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Case Report

Use of Idarucizumab for dabigatran reversal: Emergency department experience in two cases with subdural haematoma

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ABSTRACT

Introduction: Idarucizumab is the first effective humanized monoclonal antibody fragment developed specifically as a reversal agent for dabigatran, a Direct Oral Anticoagulant. Despite recent trials demonstrating reversal of clinically relevant bleeding, there is a paucity of data on use outside the trial setting. This manuscript describes the use of Idarucizumab to reverse dabigatran in two patients presenting to the emergency department of a major tertiary hospital with acute traumatic subdural haematomas (SDH).

Methods: Patients were identified through retrospective review of medication dispensing systems and electronic medical records.

Results: Two cases of Idarucizumab use were identified. Case 1 was of a 63-year-old male who presented following a motorcycle crash. Case 2 was of a 77-year-old male who presented with a 3-week history of ataxia and recurrent falls. Both patients were taking dabigatran for atrial fibrillation (AF). CT Brain revealed acute SDH with clinical indications for urgent surgical evacuation. Serum dabigatran levels were obtained on arrival in the emergency department with levels of 155 ng/ml and 110 ng/ml (reference range 117–275 ng/ml). Idarucizumab for dabigatran reversal was commenced; Case 1 received 5 g Idarucizumab as an intravenous bolus dose, while Case 2 received 5 g Idarucizumab as two 2.5 g intravenous infusions. Serum dabigatran levels for Cases 1 and 2 were 0 ng/ml at 75 min and 340 min post Idarucizumab administration respectively. Both patients proceeded to craniotomy with evacuation of the SDH. There was no extension of the SDH in either case. Anticoagulation was withheld until outpatient clinic review, and both patients transferred for rehabilitation prior to discharge home.

Conclusion: Idarucizumab was clinically effective for reversing dabigatran, resulting in undetectable serum levels, and should be considered in patients presenting to hospital with clinically significant bleeding associated with dabigatran therapy.

Introduction

In-hospital mortality in the setting of disorders of coagulation and traumatic brain injury (TBI) has been reported to be approaching 50% [1] Timely normalization of coagulopathy has also been associated with improved outcomes [2] Dabigatran, a direct thrombin inhibitor, is a novel anticoagulant. Patients treated with dabigatran who present with major bleeding or need urgent

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Table 1
Case 1 laboratory data.

Laboratory markers (reference ranges)	Admission	Post Idarucizumab Administration (T = 75 min from administration)
Dabigatran (117–275 ng/ml)	155	0
PT* (10.6–15.3 s)	17.4	14.1
APTT* (26–38 s)	63	35.5
INR* (0.9–1.3)	1.4	1.1
TCT* (14–24 s)	133.4	18.1

surgical intervention are at risk of severe complications due to the anticoagulation effects [3] Idarucizumab is the first effective humanized monoclonal antibody fragment developed specifically as a reversal agent for dabigatran [4–6] The Therapeutic Goods Administration approved the use of Idarucizumab in Australia in June 2016.

Early studies in healthy young patients and those between 45 and 80 years old with mild to moderate renal impairment have demonstrated idarucizumab rapidly reverse the anticoagulant effects of dabigatran and achieve haemostasis without pro-thrombotic effects. However, the safety and efficacy in patients with serious bleeding or who require urgent surgery is not known.

This case series documents the use of Idarucizumab to reverse dabigatran in patients presenting to the emergency department of a major tertiary hospital with acute traumatic subdural haematomas (SDH).

Methods

Patients were identified through retrospective review of medication dispensing systems and electronic medical records. Two cases were identified from 1/1/2016 to 1/6/2016 and informed consent to present this report obtained. The study was approved by The Alfred Hospital Research and Ethics Committee.

Results

Two cases were identified for inclusion. Case 1 was of a 63-year-old male who was transferred from a regional centre following a motorcycle crash. He had a history of atrial fibrillation for which he was prescribed dabigatran. Computed tomography (CT) imaging following the crash showed a SDH with mass effect. Fresh Frozen Plasma and a 3-factor prothrombin complex concentrate were administered prior to transfer. Upon arrival at our centre, and following analysis of laboratory data and multi-disciplinary medical team discussions, a decision to administer Idarucizumab was made. Laboratory results are listed in Table 1 and a timeline of events in Fig. 1. A single 5g-bolus dose of Idarucizumab was administered. The patient proceeded to the operating theatre where he underwent a craniotomy and evacuation of the SDH. Surgery was successful and haemostasis was achieved. Post-operative complications involved residual dysphasia, which resolved within 2 weeks post discharge. There was evidence of residual SDH on CT scans performed at 2 and 4 weeks post the crash but with no acute component. Anticoagulation was withheld and the patient was discharged into the care of his local medical officer who was advised to restart anticoagulation if there had been no extension of SDH on a follow-up CT scan to be performed 6 weeks post crash.

Case 2 was of a 77-year-old male who presented with an ataxic gait and recurrent falls, increasing in frequency in the preceding 3 days. He had a history of atrial fibrillation for which he was prescribed dabigatran. CT imaging revealed an acute on chronic SDH. Laboratory investigations confirmed active anticoagulation (Table 2) and a timeline of events outlined in Fig. 2. Multi-disciplinary medical discussions resulted in a decision to administer Idarucizumab. The patient was prescribed a 5 g dose of Idarucizumab, administered as two 2.5 g bolus doses spaced 5 min apart. No other blood products were administered to achieve haemostasis. The patient proceeded to the operating theatre for a frontoparietal mini craniotomy and evacuation of the SDH. The post-operative course was uncomplicated but routine CT follow-up at 4 weeks showed some residual SDH, although the patient was asymptomatic. A decision was made to remain off anticoagulation until a repeat CT was performed in 8 weeks time. CT scans performed seven months

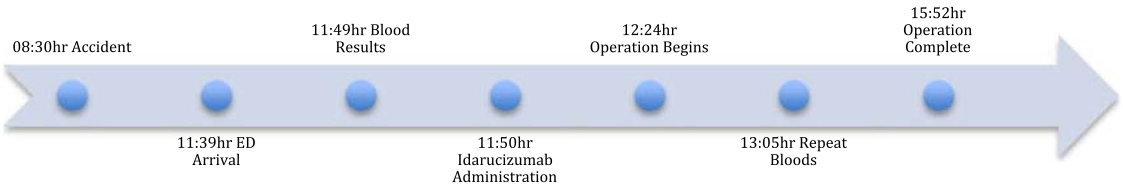

Fig. 1. Case 1 Timeline.

Table 2
Case 2 laboratory results.

Laboratory markers (reference ranges)	Admission	Post Idarucizumab Administration (T = 340 min from administration)
Dabigatran (117–275 ng/ml)	110	0
PT* (10.6–15.3 s)	17.2	15
APTT* (26–38 s)	48.4	28.6
INR* (0.9–1.3)	1.4	1.2
TCT* (14–24 s)	N/A	16.5

*PT = prothrombin time, APTT = activated partial thromboplastin time, INR = International normalised Ratio, TCT = thrombin clotting time.

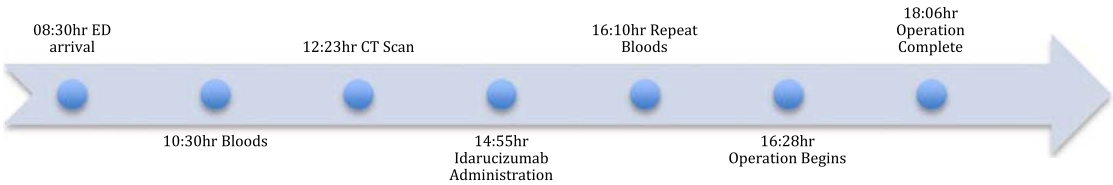

Fig. 2. Case 2 Timeline.

following injury show near complete resolution of SDH. However, the patient remained off anticoagulation under the guidance of the neurosurgical and cardiology teams.

Discussion

This manuscript describes two cases of successful reversal of the effects of dabigatran following administration of Idarucizumab. Both patients were taking dabigatran and sustained severe traumatic brain injuries requiring urgent surgical intervention. There were no obvious adverse effects observed.

Alternate options for reversal of the effects of dabigatran such as haemodialysis or waiting until anticoagulation effects cease by normal elimination, were not feasible in these cases, as rapid return to haemostasis was required. In patients with normal renal function dabigatran has a half-life of 12–14 h extending in those with renal impairment [7]. Therefore, ceasing treatment 24–48 h prior to planned procedures is a valid treatment strategy. Similarly, haemodialysis can be also considered for reversal of dabigatran effects in specific patient scenarios [8].

Idarucizumab has been developed as a specific antidote to dabigatran and is approved for use when the rapid reversal of anticoagulation effects is required for emergency surgery, urgent procedures, and in life threatening or uncontrollable bleeding. It is a humanized monoclonal antibody that binds specifically and potently to dabigatran to neutralise its effects [9]. The affinity of Idarucizumab binding to dabigatran is around 350 times greater than that of dabigatran for thrombin [9,10]. Both free and thrombin-bound dabigatran can be bound by Idarucizumab to neutralise anticoagulation activity [10]. Idarucizumab does not bind thrombin or its substrates nor does it activate platelets or convert fibrinogen to fibrin [4]. Benefits of Idarucizumab include a low rate of adverse effects, no increase risk of thrombosis and its short half-life allows for the resumption of anticoagulation therapy early after the acute episode of bleeding has resolved [6].

An important consideration when deciding on the use of Idarucizumab is the timing of the last dabigatran dose. It was confirmed with both cases that doses had been taken on the morning of their presentations and this was reflected through serum dabigatran levels measured on admission. Given the short half-life of dabigatran, if doses had been missed, it is possible that it no longer contributes to bleeding.

Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) is a prospective cohort study to examine the efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran in patients who presented with serious bleeding or who required urgent surgery or intervention. In the interim analysis of the RE-VERSE AD study, Idarucizumab was administered to around 25% of patients who had normal coagulation tests making it difficult to ascertain the benefit gained from Idarucizumab in this cohort [4,10].

The dose prescribed and administered of Idarucizumab varied between our two cases with one patient receiving a 5 g intravenous bolus dose and the other patient receiving two 2.5 g intravenous bolus doses. It is believed a 5 g total dose of Idarucizumab will reverse all available dabigatran up to the 99th percentile of dabigatran plasma concentrations measured in patients enrolled in the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial [4,10]. RE-VERSE ED administers Idarucizumab as two 2.5 g intravenous bolus doses no more than 15 min apart. While dosing of Idarucizumab in our case series did not follow the regimen

of this current Phase 3 trial, it still produced undetectable serum dabigatran levels and improvement in other markers of coagulation post administration. A study by Glund et al. conducted in healthy elderly or with mild-moderate renal impairment found that administration of 5 g or two 2.5 g Idarucizumab doses led to the sustained reversal of dabigatran induced anticoagulation [5]. Standardised dosing of Idarucizumab is of benefit in the busy clinical environment and future research could assess the efficacy of a single 5 g Idarucizumab doses to further simplify treatment.

Ongoing assessment will provide better understanding of optimal timing of serum dabigatran and coagulation laboratory tests. Timing of post Idarucizumab administration laboratory data varied in our two cases. RE-VERSE AD is performing measures between 10 and 30 min and at 1, 2, 4, 12, and 24 h following the second infusion [10]. In the busy clinical setting of an emergency department or theatre suite it may not be practical or achievable to perform laboratory testing as frequently as this. Thus, clear guidelines need to be established for clinical practice reflecting both real life data and clinical trial literature.

Conclusion

The two cases described support the use of Idarucizumab, rapidly reversing the anticoagulant effects of dabigatran. Idarucizumab can be considered in patients treated with dabigatran who present with uncontrollable or life-threatening bleeding or in need of urgent surgical intervention.

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