Clinical Case Report

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Massive intoxication with rivaroxaban, phenprocoumon, and diclofenac

A case report

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Abstract

Rationale: Oral anticoagulants and painkillers, some with an additional effect on the coagulation system, are widely used and are therefore prone to abuse and (intentional) overdose. We report the case of a patient with a massive mixed anticoagulant intoxication.

Patient concerns: The patient had ingested 1960 mg rivaroxaban, 31.5 mg phenprocoumon, 1425 mg diclofenac, and 21,000 mg metamizole in suicidal intention.

Diagnoses: Massive mixed anticoagulant overdose.

Interventions: The patient was closely monitored. The phenprocoumon overdose was treated by the administration of vitamin K and PCC.

Outcomes: Despite the massive inhibition of the coagulation system, the patient did not experience bleeding apart from a slight gross hematuria.

Lessons: Despite the ingestion of a massive amount of rivaroxaban, the plasma levels were not as high as feared, due to the ceiling effect of rivaroxaban absorption. Elimination occurred according to the half-life of rivaroxaban and was not unduly prolonged by the ingested quantity.

Abbreviations: ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, INR = international normalized ratio, LDH = lactate dehydrogenase, PCC = prothrombin complex concentrate, PT = prothrombin time.

Keywords: anticoagulant intoxication, case report, overdose, phenprocoumon, rivaroxaban

1. Introduction

A 23-year-old male patient presented himself after the suicidal ingestion of a mix of 4 different drugs (rivaroxaban, phenprocoumon, diclofenac, and metamizole), 3 of which have a known effect on the coagulation system.

Literature research revealed 3 case reports with an intentional, massive rivaroxaban overdose (1400, 1800, and 1960 mg),[1–3] with 1 patient having additionally administered enoxaparin.[1] Additionally, 1 case of surreptitious rivaroxaban intake was found.[4]

We present, to our knowledge, the first case with a massive combination overdose of rivaroxaban, phenprocoumon, and diclofenac, and also metamizole.

2. Case report

2.1. History

The patient had experienced an extensive deep vein thrombosis of the right upper leg 5 months previously (Table 1). Research revealed an aplasia of the inferior vena cava with extensive collaterals, a relevant risk factor for venous thrombosis.[5] A lifelong anticoagulation was advised. Treatment with rivaroxaban (20 mg daily) was started, but after a re-thrombosis of the right upper leg 2 months after the initial thrombosis (confirmed daily rivaroxaban intake and without further recognizable risk factors), the patient was switched to phenprocoumon with an international normalized ratio (INR) target of 3.0 to 3.5. No further relevant endogenous risk factors for venous thrombophilia were detected. One week before the suicide attempt, the hemoglobin level had been 12.6 g/dL, the hematocrit 38.3%, and the platelet count 329.000/μL.

He had a history of depression, but had not been on antidepressants during the past 5 years.

2.2. Presenting condition

A 23-year-old male (74 kg, nonsmoker) presented himself at the emergency room of an external clinic approximately 12 hours after the intentional, suicidal ingestion of 1960 mg rivaroxaban (Xarelto, Bayer Pharma AG, Germany), 31.5 mg phenprocou-

Editor: Wen Zhou.

The authors declare that they have no conflicts of interest relevant to the manuscript.

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Medicine (2016) 95:44(e5343)

Received: 14 July 2016 / Received in final form: 10 October 2016 / Accepted: 11 October 2016

http://dx.doi.org/10.1097/MD.0000000000005343

Table 1

Timeline of previous patient history, adapted according to.[6]

5 mos and 2 wks	Appendectomy
5 mos and 1 wk	Testicular torsion (right)
5 mos	Extensive deep vein thrombosis of the right upper leg
3 mos	Re-thrombosis of the right upper leg
1 wk	Thrombophilia screening
0	Suicide attempt
+3 d	Transfer from intensive care unit to psychiatric clinic
+3 mos	Discharge from psychiatric clinic

mon, 1425 mg diclofenac, and 21,000 mg metamizole (ingestion occurred around 7 p.m.). He reported 1 episode of vomiting during the night (no blood or pills were observed, time since ingestion unknown).

Upon admission, no bleeding was observed. The physical examination and the electrocardiogram showed no abnormalities. The laboratory results showed a prothrombin time (PT) higher than 34 seconds (no further specification of this result was available at that time), INR was not measurable, activated partial thromboplastin time (aPTT) was 128 seconds. The blood count was normal (hemoglobin 13.3 g/dL, hematocrit 41%, platelet count 349.000/μL). Electrolytes, liver, and kidney function were normal [calculated glomerular filtration rate 110 mL/min (modification of diet in renal disease-formula), lactate dehydrogenase (LDH) 177 U/L, alanine aminotransferase (ALT) 10 U/L]. He received 20 mg of intravenous vitamin K, 2000 IU of prothrombin complex concentrate (PCC), 50 g oral charcoal, 40 mg pantoprazole, and 1 L of intravenous electrolyte solution (Jonosteril, Fresenius, Germany).

2.3. Initial therapy

The patient was transferred to an intensive care unit in our hospital 18 hours after ingestion. The rivaroxaban level at that time was 1211 ng/mL, measured through anti Xa-inhibition (test: STA-Liquid Anti-Xa, Diagnostica Stago S.A.S., Asnières sur Seine Cedex, France. Calibrator: Multi Hep calibrator, Diagnostica Stago S.A.S., Asnières sur Seine Cedex, France). The PT was longer than 34 seconds, the INR was larger than 6, and the aPTT was 47.2 seconds (laboratory-defined reference range for the aPTT is 23.4–34.8 seconds and <16.1 seconds for the PT) [controls: STA-Quali-Clot I (Lot 113071) with 13.8 seconds (11.5–16.0 seconds) for the PT and 32.5 seconds (27.0–38.0 seconds) for the aPTT]. The blood count showed hemoglobin of 11.5 g/dL, hematocrit of 35.2%, and platelets of 316,000/μL). Analysis of the platelet function (using PFA-200 (Siemens, Germany) and Multiplate (Roche Diagnostics, Switzerland)) revealed a pronounced diclofenac-induced platelet dysfunction, but no apparent additional congenital platelet disorder.[7]

The patient was closely monitored, and, within 3 hours of admission in our clinic, received 3000 IU PCC pre-emptively, 60 mg vitamin K intravenously, a total of 32 g cholestyramine during his inpatient stay, and 40 mg pantoprazole once daily. Platelet concentrates were not transfused. PCC and vitamin K were given to counteract the massive phenprocoumon overdose. Because of the rivaroxaban overdose, an effective anticoagulation was ensured despite the temporary interruption of the phenprocoumon effect.

Apart from a slight gross hematuria upon admission, the patient never showed signs of bleeding. He was always completely oriented and never unconscious. The rivaroxaban levels (through anti-Xa inhibition) were measured every couple of hours until they were no longer detectable (Table 2). Requiring long-term anticoagulation because of his patient history, he was started on unfractionated heparin IV the moment the routine coagulation parameters (INR and aPTT) were normalized, which happened 30 hours after ingestion (approximately 18 hours after admission).

Table 2

Coagulation parameters.

Hours after ingestion	Rivaroxaban level (anti-Xa inhibition), ng/mL	PT, s	INR	aPTT, s
12	Not done	>34.0	Not measurable	128
18	1211	>34.0	>6.00	47.2
21	449	31.1	2.94	52.6
27	174	22.1	1.90	36.6
30	128	21.4	1.78	62.8*
36	70	16.2	1.21	33.0*
38	33	15.2	1.15	34.0*
46	Not done	17.5	1.33	36.5*
53	Not done	15.2	1.15	51.9*
59	<25	17.8	1.38	60.9*

Laboratory-defined reference range for the aPTT is 23.4 to 34.8 seconds, and for the PT <16.1 seconds.

aPTT = activated partial thromboplastin time, INR = international normalized ratio, PT = prothrombin time.

* At 30 hours after ingestion, the patient was started on unfractionated heparin, since his patient history required effective anticoagulation.

2.4. Follow-up and outcome

Three days after ingestion, the patient was transferred to our psychiatric clinic for further treatment. The PT upon transfer was 17.8 seconds, the INR was 1.38, the aPTT 60.9 seconds (heparin IV), and the rivaroxaban level was lower than 25 ng/mL. Hemoglobin was 13.3 g/dL and the hematocrit 41%. The patient was transferred to the psychiatry unit on unfractionated heparin. Later, he was started on oral anticoagulation with phenprocoumon (as previously done) and trained to do self-management. The lowest observed hemoglobin was 11.5 g/dL.

After stabilization and transfer to the psychiatric clinic, the exact plasma concentrations of rivaroxaban and phenprocou-

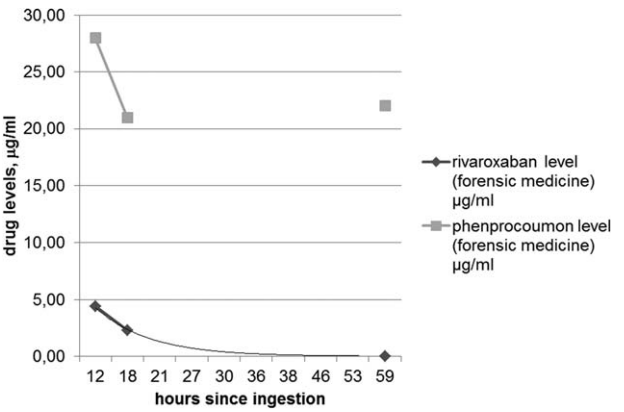

Figure 1. Exact plasma levels of rivaroxaban and phenprocoumon, evaluated by liquid chromatography tandem mass spectrometry. The routine anticoagulation phenprocoumon level is between 1 and 3 μg/mL. For rivaroxaban, no such references exist in our laboratory.

mon were evaluated by liquid chromatography tandem mass spectrometry (Fig. 1). The rivaroxaban level 12 hours after ingestion, determined by spectrometry, was extremely high (4.4 μg/mL). Eighteen hours post ingestion, the levels were still high, with a marked discrepancy between our anti-Xa measurement (1211 ng/mL) and the spectrometry measurement (2.3 μg/mL). The reason for this remains unclear, as literature research revealed a good correlation between these 2 methods with only slight differences.[8] Rivaroxaban levels dropped as expected by their half-life and the patients unimpaired renal function, whereas phenprocoumon levels did not differ significantly over the course of these 3 days. Fifty-nine hours post ingestion, rivaroxaban had been almost cleared (both measurements).

No renal and/or liver dysfunction, as a late effect especially of intoxication with diclofenac and metamizole, was observed during the following weeks. Since this is a case report, neither institutional review board approval nor patient consent was sought.

3. Medication background information

Rivaroxaban is an oral, direct, and selective factor Xa inhibitor.[9] The plasma levels and therefore the maximum anticoagulant effects of rivaroxaban are reached within 2 to 4 hours, with a half-life of 5 to 9 hours, which may be prolonged in older patients or in cases of insufficient renal function (11–13 hours).[10,11] About one-third is eliminated unchanged via the kidneys.[12] After 16 hours, the expected anticoagulant effect is low and only a minimal effect is noticeable after more than 24 hours.[11] An apparent 'ceiling effect' after (about 50 mg) was observed after the ingestion of higher doses with a limitation to the maximum potential anti-Xa inhibitory effect.[10]

Monitoring through determination of anti-Xa activity, using special calibrators, is a precise way to ascertain the quantitative anticoagulant effect, but this is seldom routinely available.[13,14] The gold standard is measurement by liquid chromatography tandem mass spectrometry.[14] PT and aPTT are affected without any linearity, depending on the reagents used, but normal PT and aPTT seem to exclude relevant rivaroxaban plasma levels.[9,15,16]

In case of acute rivaroxaban overdose, the major concern is bleeding. Since no specific antidote is available,[17] close monitoring and supportive measures are of utmost importance. Gastrointestinal decontamination using activated charcoal may be useful only if applied shortly after ingestion.[11] In our case, it is not clear whether the administration of charcoal 12 hours after ingestion was helpful. Rivaroxaban is not dialyzable due to its high plasma protein binding.[17]

Treatment of bleeding complications include mechanical methods, radiological interventions, and surgery.[11] Since a specific antidote is not available, administration of PCC seems to be the best option in cases of severe bleeding (same dosage as for vitamin K antagonist-induced bleeding, ie, 25–50 IU per kg bodyweight).[11,18] Fresh frozen plasma (FFP) or recombinant factor VIIa might also be used, although their prothrombotic potential might be higher than that of PCC.[18]

Phenprocoumon is a vitamin K antagonist with a high protein binding (> 95%), which prevents its elimination via dialysis.[9,15] Although peak concentrations are reached about 90 minutes after intake, the half-life is 5.5 days with an accordingly slow onset and end of efficient anticoagulation.[15] Because of its inhibition of the synthesis of vitamin K-dependent coagulation factors (factors II, VII, IX, and X, and also proteins C and S), onset of coagulation is slow, whereas multiple interactions with food, other drugs, and genetic variability are observed.[9,15,19] The therapeutic index is relatively small, but the anticoagulation effect can be easily monitored by the INR, which is readily available in most clinics.[9,15] Vitamin K is the preferred antidote, but requires a certain amount of time to become effective.[9,15] For a fast termination of the phenprocoumon effect, PCC or FFP can be administered, but a rebound effect is to be expected.[9,15] Whereas supratherapeutic levels of vitamin K antagonists are a common side effect in patients requiring oral anticoagulation, massive overdoses are relatively rare.[19]

Diclofenac is a reversible cyclooxygenase inhibitor with a half-life of 1 to 2 hours, an antinoceptive and a marked antiphlogistic effect.[20,21] Common side effects include gastrointestinal, cardiac, and vascular adverse events, and also a reversible inhibition of the platelet function (in accordance to the plasma half-life) and renal adverse effects.[20] Most cases of overdose show a benign outcome, with only rare serious adverse events.[22] Treatment is strictly supportive, although the administration of oral charcoal is advised.[22] Diclofenac cannot be eliminated by dialysis.[22]

Metamizole (also known as dipyrone) is a reversible cyclooxygenase inhibitor, has a half-life of approximately 2 to 4 hours, and the maximum peak level is reached after about 1 to 1.5 hours.[20,23,24] No clinically relevant inhibition of platelet function has been observed.[20] Common side effects include gastrointestinal, cardiovascular, renal, or hypertensive adverse events, whereas agranulocytosis is a rare but serious side effect.[20,23]

4. Discussion

Literature research revealed 3 case reports with an intentional, massive rivaroxaban overdose (1400, 1800, and 1960 mg),[1–3] with 1 patient having additionally administered enoxaparin.[1] Additionally, 1 case of surreptitious rivaroxaban intake was found.[4] We present, to our knowledge, the first case with a massive combination overdose of rivaroxaban, phenprocoumon, and diclofenac, and also metamizole, resulting in a massive inhibition of the secondary, and also the primary coagulation system. Despite this, the patient never showed signs of significant bleeding, thereby underlining the importance of stable blood vessels.

Due to the ceiling effect of rivaroxaban absorption, the rivaroxaban plasma levels were comparably low considering the massive ingestion. Elimination occurred according to the known half-life of rivaroxaban. The phenprocoumon overdose was well-treated by the fast and ample administration of vitamin K and PCC.

In all 3 previous case reports with a massive rivaroxaban overdose, patients were middle-aged, clinically stable, and fully conscious upon admission.[1–3] Two patients received PCC pre-emptively—in 1 case with additional active charcoal and in the other case with tranexamic acid.[2,3] No bleeding episodes were recorded.[1–3] Elimination of rivaroxaban and therefore normalization of blood coagulation (and its parameters) was observed 22 to 48 hours after ingestion.[1–3] In the case of surreptitious rivaroxaban intake, the patient presented with menorrhagia, epistaxis, and easy bruising, but no serious bleeding was observed and no treatment was necessary.[4] All 4 case reports postulated that a pre-emptive administration of coagulation factors might not be necessary, but dependent on clinical findings, and likely did not improve the clinical outcome.[1–4]

In this patient, the risk of bleeding complications was estimated to be very high. Because of the confusing coagulation situation,

with a massive inhibition of the primary, and also the secondary coagulation system, the patient was given PCC and vitamin K to counteract at least some of the phenprocoumon effect. This therapy was likely not effective in counteracting the rivaroxaban overdose, thereby ensuring an effective anticoagulation despite the massive procoagulatory therapy. In the future, with more experience concerning mixed anticoagulation overdoses, a different therapy approach or a reduced procoagulatory treatment might be possible.

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