Topical NSAID Therapy for Musculoskeletal Pain

Simon Haroutunian, MSc,*† Daniel A. Drennan, MD,‡ and Arthur G. Lipman, PharmD*‡

*Department of Pharmacotherapy, College of Pharmacy, University of Utah
†Department of Pharmaceutics, School of Pharmacy, The Hebrew University of Jerusalem, Israel
‡Department of Anesthesiology, School of Medicine; and Pain Management Center, University Health Care, Salt Lake City, Utah, USA

Reprint requests to: Simon Haroutunian, MSc, Department of Pharmaceutics, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, 91120, Israel. Tel: +972-26757667; Fax: +972-26757246; E-mail: simonh@ekmd.huji.ac.il.

Abstract

Objective. Systematic reviews previously reported in the literature document that topical nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in relieving pain in acute and chronic painful musculoskeletal disorders including osteoarthritis, tendonitis, and muscle strains. Because several topical NSAIDs are available, with important differences among the formulations, there is a need to address and summarize the evidence of their effectiveness and safety.

Design. We searched Medline and Cochrane CENTRAL databases for clinical trials and systematic reviews of topical NSAIDs in musculoskeletal pain, using the following keywords: “NSAID,” “nonsteroidal,” “anti-inflammatory,” “topical,” “cream,” “gel,” “solution,” “lotion,” “patch,” “plaster,” “musculoskeletal,” “tendonitis,” “strain,” “sprain,” “trauma,” and word roots “pain” and “arthritis.”

Conclusions. Topical NSAIDs may vary significantly in their absorption kinetics and pharmacodynamic effects, based on NSAID molecule and the formulation chosen. Some topical NSAID formulations have been shown to be more effective than placebo in multiple studies, or to have comparable efficacy and a better safety profile than oral NSAIDs for single joint osteoarthritis and acute muscle injuries. In acute and chronic low back pain, widespread musculoskeletal pain, and in peripheral neuropathic pain syndromes, the current evidence does not support the use of topical NSAIDs.

Key Words. NSAID; Nonsteroidal; Topical; Pharmacokinetics; Pain; Musculoskeletal

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs in the world [1]. They have been used in folk medicine for millennia. Initially this was as salicylate-containing willow bark, and the synthetic drug aspirin was introduced in 1897 by Bayer Fabrik in Germany. Indomethacin was introduced in 1962 [2] as the first “modern” NSAID. Now, over two dozen NSAIDs are commercially available in many countries in oral dosage forms, and a few as parenteral and topical formulations. In 2004 over 100 million prescriptions were written for NSAIDs in the United States alone. In the United Kingdom, 20–24 million prescriptions predominantly for oral NSAIDs are written each year, representing fully 5% of all National Health Service prescriptions.

NSAIDs are the cornerstone of musculoskeletal pain management. Musculoskeletal pain can result from injuries to ligaments or muscles, such as sprains and strains; from the arthridites, most commonly osteoarthritis (OA); and from disorders such as myofascial pain. The U.S. Public Health Service Centers for Disease Control and Prevention estimates that nearly seven million Americans annually seek medical care for sports-related injuries [3,4]. In the United Kingdom, ankle sprains are estimated to occur in 53 per 10,000 people [5]. OA is common and increasing in prevalence, especially in older adults; with the knee joint being the most common site [6]. Over 26.9 million adults in the United States have symptomatic OA, ranking it among the top five leading causes of disability among noninstitutionalized adults [7].

While NSAIDs are effective and extensively used for musculoskeletal pain, their adverse effects have become increasingly evident. A 1998 report of oral NSAID-associated gastropathy was the harbinger of many more toxicity reports [8]. That report documented that more than 30 million Americans were then taking NSAIDs regularly [9] and at least 107,000 patients were hospitalized for NSAID-associated gastrointestinal (GI) complications each year. Of those, an estimated 16,500 died due to NSAID-related complications among the arthritis patients alone [10]. The attributable risk of GI bleeding or ulcer complication is estimated at between 2% and 4% annually.
for regular oral NSAID users [11]—four times higher than for nonusers [12,13]. In rheumatoid arthritis (RA) this risk appears to be even higher, because RA patients often require increased NSAID doses for projected periods of time [8]. Misoprostol, a prostaglandin analogue, is effective in reducing the GI complications of NSAIDs [14]. However, misoprostol may cause serious cardiovascular and thromboembolic adverse effects and some less serious, but common adverse effects, most notably diarrhea in 14–40% of patients and abdominal pain in 13–20% of patients. Those effects frequently cause patients to be nonadherent with misoprostol use [15,16]. Cyclooxygenase (COX)-2 selective NSAIDs, for example, celecoxib, were shown to have safer GI adverse effect profiles than nonselective NSAIDs for at least 6 months of regularly scheduled use [17,18]. In arthritic patients at high risk of GI complications who need an NSAID, administration of a proton pump inhibitor with a COX-2 selective NSAID may prevent or reduce GI bleeding [19]. Other reports document additional GI, renal, hepatic, and most recently cardiovascular toxicities associated with systemic NSAID use [20–23].

NSAID Mechanism of Action

The major mechanism of analgesic action of NSAIDs is reduction of prostaglandin synthesis by COX inhibition at the site of pain and inflammation [24,25]. In recent years the relative importance of the COX-2 isoform in mediating inflammation via prostaglandin production has been highlighted [26]. Cox-2 isoenzyme is inducible in vivo; it increases quantitatively in inflammatory states [27]. Additionally, central nervous system mechanisms of analgesic and antihyperalgesic action have been proposed [28–30]. The relative importance of the central mechanisms in musculoskeletal pain remains unknown. Some evidence suggests that the inducible COX-2 isoform may play a role in development of peripheral diabetic neuropathy [31]; however, clinical trials demonstrating efficacy of COX-2 inhibition in any types of peripheral neuropathy are lacking. Other postulated mechanisms by which NSAIDs suppress inflammation include inhibition of leukocyte adherence and function, reduction of platelet aggregation, modulation of lymphocyte responsiveness, inhibition of cytokine production, suppression of proteoglycan production in cartilage, amelioration of complement mediated cell lysis, and inhibition of free radical formation [32].

The Rationale for Topical NSAIDs

Because NSAIDs are drugs of choice for musculoskeletal pain and because adverse events occur commonly with systemic NSAID therapy, formulation of topical dosage forms to limit systemic exposure was a logical pharmaceutical development. Topical formulations are those that are applied locally in proximity to the affected area and which provide effective concentrations at the local target tissues without producing the systemic levels that are associated with common adverse effects. These differ from transdermal dosage forms that deliver full systemic levels of the drug through the skin into the circulation.

In theory, an NSAID applied topically could achieve therapeutic concentrations in the tissues proximal to the application site with only low, relatively safe serum concentrations. This would avoid adverse GI events, eliminate first pass metabolism, and reduce risk of adverse events related to the high serum drug concentrations often needed for efficacy with systemic dosage forms [33]. Local gastric contact effects and the sequelae of high serum concentrations which favor drug back-diffusing into GI tissue also should decrease.

This review focuses on the differences among the various topical NSAID formulations in terms of pharmacokinetics, safety, and efficacy in acute and chronic musculoskeletal pain conditions.

Search Methods

In order to identify clinical trials and systematic reviews of topical NSAIDs in musculoskeletal pain conditions, we searched Medline and Cochrane CENTRAL databases (1966 through May 2009) using the following keywords: “NSAID,” “nonsteroidal,” “anti-inflammatory,” “topical,” “cream,” “gel,” “solution,” “lotion,” “patch,” “plaster,” “musculoskeletal,” “tendonitis,” “strain,” “sprain,” “trauma,” and word roots “pain” and “arthritis.” Additional references were sought from the reference list of the retrieved papers.

We also accessed: the Food and Drug Administration (FDA) Website for any New Drug Application (NDA) information on topical NSAIDs, the NDA Pipeline newsletter for additional topical NSAIDs in development information, and the websites of the federal drug regulatory agencies of the United States, Canada, New Zealand, Ireland, Finland, France, and Israel for information on approved topical NSAID dosage forms.

Topical NSAID Pharmacokinetics

Penetration through the Skin

Formulation of a topical dosage form to efficiently deliver an NSAID to the adjacent soft tissues and joints requires an understanding of the anatomy of the skin and physicochemical processes involved in absorption across the skin barrier. The skin layers through which any drug must be transported to reach its site of action in soft tissue, bone, or the systemic circulation are the stratum corneum, the epidermis, the basal membrane, and the dermis [32] (Figure 1). Only then can absorption into the systemic circulation or penetration into deeper tissues occur. The stratum corneum is largely lipophilic and is more easily traversed by drugs in their more lipophilic, unionized form [34], while the viable epidermal layer is predominantly aqueous. Thus, for optimal penetration through both layers, a drug must have both hydrophilic and hydrophobic properties. Drugs that are highly hydrophilic or hydrophobic are poorly absorbed without optimization of the topical formulation. NSAIDs are largely lipophilic compounds [35], they are weak acids, with pKa values between 3 and 4.6 [35,36]; consequently, at physiological
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and AUC were approximately twice as high with a topical diclofenac sodium plaster (patch) than with an equivalent dose of the drug applied as a diclofenac epolamine plaster in healthy volunteers [41].

A penetration study of another NSAID, meloxicam, both in vitro and through cadaver skin, employed different types of penetration enhancers. Menthol produced a dose-proportionate increase in meloxicam flux through the skin, while DMSO in concentrations up to 10%, polysorbate 20 (Tween 20) in concentrations up to 5%, and oleic acid in concentrations up to 5% failed to improve the flux relative to a control formulation [42]. Topical administration of diclofenac 1.5% lotion with 45.5% weight/weight DMSO as a penetration enhancer showed continuous and prolonged penetration into and through the skin, with the time to maximum plasma concentration (Tmax) measured after a mean of 30 hours. The Cmax values were comparable to or slightly higher than those obtained by repetitive topical diclofenac 1% gel administration. The Cmax following application of 1 mL of 1.5% diclofenac lotion in this study (11.8 ng/mL) was approximately 40 times lower than Cmax achieved with 100 mg oral diclofenac sustained release tablets [43]; however, the plasma AUC following the same application was only twice lower than AUC obtained after a single oral 50 mg diclofenac dose [44]. This indicates that the diclofenac lotion with DMSO penetration enhancer provides prolonged transdermal delivery without high plasma concentrations [45]. Clinicians should note that use of excessive amounts of a topical NSAID formulation may produce higher than desired systemic levels hindering the advantage of topical vs systemic administration.

Developing particulated drug carriers as microparticles and nanoparticles may also significantly alter the pharmacokinetics of a topical NSAID formulation. These formulations improve the duration of drug residence in the skin [46], and they seem more practical for dermal drug delivery to treat local skin and adjacent tissue disorders. Nanocarrier formulations usually are not intended to increase transdermal transport and systemic drug delivery. However, a study using ultrafine (188 nm) nanocapsules impregnated with indomethacin showed increased absorption and bioavailability of the compound from the nanoparticle formulation compared with a reference formulation (indomethacin incorporated in Pluronic F-127 gel) [47].

Recent study evaluated the effect of various nanocarrier formulations (nanospheres, nanocapsules, or a nanoemulsion) on penetration of the NSAID nimesulide through the different skin layers ex vivo, using Franz-type diffusion cells. For the gel containing nanoemulsion, nimesulide was not quantified in stratum corneum (as it was with the other two nanoformulations), but it directly permeated the dermis. All three formulations were able to release the drug beyond the stratum corneum in the viable skin layers, compared with a nonparticulated nimesulide-loaded hydrogel formulation at the same concentration from which the drug did not penetrate any of the skin

pH, NSAIDs are >99% ionized. The role of molecular size of the compound in absorption through the skin is not well defined, but it appears that the optimal molecular weight is less than 500 Da [37]. The molecular weight for most NSAIDs is between 200 and 400 Da. Hence, there are some physicochemical differences among the individual NSAID molecules. These differences do impact the pharmacokinetics of a topical dosage form, but evidence suggests that the formulation of a topical NSAID dosage form may also significantly affect its pharmacokinetic properties [38].

Differences in Formulations

The topical NSAID formulation may greatly impact its absorption and penetration through the skin. Differences in the formulations may be based on 1) the dosage form (e.g., gel vs solution vs patch), 2) different salts of the same molecule (e.g., diclofenac sodium vs diclofenac potassium vs diclofenac epolamine), 3) carrier-mediated transport (e.g., lipid emulsions vs solid nanoparticles), and 4) penetration enhancement methods, either chemical (e.g., addition of penetration enhancer like menthol vs dimethylsulfoxide [DMSO]) or physical (e.g., heat-mediated penetration enhancement vs electrical charge-mediated penetration enhancement such as iontophoresis).

A study comparing two topical gel formulations of the same NSAID, diclofenac, showed that administration of a solution of diclofenac incorporated into an aqueous alcoholic gel produced a mean increase of 53.8% in plasma area under the concentration-time curve (AUC) and an increase of 106% in the maximal plasma concentration (Cmax) compared with a gel prepared with diclofenac emulsified in a lipid phase [39]. The relative bioavailability of another salt, diclofenac hydroxyethylpyrrolidine (DHEP, diclofenac epolamine) from a topical patch was only about 30% of that with DHEP topical gel [40]. The mean Cmax

Figure 1 Representation of the skin layers through which a drug must be transported to reach its site of action.
A novel formulation of ketoprofen, based on Transfersome technology, delivered the active compound more effectively to muscle than a standard formulation of ketoprofen [50]. This technology utilizes ultrafroamear carriers loaded with an active substance in an aqueous suspension. When water evaporates depriving the carriers of their suspending medium, the carriers reach their solubility limit and migrate toward higher water content in the skin, apparently improving dermal penetration [51].

**Topical NSAID Absorption**

By limiting absorption primarily to the local target tissues, topical NSAIDs should produce decreased systemic adverse effects. Numerous studies have addressed this issue. For example, the systemic absorption from a diclofenac epolamine patch, when compared with other diclofenac formulations, appears to be limited. Although no solid safety data are available, one could argue that this dosage form may be safer in terms of systemic side-effects. The Cmax was obtained 10–20 hours after application of a single diclofenac epolamine patch ranged between 0.7–6 ng/mL, with steady state plasma concentrations after five consecutive days of twice daily application were 1.3–8.8 ng/mL [52]. For comparison, the mean Cmax obtained with a single oral 50 mg diclofenac dose was 1214 ng/mL, at least two orders of magnitude higher [44].

A study comparing single and multiple-dose topical diclofenac application showed that a single topical administration of 30 g diclofenac 1% gel produced a subcutaneous/plasma concentration ratio that was much higher than that achieved with multiple dose application of 60 g three times a day. The mean ± standard deviation (±SD) plasma Cmax values were 8.54 (±1.49) ng/mL and 1.45 (±0.48) ng/mL for multiple and single dose administration, respectively [53]. Hence, with multiple-dose topical gel administration, higher systemic concentrations are achieved. In another study, topical application of 1% diclofenac gel (Voltaren gel; Novartis, Parsippany, NJ) produced mean (±SD) plasma Cmax of 15 ± 7.3 ng/mL after a 4 g dose was applied four times daily for a total of 160 mg of diclofenac per day, and 53.8 ± 32 ng/mL after a 12 g dose was applied four times a day for a total dose of 480 mg diclofenac per day. The Cmax mean (±SD) after oral administration of 50 mg diclofenac three times a day was 2270 ng/mL [54]. Based on these findings, the recommended amount of diclofenac gel for upper extremities (hand, elbow, wrist) is 2 g per joint per application, with a maximum of 8 g per joint per day. For lower extremities (foot, ankle, knee) the recommended dose is four grams four times a day, with a maximum of 16 grams per joint per day. Patients should not exceed a total of 32 grams of gel per day.

Administration of topical ketoprofen 110 mg twice a day in a Transfersome drug delivery system produced a mean trough plasma concentration of 81.2 (range 4.6–677) ng/mL [51], which is only 0.1–17% of the plasma concentration achieved following oral administration of 50 mg ketoprofen four times daily [55].

Several studies have measured intramuscular and intra-articular concentrations of NSAIDs after topical administration. Rolf et al. [56] investigated intra-articular absorption and distribution following single and multiple ketoprofen plaster (patch) applications as well as oral administration. Oral administration produced high plasma, synovial fluid, and synovial tissue ketoprofen concentrations. Topical administration resulted in lower plasma (18.7 ng/mL vs 2595.3 ng/mL), synovial tissue (56.7 ng/g vs 364 ng/g), and synovial fluid (12.8 ng/mL vs 350.7 ng/mL) concentrations, but higher cartilage (568.9 ng/g vs 83.5 ng/g) and meniscus (349.3 ng/g vs 85.7 ng/g) concentrations than oral administration.

There is evidence that phonophoresis (achieved by applying either continuous or pulsed ultrasound) can increase the synovial concentration of ketoprofen 10-fold, without increasing fat tissue and plasma concentrations [57]. However, this study evaluated the Cmax only 50–70 minutes following application. Therefore, these values may result from increasing the rate but not the extent of penetration. Further pharmacokinetic trials are warranted to clarify this point.

Muscle and subcutaneous tissue concentrations of ibuprofen were evaluated by microdialysis following oral and topical administration in adults [58]. Volunteers received 800 mg of oral ibuprofen or 16 g of 5% topical ibuprofen gel (containing 800 mg ibuprofen). The Cmax after topical administration was 300-fold lower than after oral administration of ibuprofen. Following oral administration, mean muscle and subcutaneous tissue concentrations of ibuprofen were similar, 121 ng/mL and 95.6 ng/mL, respectively. Topical administration produced the same muscle concentration (100 ng/mL), but much higher subcutaneous concentration of ibuprofen (1,374 ng/mL).

Topical NSAIDs produce high drug concentration in dermis, muscle, synovium, and joint cartilage, while plasma drug concentrations are less than 10% of those obtained after oral administration. Tissue and synovial fluid concentrations obtained with NSAIDs approximate the concentration needed to inhibit 50% of enzyme activity (IC50) for prostaglandin synthetase in vitro [59]. However, substantial inter-individual variability exists in transdermal drug penetration [33]. While the anatomical site of application has little effect on systemic drug absorption [60], individual skin and connective tissue differences may alter topical absorption of drugs.

**Clinical Evidence**

Compounding pharmacists have reported various recipes for extemporaneous preparation of topical NSAID dosage...
forms for several decades. However, such formulations are rarely studied for bioavailability and objective clinical endpoints. The first reported clinical trials with topical NSAIDs emerged in the 1970s [61–63]. Since then, various topical NSAIDs formulations in creams, gels, patches (plasters), and solutions (lotions) have been used for musculoskeletal pain conditions in numerous European and other countries. Several formulations are approved by governmental regulatory agencies and are commercially available [Table 1] and others are in development. However, some authors have questioned whether these drugs having any action other than as rubefacients. The U.S. Food and Drug Administration only recently approved two topical NSAID products, both containing diclofenac, for different indications. Diclofenac sodium gel 1% (Voltaren) is indicated for symptomatic treatment of OA of joints such as the knees and hands. Diclofenac epolamine topical patch 1.3% (Flector) is indicated for treatment of acute pain due to minor strains, sprains, and contusions.

Topical NSAIDs have demonstrated efficacy in some types of musculoskeletal pain (Tables 2 and 3), but not every pain condition may benefit from this therapy. For example, studies did not show clear efficacy of topical NSAIDs in low back pain, which is the most frequent musculoskeletal pain condition [1]. A recent systematic review documented that systemic NSAIDs have only a small effect on acute and chronic low back pain [1]. There is no evidence to recommend any NSAID dosage forms other than oral capsules or tablets for these conditions [1]. Additionally, NSAIDs, in any dosage form, lack demonstrated efficacy in clinical trials for neuropathic pain including for peripheral neuropathies [64].

Several clinical trials and systematic reviews exist on topical NSAID use for the treatment of chronic conditions such as OA and tendinitis, and treatment of acute conditions such as sports injuries (Tables 2 and 3). There have been both positive and negative results, and the first quantitative systematic review on topical NSAIDs published in 1998 [65] concluded that topical NSAIDs were effective and safe in acute conditions including recent soft tissue injury, sprains, strains, and trauma, as well as in chronic conditions such as single joint arthritis and rheumatism. That review included all randomized controlled trials on topical NSAIDs for chronic and acute painful conditions, published from 1966 to 1998, as well as some unpublished clinical trials. Eighty-six reports with total of 10,160 patients were included. The conclusion of the systematic review was that topical NSAIDs were more effective than placebo, and comparable to oral NSAIDs in analgesic efficacy using ≥50% pain decrease as the primary efficacy outcome. The adverse effects and the withdrawal rates associated with topical NSAIDs were not different from placebo.

Additional clinical trials and systematic reviews on the efficacy and safety of topical NSAIDs have been published subsequently. In order to clarify the differences between acute and chronic painful musculoskeletal conditions and to differentiate between the lengths of treatment, we have summarized those studies in two tables. The systematic reviews and additional clinical trials that were not included in the systematic reviews, which evaluated the efficacy of topical NSAIDs in chronic musculoskeletal conditions, are summarized in Table 2. The systematic reviews and clinical trials of topical NSAIDs for acute conditions are summarized in Table 3.

### Ongoing Clinical Trials

Numerous topical NSAIDs formulations are in ongoing clinical trials. At the time of this writing a ketoprofen topical patch was in Phase III trials for pain associated with soft tissue injuries, acute strains, and sprains, and nonarticular rheumatism, tendinitis and bursitis. A diclofenac epolamine patch is being studied for osteoarthritis. Ketotransdel, a topical ketoprofen in a Transdel delivery system that enables transdermal penetration of drugs avoiding first pass metabolism by the liver and minimizing systemic exposure, is in clinical trials for acute soft tissue injury. Thermoprofen, a matrix transdermal ketoprofen patch integrated with a long lasting controlled heat-assisted drug delivery unit, is currently in clinical trials for the treatment of chronic pain associated with OA of the knee. We could identify no published clinical trials of Ketotransdel or Thermoprofen formulations. Diractin, a topical ketoprofen gel based on Transfersome ultra-deformable carriers, is in advanced clinical trials for muscle soreness, OA of the knee, joint pain and stiffness. However, its recent application to European Medicines Agency for symptomatic treatment of OA was judged not approvable as its efficacy has not been sufficiently demonstrated [66]. High-concentration diclofenac spray (4%) is in advanced clinical trials for OA. Topical 1.5% diclofenac lotion with DMSO as penetration enhancer (Pennsaid) is in long-term randomized controlled trials for knee OA. That formulation has consistently shown superior efficacy to placebo and equivalence to oral NSAIDs. It is approved in Canada and some European countries and was recently approved by the FDA.

### Safety of Topical NSAIDs

Most clinical trials and systematic reviews concluded that topical NSAIDs have a high safety margin. The majority of adverse events seen in clinical trials with a diclofenac patch were mild or moderate with application site reactions being the most common adverse events in both the diclofenac and placebo groups. About 3% of patients in both the diclofenac patch and placebo groups discontinued therapy due to an adverse event with no differences between the groups [67]. In clinical trials of diclofenac gel, 7% of patients experienced application site reactions compared with 2% with placebo gel (P value not reported) [54]. The most common reported reaction was dermatitis. On average, adverse drug events (ADEs) occurred in 12% (range 0–85%) of the patients in studies with topical NSAIDs, and approximately 75% of the ADEs were cutaneous rash and/or pruritus at the application site [33]. The
<table>
<thead>
<tr>
<th>Country (Database)</th>
<th>Diclofenac</th>
<th>Ketoprofen</th>
<th>Ibuprofen</th>
<th>Piroxicam</th>
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<tr>
<td>United States (FDA) <a href="http://www.fda.gov">www.fda.gov</a></td>
<td>Flector patch (diclofenac epolamine 1.3% patch, Alpharma Pharmaceuticals) Voltaren gel (diclofenac sodium 1% gel, Endo Pharmaceuticals).</td>
<td>NA</td>
<td>NA</td>
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<td>Canada (Health Canada Drug Product Database) <a href="http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php">http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php</a></td>
<td>Pennsaid (diclofenac dosium 1.5% topical solution, Squire Pharmaceuticals) Voltaren emulgel (diclofenac 1% topical gel, Novartis)</td>
<td>NA</td>
<td>NA</td>
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<td>New Zealand (MEDSAFE) <a href="http://www.medsafe.govt.nz/profs/Datasheet/DSForm.asp">http://www.medsafe.govt.nz/profs/Datasheet/DSForm.asp</a></td>
<td>NA</td>
<td>Oruval topical gel (ketoprofen 2.5% gel, Sanofi-Aventis)</td>
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<td>Ireland (Irish Medicines Board) <a href="http://www.imb.ie/EN/Medicines/HumanMedicines/HumanMedicinesListing.aspx">http://www.imb.ie/EN/Medicines/HumanMedicines/HumanMedicinesListing.aspx</a></td>
<td>Diclac 1% gel (diclofenac sodium 1% gel, Rowex Ltd.) Difene gel (diclofenac sodium 1% gel, Astellas Pharma) Difene spray gel (diclofenac sodium 4%, Astellas Pharma) Flector tissuegel 1% medicated plaster (diclofenac epolamine 1% patch, Novartis) Voltarol emulgel (diclofenac diethylamine 1% gel, Novartis)</td>
<td>Fastum 2.5 gel (ketoprofen 2.5% gel, A menarini industrie), Oruval (ketoprofen 2.5% gel, Sanofi Aventis),</td>
<td>Ibuprofen 5% gel, sanofi avertis,</td>
<td>Piroxicam gel (piroxicam 0.5% gel, Pfizer)</td>
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<td>Finland (National Agency for Medicines) <a href="http://namweb.nam.fi/namweb/do/haku/view?locale=en">http://namweb.nam.fi/namweb/do/haku/view?locale=en</a></td>
<td>EEZE spray (diclofenac 4% spray, Antula healthcare) Flector (diclofenac epolamine 1% plaster, IBSA Farmaceutici Italia Srl) Voltaren emulgel (diclofenac diethylamine 1% gel, Novartis)</td>
<td>Keterin 2.5% gel (ketoprofen 2.5% gel, Orion Oy), Orudis gel (ketoprofen 2.5% gel, Sanofi Aventis)</td>
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<td>Flector (1% diclofenac epolamine plaster, Laborabires Genievrier SA) Voltaren emulgel (diclofenac diethylamine 1% gel, Novartis)</td>
<td>Ketoprofen 2.5 % gel (multiple manufacturers)</td>
<td>Ibuprofen 5% gel, solution (multiple manufacturers)</td>
<td>Piroxicam gel (piroxicam 0.5% gel, Pfizer)</td>
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<td>Israel (The Israel Drug Registry) <a href="http://www.health.gov.il/units/pharmacy/trufot/index.asp?safa=e">http://www.health.gov.il/units/pharmacy/trufot/index.asp?safa=e</a></td>
<td>Dicloplast (diclofenac sodium patch 140 mg, CTS Chemical Industries) Voltaren emulgel (diclofenac diethylamine 1% gel, Novartis) Diclofenac sodium 1% (diclofenac sodium 1% gel, Vitamed) Diclofen gel (diclofenac sodium 1% gel, Trima)</td>
<td>Fastum gel (ketoprofen 2.5% gel, A. Menarini SRL)</td>
<td>Deep relief (ibuprofen 5% and levomenthol 3%, Mentholatum company), Nurofen gel (5% ibuprofen gel, Reckitt Benckiser Healthcare Ltd)</td>
<td>Expan (Piroxicam 0.5% gel, Perrigo Israel Pharmaceuticals), Feldene gel (piroxicam 0.5% gel, Pfizer)</td>
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NA = not available.
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<th>Study</th>
<th>Study Design and Duration</th>
<th>Intervention and Outcome Measure</th>
<th>Results</th>
<th>Adverse Effects</th>
<th>Remarks</th>
<th>Conclusion</th>
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<tr>
<td>Underwood et al., BMJ 2008.</td>
<td>Non blinded multicenter, RCT (n = 282) + patient preference study (n = 303). Duration: 24 months</td>
<td>Topical versus oral NSAIDs (preferably ibuprofen) in chronic knee pain.</td>
<td>Global WOMAC scores equivalent at 12 months in oral and topical groups</td>
<td>No difference in major AEs. In oral NSAIDs group: more respiratory and renal AEs. More patients changed treatment because of AEs. In topical NSAIDs group—more patients changed treatment because of ineffectiveness</td>
<td>In patient preference study: patients preference was 2.5:1 to topical NSAIDs</td>
<td>Topical NSAIDs are as effective as oral in knee pain for 12 months.</td>
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<tr>
<td>Mason L et al., BMC Musculoskeletal Disord 2004.</td>
<td>Meta analysis of 25 studies. From those 14 double-blind RCTs. Indications: OA (8 studies), Rheumatic Disease (3 studies), others.</td>
<td>Includes intervention with different NSAIDs, different dosage forms. Outcome measure: 50% reduction of pain at 2 weeks.</td>
<td>Topical NSAIDs superior to placebo. Relative benefit 1.9 (95% CI 1.7–2.2), NNT 4.6 (95% CI 3.8–5.9). In 3 trials of comparison to oral NSAIDs (n = 764)—no difference in efficacy.</td>
<td>Topical NSAIDs not different from placebo.</td>
<td></td>
<td>Topical NSAIDs are effective and safe in chronic musculoskeletal conditions—for 2 weeks treatment.</td>
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<tr>
<td>Lin J et al., BMJ 2004.</td>
<td>Meta analysis of 13 RCTs of topical NSAIDs in OA.</td>
<td>Outcome measure: reduction in pain (global pain or pain at rest) from baseline. Clinical response rate (% of patients reporting ≥50% pain relief or improvement in symptoms).</td>
<td>Effect size of topical NSAIDs at 1 week and 2 weeks were superior to placebo. Weeks 3 and 4—no benefit over placebo.</td>
<td>Topical NSAIDs had no more adverse effects than placebo. Compared with oral NSAIDs, fewer patients taking topical NSAIDs had any AEs, withdrawals due to AE, and GI AEs, but significantly more patients reported local AEs such as rash, itch, and burning.</td>
<td>There were only 4 trials of 4 week duration. One study with salicylate, one with prilocain (both were shown to be less effective than other topical NSAIDs in other trials) and 2 trials with Etinilen. No long-term studies with diclofenac, ibuprofen or ketoprofen. In our opinion, there is no enough data in this meta-analysis to rule out the long-term effectiveness of topical NSAIDs in OA.</td>
<td>No data support long term (beyond 2 weeks) use of topical NSAIDs in OA.</td>
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<tr>
<td>Biswal S et al., J Rheumatol 2006.</td>
<td>Meta analysis of long-term (more than 4 weeks) trials of topical NSAIDs in knee OA. Four RCTs (4–12 weeks), n = 709.</td>
<td>Primary outcome: pain intensity on VAS or WOMAC OA index.</td>
<td>Pooled effect of topical NSAIDs (diclofenac and etinilen) superior to placebo/vehicle at 4 weeks or later. AEs more common in topical NSAIDs group and included dryness, pruritus, rash, but were mild or moderate in nature.</td>
<td>Adds data to debate the conclusion of study by Lin et al. about long-term effectiveness of topical NSAIDs in OA.</td>
<td>Topical NSAIDs demonstrated efficacy in relief of knee OA pain at 4 weeks or beyond.</td>
<td>Topical NSAIDs are as effective as oral in knee pain for 12 months.</td>
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<tr>
<td>Rother M et al., Ann Rheum Dis 2007.</td>
<td>Randomized, controlled, phase II trial, n = 397. Duration: 6 weeks.</td>
<td>Arms: 110 mg Ketoprofen in Transfersome BID + oral placebo vs 100 mg PO Celecoxib BID + topical placebo vs oral-topical placebo. Primary Outcome: WOMAC pain and physical function scales and patient global assessment of response</td>
<td>Topical ketoprofen superior to placebo in two of three primary outcomes, and not different from oral celecoxib. More skin irritation and erythema with topical ketoprofen, but no statistically meaningful difference from placebo.</td>
<td>This is a long-term study showing efficacy of topical NSAID over placebo and comparability to oral NSAID.</td>
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<td>Topical ketoprofen in Transfersome appear safe and well tolerated. It was superior to placebo and similar to oral celecoxib in relieving pain of knee OA over a 6-week treatment period.</td>
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<td>Green S et al., Cochrane Database of systematic reviews 2002. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults [81]</td>
<td>Systematic review of 3 trials (n = 130). Up to 4 weeks of treatment</td>
<td>Primary outcome measure: Pain reduction on 0–10 VAS</td>
<td>Topical NSAIDs significantly more effective than placebo in alleviating lateral elbow pain. The pooled WMD was (-1.88) (95% CI (-2.54) to (-1.21)) in favor of topical NSAIDs.</td>
<td>AEs with topical NSAIDs not different from placebo.</td>
<td>Topical NSAIDs are significantly more effective than placebo with respect to lateral elbow pain and participant satisfaction for at least 4 weeks.</td>
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<td>Towheed TE, J Rheumatol 2006. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials [68]</td>
<td>Systematic review and meta-analysis of 4 trials (n = 1,412) of diclofenac 1.5% solution with 45.5% w/w DMSO penetration enhancer (Pennsaid) in Knee OA.</td>
<td>3 RCTs comparing topical diclofenac solution 1.5 mL QID versus vehicle. One trial compared topical diclofenac solution to 50 drops TID to 50 mg PO diclofenac TID. Primary outcome: WOMAC OA index pain, stiffness and physical function subscales.</td>
<td>In 3 placebo-controlled trials, diclofenac was superior to vehicle in all WOMAC subscales. In active comparison study, topical diclofenac was not different from oral diclofenac in any of WOMAC subscales.</td>
<td>Topical diclofenac produced significantly more skin dryness than the placebo vehicle. Other AEs observed included paresthesia and rash. Topical diclofenac produced significantly less GI AEs than oral diclofenac, but more dry skin and rash.</td>
<td>AEs as paresthesia, rash and skin dryness were observed, and they may be attributable to the vehicle or DMSO, as their incidence was higher than in other trials with topical diclofenac.</td>
<td>Topical diclofenac solution with DMSO penetration enhancer was effective in symptomatic OA of knee for 4 or more weeks of treatment. It was equivalent to PO diclofenac, and more tolerable.</td>
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<tr>
<td>Niethard FU et al., J Rheumatol 2005. Efficacy of topical diclofenac diethylamine gel in osteoarthritis of the knee [82]</td>
<td>Double blind, placebo controlled RCT. Assessment of safety and efficacy of diclofenac gel vs placebo for 3 weeks (n = 237).</td>
<td>Application of diclofenac gel (4 g four times daily) vs placebo. Primary objective: WOMAC OA index pain, stiffness and physical function subscales.</td>
<td>At weeks 1, 2 and 3 diclofenac was superior to placebo on all WOMAC subscales.</td>
<td>In each group, 9% of patients had AEs. Four patients in diclofenac group and 3 patients in placebo group experienced application-site reactions.</td>
<td>Topical diclofenac gel applied 4 times daily has been shown to effectively relieve the pain of OA of the knee.</td>
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* Conditions: OA, chronic tendinitis, knee pain.

WOMAC OA Index = Western Ontario and McMaster Osteoarthritis Index; AE = adverse effects; NNT = number needed to treat to achieve ≥50% reduction in pain; VAS = visual analog scale; BID = twice a day; TID = three times a day; QID = four times a day; WMD = weighted mean difference.
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<tr>
<td>Mason L et al., BMC Fam Pract 2004. Topical NSAIDs for acute pain: a</td>
<td>Meta analysis of 26 RCTs, (total n = 2,853) topical NSAIDs in acute sprains, strains and</td>
<td>Included interventions with different topical NSAIDs and different dosage forms (creams, gels,</td>
<td>Topical NSAIDs were better than placebo in 19 of 26 trials. At 7 days, pooled relative benefit of topical</td>
<td>AE of topical NSAIDs not</td>
<td>Ketoprofen appeared better than other NSAIDs; indomethacin was barely</td>
<td>Topical NSAIDs are effective and safe in treating acute pain condition for 1</td>
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<td>meta-analysis [71]</td>
<td>contusions.</td>
<td>patches, foams). Outcome measure: 50% reduction of pain at one week.</td>
<td>NSAIDs was 1.6 (95% CI 1.4–1.7), and NNT of 3.8 (95% CI 3.4–4.4). In 3 trials of comparison to oral NSAIDs</td>
<td>different from placebo</td>
<td>different from placebo.</td>
<td>week.</td>
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<td>(n = 443)—no difference in efficacy.</td>
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<td>Esparza et al., Br J Sports Med 2007. Topical ketoprofen TDS patch</td>
<td>Prospective, randomized, open, phase III trial. Ketoprofen patch vs diclofenac gel in</td>
<td>20% ketoprofen patch (100 mg) QD vs diclofenac gel 2–4 g TID. Outcome measure: pain on VAS at</td>
<td>Reduction of pain at activity and at rest with ketoprofen was not inferior to topical diclofenac. Ketoprofen</td>
<td>AE rate was 4.3% for the</td>
<td>Because patch was compared with gel, blinding was impossible in this</td>
<td>Ketoprofen transdermal patch was at least as effective as topical diclofenac</td>
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<td>versus diclofenac gel: efficacy and tolerability in benign sport</td>
<td>patients with sprains, strains, contusions. (n = 223). Duration: 7–14 days.</td>
<td>at rest and at activity.</td>
<td>patch had a higher cure rate related to the injury at day 7 (64% vs 46%, P = 0.004).</td>
<td>ketoprofen patch and 0.1% for</td>
<td>study.</td>
<td>gel in relieving acute pain after 7–14 days of treatment.</td>
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<td>related soft-tissue injuries [83]</td>
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<td>diclofenac gel. (not statistically significant)</td>
<td>diclofenac gel.</td>
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<td>00GB/Fp05-UK/German study. Diclofenac epolamine 1.3% topical patch</td>
<td>Double blind, placebo-controlled RCT. Diclofenac epolamine patch vs placebo patch.</td>
<td>Diclofenac epolamine 180 mg topical patch BID vs placebo patch. Outcome: Reduction in pain score on</td>
<td>Diclofenac more effective than placebo in reducing pain on 0–10 scale on day 14.</td>
<td>AEs were uncommon</td>
<td>Diclofenac epolamine patch more effective than placebo in alleviating</td>
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<td>(Flector patch)</td>
<td>Duration: 2 weeks (n = 418)</td>
<td>0–10 scale.</td>
<td>AEs were uncommon (in 2% of diclofenac and in 4% of placebo arm)</td>
<td></td>
<td>pain from minor sprains, strains, and contusions for 2 weeks.</td>
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<td>Formulary submission Dossier: Piscataway, NJ: Alpharma Pharmaceuticals</td>
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<td>05-05-98-French study.</td>
<td>Double-blind, placebo controlled RCT. Diclofenac epolamine 1.3% topical patch (Flectorpatch) Formulary submission Dossier, Piscataway, NJ: Alpharma Pharmaceuticals LLC; 2007. Diclofenac epolamine patch in minor sprains, strains and contusions. Not Published</td>
<td>Diclofenac epolamine 180 mg topical patch BID vs placebo patch BID. Outcome: Pain score reduction on 100 mm VAS.</td>
<td>Diclofenac more effective than placebo in reducing pain scores on day 3 and day 7.</td>
<td>No patients discontinued treatment in diclofenac group because AEs, 1 patient in placebo group discontinued treatment.</td>
<td>Diclofenac epolamine patch more effective than placebo in alleviating pain from minor sprains, strains and contusions for 1 week.</td>
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<td>Mazieres et al., J Rheumatol 2005. Topical ketoprofen patch in the treatment of tendinitis: A randomized, double blind, placebo controlled study [84]</td>
<td>Double-blind, placebo-controlled RCT. Ketoprofen TDS patch vs placebo for acute tendinitis. Duration: 2 weeks (n = 172).</td>
<td>Ketoprofen 100 mg TDS gel once daily application vs placebo. Primary Outcome: Change in global pain on 100 mm VAS from days 0 to 7.</td>
<td>Ketoprofen patch more effective than placebo, 55.6% vs 36.8% reduction on VAS (P &lt; 0.005) over 7 days of treatment.</td>
<td>Most AEs were mild or moderate and were not different between the two groups.</td>
<td>Treatment of tendinitis with the once daily 100 mg ketoprofen TDS patch is useful and well-tolerated.</td>
<td></td>
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<tr>
<td>Mazieres et al., Am J Sports Med 2005. Topical ketoprofen patch (100 mg) for the treatment of ankle sprain. A randomized, double-blind, placebo-controlled Study [85]</td>
<td>Double-blind, placebo-controlled RCT. Ketoprofen TDS patch vs placebo for ankle sprains. Duration: 2 weeks (n = 163).</td>
<td>Ketoprofen 100 mg TDS gel once daily application vs placebo. Primary Outcome: Change in spontaneous pain on 100 mm VAS from days 0 to 7.</td>
<td>Ketoprofen patch more effective than placebo, 73% vs 57% reduction on VAS (P &lt; 0.01) over 7 days of treatment.</td>
<td>Most AEs were mild or moderate and were not different between the two groups.</td>
<td>Treatment of ankle sprains with once-daily 100 mg ketoprofen TDS patch is useful and well tolerated.</td>
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</table>

* Conditions: strains, sprains, contusions and acute tendinitis.

AE = Adverse effects; NNT = number needed to treat to achieve ≥50% reduction in pain; VAS = visual analog scale; QD = once a day; BID = twice a day; TID = three times a day; QID = four times a day.
mean percentage of patients reporting adverse events from topical placebos was 14.4% (range 0–52%). Again, these events were primarily rash and pruritus, suggesting that the vehicles may be largely responsible for the adverse cutaneous reactions [33]. With the DMSO containing diclofenac formulation, there was about a 37% reported incidence of skin dryness [68], which seems higher than the rate reported in clinical trials of other NSAID formulations. The DMSO may be responsible for this effect, as the reported incidence of dryness and parasthesia at the application site were higher for DMSO containing vehicle (without diclofenac) than for the placebo application [69]. Reported paresthesias were transient and reversible upon discontinuation of therapy. Dryness is not an unexpected effect with a polar solvent that facilitates drug passage through lipoid biological structures. It seems logical that a lipid emollient might ameliorate this effect. The systemic manifestations of this formulation; however, that is, GI adverse effects, elevation of liver enzymes, and decrease in hemoglobin were significantly less common than with oral diclofenac [70].

The systemic adverse effects associated with topical NSAID treatment were generally infrequent and did not differ from placebo in the vast majority of the trials [65,69,71]. The studies comparing topical and oral NSAIDs, showed decreased incidence of systemic adverse events with topical administration. The incidence of severe GI effects and hepatic enzyme elevation was three times lower with topical application as compared with oral administration of diclofenac [70]. In a population-based retrospective study, topical NSAIDs were not significantly associated with upper GI bleeding and perforation [72].

Some preclinical data suggests that high NSAID concentrations may inhibit chondrocyte proliferation and adversely affect repair processes in joint cartilage [73,74]. Although this effect may be of theoretical concern, its clinical relevance with topical NSAIDs has not been demonstrated.

**Discussion and Conclusions**

This review summarizes the pharmacokinetic and pharmacodynamic differences among the topical NSAID formulations, and the results of clinical trials of these agents. NSAIDs remain important drugs in the armamentarium for the treatment of musculoskeletal pain. They are among the most commonly used nonprescription and prescription medications from all drug classes worldwide.

Table 2 summarizes the literature on topical NSAID use in chronic musculoskeletal painful disorders including osteoarthritis, tendinitis, and knee pain. The data clearly demonstrate effectiveness of topical dosage formulations in studies up to 12 weeks in duration. One systematic review [75] concluded that there are no data to support the effectiveness of topical NSAIDs beyond 2 weeks of therapy. However, the data in this meta-analysis are insufficient to rule out the long-term effectiveness of topical NSAIDs in OA, and clinical trials carried out later support long-term efficacy. Five studies compared four topical NSAID formulations to oral NSAIDs in OA and showed equal efficacy of the topical NSAIDs to oral NSAIDs with fewer systemic adverse effects [70,76,77]. Two of these trials compared topical 1.5% diclofenac solution with DMSO to oral diclofenac. One study each compared piroxicam 0.5% gel to oral ibuprofen, diclofenac 1% gel to oral ibuprofen, and etenidoic acid 1% gel to oral ibuprofen. The other topical NSAID formulations in development had not been compared with systemic NSAIDs in studies published at the time of this writing.

Table 3 summarizes the published reports on topical NSAIDs for acute painful disorders including sprains, strains, and contusions. There is now sufficient evidence to conclude that these drugs are effective for the aforementioned conditions, are well tolerated by patients, and present markedly less risk for systemic toxicities than oral NSAID therapy. There are, however, several common pain conditions, for which topical NSAIDs have not demonstrated efficacy. These include acute or chronic low back pain, widespread musculoskeletal pain, and peripheral neuropathic pain syndromes. Topical NSAIDs therefore cannot be recommended today for those types of pain.

Clinicians have long known that there is great interpatient variability in response to systemic NSAIDs. Clinical experience taught us to use an oral NSAID at full dose for 3 weeks, and if the desired response does not occur, rotate to a different NSAID in arthritis management.

Clinical experience also has long favored diclofenac resulting in it becoming one of the most commonly used NSAIDs in the world. Concerns about hepatotoxicity of diclofenac have caused some clinicians to hesitate to use it as first line agent. Topical diclofenac produces analgesic and anti-inflammatory effects similar to the oral, systemic dosage forms, without the systemic levels that are believed to produce the hepatotoxicity. As the amount and frequency of topical formulation applied at painful site may vary, it is important to recognize that use of excessive amounts topically may cause systemic adverse effects including major GI bleeding [78]. Both clinicians and patients should follow the manufacturers’ safety recommendations regarding the amount of drug to apply. For diclofenec 1% gel that is 16 g of gel per joint daily for a maximum 24-hour total of 32 g of the gel. The data on the two most extensively studied topical NSAIDs, diclofenac and ketoprofen, suggests that topical administration of both these agents at the recommended doses does not produce the plasma concentrations that are associated with systemic adverse effects. Diclofenac epolamine plasters produce the lowest plasma concentration of diclofenec, while diclofenec solution with DMSO appears to produce the highest penetration into the deep tissues and systemic circulation.

Interpatient variability in response to NSAIDs occurs with topical, as well as systemic dosage forms. Unlike opioids
for which we have evidence that interpatient variability is due—at least in part—to genetic polymorphism, we do not know why this occurs with NSAIDs. This variability may result from genetic factors, but with topical dosage forms, the formulation may have a larger impact than with the systemic dosage forms, due to the relatively complex absorption across the skin.

The evidence suggests that topical administration of NSAIDs produces effective drug concentrations in dermis, muscle, synovium, and joint proximal to and below the application site. However, patients’ skin and soft tissue conditions, and the anatomical site from which the pain is derived play important roles in variability in both analgesic response and systemic drug exposure. Use of a penetration enhancer may theoretically lessen this variability. Unfortunately, most of the published clinical trials evaluated only pharmacodynamic effects of topical NSAIDs in musculoskeletal pain conditions and did not measure plasma or target tissue concentrations of NSAIDs. Therefore, definitive clinical data on the correlation of systemic or tissue NSAID concentrations and clinical effectiveness are still lacking. Therefore, as with most analgesic therapies, clinicians should titrate to response within the approved dose range.

A lack of sufficient evidence hampers our ability to state which penetration enhancement method provides the best results. Different approaches vary in their results, and there are very few head-to-head clinical trials of different penetration enhancers. Formulations that facilitate extensive soft tissue and cartilage penetration of NSAIDs may be effective for disorders of deeper tissues such as joints; however, they may also produce higher systemic concentrations. For more superficial conditions such as muscle strains these formulations may produce unnecessary systemic exposure which might be avoided with a formulation possessing less vigorous penetration-enhancement effect. It is probable that several different topical NSAIDs will be needed in the armamentarium to meet most patients’ needs. Clinicians should recognize that the available topical NSAIDs and those in the pipeline differ greatly in their formulations and patient acceptance; they are not interchangeable. A good clinical strategy is to identify those dosage forms that work in the highest percentage of patients, that act rapidly and reliably, and to position those as first line therapies.

Acknowledgments

The authors acknowledge the contribution of David Peterson, PharmD, who assisted in literature retrieval and analysis. The authors received an unrestricted grant from Nuvo Research, Inc., the manufacturer of diclofenac topical solution with DMSO (Pennsaid), for manuscript development. This paper is the exclusive product of the authors, not Nuvo Research, Inc.

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