Canterbury District Health Board
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Dabigatran etexilate dosing: major considerations and audit results

Dabigatran etexilate, an anticoagulant, has been licensed and fully funded in NZ since 1 July 2011 for thromboprophylaxis in non-valvular atrial fibrillation (AF) and post-major orthopaedic surgery. There has been rapid uptake of its use, with Medsafe estimating in September 2011 that 10,000 of 40,000 patients on warfarin for AF had been changed to dabigatran etexilate. It is a substrate of intestinal P-glycoprotein (P-gp), which contributes to the low oral availability of the drug. Further, it is a prodrug i.e. itself inactive and is metabolised to the active agent, dabigatran. A major route of dabigatran clearance is renal. This bulletin focuses on 1) two major pharmacokinetic considerations of dabigatran etexilate dosing, including intestinal P-gp function and renal function and 2) results from an audit of dabigatran etexilate dosing in CDHB inpatients.

Intestinal P-glycoprotein function

P-gp is an efflux transporter present on the luminal membranes of intestinal epithelial cells and functions to keep harmful compounds out of the body. It reduces the passage of P-gp substrates, such as dabigatran etexilate, into the systemic circulation. P-gp is thus an important contributor to the low oral availability (7%) of dabigatran etexilate. Various drugs can alter the function of P-gp, either by inhibition (e.g. amiodarone, verapamil) or induction (e.g. rifampicin; see Pink Book for a more comprehensive list). The manufacturer has reported that dabigatran concentrations increased by > 50% with both amiodarone and verapamil, and decreased by 60% with rifampicin. Of interest, the manufacturer has made inconsistent dosing recommendations based on these data e.g. when given with P-gp inhibitors, doses are unaltered for AF but reduced for venous thromboembolism (VTE) prevention. We recommend that dabigatran etexilate dose-alteration should always be considered when co-prescribed with P-gp inhibitors (decrease doses) or inducers (increase doses). Advice for the individual patient may be sought from the Drug Information Service (extension 80900).

Renal function

Following absorption, dabigatran etexilate is rapidly metabolised by plasma and hepatic esterases to dabigatran. Dabigatran is not a P-gp substrate, and is mainly cleared by glomerular filtration. This is reflected in its high fraction excreted unchanged in urine (fu) of 0.8. Dabigatran concentrations are therefore expected to be closely correlated with estimated glomerular filtration rate (eGFR), which is borne out by the manufacturer's data e.g. dabigatran concentrations in a patient with eGFR 55 mL/min are almost double that of eGFR 100 mL/min, given the same dose. However, here again the manufacturer's dosing guidelines do not reflect their own data e.g. they recommend dosing for eGFR 55 mL/min is the same as that for eGFR 100 mL/min. We recommend that dosing should closely reflect eGFR using the following standard pharmacological method:

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

$$\text{Dose-rate} = \frac{\text{Dose-rate}_{\text{standard}} \times \text{eGFR}}{0.8 \times 120}$$

where the $\text{Dose-rate}_{\text{standard}}$ is the recommended dose-rate for the particular indication for patients with normal renal function.

It is important to note that dosing is necessarily restricted by the available dosage strengths, which for dabigatran etexilate includes 75 mg, 110 mg and 150 mg tablets.

Audit of dabigatran etexilate dosing

The marked disparities between the manufacturer's data and their dosing recommendations, particularly in relation to GFR, led to the development of local dosing guidelines. These were initially locally circulated in the form of a bulletin in August 2011, before being formally adopted by the current Blue Book. The following table shows the manufacturer's and Blue Book dosing guidelines for AF in relation to GFR:

Dosing for AF *	Manufacturer	Blue Book
Age < 80 years	150 mg q12h	Use eGFR
Age ≥ 80 years	110 mg q12h	Use eGFR
eGFR > 80 mL/min	150 mg q12h	150 mg q12h
eGFR 50 – <80 mL/min	150 mg q12h	110 mg q12h
eGFR 30 – <50 mL/min	110 mg q12h	75 mg q12h
eGFR <30 mL/min	Avoid	Avoid

* There are similar dosing differences for VTE prevention.

This provided the impetus for an audit of dosing in CDHB inpatients at the point of discharge. The aims were to assess dabigatran etexilate dosing in relation to a) eGFR and Blue Book guidelines and b) co-prescribed P-gp inhibitors/inducers.
The audit was for the period July 2011 to March 2012.

Demographics	
Discharges on dabigatran etexilate	193
Age, *median (range)*	72 (28 – 88)
eGFR, *median (range)*	65 (32 – 102)
Indications	
AF	179/193 (93%)
Post-orthopaedic VTE prevention	1/193 (<1%)
Other	13/193 (7%)
Dosing (cf. Blue Book and eGFR)	
Higher than recommended	**70/193 (36%)**
Appropriate	93/193 (48%)
Lower than recommended	30/193 (16%)
P-gp inhibitors *	
Co-prescribed P-gp inhibitors	30/193 (16%)
P-gp inhibitors, with lower dosing	3/30 (10%)

* Only one patient in this audit was on a P-gp inducer.

A substantial minority of patients (36%) were given higher doses than recommended by the Blue Book according to eGFR. While there may be occasions where this is clinically appropriate, this result suggests that improvements to dosing can be made.

Dabigatran etexilate study recruitment

We are currently recruiting patients on dabigatran etexilate for a study on renal function. We aim to find the formula for eGFR that best predicts dabigatran clearance, thereby providing the best guide of dabigatran dosing in relation to renal function.
If you have a potentially interested patient, please contact Dr Paul Chin: pager 8524 / phone 88354 / paulc@cdhb.health.nz.

References: Chin PKL, Vella-Brincat JWA, Barclay ML, Begg EB 2012 Brit J Clin Pharmacol. Stangier J et al 2010 Clin Pharmacokinet. van Ryn J et al 2010 Thromb Haem.