Case Report

Idarucizumab as Antidote to Intracerebral Hemorrhage under Treatment with Dabigatran

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Keywords

Intracerebral hemorrhage · Anticoagulant · Dabigatran · Idarucizumab · Antidote · Stroke

Abstract

Background and Purpose: Non-vitamin K anticoagulants (NOAC) such as dabigatran have become important therapeutic options for the prevention of stroke. Until recently, there were only nonspecific agents to reverse their anticoagulant effects in a case of emergency. Idarucizumab, an antibody fragment targeting dabigatran, is the first specific antidote for a NOAC to be approved, but real-world experience is limited. **Methods:** We report two cases of patients on dabigatran with acute intracerebral hemorrhage who received idarucizumab. **Results:** In both cases, idarucizumab promptly reversed the anticoagulant effect of dabigatran and there was no hematoma expansion in follow-up imaging. **Conclusions:** In addition to clinical and preclinical studies, our cases add to the experience regarding the safety and efficacy of idarucizumab. They show that idarucizumab may be an important safety option for patients on dabigatran in emergency situations.

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In 2010, the FDA approved the direct thrombin inhibitor dabigatran (Pradaxa) for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Thereafter, factor Xa inhibitors (rivaroxaban, apixaban, and recently edoxaban) were also approved. Both factor IIa and factor Xa inhibitors display the newly formed class of non-vitamin K oral anticoagulants (NOAC). Due to the lack of specific antidotes to rapidly reverse the anticoagulant effect of NOACs, in cases of medical emergency, the use of nonspecific agents with limited efficacy is still the method of choice for factor Xa inhibitors, where specific reversal agents are still in development.

Idarucizumab (Praxbind), the first novel antidote for a NOAC specifically antagonizing dabigatran, was recently approved by the US FDA in October and by the EMA in November 2015. We report two cases of patients on dabigatran with intracerebral hemorrhage who received idarucizumab.

Case 1

A 74-year-old woman was admitted with an acute onset of aphasia and right-sided hemiparesis (NIHSS on admission 18). She was last seen normal about 3 h earlier. Her medical history included atrial fibrillation, for which she had taken dabigatran 110 mg b.i.d. (the last dose about 9 h earlier). Further concomitant diseases included coronary heart disease and arterial hypertension. Blood pressure on admission was 180/80 mm Hg but rose subsequently to 230/120 mm Hg. CT on admission (Fig. 1) showed a large ($6.2 \times 3.9 \times 5.8$ cm) lobar intracerebral hemorrhage in the left hemisphere. Laboratory findings showed very mildly elevated activated partial thromboplastin time (aPTT) of 30.3 s (normal range 15–30 s) and a moderately elevated thrombin time (TT) of 81.6 s (normal range 17–24 s). Creatinine was slightly elevated at 103.8 $\mu\text{mol/L}$ (normal range 58.1–95.92 $\mu\text{mol/L}$), and creatinine clearance estimated according to the formula of Cockcroft and Gault was 66.8 mL/min. Dabigatran concentration on admission was measured by the Hemoclot® test and showed a result below the sensitivity range of the test (50 ng/mL). Idarucizumab was administered 45 min after arrival in the ER; when measured 3 h later, aPTT and TT were in the normal range (23.9 and 20.6 s, respectively). The patient was admitted to our stroke unit. Elevated blood pressure was treated aggressively to a target of below 140 mm Hg systolic BP. Further diagnostics did not reveal any cause of hemorrhage other than elevated blood pressure and anticoagulant treatment. During the clinical workup, no hematoma growth was detected. Sixteen days after admission, she was transferred to a rehabilitation unit. By that time, the aphasia had partially receded, but hemiparesis was still pronounced (NIHSS 9).

Case 2

A 76-year-old patient was brought to the emergency room intubated due to progressive decrease of consciousness and left hemiparesis (NIHSS 32). He had a medical history of colon cancer, hypertension, and coronary heart disease. He was on dabigatran 110 mg b.i.d. due to atrial fibrillation since 2012. Upon arrival, he presented with a hypertensive crisis (>200 mm Hg systolic) and CT revealed a right subcortical hemorrhage ($3.7 \times 3.5 \times 2.0$ cm) with severe ventricular involvement (Fig. 2). Laboratory findings showed mildly elevated aPTT of 32.6 s (normal range 15–30 s) and a moderately elevated TT of 77.8 s (normal range 17–24 s); dabigatran concentration was not measured in this patient. Renal function was

normal (creatinine 96.8 $\mu\text{mol/L}$, gender- and age-specific normal range 71.3–126.7 $\mu\text{mol/L}$, estimated creatinine clearance 64.6 mL/min).

Elevated blood pressure was lowered aggressively, idarucizumab was administered 1 h after admission, and an external ventricular drain was inserted. The repeat measure of aPTT at 3 h after administration of idarucizumab showed a normal value (28.3 s). After 2 weeks on the intensive care unit, the patient was weaned and extubated. On follow-up in week 4, he had partially recovered; he was able to speak one-word sentences, but hemiparesis was still pronounced (NIHSS 22). Also this patient did not show evidence of hematoma expansion.

Discussion

Idarucizumab is a humanized antibody fragment specifically binding to dabigatran. It has been shown to rapidly reverse the anticoagulant effect of dabigatran in healthy volunteers [1], and also in the “The Reversal Effects of Idarucizumab on Active Dabigatran” (RE-VERSE AD) study, a phase 3, global, prospective cohort study (<http://www.clinicaltrials.gov;NCT02104947>) involving patients on dabigatran requiring urgent intervention/surgery or experiencing life-threatening or uncontrolled bleeding [2]. Preliminary data are promising [3]. Our cases demonstrate that the anticoagulant effect of dabigatran can be promptly and effectively counteracted by idarucizumab under “real world conditions”, thus adding a specific safety option for emergency situations for patients on dabigatran. Further research is required for a specific antidote for factor Xa inhibitors as the clinical development program is still ongoing and approval is pending; however, it would also add further safety to patients on factor Xa inhibitors. Both cases also demonstrate the role of hypertension in patients taking oral anticoagulation and the development of intracerebral hemorrhage.

The two presented cases are in line with a recent subgroup analysis of the RE-VERSE AD trial focusing on 18 patients with intracranial hemorrhage [4]. This subgroup analysis aimed at analyzing the ability of idarucizumab to reverse the anticoagulant effects of dabigatran on the basis of an interim analysis. The analysis showed a rapid reversal of the anticoagulant activity and a mortality rate similar to patients without intracerebral hemorrhage included in the RE-VERSE AD trial.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

C.C. Eschenfelder is an employee of Boehringer Ingelheim. The other authors report no conflicts.

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Fig. 1. Case 1. Upper row: CT scan on admission shows extensive left lobar hemorrhage and sulcal blood. Middle row: follow-up CT about 10 h after admission. The patient's head was tilted during the scan, and slices are chosen to best compare the extent of hemorrhage, which is stable. Bottom row: on follow-up CT at week 12, hemorrhage has completely resolved.

Fig. 2. Case 2. Upper row: CT scan on admission shows hemorrhage originating from the right basal ganglia with extensive ventricular involvement and enlargement of the lateral ventricles. Middle row: follow-up on day 2 after insertion of an external ventricular drain shows stable hematoma size. Bottom row: follow-up CT performed at week 3 with resorption of hemorrhage, perifocal edema, and reduction of space-occupying effect.