Two Toxicologic Emergencies

Emergency physicians all too frequently diagnose and treat patients who have either intentionally or accidentally ingested toxic agents. This month, EMERGENCY MEDICINE introduces a new feature, Case Studies in Toxicology, designed to help ED physicians in the management of these patients. This feature will examine two cases, present findings, discuss possible etiologies, and suggest management strategies.

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CASE 1: Buprenorphine-Induced Opioid Withdrawal

Ryan Morrissey, MD, and Lewis S. Nelson, MD

A patient experiences untoward symptoms after he misses his regular methadone dose and takes his friend's medication instead.

A 39-year-old man presents to the ED with abdominal pain, body aches, chills, diarrhea, nausea, and vomiting. One hour earlier, the patient's friend gave him two "tablets" because he had reportedly missed his regular methadone dose of 180 mg/day. His medical history includes HIV, for which he receives highly active antiretroviral therapy, and hepatitis C.

On arrival, the patient is in moderate distress, alert, and fully oriented. Vital signs include a blood pressure of 155/93 mm Hg; heart rate, 118 beats/min; respiratory rate, 24 breaths/min; and temperature, 37.7°C. Other findings include an oxygen saturation of 99% on room air and a capillary blood glucose level of 120 mg/dL. Pupils are 6 mm, equal, round, and reactive. Copious rhinorrhea is noted. The oropharynx is clear; no thrush is observed. Lungs are clear to auscultation bilaterally, and the heart is tachycardic, with normal S_1 and S_2 and no murmur. The abdomen has hyperactive bowel sounds and is mildly tender over the epigastrium without guarding. Extremities lack cyanosis, clubbing, and edema. Neurologic examination is normal without focal deficit. The skin is diaphoretic with piloerection.

An ECG reveals a sinus tachycardia with normal QRS and QTc intervals. Serum chemistry panel results are as follows: 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.

ETIOLOGY OF CLINICAL FINDINGS

This patient manifests classic signs of 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, gradual opioid withdrawal syndrome is associated with morbidity due to the psychological distress it causes, as well as gastrointestinal manifestations, such as vomiting with potential aspiration and volume loss from diarrhea. However, precipitated opioid withdrawal, caused by administration of naloxone or another opioid antagonist, is associated with more significant morbidity and mortality. Precipitated withdrawal, which has an immediate onset, is almost always iatrogenic, typically occurring during ultrarapid detoxification or following prehospital or ED reversal of opioid poisoning. Many of

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the adverse effects of precipitated withdrawal directly result from the massive catecholamine response to rapid reversal of the opioid effect.[1]

IDENTIFYING THE PRECIPITATING AGENT

It is possible that this patient's opioid withdrawal syndrome may have been secondary to abdominal pain and emesis, which prevented him from taking his regular dose of methadone; however, given that the patient reports taking his friend's "tablets," precipitated opioid withdrawal is more likely the cause. Potential precipitating agents include full opioid antagonists (eg, naloxone, naltrexone), opioid agonist-antagonists (eg, pentazocine), and partial opioid agonists (eg, buprenorphine).

These three classes of xenobiotics differ in their pharmacodynamic relationship to a reference agonist (eg, morphine, methadone), which interacts with a biologic target (eg, the μ-opioid receptor) to produce a clinical effect (eg, central analgesia, respiratory depression). Full antagonists competitively inhibit the agonist at the target, thereby blocking the clinical effect. Agonist-antagonists have two functions: blocking the clinical effect in a manner similar to that of a full antagonist and interacting with a unique, but often related, biologic target (eg, the κ-opioid receptor) to produce a related clinical effect (eg, spinal analgesia). Partial agonists interact with the same reference biologic target but produce a lesser clinical effect. For example, buprenorphine is considered to have less μ-opioid analgesic efficacy than does morphine and is also noted to have a "ceiling effect" with regard to respiratory depression.[1,2]

When treating a patient exhibiting opioid withdrawal syndrome, identifying the specific agent helps to prognosticate the duration and degree of adverse symptoms. Opioid withdrawal due to ingestion of pentazocine typically lasts 3 to 4 hours ($t_{1/2}$ = 2 hours); ingestion of naltrexone or buprenorphine leads to symptoms lasting 24 to 36 hours. Naloxone induces withdrawal symptoms typically lasting 30 to 45 minutes. However, although it is commonly used in precipitated opioid withdrawal, naloxone has poor oral bioavailability and generally requires parenteral administration to initiate opioid withdrawal.[1]

>>FAST TRACK<<

Adverse outcomes can be minimized by clear communication of expected duration of symptoms and obtainable degree of relief.

MANAGEMENT

The patient tells the ED physicians that he has taken two buprenorphine tablets. Given buprenorphine's high affinity for the μ-opioid receptor, it displaces most opioid agonists. As a partial agonist at the μ-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 those who are highly opioid dependent, the clinical manifestations following buprenorphine administration can be nearly equivalent to those with naloxone.[3,4]

Buprenorphine's long duration of clinical effect and strong affinity for the μ-opioid receptor confer an additional degree of clinical difficulty in the management of precipitated withdrawal. Efforts to reverse withdrawal via direct competition at the μ-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 the preferred option in most situations. Thus, common practice is to compete indirectly and symptomatically using a combination of benzodiazepines, antiemetics, and sometimes clonidine.

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. The patient received IV hydromorphone, titrated by clinical response. Hydromorphone is a potent opioid with a time to onset of 10 to 15 minutes and a duration of effect of 3 to 5 hours. The patient's symptoms resolved after he received 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 return in a few hours. Despite this, the patient elected to leave the ED and was given instructions to return should the symptoms recur.

CONCLUSION

Compared with spontaneous withdrawal due to opioid abstinence, precipitated opioid withdrawal is associated with a greater degree of untoward symptoms. In opioid-dependent patients, buprenorphine can cause withdrawal symptoms that last lon-

ger than 24 hours. As in naltrexone-induced withdrawal, symptomatic and supportive management with benzodiazepines and antiemetics is generally recommended. Adverse outcomes can be minimized by clear communication of expectations regarding the duration of symptoms and the obtainable degree of relief.

CASE 2: Ethyl Chloride Neurotoxicity Following Abuse

Zhanna Livshits, MD, and Lewis S. Nelson, MD

Easily obtained and abused, this agent can cause ataxia and lower extremity weakness.

A 45-year-old man with a history of HIV presents to the ED and reports that he feels "off balance." His symptoms started the previous day, after he inhaled several canisters of a VCR head cleaner. The patient states that he sprayed approximately eight canisters of the agent into a cloth and inhaled the fumes ("huffed") in the morning. He repeated this with 10 canisters that night. After inhalation, the patient felt off balance and had slurred speech and difficulty writing. Although these symptoms disappeared after the morning inhalation, they persisted after redosing at night. A fall the next morning precipitates his ED visit.

The patient was admitted to the hospital 1 month ago with similar complaints after he inhaled more cleaner than usual. He had unremarkable findings on neurologic workup and brain MRI and has been following up with a neurologist on an outpatient basis.

Upon initial physical examination, he is alert and oriented. Vital signs include a blood pressure of 112/57 mm Hg; heart rate, 88 beats/min; respiratory rate, 18 breaths/min; and temperature, 35.8°C. His neurologic examination is significant for 4/5 strength in bilateral hip flexors and extensors, knee flexors and extensors, and foot flexor and extensor muscle groups. His bilateral lower extremities are hyperreflexic. He performs normally on finger-to-nose testing but not on the heel-to-shin maneuver. In addition, he has a positive result on the Romberg test. He has pronounced ataxia and gait spasticity and requires a walker. His speech is slightly slurred, although comprehensible. He also has difficulty writing.

Results of initial laboratory tests, including basic metabolic panel, complete blood count, and urinalysis, are normal. An ECG shows sinus rhythm with normal QRS and QTc intervals. Brain CT without contrast is normal.

DESCRIPTION OF THE INHALANT

The patient has inhaled ethyl chloride, or chloroethane. This is a colorless, volatile gas with an unpleasant odor. Ethyl chloride is used as a topical anesthetic, propellant in aerosol canisters, refrigerant, and an alkylating agent. Throughout the 20th century, ethyl chloride was used to produce tetraethyl lead, a gasoline additive that is no longer used. It is also used industrially to convert cellulose to ethyl cellulose and as a thickening agent and binder in paint and cosmetics.

Ethyl chloride is used as a recreational inhalant drug. It is usually huffed, or sprayed into a cloth and inhaled, particularly to enhance sexual experiences. It is sold on Web sites and in specialty stores and is available as a VCR head-cleaning solvent.

SIGNS AND SYMPTOMS OF TOXICITY

Ethyl chloride is a sedative that was used previously in general anesthesia, although this practice has been discontinued due to a high incidence of dysrhythmias. Sensitization of the cardiac muscle to catecholamines, stimulation of the vagus nerve, and direct myocardial depression may be responsible.

Knowledge about ethyl chloride–associated neurotoxicity is limited and is primarily derived from case reports. Patients suffer from ataxia, dizziness, and bilateral lower extremity motor (and occasionally sensory) neuropathy. They sometimes report experiencing olfactory and visual hallucinations shortly after they have huffed ethyl chloride.

Ethyl chloride is a halogenated hydrocarbon and presumably has a mechanism of action and toxicity similar to those of the entire class of xenobiotics. As such, it has a high lipophilicity that provides easy access to the central nervous system, where it produces global neuronal dysfunction through diverse and poorly understood means. Persistent dysfunction due to extensive expo-

>>FAST TRACK<<

Ideally, a plan for medical and psychosocial assessment should be set prior to discharge.

sure (as in abuse) may lead to compensatory neuronal changes that are slow to reverse.

PREVIOUSLY REPORTED CASES

A 41-year-old man presented with drowsiness, shakiness, and inability to walk due to impaired balance. On exam, the patient was tremulous, dysarthric, weak, and ataxic. After his neurologic and infectious workup produced normal findings, the patient admitted that he had been inhaling VCR head cleaner and that he usually felt similar symptoms after heavy use. His symptoms, with the exception of tremor, resolved in 5 days.[5]

A 22-year-old man presented with ataxia, blurring of vision, and diplopia associated with ataxia, horizontal nystagmus, inability to perform the heel-to-shin maneuver, and a positive result on Romberg testing. The patient later admitted to inhalation of ethyl chloride. His symptoms resolved in 7 days.[6]

A 52-year-old man presented with confusion, disorientation, visual hallucinations, and ataxia. The case was complicated by a history of alcohol and barbiturate abuse. The patient had a generalized seizure while hospitalized. He reported a 30-year history of sniffing ethyl chloride, with increased use 4 months prior to admission. He described euphoria and olfactory and visual hallucinations. On neurologic evaluation, the patient had impaired vibration sense in bilateral lower extremities with diffuse moderate motor and sensory neuropathy. He was discharged from the hospital 6 weeks after admission.[7]

As observed in these case reports, ethyl chloride neurotoxicity may persist for several days. It is prudent to perform a thorough neurologic investigation and exclude other etiologies for neurologic findings that are slow to resolve. The patient should have an ECG, since acute inhalation of ethyl chloride may lead to arrhythmia. Ideally, a plan for medical and psychosocial assessment should be set prior to discharge. Hospital admission is warranted for patients who do not return to functional baseline or who may not comply with an outpatient follow-up plan.

MORTALITY

There have been a few reports of death associated with ethyl chloride inhalation. For instance, a young, otherwise healthy college student was found face down on his pillow at home with a canister containing ethyl chloride in his hand. He could not be revived despite extensive resuscitative effort. Qualitative postmortem testing detected ethyl chloride.[8]

In another report, a 30-year-old deceased man was found surrounded by four cans that had apparently contained ethyl chloride. Three cans were empty and one was partially empty. A rag was loosely positioned in the man's mouth. Ethyl chloride was found postmortem in his body fluids and tissues.[9]

CASE RESOLUTION AND CONCLUSION

The case patient was admitted to the hospital and underwent metabolic investigation (eg, for vitamin deficiencies) as well as neurologic evaluation. Cervical, thoracic, and lumbar spine MRI findings were normal. Brain MRI, performed 1 month earlier, was not repeated. The patient's ataxia, slurred speech, and difficulty writing improved steadily, and he was discharged after 5 days with instructions to follow up with his neurologist.

Ethyl chloride is a recreational drug of abuse and can be easily obtained. The cerebellar and peripheral motor neuron components of ethyl chloride toxicity include ataxia and bilateral lower extremity weakness with hyperreflexia. The mechanism of action of ethyl chloride is unknown. Patients with ethyl chloride–associated neurotoxicity should undergo full medical and neurologic evaluation. Improvement over several days is typical. □

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