Dabigatran

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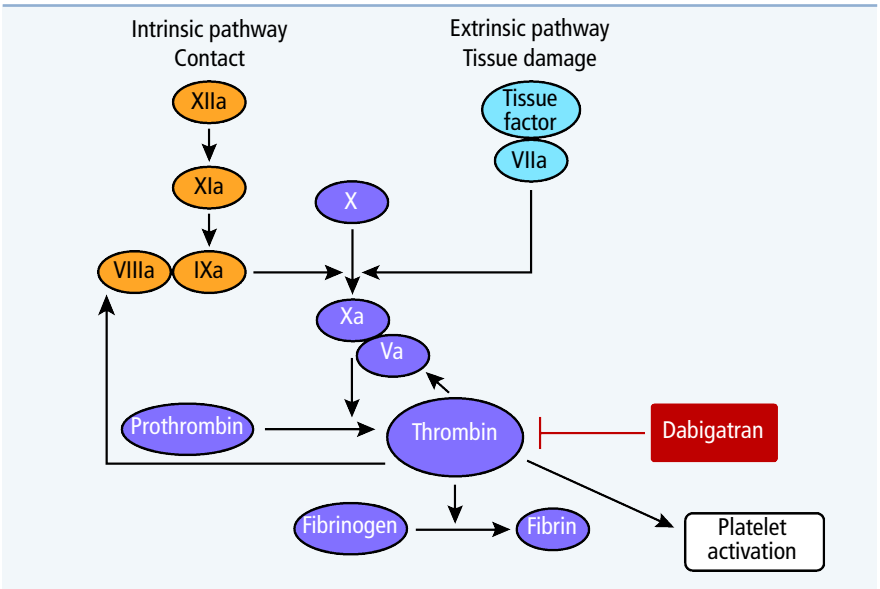

Figure 1. Pharmacological action of dabigatran etexilate. Dabigatran is a direct inhibitor of thrombin, which is central to the coagulation process. (Adapted from: Eriksson BI, *et al.* Dabigatran etexilate. *Nature Rev Drug Discover* 2008;7:557–8)

Introduction

Arterial and venous thromboembolism are major causes of death and disability. Atrial fibrillation (AF), the most common sustained cardiac arrhythmia in the UK, results in a five-fold increase in stroke risk. Anticoagulation reduces stroke risk and death in patients at risk of thromboembolism. Warfarin is currently the mainstay of treatment, but there are many problems associated with its use including the need for frequent monitoring and dose adjustment, serious adverse effects, most notably intracranial haemorrhage, and multiple food and drug interactions. The prevention and treatment of venous thromboembolism (VTE) are also labour intensive requiring parenteral anticoagulants such as low molecular weight heparins (LMWHs) or warfarin for long-term treatment. The development of a new oral anticoagulant has been keenly anticipated. Dabigatran, the first direct thrombin inhibitor to be licensed for use in the UK, represents an attractive alternative to warfarin and LMWHs in certain patient groups.

Pharmacology

Figure 1 outlines the pharmacological action of dabigatran. Dabigatran is a direct thrombin inhibitor which binds potently but reversibly to the active site of thrombin, rendering free and fibrin-bound thrombin inactive. Dabigatran inhibits platelet aggregation, tissue-factor induced thrombin generation in platelet-deplete plasma, and reduces endogenous thrombin production. Inhibition of thrombin prevents conversion of fibrinogen to fibrin, therefore preventing thrombosis. Reversible inhibition may account for safer and more predictable anticoagulation. The drug is administered as dabigatran etexilate, an oral prodrug, which is rapidly absorbed and converted by a serum esterase to the active form dabigatran. Rapid anticoagulation is achieved as it reaches peak plasma concentration within 2 hours. It is distributed over 4–8 hours, has a terminal half-life of 12–17 hours and reaches steady state concentration within three days. Dabigatran is not metabolised by cytochrome P450 isoenzymes, meaning fewer potential drug interactions than warfarin. It is primarily (80%) excreted by the kidneys so the dose will need to be reduced in renal impairment and avoided if eGFR is <30ml/min/1.73m^2.

Trials of safety and efficacy

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial recruited 18 113 patients with non-valvular AF and one or more stroke risk factors.[1] Patients were randomised to dabigatran 110mg twice daily or dabigatran 150mg twice daily, in a double blinded fashion, or open-label dose-adjusted warfarin to achieve target INR 2–3. Median follow up was two years. For the primary efficacy outcome of stroke or systemic embolism, dabigatran 110mg proved non-inferior to warfarin (annual event rate 1.53% vs 1.69%). Dabigatran 150mg was superior to warfarin in reducing the risk of stroke and systemic embolism (annual event rate 1.11% vs 1.69%). Patients receiving dabigatran 110mg had a significantly lower rate of major bleeding than those receiving warfarin (2.87% vs 3.57%). Dabigatran 150mg caused similar rates of major bleeding compared with warfarin (3.32% vs 3.57%). Rates of intracranial bleeding were higher with warfarin than dabigatran 110mg (0.76% vs 0.23%) or dabigatran 150mg (0.32%). The rate of myocardial infarction was higher with dabigatran 110mg (0.82%) and dabigatran 150mg (0.81%) than warfarin (0.64%); however, comparisons failed to show statistical significance. Dabigatran 150mg caused significantly higher rates of gastrointestinal bleeding compared with warfarin (annual rate 1.51% vs 1.02%).

The RE-NOVATE and RE-MODEL studies compared dabigatran 150mg and 220mg once daily with enoxaparin 40mg once daily for the prevention of VTE following elective hip and knee arthroplasty, respectively.[2,3] Primary efficacy outcomes were identical: a composite of total VTE and all-cause mortality during treatment. In RE-NOVATE, event rates were 6.7% with enoxaparin vs 6.0% with dabigatran 220mg and 8.6% with dabigatran 150mg. In RE-MODEL, event rates were 37.7% with enoxaparin, 36.4% with dabigatran 220mg and 40.5% with dabigatran 150mg. In both trials, dabigatran proved non-inferior to enoxaparin and safety profiles were similar.

The RE-MOBILIZE study compared the North American regimen of enoxaparin 30mg twice daily with dabigatran 150mg or 220mg once daily for the prevention of VTE following knee arthroplasty.[4] VTE rates were 31% with dabigatran 220mg, 34% with dabigatran 150mg and 25% with enoxaparin. Both doses of dabigatran were inferior to enoxaparin in terms of efficacy. Safety profiles were similar. The authors proposed that differences between these results and the results of the European studies may, in part, be explained by higher dose and more prolonged treatment with enoxaparin.

Specific evidence for use in diabetes

In the RE-LY trial, subgroup analysis of 4221 patients with diabetes revealed lower rates of stroke or systemic embolism with dabigatran 110mg (1.76%) and dabigatran 150mg (1.46%) compared with warfarin (2.32%). P-values for interaction between diabetes and rates of the primary outcome depending on treatment group were non-significant.

Discussion

Dabigatran is a promising new anticoagulant therapy which has the potential to replace warfarin and enoxaparin in certain patient groups. In the RE-LY trial, dabigatran 150mg has superior efficacy compared with warfarin for the prevention of stroke and systemic embolism in patients with AF. It has similar efficacy compared with enoxaparin 40mg, in reducing the risk of VTE following hip and knee arthroplasty. Dabigatran has demonstrated an equivalent safety profile in terms of major haemorrhage, acute coronary syndromes, pulmonary embolism and mortality rates compared with current gold standard anticoagulants. The most serious adverse effect of warfarin is intracranial haemorrhage, the rates of which are significantly lower with dabigatran, even compared to patients with good INR control. Other advantages of dabigatran over warfarin include stable and rapid onset anticoagulation, fewer drug interactions, no food interactions and no requirement for monitoring.

In the RE-LY trial, higher rates of dyspepsia and gastrointestinal bleeding were noted with dabigatran compared with warfarin. This may be explained by the acidic core of dabigatran, which is required to create the low pH necessary for optimal absorption. There is no clear explanation for increased rates of myocardial infarction observed in patients on dabigatran compared with warfarin. This requires further investigation. The lack of a specific antidote to dabigatran poses concern; however, as dabigatran is renally excreted, haemodialysis might be an option. Lack of monitoring could be problematic in patients with renal impairment in whom levels may accumulate or in those who have an ischaemic stroke where adherence/coagulation status must be assessed. Dabigatran is more expensive than warfarin (£900–1000 vs £35–50 *per annum*); however, the cost of INR monitoring must be considered when evaluating overall cost. It must be noted that in the RE-LY trial the benefits of dabigatran were diminished in comparison to patients with good INR control. Dabigatran is therefore most likely to benefit patients with AF and poor INR control.

Dabigatran is currently recommended by NICE as an option for thromboprophylaxis in patients undergoing elective hip or knee arthroplasty. Guidelines for the use of dabigatran for the prevention of stroke and systemic embolism in patients with AF are expected in 2012.

Key points

- Dabigatran 150mg twice daily is superior to warfarin for the prevention of stroke and systemic embolism in patients with AF, with similar rates of major haemorrhage, acute coronary syndromes, pulmonary embolism and significantly lower rates of intracranial haemorrhage compared with warfarin
- Dabigatran has similar efficacy compared with enoxaparin 40mg, in reducing the risk of VTE following hip and knee arthroplasty
- Subgroup analysis shows benefit of dabigatran 150mg twice daily over warfarin for diabetic patients with AF, but evidence for specific use in diabetic patients for VTE prophylaxis is lacking

Declaration of interests

Dr McKay and Professor Fisher have served on advisory boards for Boehringer Ingelheim.

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