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Case Report

Massive Intoxication with 70 Tablets of Apixaban: A Case Report

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Keywords

Antithrombin activity · Anti-Xa activity · Apixaban · Intoxication · Prothrombin time-international normalized ratio

Abstract

Apixaban is a direct oral anticoagulation agent that exerts its effect through the direct inhibition of factor Xa. We treated a case of massive intoxication with 70 tablets of apixaban and have presented the clinical course of the associated anti-Xa activities. A 49-year-old woman was admitted to the emergency department approximately 1.5 h after impulsive self-intoxication with 175 mg of apixaban. She developed coagulopathy with prothrombin time-international normalized ratio (PT-INR) of 3.65, activated partial thromboplastin time of 56.5 s, and antithrombin activity (AT) of >150% (at 1.5 h post-ingestion). The patient's initial and peak anti-Xa activity was 17.7 IU/mL, and its elimination displayed first-order kinetics with a half-life of 10.5 h. The patient's anti-Xa activity was within the therapeutic dose range at 26 h post-ingestion, and she recovered without experiencing any bleeding complications. Her coagulopathy also returned to normal level at the same timing. This result suggests that PT-INR and AT can be used as substitute markers of overwhelmed anticoagulation following massive overdose of apixaban. A case of apixaban overdose with associated anti-Xa activities was presented. There was favorable resolution of anticoagulation without specific treatments.

Introduction

Apixaban is a selective, reversible direct factor Xa inhibitor, which exerts oral anticoagulant activity through direct factor Xa inhibition. It is currently approved for the treatment of non-valvular atrial fibrillation and the prevention/treatment of deep venous thromboembolism. As

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with acute overdose of all anticoagulants, the primary concern is bleeding. We have presented a case of acute apixaban overdose without bleeding complications and described the associated anti-Xa activity and coagulation profile. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533520).

Case Presentation

A 49-year-old woman presented to our emergency department following overdose with 70 × 2.5 mg (175 mg) apixaban in the preceding 1.5 h. She had medical history of schizophrenia, allergic rhinitis, and iron-deficiency anemia, but neither atrial fibrillation nor deep venous thromboembolism, which are the indications for apixaban. She stated that she took apixaban that had been prescribed to her boyfriend and denied it was a suicide attempt. Her initial vital signs were pulse, 102 bpm (regular); blood pressure, 110/93 mm Hg; temperature, 37.1°C; oxygen saturation, 97% on room air; Glasgow coma scale, 15/15 (E4V5M6); and blood sugar concentration, 88 mg/dL.

The patient was calm and able to hold normal conversation. Although no significant hemorrhagic complications developed, we administered activated charcoal owing to the short interval since overdose (2 h post-ingestion). Initial coagulation studies, performed 1.5 h post-ingestion, showed a prothrombin time-international normalized ratio (PT-INR) of 3.65 (0.8–1.2), activated partial thromboplastin time of 56.5 s (22–32 s), and antithrombin activity (AT) of more than 150% (80–120%). The patient exhibited no indications of hepatic impairment or renal insufficiency, both of which can potentially affect the outcomes of coagulation panels (Table 1). Additionally, the medications prescribed to her included antipsychotics and antiallergic drugs (Table 2), which did not seem to have any noticeable influence on the test results.

After injection of vitamin K 20 mg at 2 h post-ingestion, the patient was transferred to an intensive care unit. After transfer, anti-Xa activity was measured, and the peak value was 17.7 IU/mL (reference range: 0 IU/mL-0.01 IU/mL, therapeutic range: 1.0 IU/mL-2.0 IU/mL) at 4.5 h post-ingestion. Due to stable condition, she was observed without any antidotes and transfusions. Upon administering vitamin K, we entertained the suspicion of warfarin ingestion due to the prolonged PT-INR. However, this possibility was later disproven by the patient's boyfriend. The patient received a psychiatric assessment while in hospital; she was advised to make an appointment with her psychiatrist after discharge and agreed to do so. She was discharged from hospital to her family 5 days after admission without any significant complications.

The patient's coagulation profile is presented in Figure 1. The observed half-life of anti-Xa activity (HaemosIL Heparin Kit; Instrumentation Laboratory, Bedford, MA, USA) was 10.5 h, and the activity appeared to correlate relatively well with PT-INR.

Discussion

Several case reports described the clinical course or toxicokinetic of apixaban overdose [1–5]. This currently reports the earliest post-ingestion measurement of anti-Xa activity. Unfortunately, we were unable to check the concentrations of apixaban owing to lack of access. However, most previous cases [1–5] showed a strong correlation between apixaban concentration and anti-Xa activity, as did pharmacokinetic studies [6]. Therefore, we had sufficient information to understand and estimate toxicokinetic from

Table 1. Blood test results on admission in emergency room

Parameters	Values				
	day 1	day 2	day 3	day 4	reference range
Hematology					
White blood cell count /μL	10,690	7,560	8,060	8,730	3,300–8,600
Red blood cell count, $\times 10^6$/μL	3.63	3.28	3.32	3.46	3.86–4.92
Hemoglobin, mg/dL	7.7	6.8	6.9	7.3	11.6–14.8
Hematocrit, %	26	23.8	24.1	25.3	35.1–44.4
Platelet, $\times 10^3$/μL	342	325	331	343	158–348
Coagulation					
PT-INR	3.65	1.14	0.96	0.96	0.9–1.1
Activated partial thromboplastin time, sec	56.5	34.4	30.9	28.7	26.5–36.1
Antithrombin, %	>150	111	87	85	83–128
D-dimer, μg/mL	0.71	0.66	0.81		0.0–1.0
Anti-Xa activity, IU/mL	17.7	1.6	0.07	0.03	0.00–0.01 (Therapeutic 1.0–2.0)
Biochemistry					
Albumin, g/dL	3.9	3.3	3.4	3.5	4.1–5.1
Total bilirubin, mg/dL	0.2	0.5	0.3	0.3	0.4–1.5
Aspartate aminotransferase, IU/L	15	15	12	12	13–30
Alanine aminotransferase, IU/L	13	11	11	11	7–23
Lactate dehydrogenase, IU/L	206	173	167	157	124–222
Blood urea nitrogen, mg/dL	12	8	9	11	8–20
Creatinine, mg/dL	0.55	0.57	0.58	0.64	0.46–0.79
C-reactive protein, mg/dL	0.12	0.16	0.11	0.11	0.00–0.14

The blood tests showed coagulopathy induced by apixaban overdose and no liver and renal failure.
PT-INR, prothrombin time-international normalized ratio.

only anti-Xa activity measurements. Anti-Xa activity was measured using HemosIL Heparin Liquid (Instrumentation Laboratory, Bedford, MA, USA) in our hospital. In this case, the patient had an uneventful course without any serious complications. We observed a significant rise in PT-INR, activated partial thromboplastin time, AT, and anti-Xa activity. Although activated charcoal and vitamin K were administered just after the first blood tests, these did not play a clinically significant role in the prevention and reversal of coagulopathy, as measured by the available tests. Andexanet-alfa, a new direct Xa inhibitor reversal agent, is a promising option for overdoses of apixaban and other Xa inhibitors [7]. However, it does not appear to have a role in the absence of critical bleeding.

Previous studies of apixaban pharmacokinetics have investigated the therapeutic dose [8]. In an escalating single-dose pharmacokinetic study, at the highest dose of 50 mg, the peak apixaban concentration was 685.2 ng/mL at 2.5 h post-ingestion, and the plasma terminal half-life was 19.7 h. This study showed that an increased apixaban dose was well correlated with a linear increase in the maximum PT-INR. The highest value of PT-INR was

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Table 2. Patient's medications

Antipsychotics	Lorazepam 3 mg/day, alprazolam 0.4 mg/day, flunitrazepam 2 mg/day, sodium valproate 400 mg/day, paliperidone 6 mg/day, risperidone 1 mg as needed
Antiallergic agents	Pranlukast 250 mg/day, fexofenadine 120 mg/day

The patient was prescribed antipsychotics and antiallergic agents.

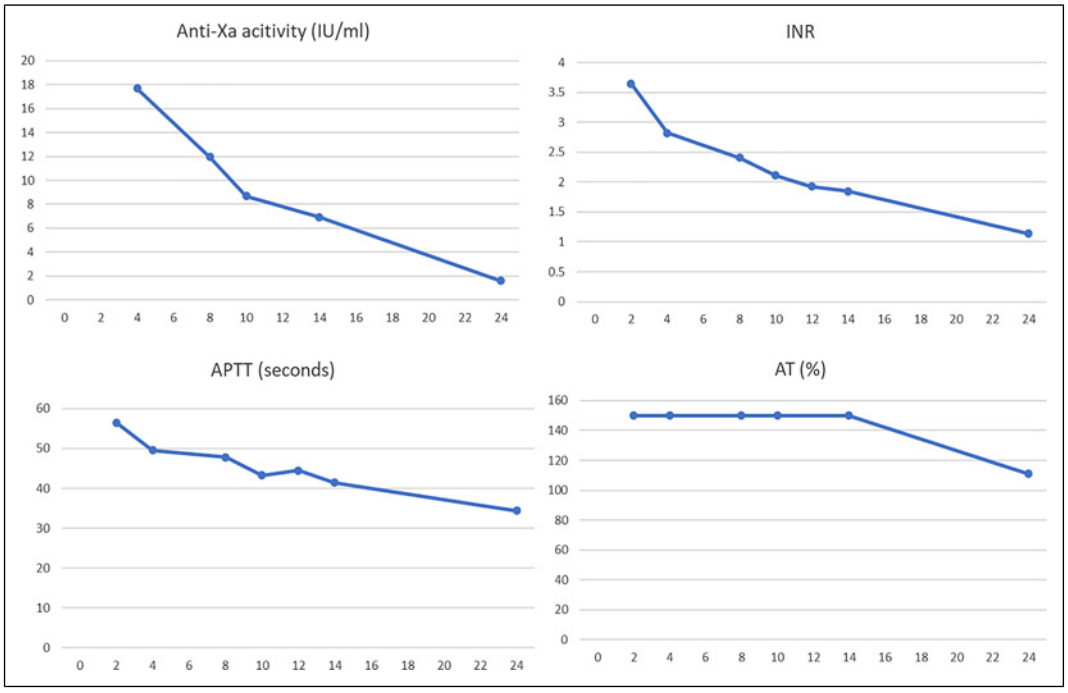

Fig. 1. The graph shows the trends of Anti-Xa activity, PT-INR, APTT, and AT. The recovery timing of anti-Xa activity, PT-INR, and AT was almost the same. APTT, activated partial thromboplastin time.

3.65 in our patient, also correlating with a linear PT-INR-anti-Xa activity correlation. Although PT-INR is not a best marker of anti-Xa activity in therapeutic dose [9], this suggests that PT-INR may be useful in the detection of apixaban overdose to determine anticoagulation effects; neither anti-Xa assays nor apixaban concentrations are available [6]. Interestingly, AT also returned to the normal range simultaneously with the return to the therapeutic range of the anti-Xa activity of apixaban (1.0–2.0 IU/mL). In our hospital, AT is detected using the Xa method, and the reagent used is HemosIL Antithrombin Liquid (Instrumentation Laboratory, Bedford, MA, USA). The Xa method for the detection of the activity of AT works through investigating the anti-Xa activity of AT-heparin conjugates. It is also known as an artifact of high value under apixaban dosing [10]. Paradoxically, we may be able to determine the disappearance of apixaban by detecting AT activity using the Xa method.

At present, apixaban concentration and anti-Xa activity are not popular laboratory tests. Therefore, it is useful to know PT-INR and AT, which may confirm the absence of an anticoagulation effect of apixaban for cases of overdose.

Conclusion

We reported a case of apixaban overdose that showed a favorable resolution of coagulopathy with no significant bleeding complications. There was a clear correlation between an increase in anti-factor Xa activity and PT-INR. AT also returned to the normal range in the same time frame as the return of anti-factor Xa activity to the therapeutic range. These results suggest that elevated PT-INR and excess AT can be used as substitute markers of overwhelmed anticoagulation following massive overdose of apixaban.

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Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Since case reports are not included in the scope covered by the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the Ministry of Health, Labor and Welfare (MHLW), it is the general interpretation in Japan that case reports are published without Ethics Committee review. And written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tadahiro Kobayashi designed the report and wrote the initial draft of the manuscript. He approved the final manuscript. Masaki Nakane substantially contributed to the conception of the report and critically revised the manuscript. He approved the final manuscript. Satoko Saito, Masayuki Takada, Kento Sakaguchi, Kazunori Takahashi, Ken Tanaka, and Kaneyuki Kawamae substantially contributed to the collection of clinical information and critically revised the manuscript. They approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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