An Observational Study of the Factor Xa Inhibitors Rivaroxaban and Apixaban as Reported to Eight Poison Centers

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Study objective: Rivaroxaban and apixaban are part of a new group of oral anticoagulants targeting factor Xa and approved by the Food and Drug Administration in 2011 and 2012. These oral anticoagulants are administered at fixed daily doses, without the need for laboratory-guided adjustments. There are limited data available on supratherapeutic doses or overdose of the oral Xa inhibitors. This study characterizes the clinical effect in patients exposed to rivaroxaban and apixaban.

Methods: A retrospective study collected data from 8 regional poison centers covering 9 states. Cases were initially identified by a search of the poison centers' databases for case mentions involving a human exposure to Xarelto, rivaroxaban, Eliquis, or apixaban. Inclusion criteria included single-substance exposure. Exclusion criteria were animal exposure, polysubstance exposure, or information call. Data for the study were collected by individual chart review, including case narratives, and compiled into a single data set.

Results: There were 223 patients: 124 (56%) were female patients, mean age was 60 years, and 20 were children younger than 12 years (9%). One hundred ninety-eight patients ingested rivaroxaban (89%) and 25 ingested apixaban (11%). Dose was reported in 182 rivaroxaban patients, with a mean dose of 64.5 mg (range 15 to 1,200 mg), and in 21 apixaban patients, with a mean dose of 9.6 mg (range 2.5 to 20 mg). For rivaroxaban, prothrombin time was measured in 49 patients (25%) and elevated in 7; partial thromboplastin time, measured in 49 (25%) and elevated in 5; and international normalized ratio, measured in 61 (31%) and elevated in 13. For apixaban, prothrombin time was measured in 6 patients (24%) and elevated in none; partial thromboplastin time, measure in 6 (24%) and elevated in none; and international normalized ratio, measured in 5 patients (20%) and elevated in none. Bleeding was reported in 15 patients (7%): 11 rivaroxaban and 4 apixaban. The site of bleeding was gastrointestinal (8), oral (2), nose (1), bruising (1), urine (1), and subdural (1). The subdural bleeding occurred after fall and head injury. All cases with bleeding involved long-term ingestions. Coagulation test results were normal in most patients with bleeding: prothrombin time 5 of 6 (83%), partial thromboplastin time 5 of 6 (83%), and international normalized ratio 5 of 9 (55%). Blood products were used in 7 rivaroxaban patients (1 suicide) and 3 apixaban patients. No bleeding or altered coagulation test results occurred in children, which all involved a one-time ingestion. All 12 suicide attempts involved rivaroxaban: altered coagulation test results occurred for 5 patients (42%), no bleeding occurred in any suicide attempt patient, 1 patient was treated with fresh frozen plasma (international normalized ratio 12.47), and dose by patient history did not predict risk of altered coagulation or bleeding. Two rivaroxaban patients experienced elevation of hepatic transaminase levels greater than 1,000 U/L.

Conclusion: Bleeding after Xa inhibitor ingestion as a single agent is uncommon. Prothrombin time, partial thromboplastin time, or international normalized ratio may be elevated in a minority of cases but appears unreliable to measure risk of bleeding. Massive acute ingestion in suicide attempt may result in significant anticoagulation. Single exploratory ingestion by children was not associated with toxicity. [Ann Emerg Med. 2016;67:189-195.]

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INTRODUCTION

Rivaroxaban and apixaban were approved by the Food and Drug Administration in 2011 and 2012 as new oral anticoagulants targeting factor Xa. They selectively bind to the active site of free and clot-bound factor Xa, which leads to inhibition of the intrinsic and extrinsic coagulation cascade, with inhibition of thrombin formation and thrombus development.[1] These oral anticoagulants are

Editor's Capsule Summary

What is already known on this topic

The toxicity of factor Xa anticoagulants has not been well described.

What question this study addressed

This study characterizes clinical effects according to poison centers contacts about patients exposed to rivaroxaban or apixaban.

What this study adds to our knowledge

Prothrombin time, partial thromboplastin time, or international normalized ratio was elevated in a minority of 223 patients regardless of the reported ingestion. Bleeding occurred only in chronic ingestions: coagulation test results were normal in most patients. No abnormal results were identified in children (single ingestions). Two adult patients had hepatic transaminase levels greater than 1,000 U/L.

How this is relevant to clinical practice

Case series such as this one help to characterize the findings one can expect for overdoses of these agents.

administered at fixed daily doses and are marketed with the claim that no coagulation laboratory monitoring for dosage adjustments is needed. However, in the case of another newer oral anticoagulant, dabigatran, that claim has been challenged as related to incomplete disclosure of trial data to drug regulators.[2] Dosage adjustments for rivaroxaban are suggested according to renal status, with a progressive reduced dosing regimen for creatinine clearance less than 50 mL/min. Dosage adjustments for apixaban are suggested for creatinine level greater than 1.5 mg/kg or age older than 80 years.

There are limited data available on supratherapeutic doses or overdose of the oral Xa inhibitors. Published information on rivaroxaban includes a case series of 12 patients and 2 individual case reports.[3-5] A literature search failed to locate any published reports of overdose for apixaban. Risk of serious bleeding is the greatest potential problem with the oral anticoagulants. Unlike other oral anticoagulants such as warfarin (targeting vitamin K–dependent factors II, VIIa, IX, and X) or dabigatran (a direct thrombin inhibitor), the Xa inhibitors appear to have a ceiling effect based on saturation binding of factor Xa sites,[3,4] which may limit the risk of bleeding after an acute overdose.[3,5] Elevated serum rivaroxaban concentration and prolonged coagulation tests, but not bleeding, have been reported after overdose.[3,5] Adverse events with chronic therapy include altered coagulation study results and gastrointestinal, genitourinary, and central nervous system bleeding.[6] Additionally, there is some difficulty in laboratory monitoring of oral Xa inhibitor ingestions. Commonly available testing using international normalized ratio, prothrombin time, or partial thromboplastin time may or may not be elevated and may not reflect risk of bleeding.[3,7-9] Serum levels of rivaroxaban or apixaban are not widely available and may be difficult to obtain in a timely manner.

The purpose of this study was to characterize the clinical effects and outcomes of single-substance factor Xa inhibitor ingestion according to review of cases reported to 8 US poison centers during a 3-year period.

MATERIALS AND METHODS

This was a retrospective observational study of exposures to rivaroxaban or apixaban reported to 8 regional poison centers covering 9 states (Florida, Indiana, Louisiana, Maryland, Minnesota, North Dakota, Ohio, Oklahoma, and South Dakota). Data were collected on patients who contacted one of the participating poison centers between January 1, 2012, and December 31, 2014. Data were recorded at the occurrence of the case by trained specialists (nurses, pharmacists, or physicians) during the routine management of the exposure. Study approval or exemption was obtained from the institutional review board of each of the 8 regional centers.

Each poison center case has a unique substance or substances associated with the exposure. The term "exposure" is used by poison centers, allowing cases of different routes of exposure (eg, ingestion, dermal, inhalation, parenteral). Cases were identified by a search of the 8 poison centers databases for mentions of a substance identified as Xarelto, rivaroxaban, Eliquis, or apixaban. Each poison center's database was queried for Micromedex product codes for rivaroxaban, Xarelto, apixaban, and Eliquis. Once a case had been identified, additional inclusion criteria included a human patient and single-substance exposure. Single-substance exposure means cases that reported only 1 substance, with no coingestants. Exclusion criteria were animal exposure, polysubstance exposure, or information call.

The initial data available to the site coinvestigators were collected during the routine management of these patients by the respective poison centers. Data for the study were collected by individual chart review, including case narratives, and compiled into a single data set after personal health information had been removed. The chart review was performed by the site coinvestigators. The abstractors