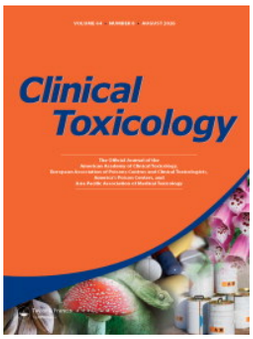

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POISON CENTRE RESEARCH

Acute unintentional single-substance pediatric exposures to direct factor Xa inhibitors reported to US Poison Centers, 2011–2019

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ABSTRACT

Introduction: Direct factor Xa inhibitors are widely used anticoagulants. Safety in adults is well studied, however limited data exist for pediatric exposures. The objective of this study is to describe referral patterns, clinical outcomes, and treatment modalities for unintentional pediatric single-substance ingestion of factor Xa inhibitors as reported to the National Poison Data System®.

Methods: This is a retrospective review of cases reported to the National Poison Data System® from January 1, 2011 to December 31, 2019. Inclusion criteria were age <6 years with single-substance, unintentional ingestion of a direct factor Xa inhibitor. Cases were excluded if the medical outcome was coded as unrelated effect, confirmed non-exposure, not followed (non-toxic/minimal toxicity), unable to follow (potentially toxic), or outcome not provided. Data abstracted included medical outcomes, level of care, clinical effects, and therapies.

Results: A total of 744 cases met inclusion criteria. Among 350 cases managed at home, outcomes included 346 cases with "no effect" and four cases with "minor effect". Among 394 cases treated/evaluated at a healthcare facility, reported medical outcomes included 337 (85.5%) cases with "no effect", 33 (8.4%) with "minor effect", 22 (5.6%) with "moderate effect", and two (0.5%) with "major effect". No clinical effects related to bleeding were reported. One hundred twenty-two patients received activated charcoal. One of the two cases with major effect involved ingestion of up to 500 mg rivaroxaban with laboratory coagulopathy, but bleeding was not coded as a clinical effect.

Discussion: In this cohort of patients less than six years of age with acute, unintentional single-substance ingestion of direct factor Xa inhibitors, no cases had bleeding coded as a clinical effect. These findings are consistent with the previously described low toxicity profile of acute ingestions of these medications in children.

Conclusions: These data suggest that asymptomatic, unintentional, single substance exposures to factor Xa inhibitors in patients <6 years of age are unlikely to develop clinically significant bleeding.

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Anticoagulant overdose; apixaban; pediatric poisoning; rivaroxaban; unintentional

Introduction

The direct factor Xa inhibitors, rivaroxaban, apixaban, and edoxaban were approved by the Food and Drug Administration in 2011, 2012, and 2015, respectively and have become frequently prescribed alternatives to vitamin K antagonists for stroke prevention and treatment of thromboembolic conditions. This trend is related to their purported ease of dosing, limited need for laboratory monitoring, as well as favorable therapeutic indices and side effect profiles [1]. Lack of significant toxicity following acute ingestion of these agents is hypothesized to result from one of two mechanisms: the apparent saturability of the binding site on factor Xa creating a ceiling anticoagulant effect, or short half-life in acute ingestion [2].

Although chronic overdose of factor Xa inhibitors has been associated with coagulation abnormalities and bleeding, few reports describe adverse effects after acute, single-substance exposures [3]. Adverse effects are typically limited to abnormalities in laboratory measures of coagulation including prothrombin time, partial thromboplastin time, and international normalized ratio. Clinically significant bleeding complications are uncommon [4].

In 2021, rivaroxaban was approved for pediatric patients for treatment of venous thromboembolism, prevention of recurrent venous thromboembolism and

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thromboprophylaxis following the Fontan procedure [5]. The expanded pediatric indications and availability of these medications raise concern for increased risk of exploratory or unintentional exposure in the pediatric population. To date, published experience with unintentional pediatric ingestion of these agents has been limited to case reports and small case series [3,4,6–13]. Our study is a timely contribution to the literature regarding the effects, therapies, and outcomes following unintentional exposure to a factor Xa inhibitor.

Our objective was to describe referral patterns, clinical effects, and outcomes for acute unintentional pediatric (<6 years) single-substance ingestions of factor Xa inhibitors. We also aimed to characterize therapies used and assess evidence of clinically significant bleeding.

Methods

Setting and participants

This is a retrospective review of the National Poison Data System (NPDS®) which, at the time of this study, received data from 55 United States Poison Centers. This study was deemed exempt from review by the institutional review board at the authors' institution.

Cases involving single-substance, unintentional exposures to rivaroxaban, apixaban, edoxaban, or unspecified factor Xa inhibitor in patients <6 years of age reported to the NPDS® between 1 January 2011 and 31 December 2019 were identified. Substance generic code 0077850 ("Other Types of Anticoagulant") was used to identify cases within the study period, further specified by product codes 1,2,3, and 4 corresponding to anti-Xa not otherwise specified, apixaban, edoxaban, and rivaroxaban, respectively.

Cases were excluded for route of exposure other than ingestion, reason for exposure other than 'unintentional', or if cases were coded as not followed-judged as non-toxic exposure, not followed-minimal toxicity expected, unable to follow-judged as a potentially toxic exposure, unrelated effect-the exposure was probably not responsible for the effect(s), confirmed non-exposure, or outcome not provided. Definitions of the terms can be found in the American Association of Poison Control Centers *NPDS® Coding Users' Manual* [14].

Data collection

Standard America's Poison Centers® medical outcome codes (no effect, minor effect, moderate effect, and major effect) were recorded. Study variables included substance ingested (apixaban, rivaroxaban, edoxaban, or factor Xa inhibitor not otherwise specified), level of care, medical outcome, related clinical effects, and therapies performed. Variables were defined by the NPDS® Coding Users' Manual [14].

For the two cases with an outcome code "major effect", de-identified case narratives were requested from the respective poison centers to provide context, although only one case narrative was obtained.

Statistical analysis

Descriptive statistics are reported for clinical effects, outcome, and therapies provided. Given the retrospective nature of NPDS® data and the descriptive objective of this study, no inferential statistics were performed.

The total number of cases per year was tabulated to evaluate for a trend in case volume per year for all factor Xa inhibitors as well as for individual xenobiotics.

Data availability

This study utilized data from the NPDS®, which is managed by America's Poison Centers®. Data requests should be directed to America's Poison Centers®.

Results

A total of 1,789 cases of unintentional single-substance exposures to factor Xa inhibitors were reported to United States Poison Centers between January 1, 2011, and December 31, 2019. Of these, 744 cases met inclusion criteria (Figure 1). Demographic and exposure characteristics of included patients are shown in Table 1. The median age was two years, and approximately half of patients were male (49.3%). Rivaroxaban was the most frequently reported xenobiotic (57.9%), followed by apixaban (38.6%) and non-specified factor Xa inhibitors (3.5%). No cases of edoxaban ingestion were identified. Activated charcoal was administered in 16.4% of cases. Among the included cases, 350 (47.0%) were managed at home and 394 (53.0%) were evaluated or treated at a healthcare facility (Table 2).

Across all factor Xa inhibitors, 683/744 (91.8%) cases had no effect; 37/744 (5.0%) minor effect; 22/744 (3.0%) moderate effect; and 2/744 (0.3%) major effect (Table 3).

Annual reported cases increased over the study period, with fewer than 20 cases per year prior to 2013 and higher annual case counts from 2014 through 2019, with a single year-to-year decrease between 2016 and 2017 (Figure 2).

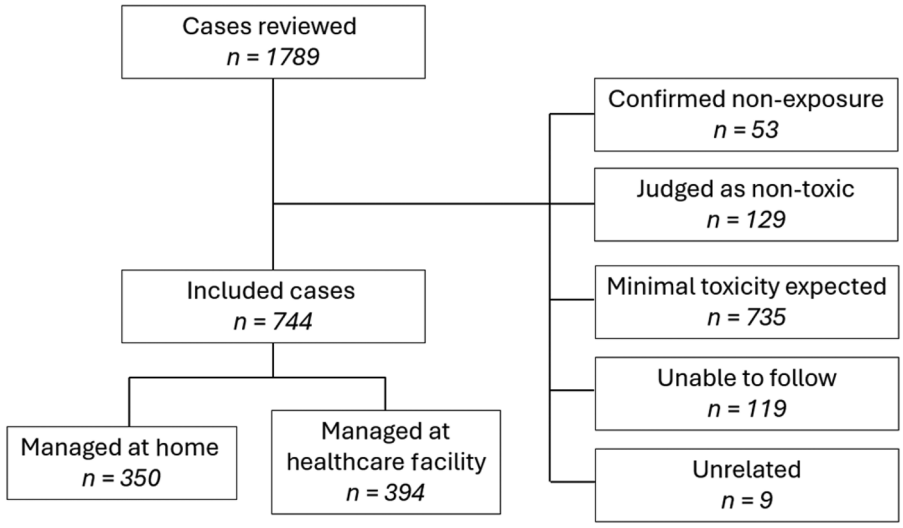

Figure 1. Case review with inclusions and exclusions.

Table 1. Demographics and exposure details of included patients ($n = 744$).

	$n = 744$
Age (median, IQR)	2 (1)
Male, *n* (%)	364 (49.3%)
Female, *n* (%)	377 (50.7%)
Unknown Sex, *n* (%)	3 (0.4%)
Rivaroxaban,*n* (%)	431 (57.9%)
Apixaban, *n* (%)	287 (38.6%)
Factor Xa Inhibitor Not Specified, *n* (%)	26 (3.5%)
Activated Charcoal Administered, *n* (%)	122 (16.4%)
Activated Charcoal Recommended and Performed, *n* (%)	111 (91.0%)
Activated Charcoal Performed (not recommended), *n* (%)	11 (9.0%)
Activated Charcoal Recommended, Known Not Performed (*n*)	6

Table 2. NPDS® medical outcome based on location of patient management.

Outcome	Managed at home ($n = 350$)	Managed at a HCF ($n = 394$)	Total ($n = 744$)
No Effect	346	337	683
Minor Effect	4	33	37
Moderate Effect	0	22	22
Major Effect	0	2	2

HCF = healthcare facility.

Among 350 cases managed at home, reported medical outcomes included 346 cases with "no effect" and four cases with "minor effect." Minor effects included vomiting in three cases and diarrhea in one case.

There were 394 cases seen at a healthcare facility of whom 120 were referred by the poison center, 274 were already in a healthcare facility at the time of first poison center contact. Reported outcomes included 337 (85.5%) with "no effect," 33 (8.4%) with "minor effect," 22 (5.6%) with "moderate effect," and 2 (0.5%) with "major effect" (Table 2). The most frequently coded clinical effect was 'prothrombin time/international normalized ratio prolonged,' recorded in 41 (10.4%) cases; however, no cases had bleeding coded as a clinical effect. One case with "moderate effect" included the coded clinical effect 'conduction disturbance, asystole,' which may represent a coding error, as no therapies were documented. Clinical effects reported for the two cases with "major effect" included 'miscellaneous-other,' 'prothrombin time/international normalized ratio prolonged,' and 'coagulopathy-other.'

Therapies recommended included cathartic, multiple-dose activated charcoal, single-dose activated charcoal, dilute/irrigate/wash, intravenous fluids, food/snack, other, and other-emetic. Activated charcoal was administered in 122 (31%) cases evaluated at a healthcare facility. Among these, administration was recommended by the poison center and performed in 111 (91.0%) of cases, while charcoal was performed without a documented poison center recommendation in 11 (9.0%) cases. Activated charcoal was recommended but known not to have been performed in six additional cases. One patient received multiple doses of activated charcoal which was performed without a specific poison center recommendation.

Clinical case narratives were requested for the two cases coded as having a "major effect." One narrative described a 22-month-old patient with a reported ingestion of up to 500 mg of rivaroxaban. Laboratory studies showed prothrombin time 31.7 s, international normalized ratio 6.30, partial thromboplastin time 115 s, and hemoglobin 13 g/dL. No clinical signs of bleeding were present. The patient received activated charcoal and one dose of vitamin K (route not specified). Approximately 10 h after ingestion, the international normalized ratio decreased to 1.5, and the patient

Table 3. Location of patient management and NPDS® medical outcome based on specific factor Xa inhibitor ingested.

Agent	Total cases	Managed at home	Managed at healthcare facility	No effect	Minor effect	Moderate effect	Major effect
Rivaroxaban, *n* (%)	431	171 (39.7%)	260 (60.3%)	383 (88.9%)	30 (7.0%)	16 (3.7%)	2 (0.5%)
Apixaban, *n* (%)	287	169 (58.9%)	118 (41.1%)	277 (96.5%)	5 (1.7%)	5 (1.7%)	0 (0%)
Factor Xa inhibitor not otherwise specified, *n* (%)	26	10 (38.5%)	16 (61.5%)	23 (88.5%)	2 (7.7%)	1 (3.8%)	0 (0%)
Total, *n* (%)	744	350 (47.0%)	394 (53.0%)	683 (91.8%)	37 (5.0%)	22 (3.0%)	2 (0.3%)

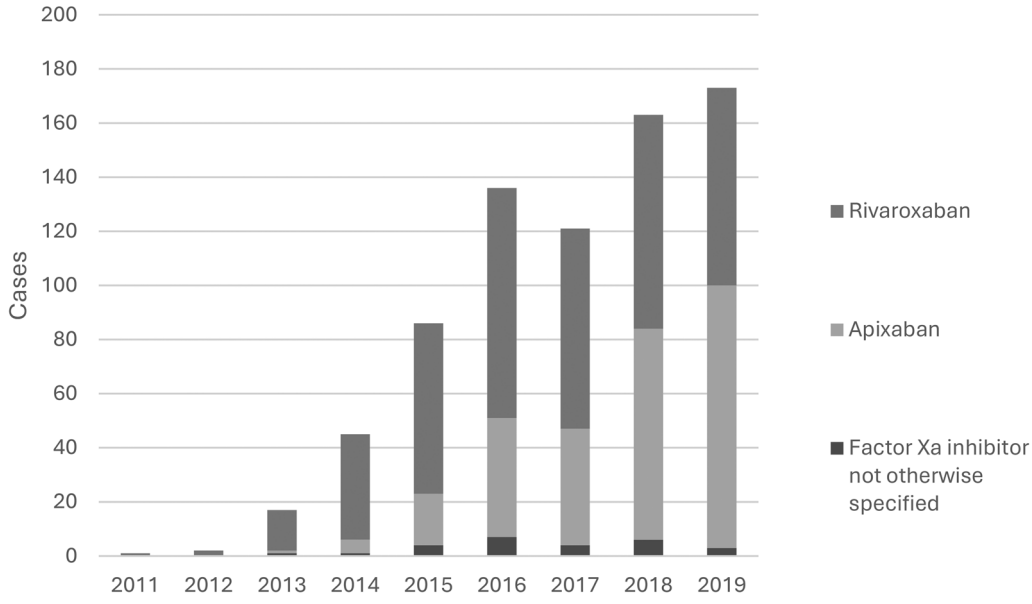

Figure 2. Cases per year stratified by specific medication reported ($n = 744$).

remained asymptomatic. Laboratory values normalized by hospital day two (partial thromboplastin time 48 s, international normalized ratio 1.0). The second narrative was not provided. That case involved a two-year-old patient with ingestion of two rivaroxaban tablets (dose unknown). The only coded clinical effect was "other-miscellaneous," and no therapies were provided.

Discussion

There is a paucity of literature describing unintentional pediatric ingestions of factor Xa inhibitors, with existing data limited primarily to case reports, case series, and small retrospective studies. Several case reports describe unintentional ingestion of rivaroxaban and apixaban characterized by coagulation abnormalities (i.e., elevated prothrombin time, international normalized ratio, activated partial thromboplastin time, and anti-Xa activity) [4,7–13,15]. To our knowledge, no case of clinically significant bleeding has been reported after acute, unintentional overdose of these medications in pediatric patients.

Spiller et al. performed a retrospective review of pediatric and adult exposures to apixaban and rivaroxaban exposures reported to eight United States Poison Centers between 2012 and 2014. Twenty patients under 12 years of age were included, the majority (60.0%) of whom had no effect. Seven cases were not followed (judged as nontoxic or only minimal effect) and one case was lost to follow up. No pediatric cases exhibited clinically significant bleeding. Notably, of the 223 total cases in this study, bleeding or bruising was reported in 7%, including 6% of cases involving rivaroxaban and 17% of cases involving apixaban. The complication of bleeding or bruising was only observed in adult patients chronically taking a factor Xa inhibitor [3].

A single poison center study conducted by Stevenson et al. identified two pediatric patients with reported rivaroxaban ingestion. Neither patient was referred to a healthcare facility or had reported clinical effects [6].

In our study, among all patients less than six years old with single substance exposure to a factor Xa inhibitor reported between 2011 and 2019, only 61/744 (8.2%) had clinical effects reported. No patients were reported to have bleeding or associated complications that required intervention. Our data are consistent with the current literature and reinforce that serious

outcomes such as bleeding are rare after acute, unintentional ingestion of a factor Xa inhibitor [3,4,6–13,15].

There were two cases with outcome code "major effect," however we suspect these cases may have been miscoded based on the coded clinical effects and therapies which did not meet the NPDS® criteria for major outcome.

Although serious outcomes were not observed in this cohort, evaluation in a healthcare facility was common: 53.0% of included cases were evaluated or treated at a healthcare facility. It is notable that the majority of cases evaluated at a healthcare facility presented prior to contact with the poison center ($n = 274$, 69.5%). Previously published poison center series provide limited detail on referral patterns, which limits direct comparison with our observed proportion evaluated in healthcare facilities [3,6].

In the present study, no cases had bleeding coded as a clinical effect and no patient received targeted reversal therapy. Activated charcoal was used in a minority of cases, consistent with expert opinion suggesting that activated charcoal may be considered for known recent ingestions, while most exploratory ingestions of factor Xa inhibitors can be managed with supportive care. Taken together, these findings support poison center triage decisions to recommend home observation for asymptomatic children with confirmed single-substance exposures when caregivers can reliably observe the child and return precautions are clearly communicated. Poison centers are well-positioned to provide this guidance and follow-up, which may reduce unnecessary healthcare utilization without compromising patient safety.

Limitations

This study has notable limitations. Poison center data is prone to reporting bias due to the voluntary nature of reporting. It is possible that a substantial number of cases are not reported to poison centers and therefore are not captured in this study. Additionally, many cases were closed without follow up and definitive outcome is not known. However, we suspect that cases with significant clinical outcomes would likely have been reported. Additionally, although all cases are coded as unintentional ingestion of a factor Xa inhibitor, lack of confirmatory testing limits confidence that ingestion truly occurred in all cases (e.g., a child may be found with a pill but without definitive history of ingestion). Furthermore, although quality assurance measures are in place, human error and variability in data entry are inevitable. Finally, the case narrative of one case with NPDS® medical outcome code "major effect" was unable to be reviewed in its entirety.

Conclusions

These data suggest that asymptomatic, unintentional, single substance exposures to factor Xa inhibitors in patients less than six years of age are unlikely to develop clinically significant bleeding.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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