News from Good Life

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Please don't hesitate to let us know how we can be of further assistance to you and your practice.

Sincerely,
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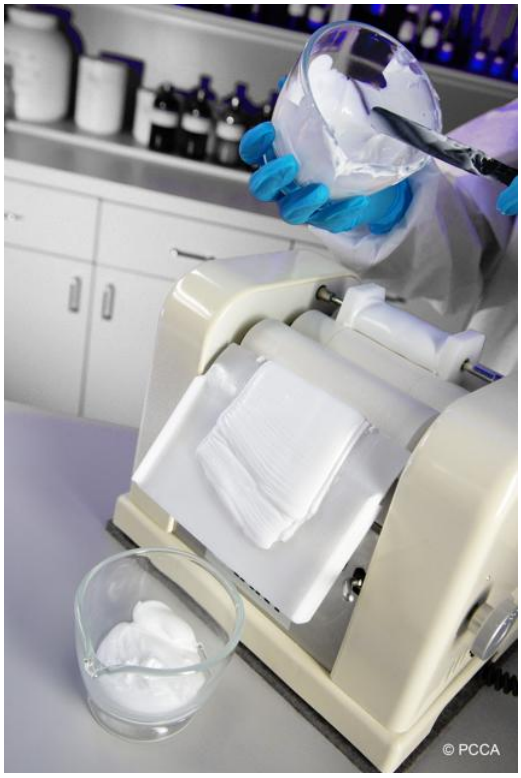
Management of Chronic Neuropathic Pain with Compounded Topical Analgesics

The recent increase in opioid use has prompted pain physicians to find new and improved solutions to tackle chronic, refractory pain syndromes. Topical analgesics are emerging as a valued solution.



Neuropathic pain (NP) is defined by the International Association of the Study of Pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". NP can present alone or in any combination with other types of pain and affects 6-8% of the population. NP can originate from focal lesions in the peripheral nervous system such as postherpetic neuralgia (PHN) or post-traumatic neuralgia, or from general lesions such as painful diabetic neuropathy, HIV-neuropathy, etc. Additionally, lesions to the CNS and other complex disorders (spinal cord injuries, stroke, complex-regional pain syndrome, etc.) can cause NP. NP can be described as burning, tingling, electric-like or a shooting sensation, with a combination of sensory loss and the paradoxical presentation of hypersensitivity in the painful area. The mechanism of NP includes peripheral sensitization, central sensitization in the dorsal horn of the spinal cord as well as changes in cortical and subcortical regions.

Topical versus Transdermal

Transdermal delivery of medication is accomplished through percutaneous absorption, and systemic therapeutic drug levels can be achieved, comparable to those of oral medication. Often, transdermal medications can be administered distal from the painful area. Transdermal drug delivery has advantages because it avoids first-pass hepatic metabolism which occurs with oral drugs, and the need for frequent painful injections associated with parenteral therapy.

Topical medication targets soft tissues and peripheral nerves underlying the site of application, and exerts its action at the site of application by penetrating the skin through passive diffusion. Therefore, topical medication does not produce systemic side effects or drug-drug interactions. One of the main targets for topical analgesics are keratinocytes. This network of skin cells includes a number of receptors, neurotransmitters and neuropeptides, which play a significant role in the development of NP.

Topical analgesics may be safer and are easier to use as compared to systemic drugs. Due to the complex nature of NP conditions, topical analgesic therapy should be employed as part of a multidrug approach. Elderly patients are a target group that can benefit from topical analgesics. The American Geriatrics Society recommends the use of topical analgesics for NP. The elderly population undergoes reduction in the fat-to-muscle ratios which makes the use of opioids less optimal. Additionally, reduction in the renal and hepatic metabolism and various comorbidities managed with multidrug therapy supports the use of topical versus systemic medication for safety concerns. However, there are some limitations to the use of topical agents in management of NP. Topical analgesics can be used on a limited skin area due to increased risk of toxicity, and for that reason they cannot be used in conditions with skin integrity disruption or large affected areas.

Many studies have been conducted on the efficacy of topical ketamine cream, clonidine gel, topical gabapentin, topical baclofen and topical phenytoin for peripheral neuropathic pain, either alone or in combination with other formulations.

Practice Points

- In order for a topical analgesic to pass through the stratum corneum of the epidermis, it has to possess both hydrophilic and hydrophobic elements.
- The choice of base determines the extent of absorption of a topically applied medication.
- Ketamine acts as an inhibitor on voltage-gated Na+ and K+ ion channels.

- Topically applied ketamine exerts its peripheral antinociceptive effect by the activation of neuronal nitric oxide synthase.
- Clonidine is lipophilic, which aids in easy skin penetration and it has a half-life of approximately 8 hours, thus requiring three-times daily topical application.
- Phenytoin 10% cream, a nonselective voltage-gated Na channel stabilizer, GABA-a receptor agonist, showed promising results in allodynia reduction.
- Topical gabapentin 10% cream reduced allodynia and hyperalgesia in chronic sciatic constriction nerve injury in rats.
- GABA-b receptors are located in cutaneous layers on nerve endings and keratinocytes.

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Topical Ketamine-Amitriptyline-Lidocaine for Chronic Pruritus

Topical analgesics have been studied extensively in the management of neuropathic pain, however, limited data is available on their role in treating pruritus.

A study at the Department of Dermatology at Temple University Hospital retrospectively examined the clinical response and tolerability of the combination of topical ketamine-amitriptyline-lidocaine (TKAL) on chronic itch. Its proposed mechanism of action is aimed at reducing hypersensitivity of peripheral nerve fibers through blockade of N-methyl-D-aspartate receptor and sodium channels. The change in numeric rating scale before and after use of TKAL was assessed as were any adverse events. In addition, rates of prescription refills as a measure of patient adherence were documented as TKAL was not covered by most insurance. A total of 96 patients (68.8% female) with a mean age of 65.6 years were identified. Patients reported a mean duration of itch of 76.7 months with 38% having failed more than 3 previous treatments. TKAL was prescribed at a standardized concentration of 10% ketamine, 5% amitriptyline, and 5% lidocaine compounded in a lipoderm cream, except for 16 patients who were prescribed the combination with 5% ketamine. Patients were instructed to apply sparingly to areas that were the most severe, up to 3 times daily. The most frequent indications were for neuropathic conditions (29%) and prurigo nodularis (19%). The average numeric rating scale was 8.63 +/- 1.62 before and 4.19 +/- 2.9 after treatment with an average reduction of 4.61 +/- 2.77. Although oral systemic medications were concomitantly prescribed, most commonly gabapentin (46%) and mirtazapine (22%), 63% of patients attributed relief directly to the use of TKAL alone with reduction in numeric rating scale seen in all pruritus subtypes. Refills were granted as needed and requested on average of 2.41 times with an average of 43.67 days between refills. Review of a pharmacy administered telephone survey that assessed medication tolerability and efficacy of 40 patients revealed that 23 patients (58%) had relief to a great extent and 14 (35%) to a moderate extent, experiencing itch relief within 4.18 +/- 3.39 minutes on average. Side effects reported by 16 subjects were primarily a mild localized burning sensation (7%) and redness (6%) at the application site. Although limited by its retrospective nature and use of concomitantly prescribed systemic oral medications, this study further supports the use of TKAL as an effective single or adjuvant therapy when treating various pruritic conditions.

NOTE: A case of encephalopathy was recently reported in an elderly patient with eczema after applying TKAL over his entire body. Thus, it is important to counsel patients on appropriate usage, including the extent of body surface application.

J Am Acad Dermatol. 2017 Apr;76(4):760-761.
JAMA Dermatol. 2016 Dec 1;152(12):1390-1391.

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