Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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July 2011 No. 010/11

Dabigatran etexilate

Dabigatran etexilate, a novel oral anticoagulant, has recently been licensed in NZ. It is a prodrug, which is metabolised to the active agent dabigatran. This bulletin focusses on its pharmacokinetics, interactions, dosing, and compares it with warfarin.

Indications

Dabigatran etexilate is currently licensed and fully funded in NZ for thromboprophylaxis in non-valvular atrial fibrillation (AF) and post-major orthopaedic surgery. Multi-centre randomised controlled studies (RCT) support these indications. For example, the RE-LY trial (N~18000) compared dabigatran etexilate 150 mg twice daily with warfarin for AF. Similar embolic rates were seen with both drugs (1.11 vs. 1.69%/yr, respectively, P = 0.34). The INR in the warfarin group was therapeutic for approximately 64% of the study period. Dabigatran etexilate is not yet licensed for treatment of venous thromboembolism in NZ, although a RCT (RE-COVER-1, 2009) reported that it is comparable to warfarin for this indication at 6 months of treatment and follow-up.

Mechanism of action

Dabigatran is a reversible direct thrombin inhibitor. Thrombin (factor IIa) is a plasma enzyme that catalyses the conversion of fibrinogen to fibrin, which is central to coagulation.

Pharmacokinetics

Dabigatran is a highly polar compound and is thus not absorbed via the gastrointestinal tract. The prodrug, dabigatran etexilate, was developed to overcome this issue. However, dabigatran etexilate still only has an oral availability of 7%. This is because the prodrug is a substrate of P-glycoprotein (P-gp), an efflux transporter localised on the luminal membrane of intestinal epithelial cells. Following absorption, the prodrug is rapidly converted to dabigatran by esterases, with peak dabigatran concentrations within 2 hours after oral administration in healthy subjects. Dabigatran is then predominantly renally cleared, with a high fraction excreted unchanged in urine (fu) of 0.8. With normal renal function, dabigatran has a half-life of 12 hours. Of note, dabigatran itself is not considered a P-gp substrate.

Interactions

Pharmacokinetic: As dabigatran etexilate is a P-gp substrate, it is vulnerable to the effects of drugs that are inhibitors (e.g. amiodarone, carvedilol, verapamil) or inducers (e.g. rifampicin) of this transporter (see the Pink Book for lists of P-gp-related drugs). As P-gp is involved in the removal of dabigatran etexilate from the intestinal epithelial cells, the oral availability of dabigatran etexilate increases with a P-gp inhibitor and decreases with a P-gp inducer. For example, peak dabigatran concentrations increased by 60% with chronic verapamil use.
Pharmacodynamic: Co-administration of dabigatran etexilate with other antithrombotic agents increases the risk of bleeding.

Dosing

In patients with normal renal function (i.e. 'standard dosing'):

- Non-valvular AF: 150mg twice daily.
- Post-major orthopaedic surgery: 110mg within hours post-surgery, followed by 220mg daily from the next day onwards.

In patients with impaired renal function, the first dose is the same as that for 'standard dosing', but subsequent doses should be adjusted for renal impairment:

1. Estimate the glomerular filtration rate (GFR, mL/min) using either the Cockcroft & Gault formula, or the MDRD value supplied by the lab (accuracy is improved by correcting for the patient's body surface area).
2. Incorporate the GFR and fu of 0.8 into the 'fu formula' (found in Prescribing in Renal Impairment, Pink Book) to calculate the maintenance dose-rate:

$$\text{Dose-rate}_{\text{patient}} = \left[(1 - \text{fu}) + \text{fu} \times \left(\frac{\text{GFR}}{100}\right)\right] \times \text{Dose-rate}_{\text{standard}}$$

These guidelines are in contradistinction to the drug company's advice, which downplays the influence of GFR on dosing.
In patients with GFR < 30 mL/min (excluded from the RCTs), use of dabigatran etexilate is not recommended.
Dosing should also take into account relevant drug interactions e.g. in the presence of P-gp inhibitors, dose-rate reduction should be considered. More specific advice may be sought from the CDHB Drug Information Service (extension 80900).

Switching to and from dabigatran etexilate

Parenteral anticoagulation to dabigatran etexilate: The first dose is given within 2 hours before the next dose of the parenteral anticoagulant would have been due (had it not been ceased).
Warfarin to dabigatran etexilate: Start dabigatran etexilate when INR < 2.0 following warfarin cessation.
Dabigatran etexilate to warfarin: If GFR > 50 mL/min, start warfarin 3 days before ceasing dabigatran etexilate; if 31-50 mL/min, start 2 days before; if 15-30 mL/min, start 1 day before.

Adverse effects

When used for AF (150mg twice daily), the major bleeding event rate with dabigatran etexilate was found to be similar to warfarin (3.1 vs. 3.4%/yr, P = 0.31). Dyspepsia is more common with dabigatran etexilate than warfarin (11.3% vs. 5.8%, P < 0.001). This is likely to be due to its tartaric acid content that provides an acidic microenvironment to enhance dissolution and absorption.

Dabigatran etexilate versus warfarin

Warfarin has occupied a unique position in therapeutics as the preeminent oral anticoagulant for decades. It is contrasted with dabigatran etexilate in the table below.

The main purported advantage of dabigatran etexilate is the apparent reduced need for lab coagulation monitoring. There may be situations where this monitoring is desirable, although there is a lack of experience with this.
The high fu of dabigatran means that renal function should be monitored, especially in those at high risk of, or already with, significant renal impairment.
Further, its poor oral availability makes it vulnerable to potentially large increments in drug exposure e.g. with P-gp inhibitors.

Finally, the uncertainty and paucity of data regarding strategies to reverse its anticoagulation is also a major concern.

Advantages and disadvantages of dabigatran etexilate versus warfarin

Advantages	● Lab coagulation monitoring not routine ● Rapid onset	● No CYP enzyme interactions ● ? safer with hepatic impairment	
Disadvantages	● Minimal experience with lab coagulation monitoring	● P-gp interactions ● ? riskier with renal impairment	● Less mature safety database ● Efficacy of reversal strategies unclear