The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran

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ABSTRACT
Dabigatran is an oral direct thrombin inhibitor (DTI) licensed for stroke prevention in atrial fibrillation and likely to be soon approved in Europe for treatment of venous thrombosis. Predictable pharmacokinetics and a reduced risk of intracranial haemorrhage do not negate the potential risk of haemorrhage. Unlike warfarin, there is no reversal agent and measurement of the anticoagulant effect is not ‘routine’. The prothrombin time/international normalised ratio response to dabigatran is inconsistent and should not be measured when assessing a patient who is bleeding or needs emergency surgery. The activated partial thromboplastin time (APTT) provides a qualitative measurement of the anticoagulant effect of dabigatran. Knowledge of the time of last dose is important for interpretation of the APTT. Commercially available DTI assays provide a quantitative measurement of active dabigatran concentration in the plasma. If a patient receiving dabigatran presents with bleeding: omit/delay next dose of dabigatran; measure APTT and thrombin time (consider DTI assay if available); administer activated charcoal, with sorbitol, if within 2 h of dabigatran ingestion; give tranexamic acid (1 g intravenously if suspected overdose, urgently needed surgery, or urgent invasive diagnostic or therapeutic procedures in patients who are taking this new drug). These comments offer little solace or guidance to a clinician faced with having to manage one of the many surgical procedures in patients who are taking this new drug.

COAGULATION ASSAYS: MEASURING THE EFFECT OF DABIGATRAN
Prothrombin time/international normalised ratio
Vitamin K antagonists, such as warfarin, reduce the levels of the coagulation factors II, VII, IX and X.9 The prothrombin time (PT) is particularly sensitive to a reduction in factor VII, and, as a result, treatment with vitamin K antagonists results in prolongation of the PT. This is usually expressed as a standardised ratio (the international normalised ratio (INR)), which is used to monitor the therapeutic anticoagulant effect of warfarin.10 The PT/INR is insensitive to dabigatran at therapeutic levels.11 It may be prolonged by supratherapeutic levels of dabigatran, but the results will vary widely between laboratories, because of variation in the sensitivity of different reagents to the effect of dabigatran.11 Neither a laboratory-based nor
point-of-care PT/INR can be used to assess the anticoagulant effect of dabigatran.

Activated partial thromboplastin time

The activated partial thromboplastin time (APTT) provides a measure of the intrinsic (factors VIII, IX and XI) and common (factors II, V, X and fibrinogen) coagulation pathway. The APTT can be used to monitor the anticoagulant effect of unfractionated heparin.12 The APTT displays a curvilinear dose response to increasing plasma concentrations of dabigatran11 and may be used to demonstrate that a patient is anticoagulated with dabigatran—for example, if a patient is bleeding or needs surgery. However, it does not provide a quantitative measurement and should not be used for routine monitoring.

In the stroke prevention trial,2 the APTT ratio was 1.4–2.3 in patients receiving 150 mg twice a day, and 1.3–2.1 in those receiving 110 mg twice a day, with a peak effect seen 2 h after administration.13 Prolongation of the APTT is maintained for at least 8–12 h, with a measurable effect still seen in some patients after 24 h.1 If the APTT is prolonged by 2–3-fold at trough (when the next dose is due), there is a higher risk of bleeding.14 15 Therefore, knowledge of the time of last dose is important for interpretation of the APTT, particularly if an invasive procedure is planned.

Thrombin time

The thrombin time (TT) provides a measurement of the conversion of fibrinogen into fibrin (clot). The TT displays a linear time response to increasing plasma concentrations of dabigatran.1 In general, the TT does not form part of a ‘routine’ coagulation profile and may not be readily available in clinical practice. In addition, the TT is exquisitely sensitive to the presence of dabigatran, and samples may be unclottable at therapeutic levels, making it unsuitable as a quantitative assay.14 15 Conversely, a normal TT indicates an absence of dabigatran anticoagulant effect and could therefore be used to exclude the drug as a cause of haemorrhage.

DTI assay

The commercially available HEMOCLOT (HYPHEN BioMed, France)16 DTI assay avoids the over-sensitivity displayed by standard TT assays. The clotting time is directly related to the concentration of active dabigatran in the patient’s plasma and can be used to measure the anticoagulant activity of dabigatran. A DTI assay may be of use in assessing patients presenting with bleeding or in those that require an urgent invasive procedure or surgery.

MANAGEMENT OF BLEEDING

There are currently no antidotes available for reversing the anticoagulant effect of dabigatran, although preclinical work is underway to develop a neutralising, dabigatran-specific monoclonal antibody.17 If a patient presents with bleeding, dabigatran therapy should be discontinued until appropriate investigations are completed and the patient is stabilised (figure 1).18–20

Activated charcoal

Activated charcoal is a processed form of carbon with a large porous surface area available to bind to oral drugs such as dabigatran21 22 and reduce absorption from the gastrointestinal tract. Binding to charcoal is reversible; sorbitol is often added for its laxative effect to speed transit through the intestines. Since dabigatran is rapidly absorbed after ingestion, activated charcoal is likely to be of greatest benefit within 2 h of ingestion. Clinicians should bear in mind that absorption of concomitant oral medication will also be impaired by administration of charcoal.

**Figure 1** Management of bleeding patient anticoagulated with dabigatran.18–20 APTT, activated partial thromboplastin time; TT, thrombin time; eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; BP, blood pressure; i.v., intravenous; Hb, haemoglobin; Plt, platelet; CNS, central nervous system; FEIBA, factor eight inhibitor bypassing activity; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.
Tranexamic acid
Tranexamic acid inhibits fibrinolysis by inhibiting the binding of plasmin to fibrin. Tranexamic acid has been shown to reduce bleeding after tissue injury associated with surgery and after trauma. Based on the results of more than 200 randomised control trials, the efficacy of anti-fibrinolytic drugs does not appear to be offset by serious side effects. In the event of major bleeding with dabigatran, 1 g tranexamic acid should be given intravenously.

General supportive measures
Maintaining renal perfusion and urine output can aid elimination of dabigatran, 80% of which is excreted through the kidneys unchanged. Mechanical methods to arrest bleeding, including compression, tamponade, surgery and radiological intervention, are essential components of managing bleeding events.

Since the half-life of dabigatran is short (12–17 h), it is envisaged that the majority of bleeding episodes will be managed by supportive methods alone. However, if bleeding continues or is life threatening, then an additional haemostatic agent should be considered. It must be remembered that there is no specific antidote for dabigatran and there is no ideal haemostatic agent for this indication.

Dialysis
Dabigatran exhibits low protein binding and therefore it may be possible to remove it from the circulation by dialysis. The plasma concentration of dabigatran can be reduced by 50–60% after 4 h of dialysis. Unfortunately, emergency access to haemodialysis may be limited, and the technical issues surrounding establishing venous access in an anticoagulated patient means that this treatment option may only be available to a few patients.

Haemostatic agents that may be of use in the management of bleeding
Prothrombin complex concentrates
Prothrombin complex concentrates (PCCs) contain factors II (prothrombin), VII, IX and X, which are the vitamin K-dependent factors affected by warfarin therapy. Dabigatran directly inhibits thrombin, and, although administration of a PCC will not influence this effect, it may provide more substrate (prothrombin) to increase thrombin generation, which is essential for the formation of a fibrin blood clot.

A number of animal studies have found that the PCCs, Beriplex and Octaplex, result in haemostasis and reversal of blood loss after supratherapeutic doses of dabigatran. In a murine ICH model, a PCC resulted in cessation of bleeding associated with dabigatran. It also prevented haematoma expansion and significantly reduced mortality. In contrast, in a study of human healthy volunteers, a PCC (Cofact) failed to normalise the prolonged APTT or TT caused by dabigatran, although the effect on bleeding was not assessed in this study. It is important to note that, in the animal models where a clinical effect was seen, there was no improvement in the laboratory tests. The inability to measure the effect of PCC administration by laboratory tests may result in larger doses of PCC being given than necessary, leading to the potential for thrombotic complications.

FEIBA
FEIBA (which has Factor Eight Inhibitor Bypassing Activity) is currently used as a haemostatic agent for patients with antibodies to factor VIII. Activated factor X and prothrombin appear to be the main components in FEIBA responsible for its haemostatic action, and they enable the generation of thrombin, independently of factor VIII. As in the case of PCCs, this thrombin may still be inhibited by dabigatran.

In a rat tail bleeding model, FEIBA significantly reduced the bleeding time associated with dabigatran. As with the PCC studies, the APTT remained prolonged after FEIBA administration despite the reduction in bleeding time. There is a single case report of the successful use of FEIBA in the management of a life-threatening bleeding event associated with dabigatran.

It is likely that the prothrombotic effect of FEIBA is greater than that of PCCs because of the coagulation factors being activated and that, if used, much smaller doses will be required than those used for treating patients with haemophilia.

Recombinant factor VIIa
Recombinant factor VIIa (rFVIIa) is another bypassing haemostatic agent used for the management of haemophilic patients with inhibitors. It is able to directly activate factors IX and X resulting in a burst of thrombin generation (and thus fibrin clot formation) independently of factor VIII. As with the other haemostatic agents, the generation of thrombin may in part overcome the effect of dabigatran.

rFVIIa has also been shown to reduce dabigatran-induced bleeding in a rat tail bleeding model with partial normalisation of the APTT. However, in contrast with PCCs, rFVIIa failed to reduce haematoma expansion or have an impact on mortality in a murine ICH model.

Following anecdotal evidence, the off-label use of rFVIIa for non-haemophilic patients who are bleeding has gained some favour in the past decade. However, there is concern that rFVIIa is associated with an increased risk of thrombotic complications. A review of 35 randomised control trials of the off-label use of rFVIIa identified a significant increase in the risk of arterial events, particularly in the elderly.

Surgery/invasive procedure
When a patient receiving dabigatran requires an elective invasive procedure, the consequences of bleeding if anticoagulation is continued, with the risk of thrombosis if it is omitted, need to be considered. In addition, as dabigatran is predominantly eliminated via the renal pathway, this will need to be taken into account when deciding for how long to stop dabigatran before a procedure (table 1).

For patients who require urgent surgery, discussion with the patient’s surgeon and anaesthetist are of paramount importance (figure 2). A baseline assessment of coagulation should be

<table>
<thead>
<tr>
<th>Renal function (CrCl (ml/min))</th>
<th>Estimated half-life(h)</th>
<th>Major surgery or high bleeding risk*</th>
<th>Non-major surgery or standard risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>~13</td>
<td>48 h before</td>
<td>24 h before</td>
</tr>
<tr>
<td>&gt;50 and &lt;80</td>
<td>~15</td>
<td>48–72 h before</td>
<td>24–48 h before</td>
</tr>
<tr>
<td>&gt;30 and &lt;50</td>
<td>~18</td>
<td>96 h before</td>
<td>48–72 h before</td>
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*Examples of major surgery/high bleeding risk: cardiothoracic surgery, neurosurgery, major abdominal or pelvic surgery, major orthopaedic surgery, insertion of cardiac pacemaker/defibrillator.
†Examples of non-major surgery/standard risk: uncomplicated laparoscopic procedure, cardiac catheterisation/ablation therapy, CrCl, creatinine clearance.
performed, including the APTT. A normal APTT suggests that the bleeding risk is low. A prolonged APTT may reflect the presence of dabigatran or, particularly in the setting of trauma or sepsis, a coagulopathy. A DTI assay, if available, could provide additional information about the risk of bleeding.

Prolongation of the APTT and/or a measurable therapeutic dabigatran concentration in the patient’s plasma should prompt a discussion as to the feasibility of delaying surgery. A delay of 24 h in a patient with normal renal function will allow the concentration of dabigatran in the plasma to fall by 75%. If urgent surgery is required, particularly within a few hours of dabigatran ingestion, an increased risk of bleeding is likely.

To support drug elimination from the kidneys, renal perfusion and urine output must be maintained. If a patient has taken...
In the event of accidental or intentional overdose, a baseline APTT or PT assay should be performed (Figure 3). If normal, they should be repeated after 2 h, since plasma levels of dabigatran may be decreased by 60% within 4 h of dialysis.

CONCLUSION

Overdose requires surgery within 24 h of ingestion, if bleeding occurs, then supportive measures should be used with simultaneous administration of activated charcoal and sorbitol for all patients with suspected dabigatran overdose. It is likely to be of most benefit administered within 2 h of ingestion. There is currently no evidence to support, if bleeding continues, the patient should be managed with the option of hematoma evacuation, according to the protocol. Activated charcoal with sorbitol may be considered during the period of concern to reduce the risk of general anesthesia should be thoroughly discussed with the patient, individual risk of bleeding and thrombotic risk should be the sole consideration of anticoagulation should be considered for all patients who are bleeding. After surgery, the patient should receive supportive management with activated charcoal, if required, and the patient should be followed to ensure that the patient is not readmitted for bleeding.

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