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Acute Flecainide Toxicity Treated with Intravenous Lipid Emulsion

Joseph S. Schreiner
Rowan University

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Joseph S. Schreiner, DO

Introduction

Flecainide is a Vaughn-Williams class IC antiarrhythmic used in the treatment of supraventricular tachycardias including atrial fibrillation.[7] While overdose is rare, its negative effects on cardiac inotropy and conduction pathways can be readily fatal. This is further complicated by the redistribution of the drug out of the plasma and deposition in tissue, rendering reversal by sodium bicarbonate (the standard first line treatment agent) relatively ineffective.[3] A case study of the successful treatment of hemodynamic collapse using sodium bicarbonate in conjunction with intravenous lipid emulsion (ILE) in a patient who ingested a large amount of flecainide in a suicide attempt will be discussed.

Case Report

A 35 year-old female presented to the emergency department after being found unresponsive at home. The patient reportedly called her friend saying she intended to commit suicide after her husband left her. The friend rushed to the patient's home to find her unresponsive on the floor next to an empty bottle of flecainide 100 mg tablets which the patient was prescribed for her paroxysmal supraventricular tachycardia. The exact time and amount of ingestion was unknown. Emergency medical services (EMS) were called immediately.

En route to the emergency department, EMS transmitted an initial electrocardiogram which demonstrated an undetermined wide complex rhythm with marked QRS and QT prolongation and a right bundle branch block (Image 1). This was compared to the patient's previous tracing from two months prior which showed normal sinus rhythm with no evidence of a right bundle branch block.

Upon arrival to the emergency department the patient was minimally responsive to external stimuli demonstrating extensor response to pain, was making incomprehensible sounds, and her eyes were closed during exam. Her Glascow Coma Scale (GCS) score was 5. The odor of alcohol was noted. Her initial blood pressure was 150/73 mmHg. Repeat blood pressure measurement several minutes later was 79/47 mmHg. Fluid resuscitation was initiated with a two liter bolus of intravenous normal saline without improvement in hemodynamic stability. The patient remained hypotensive requiring pressor support and was started on vasopressin drip at a rate of 0.04 units/minute. She was intubated to protect her airway and placed on full ventilatory support.

The patient was given 50 milliequivalents (mEq) of sodium bicarbonate on arrival secondary to her wide complex rhythm. A second electrocardiogram was obtained ten minutes following sodium bicarbonate administration and demonstrated only minimal improvement from initial tracing. A second dose of sodium bicarbonate 50 mEq was given. A call was placed to Poison Control. The case was discussed initially with the intake nurse who agreed with continuing sodium bicarbonate and recommended a goal serum pH=7.5. A third dose of sodium bicarbonate 50 mEq was given.

Approximately 35 minutes after the patient's arrival we received a return phone call from the toxicologist at Poison Control who recommended a trial of ILE. One hundred and fifty mL of 20% ILE was administered. A third electrocardiogram was obtained following ILE which demonstrated sinus rhythm with 1st degree atrioventricular block and QRS/QT prolongation, a marked improvement from initial tracing (Image 2).

Laboratory results obtained upon presentation demonstrated an acute uncompensated primary respiratory alkalosis with a pH=7.45 (normal 7.35-7.45); pCO2=35.2 (normal 35-45) mmHg; HCO3=24.3 (normal 22-28) mmol/L; pO2=207 mmHg. The patient's serum ethanol concentration resulted at 195 mg/dL (normal <5 mg/dL). Incidentally, the patient was also noted to be pregnant with a positive qualitative serum beta-HCG. A serum flecainide level was drawn on admission and sent out. It later resulted at 3.29 µg/mL (therapeutic range 0.20 - 1.00 µg/mL). The remainder of her labs on admission were within normal limits.

She was admitted to the intensive care unit secondary to cardiogenic shock. She remained intubated and on full ventilatory support at the time of transfer. A sodium bicarbonate infusion (150 mEq/1000 mL D5W, rate =125 mL/hr) was started following ILE administration. The patient returned to her baseline physiological status over the course of an 18 day hospitalization. The patient was discharged to an inpatient psychiatric facility for further specialized management.

References

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Abstract

Owing to its high lipophilicity, flecainide toxicity can be difficult to manage with traditional treatments. Flecainide quickly redistributes into fat tissue, creating a depot of the drug that overwhelms hydrophilic reversal agents, such as sodium bicarbonate, in the plasma. Creation of a lipid sink with intravenous lipid emulsion (ILE) provides a way to minimize the sequestration of flecainide in fat stores, improve the efficacy of reversal agents and hasten drug elimination to minimize toxicity.

Figures

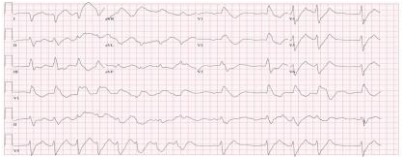

Figure 1: Electrocardiogram on initial presentation demonstrating an undetermined wide complex rhythm with marked QRS and QT prolongation and new right bundle branch block compared to prior tracing.

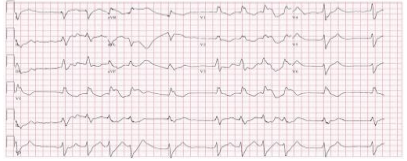

Figure 2: Electrocardiogram following initiation of sodium bicarbonate drip demonstrating an undetermined wide complex rhythm with QRS and QT prolongation; minimal improvement from initial tracing.

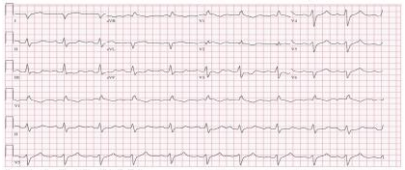

Figure 3: Electrocardiogram following administration of three amps of sodium bicarbonate and intravenous lipid emulsion (ILE) demonstrating sinus rhythm with 1st degree atrioventricular block and QRS/QT prolongation, markedly improved from initial tracing.

Discussion

Flecainide is a Vaughan-Williams class IC antiarrhythmic used in the treatment of supraventricular arrhythmias and atrial fibrillation. Flecainide overdoses are not commonly seen as demonstrated by the lack of case studies available on this topic. While rare, these overdoses are associated with a high mortality. This is not surprising given the combination of negative inotropy, proarrhythmic effects, and potent ability to slow cardiac conduction.[1] Toxicity may present with prolongation of the PR, QRS, and QTc intervals on electrocardiogram (ECG) along with bradycardia, premature ventricular contractions (PVCs), and ventricular fibrillation/ventricular tachycardia. Other features that make flecainide toxicity difficult to treat are the lack of specific antidotes and its pharmacologic characteristics (high volume of distribution and partition coefficient (4.9L/kg and log(P)=3.78 respectively), which renders hemodialysis relatively ineffective.[2]

In therapeutic doses, the plasma half-life of flecainide is approximately 20 hours (range: 12 - 27 hours) in adults. This is increased in patients with New York Heart Association (NYHA) Class III heart failure or renal dysfunction.[3] It is 95% bioavailable following oral administration and undergoes minimal first-pass effect. Metabolism takes place primarily in the liver by the cytochrome P2D6 enzyme where the drug is biotransformed via O-dealkylation into two main metabolites. These metabolites are further conjugated and excretion occurs primarily via urine with 50% of a single oral dose being excreted in 24 hours.[4] In the context of flecainide overdose, profound systemic hypotension can further limit hepatic and renal blood flow, reducing the rate of metabolism and elimination, and extending plasma half-life of the drug to 22 hours.[5] Thus, it is essential to initiate therapy to maintain end organ perfusion which will ultimately aid in drug clearance and detoxification.

Traditional treatment of flecainide overdose has included methods aimed at blocking continued intestinal absorption and reversal of the drug's cardiotoxic effects. The efficacy of reducing the rate of intestinal absorption (usually via activated charcoal) is highly dependent on the time of ingestion and may not always be effective. Additionally, the risks associated with these methods (i.e. aspiration) may not outweigh the benefits and further complicate the patient's condition.

Treatment with sodium bicarbonate has been proven to be effective in managing the cardiotoxic effects of the drug in similar cases on a two-fold basis. As a sodium salt, it is capable of competing with flecainide for cardiac sodium channels, displacing the drug and reversing its depression of inotropy and conduction. This subsequently results in narrowing of the QRS interval. Alkalinization of the plasma increases the water solubility and promotes renal excretion.[5]

Intravenous lipid emulsion (ILE) is an emerging method of treating overdose of lipophilic drugs. [6]Based upon its log(P)=3.78, flecainide is highly lipophilic and concentrates in the lipid phase at approximately 6,300 times the concentration in the aqueous phase.[6] Given the relatively high volume of distribution (Vd) of flecainide and resultant redistribution out of the plasma and into tissues, traditional therapy aimed at directly reversing or blocking the drug's effects are limited by continuous release of the drug.[4] ILE is thought to work by the phenomenon of "lipid sink", in which substances with high lipophilicity are drawn into lipid droplets in the plasma, creating a concentration gradient. This allows any drug that has redistributed to the tissue to travel back into the plasma and be emulsified.[7] The resultant effect is the drug concentration is lower both in the plasma and sequestered in tissue.

An alternate proposed mechanism for the efficacy of ILE the effects of increased intracellular lipid stores on mitochondrial damage. In the setting of an overdose of cardiotoxic substances, it is theorized that increased intracellular fatty acid content leads to improved production of ATP in cardiac myocytes.[8] Other Class 1 anti-arrythmic drugs have been shown specifically to induce toxicity in the mitochondria of cardiac myocytes by increasing the permeability of the mitochondria's inner membrane to protons, disrupting the gradient needed for ATP generation. Studies using ILE in conjunction with toxic levels of the class 1 anti-arrythmic, Bupivacaine, have demonstrated a cardioprotective effect. Rat models treated with ILE showed slower opening times of the Mitochondrial Permeability Transition Pore (mPTP), which when opened under normal ischemic conditions, allows for further leakage of protons out of the mitochondrial inner membrane space into the cytosol. Delayed opening of this pore thought to be induced by the presence of increased intracellular lipid concentration may reverse or even delay toxicity to the mitochondria.[9]

Conclusion

While the frequency of occurrence is rare, several case reports of flecainide or class IC antiarrhythmic overdoses illustrate that ILE used in conjunction with conventional therapies demonstrated long-term resolution of atrioventricular block and ECG interval abnormalities.[2] Similar outcomes were seen in the case of our patient. In order to decrease the high mortality risk in these patients, administration of intravenous lipid emulsion, sodium bicarbonate drip, and resuscitation efforts to maintain hemodynamic stability should be initiated immediately in patients where a flecainide overdose is suspected.