Paracetamol in patents with pre-existing liver disease

Dear Editor

The article 'Liver function tests' by Penelope Coates[1] (*AFP* March 2011) is an excellent summary of the use of these tests for general practitioners. However, in *Table 3* there is a note that 'patients with pre-existing liver disease, including alcohol abuse, are vulnerable to paracetamol toxicity even at a standard dose', referring to a retrospective review of cases from 1995.[2]

The safety of paracetamol use in these patients is an important issue. Paracetamol is a commonly used, effective and readily available over-the-counter analgesic and antipyretic. Liver disease and alcohol dependence are both relatively common conditions. If there were a significant problem with therapeutic doses of paracetamol in patients with pre-existing liver disease or alcohol abuse then this would be a major public health issue. Additionally, alternatives to paracetamol, including aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), carry their own risks of adverse effects.

The retrospective case reviews and case reports such as that referenced in the article[2] describe hepatic injury after repeated paracetamol ingestion with therapeutic intent, although usually not at therapeutic doses. In addition, the information contained in these reports is often incomplete and contradictory. The history of ingestion is often unknown or contradicts other clinical information provided. For example, the history may indicate a therapeutic dose, but the serum paracetamol concentration recorded can only be produced by ingestion much larger than the history would indicate.

In contrast, there are no prospective studies in humans that show an increased risk in these patient groups. Benson[3] administered 4 g/day paracetamol or placebo for 13 days to 20 patients with stable chronic liver disease in a double blinded crossover study, and detected no clinical deterioration or abnormality of liver function tests (LFTs).

Kuffner and Dart [2] conducted three randomised placebo controlled trials with a total of 484 subjects receiving 4 g/day paracetamol for periods of 3 and 5 days respectively.[4–6] These studies were performed on newly abstinent alcohol abusers, a population chosen as their state 'recreates' the scenarios postulated to increase the hepatotoxicity of paracetamol, ie. recently abstinent alcohol abusers have CYP2E1 enzyme induction and decreased glutathione stores. No difference in LFTs was detected between paracetamol and placebo groups.

Therefore, the prospective trial evidence supports the safety of short term use paracetamol in patients with stable chronic liver disease or alcohol abuse.

Thus, we disagree that patients with pre-existing liver disease or alcohol abuse are vulnerable to hepatotoxicity as a result of therapeutic dosing of paracetamol and, given the effectiveness of paracetamol, along with the potential risks of alternative analgesic and antipyretic options, we feel the evidence that paracetamol can be safely used in these situations is an important positive message for clinicians.

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Reply

Dear Editor

The issue of whether alcohol abuse increases the risk of paracetamol toxicity is important but contentious. I agree with Clunas and colleagues that often the serum paracetamol concentration is inconsistent with the history given by the patient of therapeutic dosing (<4 g/day).

The clinical trial data cited by Clunas is reassuring in that paracetamol was shown to be safe if used in short term periods in a supervised setting at therapeutic doses in patients with pre-existing liver disease or alcohol abuse. However, the fact remains that in large retrospective[1] and prospective[2] surveys of acute liver failure caused by paracetamol, alcohol abuse was present in 34% of patients and was associated with overdose with suicidal intent and with accidental overdose. Only 7% of patients in a prospective trial reported taking less than or equal to 4 g/day of paracetamol, but 65% of this group abused alcohol.[2]

A black box warning has been issued in the USA by the Food and Drug Administration suggesting people consuming more than three alcoholic drinks daily should discuss paracetamol therapy with their physician.[3]

I would therefore contend that although paracetamol should be a safe drug in the short term at therapeutic doses in patients who abuse alcohol, these patients are at higher risk of overdose, either deliberate or accidental, and that this risk should be taken into account before prescribing.

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Acute asthma in children

Dear Editor

We wish to clarify some points made by Corrales et al[1] (*AFP* January/February 2011) on the management of acute asthma in children.

The treatment of children presenting to general practice with acute severe asthma is based on immediate administration of salbutamol via pressured metered dose inhaler (MDI) plus spacer (at the doses stated, repeated after 20 minutes or as necessary until control is achieved or the ambulance arrives), oral corticosteroids and supplemental oxygen. The other treatments discussed (including IV beta 2-agonists and IV magnesium sulphate) would rarely be used outside emergency departments.

The clinical features listed as indications for 'admission to hospital', citing the Global Initiative for Asthma,[2] are actually prompts for transfer to an emergency department. These can be summarised more simply in the Australian context as follows: call an ambulance as soon as possible for any severe 'attack'.[3]

Terms to describe asthma status are notoriously open to confusion. The authors use the term 'severe asthma' to refer both to status asthmaticus and to the patient's underlying clinical status. They use the term 'severity of disease' to refer both to the patient's global clinical status and to the degree of risk associated with a particular episode of acute asthma. The National Asthma Council Australia supports the international proposal[4] to define 'asthma severity' as the intensity of treatment required to achieve good asthma control over time, and 'severe asthma exacerbations' as acute events that require urgent action to prevent hospitalisation or death.

The list of risk factors for near fatal asthma (listed in *Table 1*) includes 'insufficient or poor adherence to controller therapy'. In Australia, 'controllers' refers to long acting beta 2-agonists (LABAs), which should never be used without inhaled corticosteroids (ICS). We assume the authors intended to refer predominantly to ICS, which in Australia are termed 'preventers'.

The authors cite only USA hospitalisation rates. Readily available Australian data indicate that asthma ranks eighth among causes for hospitalisation, accounting for approximately one in 200 hospitalisations.[5] Moreover, more than twice as many people attend emergency departments for asthma each year.[6] Emergency visits are highest among children under 15 years of age, and peak each year around February and May.[6]

The National Asthma Council Australia supports publication of articles that enhance GPs' knowledge and management of asthma and appreciate the authors' contribution to this important area of clinical practice.

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Reply

Dear Editor

We thank Dr Hancock for her interest in our article and also for clarifying some points regarding the management of severe asthma in children.

We agree that initial treatment should be based on the immediate administration of salbutamol via MDI plus a spacer, steroids and oxygen. Our recommendations weren't directed to management only in the GP's office, but also in the hospital setting as we are aware that many GPs work in different settings. Although steroids should form part of first line of treatment, we stated in our article that oral corticosteroids should not be given to patients when they are vomiting or critically ill and who may require intubation. In these cases parenteral steroids should be used.

Because many GPs do work in the hospital setting, we focused more on recommendations for admission, assuming that if a patient presents with any of these criteria they would be transferred to the nearest hospital.

We agree that terms to describe status asthmaticus are quite confusing. Because our article was titled, 'Management of severe asthma in children', we made the assumption that this would refer to 'acute asthma exacerbations in children' and not to the severity of disease. The term 'severe asthma' in *Table 1* refers to the severity of the disease.

In keeping with Dr Hancock's comments about not using confusing terminology, we used terminology cited in other international guidelines (GINA[1] and British asthma guidelines[2]) where terms such as preventers and controllers are used as synonyms, both including a stepwise approach (from short acting, ICS and combination therapy).

We agree that we could have used Australian data for hospitalisation rates and thank Dr Hancock for raising this.

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