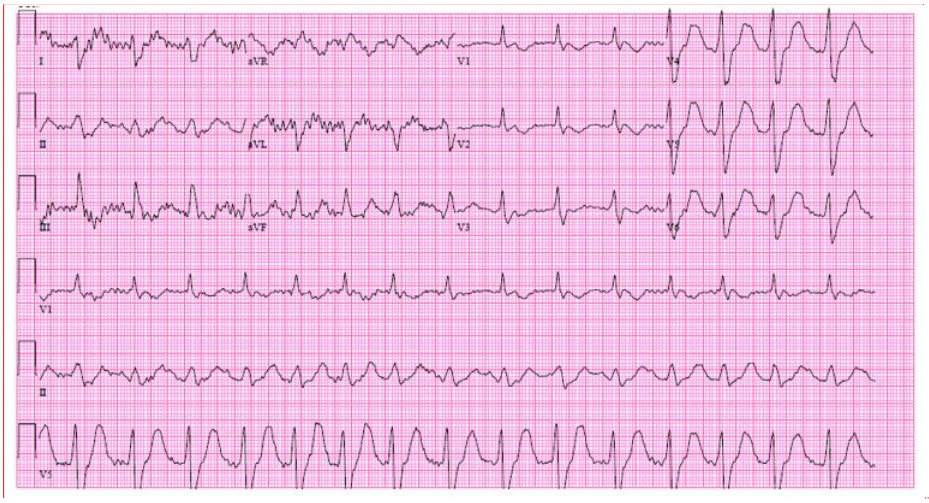
An Unexpected Etiology of Ventricular Dysrhythmia

Case

A 41-year-old man with a history of alcohol and cocaine abuse presented to the emergency department after experiencing an out-of-hospital cardiac arrest while at a party. Cardiopulmonary resuscitation was administered by bystanders and return of spontaneous circulation was achieved. He was intubated in the field. On arrival to the emergency room, he was bradycardic with a heart rate of 36, PR interval of 214 milliseconds, QRS of 148 milliseconds, and a corrected QT interval of 600 milliseconds. Vital signs were also noteworthy for hypotension to the 90s/30s mmHg. Urine toxicology was negative for cocaine and tricyclic antidepressants. He was admitted to the Medical Intensive Care Unit.

The patient was started on dopamine, norepinephrine, and isoproterenol infusions. Electrocardiography demonstrated a PR interval of 68 milliseconds, QRS of 186 milliseconds and a corrected QT interval of 641 milliseconds with the following rhythm:



His rhythm subsequently degenerated into ventricular tachycardia.

Question

1) An excessive dose of which of the following is the most likely etiology of this patient's abnormal electrocardiographic findings?

Commented [QH1]: Include an attention-grabbing title that does NOT give the diagnosis away! In addition to this title, please include a secondary title that briefly states the key diagnosis/answer (the QH Editorial staff will use this for reviewer/archiving purposes, though it will not actually be published as part of the case).

Commented [QH2]: Remember that you must adhere to a word limit of <800 words for the case and discussion (title, authors, author affiliations, and references are not included in this in this word count). Please be concise and focused. These are intended to be ***Quick*** Hits-- brevity is key!

Commented [QH3]: Use this sentence structure for the first line of your case.
"A [age] year old [gender, if provided] with a past medical history of [include elements of the PMH] presented to [the emergency room/the hospital/clinic/etc] with complaints of [chief complaint]."

Commented [QH4]: Include a **brief** description of the patient's history, as well as any pertinent hospital or outpatient course. Again, be concise and focused.

Commented [QH5]: Include 1-3 **high-quality** images (or **brief, high-quality** videos, as in the case of echocardiography, for example). Be selective with your images and only include those that you think are important to the diagnosis. The images **must** avoid patient identifiers. If you are including any patient-related images (i.e., images of the patient's body), you **must** include a patient consent form [hyperlink to this]. Radiology, echocardiograms/ultrasound images, electrocardiograms, pulmonary function testing, and sleep studies do **not** require a patient consent form.
Images should be at least 300 DPI.

Commented [QH6]: Provide 1-2 **multiple choice** questions for your readers to answer. Oftentimes, these questions will focus on selecting the correct diagnosis, identifying the cause of the patient's underlying pathology, selecting the next best option to help establish a diagnosis, or identifying the initial step in management. You should provide 3-5 possible answer choices for each question. **There must be one correct answer.**

A. Cocaine
B. Loperamide
C. Metoprolol
D. Midazolam
E. Nortriptyline

2) In addition to initiating Advanced Cardiac Life Support (ACLS) protocol, which of the following is the best treatment at this time?

A. Administer intravenous flecainide
B. Initiate transvenous pacing
C. Administer intravenous sodium bicarbonate
D. Administer intravenous beta blockade

Answers:

1) B. Loperamide
2) C. Administer intravenous sodium bicarbonate

Commented [QH7]: Provide the correct answer to each question. Readers will not immediately see the correct answer(s) and the Discussion section. Once they have read the case and answered the questions, readers will click a separate link to display the answer(s) and Discussion. For an example of this, please click here [hyperlink to this actual QH].

Discussion

The electrocardiographic findings of QT prolongation and progressive QRS widening were attributed to loperamide toxicity. Regarding Question 1, though cocaine and nortriptyline may also potentiate QT prolongation and ventricular dysrhythmias, the patient's urine toxicology was negative for both drugs. Metoprolol and midazolam do not cause QT prolongation or ventricular arrhythmias and, as such, are incorrect answer choices. Further discussion with the patient's friends and family revealed that he had been taking approximately 200 2-milligram tablets of loperamide daily in the weeks preceding this presentation. Loperamide is an opioid agonist available over-the-counter as an antidiarrheal agent. The drug slows intestinal motility by acting on opiate receptors within the gut; at appropriate dosing it has low bioavailability, poor penetration of the blood-brain-barrier, and a minimal side effect profile. At higher concentrations, loperamide can cause respiratory depression and arrhythmias. Loperamide blocks potassium channels, resulting in significant QT prolongation and torsades de pointes. At even higher plasma concentrations, loperamide causes sodium channel blockade, resulting in QRS complex widening.

Commented [QH8]: The discussion should be **brief** (limited to 2-4 paragraphs, ideally) and should begin with brief statement that provides an answer to your primary question. This initial paragraph should summarize the most important clinical pearls from the case.

Commented [QH9]: In addition to providing the correct answer to each question, you **must** provide a brief explanation as to why the other answer choices are incorrect. **This rationale must be provided in order for the Editorial staff to consider your submission for publication.**

Treatment of loperamide toxicity is focused on maintaining cardiopulmonary stability. If patients present within several hours of ingestion, gastric decontamination may minimize systemic absorption, although in many cases the highest plasma concentrations result from chronic ingestion. Opioid antagonists may mitigate respiratory depression, though some patients will require intubation and mechanical ventilation. Aggressive medical management of cardiac toxicity is required to prevent and treat arrhythmias. Electrolyte supplementation should be provided to ensure that the

patient's potassium is greater than 4 millimoles per liter and the magnesium is greater than 2 milligrams per deciliter. When significant widening of the QRS complex is noted (as seen on this electrocardiogram), intravenous sodium bicarbonate should be administered to narrow the QRS complex (Question 2). In cases of severe arrhythmias complicated by hemodynamic compromise that are refractory to initial medical management, placement of a transvenous pacer should be considered for overdrive pacing. Flecainide, a class Ic antiarrhythmic, would cause increased sodium channel blockade with QRS complex widening and, as such, is not appropriate. Beta blockade is also inappropriate, as this would exacerbate the patient's bradycardia.

In cases of bradycardia associated with ventricular ectopy, isoproterenol is typically used, though intravenous infusions can be complicated by vasodilation and worsening hemodynamics. Lidocaine may reduce the burden of ventricular ectopy. Amiodarone may worsen QT prolongation and paradoxically exacerbate arrhythmias. If pulseless ventricular tachycardia or ventricular fibrillation occurs, providers should follow ACLS protocol. Case studies support a potential benefit from intravenous lipid emulsions and veno-arterial extracorporeal membrane oxygenation in refractory cases.

In the context of today's devastating opioid epidemic, loperamide has garnered increasing attention for its ability to potentiate a "high" and to mitigate symptoms of opioid withdrawal when used in excess. The recommended dose is 2-4 milligrams in adults, not to exceed 16 milligrams daily. As a non-prescription drug, loperamide can be purchased in bulk, with many retailers selling up to 200 capsules at a time for about $25.00. Cardiotoxicity has most often been seen in chronic overuse of loperamide. In 2016, the Food and Drug Administration issued a Drug Safety Communication to warn about "serious heart problems that can lead to death" associated with inappropriate loperamide use. Anecdotally, our own intensive care unit has seen a handful of cases of ventricular arrhythmias due to loperamide over the past year and, nationally, these numbers are on the rise. Intensivists should familiarize themselves with the complications of loperamide misuse and the ways in which to manage these patients.

Commented [QH10]: It is often helpful to conclude with a description of why the case is significant and relevant.

References:

Commented [QH11]: 1-5 references are allowed per case.

1. FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium) including from abuse and misuse. Food and Drug Administration, June 2016. (https://www.fda.gov/downloads/Drugs/DrugSafety/UCM505108.pdf).
2. Litovitz T, Clancy C, Korberly B, et. al. Surveillance of loperamide ingestions: an analysis of 216 poison center reports. J Toxicol Clin Toxicol 1997; 35: 11-9.
3. MacDonald R, Heiner J, Villarreal J, et. al. Loperamide dependence and abuse. BMJ Case Reports 2015. doi:10.1136/bcr-2015-209705

4. Miller H, Panahi L, Tapia D, et. al. Loperamide misuse and abuse. Journal of the American Pharmacists Association 2017; 57: S45-S50.
5. Wu PE, Juurlink DN. Clinical Review: Loperamide Toxicity. Annals of Emergency Medicine 2017; 70: 245-52.