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Reversal of the Anticoagulation Effects of Dabigatran Etexilate by Idarucizumab in Three Patients Needing Urgent Surgical Intervention and One Case of Intravenous Thrombolysis in Ischaemic Stroke

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ABSTRACT

Objective: To describe the benefits of reversal of the anticoagulation effects of dabigatran etexilate in patients requiring urgent surgery or thrombolysis for ischaemic stroke.
Materials and methods: Four patients, treated with dabigatran etexilate and presenting with cholecystitis, tibial fracture, lower limb ischaemia and ischaemic stroke, respectively.
Results: Administration of idarucizumab normalized bleeding parameters and provided safe conditions for surgery and, in one case, successful thrombolysis of an ischaemic stroke.
Conclusion: The introduction of an effective reversal agent for dabigatran etexilate allows physicians perform surgery under conditions of normal coagulation and permits thrombolysis in patients with ischaemic stroke despite being treated with dabigatran etexilate.

LEARNING POINTS

- Novel oral anticoagulants (NOACs) are a safe alternative to warfarin to prevent ischaemic stroke.
- Ability to reverse the anticoagulant effects of NOACs could increase adherence to anticoagulation therapy, thereby decreasing the risk of ischaemic stroke.
- Reversal of the anticoagulant effect of dabigatran etexilate can improve the outcome in patients needing urgent surgery, intervention and thrombolysis.

KEYWORDS

Pradaxa; Praxbind; NOAC; surgery; thrombolysis

INTRODUCTION

Dabigatran etexilate (Pradaxa) is a specific thrombin inhibitor approved for stroke prevention in patients with non-valvular atrial fibrillation (AF) and for the treatment and prevention of pulmonary embolism (PE) and deep vein thrombosis (DVT)[1, 2].
Ever since the introduction of novel oral anticoagulants (NOACs), concern has been raised regarding the impossibility of reversing the

effects of these drugs. However, in October and November 2015, the Food and Drug Administration and the European Medicines Agency approved idarucizumab (Praxbind), a humanized monoclonal antibody fragment which reverses the anticoagulant effect of dabigatran within minutes of administration and thus is recommended as first-line treatment in patients with serious bleeding who require an urgent surgical procedure[3]. Patients with ongoing ischaemic stroke under dabigatran treatment also require acute reversal to enable thrombolysis with intravenous tissue plasminogen activator (tPA). Since its approval, idarucizumab has been used several times at the University Hospital in Malmö and here we present four of these cases where idarucizumab was used to enable optimal treatment of the patient.

CASE 1: Reversal of dabigatran etexilate for laparotomy

A 66-year-old man with hypertension, type 2 diabetes and AF on 150 mg dabigatran etexilate twice a day presented at the emergency department with abdominal pain. Initial clinical examination found evidence of cholecystitis, which was confirmed by ultrasonography later the same evening. The patient was subsequently admitted and surgery was planned for 24 hours after the last dose of dabigatran etexilate. However, the activated partial thromboplastin time (aPTT) on the day of surgery was 46, suggesting a residual anticoagulation effect. Laparoscopic surgery was commenced without idarucizumab because of a lack of knowledge of the drug by the attending surgeon. Due to extensive inflammation of the gallbladder and surrounding tissue and suboptimal control of bleeding, the procedure was converted into a laparotomy. However, this time idarucizumab was given before the procedure as the attending anaesthesiologist was aware of the possibility of reversing the effects of dabigatran etexilate. Intra-abdominal bleeding stopped and cholecystectomy was performed without complications. The patient recovered postoperatively in line with expectations.

CASE 2: Reversal of dabigatran etexilate for tPA

A 78-year-old woman with AF and on 150 mg dabigatran etexilate twice a day presented at the hospital 45 minutes after the onset of left-sided paralysis and ataxia. Initial examination showed a National Institutes of Health Stroke Scale (NIHSS) score of 11. A CT scan with angiographic and perfusion sequences revealed signs of ischaemia but no extractable thrombus. aPTT at admission was 49. Idarucizumab was administered with a second aPTT test showing complete reversal of anticoagulation effects. tPA was initiated 2 hours and 5 minutes after the first symptoms occurred and 2 hours later the patient had improved to NIHSS 2. The next day all neurological functions were normal with NIHSS 0, and a 24-hour CT scan showed no evidence of ischaemia or bleeding. The patient was discharged from the stroke unit 2 days after presentation and continued on dabigatran etexilate for anticoagulant therapy.

CASE 3: Reversal of dabigatran etexilate for endovascular intervention

An 81-year-old woman with AF and on 150 mg dabigatran etexilate twice a day presented at the emergency department with left lower limb pain. Comorbidities consisted of previous smoking, type 2 diabetes and hypertension. An initial examination was performed and the patient was diagnosed with critical ischaemia of the left leg. An acute angiographic CT scan revealed total occlusion of the left common femoral artery. The patient confirmed that she had taken dabigatran etexilate less than 6 hours previously, so idarucizumab was administered to minimize perioperative haemorrhage. Endovascular recanalization was then undertaken under the protection of 15,000 units of unfractionated heparin (UFH). Subsequently, endovascular embolectomy was performed followed by local tPA (4 mg Actilyse) and stenting of the iliac artery. Despite these efforts, a subsequent open operation was needed, resulting in endarterectomy of the common femoral artery and fasciotomy of the lower limb. However, UFH, Actilyse and ongoing treatment with dabigatran etexilate limited total blood loss to only 200 ml despite massive surgical intervention. The patient had an uneventful post-operative stay and was discharged from hospital after 7 days with dabigatran etexilate reinstated.

CASE 4: Comminuted tibia fracture

An 80-year-old woman with AF, chronic obstructive pulmonary disease, congestive heart failure and hypertension was admitted to the orthopaedic emergency room after a traumatic fall. The patient was being treated with dabigatran etexilate 150 mg twice a day. An x-ray of the right lower limb showed a comminuted diaphyseal fracture of the tibia, and subsequent clinical examination revealed a compromised arterial blood supply and impending compartment syndrome. The patient had taken the last dabigatran etexilate dose 2 hours before the fall, which was confirmed by an elevated aPTT. Due to the pathological distal status of the patient's left leg, it was decided to operate on the patient within 4 hours and the anaesthesiologist on call was contacted. Spinal anaesthesia was deemed the safest choice in light of the patient's co-morbidities. Idarucizumab was given and a subsequent aPTT test to check if the effect of dabigatran etexilate had been reversed, came back normal. The patient was then taken to the operating theatre and received standard spinal anaesthesia. Bleeding during the operation was minimal and the patient recovered without any sequelae. Dabigatran etexilate was reinstated the following day and the patient was discharged 4 days after admission.

European Journal of Case Reports in Internal Medicine

DISCUSSION

Recent comparative studies have shown that NOACs are as effective and safer options than warfarin when treating patients with AF to prevent stroke[4]. However, there are small differences in safety as regards the incidence of bleeding between the different NOACs, and a better safety profile when NOACs are taken twice daily[5]. To date, only one NOAC has an available reversal agent—idarucizumab, a specific antidote for the anticoagulation effect of dabigatran etexilate.

In this case report, we have shown that reversal of dabigatran etexilate in patents with difference conditions is effective and appears safe. Between November 2015 and September 2016, we administered idarucizumab to 18 patients in our hospital. The outcomes of these patients were similar to those seen in non-anticoagulated patients with bleeding or undergoing surgery. Our experience with idarucizumab is that it allows the physician to abruptly reverse the effects of anticoagulation and so perform advanced surgical procedures in situations where anticoagulation could be dangerous for the patient. The specificity of idarucizumab for dabigatran etexilate with no effect on other anticoagulants has allowed UFH to be used perioperatively in endovascular interventions which would not have been possible if idarucizumab had interfered with the effect of UFH. Although NOACs and warfarin lower the risk of ischaemic stroke, studies show that there still is a 0.5–2% annual risk of anticoagulated patients experiencing an ischaemic event. Consequently, thrombolysis has been contraindicated in patients on anticoagulation therapy. However, the introduction of idarucizumab has provided a method to turn off anticoagulation (apparently with no thrombogenic effects), making it possible to administer tPA to patients treated with dabigatran etexilate and with ongoing ischaemic stroke.

In this case report, we share our experience with tPA in one such patient. Several other case reports have shown that reversal of dabigatran etexilate with idarucizumab and subsequent administration of tPA is safe for patients previously considered unsuitable for this treatment. The possibility of reversing the anticoagulation effect of dabigatran etexilate also allows physicians to confidently prescribe anticoagulation to patients where uncertainty regarding bleeding risk was previously an obstacle to minimizing stroke risk.

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