Drug Monitor

Opioid Delivery and Granuloma Formation

Administering opioids into the intrathecal space means the drug is highly localized, so lower doses are possible. Nonetheless, one of the possible adverse effects is an intrathecal granuloma due to an inflammatory reaction at the level of the catheter tip. The complication is rare but very risky if not detected and treated properly.

Case reports have long implied a connection between an opioid delivered by continuous intrathecal catheter and the development of granulomas, but it wasn't clear whether the issue was dose, concentration, both, or neither. So researchers at the Midlands inpatient Regional Centre in Dudley, United Kingdom (one of the largest centers in the United Kingdom for intrathecal drug therapies) undertook a study to find out.

The control group included 31 patients who received continuous intrathecal morphine. The researchers (from Birmingham City University in Birmingham, United Kingdom, and Russells Hall Hospital in Dudley, United Kingdom) also reviewed the literature for cases of catheter-tip granulomas and included 24 patients from the review in a second group, along with 1 patient from their own center diagnosed with granuloma.

When the patients came in for a pump refill, they were asked whether the pain was being controlled and whether new symptoms had emerged, including new pain, altered sensation, or weakness of limb. If they answered yes, they were given a neurologic examination. In the case of a clear change, magnetic resonance imaging (MRI) was performed.

The average follow-up for the control group was 68 months. No masses were detected in the patients in the control group.

Both morphine dose and concentration were significantly associated with development of intrathecal masses. The morphine concentration was significantly higher in the granuloma group, compared with the control group. In the granuloma group, the mean peak dose and concentration were 23.19 mg/d (range, 3.5-120) and 37.29 mg/mL (range, 10-75), respectively. In the control group, mean peak opioid dose was 2.89 mg/d (range, 0.85-6.88), and the average peak concentration was 6.94 mg/mL (range, 1.70-18).

Early identification is critical to reduce the impact of a granuloma, the researchers advise. They note that 40% of the reviews mentioned a rapid increase in the dose administered before the diagnosis of granuloma. However, an already-formed granuloma can reduce the efficacy of the medication. That, in turn, can lead to a diagnosis of tolerance, and thus, the clinician may decide to boost the rate of infusion.

The authors advise keeping both dose and concentration as low as possible. The relative risk of granuloma, they say, can be almost halved by reducing the currently recommended maximum dose of 15 mg/d to 10 mg/d, and the recommended concentration from 20 mg/mL to 15 mg/mL. They point out, though, that even those doses are higher than the reported average needed for optimal pain control. If the maximum recommended dose and concentration do not provide desired pain relief, ziconotide is an alternative intrathecal medication. To date, the authors say, no reports have associated that drug with catheter-tip granulomas.

Source: Duarte RV, Raphael JH, Southall JL, Baker C, Ashford RL. *Clin Neurol Neurosurg.* 2012;114(6):577-584. doi: 10.1016/j.clineuro.2011.12.007.

Is Lipid Monitoring Getting Short Shrift?

Because second-generation antipsychotic drugs can cause changes to lipid metabolism, consensus statements from the American Psychiatric Association (APA) and the American Diabetes Association (ADA), among others, advise monitoring lipids at baseline, 12-week intervals, and 5-year intervals, regardless of the indication. Despite the recommendations, however, patients on those drugs are still monitored at roughly the same rate—10%—as before the APA/ADA issued the consensus statement.

And when researchers from Duke University in Durham, North Carolina, and UNC Eshelman School of Pharmacy in Chapel Hill, North Carolina, decided to find out how well their own institution was doing, they found "alarming evidence" that even in an academic setting with "active discussions" among psychiatrists about the issues of metabolic risk and appropriate monitoring, adherence to the recommendations is "disappointingly low." Worrisome, as well, since patients with schizophrenia and bipolar disorder compared with patients without mental illness have as much as double the incidence of metabolic syndrome.

The researchers analyzed data on 70 patients aged 18 to 25 years who were prescribed a second-generation antipsychotic. Roughly 70% of patients started for the first time on atypical antipsychotics had no baseline lipid panel. Of those who did have baseline monitoring, about 50% had at least 1 risk factor for atherogenic dyslipidemia (either a low HDL or elevated triglycerides).

The study yielded "intriguing" data, the researchers say. For example, women were 3 times less likely to

have lipid monitoring compared with men (16% vs 44%); a concern since studies have found that women run greater metabolic and cardiac risks. The researchers also detected a trend toward a difference in monitoring based on ethnicity (40% of African Americans had lipid panels compared with 20% of whites). But because this was a small study, they can't draw firm conclusions on the differences.

Patients taking olanzapine were also more likely to be monitored, not surprising given olanzapine's reputation as the "worst offender," the researchers say. However, they add that other second-generation antipsychotics, such as quetiapine, also carry risks of metabolic derangements, weight gain, and coronary artery disease. Yet patients on quetiapine received the lowest lipid monitoring in the study.

That 31% of patients did get baseline lipid panels puts their institution, a teaching hospital, ahead of the average, the researchers acknowledge, but they still feel the efforts have fallen short. They note that the use of second-generation antipsychotics in patients with bipolar disorder is on the rise.

Source: Laundon W, Muzyk AJ, Gagliardi JP, Christopher EJ, Rothrock-Christian T, Jiang W. *Gen Hosp Psychiatry.* 2012;34(4):380-384. doi: 10.1016/j.genhosppsych.2012.03.016.