Review Article

Topical Analgesia for Oral Mucosa: An Update

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ABSTRACT

Topical drugs used to control pain acts locally on damaged or dysfunctional soft tissues or peripheral nerves. Till date, there are only a limited number of topical therapies available for the relief of somatic pain. This article reviews various topical analgesic therapies for oral mucosa.

INTRODUCTION

Pain processing and transmission are achieved by a complex interaction of pathways and processes. Topical drugs used to control pain acts locally on damaged or dysfunctional soft tissues or peripheral nerves. They differ from transdermal delivery systems in that they target a site immediately adjacent to the site of delivery rather than using the skin as an alternate systemic delivery system. These topical applications can be in the form of cream, lotion, gel, aerosol or patch. These application methods allow for a higher local concentration of the drug at the site of initiation of the pain and lower or negligible systemic drug levels producing fewer or no adverse drug effects. However, some degree of systemic absorption will occur following localized delivery methods, especially with lipid soluble drugs, and the degree of systemic absorption needs to be assessed during the development of formulations.

Topical medications offer distinct advantages over systemic agents including greater safety, rapid onset of action and low side-effect profile. However, if local pharmacotherapeutics are to work, the targeted disorders should be regional and chronic and should demonstrate a pain relief response to topical anesthetics. Complete cessation of pain on application of topical anesthetic may not be possible, as some of the neuronal changes may be central or due to neuropathic changes not easily reached by most topical anesthetics. Nevertheless, topical medications are useful for neuropathic pain due to peripheral nerve sensitization, as well as for centralized neuropathy that is accompanied by local allodynia. In the latter situation, the topical medication is used over the trigger site to reduce the ongoing neural stimulation that maintains the central sensitization. In cases of mild-to-moderate pain, the local therapy might be the sole intervention but for moderate-to-severe pain, the use of systemic medications as well as local topical medications is required. In addition, a locally applied medication can offer faster relief while a centrally acting medication is being titrated up to effective levels.

Till date, there are only a limited number of topical therapies available for the relief of somatic pain. Analgesic therapies for acute and chronic pain conditions available are three major classes of drugs: nonsteroidal anti-inflammatory drugs (NSAIDs[1]), opioids, and a group of drugs with diverse pharmacological actions collectively known as adjuvants (e.g., antidepressants, anticonvulsants, local anesthetics, α_2-adrenoceptor agonists). Both NSAIDs and opioids exhibit a variety of adverse actions, and many chronic pain states, particularly that involving nerve injury, are not adequately controlled by these agents. With adjuvants, it is often necessary to titrate the dosage until adequate pain relief or intolerable side effects develop.

DELIVERY SYSTEM FOR OROFACIAL REGION

The purpose of a local delivery system is to apply a medication for a therapeutic action in a site-specific manner. The drug's molecular structure and its pharmacological behavior dictate the delivery site and system. Intraorally, topical agent should have a mucoadhesive base. This mucoadhesive base remains in place for several hours after application. One common mucoadhesive base is orabase compounded with a local anesthetic agent. It also is used frequently as a carrier vehicle for applying other medications (such as capsaicin) to the oral mucosa. Other common local delivery systems are dissolvable tablets and lozenges (placing drugs under the tongue), adhesive patches and powders (like lignocaine patch for oral mucosa) and tissue covering stents (like custom made intraoral stents)

This article is an effort to describe and update the use of various topical analgesics on oral mucosa.

VARIOUS TOPICAL MEDICATIONS

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs act peripherally to reduce the production of prostaglandins that sensitize nerve endings at the site of injury. This effect occurs due to inhibition of the cyclooxygenase (COX) enzyme that converts arachidonic acid liberated from the phospholipid membrane by phospholipases to prostanoids such as prostaglandins. Bioavailability and plasma concentrations following topical application are 5 to 15% of those achieved by systemic delivery. There are many clear evidences to support efficacy of topical NSAIDs given by gel, spray, or patch. When NSAIDs are administered topically, relatively high concentrations occur in the dermis, whereas levels in the muscle are at least equivalent to those following systemic administration.

Some of the medications used topically for pain include ketoprofen (a propionic acid derivative), diclofenac (a benzene-acetic acid derivative), aspirin, piroxicam and ibuprofen formulated into cream, gel, sprays or even patches. Gels are better absorbed than creams. Topical aspirin also has been specifically studied for dermal neuropathic pain, providing analgesia within 20 to 30 minutes.

Benzydamine hydrochloride is a non steroidal drug with analgesic, anti-inflammatory and antimicrobial properties. Its mechanism of action is not entirely known, but the drug may

effect formation of thromboxanes and alter the rate of prostaglandin production, and thereby inhibiting platelet aggregation and stabilizing cell membranes. It is generally been used undiluted, but if stinging occurs it may be diluted with water. When used as a rinse, its dose is 15 ml which should be held in mouth and swirled around for at least 30 seconds and use has to be repeated after every three hours. It is indicated for relief of various painful conditions of the oral cavity including radiation mucositis, aphthous stomatitis, burning mouth syndrome, post orosurgical and periodontal procedures.

Some compounds like salicylates, are related pharmacologically to aspirin and NSAIDs but their principle action is to act as skin irritant. They are also commonly used in painful oral mucosal conditions.

Opioids

The central effects of opioids on pain transmission are by actions within the dorsal horn of the spinal cord and at brainstem and other supraspinal sites have been recognized. It is known that opioid receptors also are present on the peripheral terminals of thinly myelinated and unmyelinated cutaneous sensory fibers. μ-Opioid receptor agonists are generally the most potent at producing peripheral analgesia, with δ- and κ-opioid receptor agonists being less active. In addition to the peripheral delivery of opioids by localized injection, opioids may also produce benefits following topical application to somatic sites. The topical opioids produce analgesia when applied to painful ulcers and skin lesions following burns, and in cutaneous pain in a palliative care setting. Morphine can be administered topically at any suitable dose providing relief of pain. It is given as a mouthwash, swish, shallow liquid, gel, ointment, paste, powder, film, chew, lozenge, troche, candy, sublingual or buccal tablets and oropharyngeal spray. Studies have shown that mouthwashes with a morphine containing solution decrease oral pain substantially, while not causing the side effects as seen in systemic administration of narcotic analgesics.

Depending on the type of intraoral composition and the dosage to be administered, the concentration of morphine therein can vary over a wide range. In a low-volume (about 0.5 to about 2 ml) composition, concentration of morphine can illustratively be about 5 to about 200 mg/ml; in a medium-volume (about 2 ml to about 15 ml) composition, illustratively about 1 to about 50 mg/ml; and in a high-volume (about 15 ml to about 25 ml) composition, illustratively about 0.5 to about 10 mg/ml.

The composition comprising morphine can be bioadhesive to the oral mucosal surface, exhibiting a retention time thereon of about 0.5 to about 24 hours or even longer. In various embodiments, the morphine-containing composition has at least one non-lipoidal or hydrophilic internal phase and at least one lipoidal or hydrophobic external phase that is bioadhesive to the mucosal surface.

As an alternative to, or in addition to, morphine or other opioid as an analgesic agent to be administered topically in combination with phenyloin, a non-opioid analgesic such as benzydamine or capsaicin and/or a locally acting anesthetic such as lidocaine, benzocaine, xylocaine, dyclonine or diphenhydramine can be used.

Capsaicin

Capsaicin, the compound in chilli peppers, binds to nociceptors in the skin, causing an initial excitation of the neurones and a period of enhanced sensitivity. This is usually perceived as itching, pricking, or burning, with cutaneous vasodilation, and is thought to be due to selective stimulation of afferent C fibres and release of substance P. This is followed by a refractory period with reduced sensitivity and, after repeated applications, persistent desensitisation, possible due to depletion of substance P. Depending on the concentration used and the mode of application; capsaicin can selectively activate, desensitize, or exert a neurotoxic effect on small diameter sensory afferent nerves while leaving larger diameter afferents unaffected. Topical capsaicin preparations of 0.025 and 0.075% are available for human use and are used to treat pain from postherpetic neuralgia, diabetic neuropathy, osteoarthritis and rheumatoid arthritis. Capsaicin has also been used to treat pain due to pruritus, psoriasis, oral neuropathic pain including burning mouth syndrome, trigeminal neuralgia, temporomandibular joint disorders, cluster headache (following intranasal application), dermatological and cutaneous conditions. Whereas pain relief is widely observed in these conditions, the degree of relief is usually modest, although some patients have a very good result.

Topical capsaicin is generally not considered a satisfactory sole therapy for chronic pain conditions and is often considered an adjuvant to other approaches.

The most frequently encountered adverse effect with capsaicin is burning pain at the site of application, particularly in the first week of application. Because of the limited penetration of this medication, capsaicin would be most useful when the patient's complaint is one of superficial peripheral pain, usually characterized by burning, tingling and allodynia that responds to topical or local anesthetics. It also can be used in patients who exhibit a superficial trigger area for a deeper pain. Capsaicin (0.025 percent and 0.075 percent) and can be mixed with a gelatin, pectin, methylcellulose and benzocaine cream (Orabase-B, Bristol-Myers Squibb) for intraoral use to improve its consistency and to incorporate the local anesthetic effect of benzocaine.

TOPICAL ANAESTHETIC AGENTS

As neuropathic pain frequently is associated with a peripheral ectopic generator , it is logical to use a topical anesthetic to desensitize the painful site. This approach may decrease the neuronal firing and relieve the pain. Local anesthetics are prepared for topical use in several different forms, such as aqueous or viscous gels, sprays and ointments. With neuropathic conditions, the application of the anesthetic usually is limited to a small area, and in those cases, a sticky ointment or viscous gel often is preferred. Thus, the increased sensitivity of ectopic activity to local anesthetics and the use-dependent nature of channel block allow for the block of spontaneous and evoked activity (impulse generation) without affecting nerve conduction (impulse propagation).

Topical lidocaine, xylocaine and benzocaine are used frequently on the oral mucosa. Benzocaine is available in different concentrations and presentations, the most common being paste and gel of 20 percent strength. Topical lidocaine as a 5% gel or patch

provides effective pain relief in postherpetic neuralgia with no systemic adverse effects. The general principle of treatment for topically responsive pain is to apply the anesthetic agent several times each day. The goal is to maintain local numbness, reduce ectopic neuronal firing and thereby reduce the peripheral neural sensitization. For extraoral application, covering a treatment site with a plastic adhesive sheet keeps the anesthetic in the desired area. Custom-fabricated tissue stents can be used intraorally to hold the anesthetic paste (or other topical medications) in place and protect the paste from salivary contamination and dissolution. Pretreatment with glycopyrronium enhances absorption and prolong the analgesic action of topically administered lignocaine.

A new topical anaesthetic formulation, EMLA (eutectic mixture local anaesthetics) has been reported to be one of the most effective topical anaesthetic. Recent studies shows that after 5 minutes of application EMLA shows a high degree of analgesia on oral mucosa compared to benzocaine and lidocaine although benzocaine show rapidest action. Bitter taste (pH = 9.0), low viscosity, cost, and subjects' preference are among the many disadvantages of EMLA® use in the oral mucosa. Other topical anaesthetics which have been used is ropivacaine which is a long acting amide local anaesthetic

Liposomal encapsulation of local anesthetics (e.g. liposome-encapsulated ropivacaine) enhances penetration through the epidermal barrier, carrying the encapsulated drug into the skin and providing sustained release. The permeability of the oral mucosa is estimated to be 4–4000 times more than that of skin. The better penetration of liposomal formulations and better mucosa permeability could suggest that some liposomal-encapsulated local anesthetics applied to the oral mucosa surface could penetrate the cortical bone and pulpal tissue.

Anticonvulsants.

It has long been appreciated that there a similarities between epilepsy and neuropathic pain and that drugs that are effective in reducing seizure frequency may also have an analgesic effect in neuropathic pain. Studies have suggested that an accumulation of voltage-gated sodium channels at the site of peripheral nerve injury is a primary precursory event for subsequent afferent hyperexcitability. Among the anticonvulsants drugs used topically are phenytoin, carbamazepine and gabapentin.

Carbamazepine 4% and gabapentin 4% act by suppressing paroxymal discharges and reducing neuronal hyperexcitability. Phenytoin has an unrecognized property of inhibiting mucosal degeneration and/or enhancing mucosal regeneration in a subject having oral mucositis or at risk of developing oral mucositis. It is believed that this property arises from stimulation of endothelial hyperplasia, leading to more rapid replacement of mucosal tissues lost or destroyed as a result of the mucositis. The phenytoin can be administered as straight active agent, for example in powder form, but for most purposes it will be found preferable to administer the phenytoin in a pharmaceutical composition that is adapted for intraoral administration. For each administration, a volume of about 0.5 to about 25 ml of an intraoral composition is typically administered, although lower and higher volumes can be suitable in particular situations.

Antispasmodic agents and tricyclic antidepressants

Gamma-aminobutyric acid, or GABA, is a central inhibitory neurotransmitter that also has been demonstrated to exist in the peripheral tissues. Baclofen is a GABA-B agonist and exhibits an analgesic effect via central modulation of the GABA system. There is little support for topical application of baclofen as an antispasmodic in cases of striated muscle spasm.Antidepressants produce a range of acute pharmacological actions including inhibition of noradrenaline (NA) and 5-HT reuptake, inhibition of NMDA, nicotinic, histamine, and 5-HT receptors, and block of ion channels), and a number of these actions, and even combinations of these actions, may contribute to the local peripheral efficacy of antidepressants .The antidepressant doxepin is available as a cream for the treatment of eczema. Interestingly, a recent study reported that doxepin, formulated as a mouthwash, produces analgesic actions in patients with oral mucosal pain due to cancer or cancer therapy. Antidepressants exhibit promise as a useful class of agents to be used as analgesics following topical application and other methods of local delivery.

Glutamate Receptor Antagonists

Within the dorsal spinal cord, both ionotropic glutamate receptors [NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainic acid (KA)] and metabotropic glutamate receptors are involved in nociceptive signaling and central sensitization in conditions of chronic pain. More recently, it has been appreciated that multiple glutamate receptors also are expressed on peripheral nerve terminals, and these may contribute to peripheral nociceptive signaling. Ionotropic and metabotropic glutamate receptors are present on membranes of unmyelinated peripheral axons and axon terminals in the skin.

There is some evidence in humans to support a peripheral site of action for ketamine, a noncompetitive NMDA receptor antagonist, in reducing pain responses. There are also some case reports regarding the efficacy of ketamine administered topically for sympathetically maintained pain and for pain in a palliative setting.

α-Adrenoceptor Agonists

Sympathomimetic agents may be useful in some forms of chronic neuropathic pain where nociceptor activity is being stimulated by sympathetic fiber release of norepinephrine in the periphery. It has been shown that injured C fibers express α_1 receptors on their peripheral membranes. Sympathetic activity then would excite the C fibers, signaling pain. Clonidine, an α_2-adrenergic agonist, has been used as a topical agent for neuropathic pain because it is able to interrupt the peripheral release of norepinephrine, thereby decreasing the C-fiber stimulation. Topical clonidine gel formulation contain 0.05-0.1 wt% clonidine which is applied to painful areas once a day to upto three times a day.

COMBINATION STRATEGIES

Combination strategies used to treat oral mucositis may be effective in reducing the risk of adverse drug reactions, drug tolerance and addiction. Some of the examples are magic mouthwash which contain lidocaine, diphenhydramine and magnesium aluminum hydroxide and compositions comprising a mucoadhesive (e.g., poloxamer 407), a

local anesthetic (e.g., lidocaine) and an opioid (e.g., morphine or a pharmaceutically acceptable salt thereof, such as morphine sulfate pentahydrate).

CONCLUSION

Topical medications are used to treat only a specific peripheral target with minimal or no systemic effect. These potentially help patients who are intolerant to systemic medications, older patients and medically compromised patients. These topical preparations should have penetration enhancers such as anhydrous gels and bioadhesive copolymers which are used to carry the medication transdermally and transmucosally.

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