CASE REPORT

Emergency reversal of dabigatran for emergency surgery

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SUMMARY

An 80-year-old woman had the anticoagulant effect of dabigatran etexilate reversed using factor eight inhibitor bypassing activity (FEIBA) in order to facilitate emergency surgery for an incarcerated femoral hernia. She had atrial fibrillation was taking the anticoagulant for stroke prevention. That afternoon her international normalised ratio (INR) was 1.3 and activated partial thromboplastin time ratio (APPT_r) was 2.17, having taken dabigatran that morning. 3000 units of FEIBA and 10 mg of vitamin K were administered and she was taken to theatre for emergency surgery. Surgery was successful, total blood loss was less than 100 mL and there were no complications. The following morning she had an INR of 1.1 and APPT_r of 1.49. She made an uneventful postoperative recovery and was discharged home. There is a limited evidence base guiding practice in the clinical scenario described. The only controlled studies available are animal experiments.

BACKGROUND

There is a limited evidence base guiding practice in the emergency reversal of dabigatran.

CASE PRESENTATION

An 80-year-old woman presented to the emergency department having developed a painful right lower abdominal lump, noticed earlier that day. She did not have any systemic symptoms (no fevers, rigours, nausea) had not vomited and was passing urine and stool without difficulty.

Her medical history included atrial fibrillation for several years for which she was treated with dabigatran 110 mg two times a day for stroke prevention, which she had taken that morning. She was also on treatment for congestive cardiac failure (bisoprolol 2.5 mg once daily, co-amilofruse 5/40 three times a day, furosemide 40 mg once daily, ramipril 2.5 mg once daily) and took simvastatin 20 mg once at night (ON). Her surgical history included bilateral hip replacements (10 years ago). She had no known allergies.

On examination her vital signs were in normal range and cardiac and respiratory examination were normal. She had a soft abdomen with no guarding or signs of peritonism, however, a soft lump was found in the right inguinal region. It was very tender, not reducible and did not have a cough impulse. It was not well defined and features of pulsatility, bruit and bowel sounds were not noted. It was felt that this could represent an incarcerated hernia.

INVESTIGATIONS

Routine bloods tests showed a normal full blood count, urea and electrolytes and liver function tests. Coagulation studies demonstrated the therapeutic effect of dabigatran with an activated partial thromboplastin time ratio (APPT_r) of 2.17 and an international normalised ratio (INR) of 1.3. A venous lactate was raised at 3.2 mmol/L and an ultrasound examination confirmed an incarcerated femoral hernia. The thrombin time (TT), dilute TT time-based Hemoclot™ assay and fibrinogen levels were not measured at any point.

TREATMENT

On discussion with specialist teams it was decided that reversal of the anticoagulant was necessary before emergency surgery. 10 mg of vitamin K intravenous were given immediately in an attempt to reduce INR. 3000 units of FEIBA were given over 45 min as the procedure was started. The femoral hernia was repaired that afternoon with no complications, the necrotic omentum was excised and the defect sutured. The total blood loss was less than 100 mL.

OUTCOME AND FOLLOW-UP

The patient made an uneventful postoperative recovery and was discharged home the following day. Blood tests taken that morning showed an INR of 1.1 and APPT_r of 1.49, the patient was restarted on her usual dabigatran dose.

DISCUSSION

Dabigatran etexilate is an oral direct thrombin inhibitor. When it was first licensed in the UK in 2008 it was hailed as a promising new anticoagulant due to its advantages of having a fixed dose, no clinical need for monitoring and no food restrictions.¹ Within 4 years it had garnered over \$1 billion for its manufacturers and today nearly 17% of patients with atrial fibrillation are prescribed the drug.² National Institute of Health and Care Excellence (NICE) and the European Society of Cardiology recommend the use of dabigatran in non-valvular atrial fibrillation.^{3 4} The RE-LY trial showed that dabigatran had lower rates of stroke and systemic embolisation than warfarin at the 150 mg dose.⁵

However, there is uncertainty regarding the risk of bleeding with dabigatran compared to other anticoagulants. In the RE-DEEM trial, dabigatran 110 mg was associated with 3.92 times increased risk of bleeding events compared to placebo when given with dual antiplatelet therapy and there are concerns that relevant safety data has been

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withheld from scrutiny.⁶ Conversely, 2-year data from the RE-LY trial reported lower rates of intracranial haemorrhage with dabigatran than with warfarin⁷ and provisional analysis of postmarketing data suggested that bleeding rates for dabigatran are similar to warfarin in practice despite initial high reports of serious bleeding events.

A significant weakness of dabigatran and one that deters its use is the lack of an ability to reverse the agent when necessary. Importantly, there is a lack of evidence-based guidance for scenarios such as that reported here.

Dabigatran is rapidly absorbed and can reach a peak plasma concentration within 1–3 h following ingestion. Therefore, if a patient presents within 2 h of ingestion, then activated charcoal can be given, which will impair absorption. Furthermore, because dabigatran is renally excreted and has a half-life of roughly 13 h in patients with normal renal function, a delay for 24 h will allow the concentration of dabigatran in the plasma to fall by 75%. Current perioperative advice is to maximise renal function. In addition to this, there is some experimental evidence to suggest considering Factor eight inhibitor bypassing activity (FEIBA) but guidance is unclear about whether it should be used.^{8,9}

FEIBA is an activated four factor prothrombin complex concentrate (PCC) that can be used to reverse vitamin K antagonists. Several animal studies have been described for dabigatran and FEIBA. In a rat tail bleeding model, FEIBA significantly reduced the bleeding time associated with dabigatran.¹⁰ In a rabbit model, administration of increasing doses of PCC shortened bleeding time.¹¹ There is, however, limited evidence and only one other case study which has demonstrated the use of FEIBA in reversing bleeding in a human.¹² In this study low-dose FEIBA was administered over 15 min and haemostasis was noted within minutes of infusion.

Other bypassing agents include Recombinant factor VIIa (RFVIIa) and ex vivo studies in rats and healthy volunteers suggest that it may be capable of reversing dabigatran.¹⁰ If time persists, haemodialysis over several hours could also be considered as a means for dabigatran reversal. Haemodialysis has been utilised to reverse the anticoagulant effects of dabigatran in therapeutic doses, however, this may not be feasible in haemodynamically unstable patients.¹³ Research is currently underway for specific antidotes. Recent reports show data about proposed molecules such as aDabi-Fab, a humanised monoclonal antibody fragment to bind dabigatran. It remains unclear how effective these therapies may be in excessively anticoagulated patients.¹⁴

APPT_r increases with larger doses, but not in a linear dose response manner. TT measures the direct activity of thrombin and is probably the most sensitive test for an anticoagulant effect of dabigatran. A normal TT usually excludes an anticoagulant effect due to dabigatran.¹⁵ Unfortunately TT is not routinely measured at the hospital, therefore following advice from a consultant haematologist we relied on APPT_r and INR to guide clinical judgement regarding dosing. However, there is little evidence available for FEIBA dosing and this is an area that should undergo further research.

In this case vitamin K was also administered due to the high INR. However, it is not clear that this would have made a difference to the outcome of the surgery (as its effect would have been too delayed to have had an impact) or to the anticoagulant effect of dabigatran as is a direct thrombin inhibitor rather than a vitamin K antagonist.

Wong and Keeling¹⁶ have also recently reported a case of reversal of the anticoagulant effect of dabigatran using FEIBA

for an emergency procedure. In this case the patient was also taking 110 mg two times a day for atrial fibrillation. This patient presented with septic shock and acute renal failure and after administration of 40 units/kg of FEIBA underwent percutaneous transhepatic drainage of a gallbladder empyema with no bleeding complications.

Additional studies are needed to either confirm or disprove these individual case observations. The optimal dose for off-label use of PCC agents will continue to evolve as experience with their use in the setting of novel anticoagulation reversal is gained.

Learning points

- In the case of an incarcerated hernia in a woman with atrial fibrillation on dabigatran we demonstrate the safe and rapid reversal of anticoagulant effect in a surgical emergency.
- Dabigatran can be reversed safely but further evidence is required regarding optimal dosing levels of factor eight inhibitor bypassing activity.
- Activated partial thromboplastin time ratio is a more sensitive test than international normalised ratio for detecting the therapeutic range of dabigatran. Thrombin time (TT) is probably the most sensitive test as a normal TT usually excludes the anticoagulant effect of dabigatran. Therefore TT would have been a useful test to have done in this case.

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