

Topical Analgesics for Pain

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General considerations

Topical analgesics, formulated as creams, gels, and patches are applied locally to the skin and influence pain signalling by local actions on sensory nerve endings and adjacent tissue following dermal penetration. (Note: Some analgesic patches, *e.g.*, fentanyl and buprenorphine, also function as transdermal delivery systems and recruit systemic actions within the CNS). There are several advantages to topical analgesics, as outlined in Table 1. There is currently considerable interest in developing novel topical analgesics for the following reasons:

1. Safety and adverse effect profile:

All major classes of orally administered analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors, opioids, antidepressants, and anticonvulsants exhibit adverse effects, but topical analgesics have a lesser systemic side effect profile.

2. Combination of oral and topical formulations:

In the chronic pain setting, individual drugs produce only partial analgesic efficacy, and combining oral and topical formulations, which act by different mechanisms may achieve greater effectiveness without increasing the side effect burden.

William's Case

William is a 63-year-old plumber who is looking forward to retirement but is concerned that painful osteoarthritis (OA) of his knees will limit his plans to travel and play golf. He is currently being treated for hypertension and has struggled with his weight for many years. He completely discontinued alcohol use in the past year, because it was becoming a problem that threatened his marriage. He reports that ASA gives no relief, and ibuprofen, which he purchased over-the-counter, caused indigestion. On examination, he is obese with a BMI of 32, blood pressure is elevated at 180/90, and both knees have considerable crepitus without any joint effusion. Radiographs show some loss of medial joint space bilaterally, with early osteophyte formation at both the tibial and femoral margins.

3. Knowledge of peripheral pain mechanisms:

With an increased understanding of peripheral pain signalling mechanisms, there is significant potential for drug development using this novel therapeutic approach.

Pain due to arthritis affects quality of life and presents a considerable personal and societal burden. Osteoarthritis (OA) is the most common form of arthritis. It occurs commonly in the knees, hips, and hands, and it affects about half of all persons over 65 years. Current recommendations for the management of OA pain



Table 1

Advantages and Limitations of Topical Analgesics

Advantages

- Production of low plasma drug levels and decreased systemic adverse events
- Avoidance of factors that can limit oral bioavailability (first pass metabolism, influence of gastric factors on absorption)
- Convenience and increased adherence to therapy

Limitations

- Needs appropriate physicochemical properties (molecular size, aqueous/lipid solubility) for dermal and tissue penetration
- Skin characteristics and disease states can alter the extent of dermal absorption
- Potential for local skin reactions (*e.g.*, rash, pruritus, dry skin, irritation)

for hands and knees emphasize concerns regarding the use of oral agents and suggests the use of selected topical agents.¹ Although topical agents have been used to treat rheumatic pain for decades, there has been a resurgence of interest in their use in recent years.

Two topical NSAIDs (diclofenac sodium 1% gel, and diclofenac sodium 1.5% in 45% dimethyl sulfoxide) are available in Canada for treatment of OA. Recent trials evaluating topical diclofenac formulations for knee OA indicate improved pain, physical function, and overall ratings over 12 weeks.^{2,3} Benefits are manifest at one week, develop more fully by four weeks, and are maintained to 12 weeks.² Application site reactions occurred in 5 to 18% of participants, but systemic adverse effects were minimized with topical NSAIDs, and equivalent to placebo. Meta-analysis indicates that topical NSAIDs exhibit a comparable efficacy to oral NSAIDs.⁴ While topical NSAIDs produce benefit

in OA in both younger (< 65 years) and older patients (≥ 65 years),⁵ there is some concern about long-term safety in older adults and caution is required.⁶ Topical NSAIDs are also useful for soft tissue injuries, such as sprains, strains, and contusions.⁷

Capsaicin, a constituent of hot peppers, acts on TRPV1 receptors, which are temperature sensors and regulate pain signalling on sensory nerve endings; it produces initial activation and then desensitization of these receptors. Available as a topical analgesic (generally 0.025 to 0.075%) for several decades, capsaicin has been used to treat musculoskeletal conditions; it exhibits modest efficacy (number-needed-to-treat of eight), but about one-third of users experience local adverse events (burning). It is considered for those unresponsive to, or intolerant of, other treatments.⁸ More recently, cis-capsaicin 0.075% demonstrated added efficacy (improved pain and physical function) over three months in those taking oral NSAIDs or COX-2 inhibitors for knee OA; although one-third of users reported burning, only 7% discontinued use.⁹ This agent is available in Canada as an add-on analgesic to oral NSAIDs or COX-2 inhibitors for severe OA pain. There is also a high concentration 8% capsaicin patch, available in the EU and USA but not in Canada, for treatment of neuropathic pain, such as post-herpetic neuralgia.¹⁰ A single 60-minute patch application reduces pain for 12 weeks, but application-site pain needs to be managed with oral analgesics and/or ice on the day of treatment.¹ There is no evidence available for OA with this patch.

There are many over-the-counter (OTC) preparations of topical analgesics claiming efficacy in a variety of musculoskeletal and arthritic conditions. Some are traditional formulations (*e.g.*, Tiger Balm®, Lakota), while others are newly assembled combinations of ingredients. These generally contain several natural products (*e.g.*, camphor, menthol, capsaicin, herbal extracts) and are subject to a different regulatory stream than

are pharmaceutical agents. Several ingredients have actions on different members of the TRP receptor family (e.g., camphor acts on TRPV1 and TRPV3 receptors, menthol acts on TRPM8 and TRPA1 receptors), and there is a general plausibility regarding their ability to influence sensory transduction based on homologous actions to capsaicin at TRPV1 receptors.¹¹ There are not many controlled trials of these agents, and efficacy claims are based on common usage and anecdotal claims.

Back to William

William has OA of both knees that is considered to be mild to moderate. Obesity and his occupation, which requires deep knee bends, are risk factors for OA. He presents a number of risks for the use of oral agents to help relieve his pain; thus, his hypertension is not controlled well enough and gastrointestinal irritation could be aggravated by the use of an oral NSAID. Additionally, his prior history of alcohol abuse should be a red flag for the use of opioid medications. He would be an ideal candidate for the use of topical NSAIDs in-line with the American College of Rheumatology 2012 guidelines.

Take-home Message

1. Topical NSAIDs are a rational and relatively safe treatment choice for peripheral osteoarthritis (knee, hand).
2. Topical NSAIDs exhibit local skin reactions, but they are generally well tolerated.

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