

### Serotonin Syndrome Associated With Tramadol

**To the Editor:** Serotonin syndrome is a serious condition caused by excess serotonergic activity and characterized by altered mental status and heightened neuromuscular and autonomic activity.<sup>1</sup> Serotonin syndrome is commonly associated with the use of antidepressants alone or in combination with other serotonergic medications. Tramadol is an analgesic medication with partial mu agonist activity and affects serotonin and norepinephrine. Toxicity from tramadol appears to be due to monoamine uptake inhibition rather than its opioid effects.<sup>2</sup> A literature search in April 2008 using PubMed for the English language using the keywords tramadol and serotonin syndrome noted cases involving tramadol and other serotonergic medications; reports of serotonin syndrome involving tramadol alone were absent.<sup>3</sup>

**Case report.** Ms A, a 45-year-old woman with a history of migraine headaches, was admitted to the hospital in November 2006 for hallucinations and muscle twitching. Due to poor pain control, she ingested increasing amounts of tramadol 50 mg (20 tablets) and acetaminophen 650 mg/hydrocodone 10 mg (10 tablets) in 2 days. She was also prescribed alprazolam 0.5 mg 3 times daily and topiramate 25 mg daily, although the patient reported nonadherence for several weeks.

In the emergency room, she had hallucinations of seeing and having conversations with family members who were not present as well as paranoid delusions that her pain medications were filled with illicit drugs. Ms A also believed that she was at the airport. She was noted to be tremulous, with muscular twitching of her lips and jaw muscles. She also exhibited sudden jerky movements of her extremities. Otherwise, she was alert and had no respiratory difficulties. Vital signs were within normal limits except for a temperature of 101.3°F and maximum heart rate of 101 bpm. Lumbar puncture and computed tomography of the head revealed no abnormalities. Toxicology was significant for opioids and negative for benzodiazepines.

Upon admission, tramadol was discontinued and haloperidol 0.5 mg every 6 hours as needed for agitation was prescribed along with acetaminophen 325 mg/hydrocodone 5 mg every 6 hours as needed for severe pain. Alprazolam and topiramate were discontinued from Ms A's drug regimen. She improved rapidly and was discharged from the hospital the following day.

This case illustrates an example of a toxic overdose with tramadol that resulted in features suggestive of serotonin syndrome. Concurrent administration of acetaminophen/hydrocodone certainly could have been contributory to the presentation. Although toxicology was significant for opioids, there was no clinical evidence for opioid toxicity such as diminished respiration and de-

creased pupil size; opioid toxicity was not believed to be responsible for the clinical presentation. Similarly, there were no features of acetaminophen toxicity such as gastrointestinal symptoms or diaphoresis, and, in fact, the total dose of acetaminophen was only slightly higher than the current maximum daily dose. Benzodiazepine withdrawal was also considered owing to the elevated vital signs and muscular twitching but believed to be less likely given the evidence of a negative toxicology report and nonadherence. Typically, delirium due to benzodiazepine withdrawal would worsen without the administration of a similar agent. The psychotic symptoms in this case could be related to a nonspecific delirium. However, delirium typically does not result in muscular twitching, a characteristic of serotonin syndrome. The time course of rapid improvement once tramadol was discontinued and the clinical symptoms exhibited by the patient suggest the influence of tramadol toxicity resulting in serotonin syndrome.

Most psychiatrists are aware of serotonin syndrome with antidepressants but less likely to attribute it to other classes of medications such as analgesics.<sup>4</sup> This is the first reported case in which serotonin syndrome was associated with tramadol alone without concomitant use of other serotonergic medications. Clinicians frequently prescribe tramadol as an analgesic since it is not considered a controlled substance. Awareness of its serotonergic effect is important in avoiding potential side effects and unwelcome interactions with other medications. Additionally, recognition is important regarding tramadol and its potential to cause serotonin syndrome, especially in light of concomitant usage with other serotonergic medications such as antidepressants.

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doi: 10.4088/PCC.08100690

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