

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Dabigatran – the new warfarin?

Dabigatran (Pradaxa®) is an orally administered direct thrombin inhibitor recently approved by the Australian Therapeutic Goods Administration for short term prevention of venous thrombosis in adult patients who have undergone major orthopaedic surgery. Perhaps of greater interest however is the potential for dabigatran to one day replace warfarin as a more effective, safer and more convenient long-term oral anticoagulant.

The RE-LY study *Randomized evaluation of long-term anticoagulation therapy, warfarin, compared with dabigatran* was a large scale multi-centre non-inferiority randomized trial, examining both the effectiveness and safety of dabigatran in comparison with warfarin for the prevention of stroke amongst 18,113 patients with atrial fibrillation. The study was conducted over a two year period, with blinded use of dabigatran at two doses (110 mg and 150 mg twice daily). Warfarin use was on an open label basis, with testing performed every month in order to maintain the INR within the range of 2-3. Both doses of dabigatran were found to be non-inferior to warfarin in respect to the efficacy of the drug in preventing stroke, but the 300 mg daily dose was superior to the 220 mg daily dose. The 220 mg daily dose had a better safety profile than warfarin, associated with significantly fewer major bleeds. The 300 mg daily dose of dabigatran was similar to warfarin with respect to bleeding. Of interest was the type of bleeds associated with the different anticoagulants. Warfarin was associated with a significantly increased amount of intracranial bleeding; pointing to a potential advantage for dabigatran (intracranial haemorrhages are generally difficult to treat and are associated with poor patient outcomes). Dabigatran 150 mg twice daily was associated with significantly more gastrointestinal bleeding and dyspepsia, likely due to the fact it is administered as a capsule containing dabigatran coated pellets with a tartaric acid core. This is in order to decrease gastric PH, allowing increased absorption of the drug (which has a low absolute bioavailability of 6.5%).

Warfarin has been shown in previous studies to prevent approximately 68% of strokes in atrial fibrillation, but close monitoring, drug and dietary interactions and risk of haemorrhage make it a difficult and inconvenient agent to use. Dabigatran is advantageous in many of these aspects, requiring comparatively little monitoring, having few drug interactions, being associated with an apparently decreased risk of intracranial haemorrhage relative to warfarin. However, anticoagulation with dabigatran is non-reversible and the increased rate of gastrointestinal adverse effects is concerning. Furthermore, dabigatran appeared to be associated with an increased risk of myocardial infarction, a finding not adequately explained in this study. This matter raises concerns, as another thrombin inhibitor ximelagatran (which ultimately never proceeded to marketing because of hepatotoxicity issues) was also found to be associated with increased risk of myocardial infarction.

Is dabigatran a suitable candidate to replace warfarin? While results of this study do look promising in some regards, further large scale clinical trials are required to determine its role in long term anticoagulation.

This E-Bulletin is based on work by Philip Selby, Pharmacy Intern, RGH

FOR FURTHER INFORMATION CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@health.sa.gov.au
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