The Storm After the Calm: A Case of Medetomidine Withdrawal

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ABSTRACT

We report a case of a 30-year-old woman with a history of intravenous drug use, who presented to the emergency department with nausea, vomiting, agitation, and delirium. In order to protect her airway and to facilitate further evaluation, she received endotracheal intubation, but despite maximum pharmacologic sedation, she became increasingly tachycardic and hypertensive. A comprehensive blood toxicology panel revealed medetomidine, a sedative used in veterinary medicine and a known adulterant used in illicit fentanyl. While medetomidine has permeated the fentanyl supply in the middle Atlantic states, to our knowledge this is the first case reported in Rhode Island.

KEYWORDS: medetomidine; withdrawal; intoxication; contaminant; narcotics

PRESENTATION AND HOSPITAL COURSE

The patient is a 30-year-old female who presented with complaints of abdominal pain and persistent vomiting for 24 hours. Her history was otherwise limited due to agitation and confusion. Medical history obtained through the electronic medical record was significant for intravenous (IV) drug use, including fentanyl, as well as cannabis use, for which she has had multiple prior ED visits for presumed cannabis hyperemesis syndrome, which typically improved with IV medications.

Vital signs were notable for a heart rate (HR) of 125, blood pressure (BP) 159/108 mm Hg, temperature of 97.8 Fahrenheit, and SpO2 of 99%. Her physical exam revealed confusion and agitation, mild diaphoresis, with pupils at 3 mm and equal. Cardiac exam revealed tachycardia, with a normal S1S2. The patient's lung sounds were clear, and her abdomen was soft without distention or guarding. As noted, her neurologic exam was significant for confusion and agitation, and she was unable to attend to commands. She spontaneously moved all extremities.

An initial EKG was performed and was notable for sinus tachycardia with a rate of 139, but otherwise normal intervals. Lab work revealed a white blood cell count of 23.6k, K of 2.4, and lactate of 4.3. The patient's initial urine toxicology report was positive for cannabis, benzodiazepines, and fentanyl. Her volatile alcohol levels were undetected and her acetaminophen/salicylate levels were negative. Imaging of her brain and abdomen/pelvis were unremarkable.

While in the emergency department the patient's mental status continued to worsen, causing her to become increasingly agitated, swinging at staff and herself, and she required physical and chemical restraints for patient and staff safety. The patient received multiple rounds of medications for chemical sedation, including droperidol, midazolam, fentanyl, and a dexmedetomidine drip, with no success in controlling her agitation. She continued to fight against the physical restraints and became more tachycardic to the 170s. Her diaphoresis worsened, and her pupils became more dilated. She had no hyperreflexia or ankle clonus on exam, no urinary retention, and remained normothermic. She was intubated in order to control her agitation for her safety and to facilitate work-up.

The patient was transferred to the intensive care unit for ventilator management and further evaluation and care. She was maintained on a propofol and dexmedetomidine infusion, and on day two of her hospital admission her vital signs improved and she was extubated. A comprehensive blood toxicology panel was notable for medetomidine, in addition to the drugs detected in her urine panel. She endorsed using IV opiates but left the hospital against medical advice and prior to completing her repeat laboratory studies.

DISCUSSION

Our patient suffered from medetomidine toxicity and withdrawal. Medetomidine was first brought to market in Europe in 1987 and received FDA approval for sedation in dogs in 1996.[1] It is a selective alpha-2 adrenergic receptor agonist and is widely used in veterinary medicine as a sedative and analgesic. Medetomidine is a racemic mixture of dexmedetomidine, the more pharmacologically active enantiomer which is approved for human use, and levo-medetomidine. Alpha-2 agonists are sympatholytic and inhibit norepinephrine and dopamine release, with the primary result being central nervous system (CNS) depression given the higher concentration of alpha-2 receptors centrally as opposed to peripherally.[2,3] Along with sedation, medetomidine can cause bradycardia and produce biphasic effects on blood

pressure due to the initial peripheral alpha-2 receptor activation on vascular smooth muscle, leading to vasoconstriction. This is followed by the more dominant central alpha-2 receptor activation causing the reduction in circulating catecholamines and hypotension.[3]

Medetomidine was first identified as an adulterant in the non-medical opioid supply in Maryland in July 2022. Since then, it has been found in illicit fentanyl in multiple locations in the United States, as well as in Canada, and has been linked to adverse outcomes in Philadelphia, Chicago, and Pittsburgh.[3,4] Use of medetomidine has mushroomed over the last several years. In a 2024 study in Philadelphia, medetomidine was detected in 29% of samples taken of illicit fentanyl with prevalence increasing to 87% six months later.[2,5] It has been routinely detected in wastewater in numerous states and is distributed throughout the U.S., with the greatest concentration in the Northeast and Midwest.[5]

Use of medetomidine has surpassed xylazine, which was formerly the most common adulterant in fentanyl samples.[2,4,6,7] Xylazine, a non-opioid sedative and alpha 2 adrenergic agonist medication most commonly associated with necrotic skin wounds, is sometimes combined with medetomidine and fentanyl in the non-medical opioid supply.[8] It can also cause bradycardia and hypotension, but these cardioactive effects are more predominantly noted in medetomidine toxicity as medetomidine has a 10-times greater alpha 2:alpha 1 selectivity.[9]

The combination of fentanyl and medetomidine, sometimes referred to as "demon," attenuates the respiratory drive.[3,4] In a study on Wistar rats, the combination of fentanyl and medetomidine worked synergistically, leading to earlier onset of toxicity, including respiratory depression and bradycardia compared to either drug alone.[2] While naloxone administration may reverse the impact on the fentanyl dosing, it does not countermand medetomidine toxicity.[3] At present, no reversal agents for medetomidine are currently approved for human use. Atipamezole, an imidazoline alpha-2 receptor antagonist, is a veterinary reversal agent for medetomidine and is used in dogs, but it may precipitate acute, life-threatening withdrawal symptoms in humans.[3]

Consequently, management of acute medetomidine toxicity—hypotension, bradycardia, and CNS depression—is primarily supportive. Airway protection can be achieved either through head of bed elevation or through endotracheal intubation and mechanical ventilation. Bradycardia and associated hypotension can initially be managed with fluids and vasopressors.[3,9] In patients with heavy, chronic use of medetomidine, it is paramount to closely monitor symptom progression as patients may start to display signs of withdrawal, which requires differing management.

Acute medetomidine withdrawal can lead to life-threatening hyperadrenergic symptoms, including severe hypertension, tachycardia, and agitation. Anxiety, tremor, flushing and diaphoresis can occur within hours of last drug use. Hyperthermia, a predictor of an increased risk of mortality, has been noted as well.[5] Laboratory findings are numerous. Hypokalemia, elevated lactic acid levels, and high troponin can occur. QTc prolongation, acute cardiomyopathy, and posterior resolving encephalopathy syndrome have been reported.[3,4]

Management of acute withdrawal continues to develop. In the early stages of medetomidine withdrawal (usually 4–6 hours after last use), oral and transdermal alpha-2 agonists and antiemetic therapy can be considered. Alpha-2 agonists such as clonidine, tizanidine, guanfacine, and dexmedetomidine can be utilized to directly treat the underlying pathophysiology of medetomidine withdrawal. Additionally, droperidol and benzodiazepines can be used for both agitation and as an antiemetic.[3] Progression, however, is not uncommon, and rapid escalation from agitation to autonomic dysregulation can occur during the course of an emergency department evaluation.[9] In one study, approximately two-thirds of patients required ICU admission and 16% required intubation.[4]

In our case, the patient's progressive agitation and inability to follow commands made enteral treatment untenable. The patient eventually required endotracheal intubation, ICU admission, and a dexmedetomidine infusion along with benzodiazepines. Intravenous dexmedetomidine is the mainstay of severe withdrawal symptoms, and patients may require higher than usual infusion rates.[9] Patients in severe withdrawal can continue to receive transdermal or oral clonidine (even through an orogastric tube) if there is persistent hyperadrenergic symptoms. Phenobarbital has limited effect in these patients unless there is suspicion for accompanying benzodiazepine withdrawal, and ketamine may also have limited impact in medetomidine withdrawal.[3] Patients may also require management of opioid withdrawal with antiemetics, antidiarrheals, and additional supportive medications. It is interesting to note that weaning of prolonged dexmedetomidine in the ICU setting can cause similar withdrawal symptoms to medetomidine withdrawal, given their shared mechanism of action. Signs of medetomidine withdrawal may abate after 24–48 hours.[9]

Due to the increasing prevalence of medetomidine in Rhode Island's fentanyl supply, early recognition of medetomidine toxicity and withdrawal is critically important. Management of medetomidine withdrawal is notoriously difficult, and may require intensive levels of intervention as these patients may develop life-threatening derangements with untoward consequences if not appropriately addressed.

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Disclosures

None

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