Compounded Ketamine

*A Useful Agent for Neuropathic Pain*

Neal S Taub, M.D.

Patients often suffer with continued neuropathic pain even after the typical medications have been prescribed. Prescribers can consider topical agents as an alternative in the analgesic regimen. While the more common topical analgesics include capsaicin and lidocaine, other medications can provide different types of analgesic activity such as excitatory mediators, peripheral afferents, and inhibitory influences. Topical analgesics have many advantages over systemically administered medications. The reduction or elimination of side-effects stands chief among these advantages. Topical analgesics differ from transdermal delivery methods in that prescribers use topical applications to deliver local, rather than systemic, effects. Our practice, The Center for Musculoskeletal & Pain Medicine, uses a variety of custom-compounded agents to improve your patients’ experience with pain.

One of the custom compounds useful for some patients is a topical ketamine cream. Peripheral N-methyl-D-aspartate (NMDA) receptors have been implicated in nociception.\(^1\)\(^-\)\(^3\) Ketamine blocks NMDA and 5HT receptors, Na+ and Ca+ channels, and the edema response associated with inflammation. Topical ketamine applications have documented success with neuropathic pain in terms of providing some direct analgesia and in terms of inhibiting sympathetically maintained pain. However, the most important use of custom-compounded ketamine cream is the reduction of hyperalgesia (an exaggerated sensation after a painful stimulus), the reduction of allodynia (a painful sensation elicited by a nonpainful stimulus), and as a tolerance-protective agent.\(^4\)\(^-\)\(^12\) The literature describes topical ketamine applications as being useful for pain management in cases of post-surgical neuropathic pain, complex regional pain syndrome, lumbar radiculopathy, post-herpetic neuralgia, and idiopathic proctodynia.

In 2006, Poyhai and Vainio proposed that ketamine cream worked by being absorbed into the bloodstream and reducing central sensitization.\(^7\) However, the evidence collected by Finch and colleagues (Pain 2009), suggests that ketamine cream acts only locally.\(^4\) After applying a 10% ketamine cream compound, they could not find
evidence of ketamine in the bloodstream for 20 patients, and ketamine applied to healthy limbs produced no effect in painful limbs. Custom-compounded ketamine creams have no documented side effects.

We introduce the subject of custom-compounded topical ketamine as an illustration of the many considerations and possibilities available in pain management.

References

Compounded Drug Delivery for Analgesia, and Inflammation.
Michele Koukhab, Doctor of Pharmacy Program
USC School of Pharmacy, Class of 2007

INTRODUCTION
Among the latest innovations of the pharmaceutical industry is the technology of drug delivery that overcomes the disadvantages of oral drug administration. These effects include first-pass metabolism and adverse drug side effects. An alternate route of administration that bypasses these events would offer the patient an improved substitute to conventional therapy, and would also allow for longer treatment intervals. The non-steroidal anti-inflammatory drugs (NSAIDs) have proven to be effective in the treatment of soft tissue injuries; such as sprains, strains, and contusions. They are widely used as analgesics, and in the treatment of locomotor pathologies and local inflammation. Oral NSAIDs are often adjuncts to treatment but can cause the serious systemic side effects of peptic ulcer and gastrointestinal hemorrhage, especially after long term use.

Applied topically, these drugs are formulated to penetrate the skin, subcutaneous fatty tissue, and muscle in amounts sufficient to exert local therapeutic effects, without reaching higher plasma drug concentrations. Therefore, NSAIDs offer the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse events.

A case-controlled study demonstrated that when adjustments were made for the confounding effects of concurrent oral NSAID use, topical NSAID administration was not significantly associated with upper gastrointestinal bleeding or perforation. The study also showed that the topical dosage was well tolerated and had clinically significant, less adverse events. Furthermore, it was found that the use of topical NSAID in soft tissue injury (tendonitis and sprain) resulted in more rapid healing (compared with no intervention).

KETOPROFEN

Ketoprofen is a potent NSAID that is widely used in clinical practice for the control of acute and chronic pain of soft tissues and skeletal muscle system. The importance of ketoprofen in the therapeutic field has stimulated the development of topical dosage forms to improve its percutaneous absorption through the application site. Moreover topical dosage forms could provide relatively consistent drug levels for prolonged periods and avoid gastric irritation, as well as the other typical side effects of oral NSAID administration.

Ketoprofen belongs to the group of substituted 2-phenylpropionic acids which has analgesic, anti-inflammatory and antipyretic effects. Ketoprofen exerts the majority of its analgesic actions through inhibition of the synthesis of prostaglandins by inhibiting the enzyme cyclooxygenase. Ketoprofen has also been shown to stabilize lysosomal membranes, inhibit leukotriene synthesis through inhibition of lipoxygenase, exhibit anti-bradykinin activity and scavenge hydroxyl radicals, any of which may contribute to the peripheral analgesic effects of ketoprofen.

A study performed by Alarcon, et al, comparing the topical penetration of various NSAIDS (ketoprofen, ketorlac, indomethacin, etc), found that Ketoprofen had the best permeating ability within its class. Other studies have found that topical formulations of ketoprofen demonstrate effectiveness for the treatment of well-localized soft-tissue injury and joint pain, as well as being effective in reducing muscle soreness after repetitive muscle contraction. These studies also demonstrate the maintenance of a low rate and extent of systemic absorption with no reported adverse events.

Transdermal ketoprofen has a relatively fast onset of action, being able to suppress pain ratings by 51% in patients within an hour of application, when compared with placebo.
**GABAPENTIN**

Gabapentin, a second-generation anti-epileptic drug, appears to have some beneficial effects on post-spinal cord injury pain. Agents that reduce hyperexcitability (by blocking sodium and/or glutamate channels) may reduce central pain symptoms. Analgesic action of gabapentin is mainly mediated by actions on the spinal cord. Gabapentin is useful in the treatment of neuralgia in all areas of the body. Its positive effect on neuralgia includes trigeminal neuralgia, glossopharyngeal neuralgia refractory to the usual medical treatments, and facial neuritis. Neuropathy can also be treated with gabapentin. Gabapentin is effective in the treatment of human immunodeficiency virus (HIV) neuropathy, and painful diabetic neuropathy. It is also useful in treating inflammatory pain.

Gabapentin is effective in the treatment of acute herpetic pain without apparent adverse effects. These roles have been confirmed in reviews of controlled studies. Gabapentin was the first anticonvulsant with proven benefit in post-herpetic neuralgia. A randomized, double-blind study comparing gabapentin to placebo showed reduced pain and sleep interference, and improved mood and quality of life. Minor adverse events were reported and included somnolence, dizziness, ataxia and peripheral edema. Although its side effect profile is mild, the occurrence of adverse events could be minimized with transdermal use. Gabapentin has induced cholestasis, hepatotoxicity, anorgasmia in women, and has also been associated with dyskinesia. It should be used with caution in myasthenia gravis. It does not seem to interact with warfarin.

**LIDOCAINE**

Local anesthetics such as lidocaine prevent transmission of nerve impulses by inhibiting passage of sodium ions through ion-selective sodium channels in nerve membranes. Systemic absorption remains minimal, with the highest recorded concentrations remaining at an order of magnitude below the minimum anti-arrhythmic levels. Lidocaine is well tolerated with few systemic adverse events and may provide beneficial pain relief for patients receiving multidisciplinary treatment without increasing risks for adverse drug interactions. Transdermal lidocaine has been shown clinically to reduce pain associated with post-herpetic neuralgia and back injury. Lidocaine is effective for the significant reduction in the intensity of commonly reported pain qualities in patients with neuropathic and non-neuropathic chronic pain due to low-back pain, osteoarthritis, post-herpetic neuralgia, and painful diabetic neuropathy.

**KETAMINE**

Ketamine hydrochloride is an NMDA receptor antagonist with opioid receptor activity that has been useful for anesthesia and analgesia. It has been shown in clinical study that topical ketamine reduced pain in patients with no systemic side effects, indicating negligible or no generalized absorption. Ketamine has been proposed recently for neuropathic pain secondary to its NMDA receptor activity. The current application as a topical drug stems from the theory that ketamine has peripheral action at both opioid and Na+-K+ channels. Controlled studies and case reports on ketamine demonstrate efficacy in neuropathic and nociceptive pain. Patients reported alterations in temperature sensation, feelings of relaxation and decreased tension in the area of application, and pain relief. Reduction in numerical pain scores after application of ketamine ranged from 53-100%. Patients who respond to ketamine tend to demonstrate dramatic pain relief that precludes the desire to stop treatment due to psychotomimetic effects. Ketamine also has been reported to produce opioid dose sparing and good patient acceptance.
No significant side effects were reported with topical ketamine. Topical ketamine may provide clinicians with a new option in the battle against chronic neuropathic pain, especially in patients who have been refractory to standard analgesic medication regimens.

Copyright protected, Living Well Pharmacy Inc. 2005
References


2. Mazieres, B, Rouanet, S, Velicy, J; Topical Ketoprofen Patch (100 mg) for the treatment of Ankle Sprain, a randomized, double-blind, placebo-controlled study; American Journal of Sports Medicine, 2005, 33 (4) 515-524

3. Moretti, MD, Gavini, E, Peana, AT; In vitro release and antiinflammatory activity of topical formulations of ketoprofen; Bollettino Chimico Farmaceutico; 2000, 139(2):67-72

4. Steen KH, Wegner H, Meller ST; Analgesic profile of peroral and topical ketoprofen upon low pH-induced muscle pain; Pain; 2001, 93 (1) 23-33

5. Dowling, T, Arjomand, M, Lin, E; Relative bioavailability of ketoprofen 20% in a poloxamer-lecithin organogel; AJSHP, 2004, 61(23) 2541-2544


8. Takasaki, I, Andoh, T, et al; Gabapentin antinociception in mice with acute herpetic pain induced by herpes simplex virus infection; Journal of Pharmacology and Experimental Therapeutics; 2001, 296(2) 270-5

9. Scheinfeld, N; The role of gabapentin in treating diseases with cutaneous manifestations and pain; International Journal of Dermatology; 2003, 42 (6) 491-5


11. Liem, E, Joiner, T, Tsueda, K; Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads; Anesthesiology; 2005, 102(3) 509-514

12. Rowbotham, M, Galer B, et al; Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study; Pain; 1999, 80 (3) 533-538

13. Argoft, C; Conclusions: chronic pain studies of lidocaine patch 5% using the Neuropathic Pain Scale; Current Medical Research & Opinion; 2004, 20 (2) S29-31

14. Kronenberg, R; Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration; Journal of Pain & Palliative Care Pharmacotherapy; 2002, 16 (3) 27-35


16. Quan, M, Wellish, Gilden, D; Topical ketamine treatment of postherpetic neuralgia; Neurology; 2003, 60, 1391–1392

17. Gammaitoni, A, Gallagher, R, Welz-Bonsa, M; Topical Ketamine Gel: Possible Role in Treating Neuropathic; Pain Medicine; 2000, 1 (4) 97-100