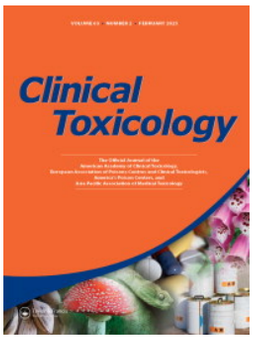

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POISON CENTRE RESEARCH

Ivabradine exposures reported to United States poison centers 2015–2023

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ABSTRACT

Introduction: Ivabradine was approved for use in the United States in 2015 for the management of heart failure. It acts through inhibition of sodium channels found in cardiac myocytes (the "funny" pacemaker current, I_f), which reduces heart rate without significantly affecting inotropy.

Methods: We queried the National Poison Data System® for reported ivabradine exposures from April 15, 2015–December 31, 2023. Age was stratified into child (0–5 years), adolescent (6–17 years), adult (18–64 years) and geriatric (65+ years). Other descriptive statistics gathered included patient sex, management site, and medical outcome as coded by America's Poison Centers®.

Results: There were 240 ivabradine exposures, with 55.0% managed on-site and not transferred to a healthcare facility. The most common reported symptom was bradycardia, reported in 36 patients (15.1%). There were 139 cases that were followed to a known outcome. Within this cohort, 60%, 14%, and 27% of patients suffered no effect, minor effect, or moderate effect, respectively. Exposures in children comprised 18.8% of cases; none required intervention. Intentional self-harm exposures comprised 17.1% of all cases and were more likely to have worse outcomes. Five adult patients received intensive therapy (endotracheal intubation, vasopressors, cardiac pacing, hemodialysis). There were no reported deaths from ivabradine exposure.

Discussion: This study has limitations. First, our data source was limited by being retrospective and incomplete; we could only study the information that was reported to poison centers, and exposures were not confirmed by laboratory testing. It is possible that cases without further follow-up had other treatments and clinical effects not reported here. Finally, reports to poison centers likely underestimate the true number of ivabradine exposures.

Conclusion: Adults with unintentional, asymptomatic exposures to ivabradine may be candidates for home monitoring. In ivabradine exposures refractory to medical management, clinicians should consider cardiac pacing or other supportive measures as a temporizing measure.

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KEYWORDS
Bradycardia; Corlanor®; exposure; ivabradine; poison center

Introduction

Ivabradine was approved by the United States (US) Food and Drug Administration (FDA) in April 2015 for use as an adjunct therapy in patients with systolic heart failure and an ejection fraction less than 35% refractory to beta-adrenoceptor blocking drugs, with off-label uses for sinus tachycardia and stable anginal chest pain [1,2]. It is also approved for use in pediatric populations as a treatment for heart failure secondary to dilated cardiomyopathy [3]. Its primary mechanism of action is through inhibition of the cardiac pacemaker current, which is a mixed sodium and potassium current activated by hyperpolarization and known as the "funny" current I_f [4]. The resulting effect is a prolonged diastolic time, ultimately reducing heart rate without affecting inotropy [1,2].

Due to the relative infancy of ivabradine use in the US market, overdose information consists primarily of case reports [5–10]. Minimal information is available to inform triage decisions, in particular regarding exposures in children and inadvertent double dosing where there is a potential for home management. Additionally, little is known about the expected course of intentional overdose. To define expected clinical courses better, we reviewed all cases of ivabradine exposure reported to US poison centers since the US FDA approved the drug.

Methods

We queried the National Poison Data System® for cases of ivabradine exposure of any age that were reported from April 15, 2015, to December 31, 2023. The National Poison Data System® database is a repository of all calls made to US poison centers. Calls are managed by trained healthcare professionals, known as certified specialists in poison information, who assist in managing the exposed patients and document the medical care in a standardized format. The cases are uploaded in near-real time to the National Poison Data

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System® database. Captured data reflect the information provided by the caller at the time of the enquiry.

The query was performed using Poisindex® product ID codes 7920477, 7920709, 8175683, and 7920360, as well as the plain language terms "ivabradine" and "Corlanor." Inclusion criteria were single-substance human exposures to ivabradine. Cases were included if there was an ingestion of the medication for any reason reported to a poison center. We excluded any cases with multi-substance exposure (e.g., exposure to multiple different non-prescribed medications, intentional ingestion of multiple medications). Cases were also excluded if they were not followed to a known outcome.

Age was stratified into "child" if 0–5 years, "adolescent" if 6–17 years, "adult" if 18–64 years, and "geriatric" if 65 or older. The National Poison Data System® database allows for coding by exact age, by age status (e.g., unknown age adult, unknown age child), or by decade (e.g., 70's, 80's, 90's). Missing data for age was handled by assigning the age group of "adult" if the age unit was coded as "unknown adult" and "geriatric" if the age unit was consistent with age greater than 65 years.

Descriptive statistics were used for age, sex, the reason for exposure, the estimated amount ingested, management site, medical outcome, clinical effects reported, and therapies provided. America's Poison Centers® coding criteria dictate that all exposures in children <6 years old are considered unintentional.

Outcomes were separated into five possible categories as coded using America's Poison Centers® coding criteria: no effect, minor effect, moderate effect, major effect, or death. In brief, "no effect" is defined as a patient not developing any symptoms as a result of the exposure. "Minor effect" is defined as minimally bothersome symptoms, which may include drowsiness or self-limited gastrointestinal symptoms. "Moderate effect" is defined by more pronounced or prolonged symptoms, such as bradycardia, disorientation or hypotension that is rapidly responsive to treatment. "Major effect" is defined as the development of life-threatening symptoms, such as cardiac arrest or respiratory failure requiring endotracheal intubation. "Death" is defined as a patient dying as a result of or as a complication of the exposure [11].

An odds ratio was used to assess the difference in moderate severity outcomes compared to minor severity or no effect in the adult age group to determine if "intentional-suspected suicide" as the reason was associated with a higher likelihood of worse outcomes.

The institutional review board of the Medical College of Wisconsin deemed this study not to be human subject research.

Results

A total of 240 cases were identified, with an increase in cases noted by year (Figure 1). Children accounted for 45 cases, adolescents 14, adults 167, and geriatrics 13. One case was missing age data. One hundred and thirty-two cases (55.0%) were managed on-site, 36 (15.0%) were referred to a healthcare facility, and 71 (29.6%) were either in or en route to a healthcare facility; one case was reported with "other" as the management site (Supplementary Figure 1).

Most exposures (81.7%) were unintentional, 17.1% were intentional, and the reason was unknown in 1.2%. Among unintentional exposures, 74% were due to therapeutic errors, 25% were inadvertent exposures (including exploratory ingestions in children and taking someone else's medications), and 1% were adverse effects of normal dosing. Most intentional exposures (95%) were related to suspected suicidal intent, and 5% were otherwise intentional misuse.

Clinical effects reported for all exposures are summarized in Table 1. The most commonly reported symptom was bradycardia ($n=36$). Following this were dizziness/vertigo ($n=16$), mild central nervous system depression ($n=9$), and hypotension ($n=7$). Therapies reported for all exposures are summarized in Table 2. The most common treatment was food or oral fluids ($n=33$), followed by intravenous fluids ($n=25$) and single-dose activated charcoal ($n=10$). Treatments reported

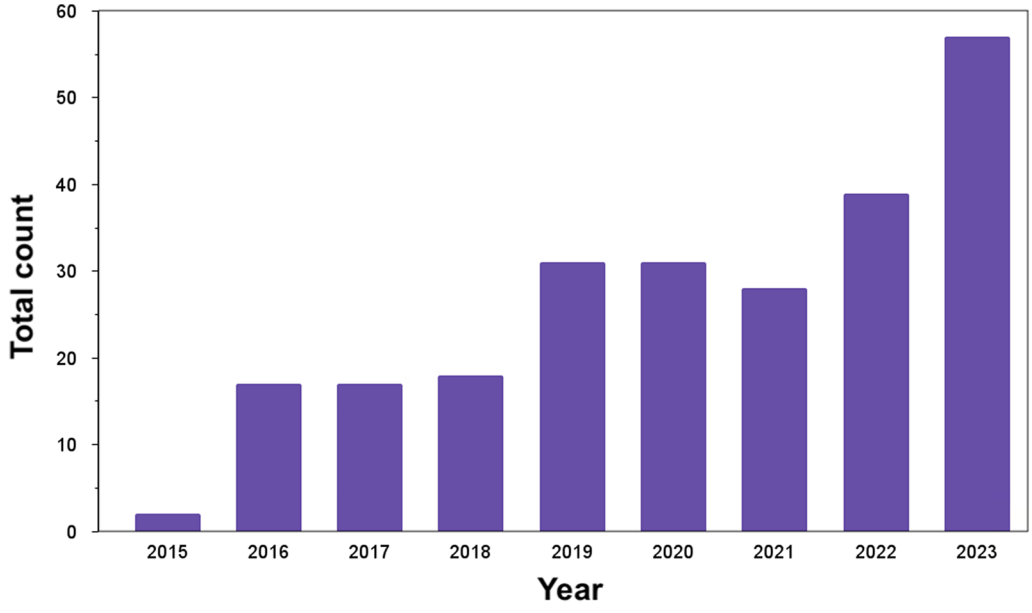

Figure 1. Annual calls to United States poison centers for ivabradine exposures 2015–2023.

Table 1. Reported adverse effects from ivabradine exposure.

Reported effects[a]	*n* (%)
Cardiovascular	
Bradycardia	36 (15.1)
Hypotension	7 (2.9)
Hypertension	3 (1.3)
Chest pain	4 (1.7)
QTc interval prolongation	1 (0.4)
Other electrocardiographic changes	3 (1.3)
Tachycardia	3 (1.3)
Conduction disturbance	2 (0.8)
Neurological/ocular	
Dizziness/vertigo	16 (6.7)
Central nervous system depression (mild)	11 (4.6)
Visual defect	5 (2.1)
Central nervous system depression (moderate)	2 (0.8)
Drowsiness/lethargy	2 (0.8)
Syncope	2 (0.8)
Agitation	2 (0.8)
Slurred speech	2 (0.8)
Tremor	2 (0.8)
Headache	1 (0.4)
Tinnitus	1 (0.4)
Muscle weakness	1 (0.4)
Other neurologic symptom	1 (0.4)
Gastrointestinal	
Vomiting	3 (1.3)
Nausea	2 (0.8)
Diarrhea	2 (0.8)
Respiratory	
Dyspnea	1 (0.4)
Cyanosis	1 (0.4)
Miscellaneous	
Erythema/skin flushing	1 (0.4)
Electrolyte abnormality	1 (0.4)
Creatinine concentration increased	1 (0.4)
Diaphoresis	1 (0.4)
Rhabdomyolysis	1 (0.4)
Other/not specified	1 (0.4)

Total count includes all reported symptoms, both related and unknown if related to ivabradine exposure.
[a]Reported effects include symptoms reported to the National Poison Data System® as related or unknown if related to exposure.

Table 2. Therapies utilized in patients exposed to ivabradine and reported to the National Poison Data system®.

Therapy	*n* (%)
Food, drink	33 (13.8)
Oral and intravenous fluids	25 (10.5)
Single-dose activated charcoal	10 (4.2)
Atropine	5 (2.1)
Oxygen	3 (1.3)
Other emetic	4 (1.7)
Antiemetics	3 (1.3)
Benzodiazepines	3 (1.3)
Vasopressors	3 (1.3)
Antipsychotics	2 (0.8)
Magnesium	2 (0.8)
Antihistamines	2 (0.8)
Antibiotics	1 (0.4)
Calcium	1 (0.4)
Glucagon	1 (0.4)
Hemodialysis	1 (0.4)
Endotracheal intubation/ventilation	1 (0.4)
Opioid analgesia	1 (0.4)
Cardiac pacing	1 (0.4)
Potassium	1 (0.4)
Thiamine	1 (0.4)
Sodium bicarbonate	1 (0.4)
Other unspecified	8 (3.3)

for children were oral fluids or snacks ($n=6$), single-dose activated charcoal ($n=5$), intravenous fluids ($n=2$), oxygen by nasal cannula ($n=1$), or otherwise unspecified ($n=3$).

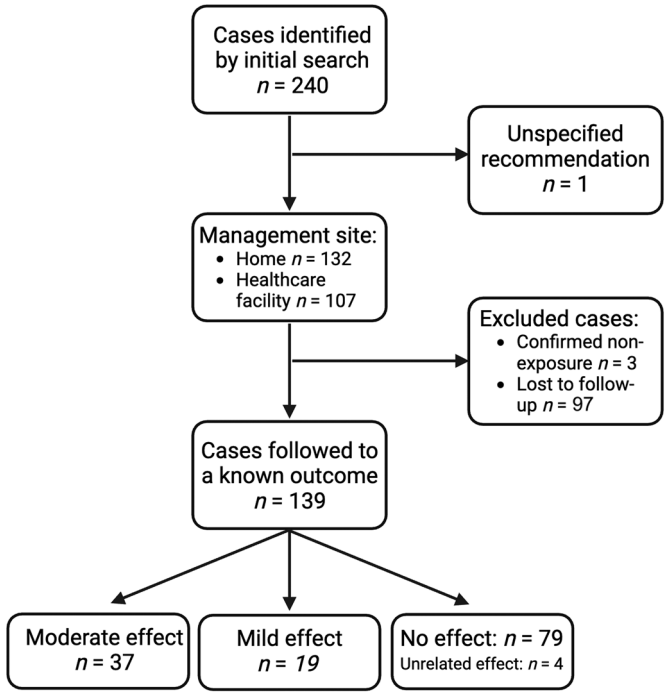

Figure 2. Flow diagram of total cases, excluded cases, and case outcomes for patients exposed to ivabradine.

There were 139 cases that were followed to a known outcome; a summary of excluded cases is shown in Figure 2. Overall medical outcomes included 37 moderate effects, 19 minor effects, 79 no effects, and four unrelated effects. The remaining cases were confirmed as non-exposure ($n=3$) or were not followed to a known outcome ($n=97$). No cases were coded as major effect.

Despite no reported major effects, five patients underwent invasive therapies during management, including treatment with vasopressors and endotracheal intubation. One underwent cardiac pacing, two received vasopressors, one was treated with vasopressors and hemodialysis, and one was endotracheally intubated. On further review of these patients (Supplementary Table 1), the estimated amount ingested ranged from 100–300 mg, and one patient had ingested an unknown amount. Three out of five were reported as intentional ingestions; one was due to a dosing error, and one was an adverse drug reaction.

Outcomes are summarized by age group in Figure 3. In children, the majority of the outcomes were no effect ($n=32$, 71% of child exposures), followed by minor effect ($n=3$) and moderate effect ($n=1$). We reviewed the single moderate effect case with details as follows: a one-month-old patient had an iatrogenic dosing error and received endotracheally ivabradine 5 mg. The patient was observed in the critical care unit of the hospital. Clinical effects included bradycardia and hypotension, but no therapies were reported. All children with reported outcomes are summarized in Table 3.

The majority of moderate effects cases occurred in adults ($n=33$, 19.7% of adult exposures). After stratifying adult exposures by reason, the majority of moderate effect cases were reported in patients who had "intentional-suspected suicide" coded as the reason ($n=23$, Figure 4). Patients with suicidal intent had 8.91 increased odds of developing a

moderate effect (95% CI: 3.08–28.12) compared to all other reasons for exposure.

A post hoc analysis was performed in an attempt to account for minor dosing errors, including any unintentional exposures of less than 20 mg, which included 53 total cases of all ages. Thirty-six of 53 (68%) patients had no reported adverse effects, 12 of 53 (23%) reported a minor effect, and five of 53 (9%) reported a moderate effect. One patient with a reported double dose was given atropine and intravenous fluids for bradycardia, nausea, and tremor. All other patients had symptom resolution with supportive care.

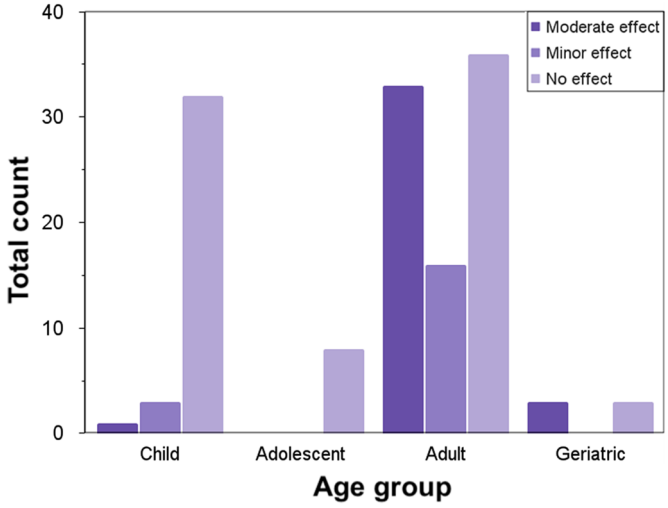

Figure 3. Medical outcomes by age.

Discussion

In our study ivabradine exposures reported to US poison centers have increased in frequency since the drug was approved by the US FDA in 2015. This number will likely continue to increase as it is used to treat a wider spectrum of cardiac conditions [12].

Ivabradine is typically administered by mouth in tablet form twice daily, ranging from 2.5–10.0 mg/dose in adults and age-dependent dosing in children, typically between 0.02–0.2 mg/kg/dose. Ivabradine is metabolized by cytochrome P450 3A4 (CYP3A4), so its use is typically contraindicated in patients taking CYP3A4 inhibitors, such as verapamil and diltiazem [1,2].

As ivabradine is specific to the cardiac pacemaker current, adverse effects include bradycardia or dysrhythmias, including atrial fibrillation, heart block, ventricular dyssynchrony, and sinus arrest [1,12]. A limited number of case reports on ivabradine toxicity have demonstrated that bradycardia is

Table 3. Exposures in children followed to a known outcome.

Age	Quantity	Reason	Treatments	Adverse effects	Medical outcome
1 month	5 mg[a]	Therapeutic error	–	Bradycardia, hypotension	Moderate effect
3 months	0.8 mg[a]	Therapeutic error	–	–	No effect
10 months	One tablet	Unspecified	–	–	No effect
12 months	One tablet	Unspecified	–	–	No effect
14 months	Unknown	Unspecified	–	–	No effect
15 months	5 mg	Unspecified	–	–	No effect
16 months	10 mg	Unspecified	–	–	No effect
20 months	One tablet	Unspecified	–	–	No effect
20 months	Unknown	Unspecified	–	–	No effect
20 months	0.5 tablet	Unspecified	–	–	No effect
22 months	5 mg	Unspecified	Oxygen, other (unspecified)	–	No effect
22 months	5 mg	Therapeutic error	Snack	–	No effect
23 months	One tablet	Unspecified	–	–	No effect
2 years	2.5 mg	Unspecified	–	–	Minor effect
2 years	One tablet	Unspecified	–	–	No effect
2 years	One tablet	Unspecified	–	–	No effect
2 years	Unknown	Unspecified	–	–	No effect
2 years	One tablet	Unspecified	–	–	No effect
2 years	5 mg	Unspecified	–	–	No effect
2 years	Unknown	Unspecified	–	–	No effect
2 years	One tablet	Unspecified	Single-dose activated charcoal	–	No effect
2 years	Four tablets	Unspecified	Single-dose activated charcoal	–	No effect
2 years	5 mg	Unspecified	Single-dose activated charcoal, snack	–	No effect
2 years	5 mg	Unspecified	Single-dose activated charcoal, intravenous fluids	–	No effect
2 years	Unknown	Unspecified	Snack	–	No effect
3 years	Unknown	Unspecified	–	–	Minor effect
3 years	5 mg	Unspecified	–	–	No effect
3 years	Unknown	Unspecified	–	–	No effect
3 years	15 mg	Unspecified	–	–	No effect
3 years	Unknown	Unspecified	Single-dose activated charcoal, intravenous fluids	–	No effect
3 years	One lick	Unspecified	Drink	–	No effect
3 years	2.5 mg	Unspecified	Food, drink	–	No effect
4 years	2.5 mg	Unspecified	–	–	No effect
5 years	5 mg	Therapeutic error	–	–	Minor effect
5 years	5 mg	Unspecified	–	–	No effect
5 years	10 mg	Unspecified	–	–	No effect

Exposures are tablet formulations unless otherwise specified.
[a]Liquid formulation.

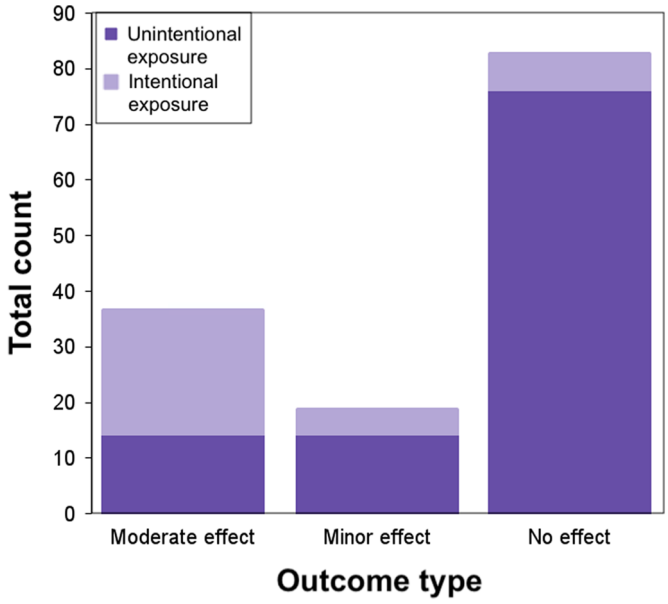

Figure 4. Outcome effect for adult and geriatric patients based on exposure type. Unintentional exposure includes any reported adverse drug reactions, general unintentional exposure, or therapeutic error. Intentional exposure includes any intentional misuse or suspected suicide.

the primary clinical effect, which can be counteracted with medications, including atropine [5,9] or more intensive measures, such as transvenous pacing [6,10]. Other reported side effects from ivabradine include visual disturbances, hypotension, and vertigo [2]. Fetal toxicity was reported in animal studies [2], but a retrospective analysis of women taking ivabradine during pregnancy suggested minimal risk as a teratogen [13].

Our retrospective review of National Poison Data System® data suggests that there is a wide spectrum of clinical effects after exposure to ivabradine. Consistent with past literature, bradycardia was common, with 16.3% of all exposures reporting bradycardia. Fortunately, in most cases, particularly exposures in children or therapeutic errors with low total doses, patients improved after observation or with minor interventions, such as intravenous fluids or oral intake. These data may be useful for healthcare workers tasked with prognosticating clinical effects from three important exposure scenarios: unintentional exposures in children, unintentional therapeutic errors, and intentional adult exposures.

Exposures in children occur most often when a child inadvertently ingests a pill or otherwise puts medication into their mouth or may result in a caregiver or healthcare worker dosing error. Patients less than 2 years old are more likely to have liquid formulations and weight-based dosing, making this age group more prone to dosing errors. Our findings demonstrate that no exposure in a child required medications or procedural interventions for the resolution of symptoms related to ivabradine exposure. This supports the recommendation that exploratory ingestions in children may be candidates for home management with close telephone follow-up, though there is insufficient data to provide definitive recommendations on dosing errors, particularly in children less than 2 years old. Further research is needed to determine vulnerable populations and appropriate triage thresholds.

Therapeutic errors overall had low rates of moderate effects, and no minor dosing errors required invasive measures, such as vasoactive medications or respiratory support. It should be noted that there was one patient with a minor dosing error requiring atropine for the resolution of symptoms. The nature of National Poison Data System® data does not allow for more granular analysis, such as home medications or comorbid illness, which may predispose to the development of adverse effects after a minor dosing error. Future research into this area may aid in the development of triage guidelines after unintentional excess dosing.

There were also multiple instances of adverse reactions to ivabradine during the course of therapeutic use, one of which was treated with vasopressors and hemodialysis (Supplementary Table 1). Determining who is at risk is an area of future research. It is likely that patient factors, such as age, comorbid medical conditions, or coingestion of cytochrome P450 inhibitors, play an important role.

Although our study demonstrated that ivabradine exposures were largely benign and self-resolving, and no major effects were reported, it is important to note that intensive therapy (endotracheal intubation, vasopressors, cardiac pacing, hemodialysis) was performed in five adult patients. In reviewing these patients (Supplementary Table 1), we found that four of five patients had reportedly taken at least five times the usual daily recommended dose (estimated 100–300 mg). Estimating the amount ingested can prove useful in risk stratification for a patient known to be exposed to ivabradine.

Another important consideration is the reason for exposure. We found that ivabradine was more likely to be associated with intentional versus unintentional exposures, and while we suspect this may be due to the greater dose ingested, the reported dosing was not specific enough to carry out any analysis to prove this hypothesis.

This study has limitations. First, we are only able to study the information that was reported to poison centers, and exposures were not confirmed by laboratory or other objective testing. It is possible that cases without further follow-up had other treatments and clinical effects not reported here. It is also likely that the number of exposures reported to poison centers is an underestimate of the true number of ivabradine exposures. Although we report ivabradine single-substance exposures, this data cannot be extrapolated to any polysubstance exposure, whether unintentional or intentional. We also are unable to account for medical comorbidities that may have contributed to patient presentations, and we are unable to verify the causality of any reported effects solely to ivabradine exposure.

Although National Poison Data System® has established guidelines for data entry, the data still rely on the subjective assessment of the certified specialists in poison information who enter the data and which are subject to interpretation. This is shown by the five adult patients with reported invasive interventions that were coded as "moderate effect". Further, the data set only provides categorical data rather than numerical data, as defined using America's Poison Centers® coding criteria. For example, "bradycardia" is defined

as a heart rate below 60 beats/min in adults, and age-related standards are recommended for children. "Hypotension" is defined as a systolic blood pressure below 90 mmHg or more than 15 mmHg below the patient's usual systolic pressure, without age-related standards recommended [11]. For this reason, we are able to identify the number of patients with bradycardia or hypotension but cannot discern specific heart rates or blood pressures. Therefore, we are unable to verify any reported instances of hypotension or bradycardia as these data are provided as categorical variables.

Conclusions

Ivabradine exposures reported to US poison centers are most often asymptomatic, and its effects are typically self-limited or resolved with only supportive care. Despite the typically benign course, in some cases, cardiac pacing, intubation, and/or hemodialysis have been employed when encountering bradycardia and/or central nervous system depression. Clinicians should consider cardiac pacing or other supportive measures in patients with known ivabradine exposure with bradycardia refractory to conservative measures.

There have been no reported major effects in children since the drug was approved in 2015, but there are limited data on dosing errors, particularly in children younger than 2 years old. In adults, more serious adverse effects are often seen in intentional exposures. Although further studies are necessary given the infancy of the drug, we hypothesize that unintentional asymptomatic exposures or double doses in adults may be candidates for home monitoring, while intentional exposures, dosing errors greater than the daily maximum dose or other symptomatic exposures should be referred for evaluation in a healthcare facility. To aid in triage, further study is needed to determine risk factors for the development of clinically significant effects after unintentional therapeutic errors, particularly in children more prone to errors due to weight-based dosing.

Disclosure statement

America's Poison Centers® maintains the National Poison Data System®, which houses de-identified records of self-reported information from callers to the country's poison centers. National Poison Data System® data do not reflect the entire universe of United States exposures and incidences related to any substance(s). Exposures do not necessarily represent a poisoning or overdose, and America's Poison Centers® is not able to completely verify the accuracy of every report. National Poison Data System® data do not necessarily reflect the opinions of America's Poison Centers®.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, LS, upon reasonable request.

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