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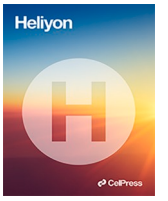

Case report

Reversal of dabigatran and apixaban-induced coagulopathy using idarucizumab, fibrinogen, and prothrombin complex concentrate: A case report

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ABSTRACT

This case report examines the combined use of fibrinogen concentrate, four-factor prothrombin complex concentrate (PCC), and idarucizumab, a specific antidote for dabigatran, to reverse the anticoagulant effects of dabigatran and apixaban-induced coagulopathy. An 86-year-old patient, receiving apixaban therapy, presented to the Emergency Department after intentionally ingesting 50 tablets of dabigatran. The combination therapy contributed to the rapid normalization of coagulation parameters and stabilization of the patient's clinical status without subsequent thromboembolic complications. This case adds to the limited evidence on the effectiveness and safety of combining PCC with idarucizumab in cases of multiple anticoagulant intoxication.

1. Introduction

Direct oral anticoagulants (DOACs) have significantly transformed anticoagulation therapy, offering a safer and more convenient alternative to traditional vitamin K antagonists for the prevention and treatment of various clinical conditions [1,2]. Nonetheless, bleeding complications pose a critical challenge in clinical management [3].

Effective management of DOAC-induced bleeding necessitates the prompt reactivation of the coagulation cascade while ensuring hemodynamic stability, thereby mitigating both hemorrhagic and thromboembolic risks. Idarucizumab, a humanized monoclonal antibody fragment (Fab), serves as a targeted reversal agent for dabigatran, whereas prothrombin complex concentrate (PCC) or andexanet alfa may be used for other DOACs [4,5]. To the best of our knowledge, clinical reports on the combined use of idarucizumab and PCC are lacking, with few preclinical studies analyzing their synergistic potential in the treatment of dabigatran-induced bleeding and restoring coagulation functionality [6,7]. Additionally, massive combined DOAC intoxication is rare, and emergency treatment is not addressed by current guidelines [1,7,8].

This case report describes the clinical reasoning that led to the practical application of dabigatran and PCC combined therapy in

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managing dabigatran intoxication.

2. Case report

We present the case of an 86-year-old Caucasian female who was admitted to the Emergency Department (ED) of the Teaching Hospital of Verona following the intentional ingestion of 50 tablets of dabigatran, which belonged to her husband, as part of a self-harm attempt. She arrived at the hospital at 5:30 p.m. and was assessed by an emergency physician within 20 min. The overdose had occurred around 1:00 p.m., and her last dose of apixaban had been taken earlier that morning. Approximately thirty minutes prior to her arrival at the hospital, the patient experienced a fall and was promptly transported to the ED.

The patient's medical history included several episodes of superficial venous thrombosis three years prior, for which she initiated treatment with apixaban 2.5 mg twice daily (Table 1). Additionally, she had a history of non-critical carotid atherosclerosis, hypertension, and frequent falls with previous vertebral fractures. Upon arrival, the patient was conscious with stable vital signs (afebrile, blood pressure 130/65 mmHg, heart rate 61 bpm, respiratory rate 16/min, and SpO_2 of 96 % in room air). Physical examination revealed contusive trauma to the right shoulder (subsequently diagnosed as a rupture of the supraspinatus tendon) and right hip, and extensive hematoma in the bilateral lumbar region, as well as the right thigh and leg. There was no reported pain, no motor disturbances, and no immediate signs of external bleeding; however, the patient's mental status and the risk of internal bleeding warranted further investigation. A comprehensive polytrauma computed tomography (CT) scan was performed, revealing an oval hematoma measuring 6 cm × 7 cm in the right gluteal region, with a small focus of active arterial extravasation in the post-contrast phase. Initial laboratory tests showed an International Normalized Ratio (INR) of 17.34 and a non-measurable partial thromboplastin time (PTT) ratio, both indicative of significant coagulopathy. Hemoglobin was measured at 112 g/L, and renal function was within normal limits (Table 2). Given the severity of the coagulation disturbance induced by the dabigatran overdose, the local Poison Control Center recommended an immediate reversal protocol. The patient was administered idarucizumab 5 g (2 vials of 2.5 mg/mL each) in a 250 mL 5 % glucose solution over 1 hour, followed by the administration of 2 g of fibrinogen concentrate. In this case, although more than 2 h had likely elapsed since the ingestion (based on an estimated but unverified timeline), we decided to proceed with supportive measures due to the substantial number of tablets ingested. These included gastric lavage followed by the administration of 100 g of activated charcoal via a nasogastric tube to reduce further dabigatran absorption, performed within 15 min of the patient's arrival at the ED. Additionally, 1 g of amoxicillin-clavulanate was administered prophylactically to prevent potential infections. Subsequently, 150 g of polyethylene glycol in 1 L of saline was provided for bowel cleansing.

Despite initial improvement in coagulation parameters (INR of 13.54 and PTT ratio of 7.44), an increase in the size of the gluteal hematoma and a decrease in hemoglobin levels to 82 g/L were observed (Table 2). This prompted the additional administration of four-factor PCC at 30 U/kg over 30 minutes, with a repeat dose planned if INR remained above 6 since we suspected a synergistic effect of dabigatran and apixaban on the coagulation cascade. The patient's coagulation parameters significantly improved by the following morning, with INR and PTT ratios normalizing to 3.22 and 3.71, respectively (Table 2). The hematoma and hemoglobin levels remained stable, facilitating a transition to inpatient care (geriatric ward) for further monitoring and recovery. Throughout the treatment and observation period in the geriatric ward, the patient showed no clinical or eco/radiographic signs of thromboembolic events, a potential complication of concern of the administered therapy. At discharge, part of the antihypertensive therapy was suspended and antidepressant therapy was initiated (please see Table 1 for full therapy at discharge). At one year of follow-up, the patient had no thromboembolic or hemorrhagic episodes.

3. Discussion

The management of dabigatran-induced coagulopathy, particularly in overdose scenarios, poses significant clinical challenges. This case report highlights the potential of combining idarucizumab with fibrinogen concentrate and four-factor PCC, a strategy, to our knowledge, not documented in the current medical literature. While idarucizumab is a well-established antidote for dabigatran reversal, the role of PCC in this context remains less clear [9–11]. PCC alone might be able to reverse dabigatran-induced anticoagulation in a dose-dependent manner, increasing the concentrations of several coagulation factors, including prothrombin, which has a half-life of 60–72 hours [11,12]. Consequently, thrombin generation may be enhanced for several days following the use of PCC to treat bleeding, potentially increasing the risk of thromboembolic events. Therefore, the lack of high-level evidence regarding the

Table 1
Pharmacological therapies at Emergency Department admission and at discharge.

ED admission therapy	Geriatric ward discharge therapy
Bisoprolol 1.25 mg BID	Bisoprolol 1.25 mg BID
Apixaban 2.5 mg BID	Apixaban 2.5 mg BID
Amiloride 5 mg QD	Mirtazapine 15 mg QD
Hydrochlorothiazide 50 mg QD	Lansoprazole 30 mg QD
	Potassium chloride retard 600 mg QD
	Alprazolam 0.75 mg/mL 5 drops PRN
	Iron 30 mg QD (for 30 days)

Abbreviations: BID = Twice a day; ED = Emergency Department; PRN = As needed; QD = Once a day.

Table 2
Laboratory tests of interest during the Emergency Department and hospital stay.

	Day 1 (ED[a])	Day 1 (ED)[b]	Day 1 (ED)[c]	Day 2 (ED)	Day 4 (GW)	Day 15[d] (GW)	Reference values	Unit of measurement
Hemoglobin	112	103	89	82	96	91	120–140	g/L
Hematocrit	0.354	0.325	0.271	0.248	0.287	0.286	0.350–0.470	L/L
PT	17.34	13.54	6.80	3.22	1.14	1.06	0.80–1.17	INR
PTT	Does not clot	7.44	5.46	3.71	0.67	0.77	0.80–1.20	Ratio
Fibrinogen[e]	–	0.55	0.84	2.28	–	–	2–4	g/L
Antithrombin[f]	–	99	–	–	–	–	70–130	%
D-dimer	–	871	–	–	–	–	2–500	µg/L
WBC	11.24	–	–	12.22	10.05	7.42	4.30–10.00	10^9/L
Glucose	7.3	6.2	7.8	6.0	4.6	4.2	3.3–5.5	mmol/L
ALT	22	–	–	–	18	16	5–45	U/L
CRP	6	–	–	15	60	38	0–5	mg/L
Sodium	140	134	132	137	138	144	135–145	mmol/L
Potassium	3.63	4.2	2.9	3.29	3.03	3.31	3.40–4.80	mmol/L
Serum creatinine	85	–	–	64	63	57	44–106	µmol/L
eCrCl[g]	47.7	–	–	63.4	64.3	71.2	80–125	mL/min
Dabigatran[h]	Not measurable	4900	3320	–	–	–	0[j]	ng/mL
Apixaban[i]	226.1	–	–	–	–	–	32-97[k]	ng/mL

Abbreviations: ALT = Alanine transaminase; CRP = C-reactive protein; ED = Emergency Department; eCrCl = Creatinine Clearance estimate; GW = Geriatric ward; INR = International normalized ratio; PT = Prothrombin time; PTT = Partial thromboplastin time; WBC = White blood count.

[a] Time zero.
[b] Three hours after the ED admission.
[c] Eight hours after the ED admission.
[d] Day of hospital discharge.
[e] Clauss method (thrombin-based clotting assay).
[f] Chromogenic anti-Xa assay for antithrombin activity.
[g] Using Cockcroft-Gault equation.
[h] Diluted Thrombin Time (dTT).
[i] Chromogenic anti-Xa assay calibrated for apixaban.
[j] Based on the patient's medication regimen.
[k] Therapeutic levels, according to our laboratory's recommendations.

indication for use and dosing of PCC in dabigatran reversal suggests that it should be considered a second-line choice after idarucizumab, with the minimum effective dose being used if necessary [7,8,11]. However, in this case, chronic accumulation of apixaban was also suspected, since not taken in excess according to the patient's declaration, for diverse reasons. Primarily, supratherapeutic concentrations of apixaban were detected using a chromogenic anti-Xa assay. Secondly, the massive elevation in INR (17.34) - to our knowledge, never described before in isolated dabigatran overdose - suggested a possible synergistic effect between dabigatran and apixaban. Lastly, the increase in the size of the gluteal hematoma and the decrease in hemoglobin levels to 82 g/L after idarucizumab administration further supported this suspicion. Therefore, the administration of a second dose of idarucizumab was postponed, and the clinical decision-making for the four-factor PCC choice was guided by several objectives a) restoring coagulation functionality, b) primarily reversing dabigatran effect but taking into account also apixaban overdose (as factor Xa inhibitor not addressed by idarucizumab), and c) a second-dose of idarucizumab would have been, probably, not sufficient based on our knowledge [13,14]. This approach appears to have contributed to the arrest of bleeding and stabilization of the patient. However, the concern for thromboembolic events post-reversal is a risk that warrants further exploration. Moreover, a limitation of our report is also the inability to monitor the natural clearance of the drugs, as testing for dabigatran and apixaban was unfortunately discontinued in the geriatric ward.

4. Conclusion

This case report suggests that the concomitant administration of idarucizumab, fibrinogen concentrate, and four-factor PCC (an approach not currently described in reversal guidelines) might be safe in terms of thromboembolic risks in scenarios involving combined dabigatran and apixaban overdose. However, further studies are warranted to establish clear emergency toxicology guidelines on this topic.

CRediT authorship contribution statement

Elia Morando: Writing – original draft, Data curation, Conceptualization. **Lorenzo Losso:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Massimo Carollo:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Ilaria Costantini:** Writing – review & editing, Methodology, Data curation. **Matilde Bacchion:** Writing –

review & editing. **Lucia Drezza:** Writing – review & editing. **Giorgio Ricci:** Writing – review & editing, Validation, Supervision, Data curation, Conceptualization.

Consent for publication

Informed consent was obtained in accordance with the Italian law.

Data availability

Anonymized data will be made available upon reasonable request and with the provision of additional informed consent from the patient.

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Declaration of competing interest

None.

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