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Idarucizumab for dabigatran overdose

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ABSTRACT

Context: An overdose of oral anticoagulants represents a challenging scenario for emergency physicians. Dabigatran, an oral direct thrombin inhibitor, is increasingly used in place of warfarin. The lack of an antidote is a concern in patients who overdose on dabigatran, even though the drug can be eliminated with hemodialysis. Idarucizumab is an antibody fragment that binds dabigatran with high affinity. It reverses the anticoagulant effect of dabigatran within minutes and is approved for the reversal of dabigatran during emergency situations.

Case details: We describe the use of idarucizumab in the management of a 68-year-old woman who was taking dabigatran 150 mg twice daily and ingested 125 capsules. Despite gastric lavage and administration of activated charcoal within two hours of drug intake, the activated partial thromboplastin time (aPTT) from 75 to 26 s, PT from 26 to 11 s and diluted thrombin time from 92 to 27 s. The initially planned emergency hemodialysis was canceled.

Discussion: This case highlights the potential use of idarucizumab for the management of massive dabigatran overdoses.

Introduction

Dabigatran, an oral direct thrombin inhibitor, is used in place of vitamin K antagonists for stroke prevention in patients with nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism.[^1] An overdose of dabigatran may prompt bleeding and constitutes a challenging clinical problem in the emergency department.

Different strategies are advocated for the management of an overdose. Oral activated charcoal will prevent the absorption of recently ingested drug.[^2,^3] The relatively short half-life of dabigatran (12–17h) in patients with normal renal function supports a conservative approach in the absence of active bleeding.[^2,^3] However, in case of bleeding or massive overdose, hemodialysis has been recommended,[^4] but it requires the insertion of a large bore catheter in an anticoagulated patient. Furthermore, dabigatran removal with this technique is slow and incomplete.[^5,^6] In a reported case series, dabigatran concentrations decreased by 52–77% during hemodialysis.[^7] However, in many cases, a rebound effect was observed.[^5,^7] The administration of coagulation factors, such as three- or four-factor prothrombin complex concentrates (PCCs) or activated PCCs (aPCCs), may support hemostasis in case of bleeding. High doses of (a)PCCs are recommended to counteract the anticoagulant effect of dabigatran.[^2–^4] The administration of (activated) coagulation factors is associated with an increased risk of thromboembolic events, which should be taken into account especially in the absence of active bleeding.[^3] The evidence base for the use of these nonspecific prohemostatic interventions for the reversal of the anticoagulant effect of dabigatran is based on partly contradictory animal data, ex vivo studies and case reports.[^2–^4,^8]

Idarucizumab is a specific reversal agent for dabigatran that was recently approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). We describe the use of idarucizumab to reverse the anticoagulant effect of dabigatran in a patient with massive overdose.

Case details

This 68-year-old female had atrial fibrillation, for which she took sotalol and dabigatran (150 mg bid), and depression treated with citalopram and topiramate. She had a history of repeated suicide attempts, including an overdose of warfarin. The patient was hospitalized after calling emergency services, reporting that she had overdosed on dabigatran. She admitted taking all her remaining dabigatran capsules, a total of 125 capsules of 150 mg, as verified by the ambulance personnel.

On presentation, her blood pressure was 139/78 mmHg and her heart rate was 63 per minute and regular. There was...
no overt bleeding. Gastric lavage was performed within two hours of dabigatran ingestion and retrieved a number of dabigatran capsules and no other medications. Activated charcoal (2 × 50 g) was administered to limit residual dabigatran absorption. Intravenous saline infusion at a rate of 167 mL/h was given to maintain diuresis, and a proton pump inhibitor was administered (omeprazole 40 mg). The patient was then transferred to a tertiary care facility for emergency hemodialysis.

On arrival five hours after dabigatran intake, aPTT was 75 s (normal 25–37 s) and PT was 26 s (normal 9–12.5 s). Renal function was normal (creatinine 0.58 mg/dL, normal 0.30–1.20 mg/dL). The plasma dabigatran concentration, as assessed by the diluted thrombin time (dTT), was 735 ng/ml. Other laboratory results were normal, except for an elevated ethanol level (1.33 g/L).

Because emergency hemodialysis requires the placement of a large bore catheter, the patient was considered eligible for the RE-VERSE AD trial, a cohort study of idarucizumab for dabigatran reversal in patients with serious bleeding or who require an emergency procedure. After giving written informed consent, she was given intravenous idarucizumab in the form of two 2.5 g boluses administered 15 min apart, as specified in the RE-VERSE AD protocol. Immediately after the first bolus, the aPTT and PT were 26 s and 11 s, respectively, consistent with complete reversal. These tests remained normal after the second idarucizumab bolus and for 24 h thereafter. As illustrated in Figure 1, normalization of the aPTT coincided with normalization of the diluted thrombin time (dTT), a specific coagulation test to quantitatively assess the anticoagulant activity of dabigatran. Unbound dabigatran concentration, assessed by liquid chromatography,[9] dropped from 643 ng/mL to <1 ng/mL. Dialysis was subsequently canceled, because there was no bleeding and the coagulation tests normalized with idarucizumab administration.

The patient was discharged home with psychiatric follow-up. Dabigatran administration was resumed four days after the overdose. One year later, the patient is doing well and remains on dabigatran.

**Discussion**

The availability of idarucizumab, a specific reversal agent for dabigatran, may facilitate the management of patients in emergency situations. Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with high affinity and has no intrinsic procoagulant activity. Idarucizumab reversed the anticoagulant activity of dabigatran in preclinical bleeding models and in healthy volunteers.[4,8–11] The interim results of the phase-III RE-VERSE AD study showed that idarucizumab was able to neutralize dabigatran within minutes in patients with serious bleeding or emergency procedures.[12]

We describe the effect of idarucizumab in a patient who overdosed on dabigatran. In this patient, who presented shortly after the overdose, gastric lavage and activated charcoal were used in agreement with guidelines.[4] Still, dabigatran anticoagulant activity remained high as assessed by coagulation tests.

Standard coagulation tests, such as aPTT, can provide qualitative information on the anticoagulant activity of dabigatran. Quantitative measurement of dabigatran can be performed with diluted thrombin time (dTT), which is however not readily available in most emergency settings. The initial plasma concentration of dabigatran, as assessed in our patient by dTT (and confirmed by liquid chromatography mass spectrometry) was >600 ng/mL. In comparison, in patients on dabigatran 150 mg bid in the RE-LY study, the median trough plasma concentrations at steady state were 93 ng/mL (10th–90th percentile 39.8–215 ng/mL) and median peak plasma concentrations 184 ng/mL (10th–90th percentile 74.3–383 ng/mL). No clinical anticoagulant effect is expected at plasma concentrations below 20 ng/mL.[13]
Because of the massive overdose, the patient was referred for hemodialysis to accelerate clearance of dabigatran. In the context of the ongoing RE-VERSE AD study, we opted to first treat the patient with idarucizumab. In this overdose case, we observed a prompt correction of dabigatran anticoagulation, and hemodialysis was canceled. No bleeding events occurred, and additional measures to support hemostasis were not needed.

Whereas no measurable levels of dabigatran were detected in the four hours after administration of idarucizumab, low levels of unbound dabigatran were measured thereafter (Figure 1). This is probably explained by the high body load of dabigatran in this patient, the continued absorption, the short half-life of idarucizumab and the redistribution of extravascular dabigatran to the vascular compartment. The RE-VERSE AD trial evaluates a 5 g dose of idarucizumab, calculated to reverse the dabigatran body loads that correspond to the 99th percentile of dabigatran levels in the RE-LY study.[12,13] Hence, for massive overdoses, repeat dosing can be considered, guided by clinical and laboratory parameters.[14]

Other reversal agents for novel oral anticoagulants currently under development include andexanet, a modified factor Xa that neutralizes factor Xa inhibitors and ciraparantag or PEA977, which may bind both dabigatran, factor Xa inhibitors and enoxaparin.[2,3,15]

Conclusion

In conclusion, this case report demonstrates a prompt reversal of the anticoagulant effect after the administration of idarucizumab in a massive dabigatran overdose. The availability of reversal agents such as idarucizumab may facilitate the management of these challenging cases in the emergency care setting.

Disclosure statement

These authors have no conflicts of interest to declare.

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