Typically but not exclusively these affect sites such as the shoulder, elbow, knee, or ankle. The common feature of these conditions is that they affect superficial musculoskeletal soft-tissues that are accessible to transcutaneously delivered NSAIDs.

Advertising of over-the-counter salicylate preparations suggests that they work by their "soothing, warming sensation" "to relieve pain and increase flexibility of joints—relief you can actually see," accompanied by thermographic images that document the increase in surface temperature.[74] With uncertainty as to whether the benefits are related to the counterirritant properties of the preparations, studies of salicylate preparations without ingredients that have a characteristic odor (typically from menthol) or thermogenic effects have been performed. Most recently, trolamine salicylate (e.g., Aspercreme, Thompson Medical Company, West Palm Beach, FL) treatment offered consistently superior effects over placebo in improving pain and stiffness.[50] Although there are a plethora of studies like these attesting to the efficacy of topical NSAIDs relative to placebo or similar topical preparations, there is a need for more well-designed and adequately powered clinical studies to be conducted, ideally involving comparisons with systemic NSAID therapy, to demonstrate unequivocally the effectiveness of topical NSAID therapy. Difficulties with trial design include lack of clearly defined diagnostic criteria and outcome measures and the tendency for the underlying condition to undergo spontaneous improvement.[21] Other problems include the practical difficulty of disguising dissimilar topical formulations in blind comparative studies and the subjectiveness of the experience of patients in applying topical treatments, which is characterized by a marked placebo response (40%–60%).[27]

Salicylates

In the United States and Canada, there are more than 40 nonprescription preparations that contain either methyl or trolamine salicylate.

In 1971, White and Sage[69] reported on 14 patients with osteoarthritis and 16 patients with RA who were treated in a prospective placebo-controlled study with Ben-Gay. After having demonstrated increased activity around inflamed joints prior to treatment, decreased levels of motor unit activity were noted after the use of Ben-Gay. Additionally, based on the use of a thymometer, a device whereby the patient adjusts a decibel level to correspond to the degree of pain, the effectiveness of Ben-Gay treatment was noted at the shoulders, elbows, and wrists. A subsequent report documented improved digital dexterity (measured by a "digital dexterity quantifier") and range of motion (measured by a "fleximeter") after Ben-Gay use.[70] Although these studies are difficult to evaluate because of lack of standardization of measurement techniques, a subjective sense of pain relief and overall improvement was noted, without development of significant complications.

In two separate double-blind studies of 90 patients with various musculoskeletal disorders, 2600 mg of oral aspirin daily was compared with topically applied trolamine salicylate. By several criteria, topical salicylate was demonstrated to be comparable to oral aspirin in relieving pain of varying severity. Trolamine salicylate was superior to aspirin in time of onset, patient acceptance, and incidence of side effects. This report was of particular note in that one of the studies included a majority (70%) of patients with rheumatoid arthritis.[55]

A double-blind study involving 113 patients with mechanical back pain revealed statistically significant relief of pain using topical hydroxyethylsalicylate as compared to placebo. An open study of bioavailability after local application in 16 patients showed a mean salicylate concentration of 0.93 μg/mL in the synovial fluid and 0.40 μg/mL in the synovial membrane as compared with 0.14 μg/mL in the serum.[51]

Nonsalicylate Nonsteroidal Anti-Inflammatory Drugs

Moore et al[37] recently reviewed the evidence that topical NSAIDs (primarily non-salicylates) are effective and safe and attempted to determine whether differences could be ascertained between topical preparations. A total of 86 reports involving 10,160 patients were included. For acute conditions (including strains, sprains, and sports injuries), 37 reports of 40 placebo-controlled trials were found. Twenty-seven of the reports showed a significant superiority of topical NSAIDs as compared to placebo. Seventy-one percent of 1747 patients allocated to treatment had a successful outcome, with 39% of 1492 patients allocated to placebo. Pooling data for specific drugs (≥3 studies) showed ketoprofen, felbinac, ibuprofen, and piroxicam to be significantly superior to placebo, whereas indomethacin and benzydamine were no better than placebo. For chronic

conditions, typically single joint arthritis and localized soft-tissue syndromes (tendinitis), 13 placebo-controlled trials and 12 active comparator trials were identified. All 13 placebo-controlled trials reported a statistical benefit of topical NSAIDs over placebo. Sixty-five percent of 547 patients receiving treatment compared with 30% of 550 patients receiving placebo had a beneficial response. Five studies compared topical NSAIDs with oral NSAIDs. In three studies of acute conditions and two studies of chronic conditions, no advantage of oral agents over topical agents was seen (Fig. 1). The results of this meta-analysis support the efficacy of topical NSAIDs. Despite attempts to review only rigorously designed studies, several of the reports included in this meta-analysis employed questionable methodology, low numbers of patients, and short duration of treatment. As with any meta-analysis, there remains the dilemma of interpreting results that reflect an inherent positive publication bias.[37]

Of particular note, a double-blind placebo-controlled trial was car-

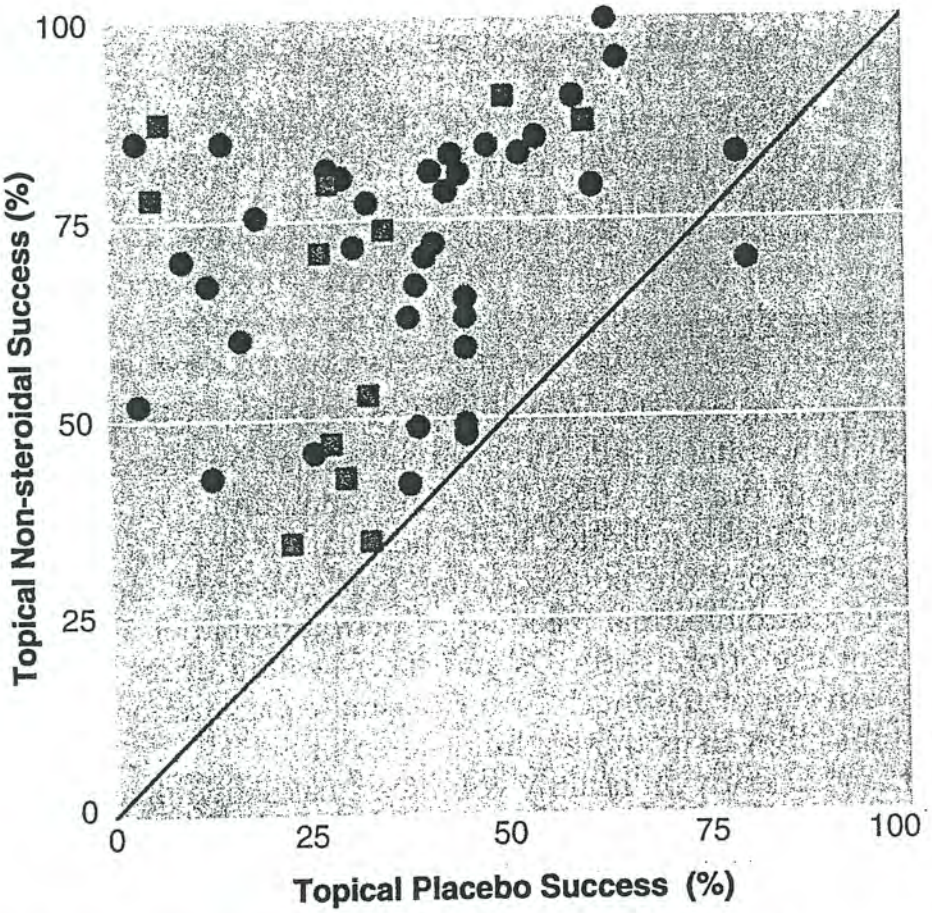

Figure 1. Success rates of topical nonsteroidal drugs for treatment of acute *(circle)* and chronic *(square)* musculoskeletal conditions. Each symbol represents one comparison of topical nonsteroidal with placebo. Percentage with successful outcome was at 1 week for acute conditions and 2 weeks for chronic conditions. (*From* Moore RA, Tramer MR, Carroll D, et al: Quantitative systemic review of topically applied non-steroidal anti-inflammatory drugs. BMJ 316:333–338, 1998; with permission.)

ried out in 155 patients with symptomatic osteoarthritis of the knee treated with either 180 mg of topical diclofenac (in the form of hydroxyethylpyrrolidine plasters) applied twice daily for 15 days or placebo. Significant improvement was seen in pain relief, overall assessment, and acetaminophen intake. Adverse effects and terminations for inefficacy were greater in the placebo-treated group.[16] In another study on the treatment of soft-tissue rheumatic disorders, the use of topical flurbiprofen cut the need for local hydrocortisone injection by 50%.[44] The efficacy and safety of topical flurbiprofen patches and oral diclofenac were compared in the treatment of soft-tissue rheumatism. Flurbiprofen was superior to oral therapy in terms of both efficacy and gastrointestinal tolerability.[33]

In the report of a randomized, double-blind, placebo-controlled trial of 290 patients with osteoarthritis of the knee published in 1997, a topical NSAID (eltenac) was compared with oral diclofenac and topical placebo. The main outcome, Lequesne's Index, and pain by visual analog scale (VAS) showed no statistically significant differences among the study groups. In patients with more severe symptoms, however, both active agents showed statistically significant differences from placebo. No serious adverse events were seen, but the incidence of gastrointestinal reactions was three times higher in the diclofenac group compared with the topical treatment group.[53]

ADVERSE EFFECTS

An argument for the use of topical NSAIDs has been the high incidence of hospitalization for gastrointestinal problems reported in regular users of oral NSAIDs (1.3%–1.6% annually).[18] In a case-control study of 1103 patients admitted to the hospital for upper gastrointestinal bleeding or perforation, no association was noted for topical NSAIDs with upper gastrointestinal bleeding or perforation after adjustment for concomitant use of oral NSAIDs and ulcer-healing drugs. This is most probably a result of the much lower plasma concentrations from doses applied topically versus those administered orally.[8]

Although a study on healthy volunteers has shown that blood levels of diclofenac after cutaneous application of the emulsion gel were less than 10% of those observed after parenteral administration, systemic absorption of topically administered drug may be sufficient to cause serious gastrointestinal complications. Upper gastrointestinal hemorrhage associated with the use of cutaneous diclofenac had been reported in four patients. In two of these cases, however, the medication had been used to treat backache (in 1 patient for only 3 days), which, in retrospect, was attributable to peptic ulcer. The other two patients had prior history

of peptic ulcer disease.[78] There have in fact been reports of adverse events involving the gastrointestinal tract with several other NSAIDs, including topical ibuprofen, ketoprofen, piroxicam, and felbinac (an active metabolite of fenbufen).[16] Local skin reactions are rare (2% to 3.6%), and systemic effects were even less common (<0.5%). Dermatologic reactions are mainly limited to mild skin irritation (erythema, dermatitis, pruritus) which resolves spontaneously and affects approximately 2% of users.[27] Contact dermatitis to topical NSAIDs or excipients in the formulation has been reported and documented with almost all topically applied NSAIDs. Cross-sensitization between agents (particularly proprionic acid derivatives) has been reported.[21] Asthma has been reported after the use of diclofenac sodium and ketorolac tromethamine ophthalmic solution.[56, 58] Acute renal failure has recently been reported after topical use of ibuprofen, piroxicam, and benzydamine.[37] A patient experienced full-thickness skin and muscle necrosis as well as interstitial nephritis as a result of topical application of methyl salicylate and menthol followed by the use of a heating pad, despite the manufacturer's warnings.[23]

The usual contraindications to the use of these compounds need to be observed; they should be avoided in patients in whom NSAIDs are known to cause urticaria, angioedema, or bronchospasm. Their use in patients receiving warfarin therapy may result in alterations in protein binding and risk of bleeding. Overall, the low level of systemic absorption can be advantageous, allowing the topical use of these medications when systemic administration is relatively contraindicated such as is the case in patients with hypertension, cardiac failure, or renal insufficiency. The safety of topical NSAIDs in pregnancy is untested.

Of course, oral ingestion of topical preparations poses unanticipated toxicities. This is particularly so with several of the salicylate preparations that come in liquid form, especially when they are ingested by children. Acute salicylate toxicity, including death, has been commonly reported, particularly with methyl salicylate because of its concentrated form and lipid solubility. One teaspoon of oil of wintergreen is equivalent to 7000 mg of salicylate or over 21 adult aspirin tablets. The use of Asian medicated oils or liniments may pose additional problems because of additional ingredients (e.g., turpentine oil in Hung Far and menthol and camphor in Pak Far or Kwan Loong, also known as Tiger Balm). Camphor is a lipophilic rapid-acting neurotoxin that has both excitatory and depressant actions. Death after camphor ingestion results from respiratory depression or status epilepticus. Turpentine, a pine oil, is a marked gastrointestinal irritant and central nervous system depressant.[10, 74]

COST IMPLICATIONS

In this time of managed care and evidence-based medicine, here lies the greatest failing of these studies. There are no data to support that the use of topical NSAIDs offers any cost benefit over the use of oral NSAIDs or other agents such as rubefacients or acetaminophen. There is little doubt that the cost of treatment with a topical NSAID is significantly greater than the cost of using the same drug administered by the oral route. For example, in the United Kingdom and Canada, a 100-g tube of diclofenac gel is three times the cost of oral diclofenac.[21] Other than the topical salicylates available over the counter, the topical NSAIDs are currently unavailable in the United States. How these agents would be priced in the American marketplace will be seen with the imminent release of the first FDA approved topical non-salicylate NSAID by late 1999 or by 2000. Aside from the purchase price, a true cost-benefit analysis of topical versus oral therapy must consider the total cost of care, which would include the cost of adverse events (gastrointestinal complications), laboratory monitoring, and prophylactic measures such as gastric cytoprotective medications.[24] As previously noted, the use of topical NSAID therapy may reduce the need for acetaminophen and minimize the frequency of local corticosteroid injection in cases of soft-tissue rheumatism.

PHONOPHORESIS AND IONTOPHORESIS

Physical modalities are an essential component in the care of many musculoskeletal conditions, and they have been reviewed recently.[41] Several physical modalities have been employed to improve the effectiveness of topical medications.

Phonophoresis

Phonophoresis, the use of ultrasound to introduce medications transdermally, is typically performed with anti-inflammatory medications such as corticosteroids and salicylates. Diffusion of medications through tissues is believed to be through an alteration in tissue permeability. Acoustic streaming, the movement of fluids caused by mechanical pressure, may be a contributing mode of dispersal. Phonophoresis does not appear to cause systemic absorption of salicylates or NSAIDs, at least as measured by serum drug levels.[7, 42]

Cortisol has been shown to penetrate into skeletal muscle and paravertebral nerve after ultrasound application. Some studies have indicated that clinically relevant concentrations can be found 10 cm deep to the treatment site after a 5-minute treatment. In other studies

comparing different ultrasound frequencies, significant concentrations of hydrocortisone in subdermal muscle were seen only at frequencies that resulted in dermal burns or at lower ultrasound frequencies that required inordinately long treatment lengths. Based on clinical response in the treatment of soft-tissue disorders in human subjects, Kleinkort and Wood[28] showed that phonophoresis with 10% hydrocortisone was superior to phonophoresis with 1% hydrocortisone. Antich[4] compared dexamethasone and lidocaine administered with ice, phonophoresis, iontophoresis, or ice alternating with phonophoresis. Although the last modality was believed to be most effective, phonophoresis alone provided subjective improvement after four treatments. Smith et al[60] could not determine a superior therapy when comparing ice massage, ultrasound alone, and iontophoresis and phonophoresis with dexamethasone and lidocaine, but all were more effective than a control treatment. Griffin et al[22] compared phonophoresis with hydrocortisone with ultrasound alone and found an improved range of motion and decreased pain in more patients with fewer treatments in the phonophoresis-treated patients.

The use of corticosteroids with phonophoresis is not without hazard, however. Studies involving the use of topical hydrocortisone suggest that, like injectable corticosteroids, frequent administration of topical hydrocortisone may result in soft-tissue atrophy and disruption of tendinous and ligamentous structures.

Clear conclusions as to the efficacy of phonophoresis are difficult to generate. The literature suggests that the response to phonophoresis may be substrate specific, that is, corticosteroids are more effective and may require repeated administration to achieve therapeutic results.

Iontophoresis

Iontophoresis is a popular mode of delivery of topical drugs, again most often used with corticosteroid preparations. For iontophoresis to succeed, the drug must be charged (or modified to a charged state). Patients with various dermatologic conditions have been treated with iontophoresis. Although the principle behind the process involves the use of electromotive force to transport charged molecules into tissues, animal studies and a small controlled trial in human subjects which involved high-pressure liquid chromatography quantification of steroid concentrations from skin biopsy specimens and serum have shown iontophoresis to be more effective than passive diffusion alone in delivering steroid medications to subdermal tissues.[73] With regard to NSAID therapy in combination with iontophoresis, a double-blind study involving 60 patients with various arthritic and soft-tissue disorders examined the

effect of ketorolac compared with normal saline delivered by iontophoresis and applied on alternate days for five sessions. Both ketorolac and placebo provided immediate significant pain relief, but only those patients who received ketorolac experienced a further statistically significant reduction in pain 7 days after treatment. Missing from this study, however, was an active treatment group that received ketorolac but avoided the use of ionotrophoresis.[52]

CAPSAICIN

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), which is derived from *Capsicum frutescens*, the common pepper, is thought to work by depleting the small, unmyelinated, type C sensory neurons of substance P, the neuropeptide implicated in the transmission and modulation of pain and the pathogenesis of various arthritic conditions. It further inhibits its reaccumulation from cell bodies and nerve terminals, resulting in analgesia. Touch, temperature, and proprioception are unaffected.[30,31] Capsaicin has been used to treat several painful disorders, including postherpetic neuralgia, postmastectomy pain, cluster headaches, diabetic neuropathy, and phantom limb syndrome.[76] Four randomized placebo-controlled studies have shown significantly better pain and tenderness relief with topical capsaicin cream than with placebo (vehicle).[2,13,35,54] There was a 40% improvement in dolorimeter scores in osteoarthritis. For the most part, no effect was demonstrated on joint swelling, grip strength, duration of morning stiffness, or functional capacity. Capsaicin cream is especially useful in patients with osteoarthritis of the hands and knees. The effects in patients with rheumatoid arthritis, who were only evaluated in two of the four trials, have been inconsistent. The patient populations were too small to make meaningful comparisons, however. Capsaicin can be purchased over the counter, and in the United States, it is available in three strengths: 0.025%, 0.075% applied four times daily, and 0.25% applied twice daily. Beneficial effects are usually seen after 3 to 7 days of application. Although it is quite safe, effective use of capsaicin is limited by the local stinging or burning sensation that typically dissipates with regular use after the first 7 to 10 days of therapy. Initially thought to contribute to a patient's perception of effectiveness (and resulting in unblinding of trials), the response of capsaicin-treated patients who had the burning sensation was slightly less than those who did not have the burning sensation.[13] Patients should be advised to apply the cream on affected areas with a plastic glove or cotton applicator and to avoid inadvertent contact with the eyes or mucous membranes. Drying of the cream and inhalation have been reported to result in coughing[2,54] and, anecdotally, asthma.

DIMETHYL SULFOXIDE

DMSO, first synthesized in 1866, has been used for over 30 years in the treatment of various disorders. Commercially prepared from lignin, a byproduct of paper manufacturing, DMSO has been used as an industrial solvent for decades. Many studies in animals demonstrated multiple diverse pharmacologic actions.[25] Despite the initial enthusiasm and media attention, there is inconsistent evidence that DMSO is effective for the treatment of musculoskeletal disorders in man.

After skin application, DMSO penetrates all tissues well, except teeth and nails. The most common side effect of DMSO therapy is a garlic-like taste and odor on the breath that occurs within 5 minutes of administration and interferes with the double-blind nature of any study of its effectiveness. Although it has been noted to cause changes in the refractive index of the lens in laboratory animals, this has not been seen in human studies. Although demonstrated to have anti-inflammatory effects in several classic models of experimental inflammation in rats, including effects as a scavenger of reactive oxygen metabolites and stabilizer of lysosomal membranes, DMSO has not consistently had ameliorative effects in animal models of arthritis, with differing responses depending on the dose, route of administration, species tested, and particular model of arthritis.[6, 59, 63, 66, 67]

The experience with human trials of DMSO has been well summarized in reviews from the mid-1980s by Trice and Pinals[64] and Jimenez and Willkens.[25] In the earliest reports dating from 1964 and 1965, Rosenbaum et al[49] related the effects of topical DMSO in an uncontrolled study on the treatment of bursitis, tendonitis, and sprains. Application of 60% to 95% DMSO resulted in a rapid improvement in range of motion and diminution of pain. Most reports of uncontrolled trials with DMSO have shown favorable results. John and Laudahn[26] evaluated 4180 patients with various musculoskeletal conditions, including over 1500 patients with acute trauma and acute or chronic tendonitis or bursitis. Over 50% of patients achieved complete remission of symptoms, with less than 15% of patients considered to be treatment failures. Demos et al[14] reviewed the results of 76 clinical studies comprising 1917 patients, with improvement noted in 72%.

Brown[9] reported a blind assessment of DMSO treatment in various acute musculoskeletal conditions using various concentrations (60%–90%) compared with 10% DMSO as a control. Excellent results were seen in 60% to 80% of patients using the high-dose DMSO as compared to none of the patients who used the 10% solution. In a more recent study of 157 patients with rotator cuff tendonitis or lateral epicondylitis, DMSO 10% gel applied three times daily for 14 days resulted in decreased pain and improved range of motion in 44% of patients as

compared to 9% of placebo-treated patients.[29] Other investigators, however, have found DMSO therapy to be relatively ineffective.[64] In a double-blind study of 102 patients with tennis elbow and rotator cuff tendonitis, DMSO 70% aqueous solution offered no beneficial effect beyond that seen with 5% DMSO.[43] As seen above, the uncontrolled experience with the large number of patients, using a patient's prior response to other treatment modalities as the basis for determining efficacy, is suggestive of beneficial effects. The double-blind studies show inconsistent results, however, and cause one to hesitate accepting DMSO as an effective intervention without further confirmatory investigations.

The experience with osteoarthritis is quite similar to that with soft tissue rheumatic conditions, with most of the early uncontrolled studies showing beneficial results. The review of Demos et al[14] identified 106 patients with osteoarthritis, 50% of whom had an excellent or good response to DMSO. Steinberg[61] reported a favorable response demonstrated by decreased pain and swelling in 85% of 152 patients. Contrariwise, Marmor and Walike[32] treated 22 patients and found a favorable response in only 3. In a randomized double-blind study involving 112 patients with symptomatic knee osteoarthritis, the effectiveness of DMSO 25% gel was assessed as compared to placebo gel.[17] Significant improvement in rest pain and pain on weight bearing was demonstrated.[17] Vuopala et al[65] studied 100 patients with knee osteoarthritis and assessed the effectiveness of DMSO 50% ointment compared with placebo. In both groups, 76% of patients responded favorably.

Uncontrolled trials of DMSO in rheumatoid arthritis have similarly shown inconsistent results. As reported by Rosenbaum et al,[49] 150 patients were treated with 60% to 90% DMSO for 10 months. Improvement was noted in 75% of milder cases, with 44% of the more severely affected patients responding. Marmor and Walike[32] reported on 53 patients with advanced rheumatoid arthritis who were treated with 70% DMSO for 8 weeks. None of the patients had an excellent response, and only 8 had good symptomatic relief, whereas 33 patients had no relief. John and Laudahn[26] reported complete remission in 74 of 177 patients treated. Demos et al[14] reported on 76 patients with rheumatoid arthritis, of whom half had a good or excellent response. A favorable response was seen in 77% of the 36 patients treated in Steinberg's series.[61] Vuopala et al[65] examined 97 patients with rheumatoid arthritis in their double-blind study. Patients were treated with either 10% DMSO, 10% DMSO with 10% diethyl salicylate, or placebo. All treatments resulted in an improvement rate of 50% to 60%; however, the concentration of DMSO was substantially lower in this study than in the uncontrolled studies in which treatment appeared to be more effective. Studies from the former Soviet Union in the late 1980s demonstrated beneficial effects of DMSO when it was given as an intra-articular injection with corticosteroids[40]

and when application of 50% DMSO was compared with physiotherapy modalities.[1] The most impressive results are those of Matsumoto,[34] who treated 274 patients with rheumatoid arthritis in a single-blind trial. Patients received either 90% DMSO, 50% DMSO, or placebo for 4 weeks. Both concentrations of DMSO resulted in improvement in pain, grip strength, and tenderness, with inconsistent results in range of motion and no change in joint circumference and laboratory parameters. Although the placebo group was clearly identifiable, the findings suggested analgesic and perhaps some anti-inflammatory effects.[34] More recently, DMSO has been examined as a treatment for reflex sympathetic dystrophy. In a study of 26 patients, 13 were treated with regional guanethidine sulfate blocks, whereas the other 13 were treated with topical DMSO.[19] After 9 weeks of therapy, the patients treated with DMSO had statistically significant improvement in pain, edema, discoloration, range of motion, and function when measured as a total score, although there was no statistically significant change in individual parameters.[19]

In vitro, DMSO has been noted to dissolve amyloid fibrils and to prevent or reverse the thermal precipitation of Bence-Jones proteins. In uncontrolled studies and in comparison with colchicine, oral DMSO provided mild improvement in renal function and proteinuria in patients with secondary amyloidosis.[25, 40, 64] Reduction in salivary gland swelling and improvement in oral mucosal appearance have been demonstrated in patients with Sjögren's syndrome.[3] Several studies have suggested that DMSO promotes healing of hand ulcerations in patients with systemic sclerosis.[3, 64] The most rigorous study of DMSO's effects in scleroderma did not clearly document efficacy, however.[72]

Although there is extensive, unblinded, uncontrolled experience with DMSO that suggests its effectiveness in the treatment of acute soft tissue conditions, osteoarthritis, and rheumatoid arthritis, controlled trials yield conflicting results. Because of the difficulty in masking the administration of the medication, clinically meaningful trials require administration of low concentrations of DMSO in the control group.

CONCLUSIONS

Topical drug delivery may be the optimal route for the treatment of localized musculoskeletal disorders, because higher drug concentrations can be achieved at the sites of clinical significance. Salicylates and nonsalicylate NSAIDs have been shown to achieve tissue levels that are potentially therapeutic, at least with regard to COX inhibition. Many topical NSAID preparations are effective in relieving pain in acute and chronic musculoskeletal conditions. The evidence that they achieve ther-

apeutic levels in synovium and synovial fluid and that they are effective in treating osteoarthritis of accessible joints is less conclusive. Substantiation of their efficacy in the treatment of rheumatoid arthritis is scanty. Other than local skin reactions, the side effects of therapy are minimal although not nonexistent, and the usual contraindications to the use of these compounds need to be considered. For those physicians and patients in the United States who are interested in pursuing these modalities, compounding pharmacies can prepare ointments of varying composition and strength. The first topical non-salicylate NSAID is anticipated to have US Food and Drug Administration approval soon.

Capsaicin application similarly offers a safe and effective alternative to systemic NSAID therapy for patients with osteoarthritis of the small joints of the hands, knees, and other superficial joints.

Uncontrolled studies of DMSO have supported an analgesic effect in the treatment of acute musculoskeletal syndromes and articular disorders. The inability to perform adequate controlled studies prevents the substantiation of its efficacy and its acceptance as a legitimate therapeutic modality. The lack of pharmaceutical industry interest in this inexpensive and apparently safe treatment destines DMSO to remain on the fringe of accepted medical practice.

In the near future, the emergence of fixed-dose locally acting patch formulations and the use of liposomes or submicron oil droplets for transcutaneous delivery provide an opportunity to more effectively and precisely deliver topical anti-inflammatory medications.

The pivotal studies to determine the cost-effectiveness of these agents have yet to be done. In addition to comparing these agents with other topical and mechanical modalities, more rigorous comparisons with acetaminophen, traditional NSAIDs, and the recently released selective COX-2 inhibitors are necessary to more firmly establish the place of topical anti-inflammatories in the therapeutic armamentarium.

In the interim, because of the symptomatic improvement and lack of important toxicities noted with their use, patients should not be discouraged from trying ointments such as these. Because of their general safety, however, directions for application are often left vague, with instructions to use "prn" or "as often as needed." It is necessary that these agents be used rigorously, with instructions provided for an interval between applications and a maximum number of applications daily, to obtain the desired benefit and avoid potential toxicity.

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Address reprint requests to

Elliot D. Rosenstein, MD
Arthritis and Rheumatic Disease Center
Saint Barnabas Medical Center
200 South Orange Avenue
Livingston, NJ 07039