January 2019 Critical Care Case of the Month: A 32-Year-Old Woman with Cardiac Arrest

Sarah A. Watkins, DO[1]
Geoffrey Smelski, PharmD[1]
Robert N.E. French, MD[1]
Michael Insel, MD[2]
Janet Campion MD[2]

[1]Arizona Poison and Drug Information Center and [2]Division of Pulmonary, Allergy, Critical Care and Sleep
University of Arizona
Tucson, AZ USA

History of Present Illness

A 32-year-old woman with history of chronic neck pain and opioid abuse complained of dizziness and palpitations shortly before suffering a witnessed cardiac arrest in her home. She was given bystander cardiopulmonary resuscitation until emergency medical services arrived on scene, at which point intermittent polymorphic ventricular tachycardia with a pulse was noted on the cardiac monitor and physical exam (Figure 1).

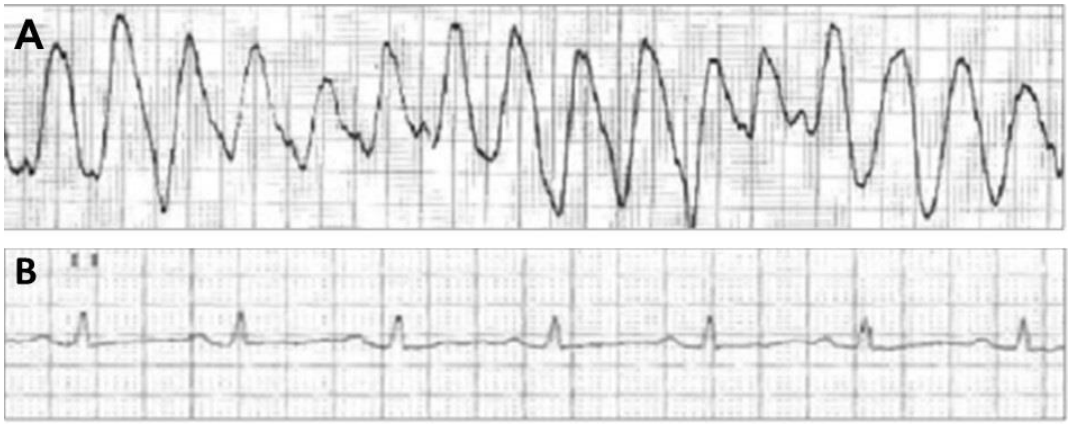

Figure 1. Rhythm strips showing ventricular tachycardia (A) and a prolonged QT interval (B).

Which of the following is (are) the ***most likely cause(s)*** of the cardiac arrythmia?

1. Cardiomyopathy
2. Coronary artery disease
3. Drug-induced arrythmia
4. 1 and 3
5. All of the above

Correct!
3. Drug-induced arrythmia

The rhythm strip (1A) shows Torsade de Pointes (TdP) during which time she became hypotensive, at times losing pulses. The TdP was intermittent and a rhythm strip between TdP episodes showed normal sinus rhythm with prolonged QRS and QTc (1B). These suggest a drug-induced arrythmia (1).

She was transported to the emergency department (ED) by EMS. On arrival to the ED, the patient had a heart rate in the 80s and was normotensive. She was intubated for airway protection. She was electrically cardioverted and defibrillated over 10 times for recurrent TdP in the emergency department. While central IV access was being obtained, multiple medical therapies were attempted without success. Central intravenous (IV) access was obtained to place a transvenous pacemaker. Her family arrived to the ED and reported they had found multiple boxes of a medication hidden under the patient's bed.

Overdose of which ***medication most likely*** caused this patient's presentation?

1. Alcohol intoxication
2. Amphetamine/dextroamphetamine
3. Gabapentin
4. Guanfacine
5. Loperamide

Correct!
5. Loperamide

Loperamide is a widely available anti-diarrheal medication that is becoming more popular amongst patients suffering from opioid misuse disorder (2,3). In therapeutic dosing, its opioid mu agonistic effects are localized to the GI tract, causing decreased gut motility and resolution of diarrhea. In overdose, however, loperamide is able to cross into the central nervous system, where it exerts central opioid effects. This leads to the classic opioid toxidrome of decreased respirations, decreased mentation, and decreased pupil size. Loperamide also acts on cardiac myocytes via blockade of potassium (hERG) channels, which leads to prolonged QT and Torsade de Pointes.

After pacemaker placement, the patient was successfully electrically overdrive paced.

Which ***over-the-counter product is commonly used to increase the desired effects*** of the medication on which this patient overdosed?

1. Aspirin
2. Bismuth Subsalicylate
3. Black Cohosh
4. Cimetidine
5. Omeprazole

Correct!
4. Cimetidine

Cimetidine is a potent inhibitor of the P-glycoprotein (PGP) efflux pump (4). PGP efflux pumps are found throughout the GI tract as well as in the blood brain barrier. Loperamide is a substrate with considerable affinity for the PGP pump. With therapeutic doses of loperamide, the bioavailability is around 0.3%, and plasma loperamide is 97% protein bound (inactive). After absorption from the GI tract, the remaining non-protein-bound loperamide must then pass through the second layer of PGP pumps in the BBB. Loperamide then enters the CNS, where it exhibits opioid agonistic effects. PGP inhibitors such as cimetidine can drastically reduce the quantity of loperamide capsules needed to ingest in order to create opioid agonist effects.

Black cohosh is known to cause numerous metabolic drug interactions through inhibition or induction of most major CYP enzyme pathways, but it is not associated with significant PGP inhibition. Bismuth subsalicylate, omeprazole and aspirin would not be expected to increase CNS dose of loperamide.

What is the ***best treatment*** for a patient suffering from loperamide toxicity?

1. Amiodarone
2. Calcium gluconate
3. Magnesium sulfate
4. Overdrive pacing
5. Sodium bicarbonate

Correct!
4. Overdrive pacing

Overdrive pacing, either electrical or chemical (e.g., with a beta agonist such as isoproterenol), has been shown to be the most effective therapy in a case series of patients with loperamide toxicity (2,3). Loperamide toxicity can lead to prolongation of both the QRS and QT. While sodium channel blockade is frequently cited as a cause of wide QRS, it is more likely that wide QRS is caused by gap junction inhibition in the setting of loperamide toxicity. Unlike sodium channel blockade, gap junction inhibition does not typically respond to administration of sodium bicarbonate or hypertonic saline solutions. It may still be prudent to trial administration of sodium bicarbonate and assess QRS response, however the risk of hypokalemia with repeated administration may outweigh the benefit. Magnesium sulfate should nearly always be administered to a patient with polymorphic ventricular tachycardia to stabilize the cardiac membrane, however in a patient with refractory TdP magnesium will likely not be adequate. Calcium gluconate is used to stabilize the cardiac membrane in patients with critical hyperkalemia and EKG changes, however it would likely not be useful in loperamide toxicity.

After stabilizing, she had a recurrence of her ventricular tachycardia. The fluoroscope which had been used to place the pacing catheter was still at her bedside and an image was obtained (Figure 2).

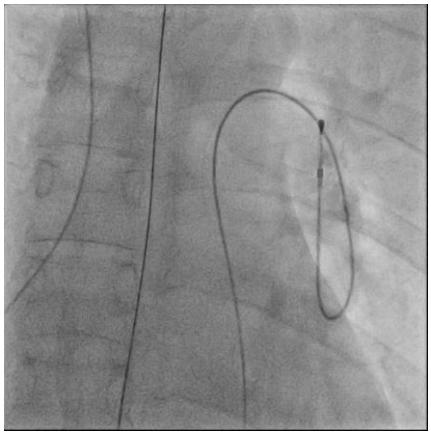

Figure 2. Image from the fluoroscope taken shortly after recurrence of the ventricular tachycardia.

What does the ***chest x-ray show***?

1. A severed central venous line lodged in the pulmonary artery
2. Swan Ganz catheter in the aorta
3. Swan Ganz catheter in the pulmonary artery
4. Transvenous pacemaker in the aorta
5. Transvenous pacemaker in the pulmonary artery

Correct!
5. Transvenous pacemaker in the pulmonary artery

The catheter migrated into the pulmonary artery as seen in the fluoroscopic image. No complication occurred and the catheter was returned to the correct location using fluoroscopic guidance. There are no absolute complications of transvenous pacemakers with life threatening conditions such as recurrent TdP with hemodynamic instability (5). Relative contraindications are minimally symptomatic bradycardia, prosthetic tricuspid valves or active anticoagulation. Complications of transvenous pacemakers include lead dislodgement or disconnection, bleeding, infection, myocardial perforation, pulmonary embolism, pneumothorax and air embolism.

She was admitted to the medical intensive care unit, where she was able to be extubated and the pacemaker removed on hospital day four. She was neurologically intact and able to confirm that she had ingested loperamide.

Which medication is the ***most appropriate*** to prescribe for this patient after the acute toxicity has fully resolved?

1. Buprenorphine
2. Cimetidine
3. Clonidine
4. Methadone
5. Sertraline

Correct!
1. Buprenorphine

Buprenorphine is a partial opioid agonist with highly competitive binding affinity. Buprenorphine is FDA indicated for the management of opioid dependence and prevention of opioid withdrawal.

Methadone is also indicated for opioid dependent patients but would not be the best choice in this scenario due to risk of QT prolongation. If the patient was to relapse and again start abusing loperamide in addition to the methadone, additive effects on QT prolongation would be expected.

Clonidine can be used as an adjunct for patients experiencing acute symptoms of withdrawal but is not indicated for chronic treatment of dependence. Sertraline and cimetidine are not indicated for the treatment of opioid misuse or withdrawal.

References

1. Dave J. Torsade de Pointes. Medscape. Jan 31, 2017. Available at: https://emedicine.medscape.com/article/1950863-overview#a1 (accessed 12/14/18).
2. Wu PE, Juurlink DN. Clinical review: Loperamide toxicity. Ann Emerg Med. 2017 Aug;70(2):245-52. [CrossRef] [PubMed]
3. Nattel S. An emerging malignant arrhythmia epidemic due to loperamide abuse: underlying mechanisms and clinical relevance. JACC Clin Electrophysiol. 2016 Dec;2(7):790-2. [CrossRef] [PubMed]
4. Hughes A, Hendrickson RG, Chen BC, Valento M. Severe loperamide toxicity associated with the use of cimetidine to potentiate the "high". Am J Emerg Med. 2018 Aug;36(8):1527.e3-1527.e5. [CrossRef] [PubMed]
5. Nickson C. Temporary pacemaker troubleshooting. Life in the Fast Lane. May 17, 2016. Available at: https://lifeinthefastlane.com/ccc/temporary-pacemaker-troubleshooting/ (accessed 12/14/18).