Drug Monitor

Methadone and Sudden Cardiac Death

The use of methadone for such therapeutic purposes as analgesia and opioid withdrawal is increasing steadily, due largely to the drug's low cost in comparison to other opioids. Several case reports, however, have associated methadone use with sudden cardiac death.

To investigate this possible association, researchers from Oregon Health and Science University, Portland prospectively studied consecutive cases of sudden cardiac death among Portland residents between 2002 and 2006. They sought to determine whether there was a low prevalence of underlying cardiac abnormalities—and, thus, a greater likelihood that methadone was associated with death—in people who had therapeutic serum levels of methadone when they died.

Of the 183 total cases of sudden cardiac death identified, the researchers eliminated 12 cases that lacked a full autopsy report and 43 that had evidence of methadone overdose or recreational drug use. Of the remaining cases, 22 showed therapeutic methadone levels at the time of death and 106 did not.

In the group without therapeutic methadone levels, 60% had a cardiac abnormality identified that could have caused sudden cardiac death. By contrast, only 23% of the group with therapeutic methadone levels had such an abnormality. According to the researchers, this finding strongly implicates methadone in the deaths of the latter group.

The absence of structural cardiac abnormalities, they say, can point to a fatal cardiac arrhythmia as the cause of sudden cardiac death. And methadone has been associated with a potentially fatal arrhythmia, torsades de pointes, likely arising from the drug's blockade of cardiac potassium ion channels, which results in prolongation of cardiac repolarization and a prolonged QT interval. They note, however, that some subjects who met the criteria for sudden cardiac death actually might have died from respiratory suppression, another potentially fatal adverse effect of methadone.

Given the widespead therapeutic use of methadone, the researchers call for a large, prospective evaluation of the therapy. To ensure its safety, they say, it may be prudent to perform electrocardiography and assess patients' potential for respiratory suppression before initiating methadone therapy.

Source: *Am J Med.* 2008;121(1):66–71. doi:10.1016/j.amjmed.2007.10.009.

Can Preoperative COX-2 Inhibition Reduce Pain and Inflammation After Knee Replacement?

In patients recovering from total knee replacement (TKR), pain, swelling, and internal joint bleeding can hinder postoperative exercise efforts, which are vital to successful outcomes. Because inflammatory reactions to surgical trauma and ischemic reperfusion injury during the procedure are largely responsible for these obstacles, researchers from Peking University People's Hospital, Beijing, People's Republic of China hypothesized that preoperative use of an anti-inflammatory agent might ameliorate these effects.

For their randomized, placebo-controlled trial, the researchers chose to investigate rofecoxib, a highly selective cyclooxygenase (COX)-2 inhibitor with a long half-life. In 2004, rofecoxib's manufacturer voluntarily withdrew the drug from markets worldwide due to concerns over adverse cardiovascular and cerebrovascular effects. This study was completed in 2003, however, and the researchers point out that these adverse effects occurred specifically in patients taking long-term, high dose rofecoxib therapy.

In their study, the researchers assigned 37 patients scheduled to undergo elective TKR to receive one 25-mg dose of oral rofecoxib (17 patients) or placebo (20 patients) one hour before the procedure. All patients had the same anesthetic and analgesic protocols and the same operating surgeon. The two groups were similar demographically, and there were no significant differences in operation time or local anesthetic dosages between the groups.

The researchers collected data on patients' postoperative pain severity, satisfaction with analgesia, morphine consumption, and adverse effects. To compare the inflammatory responses of the two groups, they also measured levels of inflammatory markers in patients' blood and knee joint drainage fluid, measured the circumference of their lower limbs to track edema, and monitored their body temperature.

The researchers found that, compared to patients in the control group, patients in the rofecoxib group reported significantly lower pain scores (both at rest and with knee movements) on days one and two after the surgery, used significantly less morphine during the first 24 hours, and reported significantly more satisfaction with analgesia at the 24-hour point. Both groups had substantial increases in the inflammatory cytokines interleukin (IL)-6 and IL-8 in the joint

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drainage fluid starting two hours after the surgery, but the rofecoxib group's IL-6 levels were 50% to 60% lower than those in the control group at six, 12, and 48 hours. Levels of tumor necrosis factor–α in the joint fluid also were significantly lower in the rofecoxib group, compared with the control group, immediately after the surgery and at six and 12 hours. Additionally, the incidence of fever and degree of knee edema was significantly reduced in the rofecoxib group.

The researchers acknowledge the limitations of their small sample size, but they note that expanding the study was not possible after rofecoxib was withdrawn from the market. They say their results suggest that short-term, perioperative use of small doses of COX-2 inhibitors may improve recovery after TKR. Further investigation is needed to establish the cardiovascular safety of this use, however. ●

Source: *J Pain.* 2008;9(1):45–52. doi:10.1016/j.pain.2007.08.003.