

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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Paracetamol: a question of dose

Paracetamol is the analgesic and antipyretic of choice for nearly all patients. Adverse effects are rare, with hepatotoxicity the principle safety concern. Acute hepatotoxicity typically occurs when doses >150 mg/kg are consumed, and results from accumulation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). About 5–9% of the dose is metabolized by CYP-450 enzymes (primarily CYP2E1) to NAPQI, which is then conjugated with glutathione to form non-toxic products.

Several patient groups may be at increased risk of hepatotoxicity:

- Patients with depleted glutathione stores (e.g. prolonged fasting or malnourished patients).
- Patients concurrently taking CYP-450 enzyme inducing medications such as carbamazepine.
- Those with severe renal, hepatic or cardiac impairment or dehydration (although evidence implicating these conditions as risk factors is limited).

Trials of paracetamol use for patients with chronic liver disease (e.g. chronic hepatitis C) and chronic alcoholism have not consistently demonstrated an increased risk of hepatotoxicity associated with paracetamol when used at therapeutic doses. The Australian Therapeutic Goods Administration (TGA) concluded the evidence does not support adding a warning statement addressing alcohol consumption to paracetamol labelling. Elderly age *per se* is also not considered to be a risk factor.

For patients without risk factors the recommended dose is 500–1000 mg every 4–6 hours prn (standard-release formulation), or 1330 mg every 6–8 hours of the extended-release formulations, to a maximum of 4000 mg daily. Patients with chronic pain should receive regular effective doses rather than as-needed.

Dose modification of paracetamol should be considered in at risk patients, but guidelines are lacking. A policy directive from NSW Health in January 2006 highlights the risk of overdose and subsequent hepatotoxicity for patients who are underweight, or malnourished, as well as for those who are obese. The policy suggests a maximum dose of 60 mg/kg daily, based on lean body weight (LBW). For adult patients of low body weight (e.g. < 40 kg) it may be prudent to use the dose recommended for children (15 mg/kg every 4–6 hours to a maximum of 60 mg/kg (LBW) per day). However, in palliative care and end of life settings it is important the dose be adequate to provide effective pain relief. There are no trials to either support or refute these recommendations, and trials that have investigated paracetamol at therapeutic doses in at risk patients (chronic undernourished alcoholics) have not shown changes in liver function indicative of hepatotoxicity. Monitoring liver function patients at risk is unlikely to be of predictive or clinical value. Importantly patients should be counselled to use only one source of paracetamol, to avoid inadvertent overdose.

LBW (males) = $(1.1 \times \text{actual weight in kg}) - (0.0128 \times \text{BMI} \times \text{actual weight in kg})$
LBW (females) = $(1.071 \times \text{actual weight in kg}) - (0.0148 \times \text{BMI} \times \text{actual weight in kg})$

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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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