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A Case of Flecainide Toxicity in a Young Male

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Introduction:

Flecainide is an antiarrhythmic drug with a narrow therapeutic window. It is a powerful sodium channel blocker that can be used to treat various types of supraventricular tachycardias. However, due to its narrow therapeutic window, there is potential for a fatal overdose. Flecainide overdose is a rare phenomenon with only a few case reports and their subsequent clinical outcome published. We present a case of a 24-year old male who presented with cardiac arrest after an intentional ingestion of large quantities of flecainide. Our goal is to raise awareness for characteristic signs and symptoms, highlight therapeutic options and discuss the pathophysiology of the overdose.

Case description:

A 24-year-old male with a known history of schizophrenia was brought in to the emergency room by ambulance after being found unresponsive at home. Family members noted that he was vomiting, seizing and was found unresponsive 20 minutes later. Emergency medical services were called and by the time they arrived, he had been unresponsive for about 40 minutes. Given the clinical picture and psychiatric history, there was a high index of suspicion for overdose. Eventually, an empty bottle of flecainide was recovered by the family. Initial electrocardiogram (EKG) in the emergency room revealed an undetermined rhythm with wide and varying QRS complexes, as well as a prolonged QTc at 650 ms. Soon after arrival, the patient went into cardiopulmonary arrest and cardiopulmonary resuscitation (CPR) was started per Advanced Cardiac Life Support protocol. The initial rhythm was pulseless electrical activity arrest. Return of spontaneous circulation was achieved after 2 cycles of CPR. The rhythm post-arrest was wide complex bradycardia. The patient was hemodynamically unstable with low blood pressure. The decision was made to undergo synchronized cardioversion with conversion to a wide complex rhythm with marginal improvement in blood pressure. Norepinephrine infusion was initiated to sustain adequate cerebral perfusion pressures. Initial arterial blood gas demonstrated a severe mixed respiratory and metabolic acidosis. The patient was hyperventilated in order to correct the underlying respiratory acidosis and on advice from local poison control center he was started on a sodium bicarbonate drip to be titrated to the normalization of the QTc interval. Electrolytes were monitored and replenished as needed. Intralipid bolus was given in an attempt to ameliorate the effects of drug-induced cardiotoxicity. Targeted temperature management was initiated due to unresponsiveness post-arrest.

In the Intensive Care Unit, the patient was found to have a profoundly resistant acidemia requiring well over 750 mEq of sodium carbonate over the next 24 hours. Serial EKGs were done (below) which demonstrated gradual normalization of the QTc interval after serum alkalinization. Serum flecainide levels were obtained on the second day of admission and were elevated at 1.31 microgram/ml (reference range 0.2-1.00). During targeted temperature management the patient developed (narrow complex) bradycardia which corrected with a dopamine infusion. After rewarming, the patient was unresponsive, with brain imaging revealing the diffuse global hypoxic injury. The patient subsequently underwent tracheostomy and percutaneous endoscopic gastrostomy tube placement and was transferred out of the ICU.

Discussion:

Flecainide, a class IC antiarrhythmic, causes rate-dependent slowing of sodium channels (citation). In therapeutic doses, this effect will lead to membrane stabilization and decreased conduction velocity of the His-Purkinje and ventricular systems with the therapeutic goal of achieving and maintaining sinus rhythm [11]. However, in higher doses, flecainide may lead to inhibition of calcium-induced calcium secretion from the sarcoplasmic reticulum during phase 2 of the cardiac action potential [11]. This process is thought to be mediated by the blockage of the ryanodine receptor [12]. Thus, flecainide overdose may be clinically apparent in an EKG which would demonstrate an increase in PR interval, QRS complex, and QTc prolongation [13](additional citation).

In our patient, several EKGs were performed that demonstrated abnormalities consistent with flecainide toxicity. The first EKG in Figure 1 (Initial EKG) demonstrated a QRS > .200 ms, severely prolonged QTc, loss of *P* waves, heart rate of 100, and borderline extreme axis deviation. A systematic review of flecainide toxicity and corresponding EKG findings demonstrated that there doesn't appear to be a relationship between the amount of flecainide consumed and QRS duration or associated features (valentino). However, the degree of widening of the QRS complex is rate-dependent, increasing as the heart rate increases (andri). In Figure 2 (EKG @ 18:30), a rate-dependent decrease of the QRS to .160 ms is demonstrated with an associated heart rate in the 70s.

Drug overdose has an overall mortality of <1%, however, overdose with class IC antiarrhythmics was associated with higher mortality rates at 22.5% [1]. Though the therapeutic implications of flecainide are well known, prior to initiating treatment clinicians should evaluate for contraindications such as structural heart disease, AV block, left bundle branch block, right bundle branch block (when associated with left hemiblock), asymptomatic nonsustained ventricular tachycardia, cardiogenic shock, reduced cardiac output (LVEF < 35%), post-MI, and significant renal or hepatic impairment [4]. Flecainide metabolism and excretion is mediated by the liver and kidney respectively (andri). Significant impairment of either organ system should be evaluated prior to initiation. After initiation of flecainide, use-dependent QRS widening may be assessed during a formal exercise test. As previously mentioned, the QRS width is directly related to the heart rate and an increase in heart rate (via exercise) should mediate a corresponding increase in the width of the QRS complex. During treatment, the QRS interval should be regularly monitored[7](additional citation).

Flecainide is known to have a narrow therapeutic index, with a peak plasma time 2-3 hrs (PO) and therapeutic range 0.2-1mcg/mL. Oral administration of flecainide results in extensive absorption (bioavailability of 90–95%). Flecainide does not appear to undergo significant hepatic first-pass metabolism; a 200–500 mg daily dose produced plasma concentrations within the therapeutic range of 200–1000 µg/L (the maximum daily dose is 300 mg) [5,6]. The elimination half-life is 12–27 h [5]. Flecainide undergoes extensive hepatic biotransformation via cytochrome P450 CYP2D6; inactive metabolites are excreted mostly (85%) in urine and excretion increases with low urine pH. Some metabolites are excreted via feces. There are also increased serum levels in renal impairment. Total plasma clearance 10 mL/min/kg.

Treatment of flecainide overdose requires a high level of suspicion and appropriate clinical history. However, even with optimal management, overdose carries a significant mortality rate. Several options are available that have been studied for the management of flecainide toxicity. Standard treatment involves aggressive electrolyte correction, fluid resuscitation and addressing conduction abnormalities. Determining the onset of ingestion has significant implications. If the patient presents within one hour

gastric lavage or activated charcoal are acceptable options for rapid decontamination and minimize the amount of circulating medication[3].

The use of sodium bicarbonate infusion serves two important functions. Firstly, the increase in sodium concentration displaces flecainide from its receptor sites on cardiac myocytes. Secondly, sodium bicarbonate causes alkalinization of the serum which causes a reduction in the degree of sodium channel blockade. There is support for sodium bicarbonate infusion to a goal of pH 7.50 to 7.55 when the QRS duration is greater than 160ms [8]. However, the one caveat is hypothetically alkalinization of urine increases elimination half-life and decreases the overall urinary clearance of flecainide (citation).

Local poison control suggested initiating infusion of intravenous fat emulsion (IFE). The mechanism of action of IFE is unclear, however, it is postulated that it follows the mechanisms of the "lipid-sink theory" whereby IFE acts to sequester lipophilic drugs such as flecainide, thereby reducing toxic activity on cardiac myocytes [9]. If the hemodynamic compromise is persistent and severe, consideration is given to extracorporeal membrane oxygenation (ECMO). ECMO provides respiratory and more importantly cardiac support, preventing end-organ damage such as renal dysfunction which is integral to the elimination of the drug. The length of the ECMO support may be determined by serum flecainide level and cardiac stability [10]. Finally, flecainide is a dialyzable medication which gives it a consideration for treatment in overdose, particularly in patients with renal impairment.

Conclusion:

Flecainide toxicity is a rarely encountered, but potentially lethal presentation that can lead to life-threatening arrhythmias. It is important to identify and begin treatment early with sodium bicarbonate, EKG monitoring, IFE infusion, and consideration for dialysis or ECMO to promote renal clearance.

REFERENCES

1. Koppel C, Oberdisse U, Heinemeyer G. Clinical course and outcome in class Ic antiarrhythmic overdose. *J Toxicol Clin Toxicol* 1990; 28:433–444.
2. Ellsworth H, Stellpflug SJ, Cole JB, Dolan JA, Harris CR. A life-threatening flecainide overdose treated with intravenous fat emulsion. *Pacing Clin Electrophysiol.* 2013;36:87-89.
3. Cheung I, Man C. Review of flecainide poisoning. *Hong Kong J Emerg Med* 2002;9:150-3
4. Aliot E, Capucci A, Crijns HJ, et al. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. Europace. 2011;13:161–173.
5. Holmes B, Heel RC. Flecainide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. Drugs. 1985;29:1–33.
6. Roden DM, Woosley RL. Drug therapy: flecainide. N Engl J Med. 1986;315:36–41.
7. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace. 2006;8:651–745.

8. Goldman MJ, Mowry JB, Kirk MA. Sodium bicarbonate to correct widened QRS in a case of flecainide overdose. J Emerg Med. 1997;15:183–186.
9. Fettiplace MR, Ripper R, Lis K, Feinstein DL, Rubinstein I, Weinberg G. Rapid cardiotonic effects of lipid emulsion infusion. Crit Care Med 2013;41(8):e156–62.
10. Auzinger GM, Scheinkestel CD. Successful extracorporeal life support in a case of severe flecainide intoxication. Crit Care Med 2001;29(4):887–90.
11. Valentino, Michael A., et al. "Flecainide toxicity: a case report and systematic review of its electrocardiographic patterns and management." Cardiovascular toxicology 17.3 (2017): 260-266.
12. Hilliard, Fredrick A., et al. "Flecainide inhibits arrhythmogenic Ca2+ waves by open state block of ryanodine receptor Ca2+ release channels and reduction of Ca2+ spark mass." Journal of molecular and cellular cardiology 48.2 (2010): 293-301.
13. Levis, Joel T. "ECG diagnosis: flecainide toxicity." The Permanente journal 16.4 (2012): 53.
14. Barman M. Proarrhythmic Effects Of Antiarrhythmic Drugs: Case Study Of Flecainide Induced Ventricular Arrhythmias During Treatment Of Atrial Fibrillation. *J Atr Fibrillation*. 2015;8(4):1091. Published 2015 Dec 31. doi:10.4022/jafib.1091
15. Gardner, Jonathan D., Jr JB Calkins, and Glen E. Garrison. "ECG diagnosis: The effect of ionized serum calcium levels on electrocardiogram." The Permanente Journal 18.1 (2014): e119-20.
16. Andrikopoulos, George K., Sokratis Pastromas, and Stylianos Tzeis. "Flecainide: current status and perspectives in arrhythmia management." World journal of cardiology 7.2 (2015): 76.
17. Hellestrand, K. J., et al. "Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man." Heart 48.2 (1982): 140-148.
18. Muhiddin, K. A., A. Johnston, and P. Turner. "The influence of urinary pH on flecainide excretion and its serum pharmacokinetics." British journal of clinical pharmacology 17.4 (1984): 447-451.