Drug Monitor

Comparing Adverse Effects of Analgesic Strategies for Chronic Cancer Pain

Nausea, vomiting, drowsiness, lack of energy, urinary retention—sometimes the adverse effects of the analgesic medication are enough to derail pain management for patients with cancer. It would help to understand the relationships between the type of analgesic prescription and the prevalence and severity of adverse effects. But not much information is available, say researchers from the University of California, San Francisco; the University of Nebraska, Omaha; and the University of Texas Southwestern Medical Center, Dallas. They conducted a descriptive, correlational study of 174 patients with bone metastasis—as part of a larger clinical trial evaluating the PRO-SELF Pain Control Program (University of California Regents, Oakland, CA)—and found that adverse effects were particularly prevalent with either around-the-clock (ATC) opioids alone or ATC opioids in combination with as-needed (PRN) opioids.

The study participants, adult outpatients from several sites in Northern California (including a VA facility and a military hospital), had been prescribed one of four analgesic strategies: no opioids (11%), only PRN opioids (42%), only ATC opioids (18%), or ATC plus PRN opioids (29%). The most common short-acting opioid products used were acetaminophen with codeine and acetaminophen with hydrocodone. The most common long-acting opioids were controlled-release morphine and transdermal fentanyl.

Patients kept a pain management diary and a checklist of 11 adverse effects. They rated the amount of daily and weekly time during which their pain interfered with their mood or activities, and they indicated the amount of relief they received from their pain medicine in the previous week. They also completed the Karnofsky Performance Status (KPS), which measures patients' ability to perform activities of daily living and their need for caregiver assistance.

There were no significant differences between any of the four groups in terms of pain intensity or amount of time spent in pain. Total pain interference scores, however, were significantly higher in the ATC plus PRN opioids group than in the no opioids group. The ATC plus PRN opioids group also had significantly lower functional scores on the KPS than the no opioids and the only PRN opioids groups, suggesting that the former patients may have been grappling with more extensive, painful disease. The percentage of pain relief was significantly lower in the no opioids group than in the only PRN opioids group.

The prevalence of most adverse effects ranged from about 25% to 80%—which is consistent with rates reported previously in the medical literature. Notably, mean severity ratings for most adverse effects were in the mild to moderate range, regardless of analgesic strategy. The researchers speculate that the patients may have learned to tolerate or use strategies to manage some of the adverse effects.

The highest prevalence rates and severity ratings for most adverse effects were found in the only ATC opioids and ATC plus PRN opioids groups. A higher total opioid dose increased the risk of many of the adverse effects studied. The total opioid dose taken by patients in the ATC plus PRN opioids group was more than three times higher than that of the only ATC opioids group and 17 times higher than that of the only PRN opioids group.

Source: *J Pain Symptom Manage.* 2007;33(1):67–77.

Clopidogrel: Best Results Pre- or Post-PCI?

When is the best time to give the antiplatelet clopidogrel to patients scheduled for diagnostic coronary angiography—before ad hoc coronary stenting or immediately after? Researchers from University of Debrecen, Debrecen, Hungary and Medical University of Vienna and Wilhelminenhospital, both in Vienna, Austria say starting treatment before percutaneous coronary intervention (PCI) has several benefits.

The researchers assigned 4,160 patients with suspected coronary artery disease to receive a loading dose of clopidogrel 300 mg either six to 24 hours before stenting (n = 1,481) or immediately afterward (n = 2,679). At 30 days, the composite primary endpoint of acute myocardial infarction (AMI), urgent repeat target vessel revascularization (TVR), or all-cause death was nearly twice as common in the patients who received post-PCI treatment (4.47%) than in those who received pre-PCI treatment (2.77%). When the endpoint components were considered individually, there remained a significant reduction in AMIs with pre-PCI treatment, although the differences in TVR and all-cause death were nonsignificant.

The post-PCI treatment group also was significantly more likely to have stent thrombosis. Pre-PCI treatment was associated with more major bleeding: 1.35% versus 0.41% in the post-PCI group. The researchers note, however, that major bleeding occurred

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less frequently than either AMI or the composite endpoint.

This study's findings were consistent with previous research showing the risk of acute and subacute stent thrombosis to be highest within the first few postimplantation days. The benefit of giving clopidogrel more than six hours before the planned PCI, say the researchers, may be in preventing acute thrombotic occlusion during the first two to six hours after stenting. They explain that, within this timeframe, the full dose of unfractionated heparin applied during PCI has mostly an anticoagulant effect and only a moderate influence on platelet activity. They also note that increased platelet reactivity has been documented in patients undergoing PCI.

Source: *Am J Heart.* 2007;153(2):289–295. doi:10.1016/j.ahj.2006.10.030.

When Succinylcholine Inhibits Urgent Intubation

With a rapid onset and short duration of action, the depolarizing neuromuscular blocker succinylcholine is an emergency department (ED) standby for rapid sequence intubation. On rare occasions, though, it can cause masseter muscle rigidity (MMR), which can complicate intubation and be life threatening. Physicians from Carl R. Darnall Army Medical Center, Fort Hood, TX report a case of succinylcholine-induced MMR that illustrates why clinicians need to be ready with a prompt response.

The patient, a 36-year-old man, had taken an overdose of clonidine and consumed an unknown quantity of alcohol approximately three hours before he was medically evaluated. When he was found, he was unresponsive to verbal or painful stimuli. Emergency medical services inserted two 18-gauge intravenous catheters into the bilateral antecubital fossa, placed the patient on a nonrebreather face mask, and administered 4 mg of naloxone but observed no response from the patient.

At the ED, the staff administered another 4 mg of naloxone. After his Glasgow Coma Scale score dropped from 7 (on ED arrival) to 3, the staff decided to intubate him. They preoxygenated him with a bag valve mask and gave him etomidate 30 mg IV followed by succinylcholine 1.5 mg/kg. Two intubation attempts, however, were impeded by an inability to open his mouth fully. Suspecting MMR, the staff gave the patient vecuronium 10 mg, which relieved the masseter rigidity and allowed successful intubation.

Typically, the authors say, MMR is managed by stopping the paralytic agent and rescheduling the procedure after an evaluation for malignant hyperthermia. But this isn't a practical option when an intubation is urgent, as is often the case in the ED. In this situation, early detection and rapid management are key.

Source: *Am J Emerg Med.* 2007;25(1):102–104. doi:10.1006.j.ajem.2006.05.032.

Tiagabine vs. Gabapentin for Cocaine Dependency

It came as a bit of a surprise, but tiagabine proved much better than gabapentin for reducing cocaine use among patients with cocaine dependency who were receiving methadone treatment, say researchers at Yale University, New Haven, CT; the VA Connecticut Healthcare System, West Haven; and the University of Arkansas, Little Rock.

The researchers randomly assigned 76 patients, all of whom were seeking help for cocaine and opioid dependency, to receive tiagabine 24 mg/d, gabapentin 2,400 mg/d, or placebo—in conjunction with methadone treatment—in a 10-week, double-blind trial. Study medications were titrated slowly to the full dosages by the end of week five and maintained through week 10.

Patients in all three study groups were predominantly young, white men. During weeks six through 10, the proportion of cocaine free urine samples was significantly greater in the tiagabine group (43%) than in the gabapentin and placebo groups (31% and 35%, respectively). Between the first and last weeks, cocaine free urine samples and abstinent rates increased substantially in the tiagabine group: from 27% to 48% and from 13% to 35%, respectively. By contrast, these rates rose less dramatically in the placebo group—and remained virtually unchanged in the gabapentin group.

The gabapentin group had significantly lower treatment retention (65%) compared with the tiagabine and placebo groups (80% and 92%, respectively). The only adverse effect attributed to the study medication was headache in one patient taking tiagabine. Generally, tiagabine was well tolerated, with no evidence of oversedation, seizures, or other significant adverse reactions. The researchers suggest initiating tiagabine at night, then increasing the dose on a twice daily schedule until reaching the target dosage.

Although the researchers are not clear about why gabapentin did not increase cocaine free urine samples, they propose a few possibilities. One is that tiagabine increases gamma-aminobutyric acid (GABA) levels to brain areas directly related to reinforcing the effects of cocaine. While gabapentin also increases GABA levels in a dose dependent fashion, the areas in the brain it affects are not fully understood. Therefore, gabapentin not only may fail to reduce cocaine reinforcement in certain areas but also may trigger brain areas that prompt cocaine use. ●

Source: *Drug Alcohol Depend.* 2007;87(1):1–9. doi:10.1016/j.drugalcdep.2006.07.003.