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CASE REPORT
Other

Idarucizumab to revert the anticoagulant effect of dabigatran in traumatic acute subdural haematoma: a case report of first use in Latin America

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Background Direct oral anticoagulants (DOAC) are an attractive alternative over vitamin K antagonists. They have several advantages in primary and secondary prevention of thromboembolisms due to atrial fibrillation, as well as in prevention and treatment of thromboembolic venous disease. They have fast onset action, do not need laboratory controls in patients with normal renal function, and they have practically no interference with the patient's diet or medications. The strongest objection to their use was the lack of reversal agents that could be used in case of life-threatening haemorrhage or the need for emergency surgery. Dabigatran was the first DOAC to have its own specific reversal agent: idarucizumab, a monoclonal antibody.

Case summary We report here the case of a patient undergoing treatment with dabigatran that suffered an expansive subdural haematoma secondary to a cranial injury. The condition was life-threatening and required emergency surgery. Anticoagulation was successfully reversed with idarucizumab.

Discussion Emergency surgery in patients in treatment with DOAC is associated with an increased risk of bleeding. With the use of a specific antidote to block the action of the anticoagulant, as in the case of idarucizumab with dabigatran, the risk of complications during and after emergency surgery is reduced. This is the first case report with which the successful use of idarucizumab in Latin America is documented.

Keywords Oral anticoagulant • Dabigatran • Idarucizumab • Case report

Learning points

- The use of idarucizumab in a patient with renal failure is safe and effective.
- In patients on dabigatran with bleeding complications, idarucizumab can facilitate successful emergency surgery.

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Introduction

Direct oral anticoagulants (DOAC) are an attractive alternative over vitamin K antagonists. They have several advantages in primary and secondary prevention of thromboembolisms due to atrial fibrillation, as well as in prevention and treatment of thromboembolic venous disease. They have fast onset action, do not need laboratory controls in patients with normal renal function, and they have practically no interference with the patient's diet or medications.[1] The strongest objection to their use was the lack of reversal agents that could be used in case of life-threatening haemorrhage or the need for emergency surgery. Dabigatran was the first DOAC to have its own specific reversal agent: idarucizumab, a monoclonal antibody.[2] This therapeutic tool allows to safely and effectively reverse the anticoagulant effect of dabigatran in case of emergencies, as is the case presented here.

Case presentation

A 92-year-old woman with non-valvular atrial fibrillation on 110 mg twice a day of dabigatran (Pradaxar®) came to the emergency room after suffering a fall from her own height. In addition to her current condition, she had a history of asymptomatic hyperuricaemia, systemic arterial hypertension, and hypothyroidism. As she fell, she hit the ciliary region of the skull but did not suffer from convulsions, loss of consciousness or abnormalities in speech or movements. During the initial assessment, the patient was awake and speaking fluidly. Her blood pressure was 140/100 mmHg, and her heart rate was 90 b.p.m., with atrial fibrillation, jugular engorgement, and peripheral oedema. She had no signs of lateralization, and swelling in the region of trauma. Her clinical condition suddenly deteriorated, starting with hemiparesis, and a drop in Glasgow score from 15 to 11 within minutes. Her CHA_2-DS_2-VAS_C score was 4 [hypertension (1), age ≥75 years old (2), and female gender (1)], and her HAS-BLED score was 4 [hypertension (1), abnormal renal function (1), age ≥65 years-old (1), and drugs or alcohol (1)].

Blood tests on admission showed slightly altered kidney function [creatinine clearance 27 mL/min (reference value 88–128), prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) times, and 850 ng/mL of dabigatran (expected range 52–275)] (*Table 1*). Computed tomography (CT) of the head showed a large right-sided subdural haematoma, with mass effect and displacement of the median line (11 mm) inducing uncal and subfalcine herniation (*Figure 1A*). A diagnosis of traumatic acute subdural haematoma was made which required emergency surgical decompression.

The patient's last dose of dabigatran had been taken 9 h prior to admission so it was decided to administer idarucizumab (Praxbind®), 5 g as a single intravenous bolus. Seven minutes after administration of idarucizumab blood tests showed significant reduction in aPTT and PT times, and dabigatran plasma levels were <15 ng/mL (*Table 1*). The patient underwent decompressive craniotomy after the administration of idarucizumab; the surgery was performed without complications, and a 160 mL haematoma was drained. The drug was well tolerated with no haemorrhagic or procoagulatory complications. Her post-operative course was uncomplicated, and 24 h after surgery, the patient was in a clear recovery, conscious, without motor deficit, breathing on her own and starting oral fluids (*Figure 2*).

A follow-up CT after surgery showed complete resolution of the subdural haematoma, with no signs of displacement or herniation (*Figure 1B*). To reduce the risk of stroke (the patient had high-risk value of Caprini score), anticoagulant therapy with dabigatran was suspended. At follow-up 2 weeks post-surgery, the patient was neurologically intact with no residual deficits.

Timeline

Prior to presentation	Non-valvular atrial fibrillation Dabigatran (Pradaxar®) 110 mg twice a day Hyperuricaemia and systemic arterial hypertension
9 h prior to presentation	Last dose of dabigatran
Upon presentation to the emergency room	Patient was awake and speaking fluidly Blood hypertension Tachycardia with atrial fibrillation Swelling in the right ciliary region of the skull Glasgow score dropping from 15 to 11 within minutes Slightly altered kidney function Prolonged activated partial thromboplastin time, prothrombin time, and International normalized ratio times Computed tomography of the head showed a large right-sided subdural haematoma, with mass effect and displacement of the median line
4 h post-admission	Idarucizumab administration
4 h and 10 min after admission	Normal haemostasis
15 h post-admission	Craniotomy is done
24 h post-surgery	Patient stable at hospital room
2 weeks post-surgery	Patient neurologically intact with no residual deficits

Discussion

Idarucizumab is a humanized monoclonal antibody with very high affinity for dabigatran, roughly 300 times higher than the affinity of the latter for thrombin.[1] Upon binding to dabigatran, idarucizumab inactivates it, reversing its anticoagulant effect. Idarucizumab's main indications are surgery or emergency

Table 1 Blood test to evaluate coagulation, kidney function, and dabigatran plasma levels (pre- and post-idarucizumab)

Test (units)	On admission	7 min after idarucizumab	Reference values
Activated partial thromboplastin time (aPTT) (s)	84.1	31.7	25–35
Prothrombin time (PT) (s)	37.7	13.4	11–14
International normalized ratio (INR) (s)	3.3	1.8	<1.5
Platelets (count per μL)	285 000	ND	150 000–400 000
Haemoglobin (mg/dL)	15.9	ND	12–16
Creatinine (mg/dL)	1.38	ND	1.2
Creatinine clearance (mL/min)	27	ND	88–128
Blood urea nitrogen (BUN) (mg/dL)	27.3	ND	7–20
Dabigatran plasma level (ng/mL)	850	<15	133 (52–275)[a]

ND, not determined.
[a]Values are 2-h post-dose plasma concentration at steady state, median (10th and 90th percentiles) are shown; data from Ref.[12]

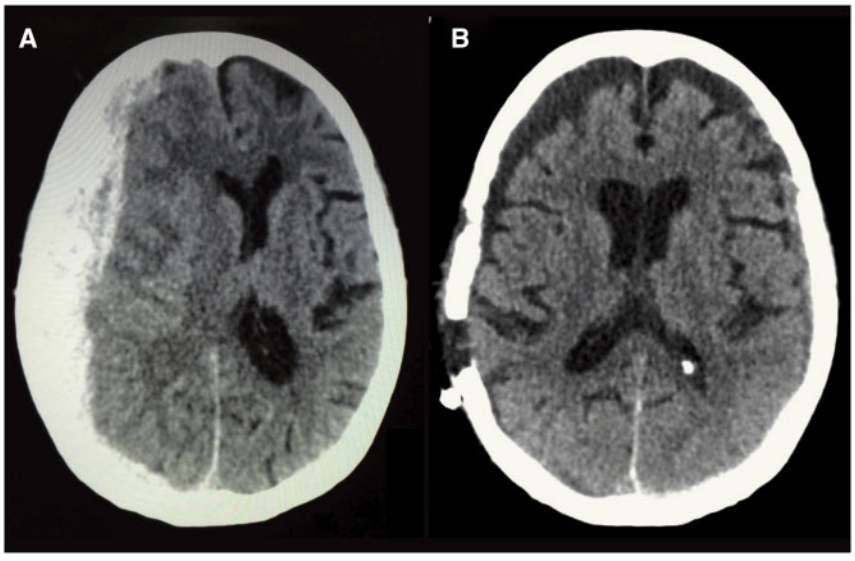


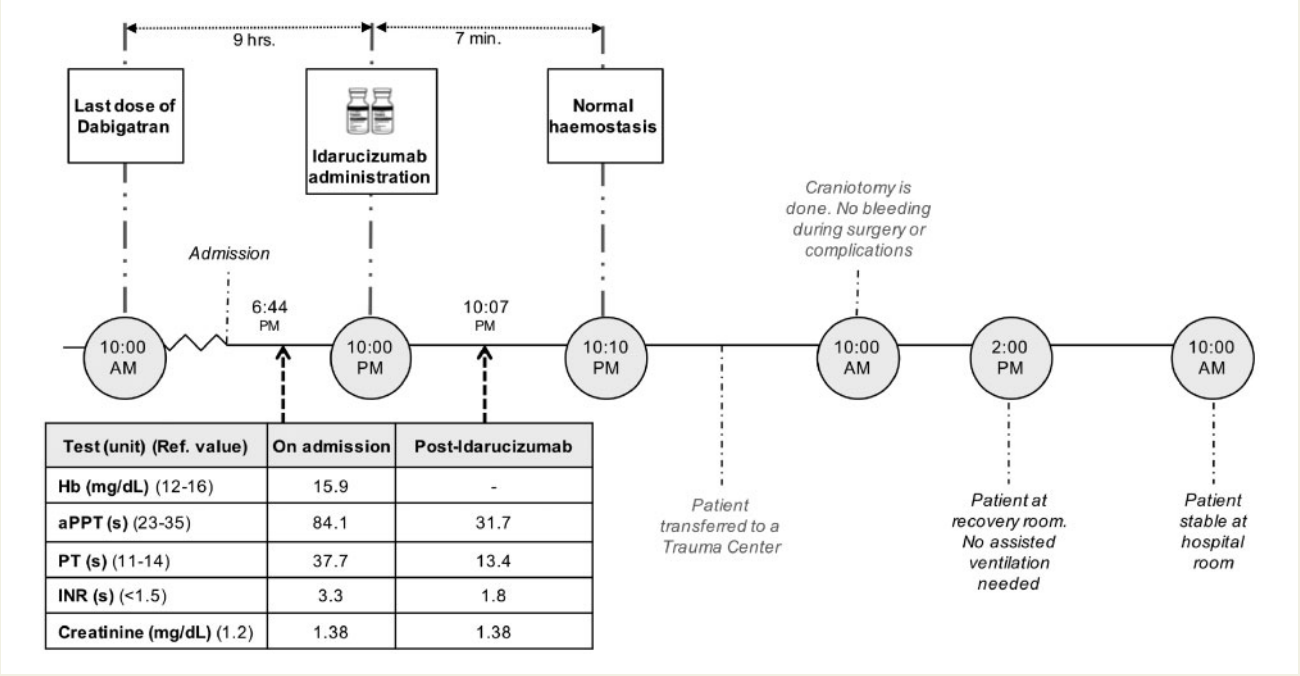
Figure 1 Computed tomographic scan of the patient taken at admission (*A*); and a control computed tomography after decompressive craniotomy (*B*) (see text for description).

procedures in patients using dabigatran as oral anticoagulant, patients with acute life-threatening bleeding,[2] or patients with accidental dabigatran overdose.[3]

Dabigatran was the first direct oral anticoagulants to have its own specific reversal agent: idarucizumab, a monoclonal antibody, and the clinical experience of use grow every day. Up-to-now, idarucizumab has been approved in more than 30 countries (including Mexico) to be used as an antidote to the anticoagulant effect of dabigatran, and reports of its successful use are becoming more and more frequent.[4,5] Recently, Andexanet Alfa, a recombinant modified factor Xa protein, has been approved in the United States and Europe to reverse the action of apixaban and rivaroxaban.[6,7] To the best of our knowledge, this is the first report of the efficacious use of idarucizumab to successfully reverse the anticoagulant effect of dabigatran in a patient with a main indication in Latin America.

Because of its high specificity, use of idarucizumab has been relatively low, however, clinical experience in controlled studies,[2,8] and first uses in real-life conditions have shown that it has an adequate safety profile, which is only complemented by the benefits obtained by its use.[9]

There has been some concern regarding emergence of anti-idarucizumab antibodies as a result of therapy which could inactivate the molecule and have a negative impact on future drug efficacy. However, the presence of such antibodies as a result of treatment or



Test (unit) (Ref. value)	On admission	Post-Idarucizumab
Hb (mg/dL) (12-16)	15.9	-
aPPT (s) (23-35)	84.1	31.7
PT (s) (11-14)	37.7	13.4
INR (s) (<1.5)	3.3	1.8
Creatinine (mg/dL) (1.2)	1.38	1.38

Figure 2 Schematic timeline with the main events of the clinical case.

as a pre-existent condition have been shown not to affect the pharmacodynamics or pharmacokinetics of idarucizumab, even in patients with impaired renal function, such as the one reported here.[10]

Dabigatran is excreted mainly through urine and patients with renal failure accumulate the drug which is why it is contraindicated when creatinine clearance drops below 30 mL/min. Accidental overdose while receiving normal doses of dabigatran has been reported in patients with impaired renal function.[11] The use of idarucizumab in our patient with renal failure was safe and effective. As more evidence of the use of idarucizumab is generated in patients with renal insufficiency and abnormal levels of dabigatran, a general recommendation may be issued for its use in cases of overdose or haemorrhagic emergencies.

Surgery in patients taking anticoagulants is fraught with risk, particularly when the anticoagulant therapy cannot be discontinued in a timely fashion, as in the case of emergencies; the use of a treatment that counteracts the effect of the anticoagulant medication is a useful alternative for these patients.

Conclusion

This case report highlights the successful use of idarucizumab in a 92-year-old woman taking dabigatran, with intracranial haemorrhage (traumatic acute subdural haematoma) that required emergency surgery and presented with moderate renal dysfunction and multiple pre-existing conditions.

Lead author biography

Dr Raúl Izaguirre Ávila is a specialist in Internal Medicine and Haematology. He works at the National Institute of Cardiology in Mexico City as Head of the Department of Haematology, which includes the Anticoagulation Clinic and the Thrombosis, Fibrinolysis and Platelet Function Laboratory. He is Professor of Haematology and the Thrombosis and Haemostasis Course at the Faculty of Medicine of the National Autonomous University of Mexico.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: The authors declare that Boehringer-Ingelheim Mexico gave unrestricted support for publication.

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