There is increasing recognition that pain is one of the most common symptoms experienced by patients with chronic renal failure. The pain that these patients experience impairs their quality of life and is dramatically undertreated.1-3 The World Health Organization (WHO) analgesic ladder4 can be applied to the treatment of patients who have end-stage renal disease (ESRD) and are in pain. Barakzoy and Moss4 conducted a landmark study to evaluate the efficacy of the WHO 3-step analgesic ladder as used to treat pain in patients with ESRD. There are several pharmacologic challenges in providing pain relief for patients with ESRD. In this article, several options are presented along with an algorithm to guide therapy.

They reported 4 major findings:

1. Use of the WHO 3-step analgesic ladder approach to treating pain led to effective pain treatment in more than 90% of patients undergoing hemodialysis.
2. Treatment of pain was more difficult in elderly patients undergoing hemodialysis.
3. There was a high prevalence of pain in the hemodialysis population, and it was accompanied by undertreatment of pain in the majority of patients undergoing hemodialysis.
4. The Short Form McGill Pain Questionnaire (SF-MPQ) was a useful and efficient tool to assess pain in patients undergoing hemodialysis.

Learning Objectives: After participating in this activity, the physician should be better able to:

1. Evaluate the extent of undertreatment of pain in patients with chronic renal failure.
2. Assess which opiates are appropriate for pain control in patients with chronic renal failure.
3. Distinguish 2 opiates that are contraindicated in patients with chronic renal failure.

CME Article: Pain Management in Patients With Chronic Renal Failure

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All faculty and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

The author has disclosed that off-label use of pregabalin, gabapentin, amitriptyline, and nortriptyline is discussed in this article.

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NMDA-Receptor Antagonist Memantine, Combined With Morphine, Decreases Pain of CRPS

Sonia Elabd, MA

In the treatment of patients with complex regional pain syndrome (CRPS), some of the most promising clinical trials have involved the use of N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine, which investigators have administered to patients in regular infusions over the course of several weeks, reporting promising results. (See Topics in Pain Management, vol. 25, no. 7 and vol. 25, no. 8). In Mexico and Germany, trials have reported that some patients with CRPS were cured when anesthetic doses of ketamine were administered for extended periods. Patients have not received doses that high in a CRPS clinical trial in the United States because of the inherent challenges of cost and how to provide a placebo control group.

A recent study provides yet more evidence supporting the use of an NMDA antagonist—this time in combination with morphine. The investigators, Gustin et al., demonstrated that a combination regimen of an NMDA antagonist—memantine—and morphine was more effective than morphine alone in decreasing neuropathic pain in patients with CRPS.

The double-blind, randomized, placebo-controlled study comprised 20 patients suffering from both types of CRPS in their hands. Patients were started on a 10-mg dose of morphine that was increased to 30 mg for a total of 56 days. On day 8, patients were given either oral memantine, starting with 5 mg and increasing to 40 mg for a total of 49 days, or placebo. The authors chose the NMDA antagonist memantine because it “displays the lowest number of side effects but has been shown to be at least as effective as ketamine and dextromethorphan in animal experiments.”

Using a visual analog scale, patients in the morphine-plus-memantine group reported a significantly greater decrease in pain upon rest (from 5.47 to 1.40) and movement (from 8.03 to 2.84) compared with the morphine-plus-placebo group. In addition, the combination therapy also improved mood and disability. The researchers used functional MRI to observe changes in the brain when the affected hand was moved, and they observed that the combination therapy resulted in decreased activation in the contralateral S1 (cS1) and anterior cingulated cortex. Decreased activation in the cS1 and secondary somatosensory cortex (S2) correlated with pain relief that the patients experienced.

“Our data suggest that the combination of morphine with an NMDA antagonist interacts at the central level of pain processing in CRPS,” said senior author Martin Lotze, MD, neurologist at the Center for Diagnostic Radiology and Neuroradiology at the University of Greifswald in Germany, in an e-mail interview with Topics in Pain Management.

“The correlation of pain relief and decrease in cortical activity in cS1 and S2 are in accordance with the expected impact of the NMDA-antagonist on cortical regions associated with discriminative pain processing,” he wrote.

The study adds to the theory that cortical areas have a significant role in processing chronic pain and that the processes may be NMDA-receptor dependent.

“NMDA-receptors play an important role in learning processes and might be related to learning-associated processes important for the development of chronic pain,” Lotze said. “The blockade of these processes in the subacut phase of CRPS might help to reverse the adaptation of the cortex to chronic pain. However, since NMDA-receptors have such an important function in multiple levels of pain processing, it is no indication for a necessary cortical pharmacological effect. On the other hand, these processes might also be related to an adaptation to morphine in respect to habituation, which might be positively influenced by NMDA-receptor antagonists,” said Lotze.

Although this study was small, and further research needs to be conducted to provide conclusive effects of memantine and other NMDA-receptor antagonists, such as ketamine and dextromethorphan, on various chronic and neuropathic pain conditions, other small studies have reported similar results in pain relief. A study of IV administration of ketamine for 10 days in patients with CRPS demonstrated that pain relief decreased significantly after ketamine administration compared with placebo. A systematic review of 28 studies of ketamine used in patients with CRPS, postherpetic neuralgia, and postamputation pain, and memantine used for treatment of postherpetic neuralgia and postamputation pain, showed that treatment with ketamine significantly decreased spontaneous postamputation pain.

The review pooled the results of studies with similar routes of administration, interventions, and patient samples. The authors concluded, “[Randomized controlled trials] including well-defined neuropathic pain disease groups, are needed to elucidate the effects of NMDA-receptor antagonists on neuropathic pain. Evidence in favor of the effectiveness of NMDA-receptor antagonists for the treatment of neuropathic pain, of which ketamine seems to be the most potent, is accumulating.”

“NMDA-receptor antagonists alone and in combination with morphine may play an important role in chronic pain processing, but further evidence needs to be obtained and the mechanism of action needs to be further elucidated for patients’ benefit,” Lotze said.

He added, “I think it is worthwhile to use the dosage and combination we used here at least for patients in the subacute phase of CRPS I. Cortical maladaptive processes in chronic pain are important. Any therapy targeting cortical maladaptive processes might be beneficial for the therapy of chronic pain. A combination of analgesic medication and NMDA-receptor antagonists is
extremely helpful to avoid the consolidation of these maladaptive processes.”

References

FDA Prompts Xanodyne to Withdraw Propoxyphene (Darvon and Darvocet)

First Complaints About Cardiac Side Effects Surfaced More Than 30 Years Ago

The impact of propoxyphene’s removal from the United States market in November 2010, after recent evidence of cardiotoxicity, will be felt more in the pocketbook than in, say, the lower back. Although other opioids can offer as much or more pain relief with lower risks, propoxyphene’s significance was its low cost for patients, who may have a hard time paying the higher cost of newer brand-name opioids.

There is also some value in observing the entire process, from the drug’s initial approval in 1957, its first safety issues in 1978, and its removal from the market 32 years later: some have noticed parallels to concerns about methadone—another inexpensive older opioid with unique safety concerns that some say outweigh its value as an inexpensive option for people in pain.

Complaints about propoxyphene began surfacing more than 30 years ago, with citizen petitions to the FDA to ban the drug or take other measures to curb its use. Concerns included its abuse potential, overdose risk, and cardiotoxicity.1

One concern, in particular, was that in the event of an overdose of propoxyphene, administration of an opioid antagonist would not reverse the cardiotoxicity.2

But each time FDA officials had to make a decision, the vote favored keeping propoxyphene available as a pain medication. The agency determined that the drug’s benefits outweighed its risks. This happened even as recently as 2009, in a response to a complaint by American and Swedish citizens. That complaint was filed in 2008 by Sidney Wolfe, MD, and Dan Suzman of Washington, DC.

A Summary of FDA Decisions on Propoxyphene-Containing Products

Propoxyphene was first approved by the FDA in 1957.1 It has been marketed in the United States since 1976 as a schedule IV controlled substance used either as a single ingredient (eg, Darvon) or in combination with acetaminophen (eg, Darvocet) to treat mild to moderate pain.

Since 1978, the FDA has received 2 citizen petitions asking the FDA to remove propoxyphene from the market or to reschedule the drug from schedule IV to schedule II. Based on all evidence available, the FDA concluded that the benefits of propoxyphene for pain relief at recommended doses outweighed the safety risk and that neither withdrawal nor changes in scheduling were warranted.

In January 2009, the FDA held an advisory committee meeting to address the efficacy and safety of propoxyphene. The committee voted 14 to 12 against the continued marketing of propoxyphene products but noted that additional information about the drug’s cardiac effects would be relevant in weighing its risks and benefits.

In July 2009, the FDA decided to permit continued marketing of propoxyphene with a new boxed warning added to the drug label alerting patients and health care professionals to the risk of a fatal overdose.

Meanwhile, Xanodyne conducted a study in healthy volunteers to determine an appropriate dose that could be used in the definitive cardiac study. Data from that study demonstrated that even when propoxyphene was taken at recommended doses, there were significant changes to the electrical activity of the heart including prolonged PR interval, widened QRS complex, and prolonged QT interval.

In light of these new scientific findings, the FDA determined the postmarketing safety signals for this drug have taken on new importance, and the overall balance of risk and benefit can no longer be considered favorable. The agency recommended that propoxyphene products be removed from the market.

Reference