CONSULTANT'S CORNER

Ketamine for Pain Management

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One of my favorite phone calls from a doctor is when they start with, "We have a pain patient and we have tried everything – do you have any ideas?" I know at this moment the doctor is open and ready to try an alternate treatment that normally might be off the table. As compounders, this is the moment we can shine and demonstrate the value of a pharmacist on the healthcare team.

My ace in the hole for pain is ketamine. Many of you thought just now, "WHAT?! No way, no way." Well, let's work through the issues surrounding ketamine and make it an option for you to recommend, too. For others, let's see if we can add some other options to your arsenal.

Ketamine is a rapid-acting, non-barbiturate dissociative anesthetic, which is a derivative of phencyclidine that was initially approved for anesthetic use in 1970. It has a short duration of action when used as an anesthetic, but can have a sustained effect for up to six hours orally. It was then used in the non-medical community as a drug of abuse starting in the early 1970s, and still is being used recreationally today. The desired effects of ketamine in the party scene include hallucinations, an out-of-body experience, and "feeling no pain." Most of the stigma of ketamine comes from the idea that it is a horse tranquilizer and people will go into a "K-hole" if they use too much (K-hole: immobility and non-communicative derealization). This is the information that our medical doctors are taught: that it is a drug of abuse, only anesthesiologists will use it, so don't prescribe it. Not such a rosy picture thus far…but here comes the good news! There is evidence to support the use of ketamine topically and orally for many pain patients in the community. Going back to 2000 (and again in 2002), Marty Jones, RPh, wrote in the *International Journal of Pharmaceutical Compounding* (IJPC) about the discovery of NMDA (N-methyl-D-aspartate) receptor sites in the neural periphery as well as the synergistic effect of NMDA antagonists, AMPA receptor and Glutamate agonists, alpha-2 agonists and other neuron modifiers. It also was noted that narcotics, when used as mono-therapy agents, were not effective in neuropathic pain. However, when given with NMDA antagonists, there was an increase in pain relief with a reduction of opioid need.[1,2] This simple synopsis is crucial to the underlying basis for transdermal pain management. Almost all compounders are comfortable with most of the agents described in this paper (gabapentin, baclofen, amitriptyline, etc.) transdermally, but ketamine is still resisted by prescribers today. The multiple studies going back to this same time frame indicate that topically applied ketamine is effective in pain management either individually or in conjunction with other medications.[3]

A paper published in the *Journal of Pain* in 2005 indicated that topical amitriptyline 2% and ketamine 1% was associated with long-term pain reduction and was well tolerated for patients with neuropathic pain, with no significant systemic absorption of either molecule. One of the most interesting points made in the discussion is that of dose titration optimization. It may be required because another study has revealed that higher concentrations of these agents combined do produce significant analgesia.[4] Another small study indicated that ketamine, when used topically at 50 mg/mL of transdermal gel, reduced pain significantly after capsaicin injections.[5] Then in 2007 in *Anesthesiology Clinics Journal*, it was noted that, "(We) … appreciate that peripheral mechanisms of (action for a variety) of preparations rationalizes their topical application and gives further opportunity to target peripheral receptors and neural pathways that previously required systemic administration to achieve therapeutic effect. Therefore, a peripheral effect can be generated by using locally applied drug and, consequently, systemic concentrations of that drug may not reach the level at which systemic side effects can occur."[6] Most recently, PCCA published a paper indicating it can successfully transport four drug molecules, including ketamine, through the skin concomitantly.[7]

Transdermal dosing for ketamine usually starts at 3% or 30 mg/mL in Lipoderm® or higher. I always combine it with an AMPA agonist, an alpha-2 agonist, and a tricyclic antidepressant (see Jones, M[2] or **PCCA Document #94064**, or contact PCCA's Pharmacy Consulting

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Department for algorithm for pain). Some other combinations include the addition of a muscle relaxant, NSAID and a low-dose narcotic, dependent on patient needs. The transdermal medication should be applied up to six times daily with a review of efficacy at three-day intervals, with adjustments being made on patient response. Dose adjustments of ketamine up to 15% in combination with other molecules is not uncommon, but if going higher than this concentration, other molecules should be reassessed for efficacy and possibly removed if unnecessary.

Some other options for ketamine include the oral route as a baseline pain control for hospice care patients. Oral dosing for adults usually starts at 35 mg three times daily and is titrated up based on patient response.[8] This dose generally will stop the upward progression of narcotic dosing, and in many cases reduces narcotic load. Lastly, for patients with breakthrough pain, intranasal ketamine can be used as 100 mg/mL in combination with lidocaine HCl 40 mg/mL. An intranasal spray of 0.1 mL contains only 10 mg ketamine, but can alleviate pain immediately (similar onset as IV). Intranasal dosing should be started for only significant cases at one spray bilaterally up to three times daily as needed. Please contact PCCA Pharmacy Consulting for further discussion.

Important Notes

Salt conversion for ketamine has to be taken into account. If you are going to start using ketamine in your practice, it is important to know that 1 mg ketamine = 1.15 mg ketamine HCl, and your calculations should include this conversion.

Diazepam and other CYP3A4 inhibitors increase ketamine levels, so watch for diazepam and some ABX and SSRIs that may influence (increase) on profile.

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