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CASE REPORT

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Conservative management of massive rivaroxaban overdose: A case report and literature review

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Abstract

In the cases of acute rivaroxaban overdose, conservative management without prothrombin complex concentrate or other coagulation factors may be sufficient if renal function is normal and there is no bleeding.

KEYWORDS

case report, intoxication, overdose, rivaroxaban

1 | INTRODUCTION

A 31-year-old woman with a normal renal function ingested intentionally 1200 mg of rivaroxaban. The patient's standard coagulation markers revealed coagulopathy, but no systemic or local hemorrhage occurred during the hospitalization. No blood products or reversal agents were used, and coagulation markers were reduced with conservative treatment.

Anticoagulant therapy is required in several clinical applications such as the treatment of coronary artery disease, deep venous thrombosis, pulmonary embolism, and cerebrovascular events.[1] New anticoagulants are known as direct oral anticoagulants or novel oral anticoagulants (NOACs).[2] NOACs are increasingly replacing vitamin K antagonists because of benefits such as no need for monitoring, short half-lives, and less drug interaction.[3] Their mechanism of action includes a direct thrombin inhibitor (dabigatran) and a direct inhibitor of factor Xa (rivaroxaban, edoxaban, and apixaban).[4] Rivaroxaban, one of the NOACs, is a direct factor Xa inhibitor administered orally. It has at least a 50% lower risk of bleeding compared to warfarin, but bleeding is still the most common side effect.[5] No quantitative rapid measurement tests are available to demonstrate the extent of blood coagulation timing with rivaroxaban in cases where measuring anticoagulant activity is clinically relevant, including the cases of rivaroxaban overdose. Prothrombin time (PT) is described as a potential emergency test because a normal PT indicates that its associated clinical anticoagulant effect is unlikely.[6] There are very few reports of rivaroxaban overdose. Here, we present a case of intoxication with

rivaroxaban who developed and subsequently manifested abnormal coagulation function tests and compare this case with existing case reports.

2 | CASE PRESENTATION

A 31-year-old female patient presented, herself, to a regional hospital on the outskirts of Mashhad (Iran), 10 h after suicidal ingestion of 1200 mg rivaroxaban (60 tablets of 20 mg). She was referred to the Clinical Toxicology Department of Imam Reza Hospital of Mashhad, associated with the Mashhad University of Medical Sciences (CTD-IRH-MUMS) about 3 h later. The patient had experienced a myocardial infarction one month ago and had a history of depression.

At the initial visit in the regional hospital, she was awake and oriented and had a heart rate of 52 beats/min, respiratory rate of 16 breaths/min, an axillary temperature of 36.5°C, systolic/diastolic blood pressure of 110/80 mmHg, and oxygen saturation of 98% in room air. Initial laboratory results before transferring the patient revealed a hemoglobin level of 11.3 g/dl, PT of 31.8 s, international normalized ratio (INR) of 3.6, and activated partial thromboplastin time (aPTT) of 45 s. Biochemistry tests and platelet counts were normal. The results of the patient's previous control tests were not available in her medical record.

At the admission time in CTD-IRH-MUMS, she was conscious (The Glasgow Coma Scale (GCS): 15/15) without any symptoms of hemorrhage. The patient's vital signs at that time were as follows: blood pressure of 120/70 mmHg, heart rate of 80 bpm, respiratory rate of 17 cycles/min, and oxygen saturation of 99% in room air.

The patient was closely monitored in bed rest and treated with 40 mg pantoprazole every 12 h and 1 L of intravenous electrolyte solution three times a day.

The results of the daily coagulation parameters are summarized in Figure 1. The electrocardiogram showed no new abnormalities. Electrolytes, kidney, and liver function were normal. Psychiatric and cardiovascular consultations were performed for the patient. In the cardiovascular consultation, rivaroxaban was held, but it was recommended to start rivaroxaban with the previous dose 72 h later if there was no bleeding. An outpatient echocardiography was also recommended. The psychiatric consultation suggested the admission of the patient to the psychosomatic ward after discharge from the toxicology department.

At 72 h after the ingestion, the patient's coagulation parameters returned to normal, and she was transferred to the psychosomatic ward for further treatment. There was no bleeding during her clinical course.

3 | DISCUSSION

Here, we reported a case of rivaroxaban overdose that had a favorable outcome with conservative management and did not require the administration of any fresh frozen plasma, blood products, or prothrombin complex concentrate (PCC). We conducted a literature search to identify similar cases, and the characteristics of the patients, along with the treatment, are shown in Table 1.[7-18]

The use of rivaroxaban in anticoagulant treatment has increased, and its administration is expected to rise significantly.[5] One of the problems with rivaroxaban overdose is how to measure and monitor its impacts on the coagulation system. Mueck et al. showed that PT is associated with plasma rivaroxaban concentrations in healthy subjects.[19] Anti-Xa assay is a better indicator of plasma concentration of rivaroxaban than PT for measuring the factor Xa inhibition, but it is rarely available.[20] This method is not available in our center, so we used PT and aPTT for the patient follow-up.

The maximum anticoagulant effect of rivaroxaban is 2–4 h, and its half-life is 5–9 h, which may increase to 11–13 h in elderly patients or cases with insufficient renal function.[21] We observed that the PT level did not decrease in a pharmacokinetic manner compatible with the therapeutic doses of rivaroxaban.

Bleeding is a prime concern in rivaroxaban overdose, and the goal of treatment is to reduce its complications such as bleeding and prevent the progression of bleeding. Rivaroxaban has a short half-life and does not require any drug intervention, even in the cases of minor bleeding with a normal renal function.[22] Close monitoring and supportive treatment are very important as no

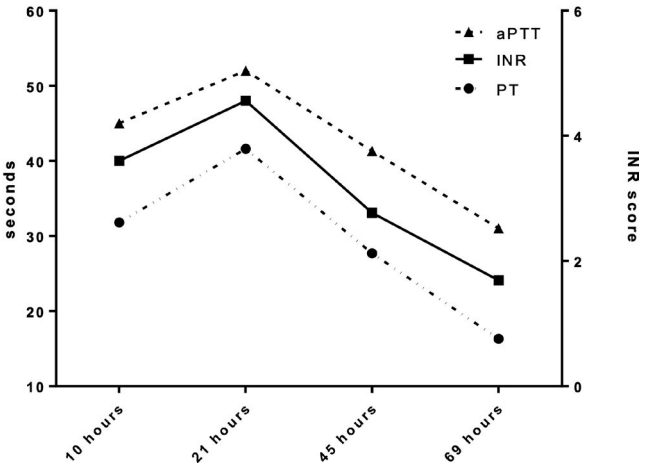

FIGURE 1 Serial post-ingestion coagulation parameters of the intoxicated patient with rivaroxaban. aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time

TABLE 1 Characteristics of other rivaroxaban overdose cases

First author (year), reference	Age	Sex	PMH	Intentional	Rivaroxaban dosage (mg)	Co-ingestion	Time to presentation	Treatment	Bleeding	Outcome
Lehmann et al. (2014)[7]	63-year-old	Male	CAD, chronic AF, idiopathic thrombocytopenia, and chronic vertigo	Yes	1960	50 mg zolpidem, 1 g quetiapine, 90 mg diazepam	2.5 h	Oral AC + 18 U/kg of four-factor PCC	None	48 h post-ingestion, his coagulation parameters were normalized
Linkins and Moffat (2014)[8]	42-year-old	Male	Hypertension, recurrent venous thromboembolism, chronic back pain, obstructive sleep apnea, and depression	Yes	1400	1200 mg codeine, 24 g acetaminophen, 8 mg lorazepam, 600 mg diphenhydramine; unknown amount of naproxen	5 h	1 g tranexamic acid + 20 U/kg of four-factor PCC	None	37 h post-ingestion, his coagulation parameters were normalized
Carr et al. (2018)[9]	35-month-old	Male	Previously healthy	No	200	None	15 min	Oral AC	None	He was discharged <24 h post-ingestion, without any complication
Repplinger et al. (2016)[10]	71-year-old	Male	AF, porcine aortic valve replacement, and CHF	Yes	1940	None	2 h	None	None	5 days post-ingestion, his coagulation parameters were normalized
Pfeiffer et al. (2016)[11]	23-year-old	Male	Extensive DVT of the right upper leg	Yes	1960	1425 mg diclofenac, 21 g metamizole, 31.5 mg phenprocoumon	12 h	3000 IU PCC, 60 mg vitamin K, 32 g cholestyramine, 40 mg pantoprazole once daily	One episode of gross hematuria	30 h post-ingestion, his coagulation parameters were normalized
Sajkov and Gallus (2015)[12]	50-year-old	Male	DVT	No	300 (Two 150 mg doses 12 h apart)	None	10 min after the second dose	Oral AC	None	There were no complications, and the previous treatment dose was restarted on the second day for the patient
Stevenson et al. (2014)[13]	59-year-old	Male	AF, hypertension, and diabetes	Yes	Unknown	Unknown amount of dutasteride	Unknown	4 U of FFP and vitamin K	None	10 days after admission, the patient was medically cleared

(Continues)

TABLE 1 (Continued)

First author (year), reference	Age	Sex	PMH	Intentional	Rivaroxaban dosage (mg)	Co-ingestion	Time to presentation	Treatment	Bleeding	Outcome
Blickstein et al. (2016)[14]	47-year-old	Female	Left leg DVT, combined thrombophilia (low protein S level and heterozygote for factor V Leiden) and chronic severe iron deficiency anemia	Yes	400	None	1.5 h	Oral AC	None	The plasma level of rivaroxaban was 0.0 ng/ml 36 h after ingestion
Levine et al. (2018)[15]	59-year-old	Female	-	Yes	Unknown	-	-	FFP, Vitamin K	Gingival bleeding	Survived
	49-year-old	Male	-	Yes	Unknown	-	-	FFP, DDAVP	Intracranial hemorrhage	Survived
	63-year-old	Female	-	Yes	Unknown	-	-	PRBC, PCC	GI bleeding	Survived
	63-year-old	Female	-	Yes	Unknown	-	-	PCC	GI bleeding	Survived
	69-year-old	Female	-	Yes	Unknown	-	-	FFP, PRBC	GI bleeding	Survived
	42-year-old	Male	-	Yes	Unknown	-	-	3 day observation	GI bleeding	Survived
Bandali et al. (2014)[16]	54-year-old	Male	CAD, AF, pulmonary embolism, diabetes, hypertension, depression, and borderline personality disorder	Yes	1800	1800 mg enoxaparin	3 h	None	None	22 h post-ingestion, his coagulation parameters normalized
Weirthein et al. (2019)[17]	18-month-old	Male	-	No	Unknown	None	2 h	20 ml/kg FFP	None	One day after admission, his coagulation parameters normalized
Katragadda et al. (2015)[18]	28-year-old	Female	Unknown	Yes	Unknown	Unknown	3 months	Unknown	Abnormal uterine bleeding, recurrent epistaxis and easy bruising	Unknown
Current case	31-year-old	Female	Myocardial infarction, depression	Yes	1200	-	10 h	None	None	72 h post-ingestion, her coagulation parameters were normalized

Abbreviations: AC, activated charcoal; AF, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; DDAVP, desmopressin; DVT, deep vein thrombosis; FFP, fresh frozen plasma; GI, gastrointestinal; PCC, prothrombin complex concentrate; PMH, past medical history; PRBC, packed RBCs.

specific antidote is available. Gastrointestinal decontamination by activated charcoal can prevent the absorption of rivaroxaban if administered within the first 1–2 h after ingestion.[12] Charcoal was not prescribed for our patient because the ingestion had occurred 10 h earlier. A PCC injection is used to compensate for excessive inhibition of factor Xa, but it can be withheld, especially in cases where the risk of bleeding is low[23] such as our case. Due to high plasma protein binding, hemodialysis has no role in the management of the bleeding associated with the use of rivaroxaban.[12]

In a similar case report, Repplinger et al. reported a 71-year-old man with an intentional ingestion of 1940 mg rivaroxaban.[10] His coagulation parameters decreased during the course of hospitalization, and he had no severe bleeding events that caused hemodynamic instability or needed the administration of reversal agents or blood products. His coagulation parameters had returned to normal 120 h after the ingestion.[10] The management of this case was similar to our study, but his coagulation parameters returned to normal after 5 days, which was longer than our case.

4 | CONCLUSION

In the cases of acute rivaroxaban overdose, conservative management without PCC or other coagulation factors may be sufficient if renal function is normal and there is no bleeding. The most important management in these patients is hospitalization and monitoring, and if the patient presents shortly after ingestion, charcoal can be helpful too. The standard coagulation markers such as PT, aPTT, and INR can be used to evaluate the drug clearance.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Alireza Ghodsi, Bita Dadpour, Babak Mostafazadeh, and Mohammad Moshiri performed material preparation, data collection, and acquisition. Alireza Ghodsi, Leila Etemad, and Mohammad Moshiri involved in writing the first draft of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. All experiments were performed in accordance with relevant guidelines and regulations recommended by the institution. Moreover, written informed consent was obtained from the patient for publication of this case report.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

DATA AVAILABILITY STATEMENT

The data are also available on request.

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