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### **HOURS:**

**9 AM - 6 PM**

**Monday - Friday**

## **Topical Medications for Orofacial Neuropathic Pain**

**There are an ever-increasing number of medications that can be used to help patients with neuropathic-based oral and perioral pain problems. Advancements in the delivery of medications include the development of vehicles (Pluronic lecithin organogel [PLO]) that can penetrate the mucosa and cutaneous tissues, carrying active medication to the affected site.**

Systemic administration of medication for patients with regional or local conditions poses several disadvantages over the preferred oral route. Most notable include hepatic first-pass metabolism, enzymatic degradation, and presystemic elimination within the gastrointestinal (GI) tract.<sup>1</sup> In contrast, administration of a medication directly to a target area, including local injection and transdermal application at the affected site, offers distinct advantages over systemic administration including more rapid onset of action and lower side-effect profile. The oral mucosa, specifically, has a rich blood supply, is relatively permeable, demonstrates short recovery times after stress or damage,<sup>2,4</sup> and is tolerant to potential allergens due to the virtual lack of Langerhans cells.<sup>5</sup> For orofacial disorders that are regional, near the surface or chronic, topical medications offer a clear advantage over systemic treatment options.<sup>6</sup> For the clinician, an understanding of the various drug delivery mechanisms available for topical, transdermal, intraoral, and extraoral use can be of great benefit in the management of neuropathic orofacial pain.

salivary lubrication, the presence of inflammatory conditions, and physical damage to the oral mucosa.

### **Orofacial Neuropathies**

Chronic neuropathic pain, including diabetic peripheral neuropathy, postherpetic neuralgia, and orofacial pain syndrome is the result of multiple, often unknown etiologies sharing a single pathophysiological pathway.<sup>6</sup> An understanding of both the peripheral and central changes that occur in neuropathic pain syndromes, as well as the relationships between the various neurotransmitters and nociceptors, which as of yet are not completely understood, is vital to the development of customized treatment protocols. Chronic peripheral nociceptor irritability, as a result of neuronal injury, demyelination, or vascular compression occurs subsequent to a release of excitatory and inflammatory mediators as well as functional changes in the peripherally located sodium channels. Central neuronal changes and the activation of *N*-methyl-D-aspartate (NMDA) receptors start a chain of events that

### **Orofacial Drug Delivery**

Transdermal delivery of medication in the oral and perioral region is dependent upon the agent's ability to penetrate the stratum corneum of the extraoral skin or the oral mucosa, which can be affected by the patient's skin integrity, age, the presence of any dermal conditions and natural variations in thickness, and keratinization of the epithelial tissue.<sup>7</sup>

The barrier capabilities of the oral mucosa are greater than that of the intestinal mucosa, but in general are far less effective than the skin. The results are dependent upon the patient's age,



## TOPICAL FORMULATIONS FOR THE TREATMENT OF OROFACIAL NEUROPATHIC PAIN

### Rx

Capsaicin 0.05% and Ketamine Hydrochloride 2% in Pluronic Lecithin Organogel

### Rx

Ketoprofen 10% and Lidocaine Hydrochloride 5% in Pluronic Lecithin Organogel

can result in the development of allodynia and hyperalgesia.<sup>1</sup>

## Topical Medications

For successful treatment of orofacial neuropathies the disease should be regional and chronic and should indicate a response to topical anesthetics, thereby differentiating itself from a centrally driven pain mechanism. Novel approaches to the clinical management of chronic neuropathies, in general, include NMDA receptor antagonists,  $\alpha_2$ -agonists, sodium channel blockers, GABA agonists,  $\alpha_1$ -antagonists, and opioids in various combinations. Transdermal lidocaine has been shown clinically to reduce postherpetic neuralgia pain.<sup>4</sup> Depending upon the mechanism driving the pain, application of topical anesthetics may not completely eliminate the pain response. This partial or incomplete response is especially true in the case of central neuronal changes or inaccessible regions. Topical anesthetics, however, are still useful for pain from peripheral nerve hyperexcitability or allodynia, which may accompany central pain conditions. Lidocaine, benzocaine, tetracaine, and prilocaine in

the form of gels, pastes, spray, and lozenges are frequently used topically for oral mucosal conditions as well as transdermally for facial neuropathies.

Additional agents with reported benefits for orofacial neuropathic pain include: capsaicin, NSAIDs, clonidine, ketamine, carbamazepine, amitriptyline, and baclofen. Capsaicin has demonstrated efficacy in traumatic neuropathy, trigeminal neuralgia, postherpetic neuralgia, and chemotherapy or radiation-induced oral mucositis.<sup>1</sup> While NSAIDs can cause serious GI side effects when taken orally, transdermal formulations avoid GI tract irritation and first pass metabolism. Few if any systemic side effects and improved patient compliance have been reported with local application of NSAIDs, including ketoprofen, diclofenac, and ibuprofen.<sup>8,9</sup>

Controlled studies and case reports on transdermal ketamine, an NMDA blocking agent, demonstrate efficacy in neuropathic and nociceptive pain with no systemic side effects.<sup>10-12</sup> Administered transdermally, clonidine (a sympathomimetic) has been

shown to relieve hyperalgesia in patients with sympathetically maintained pain.<sup>1</sup> Anticonvulsants, including carbamazepine, have demonstrated efficacy in the periphery theoretically by blocking the sodium channels that appear to accumulate at the site of peripheral nerve damage leading to hyperexcitability. Amitriptyline and baclofen have been used for their analgesic effect by the central modulation of the GABA and serotonin systems, respectively. Anecdotal reports indicate that the use of multiple agents with various mechanisms of action increases efficacy while decreasing adverse events.<sup>13</sup>

## Drug Delivery Systems

Improvements in the delivery options for medications for intra- and extraoral use include the development of vehicles designed to penetrate the mucosa and cutaneous tissues, carrying active agent to the affected site, as well as mucoadhesive dosage forms devised to prolong the time in which an active moiety can remain at the site.

The ability of an agent to penetrate either the facial skin or the oral mucosa can be increased by the use of delivery vehicles that increase the lipid solubility of the medication. The development of oil/water microemulsion systems has provided transdermal vehicles that are balanced for delivery of both hydrophilic and hydrophobic drugs.<sup>14</sup> The standard of transdermal delivery systems is PLO, which is composed of Pluronic gel (the water phase) and lecithin/isopropyl palmitate (the oil phase). This microemulsion has been shown to have the ability to deliver

a multitude of pharmacological agents, including NSAIDs, across the epidermal barrier through either simple diffusion through the lipid intercellular matrix or by the slight disorganization of the skin which allows the drug to pass through the stratum corneum.<sup>8,15</sup> Unlike dimethyl sulfoxide (DMSO), which damages the stratum corneum by dissolving the lipid layers, PLO harmlessly disrupts the layers allowing the medication to slip through.<sup>16</sup> PLO has been shown both *in vivo* and *in vitro* to facilitate the release and permeation of drugs applied transdermally.<sup>17</sup>

Medication impregnated mucoadhesive bases and pastes reduce the inconvenience of repeated reapplication of topical agents for intraoral use. Topical agents without adhesive properties can dissolve, spread throughout the mouth and can ultimately be swallowed. Additional delivery systems for the orofacial region include:

- Adhesive patches and powders
- Aqueous gels
- Dissolving polymeric devices
- Dissolving tablets or lozenges
- Medicated chewing gum, candy and lollipops
- Medicated lipbalms
- Mouthwashes
- Tissue-covering stents
- Toothpastes

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