

Buprenorphine-Induced Opioid Withdrawal

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Case Summary:

A 39 year-old man presented to the emergency department with abdominal pain, body aches, chills, diarrhea, nausea and vomiting. One hour prior to arrival his friend had given him two “tablets” because he had reportedly missed his regular methadone dose of 180 mg/day. His past medical history included HIV, for which he was on highly-active antiretroviral therapy (HAART), and hepatitis C.

On arrival he was in moderate distress, and was alert and fully oriented. Vital signs were: blood pressure, 155/93 mmHg; heart rate, 118/min; respiratory rate, 24/min; temperature, 99.9 °F; oxygen saturation, 99% on room air; and capillary blood glucose, 120 mg/dL. Pupils were 6 mm, equal, round, and reactive. Copious rhinorrhea was noted. The oropharynx was clear; no thrush was observed. Lungs were clear to auscultation bilaterally, and his heart was tachycardic, with normal S₁ and S₂, and without murmur. Abdomen had hyperactive bowel sounds, and was mildly tender over the epigastrium without guarding. Extremities lacked cyanosis, clubbing, or edema. Neurological examination was normal without focal deficit. Skin was diaphoretic with piloerection.

An ECG revealed a sinus tachycardia with normal QRS and QTc intervals. Serum chemistry panel results were: sodium, 136 mEq/L; potassium, 4.2 mEq/L; chloride, 113 mEq/L; bicarbonate, 23 mEq/L; blood urea nitrogen, 22 mg/dL; creatinine, 0.9 mg/dL; and glucose, 122 mg/dL.

What is the likely cause of this patient’s clinical findings?

This patient manifested classic findings of the opioid withdrawal syndrome. Generally, opioid withdrawal is characterized by a minor amount of increased central sympathetic outflow: mild hypertension and tachycardia, diaphoresis, piloerection, reactive mydriasis, tremor, and discomfort. Agitation, delirium, and severe abnormalities of vital signs are not expected. While not directly life-threatening to most adult patients, spontaneous, and therefore gradual, the opioid withdrawal syndrome carries morbidity from its psychological distress as well as gastrointestinal manifestations, such as vomiting with potential aspiration and volume loss from diarrhea. However, more significant morbidity and mortality is associated with precipitated opioid withdrawal, when naloxone or another opioid antagonist is administered and results in the immediate onset of opioid withdrawal. Precipitated withdrawal is almost always iatrogenic, as occurs during ultrarapid detoxification or following prehospital or ED reversal of opioid poisoning. Many of the adverse effects are a direct result of the massive catecholamine response to rapid reversal of the opioid effect.¹

What “tablets” could have induced this patient’s findings?

It is possible that this patient’s opioid withdrawal syndrome may have been secondary to the abdominal pain and emesis, which prevented him from using his regular dose of methadone.

However, given the historical association with his friend's "tablets," precipitated opioid withdrawal is more likely. Potential precipitating agents include: full opioid antagonists (e.g., naloxone, naltrexone), opioid agonist-antagonists (e.g., pentazocine), and partial opioid agonists (e.g., buprenorphine).

The difference between these three classes of xenobiotics is their pharmacodynamic relationship to a reference agonist (e.g., morphine or methadone) which interacts with a biologic target (i.e., the mu-opioid receptor) to produce a clinical effect (i.e., central analgesia or respiratory depression). Full antagonists competitively inhibit the agonist at the target, thereby blocking the clinical effect. Agonist-antagonists have two functions: they block the clinical effect in a manner similar to a full antagonist, and they interact with a unique, but often related, biologic target (e.g., the kappa-opioid receptor) to produce a related clinical effect (i.e., spinal analgesia). Partial agonists interact with the same reference biologic target, but produce a lesser degree of clinical effect. For example, buprenorphine is considered to have less mu-opioid analgesic efficacy than morphine, and is also noted to have a "ceiling effect" in regard to both analgesia and respiratory depression.^{1,2}

Identification of the specific agent, if possible, would be useful clinically to prognosticate the duration and degree of adverse symptoms based on the pharmacology of the antagonist. Opioid withdrawal is expected to last for 3-to-4 hours when an opioid-dependent patient ingests pentazocine ($t_{1/2} = 2$ hours), but to be sustained for 24-to-36 hours following ingestion of either naltrexone or buprenorphine. For the sake of comparison, naloxone induces withdrawal symptoms that typically last about 30-45 minutes. However, although it is a common cause of precipitated opioid withdrawal, naloxone has poor oral bioavailability and requires parenteral administration to initiate opioid withdrawal.¹

Case continued:

The patient endorsed taking two buprenorphine tablets. Given buprenorphine's high affinity for the mu-opioid receptor, it displaces most opioid agonists. As a partial agonist at the mu-opioid receptor, the withdrawal syndrome induced by buprenorphine is not typically as severe as that induced by a full antagonist such as naloxone. However, this temperance is not universal, and in some patients, particularly in those who are highly opioid dependent, the clinical manifestations following buprenorphine administration can be equivalent to those following naloxone.^{3,4}

How should this patient be managed?

The long duration of clinical effect and strong affinity for the mu-opioid receptor of buprenorphine, confer an additional degree of clinical difficulty when managing precipitated withdrawal. Efforts to reverse withdrawal via direct competition at the mu-opioid receptor may require unconventionally high doses of potent opioids. Since use of this method requires close monitoring for side effects, overdose, and recurrent withdrawal, it is not preferred in most situations. Thus, common practice is to compete indirectly and symptomatically using a combination of benzodiazepines, antiemetics, and sometimes clonidine.

Case management:

Based on the patient's mild withdrawal syndrome and the lack of published clinical experience for the management of opioid withdrawal precipitated by buprenorphine, the clinician chose to

attempt reversal using an opioid agonist. This patient received intravenous hydromorphone, titrated by clinical response. Hydromorphone is a potent opioid, with a time to onset of 10-15 minutes and a duration of effect of 3-5 hours. Symptoms resolved after he received a total of 8 mg administered over 45 minutes. During a period of observation the patient demonstrated understanding that the relief would be temporary and that withdrawal symptoms would likely reappear in a few hours. Despite this he elected to leave the ED and was given instructions to return should the symptoms recur.

Conclusions:

Precipitated opioid withdrawal can manifest untoward symptoms to a greater degree than spontaneous withdrawal due to opioid abstinence. In opioid dependent patients buprenorphine can cause withdrawal symptoms that may last more than 24 hours. Similar to patients with naltrexone induced withdrawal, symptomatic and supportive management with benzodiazepines and antiemetics are generally recommended. Adverse outcomes can be minimized by clear communication of expectations regarding the duration of symptoms and the degree of relief that may be achieved.

References:

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