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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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Anticoagulation – bleeding and anticoagulant variability

The single most major concern in connection to anticoagulant use is the risk of bleeding. Perhaps the biggest driver of this concern is increasing intensity of anticoagulation. Often there is unpredictable variability in patient response to anticoagulant therapy that may inadvertently lead to overanticoagulation and subsequent bleeding.

Most variability in response to warfarin is driven by two genetic elements - the vitamin K epoxidase system, which is the basis for the action of warfarin, and the cytochrome P450 2C9 liver enzymes responsible for warfarin metabolism. As a result, daily maintenance doses can range from 0.5 mg – 20 mg/day. Those who are extremely poor 2C9 metabolisers face an increased risk of overanticoagulation and thus increased likelihood of bleeding. Further to this, a small number of patients may be experiencing unrecognised sub-clinical bleeding prior to commencement of therapy. Once anticoagulated, this sub-group are at risk for a high incidence of major bleeds during the first month of treatment, a time when these patients are also more likely to experience an elevated INR due to instability in the initiation process.

Unfractionated intravenous heparin infusions can be rapidly reversed if required, but the huge within patient and between-patient therapeutic variability seen with this drug makes it notoriously difficult to control. In one case series patients experiencing a major bleed had a mean APTT of >120 seconds, despite constant monitoring. Most clinicians now prefer the use of Low Molecular Weight Heparins (LMWHs) due to more predictable therapeutic reproducibility. This expresses clinically as improved outcomes and lower rates of bleeding.

The impact of drug level variability has now even become evident with enoxaparin. Transiently high anti-Xa peaks seen soon after administration are linked to increases in bleeding. Subtle alterations of the dosing approach to enable smoother anti-Xa profiles have reduced major and minor bleeding by 80% and 90% respectively, without apparent loss of efficacy. Further to this, recent data from OASIS-5 (comparing fondaparinux and enoxaparin) indicated fondaparinux displayed similar efficacy, but with reduced bleeding. This result was to some extent surprising, as it is generally considered that by increasing anticoagulation intensity one could improve efficacy, but always at the expense of an increased bleeding incidence.

While enoxaparin was shown to have much higher overall anticoagulant activity than fondaparinux in this study, as determined by a range of markers, the variability around fondaparinux anticoagulant activity over the dosing interval was much less. It appeared that the more consistent, less variable effect of fondaparinux across the dosing interval enabled maintenance of efficacy, while reducing bleeding, relative to enoxaparin.

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

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