

New oral anticoagulant drugs – mechanisms of action

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Summary

In 2008, two new oral anticoagulant drugs were registered in Australia for the prevention of venous thrombosis after elective knee or hip replacement. Rivaroxaban is a direct reversible competitive antagonist of activated factor X. Dabigatran etexilate is a direct reversible competitive antagonist of thrombin. Both drugs are effective anticoagulants which offer potential advantages over heparin and warfarin.

Key words: dabigatran etexilate, rivaroxaban.

(*Aust Prescr 2010;33:38–41*)

Introduction

Since the 1960s warfarin has been the only oral anticoagulant drug in regular use for treating patients with thromboembolic disease. In November 2008 the Therapeutic Goods Administration approved two new oral anticoagulant drugs – rivaroxaban and dabigatran etexilate – for the prevention of venous thrombosis in patients having elective knee or hip replacement.

Mechanisms of action

Rivaroxaban and dabigatran etexilate have low molecular weights. They have specific and restricted anticoagulant activities (Fig. 1). Although their mechanisms of action are different, the specificity of activity has no known clinical relevance and both drugs are effective anticoagulants.

Rivaroxaban is a competitive reversible antagonist of activated factor X (Xa). Factor Xa is the active component of the prothrombinase complex that catalyses conversion of prothrombin (factor II) to thrombin (factor IIa).

Dabigatran etexilate is a competitive reversible non-peptide antagonist of thrombin. Thrombin is a multifunctional enzyme which converts fibrinogen to fibrin, cross-linking fibrin monomers via activation of factor XIII and augmenting further thrombin production via the activation of factors V and VIII. It also activates platelets, generates anticoagulant activity via

activation of protein C and initiates numerous cellular processes including wound healing. Most of the actions of thrombin are inhibited *in vitro* by dabigatran etexilate.

Pharmacokinetics

The essential properties of the new anticoagulants are compared to warfarin in Table 1. Their main advantages are a rapid onset of anticoagulant effect, more predictable pharmacokinetics, and a lower potential for clinically important interactions with food, lifestyle and other drugs. There is no requirement for routine monitoring and dose adjustment as required with warfarin.

Rivaroxaban

Rivaroxaban¹ 10 mg tablets are well absorbed (80% bioavailability) with no effect of food on absorption or pharmacokinetic parameters. Plasma concentrations peak at 2.5–4 hours. The plasma elimination half-life is 5–9 hours in young adults and 11–13 hours in older people due to the age-related decline in renal function. This permits once- or twice-daily dosing.

Rivaroxaban is metabolised by liver enzymes, principally cytochrome P450 3A4, and also by cytochrome-independent mechanisms. There are no known active metabolites.

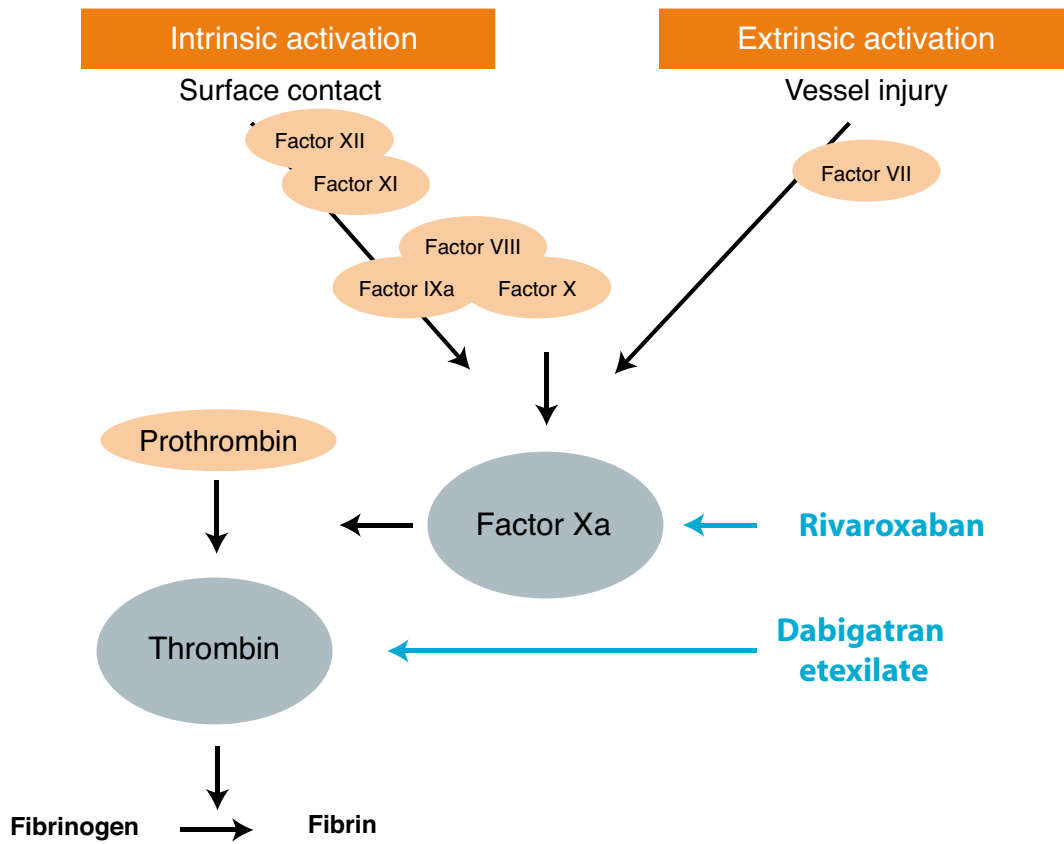
Rivaroxaban has a dual mechanism of excretion. Approximately 66% of the dose is excreted via the kidneys, in roughly equal proportions of rivaroxaban and inactive metabolites. The remainder is excreted by the faecal-biliary route. Intestinal excretion of rivaroxaban appears to be mediated, at least in part, by P-glycoprotein, a transport protein, because potent P-glycoprotein inhibitors will increase plasma concentrations of rivaroxaban.

Dabigatran

Dabigatran is a hydrophilic polarised membrane-impermeable molecule which is not absorbed after oral dosing. The oral formulation, dabigatran etexilate,² is a prodrug with low bioavailability (approximately 6.5%) and its absorption in the stomach and small intestine is dependent on an acid

Fig. 1

Site of action of new anticoagulant drugs



environment. To promote this microenvironment, dabigatran etexilate is formulated in tartaric acid-containing capsules. Esterases found in enterocytes, plasma and the liver rapidly convert dabigatran etexilate to dabigatran. The drug enters the portal vein as a combination of prodrug and active compound, but once in the liver bioconversion of the prodrug is completed. Plasma concentrations of dabigatran peak 0.5–2 hours after an oral dose.

The plasma elimination half-life is 7–9 hours, and 12–14 hours in older people. This permits once- or twice-daily dosing. About 20% of dabigatran is conjugated and excreted via the biliary system. The cytochrome P450 system plays no part in the metabolism of dabigatran and there are no active metabolites. The remaining 80% of circulating dabigatran is excreted unchanged via the kidneys. The medication is presented in two formulations, 75 mg and 110 mg capsules.

Interactions

Diseases and drug interactions may alter the anticoagulant effect of these drugs. This can reduce efficacy or increase the risk of bleeding.

Rivaroxaban

Disease- or drug-induced reductions in faecal and renal clearance can increase the anticoagulant effect of rivaroxaban. It is currently contraindicated in patients with severe liver disease because metabolic inactivation may be impaired, and in patients with severe renal impairment (creatinine clearance under 30 mL/min).

To date, clinical trials have found no significant pharmacokinetic interactions with aspirin, non-steroidal anti-inflammatory drugs, antacids, histamine H₂-receptor antagonists or digoxin. Caution is needed in patients receiving treatment with potent inhibitors of both CYP3A4 and P-glycoprotein, such as ketoconazole, macrolide antibiotics (for example clarithromycin) or protease inhibitors (for example ritonavir, atazanavir). These drugs increase the anticoagulant effect.

Dabigatran

Reduced renal clearance increases the total exposure (area under the concentration-time curve – AUC) and the elimination half-life of dabigatran. This can cause an exaggerated anticoagulant effect. In elderly patients with

Table 1

Comparison of oral anticoagulants

Property	Warfarin	Rivaroxaban	Dabigatran etexilate
Anticoagulant action	Reduced synthesis of functional clotting factors II, VII, IX and X	Direct competitive reversible inhibition of activated factor X	Direct competitive reversible inhibition of thrombin
Prodrug	No	No	Yes
Bioavailability	Almost 100%	80%	6.5%
Onset of anticoagulant action	36–72 hours	Within 30 minutes T_{max} 2.5–4 hours	Within 30 minutes T_{max} 0.5–2 hours
Duration of anticoagulant action	48–96 hours	24 hours	24–36 hours
Elimination half-life (anticoagulant activity)	20–60 hours	5–9 hours in young adults 11–13 hours in older adults	7–9 hours in young adults 12–14 hours in older adults
Predictable pharmacokinetics	No	Yes	Yes
Interactions with diet or alcohol	Yes, clinically significant	Low potential	Low potential
Drug interactions	Numerous clinically significant interactions	Potent cytochrome P450 3A4 and P-glycoprotein inhibitors augment anticoagulant effect (e.g. ketoconazole, clarithromycin, ritonavir)	Proton pump inhibitors reduce absorption Possible interactions with P-glycoprotein inhibitors and inducers
Dosing and dose adjustments	Dose individualised for each patient, requires frequent INR monitoring and adjustment	Fixed according to clinical indication	Fixed according to clinical indication
Monitoring	INR every 1–2 weeks	No routine monitoring required	No routine monitoring required
Use in liver failure	Contraindicated or caution advised	Contraindicated as hepatic metabolism	Possibly safe as no hepatic metabolism but caution advised
Use in severe renal impairment	No dose adjustment required	Increased drug exposure and elimination half-life in renal impairment Safety and dosing not yet established Contraindicated in severe renal impairment	Increased drug exposure and elimination half-life in renal impairment Safety and dosing not yet established Contraindicated in severe renal impairment
Use in pregnancy	Category D Teratogenic in first trimester	Contraindicated as safety not established (excluded from clinical trials)	Contraindicated as safety not established (excluded from clinical trials)
Reversibility after cessation	Several days, requires synthesis of clotting factors	24 hours, dependent on plasma concentration and elimination half-life	24–36 hours, dependent on plasma concentration and elimination half-life
Antidote	Immediate reversal with plasma or factor concentrate Reversal within hours with vitamin K	None available	None available

INR international normalised ratio

 T_{max} time to maximum concentration

calculated moderate (creatinine clearance 30–50 mL/min) or severe (creatinine clearance 10–30 mL/min) renal insufficiency, the AUC was increased 2.7 and 6-fold respectively, while the plasma elimination half-life increased at least twofold. Dabigatran should not be used in patients with severe renal impairment (creatinine clearance under

30 mL/min). It does not undergo hepatic metabolism and no change in total dabigatran exposure was seen in 12 patients with moderate hepatic insufficiency (Child-Pugh B classification).

The absorption of dabigatran etexilate is reduced by 20–25% if patients are also given proton pump inhibitors.

Co-administration of dabigatran etexilate with food delays the peak plasma concentration by two hours and increases the AUC of dabigatran by 27%. In postoperative patients, the peak plasma concentrations are not achieved for 7–9 hours if dabigatran is given on the day of surgery. These two observations do not seem clinically important.

Clinical studies have not found pharmacokinetic interactions with atorvastatin or diclofenac, consistent with the observation that the cytochrome P450 system plays no role in the metabolism of dabigatran. Interactions have been found with P-glycoprotein inhibitors (quinidine, amiodarone) with increased total dabigatran exposure (AUC increased up to twofold). P-glycoprotein inducers may reduce systemic exposure of dabigatran. No changes in digoxin (a P-glycoprotein substrate) or dabigatran concentrations were noted when the drugs were co-administered.

Safety

Rivaroxaban and dabigatran etexilate have not been shown to be safe and effective in important groups of patients who may require anticoagulant therapy. These groups include patients with severe renal or hepatic impairment (dabigatran does not undergo hepatic metabolism and may be safe in patients with hepatic disease), children, and pregnant or lactating women.

The major adverse effect of all anticoagulant medications is bleeding. There is no published evidence yet that the new anticoagulant medications cause less bleeding than heparin or warfarin. Fatal and major bleeding will be further increased with concomitant anticoagulant and antiplatelet therapies. Antiplatelet medications should be avoided while on new anticoagulant medications, unless the benefits of combined therapy outweigh the risks. No antidotes to reverse rivaroxaban or dabigatran anticoagulant effects are available. The anticoagulant effect will not be reversed by administration of vitamin K or plasma infusion.

Compared to enoxaparin, there is no significant increase in abnormal liver function tests with either drug. The possibility of hepatotoxicity with rivaroxaban cannot be excluded until data are available from longer-term usage (up to 24 months) in venous thrombosis treatment, and stroke prevention studies.³

Conclusion

Rivaroxaban and dabigatran etexilate are two oral anticoagulant medications recently registered in Australia for prevention of venous thrombosis after lower limb arthroplasty. Both drugs have specific but different mechanisms of action, a rapid onset of anticoagulant activity, less variable pharmacokinetics than warfarin, and a low

potential for interactions with diet and other drugs. They are given in fixed doses and do not require routine monitoring. The safety and efficacy of these drugs in the prevention of venous thrombosis in patients other than those having arthroplasty remains to be established in clinical trials.

References

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Dr Brighton has received an honorarium from Bayer for an advisory role on steering committees for the EINSTEIN phase II and III clinical studies (rivaroxaban). He has received honoraria from Boehringer Ingelheim for an Australian advisory committee role and lectures.

Self-test questions

The following statements are either true or false (answers on page 59)

1. The doses of rivaroxaban and dabigatran etexilate are adjusted according to the patient's INR.
2. The anticoagulant effects of rivaroxaban and dabigatran etexilate are reversed by vitamin K.

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