



Use of Topical Analgesics in Treating Neuropathic and Musculoskeletal Pain

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Topical administration of anesthetics and analgesics can allow for the efficient, painless delivery of medications that may reduce systemic side effects associated with the medication while providing clinical advantages over injected or oral administration for the same clinical situation. Topical administration of nonsteroidal anti-inflammatory drugs (NSAIDs), lidocaine, capsaicin, and other agents is useful for a range of conditions including acute and chronic musculoskeletal pain.

Background

Topical medications target the site of application and ideally produce effective drug concentrations locally with minimal systemic absorption. Topical anesthetics and analgesics target the peripheral nerves and soft tissue at that site.¹ A number of topical medications are beneficial for chronic musculoskeletal pain. In contrast, transdermal medications do not have to be applied over an involved site and attempt to reach systemic drug concentrations to achieve therapeutic results.² This review will focus on topical medications (Table).

Benefits of topical drug delivery include the potential for local therapeutic drug levels with reduced side effects, painless drug delivery, improved patient adherence and acceptance, ease of dose termination, avoidance of first-pass metabolism, and direct access to the target site.

The skin is a barrier to drug delivery, its primary role being to prevent the ingress or egress of compounds across it.³ The stratum corneum, the upper most layer of the skin, is a thin layer of cornified nonviable keratinocytes that is an effective barrier to water-soluble

substances, which typically include anesthetics. Topical medications must traverse the stratum corneum to reach their site of action, which may be the peripheral transducing terminals of cutaneous sensory fibers located in the dermis and epidermis,⁴ or the local soft tissues including synovial fluid, synovial tissue, and cartilaginous structures.⁵

Three delivery methods have been used to bypass the stratum corneum barrier.⁶

1. Injection of local anesthetics or other medications, usually via a small-gauge hypodermic syringe, is the oldest of the methodologies.
2. Passive diffusion from creams, gels, or patches comprises the second general class of methodologies. Passive diffusion of topical agents require that they have a molecular weight under 500 DA, with a hydrophobic component to allow it to transverse the stratum corneum but also some hydrophilic features to penetrate the epidermis.⁷
3. Active drug delivery methods that enhance the rate of drug passage through the skin and shorten the time to onset of action. There are a diverse group of

Table. Common Topical Anesthetics and Analgesics for Chronic Pain

Drug	Brand or Other Names	Use	Formulation
Arnica		MSK pain	Gel, cream
Capsaicin	Zostrix, Qutenza, others	Neuropathic pain, MSK pain	Patch, gel, cream
Lidocaine	Lidoderm	Neuropathic pain, MSK pain	Patch
Menthol and methyl salicylates	Many	MSK pain	Ointment, liniment, cream
Topical NSAIDs	Flector, Voltaren, Pennsaid, others	MSK pain	Patch, gel, cream

NSAID, nonsteroidal anti-inflammatory drug;
MSK, musculoskeletal

technologies that facilitate the drug delivery process. These include heat-enhanced diffusion, iontophoresis, sonophoresis, laser-assisted transdermal passage, or pressurized gas delivery of powdered drug particles.⁶ Microporation, a newer technology, uses tiny microneedles to penetrate the stratum corneum and are directly placed within the epidermis.

Topical as well as transdermal drug delivery is a rapidly expanding field. Most of the drugs and technologies used for procedural topical anesthesia have been well studied; however, this is not universally the case for topical medications used for musculoskeletal pain, which will be discussed in this review. Additionally, most of these topical agents have been studied exclusively in adults. The extrapolation of use of these agents in children seems reasonable given several factors, the pharmacodynamic response to most medications including local anesthetics, opioids, and NSAIDs are substantially mature by the age of 2 years, the degree of systemic absorption of these topical medications is low, and the local skin effects are, for the most part, minimal and short-lived.⁸

Topical Medications for Treatment of Musculoskeletal Pain

LIDOCAINE

Although indicated for the treatment of postherpetic neuralgia (PHN) in the United States, lidocaine 5% topical anesthetic patch (Lidoderm, Endo) has gained usage in a variety of neuropathic and musculoskeletal clinical conditions. The 5% lidocaine patch is composed of an adhesive material containing lidocaine, which is applied to a nonwoven polyester felt backing that allows for slow medication release. The patch provides analgesic action, reducing pain with some decrease in sensory function but without the complete loss of sensation; thus, it is not effective for procedural pain.^{9, 10} The size of the patch is 10-14 cm.¹¹

In addition to treatment of PHN, the 5% lidocaine patch has been used with efficacy in a variety

of neuropathic pain conditions, such as post-thoracotomy pain, complex regional pain syndrome, and post-amputation pain.¹² The lidocaine patch also is effective for musculoskeletal conditions. The 5% lidocaine patch is effective in adults with osteoarthritis (OA)^{13,14} lower back pain.^{15,16} It also has shown efficacy for myofascial pain syndrome.¹⁷

The lack of significant side effects makes topical 5% lidocaine an appropriate option for any focal neuropathic pain with allodynia or hyperalgesia.¹⁸ The patch must be placed at the site of pain in order to be effective.

Although it has not been studied specifically in children, we have used the 5% lidocaine patch successfully in many of the conditions described above, especially low back pain and focal neuropathic pains. Lidocaine absorption in adult usage amounts to only 3% to 5% of the total dose available in the patch and systemic levels do not increase with daily use. Systemic toxicity in adults is not considered a significant risk.^{19,20} For children under 50 kg, we limit the treatment to 1 to 2 patches for 12 hours per day to ensure safety. For children weighing more than 50 kg the adult dose of 3 patches for 12 hours per day is recommended. Often, 7 to 10 days of treatment is necessary before efficacy is noted. Side effects usually are limited to redness or other signs of skin irritation.

NSAIDs

Topical NSAIDs can provide local relief without the risks of an orally or parenterally delivered NSAID. Primarily, they have been evaluated for OA and acute musculoskeletal injury. These drugs are applied over the injured or painful body part and penetrate into the subcutaneous tissues, musculature, and tendons, where they exert their therapeutic action.²¹

After administration of topical NSAIDs, peak plasma concentrations are 0.2% to 8% of concentrations achieved with appropriate oral dosing.²² However, levels of NSAID in the meniscus and cartilaginous structures as well as in muscular tissues are 4 to 7 times greater after topical administration than oral administration.^{5,23} Concentrations in the tendon sheath are several hundred times greater than plasma concentration after topical administration. Length of time to peak concentration (C_{max}) is about 10 times longer in topically rather than orally administered NSAIDs with C_{max} for topical preparations ranging from 2.2 to 23 hours.²²

Unlike orally administered NSAIDs, topical NSAIDs have not been associated with increased risk for bleeding, and the risk for any gastrointestinal side effects for topical administration is considerably lower.⁵ Adverse events with topical NSAIDs are predominately local cutaneous reactions. Photosensitivity is a rare adverse reaction to topical NSAIDs.⁵ Although there are fewer comparative trials, in general, topical NSAIDs appear as effective and have a better safety profile in adults than oral NSAIDs, although onset of action is slower.^{22,24}

There are a variety of topical NSAID preparations including creams, gels, patches, and plasters. NSAIDs

delivered topically include diclofenac, ketoprofen, and ibuprofen. Superiority of topical NSAIDs compared with placebo has been demonstrated for both diclofenac (Flector Patch, Pfizer) and ketoprofen patches (various) for acute musculoskeletal conditions.²⁵ Based on a large meta-analysis, ketoprofen may be the most effective of the topical NSAIDs for acute pain.²⁶ Diclofenac topical solution (Pennsaid, Mallinckrodt) was superior to placebo and as effective as 3 times-a-day oral diclofenac for knee OA.²⁸ Diclofenac gel (Voltaren, Endo, Novartis) was superior to placebo in a 12-week study of knee OA, with decreased pain and improved function seen.²⁹

There are no randomized trials of topical NSAIDs in the pediatric age group. Given the excellent safety profile and low systemic absorption, use of topical NSAID treatment in children and adolescents with acute or chronic musculoskeletal pain is a reasonable option.

CAPSAICIN

Capsaicin, the active compound in chili peppers, is a counter-irritant (a substance applied to the skin that, by acting as an irritant on a painful zone, attenuates the sensation of pain) that provides some relief in neuropathic pain conditions. Capsaicin is a TRPV1 agonist that first activates nociceptive nerve fibers in the skin and causes the release of substance P, which results in neurogenic inflammation. This is followed by reversible defunctionalization of nerve endings resulting in the inhibition of pain transmission.³⁰⁻³²

Low-concentration (0.025% and 0.075%) capsaicin creams have shown mild efficacy in a variety of neuropathic conditions, including PHN, diabetic neuropathy polyneuropathy, and postsurgical neuropathic pain. These creams must be applied several times a day and can take several weeks of application to have effect.³² More recently, an 8% capsaicin patch (Qutenza, Acorda Therapeutics) has been developed for one-time use and has shown efficacy in PHN and HIV neuropathic pain.³⁰

In patients with musculoskeletal pain, capsaicin was superior to placebo in 154 patients with chronic low back pain. A systematic review of topical capsaicin for musculoskeletal pain demonstrates superiority over placebo.³³ Another meta-analysis showed superiority of placebo of capsaicin for OA pain.³⁴ A recent non-blinded, comparative, 6-week trial of topical capsaicin plus routine treatment versus routine treatment alone in 130 adults with fibromyalgia demonstrated decreased myalgic score and global subjective improvements in the capsaicin group. The experimental group showed continued improvements in symptoms 6 weeks after the end of treatment.³⁵

Local skin irritation with capsaicin cream use is common with burning and erythema and itching being the predominant side effects. These effects usually diminish after 1 to 2 weeks of use. Pretreatment of the skin with topical anesthetic is necessary before the use of the capsaicin 8% patch to improve tolerability.

Use of capsaicin in pediatrics is limited to case reports. Given the rare incidence of systemic side effects, use of capsaicin for chronic pain in children and adolescents could be considered and will be limited by tolerance to the application.

Other counter-irritants such as methyl salicylates and menthol also have been used for musculoskeletal pain. Methyl salicylate may have direct analgesic effects but also provides tissue warming by its vasodilatory effects.³⁶ Menthol's mode of action is likely the cooling effect it has on the skin. There is limited evidence for the efficacy of these compounds; however, a recent study of a 10% methyl salicylate 3% menthol patch demonstrated greater pain relief than placebo in 208 adults with muscle strains.³⁶

DEXAMETHASONE

Dexamethasone, a steroid, can be delivered iontophoretically for a variety of inflammatory conditions such as knee OA, medial and lateral epicondylitis, Achilles tendonitis, and plantar fasciitis.³⁷⁻³⁹ The data supporting the efficacy of dexamethasone iontophoresis is variable. The largest study that evaluated dexamethasone iontophoresis for epicondylitis demonstrated reduced pain in the active drug group versus placebo; however, the results of several other smaller trials including one for epicondylitis were mixed. It is likely that dexamethasone iontophoresis provides short-term benefits including pain relief in acute musculoskeletal injuries.⁴⁰

One pediatric study of dexamethasone iontophoresis demonstrated efficacy in a case series of 28 patients with juvenile idiopathic arthritis treated for temporomandibular joint involvement.⁴¹

ARNICA

Arnica is a perennial herb indigenous to central Europe. It has been used topically to reduce inflammation, soothe muscle aches, and decrease swelling and bruising associated with injuries.⁴² Two studies have evaluated arnica gel for topical treatment of OA. Knuesel evaluated arnica gel in an open-label trial of 79 patients with mild to moderate OA, demonstrating improved function and decreased pain.⁴³ A subsequent double-blind randomized trial of 204 patients with radiologically confirmed active hand OA compared arnica gel with 5% ibuprofen gel and demonstrated no difference between the groups with decreased pain intensity and improved function in both treatment arms.⁴⁴ Adverse reactions associated with arnica use are limited to mild local skin reactions.

Conclusions

There are a variety of effective topical medications for musculoskeletal pain. Given the excellent safety profile, including lack of systemic absorption and minimal local side effects, the more extensive use of these medications in treating chronic musculoskeletal conditions should be considered.

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