Reversal of direct oral anticoagulants

An understanding of how to counteract the anticoagulant effect of direct oral anticoagulants is essential in the event of haemorrhage, emergency surgery and overdose. This review summarizes strategies for the reversal of direct oral anticoagulants, including the use of novel agents.

The direct oral anticoagulants (apixaban, edoxaban, rivaroxaban and dabigatran) have demonstrated non-inferiority to warfarin in randomized controlled trials for stroke prevention in patients with non-valvular atrial fibrillation and treatment of acute venous thromboembolism. Together with their predictable pharmacology and ease of use, this has led to National Institute for Health and Care Excellence approval and increasing clinical use. Reversal of the anticoagulant effects of direct oral anticoagulants in emergency situations has been challenging given the lack of specific antidotes. Using a case-based approach, this article discusses currently available strategies for direct oral anticoagulant reversal, including how the novel reversal agents can be used.

Case history

A 75-year-old man was brought to the emergency department by ambulance with a 2-hour history of right-sided weakness. His observations were stable on arrival, with a blood pressure of 180/90 mmHg and heart rate of 100 beats per minute. Glasgow Coma Score was 15. A faxed letter from his GP revealed a history of hypertension and atrial fibrillation (CHADS2-VASc score = 3), for which he was receiving dabigatran 150 mg twice daily. His wife, who accompanied him to the emergency department, reported that he was fit and active and had taken a dose of dabigatran that morning, approximately 4 hours before becoming unwell. His other medications were ramipril 10 mg once daily, amlodipine 10 mg once daily and simvastatin 40 mg once daily. He was a non-smoker and only drank alcohol socially.

Blood tests on arrival were haemoglobin 132 g/litre, white cell count 10.5 x10^9/litre, platelet count 258 x10^9/litre, prothrombin time 14 seconds (normal range 8–12 seconds), activated partial thromboplastin time 40 seconds (normal range 26–36 seconds), thrombin time >120 seconds (normal range 14–19 seconds), fibrinogen 1.5 g/litre and creatinine 98 µmol/litre (estimated glomerular filtration rate of 69 ml/min/1.73m^2). A dabigatran level was requested but was not immediately available. Urgent computed tomography of the head revealed a 5 ml left supratentorial lobar intracranial bleed without mass effect.

The haematology registrar was contacted for advice regarding reversal of the anticoagulant effect of dabigatran. Given the critical bleed, the haematology registrar advised giving 5 g idarucizumab (Praxbind) immediately as two 2.5 g vials by slow bolus. Subsequently the dabigatran level sent on admission was 264 ng/ml (local reference range for peak concentration 64–443 ng/ml).

He was transferred to the acute stroke unit for further management. Blood pressure control was optimized. Neurosurgical opinion was sought. Given that he was neurologically stable, no surgical intervention was considered necessary. He was closely monitored for any signs of deterioration. Intermittent pneumatic compression was applied to reduce the risk of venous thromboembolism.

As he recovered from the initial event, the risks and benefits of future anticoagulation therapy were carefully considered. In this case, the risks of anticoagulation were considered to outweigh the benefits, and a decision was made jointly between the patient, stroke physicians and neurosurgeons to stop anticoagulation. He was referred to the cardiologists for consideration of left atrial appendage occlusion.

Risk of bleeding on direct oral anticoagulants

Individual phase III randomized controlled trials of direct oral anticoagulants demonstrated either no significant difference in the risk of major bleeding compared to warfarin with a target international normalized ratio of 2.5, or in some cases a reduction in bleeding risk (Chai-Adisaksopha et al, 2014; Ruff et al, 2014). While these clinical trials had differences in both patient characteristics at baseline and time in therapeutic range for the warfarin comparator, meta-analysis provides a useful tool to examine the risk of bleeding on direct oral anticoagulants compared to warfarin.

Dr X-Y Zhang, Haematology Specialist Registrar, Department of Haematology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford

Dr MJ Desborough, Clinical Research Fellow, NHS Blood and Transplant, John Radcliffe Hospital, Oxford, and Oxford Clinical Research in Transfusion Medicine, Nuffield Division of Clinical Laboratory Sciences, University of Oxford, Oxford

Dr S Shapiro, Consultant Haematologist, Oxford Haemophilia and Thrombosis Centre, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE

Correspondence to: Dr S Shapiro (susie.shapiro@ouh.nhs.uk)

Table 1. Direct oral anticoagulant pharmacology

Direct oral anticoagulant	Time to peak concentration (hours)	Half life (hours)	Active renal clearance
Dabigatran	1.25–3	12–14	85%
Apixaban	1–3	8–15	27%
Edoxaban	1–2	9–11	35%
Rivaroxaban	2–4	9–13	33%

From Bounameaux and Camm (2014), Dale et al (2015)

Table 2. British Committee for Standards in Haematology recommendations for the time before surgery that direct oral anticoagulants should be stopped, based on renal function (creatinine clearance)

Direct oral anticoagulant	Creatinine clearance (ml/min)	Low bleeding risk surgery (hours)	High bleeding risk surgery (hours)
Dabigatran	≥80	24	48
	50–80	24–48	48–72
	30–50	48–72	96
Apixaban, edoxaban and rivaroxaban	≥30	24	48
	<30	48	72

From Keeling et al (2016)

Systematic review and meta-analysis of direct oral anticoagulants in both atrial fibrillation and venous thromboembolism (Chai-Adisaksopha et al, 2014; Ruff et al, 2014) demonstrated that direct oral anticoagulants were associated with a significant reduction in the risk of major bleeding (relative risk 0.72, number needed to treat 156), clinical relevant non-major bleeding (relative risk 0.78, number needed to treat 99), and total bleeding (relative risk 0.76, number needed to treat 18). There was also a significant reduction in the risk of fatal bleeding (relative risk 0.53, number needed to treat 454).

Additionally direct oral anticoagulants halve the risk of intracranial haemorrhage compared to warfarin (Chai-Adisaksopha et al, 2014; Ruff et al, 2014): intracranial haemorrhage on warfarin occurred in 1.08% of patients compared to 0.51% of patients on a direct oral anticoagulant (relative risk 0.43, *P* value 0.01), resulting in a number needed to treat of 185. Furthermore, a small prospective observational study showed that patients with direct oral anticoagulant-associated intracranial haemorrhage had smaller intracranial haemorrhage volumes and better clinical outcomes (as measured by modified Rankin score) compared with warfarin-associated intracranial haemorrhage (Wilson et al, 2016) despite a specific reversal agent not being available at the time of this trial.

In individual randomized controlled trials compared to warfarin, gastrointestinal bleeding was more common in patients who received dabigatran 150 mg twice daily, rivaroxaban and edoxaban (not apixaban) (Connolly et al, 2009; Patel et al, 2011; Giugliano et al, 2013). These trial findings for dabigatran and rivaroxaban were corroborated by a cohort study demonstrating an increased risk of gastrointestinal bleeding for patients aged over 75 years (Abraham et al, 2015); however, no increase in gastrointestinal bleeding was found for those under the age of 75 years (Chang et al, 2015).

Direct oral anticoagulant pharmacology and laboratory testing

A basic knowledge of direct oral anticoagulant pharmacology is helpful for understanding their reversal strategy. Direct oral anticoagulants have a rapid onset of action with relatively short half-lives (*Table 1*). The anticoagulant activity of direct oral anticoagulants can be estimated from knowledge of time of last dose, half-life and renal clearance. They are all cleared to some extent by the kidneys and their half-lives prolonged by renal impairment. In a patient with normal renal function, the direct oral anticoagulant will usually only be present at very low levels 24 hours after a dose is taken. This not only forms the basis of advice on when to stop a direct oral anticoagulant before elective surgery (*Table 2*), but similar principles can be applied to emergency surgery which is discussed below.

While it is accepted that the anticoagulant effects of the direct oral anticoagulants do not need to be routinely monitored, there are situations in which measuring the anticoagulant activity can help guide treatment, such as in the event of major bleeding or suspected overdose. Traditional coagulation tests, such as prothrombin time and activated partial thromboplastin time, are inexpensive and widely available, but they have extremely limited use in assessing the anticoagulation effect of direct oral anticoagulants. Crucially, a normal prothrombin time and activated partial thromboplastin time do not exclude therapeutic levels of anticoagulation. The prothrombin time and activated partial thromboplastin time show different sensitivities depending on the reagents used by the local laboratory, but an overall summary of the effect of each of the direct oral anticoagulants on common coagulation tests is shown in *Table 3*. Arguably the most useful standard coagulation test for the direct oral anticoagulants is the thrombin time for patients on dabigatran. The thrombin time is highly sensitive to dabigatran and a normal thrombin time therefore suggests absent or very low dabigatran levels.

Direct oral anticoagulant levels can be quantified more accurately with specialized tests. Dabigatran can be measured with the dilute thrombin time or ecarin clotting time, and apixaban, edoxaban and rivaroxaban can be measured with reagent specific anti-Xa assays (Dale et al, 2015).

These tests are not available in all centres. Guidance from the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis on the use of antidotes advises: 'in patients with serious bleeding, a drug concentration >50 ng/ml is likely

sufficiently high to warrant antidote administration, whereas in those requiring an urgent intervention associated with a high risk of bleeding, antidote administration should be considered if the drug concentration exceeds 30 ng/ml' (Levy et al, 2016). However, this is only a guide and, as in this case, when there is a critical bleed the authors would use the direct reversal agents without delaying until drug levels are known. *Table 4* summarizes the usual trough and peak levels of the direct oral anticoagulants in order to give a framework for the significance of different drug levels.

General measures for management of bleeding patients on direct oral anticoagulants

Interestingly studies have shown that outcomes of major bleeds associated with direct oral anticoagulants are no worse than those with warfarin even in the absence of specific reversal agents (Majeed et al, 2013; Hylek et al, 2014; Piccini et al, 2014). In the event of significant bleeding, both general and direct oral anticoagulant-specific measures should be considered. The authors recommend that non-specialists are aware of local protocols and guidelines and contact a haematologist for advice.

The direct oral anticoagulant should be discontinued until after bleeding is controlled. Local measures to stop bleeding should be used when possible. The authors advise administering tranexamic acid 1 g intravenously if there is significant bleeding. Although there is little evidence for the efficacy of tranexamic acid in this setting, there is good evidence of its benefit in traumatic bleeds (Shakur et al, 2010), and no evidence that it increases arterial or venous thrombosis risk (Myles et al, 2017). The hospital's major haemorrhage protocol should be used to guide transfusion of blood components if necessary.

Prohaemostatic agents

In situations where a specific antidote is not available, the use of prohaemostatic agents, e.g. prothrombin complex concentrate or activated prothrombin complex concentrate, can be considered to promote haemostasis. Clinical data on their efficacy and safety in this setting are relatively limited and are based on animal studies showing a reduction in bleeding with the use of prothrombin complex concentrate or activated prothrombin complex concentrate (Dickneite and Hoffman, 2013) and also case reports. Arterial or venous thrombotic events are the main risks associated with both prothrombin complex concentrate and activated prothrombin complex concentrate, although other side effects include headache, nausea or vomiting, arthralgia and hypotension.

The prothrombotic potential of activated prothrombin complex concentrate is considered to be higher than that of prothrombin complex concentrate, and so prothrombin complex concentrate may be preferred in situations where there is a particularly high risk of thrombosis, but there are few data to quantify this risk in this setting (Sridharan et al, 2015). Given the lack of clinical data to guide their use, these agents should be reserved for significant haemorrhage when specific antidotes are not available – the authors would not advise their use in cases of overdose without bleeding or in general before emergency surgery. The authors recommend that these agents are only considered after a discussion with a haematologist.

Table 3. Effect of direct oral anticoagulants on common coagulation tests

Direct oral anticoagulant	Prothrombin time	Activated partial thromboplastin time	Thrombin time
Dabigatran	Minimal prolongation in usual treatment range	Prolonged activated partial thromboplastin time suggests dabigatran level within or above usual treatment range	Normal thrombin time is highly suggestive of little or no dabigatran present
Apixaban	Not useful	Not useful	Not applicable
Edoxaban	Often prolonged but normal prothrombin time does not exclude therapeutic anticoagulation	Not useful	Not applicable
Rivaroxaban	Often prolonged but normal prothrombin time does not exclude therapeutic anticoagulation	Not useful	Not applicable

Table 4. Therapeutic peak and trough anticoagulant levels

Direct oral anticoagulant	Usual trough* (ng/ml)	Usual peak* (ng/ml)
Dabigatran 150 mg twice daily	90 (31–225)	184 (64–443)
Apixaban 5 mg twice daily	103 (41–230)	171 (91–321)
Edoxaban 60 mg once daily	36 (19–62)	–
Rivaroxaban 20 mg once daily	22 (4–96)	223 (160–360)

*From Mueck et al (2008), van Ryn et al (2010), Ruff et al (2015), Bristol-Myers Squibb-Pfizer (2016). These ranges are for guidance only and vary considerably between patients and between studies. *Trough and peak anticoagulant levels are presented as 90% confidence intervals except for edoxaban, which is presented as median (interquartile range).*

Novel antidotes for direct oral anticoagulants

Idarucizumab (Praxbind), a humanized monoclonal antibody fragment against dabigatran, is now licensed in the United States and Europe. It binds free and thrombin-bound dabigatran with high affinity and neutralizes its activity. Studies in patients with major bleeding or those requiring emergency surgery or invasive procedures have shown that it completely reverses the anticoagulant effects of dabigatran within minutes in the majority of patients (Pollack et al, 2015). No serious adverse events or thrombotic complications were observed in phase I studies (Glund et al, 2015). A single administration of the standard 5 g dose effectively and completely reverses very high concentrations of dabigatran associated with overdose (Peetermans and Verhamme, 2016; Shapiro et al, 2016).

Figure 1. International Standards on Thrombosis and Haemostasis recommendations for antidotes for direct oral anticoagulants (Levy et al, 2016). The authors recommend that the two situations marked with * are considered on a case-by-case basis.

When to consider an antidote for a direct oral anticoagulant
- Life-threatening bleeding
- Bleeding in a critical space or critical organ
- Persistent major bleeding despite normal haemostatic measures
- Urgent intervention or surgery with a high risk of bleeding that cannot be delayed

Antidotes should not be used in:
- Elective surgery
- Gastrointestinal bleeds that respond to supportive measures*
- High drug levels or excessive anticoagulation without bleeding*
- Need for surgery that can be delayed for long enough to permit drug clearance

Andexanet alfa is a recombinant modified human factor Xa decoy protein, which binds to factor Xa inhibitors at their active site with high affinity and neutralizes the anticoagulant effects of both direct and indirect factor Xa inhibitors. Owing to its short half-life (approximately 1 hour), it is administered as a bolus followed by an infusion, which needs to be continued for the duration that reversal is required. Different doses are given dependent on the time from ingestion and the type of antiXa drug. Two phase II trials (ANNEXA-A and ANNEXA-R) showed that andexanet alfa reversed the anticoagulant effect of apixaban and rivaroxaban within minutes of administration in older healthy volunteers (Siegal et al, 2015). No serious adverse or thrombotic events were reported. Interim results of the ongoing open-label, single-arm phase III trial (ANNEXA-4), evaluating the efficacy and safety of andexanet alfa in patients with acute major bleeding, showed that 79% had a good to excellent haemostatic response post-andexanet infusion (Connolly et al, 2016). Thrombotic events occurred in 18% of the safety population, which was somewhat higher than in previous idarucizumab and prothrombin complex concentrate trials.

Ciraparantag (PER977) is a broad-spectrum anticoagulant reversal agent at an earlier stage of development. It is a synthetic, small cationic molecule, which binds to direct thrombin inhibitors, factor Xa inhibitors, unfractionated and low molecular weight heparin through non-covalent hydrogen bonds and charge-charge interactions. In phase I/II studies, a single intravenous dose of ciraparantag lead to rapid and full reversal of anticoagulation in healthy volunteers given edoxaban (Ansell et al, 2014) or enoxaparin (Ansell et al, 2016). The effect was sustained for 24 hours and no procoagulant effect was observed. It was well tolerated with only transient, minor side effects. Phase III trials using ciraparantag to reverse edoxaban have been planned.

The Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis has produced guidelines on when antidotes to direct oral anticoagulants should be used, which are summarized in *Figure 1* (Levy et al, 2016).

Emergency surgery

In addition to patients who are actively bleeding, the management of patients who require emergency surgery is also challenging. If safe to do so, delaying surgery until the direct oral anticoagulant is cleared from the circulation will result in normal haemostasis (*Table 2*). In the event that it is not possible to wait, discussion with a haematologist is advised. Potential treatment options, when a direct reversal agent is not available, are similar to those for acute bleeding: tranexamic acid, prothrombin complex concentrate or activated prothrombin complex concentrate (but generally withheld unless patient is actively bleeding in theatre). Of note, spinal or epidural anaesthesia would be absolutely contraindicated in this scenario when a direct reversal agent is not available.

Overdose

In the event of an overdose of a direct oral anticoagulant in a patient who is not actively bleeding, options include:
- Activated charcoal (within 2 hours of dabigatran and 6 hours for rivaroxaban ingestion) to reduce further absorption (Makris et al, 2012)
- Tranexamic acid 1 g
- Idarucizumab and andexanet alfa do not necessarily need to be used for non-bleeding patients, although this should be assessed on a case-by-case basis
- Consideration of haemodialysis for dabigatran overdose if idarucizumab is not available – 4 hours of intermittent haemodialysis has been shown to halve dabigatran levels (Khadzhynov et al, 2013). Haemodialysis is ineffective for clearance of other direct oral anticoagulants as they are much more highly protein-bound than dabigatran.

Drug levels can be monitored to ensure clearance.

Conclusions

In the absence of a specific reversal agent for direct oral anticoagulants, a number of general measures can be applied in emergency situations and the outcomes of major bleeds are no worse than those with warfarin. Standard tests of coagulation have limited use in assessing the anticoagulation effect of the direct oral anticoagulants and specific assays should be used. Idarucizumab is a specific reversal agent for dabigatran and is now licensed and National Institute for Health and Care Excellence approved. Andexanet alfa, a specific reversal agent for factor Xa inhibitors, is in phase III trials. **BJHM**

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KEY POINTS

- Direct oral anticoagulant therapy is associated with a reduced risk of intracranial bleeding and major bleeding when compared with warfarin.
- The anticoagulant activity of direct oral anticoagulants can be estimated from knowledge of time of last dose, their half-life and renal clearance.
- Traditional coagulation tests (prothrombin time and activated partial thromboplastin time) provide limited information on the residual anticoagulant effect of direct oral anticoagulants. A normal prothrombin time and activated partial thromboplastin time does not exclude a significant anticoagulant effect of a direct oral anticoagulant.
- Specialized tests can be used to quantify direct oral anticoagulant effects more accurately.
- Idarucizumab (Praxbind), a direct reversal agent of dabigatran, is now licensed and National Institute for Health and Care Excellence approved in the UK. The factor Xa reversal agent andexanet alfa is in phase III trials.
- If direct reversal agents are not available in the event of significant bleeding on direct oral anticoagulants, consider 1 g intravenous tranexamic acid, prohaemostatic agents such as prothrombin complex concentrate or activated prothrombin complex concentrate, or haemodialysis for patients on dabigatran.
- Non-specialists should be aware of local protocols and consult a haematologist for advice on management of patients with major bleeding taking a direct oral anticoagulant.

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