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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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Non-Steroidal Anti-inflammatory drugs & cardiovascular risk

Non steroidal anti-inflammatory drugs (NSAIDs) are used for their anti-inflammatory, analgesic and anti-pyretic properties. NSAIDs exert their effect by inhibiting the cyclooxygenase (COX) enzyme. All NSAIDs inhibit the isoenzyme COX-2, however non-selective NSAIDs also inhibit COX-1. Inhibition of COX-1 results in decreased production of prostaglandins and thromboxane, which are involved with gastroprotection and thrombotic effects. Inhibition of COX-2 results in decreased production of prostaglandins and prostacyclins, which are involved with inflammation and decreased platelet aggregation. It is believed that the mechanism for increased cardiovascular adverse outcomes with the use of selective COX-2 inhibitors is due to the lack of inhibition of thromboxane production, in conjunction with inhibition of prostacyclins. The most likely theory for the differences between the NSAIDs in terms of cardiovascular risk is their degree of selectivity for COX-2 compared with COX-1.

Since the withdrawal of rofecoxib (Vioxx) from the market in 2004, the cardiovascular safety of all NSAIDs has been under scrutiny. The results of a meta-analysis in 2006 suggested that high dose regimens of diclofenac and ibuprofen were associated with an increase in cardiovascular events, however high dose naproxen was not. In October 2006, the Commission on Human Medicines (CHM) published a review of safety data and concluded that diclofenac has a thrombotic risk similar to at least one other COX-2 inhibitor (etoricoxib), but there was no evidence suggesting an increased risk with ibuprofen or naproxen. The CHM published a further safety update in 2009. This was in response to the results of two epidemiological studies which suggested that the adverse cardiovascular events associated with NSAIDs were common in the general population, regardless of baseline risk, or duration of use.

Earlier this year, a network meta-analysis was published by Trelle et al, which compared naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, lumiracoxib, rofecoxib and placebo. This analysis included 116,429 patients from 31 trials. The primary outcome of the study was fatal or non-fatal MI, and secondary outcomes included stroke and cardiovascular death. Two of the COX-2 inhibitors, which were previously withdrawn from the market (rofecoxib and lumiracoxib) had the highest rate ratio of myocardial infarction (MI). Ibuprofen was associated with the highest risk of stroke, followed by diclofenac. Etoricoxib, followed by diclofenac, and then ibuprofen had the highest risk of cardiovascular death. Naproxen had the lowest rate ratios for myocardial infarction and cardiovascular death. The authors concluded that naproxen seemed the least harmful NSAID (although they did acknowledge its propensity to cause gastrointestinal adverse effects). Interestingly, this meta-analysis found no clear relation between the specificity for COX-2 and cardiovascular risk, which suggests that other mechanisms may contribute. This study has many of the usual limitations associated with a meta-analysis, however the results are in line with previous findings. Currently, a randomized controlled trial (the PRECISION trial) comparing celecoxib, naproxen and ibuprofen in patients with moderate cardiovascular risk, is underway.

The National Prescribing Centre UK recommends that NSAIDs should be used at the lowest dose for the shortest possible time and that gastric protection with a Proton Pump Inhibitor should be considered. They also recommend that naproxen or low dose ibuprofen (<1200 mg/day) are the most reasonable options for NSAID use, and that diclofenac should be avoided if possible, especially for those with high cardiovascular risk.

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