Topical Analgesics for Chronic Pain

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Abstract Such medications as anticonvulsants, nonsteroidal anti-inflammatory drugs, antidepressants, and opioid analgesics enable effective treatment of a variety of chronic pain conditions, but all have the potential for severe adverse effects. Because few patients with chronic pain respond adequately to monotherapy, drug combinations are common, and the risk of side effects increases accordingly. When chronic pain is experienced in a localized area of the body, applying medications topically may have the desired therapeutic effects while reducing potential morbidity. Several commonly used medications are now known to penetrate the skin in therapeutic concentrations, and topical analgesic preparations are becoming more widely used as valuable additions to medical practice. Here we examine the different classes of topical analgesic used to treat chronic pain and the evidence of their efficacy for specific pain conditions.

Keywords Topical analgesics · Lidocaine · Diclofenac · Capsaicin · Clonidine · Chronic pain · Neuropathic · Treatment · Pharmacology · Review

Introduction

Topical analgesics have probably been around for as long as medicine itself. Chinese medical texts in a tomb dated to 186 BCE described the topical application of herbs for pain relief, and the technique may date back centuries earlier

[1]. Topical “patent medicines” for pain relief flourished in the 1800s, although many contained toxic ingredients, for example turpentine, chloroform, or mercury [2]. In recent years, as medical recognition and understanding of chronic pain conditions has grown, the topical route for pain management has seen a resurgence of interest because of its potential to deliver therapeutic doses of medication directly to a painful site, bypassing the GI tract and without the need for a needle. Numerous topical preparations, old and new, are now marketed for the purpose of pain relief. This review is a guide to currently available topical analgesics and their specific applications in chronic pain management.

Topical Drug Delivery

The efficacy of topical drug delivery depends on numerous factors including:

- 1 the depth of the desired drug target below the skin surface;
- 2 the physical properties of the drug to be delivered;
- 3 the rate of drug metabolism and/or circulatory clearance; and
- 4 the vehicle used to deliver the agent.

The top two skin layers are the lipophilic stratum corneum and the largely aqueous epidermis. For drugs to penetrate these layers they must, therefore, have both lipophilic and hydrophilic properties, or be accompanied by a “penetration enhancer”, for example alcohol, propylene glycol, or DMSO [3]. Traditional vehicles for topical administration include poultices, aqueous solutions or suspensions, creams, oils, and oil-based ointments. Newer vehicles include topical gels and a variety of transdermal drug-delivery systems (usually patches). Drugs which are

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ionic salts can be driven through the skin by application of an electric field (iontophoresis) [4]. Portable iontophoretic systems, which carry a small battery for delivery of the electric field, are a promising addition to topical therapy [5] and are already available for use with some drugs.

Table 1 lists topical analgesic preparations commonly used for the treatment of chronic pain. This review examines each listed analgesic and the rationale for its use, as well as others in less common use or still under investigation.

Lidocaine

Lidocaine, an amide-type local anesthetic, reduces voltage-gated sodium-channel activation, blocking generation of action potential and thus inducing anesthesia. Topical lidocaine reduces neuropathic pain by producing a selective block of A δ and C fibers sufficient to attenuate pain but leaving normal sensation intact [6•]. It also activates the irritant receptor TRPV1 [7], which probably explains the burning sensation experienced on initial exposure. Prolonged application leads to elevated thresholds for touch, pinprick, and mechanical windup, and a moderate decrease in epidural nerve fiber density. The latter does not seem to account for the changes in sensory threshold [8••].

Dosage Forms

Topical lidocaine is commonly prescribed as a 5 % transdermal lidocaine patch (LP), which is applied for up to 12 continuous hours per day and can be cut to more precisely match the dimensions of a painful area. Lidocaine patches are recommended for use on intact skin only, to minimize the risk of excessive systemic lidocaine absorption. They are approved in the US for treatment of postherpetic neuralgia (PHN) [9].

Lidocaine is also available in gel and ointment forms. These require more frequent application and tend to rub off on clothing, but may be more practical than patches for use on painful toes or other small areas. A prilocaine–lidocaine cream has also been used for pain treatment and for pre-procedure cutaneous anesthesia [10].

Efficacy

Compared with placebo, the lidocaine patch significantly reduces spontaneous pain and mechanical allodynia in PHN [11] with excellent safety and tolerability [12]. In a randomized, controlled, open-label trial, LP was superior to 300–600 mg/day of the $\alpha 2\delta$ ligand pregabalin for treating PHN pain, but approximately equivalent to pregabalin for treating painful diabetic neuropathy (PDN). For patients already experiencing some relief with monotherapy, the

combination of LP and pregabalin yielded more pain reduction and increased patient satisfaction [13]. LP provided safe and significant pain relief in small uncontrolled trials for children with post-burn neuropathic pain [14] and for cancer patients with focal neuropathic pain [15].

Lidocaine patches are less effective for non-neuropathic pain conditions. A trial of LP for myofascial pain of the upper trapezius revealed modest effect for LP at day 7 of treatment but no difference from placebo by day 28 [16]. A different myofascial pain trial showed LP to reduce pain as well as bupivacaine trigger-point injection and better than placebo, but the study period was only nine days [17]. In a comparison of LP and placebo for chronic low back pain, both groups reported 50 % relief and there were no changes on functional MR brain imaging [18].

Adverse Effects

Topical lidocaine is usually safe when applied to intact skin. Lidocaine patches may cause irritant contact dermatitis among up to one-third of users. Prilocaine–lidocaine cream has been used for anesthesia during minor vulvar procedures; although usually well tolerated, some patients have experienced local irritation accompanied by histopathological changes [19]. There is one case report of methemoglobinemia resulting from chronic topical lidocaine therapy [20].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs inhibit the action of cyclooxygenase, reducing levels of prostaglandins, prostacyclins, and thromboxanes [3], thereby attenuating inflammatory pain. NSAIDs may also reduce pain by a second mechanism, attenuating spinal nociceptive transmission by inhibiting the COX-2 subtype of cyclooxygenase [21].

Topical NSAID application can deliver therapeutic drug concentrations to local tissue. A 100 mg topical ketoprofen patch enables high penetration to synovium and tendons, but with plasma concentrations 10 % or less than with oral administration [22]. After three days of topical diclofenac 4 % spray treatment to osteoarthritic knees, diclofenac had penetrated skin locally in substantial amounts and was found in synovial tissue at 10–20 times the concentration in synovial fluid or plasma [23]. Studies on hairless rats suggest that penetration of topical diclofenac may be enhanced by iontophoresis [4].

Dosage Forms

The US Food and Drug Administration (FDA) has approved two topical NSAID formulations for treating OA: diclofenac sodium topical 1.5 % solution in 45.5 %

dimethyl sulfoxide (D/DMSO), approved for knee OA only [24], and diclofenac sodium 1 % gel (DG), approved for OA of elbows, wrists, hands, knees, ankles, and feet [25]. A diclofenac epolamine 1.3 % patch (DP) is also available in the US but is only approved by the FDA for use to treat sprains and strains. Other NSAID preparations are available internationally.

Efficacy

Strong evidence supports effective pain relief from topical NSAIDs in knee and hand OA. A randomized double-blinded controlled trial of DG resulted in significant pain reduction and functional improvement for patients with unilateral or bilateral knee OA; effect was independent of disease severity or patient age [26]. DG also effectively reduced pain for patients with primary hand OA [27]. D/DMSO reduced knee OA pain and improved function in multiple well-designed clinical trials [28]. DP reduces the acute pain of a variety of minor soft tissue injuries [29] and ankle sprains [30]. The American College of Rheumatology considers topical NSAIDs to be first-line treatment for hand and knee OA [31].

Adverse Effects

Compared with systemically delivered NSAIDs, topical preparations cause more local adverse effects (mainly mild skin reactions) but much less gastrointestinal toxicity [32]. Safety and tolerability of D/DMSO for knee or hand OA were excellent in a pooled analysis of multiple controlled trials [33]. Long-term use of DG (up to 12 months) was safe and well tolerated by the elderly and individuals with hypertension, diabetes, and cerebrovascular and cardiovascular disease [34]. Incidence of GI side effects is low for DP, comparable with that for placebo [35].

Capsaicin

The compound that puts the “heat” into chili peppers has found new medical uses. Capsaicin has profound sensitizing effects on peripheral and central nerve fibers. Capsaicin binds to the TRPV1 ion channel on nociceptive nerve terminals, causing sodium and calcium influx. The resulting depolarization is perceived as a painful burning sensation. Repeated or high-dose cutaneous application can cause desensitization of epidermal nociceptive fibers, causing analgesia [36], and possibly the reversible degeneration of nerve terminals. This effect has been termed “dysfunctionalization” and may be caused by a combination of effects which disable the cell’s normal functions. Originally, capsaicin was thought to induce analgesia by

depleting substance P from nociceptive nerve terminals, but this is no longer believed to be the primary mechanism [37].

Capsaicin is readily absorbed through the skin. Combination with isopropyl alcohol markedly enhances delivery compared with mineral oil or propylene glycol [38].

Dosage Forms

Capsaicin is frequently applied as a cream at 0.025 or 0.075 % concentration. Both of these low-concentration capsaicin creams (LCCC) are available without prescription in the US and are marketed for treatment of muscle and joint pain, arthritis, and neuralgia [39]. As over-the-counter medications, they do not have specific FDA indications.

A high-concentration (8 %) capsaicin patch has FDA approval for treatment of PHN. The FDA has declined to approve this preparation for treating HIV-associated neuropathy (HIV-AN). Because capsaicin at this dose can be quite painful, topical lidocaine is applied to anesthetize the skin before patch application, which typically lasts 60 min. The patch is carefully cut to fit the skin region affected by PHN [40]. A higher-dose capsaicin liquid requiring a shorter application time has shown promise in Phase 2 trials for PHN [41], but its development is stalled pending sale of the product to a new company [42].

Efficacy

There is little evidence to support the efficacy of LCCC in neuropathic pain; studies have been scant and sample sizes small [43]. There is modest support for the use of LCCC to treat OA pain [44], and the American College of Rheumatology conditionally recommends their use for treating hand OA [31]. A 1 % capsaicin hydrogel patch was no better than placebo for treating myofascial pain [45].

The 8 % capsaicin patch has yielded better results for treating neuropathic pain. In well-designed studies, patients with PHN or HIV-AN experienced less pain and better quality of life on the 8 % capsaicin patch than control subjects receiving LCCC [46, 47]. Despite the high dose given at skin level, systemic absorption of capsaicin is low for patch-treated patients and elimination is rapid, supporting the safety of this novel treatment [48]. Tolerability of the patch is improved by application of topical anesthetics before the capsaicin, with several different anesthetics having equivalent efficacy [49, 50].

Other Agents

Many other drugs are applied topically to treat chronic pain, but few have been well-studied. Compounding

Table 1 Topical analgesics commonly used for treatment of chronic pain

Drug name/class	Dosage form	Uses	Comments
Lidocaine (local anesthetic)	2 % gel	PHN, PDN, other neuropathic pain	Irritant contact reaction possible
	5 % ointment	Gel: urethral anesthesia for bladder instrumentation	
	5 % patch	PHN ^a , PDN, other neuropathic pain	Intact skin only; contact skin reaction possible
	2.5 % Prilocaine–2.5 % lidocaine cream	Pre-procedure cutaneous anesthesia ^a Neuropathic pain	
Diclofenac (NSAID)	1 % gel	OA of elbows, wrists, hands, knees, ankles, and feet ^a	Contact skin reaction possible; intact skin only; avoid large surface area for patients susceptible to NSAID side effects
	1.5 % solution in 45.5 % DMSO	Sprains and strains OA of knees ^a	
	1.3 % patch	Sprains and strains ^a	
		OA	
Capsaicin	Low-dose creams: 0.025 %, 0.075 %	Arthritis, muscle pain, joint pain, neuralgias	Burning discomfort; contact skin reaction possible; avoid contact with mucous membranes and eyes; intact skin only
	High-dose patch: 8 %	PHN ^a Other localized neuropathies	

NSAID nonsteroidal anti-inflammatory drug, PHN postherpetic neuralgia, PDN painful diabetic neuropathy, OA osteoarthritis

^a Drug has US Food and Drug Administration (FDA) indication for the condition

pharmacies often prepare creams or gels containing medications in different combinations. These often contain drugs of multiple classes (e.g., an NSAID, an anticonvulsant and/or antidepressant, and a local anesthetic), making it impossible to identify individual treatment effects. The drugs discussed below have been studied as single agents or in two-drug combinations.

Clonidine

This antihypertensive agent, an α_2 -adrenergic agonist, was found to reduce hyperalgesia in patients with sympathetically maintained pain when applied via a transdermal patch to the painful area. Sample size was small but pain relief was marked. The analgesic effect was confined to the area of skin beneath the patch [51]. Topical clonidine gel also reduced pain in patients with PDN in a randomized, double-blind, placebo-controlled trial. Clonidine was superior to placebo only for patients who experienced pain when given topical capsaicin, and those with more capsaicin-induced pain had a better response to clonidine. This suggests that functional, sensitized nociceptors must be present for clonidine to be effective [52••].

Ketamine

A glutamate NMDA-receptor antagonist, ketamine is potentially active centrally as an analgesic and anesthetic, but severe psychomotor side effects have limited its use in pain

management. NMDA receptors are highly expressed in the central nervous system and are involved in the development of dorsal horn “windup” underlying central sensitization [53]; they are also distributed on cutaneous nerve terminals [54], suggesting a possible target for topical therapy. Ketamine is frequently found in custom-compounded topical preparations. However, in a small randomized placebo-controlled study, a 5 % topical ketamine cream was no better than placebo for treating diabetic neuropathy pain [55]. A retrospective chart review found relief of neuropathic pain for 73 % of patients treated with ketamine–lidocaine topical cream, but wide variations in drug concentration, cream base, and type of pain condition limit the applicability of the data [56].

Tricyclic Antidepressants

These are also often seen in compounded preparations. Topical amitriptyline is the best studied. It was effective in two cases of painful peripheral neuropathy at 5 and 10 % concentrations, but systemic adverse effects, including drowsiness, were notable with the 10 % dose [57]. Another group found 2.5 % topical amitriptyline to provide potent local analgesia for rats, though with some toxic effects on the skin; combining amitriptyline with capsaicin prolonged the analgesic effect and caused no adverse skin reactions [58], suggesting potential clinical applications.

Doxepin, another tricyclic drug, has antihistaminic properties and is available as a topical 5 % cream for

treatment of pruritus, but it has also shown promise as an analgesic. Doxepin inhibits inflammatory histamine and substance P responses in human skin [59]. A 0.5 % doxepin oral rinse provided significant pain relief in an open-label study of 41 patients with mucosal pain as a result of cancer or cancer treatment [60]. A combination of 3.3 % doxepin and 0.025 % capsaicin produced analgesia in patients with chronic neuropathic pain, with efficacy similar to either agent used alone but with more rapid onset of analgesia [61]. Unfortunately, topical doxepin may have substantial sedative [62] and anticholinergic [63] effects.

Opioids

Opioid receptors are expressed on peripheral nerve terminals in inflamed tissue [64], prompting investigation of opioids as topical analgesics. The literature thus far has been largely limited to case reports showing some efficacy of topical opioids for chronic superficial wounds [65]. A small randomized controlled trial of topical morphine for chronic painful leg ulcers did not show significant effect; systemic absorption of morphine was minimal [66].

General Considerations

Skin penetration of topical agents may vary between individuals and between body sites with different skin thicknesses, complicating calculation of appropriate doses. For drugs such as tricyclic agents, for which systemic side effects can be substantial, a good general principle is to start with a low concentration and/or cover a small surface area, assess the patient's response, and then titrate the concentration and surface area as appropriate. Cut or burned skin may result in increased systemic exposure to topical agents, risking toxicity. Cutaneous reactions may occur with any transdermal drug-delivery system; irritant contact dermatitis is most common and is usually addressed satisfactorily by careful skin cleansing and careful adhesive removal to avoid skin injury. Allergic contact dermatitis is less common [67].

Conclusion

Topical analgesics are a promising class of agents for treatment of chronic pain. They can be used to supplement or replace systemic analgesics, improving clinical outcome while reducing the side effects and morbidity associated with systemic agents. Lidocaine, diclofenac, and capsaicin are now proved additions to the health-care provider's toolkit, although care should be taken to select the most appropriate drug or drugs for each clinical situation. Other

drugs, many in common use as systemic agents, show promise as topical analgesics and warrant further investigation. Modern medical advances notwithstanding, the ancient Chinese physician's axiom still holds true: "Sometimes, when you rub it on the skin, it really works."

Compliance with Ethics Guidelines

Conflict of Interest NJ Rudin declares he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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