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Case Report

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Idarucizumab in the management of a severe upper gastrointestinal bleeding

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Abstract

Dabigatran, an oral direct thrombin inhibitor, is a non-AVK oral anticoagulant (NOACs) increasingly used for stroke prevention in patients with nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism. At the moment it is the only oral anticoagulant with a specific reversal agent, idarucizumab. Idarucizumab is a fully humanized Fab antibody fragment that binds specifically and with high affinity to dabigatran. It provides specific, immediate, complete, and sustained reversal of the anticoagulant effect of dabigatran. We describe the use of idarucizumab in the management of a 78 years old female patient in treatment with dabigatran 150 mg twice daily who is admitted to the hospital with the symptoms of acute upper gastrointestinal bleeding accompanied by hemorrhagic shock and secondary anaemia. The endoscopic exam reveals gastric erosions and a possible diffuse bleeding. Because the patient was on dabigatran it is decided that she will receive the specific reversal agent, idarucizumab beside the gastro-protective and haemostatic medication. Under haemostatic treatment and iso-group, iso-Rh blood transfusion the evolution was favorable. This case confirms in the clinical practice the efficacy and safety of idarucizumab in reversal of the anticoagulant effect of dabigatran.

Keywords: dabigatran, idarucizumab, NOACs, severe upper gastrointestinal bleeding, specific reversal agent

Introduction

Dabigatran, an oral direct thrombin inhibitor, is the first representative of a new class of oral anticoagulants, non-AVK oral anticoagulants (NOACs) increasingly used for stroke prevention in patients with nonvalvular atrial fibrillation and for the prevention and treatment of venous thromboembolism [1].

Dabigatran has ~7 years of experience, with long-term and real-world clinical safety data. Its major indication, stroke prevention in patients with AF, was based on the results of the RE-LY trial. This study in >18 000 patients was conducted without a specific reversal agent to dabigatran. RE-LY demonstrated, for the

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two randomized test doses, a favorable efficacy and safety profile of dabigatran compared with warfarin [2–4]. Importantly, both doses of dabigatran significantly reduced the risk of ICH, the most devastating complication of oral anticoagulant therapy.

A growing body of real-world experience is confirming the safety and efficacy profile of dabigatran [5–12]. The results from RE-LY were confirmed in an independent US FDA study involving 134414 Medicare patients. Among new users of anticoagulants, dabigatran demonstrated its favorable benefit–risk profile with a lower risk of ischaemic stroke, ICH, and death compared with warfarin [5]. Similar results have been observed in other US health insurance databases [6–7], and in a US Department of Defense database [8]. Likewise, in Europe, results from Danish observational studies showed that both doses of dabigatran were associated with significant reductions of ≥28% in the risk of any bleeding compared with warfarin [9]. More recent data from the Danish health databases show that the risks of death, any bleeding or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin [10]. Clinical practice data from the USA and Denmark have also shown safety benefits of dabigatran over rivaroxaban in terms of reduced risk of bleeding with a similar stroke-prevention effectiveness [11,12].

With appropriate risk identification, dose selection, and management of any bleeding episodes, dabigatran represents a favorable option for the prevention of stroke in patients with AF, and the treatment and prevention of VTE. It is important to note that all anticoagulant therapies must be administered in accordance with the guidance provided within their respective product label. Clinicians should carefully evaluate individual risk factors for patients and closely follow up patients, especially those who may be at increased risk of bleeding.

Despite this data, there is still a barrier to prescribing oral anticoagulation without the availability of a reversal agent, resulting in some patients with AF being denied the optimal protection against stroke and VTE [13].

Idarucizumab, a humanized Fab antibody fragment that binds specifically and with high affinity to dabigatran [14], has been approved in the United States and Europe for use in adult patients treated with dabigatran when rapid reversal of its anticoagulant effect is required. The efficacy and safety of idarucizumab (5 g administered intravenously as two 2.5 g/50 mL infusions or as a bolus injection) in dabigatran-treated patients with uncontrollable or life-threatening bleeding and in those requiring an urgent surgical or invasive procedure are being investigated in RE-VERSE AD, a global phase 3 prospective cohort study [15]. An interim analysis including the first 90 patients enrolled in the study (51 with serious bleeding and 39 requiring an urgent procedure) reported rapid, complete and sustained reversal of the anticoagulant effect of dabigatran following idarucizumab administration [16].

Clinical experience with the use of idarucizumab for urgent reversal of the anticoagulant effects of dabigatran is currently limited.

In the present article, we describe the use of idarucizumab to reverse the anticoagulant effect of dabigatran in a patient with a severe upper gastrointestinal bleeding.

Case Presentation

Female patient, aged 78, known with cardiovascular disease and permanent atrial fibrillation (CHA2DS2-VASc score=5, HAS-BLED score=2) in treatment with dabigatran presents to the hospital with the symptoms of a severe upper gastrointestinal bleeding (numerous melenic stools), hemorrhagic shock and secondary anaemia (Hgb 4.7). The patient has indication for chronic anticoagulation due to higher risk of cardioembolic events (15.26% annual event rate of stroke or systemic embolism)

The ECG exam reveals atrial fibrillation with a ventricular rate of 70 beats per minute, intermediate QRS axe, negative T wave V3–V6, without other lesional modifications.

The gastroscopy shows a stomach with erosions and a possible diffuse bleeding.

The thoracic radiography reveals aspects that confirm the pathological context of the patient: cardiomegaly, expanded inferior left heart border, calcified aortic knob and no active pleuropulmonary lesions.

The laboratory tests show a severe normochromic, normocytic anaemia (4, 8g/dl), mild neutrophilic leukocytosis and a normal number of thrombocytes. Clinical biochemistry reveals the presence of increased

BUN, mild hyperkalaemia and normal transaminase levels.

Taking into consideration the urgent character of the emergency situation, the patient receives besides the gastro-protective and haemostatic medication, a fast i.v. infusion of 5 g idarucizumab (2 vials of 2.5 g/50ml for 5–10 minutes each) with good tolerability and no immediate or late toxicity.

The coagulation parameters (aPTT) are rapidly normalized and in the context of the haemostatic treatment and iso-group, iso-Rh blood transfusion the evolution is favorable and the bleeding ceased in the same day.

The patient is discharged after 6 days of hospitalization with parenteral anticoagulant treatment until the next gastroscopy for the confirmation of bleeding cessation and the cure of the gastric lesions. Afterwards, oral anticoagulation with Pradaxa 110 mg twice daily will be taken into consideration.

Discussion

The recent ESC guidelines for the management of atrial fibrillation, presented during the European Society of Cardiology Congress in 2016, include in the management of severe bleedings as a therapeutic option for the patients treated with NOACs the specific reversal agents. Idarucizumab is currently the only specific reversal agent approved by EMA and FDA. In the REVERSE-AD clinical study, the administration of idarucizumab resulted in immediate, complete, and sustained reversal of dabigatran anticoagulation.

In the reported case, the administration of idarucizumab rapidly normalized the coagulation parameters (aPTT) and in the context of a multidisciplinary management of the bleeding had an important contribution in obtaining an adequate haemostasis in the same day.

Conclusion

The administration of idarucizumab in real life resulted in immediate, complete and sustained reversal of dabigatran anticoagulation, without side effects (no allergic reaction and excellent tolerability) for a female patient with a severe upper gastrointestinal bleeding and consequently the presented case confirms the results of the RE-VERSE AD study.

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