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The reversal of anticoagulation in clinical practice

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ABSTRACT

Widespread use of anticoagulant drugs for treatment and prevention of thromboembolic events means it is common to encounter patients requiring reversal of anticoagulation for management of bleeding or invasive procedures. While supportive and general measures apply for patients on all agents, recent diversification in the number of licensed agents makes an understanding of drug-specific reversal strategies essential. Recognising effects upon, and limitations of, laboratory measures of coagulation also plays an important role. An understanding of reversal strategies alone is insufficient to competently care for patients who may require anticoagulation reversal. It is also necessary to reduce the need for reversal through correct prescribing and by employing appropriate periprocedural bridging strategies for elective and semi-elective procedures. Finally, consideration of whether and when to reintroduce an anticoagulant drug following reversal is important not only to balance bleeding and thrombotic risks for individual patients but also for timely management of discharge.

Introduction

Since the earliest clinical investigation of heparin in the 1930s,[1] the indications for anticoagulant drugs and the number of commonly encountered agents has increased (Table 1). These drugs act by inhibiting different stages of the coagulation cascade that culminates in the formation of cross-linked fibrin (Fig 1). It is common in clinical practice to encounter patients requiring anticoagulation reversal. Indications for anticoagulation reversal include:

- bleeding
- elective or emergency invasive procedures or surgery
- over-anticoagulation, due to accidental or intentional overdose, drug interactions or reduced excretion.

A decision to reverse anticoagulation must weigh the benefits of anticoagulation reversal in terms of stopping bleeding or reduction of bleeding risk against the risk of development or extension of thrombosis while anticoagulation is reversed. This can be particularly challenging in situations such as bleeding in patients with mechanical heart valves.

This article will focus on urgent reversal of anticoagulation. It is important that care of patients on anticoagulant drugs is optimised so that the need for urgent reversal is minimised. The benefits should be weighed against a patient's individual bleeding risk when deciding to anticoagulate and in choice of anticoagulant, and factors including potential drug–drug interactions and the need for dose reduction considered.[2] Antiplatelet agents should be discontinued when an anticoagulant is used, except in certain circumstances.[3] An anticoagulation plan should be prepared in advance of elective procedures so that urgent reversal is not required. Table 2 summarises the length of time for which different anticoagulants should be stopped prior to an invasive procedure. Some procedures (eg joint injections,

Key points

The type of anticoagulant, dose, timing of last dose and indication are significant points to establish when making decisions about anticoagulation reversal

For elective procedures and surgery, the need for anticoagulation reversal should be avoided by determining whether cessation of anticoagulant is required, and by following local bridging protocols

In patients bleeding while on anticoagulants, supportive treatment including blood components and local measures should be employed alongside the steps taken to reverse the anticoagulant effect

INR and APTT can be used to assess anticoagulant activity of vitamin K antagonists and unfractionated heparin respectively, but therapeutic ranges for these drugs cannot be used to interpret clotting tests in patients on other anticoagulants

Specific reversal agents exist for vitamin K antagonists (vitamin K and prothrombin complex concentrate), heparins (protamine sulphate) and dabigatran (Idarucizumab) but there is currently no specific reversal agent for fondaparinux or for the oral factor Xa inhibitors

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Table 1. Key pharmacokinetic features of common anticoagulant drugs

Name	Excretion	Plasma half-life
Warfarin	Hepatic metabolism to inactive metabolites excreted in urine	Effective half-life 40 h
UFH	Rapid endothelial cell internalisation (saturateable), slower renal clearance	45–90 min
LMWH	Predominantly renal	4 h
Fondaparinux	70% renal	17–21 h
Argatroban	Hepatic	45 min
Dabigatran	80% renal	13 h
Apixaban	25% renal, 75% hepatic	12 h
Edoxaban	35% renal, 65% hepatic	10–14 h
Rivaroxaban	25% renal, 75% hepatic	5–9 h

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

endoscopic procedures with a low risk of bleeding and cataract surgery) can be performed without stopping anticoagulants. If anticoagulation is not lifelong, consideration should be given to deferring the procedure until treatment is completed. If anticoagulant treatment must be interrupted, bridging protocols should be employed that take into account drug pharmacokinetics and bleeding and the thrombotic risk.[4]

In urgent situations where reversal is required a combination of general measures which apply regardless of which anticoagulant a patient is taking, and drug-specific management is used. Drug specific reversal strategies are summarised in Table 3. General measures include making an assessment of the dose and timing of the drug, considering its rate of elimination, and in the case of bleeding resuscitating the patient and identifying and treating the source of bleeding. The efficacy and evidence base for specific reversal strategies varies between anticoagulants, and an understanding of this, is important when making choices about reversal.

General measures for anticoagulation reversal

Baseline information and investigations

It is important to establish what anticoagulant a patient is taking, the dose, frequency, timing of last dose and indication. The anticoagulant should be stopped. Other drugs that can affect bleeding (eg antiplatelet agents and non-steroidal anti-inflammatory drugs) should also be noted. Blood tests must include a full blood count and clotting screen (prothrombin time [PT], activated partial thromboplastin time [APTT], thrombin time [TT] and fibrinogen). Additional clotting samples for drug-specific tests may be requested, guided by discussion with haematology or the coagulation laboratory. Liver function tests and renal function tests are essential to provide information on drug elimination.

Supportive measures

Bleeding patients should receive appropriate resuscitation and blood-component support, which in the situation of major haemorrhage should follow national guidelines.[5]

Pharmacological measures

Tranexamic acid 1 g every 8 hours should be considered for patients requiring reversal of anticoagulation. Tranexamic acid is beneficial in patients bleeding following trauma, although these

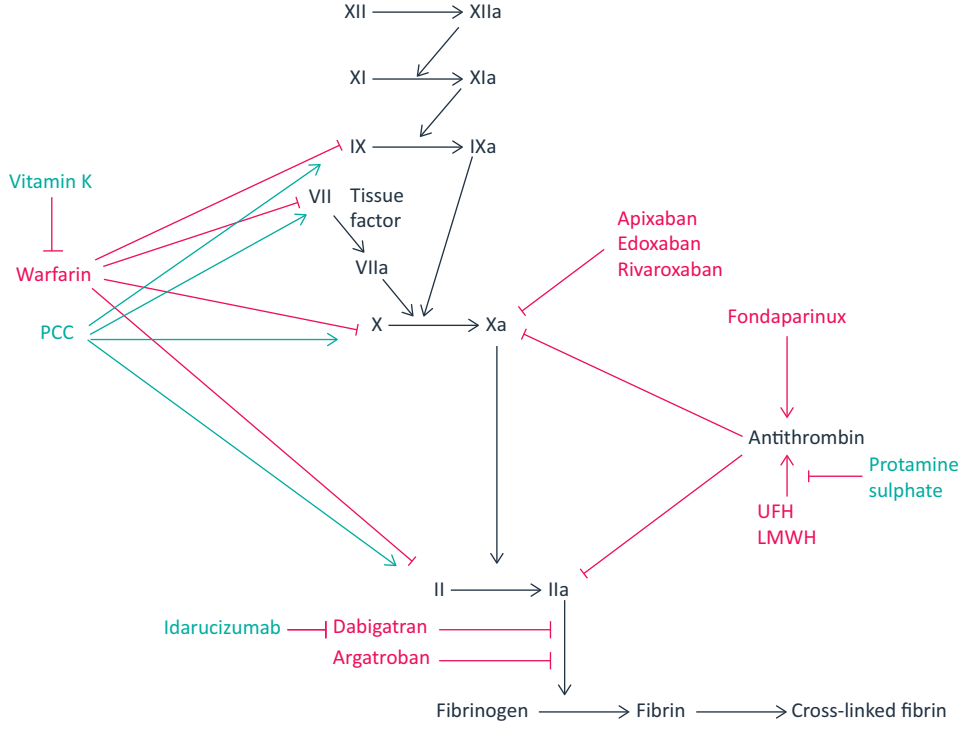

Fig 1. Representation of stage of action of anticoagulants and their reversal agents on a schematic clotting cascade. This diagram is intended to summarise drug actions but does not reflect the complexity of haemostasis believed to occur physiologically, where cell surface molecules regulate initiation, amplification and propagation of thrombus.[31] Please see the main text for details on specific drug and reversal agent mechanisms. PCC = prothrombin complex concentrate; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; → = promotes; ⊢ = suppresses

Table 2. Approximate time prior to surgery or invasive procedure for which anticoagulant drug should be stopped. National[4] and local guidelines and product literature should be consulted for specific details

Drug	Duration between stopping and invasive procedure or surgery		Duration before stopping and invasive procedure or surgery in impaired renal function – creatinine clearance <30	
	Low bleeding risk procedure	High bleeding risk procedure	Low bleeding risk procedure	High bleeding risk procedure
Warfarin	5 days			
UFH	4 hours			
LMWH	Prophylactic dose, 12 hours Treatment dose, 24 hours		If used, discuss dose and timing with haematology	
Fondaparinux	24–42 hours		If used, discuss dose and timing with haematology	
Argatroban	4 hours			
Dabigatran	24 hours	48 hours	Cr Cl > 50 to <80: 24–48 hours Cr Cl > 30 to <50: 48–72 hours	Cr Cl > 50 to < 80: 48–72 hours Cr Cl > 30 to <50: 72–96 hours
Apixaban	24 hours	48 hours	48 hours	72 hours
Edoxaban	24 hours	48 hours	48 hours	72 hours
Rivaroxaban	24 hours	48 hours	48 hours	72 hours

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

data do not relate specifically to those taking anticoagulants.[6] It is reasonable to consider tranexamic acid for patients on anticoagulants with non-traumatic bleeding, provided there are not contraindications. Consideration of tranexamic acid is recommended prior to urgent surgery[4] and in adults having surgery who are expected to have moderate blood loss.[7]

Local measures and intervention

Attempts should be made to identify the site of bleeding and where possible apply local measures to stop it eg pressure, endoscopy, surgery and interventional radiology.

Drug elimination

The extent to which an anticoagulant drug is contributing to bleeding or bleeding risk should be considered. If the timing, excretion route and elimination time (Table 1) suggest the drug has been cleared, specific reversal agents should not be employed. Haemodialysis and haemofiltration have little utility in anticoagulant reversal.

Table 3. Current drug-specific reversal strategies and novel agents under development

Drug	Drug-specific reversal strategy	Agents likely to be available in the future
Vitamin K antagonists	Vitamin K, four-factor PCC	
Unfractionated heparin	Protamine sulphate	Ciraparantag
Low molecular weight heparin	Protamine sulphate	Andexanet alfa, Ciraparantag
Fondaparinux	Consider recombinant activated factor VII	Andexanet alfa, Ciraparantag
Dabigatran	Idarucizumab	Ciraparantag
Factor Xa inhibitors	Four-factor PCC	Andexanet alfa, Ciraparantag

PCC = prothrombin complex concentrate

Specific management

Vitamin K antagonists

Vitamin K antagonists exert their anticoagulant effect by inhibiting the vitamin K dependent carboxylation of coagulation factors II, VII, IX and X (Fig 1). In the UK, warfarin is the most commonly prescribed vitamin K antagonist and we will focus on reversal of warfarin in this article. Acenocoumarol and phenindione may be encountered, and urgent reversal of all three agents follows similar principles.[8] Where cessation or dose-reduction is insufficient, reversal can be achieved with oral or intravenous vitamin K or by replacement of the affected factors, a choice determined by the desired rapidity and depth of reversal.

In patients with a moderately elevated international normalised ratio (INR) (5–8) without bleeding, reversal is usually achieved by withholding one or two doses of warfarin, followed by dose reduction. INRs above 8 confer a substantially increased bleeding risk so anticoagulation should be reversed with oral vitamin K 1–5 mg. Oral vitamin K could also be considered in INRs of 5–8 when additional bleeding risk factors are present.[9]

Oral or intravenous vitamin K administration achieves a similar INR after 24 hours, but a more rapid initial effect occurs with the intravenous route, making it preferable in bleeding patients.[10] For non-major bleeding, anticoagulation reversal can be managed with 1–3 mg intravenous vitamin K.[9]

In major bleeding or for emergency procedures which cannot be delayed until vitamin K has taken effect, rapid reversal of warfarin can be achieved using four-factor prothrombin complex concentrates (PCC) at a dose of 25–50 units/kg. These contain factors II, VII, IX and X and the vitamin K dependant anticoagulant proteins protein C and protein S. PCC containing lower levels of factor VII are termed three-factor PCC. They do not

produce a good correction of the INR and are not recommended.[9] PCC is superior to fresh-frozen plasma in achieving rapid correction of INR in patients with bleeding[11] and those requiring urgent warfarin reversal for surgery or procedures.[12] 5 mg vitamin K should be given concurrently to maintain reversal when factor levels fall. PCCs should be avoided outside emergency situations; they carry risks associated with plasma-derived products (such as viral infection) and are associated with a risk of thrombosis. The limited data on thrombosis suggests the risk is relatively low and it is difficult to distinguish from other patient risk factors.[13,14] Nonetheless, caution is advised in patients with recent thrombosis or surgery, cardiovascular disease, or liver disease.

Unfractionated heparin

Unfractionated heparin (UFH) enhances the activity of antithrombin, an endogenous negative regulator of the clotting cascade that inactivates thrombin and factor Xa (Fig 1) as well as factors IXa, XIa, XIIa. UFH has a short half-life (Table 1) so rapid reversal is achievable by stopping the infusion.[15] Protamine sulphate is licensed for reversal of UFH, acting by preventing its interaction with antithrombin. Protamine sulphate is given as a slow intravenous bolus at a dose calculated from the number of units of UFH received in the last 2 hours, with 1 mg protamine sulphate neutralising approximately 80–100 units of UFH. In excess, protamine itself acts as an anticoagulant. Protamine is derived from fish sperm and there is a risk of allergic reactions, especially in individuals with previous protamine exposure, fish allergies and following vasectomy.

Low molecular weight heparin

Low-molecular-weight heparins (LMWH) contain shorter polymers than UFH, and their interaction with antithrombin affects Xa more than thrombin.[1] Protamine sulphate is less effective at reversing anti-Xa activity than antithrombin activity but is recommended for LMWH reversal based on an absence of alternatives and evidence from animal studies and small retrospective studies.[16] Up to 8 hours from LMW heparin administration protamine sulphate 1 mg/100 units can be considered, with a further dose of 0.5 mg/100 units if there is ongoing bleeding. If LMWH was given over 8 hours earlier, lower doses may be used.[15]

Fondaparinux

Fondaparinux is a synthetic pentasaccharide not a LMWH but is considered here as it is used in similar indications and has a similar mechanism of action, by promoting the interaction of antithrombin and factor Xa (Fig 1). Protamine sulphate has no activity against fondaparinux. Recombinant activated factor VII can be considered for critical bleeding,[17] but this is an unlicensed indication.

Direct thrombin antagonists

Dabigatran and argatroban are direct thrombin antagonists. Dabigatran is given as an oral pro-drug dabigatran etexilate. Argatroban is given intravenously, its main use being in heparin-induced thrombocytopaenia. By inhibiting thrombin these drugs reduce the conversion of fibrinogen to fibrin (Fig 1). Argatroban has a short half-life of around 45 minutes – stopping the infusion and initiating general measures should achieve reversal.

There is a licensed antidote, idarucizumab, for rapid reversal of dabigatran for emergency surgery and procedures or in life-threatening or uncontrolled bleeding. It is an engineered antibody fragment that mimics structural features of thrombin to bind dabigatran with high affinity, without binding other thrombin substrates.[18] In an open-label study, idarucizumab rapidly and completely reversed laboratory measures of anticoagulation in patients taking dabigatran.[19]

Factor Xa inhibitors

Rivaroxaban, apixaban and edoxaban act by inhibiting Xa (Fig 1). Minor bleeding should be managed using local measures and delaying the next dose or discontinuing the drug. For more severe bleeding, tranexamic acid and supportive measures should be used but there no licensed reversal agent. For life-threatening bleeding PCC may be considered;[17] however, this is an unlicensed indication and should be discussed with a haematologist. The rationale is that elevation of factor levels above normal will promote haemostasis, but there is limited evidence to suggest an improvement in laboratory measures of clotting and in bleeding from studies in animals and healthy individuals.[20] Prospective cohort studies have reported effective haemostasis using PCC, with rates of thromboembolic complications comparable to patients receiving PCC for warfarin reversal.[21,22]

What is the role of laboratory measurement?

Vitamin K antagonists and UFH are routinely monitored using the INR and APTT respectively. Anti Xa activity is a measure of LMWH anticoagulant effect, which may guide protamine doses.[16]

The effect of direct thrombin antagonists and factor Xa inhibitors on routine clotting tests, and the utility of these tests in guiding reversal of anticoagulation is more complex. Therapeutic ranges for vitamin K antagonists and UFH should not be used to interpret clotting results in the presence of other agents. Drug-specific assays may not be available in all laboratories or out of hours. It is important to inform the laboratory of the type of anticoagulant and the timing of the last dose. The effect on routine clotting tests can depend upon which laboratory reagents are used.[23,24] Furthermore, the degree of intra-individual variation in drug levels (between peak and trough levels) and the degree of variation between individuals taking therapeutic doses must be taken into account when interpreting drug levels.[25]

Table 4 summarises possible interpretations of normal and prolonged PT, APTT and TT in the presence of thrombin antagonists and Xa inhibitors, and the commonest drug-specific assays for each agent.

Whether and when to restart anticoagulant drugs following reversal

The bleeding risk associated with restarting a drug must be balanced against the thrombotic risk while off anticoagulation. If haemostasis is secured following a procedure or an intervention for bleeding, a pragmatic approach is to restart anticoagulation following local bridging protocols and monitoring for further bleeding.[4] Often a prophylactic dose of LMWH or a direct oral anticoagulant (DOAC) can be started 6–8 hours post procedure. Decisions are more challenging following reversal for bleeding when no procedure to achieve haemostasis is performed, for example

Table 4. Effect of direct thrombin antagonists and Xa inhibitors on clotting tests, and drug-specific assays

Drug	PT		APTT		TT		Drug specific assay
	Normal	Prolonged	Normal	Prolonged	Normal	prolonged	
Dabigatran	Below or within therapeutic levels	Supra-therapeutic levels	Below or within therapeutic levels	Within or above therapeutic levels	Likely little or no drug present	Cannot interpret	Dilute thrombin time or ecarin clotting time
Rivaroxaban	Therapeutic levels unlikely but cannot be excluded	Therapeutic or supratherapeutic levels	Therapeutic or subtherapeutic levels	Therapeutic or supratherapeutic levels	Unaffected		Rivaroxaban-specific anti Xa activity
Apixaban	Insensitive, cannot be assessed with these methods				Unaffected		Apixaban-specific anti Xa activity
Edoxaban	Therapeutic levels cannot be excluded		Not useful		Unaffected		Edoxaban-specific anti Xa activity

APTT = activated partial thromboplastin time; PT = prothrombin time; TT = thrombin time

in intracranial haemorrhage. For some patients, especially those with traumatic intracranial haemorrhage and a persistent risk of falls, consideration may be given to discontinuing anticoagulation. Data on the optimal time to reintroduce anticoagulation following intracranial haemorrhage is minimal and conflicting, with suggested times ranging from 4–7 days[26] to 10–30 weeks.[27]

Future prospects

Two 'universal' reversal agents are under development. Andexanet alfa, recently licensed in America, is a recombinant Xa modified to lack catalytic and membrane-binding activity but retain affinity to Xa inhibitors, LMWH, fondaparinux and antithrombin.[28] It corrects laboratory measures of coagulation in patients with major bleeding taking direct Xa inhibitors or the LMWH enoxaparin. Rates of thrombosis are higher than in studies examining PCC, but it is unclear to what extent this reflects interruption of anticoagulation and underlying pathology.[29] Ciraparantag is a synthetic molecule that binds UFH, LMWH, fondaparinux, Xa inhibitors and dabigatran. It has been examined in healthy volunteers given edoxaban where it corrected laboratory measures of clot formation.[30] ■

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