

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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Factors influencing anticoagulation with rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders. As clinical use increases for this new drug it is important to be aware of factors influencing its clearance and hence anticoagulant potency. This is particularly important in the early part of the clinical use of a new drug, as sponsored clinical trials may have inclusion and exclusion criteria that might tend to be selective for healthier patients.

Rivaroxaban has a half-life of 6-7 hours, with about 30% excreted unchanged in the urine, and a significant hepatic metabolism via the cytochrome P450 3A4 system (CYP 3A4). Increasing rivaroxaban concentrations cause increasing prothrombin time and decreasing anti-Xa activity in a predictable linear manner. Whilst the INR is also increased, this cannot be interpreted in any meaningful manner due to non-standardisation across laboratories.

In patients with renal insufficiency, rivaroxaban AUC was 44%, 52% and 64% higher in mild (GFR 50-79ml/min), moderate (30-49ml/min) and severe (<30ml/min) renal impairment, respectively. Subsequently, Factor Xa inhibition increased by 50%, 86% and 100% respectively, while the prothrombin time increased by 33%, 116% and 144% respectively. In one study there was an increase in prothrombin time of 0.45 - 0.8% from baseline for each 1.0ml/min decrease in estimated GFR. While there is currently no formal recommendation to adjust doses for renal impairment, a dosage adjustment has been used in trials for patients with a GFR 30-49ml/min, and patients with a GFR<30ml/min have been excluded from studies.

When rivaroxaban was evaluated in patients >75 years of age there was a significant increase in rivaroxaban concentrations reflected by increased prothrombin time and Factor Xa inhibition. This was largely associated with the age-related decline in renal function in this group, and whether the dose should be adjusted for the elderly is still remains unclear. A further consideration in the elderly is they are a group more at risk of bleeding, simply due to physiological changes of aging.

Strong inhibitors of CYP 3A4 such as ketoconazole and ritonavir have been shown to cause 2.5-fold increases in rivaroxaban concentrations, which are likely to be clinically important. Clarithromycin and erythromycin are known to cause 30-50% increases in rivaroxaban concentrations. Likewise, strong inducers of CYP 3A4 such as rifampicin are known to cause a 50% decrease in rivaroxaban concentrations.

While there appears to be no need for routine coagulation monitoring with rivaroxaban at this stage, it may be possible to use this approach to enhance the safety of the drug amongst in selected patients: target ranges for coagulation parameters in this context have not yet been established.

This E-Bulletin is based on work by Greg Roberts, Senior Research Clinical Pharmacist, RGH

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