Acute on Chronic Ivabradine Overdose: a Case Report

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Abstract Ivabradine is a newly approved medication which reduces the heart rate by antagonizing the I_f channel. We report a case of intentional overdose on ivabradine. A 26-year-old female presented after taking 250 mg ivabradine. On arrival, her vital signs and neurologic exam were unremarkable. Within 30 min, her heart rate decreased to 31 bpm, but she remained normotensive with no change in mentation. Her bradycardia resolved after treatment with atropine. She experienced two further bradycardic episodes responsive to atropine; the second episode was associated with hypotension, responsive to a fluid bolus. For the remainder of her hospitalization, she remained hemodynamically stable without further interventions. She was dispositioned to the psychiatry service approximately 36 h post-ingestion with a heart rate of 67 bpm. Laboratory analysis confirmed a serum ivabradine concentration of 525 ng/mL, greater than 50 times the mean level in therapeutic trials. Proposed treatments for ivabradine include activated charcoal, atropine, isoproterenol, and intravenous pacing. Further study is needed to identify ideal treatment modalities.

Keywords Ivabradine · Cardiotoxicant · Bradycardia

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Introduction

Ivabradine is a recently FDA approved medication indicated to reduce hospitalization from worsening heart failure [1]. Therapeutically, it antagonizes the I_f or “funny” current, resulting in a reduced heart rate. While it has been extensively studied in heart failure, myocardial ischemia, and postural orthostatic tachycardia syndrome (POTS), there are few reported cases of overdose [2, 3]. We report a case of acute on chronic intentional ivabradine overdose in a 26-year-old female on ivabradine for POTS.

Case Report

A 26-year-old female presented to the emergency department (ED) after an intentional overdose of 250 mg (50 tablets, 5 mg each) of ivabradine approximately 30 min prior to arrival. The patient was prescribed ivabradine for POTS and had no access to any other prescription medications. She denied coingestions other than an unknown amount of alcohol. She had no physical complaints at her initial presentation. Her triage vital signs were heart rate 81 beats per minute (bpm), respiratory rate 16 breaths per minute, blood pressure 115/73 mmHg, temperature 98.4 °F (36.9 °C), and oxygen saturation 100 % on room air. She was well appearing, answering questions appropriately with a normal neurological exam. Within 30 min of arrival, her heart rate decreased to 31 bpm. She remained normotensive with palpable pulses in all four extremities and had no change in her mental status. Twenty-five grams of oral activated charcoal and 0.6 mg of intravenous (IV) atropine were given at this time, and her heart rate improved to 60 bpm. A 1-mg IV dose of glucagon was given at the same time without apparent effect. An hour after the initial dose of atropine, her heart rate decreased to 43 bpm

with no other change in her vital signs or mentation. A second dose of 0.6 mg IV atropine was given, resulting in improvement in her heart rate to 60 bpm. Forty-five minutes after the second dose of atropine, her blood pressure was 89/43 mmHg with a pulse of 59 bpm. She was asleep at the time but easily awakened. A third dose of 0.6 mg IV atropine was given and her heart rate improved to 63 bpm while her blood pressure remained unchanged. She then received one liter of IV fluids and her blood pressure increased from its nadir of 89/43 to 102/67 mmHg. Her pulse remained above 60 bpm. Serum chemistry revealed sodium 145 meq/L, potassium 3.8 meq/L, chloride 106 meq/L, bicarbonate 21 meq/L, blood urea nitrogen 6 mg/dL, creatinine 0.7 mg/dL, and calcium 8.8 mg/dL. Acetaminophen and salicylates were undetectable; serum ethanol concentration was 150 mg/dL; a urine drug screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates was negative. The initial EKG showed a normal sinus rhythm of 56 bpm with intervals PR 116 ms, QRS 84 ms, and QT/QTc 452/437 ms, respectively. For the remainder of her stay in the ED, she remained hemodynamically stable and required no further interventions. She was observed overnight in the intensive care unit with no further bradycardic or hypotensive events and was dispositioned to the psychiatry service approximately 36 h post-ingestion with a heart rate of 67 bpm. Blood obtained at time of arrival was later analyzed and confirmed an ivabradine concentration of 525 ng/mL.

Discussion

Currently, ivabradine is the only specific bradycardic agent available [4]. Since it recently became available in the USA in April 2015, there are few case reports of overdose [2, 3]. As ivabradine slows the sinoatrial (SA) node, one commonly reported adverse effect is bradycardia [4, 5]. The bradycardia, however, is typically not severe. Several mechanisms might explain this. First, the medication exhibits use-dependent properties, making the effects more pronounced at higher heart rates, and less pronounced at lower heart rates [5]. Second, while ivabradine does demonstrate a dose-dependent heart-rate lowering effect, there appears to be a plateau effect at doses greater than 40 mg daily [5]. Therefore, patients might be protected from severe bradycardia at supratherapeutic doses. We hypothesize that these mechanisms led to the attenuated bradycardia in this case, which occurred but did not alter mentation.

The primary mechanism of action for ivabradine is antagonism at the I_f channel, which is located in the SA node and spontaneously generates pacemaker activity [6]. When activated between -40 and -50 mV, it allows an influx of Na^+ and K^+ ions, facilitating depolarization of the myocardium. Ivabradine antagonizes the I_f channel in its open state, which

then inhibits the SA nodal pacemaker, leading to bradycardia [6]. Ivabradine is a pure heart rate-lowering medication without negative inotropic properties. Therefore, severe hypotension is not expected.

Ivabradine is metabolized primarily via oxidation by cytochrome P450 isoenzyme 3A4 (CYP3A4) [7]. It is not noted to be an inducer or inhibitor at any cytochrome P450 isoenzymes. Ivabradine generates an active *n*-desmethyl metabolite which is also metabolized by CYP3A4 [7]. In human trials, ivabradine showed two compartment kinetics with a main half-life of approximately 2 h and an effective half-life of approximately 11 h [7].

In therapeutic use, ivabradine is also known to inhibit human ether-à-go-go-related gene (hERG) potassium channel, which results in QTc prolongation [4]. QTc prolongation occurs most commonly when ivabradine is used concomitantly with other QTc prolonging medications or with CYP3A4 inhibitors. The cumulative effects of QTc prolongation and bradycardia could result in torsades de pointes (TdP) arrhythmia [4]. TdP has been reported at least 24 times to the European Medicines Agency and in two cases in the literature [4, 8, 9]. The first case report was complicated by coingestion of diltiazem and ranolazine [8]. Both of these are metabolized by CYP3A4, and diltiazem also inhibits CYP3A4 [8]. The second case was complicated by the patient's baseline prolonged QTc as shown on EKG prior to ivabradine administration, and by coingestion of azithromycin [9]. Neither case involved supratherapeutic dosing of ivabradine.

Another described effect of ivabradine with therapeutic use is atrial fibrillation (AF). A meta-analysis of 11 studies demonstrated that therapeutically ivabradine was associated with an approximately 15 % increase in the relative risk of developing AF [10]. The 11 studies included patients predominately with heart failure, but also patients with angina, myocardial infarction, and the syndrome of inappropriate sinus tachycardia. The mechanism for AF with therapeutic ivabradine use appears to be related to inhibition of the I_f current which predisposes to this arrhythmia.

This patient's serum ivabradine concentration was measured in three tubes: EDTA, serum separator, and plasma separator. Her concentration at time of arrival was 525 ng/mL from the EDTA tube. The measured concentration in the serum separator and plasma separator tubes were lower (464 and 460 ng/mL, respectively), potentially reflecting a degree of drug binding to the separator gel in the blood collection tubes. The patient's ivabradine concentration 3 h post-admission was 130, 120, and 110 ng/mL, using EDTA, serum separator, and plasma separator tubes, respectively. For comparison, one prior overdose case reported a concentration of 375 ng/mL after gastric lavage but did not provide any subsequent concentrations [2]. In a trial of ivabradine at therapeutic doses, patients were noted to have a mean concentration of 9.7 ng/mL 13 h post-ingestion, with a maximum concentration of 25 ng/mL [2, 11].

In patients presenting shortly after ingestion of ivabradine, gastrointestinal decontamination with activated charcoal is reasonable in the absence of contraindications. Given the described toxic effects of ivabradine, further management should predominately be directed at treating bradycardia. In animal studies, it was noted that either isoproterenol or dobutamine would readily reverse bradycardia from ivabradine, while atropine did not have a consistent effect [7]. In the limited number of reported human overdose cases to date, the opposite has been noted. Two cases (including this case report) exist describing successful reversal with atropine [2]. In another case isoproterenol was ineffective [3]. Further study on this is needed to elucidate the ideal treatment for ivabradine-associated bradycardia. However, it seems reasonable to administer atropine for clinically significant bradycardia in cases of ivabradine overdose. If bradycardia is refractory to medical management, intravenous pacing can be attempted and has been successfully described in one case [3].

Cases of ivabradine overdose can appear clinically similar to other cardiotoxins such as beta blocker or calcium channel blocker overdoses. In the undifferentiated patient with hypotension and bradycardia, therapies such as glucagon or calcium salts are reasonable. While the positive effects of SA nodal chronotropy from glucagon could be beneficial in symptomatic bradycardia, the subtherapeutic dose used in this case makes it difficult to interpret its lack of effect. Further studies on glucagon efficacy need to be performed before recommendation can be made for use in ivabradine overdose.

Conclusion

Ivabradine is a newly approved negative chronotrope acting at the I_f current. In reported cases to date, the most pronounced clinical effect has been bradycardia responsive to atropine, though AF and QTc prolongation have also been noted with therapeutic use. Given the limitations of single case reports, further study is needed to elucidate other toxic effects and clarify the ideal treatment modality.

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