November 2014 Critical Care Case of the Month: I Be Gaining on My Addiction

Nathaniel R. Little, MD
Carolyn H. Welsh, MD

University of Colorado and the Eastern Colorado Veterans Affairs Medical Center
Department of Medicine
Division of Pulmonary Sciences and Critical Care Medicine
Denver, CO

History of Present Illness

A 33 year-old man came by ambulance to the Emergency Department for progressive altered mental status and bizarre behavior. Per history from his significant other, the patient had a long-standing history of heroin addiction and diazepam abuse. Despite multiple failed attempts at prior detoxification, he had recently resolved to “take matters into his own hands.”

The patient had informed his girlfriend that he quit heroin “cold turkey” 3 days prior to admission. On the first day after his last heroin use, he was communicative, energetic, and appeared normal. On the second day, he was increasingly introspective, somnolent, and mute. He spent the majority of the day in bed, and had tremors of all extremities. On the third day, he experienced increased arousal, with auditory and visual hallucinations. His speech was “very technical and scientific” with episodes of “waxing philosophic.” Given increasingly erratic behavior, worsening tremors, and inability to ambulate; emergency services were called for transport to the hospital.

Past Medical History, Social history and Family History:

The patient had a history of heroin and diazepam addiction, with failed attempts at cessation. He carried prior diagnoses of depression and anxiety, with a history of suicide attempts in his youth. He took no prescribed medications. He was employed as a software engineer. Aside from daily intravenous heroin use, he did not smoke nor drink alcohol. Family history was non-contributory.

Physical Examination:

On admission , he was hypothermic (35.8 C), hypotensive (BP = 81/48), and bradycardic (HR =41). Respiratory rate and oxygen saturations were normal. He was pale, diaphoretic, altered, and responsive only to internal stimuli. Additional findings included nystagmus, with oral exam showing dry mucus membranes. Per cardiovascular exam, he had profound bradycardia, with diminished radial and dorsalis pedis pulses. His extremities were cool to the touch. Pulmonary and abdominal exams were normal. On neurologic evaluation, the patient demonstrated a Glasgow Coma Score of 9, opened eyes only to command, demonstrated mumbled speech, and had tongue fasiculations. He was able to move all extremities, but with severe ataxia. Deep tendon reflexes were normal.

Laboratory Studies:

Complete Blood Count: White blood cell count (WBC) 9.0 x 1000 cells/µL, hemoglobin 14.5 g/dL, hematocrit 43.0, platelets 220,000 cells/µL
Chemistry: Sodium 150 meq/L, potassium 3.6 meq/L, chloride 113 meq/L, bicarbonate (CO2) 25 meq/L, blood urea nitrogen (BUN) 31 mg/dL, creatinine 1.14 mg/dL, glucose 114 mg/dL, magnesium 1.6 meq/L, phosphorus 4.1 mg/dL, creatinine kinase 33.
Toxicology Screen: Urine drug screen positive only for benzodiazepines, negative for opiates.
Urine: trace ketones, otherwise unremarkable.

Imaging:

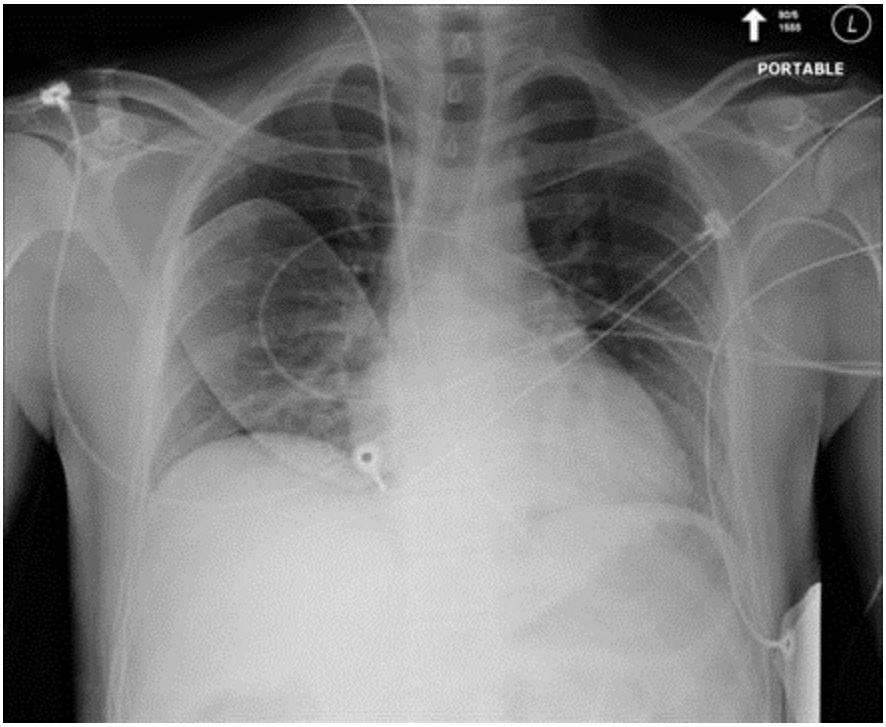

Figure 1. Admission AP of chest.

The patient's clinical presentation thus far is most consistent with what type of shock:

1. Cardiogenic
2. Distributive
3. Hypovolemic
4. Neurogenic
5. Obstructive
6. Both 1 and 3
7. All of the above

Correct!
6. Both 1 and 3

The patient demonstrates multiple findings suggestive of both hypovolemic and cardiogenic shock. Clinical elements suggesting hypovolemia are dry mucus membranes, the history of poor intake over the last 3 days and hypernatremia. Impaired cardiovascular function is reflected by bradycardia, cool extremities, and diminished pulses. The patient was aggressively resuscitated with intravenous fluids with minimal benefit. A transthoracic echocardiogram was obtained which demonstrated normal appearing left and right ventricular size/wall motion, contractility, and normal valves. No pericardial effusion was observed. Despite volume resuscitation, the patient's blood pressure continued to drop, along with further slowing of his heart rate. EKG findings are shown in Figure 2.

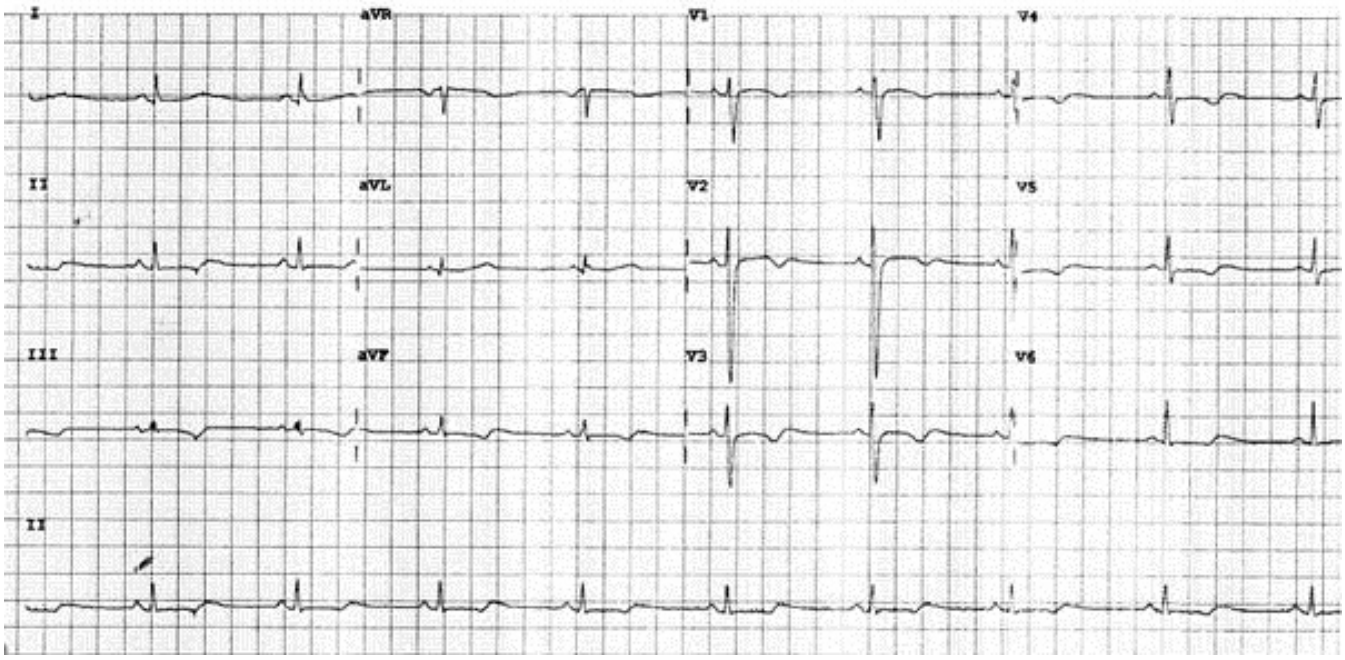

Figure 2. Admission EKG.

What are the EKG findings of concern for a toxidrome?

1. Bradycardia
2. First degree AV block
3. QT prolongation
4. ST depressions in II, III, AVF and the precordial leads
5. Both 1 and 3
6. All of the above

Correct!
5. Both 1 and 3

This EKG shows bradycardia although tachycardia would be expected in the presence of hypotension. The ST depressions in inferior and lateral leads are nonspecific. The QTc interval is prolonged and eventually was more than 600 milliseconds for this patient. He does not have first degree AV block.

Acquired prolonged QT syndrome can be seen with many drugs including most antiarrythmics, haloperidol, macrolide antibiotics or methadone, which was of potential concern for this patient. Use of cocaine, cinchona(from which quinine is derived), and licorice extract have led to prolonged QT intervals. Electrolyte abnormalities including hypokalemia, hypomagnesemia and hypocalcemia predispose to prolonged QT and risk for the torsades de pointes form of polymorphic ventricular tachycardia.

The next appropriate step in the management of this patient's bradycardia and associated shock are the following:

1. Additional intravenous fluids
2. Atropine
3. Transcutaneous/transvenous pacing
4. Vasopressors
5. 1 and 3
6. All of the above

Correct!
6. All of the above

All of these choices may be helpful is resolving his shock. If atropine does not correct the bradycardia, rapid placement of pacing or an adrenergic agent may be helpful. IV fluids and vasopressors can treat the hypovolemia.

The toxidrome most associated with this patient's clinical presentation is due to which of the following medications:

1. Buprenorphine
2. Clonidine
3. Ibogaine
4. Methadone
5. 1 and 3
6. All of the above

Correct!
3. Ibogaine

Ibogaine is an indole alkaloid with psychoactive and dissociative properties, widely regarded by tribes in West Africa as a cure for hunger, thirst, and even fatigue at low doses (1). Higher doses play a central role in tribal rites of passage and ritualistic attempts to communicate with ancestors. Today, ibogaine is best known for its purported anti-addiction properties and potential role in polysubstance detoxification as well as its toxicity (2).

A former heroin addict turned ibogaine researcher inadvertently stumbled upon this agent in the 1960's when after ingestion, five of six users completely lost the urge for further opioid use. After years of *in vitro* and *in vivo* studies characterizing the anti-addictive properties of ibogaine, the FDA approved a clinical trial exploring the compound (3). However, owing to conflicting *in vivo* data suggesting cerebellar neurotoxicity and institutional financial constraints, the National Institute on Drug Abuse abandoned plans for ongoing investigational trials in 1995.

Due to its psychedelic/dissociative properties, ibogaine remains as a Schedule I drug in the USA. Nevertheless, ibogaine continues to be explored by individuals seeking detoxification from a variety of substances, opioids being the most common. It can be obtained through non-legal means and self-administered, or can be administered by medical personnel in countries without current bans.

Ibogaine use can lead to death (2). In a multinational forensic case series, 19 deaths were temporally associated with ibogaine ingestion (4). Cardiac disease, specifically cardiac arrhythmias are considered of greatest concern. QT prolongation is common with ibogaine toxicity (5). With blockage of the potassium voltage-gated ion channels encoded by the human ether-a-go-go-related gene there is a heightened risk of polymorphic ventricular tachycardia, torsades de pointes. Also, those presenting with toxicity are often at elevated risk for electrolyte and nutritional disturbances which themselves predispose to cardiac irritability and arrhythmia.

In rats given ibogaine, neurotoxicity was seen with high doses particularly in the olivocerebellar neural projections. This parallels the human side effects seen after acute ingestion, that of tremor and ataxia (6), demonstrated in the current case.

References

1. Mash DC, Kovera CA, Pablo J, Tyndale RF, Ervin FD, Williams IC, Singleton EG, Mayor M. Ibogaine: complex pharmacokinetics, concerns for safety, and preliminary efficacy measures. Ann N Y Acad Sci. 2000;914:394-401. [CrossRef] [PubMed]
2. Jalal S, Daher E, Hilu R. A case of death due to ibogaine use for heroin addiction. Am J Addict. 2013;22(3):302. [CrossRef] [PubMed]
3. Maciulaitis R, Kontrimaviciute V, Bressolle FM, Briedis V. Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. Hum Exp Toxicol. 2008;27(3):181-94. [CrossRef] [PubMed]

4. Alper KR, Stajic M, Gill JR. Fatalities temporally associated with the ingestion of ibogaine. J Forensic Sci. 2012;57(2):398-412. [CrossRef] [PubMed]
5. Hoelen DW, Spiering W, Valk GD. Long-QT syndrome induced by antiaddiction drug ibogaine. N Engl J Med. 2009;360(3):308-9. [CrossRef] [PubMed]
6. O'Hearn E, Molliver ME. The olivocerebellar projection mediates ibogaine-induced degeneration of Purkinje cells: a model of indirect, trans-synaptic excitotoxicity. J Neurosci. 1997;17(22):8828-41. [PubMed]