SHORT COMMUNICATION

Drugs 2003; 63 Special Issue 2: 39-42
0012-6667/03/0002-0039/$33.00/0

Tolerability of Paracetamol*

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Abstract

Paracetamol (acetaminophen) is a well-tolerated drug at therapeutic doses and this safety profile is a major factor in the very wide use of the drug. It is well known that paracetamol is converted by the hepatic cytochrome P450 system to reactive compounds. Less well known is that paracetamol is also metabolized to the same reactive compounds by myeloperoxidase and the peroxidase function of cyclo-oxygenase (COX)-1. The reactive metabolites lead to hepatotoxicity following overdosage. Similar hepatotoxicity has been reported after therapeutic doses, but critical analysis indicates that most patients with alleged toxicity from therapeutic doses have taken overdoses.

Associations between the use of paracetamol and chronic renal diseases, gastrointestinal toxicity and asthma may be due to bias in case–control studies. In particular, bias may be caused by the perceived safety of paracetamol in these diseases. Selective inhibition of the delayed pathway of prostaglandin synthesis is consistent with the gastrointestinal safety of paracetamol and its safety in the majority of aspirin-sensitive asthmatics. Despite the conversion of paracetamol to reactive compounds, hypersensitivity reactions are rare, although urticaria is produced in occasional patients.

1. Metabolism and Hepatotoxicity

The hepatotoxicity of paracetamol overdose is a significant clinical problem. The mechanism is that the cytochrome P450 system in the liver catalyses the conversion of paracetamol to a quinoneimine, which reacts with glutathione. When the concentrations of glutathione are greatly depleted, there is reaction with the thiol groups of liver proteins, leading to the characteristic centrilobular necrosis. Depletion of glutathione could also provide an oxidant stress to the liver or inhibit enzymes for which glutathione is a cofactor, or both. It has therefore been suggested that conditions which lead to low concentrations of glutathione, such as alcoholism, malnutrition, hepatitis C, cirrhosis or AIDS, should cause hepatotoxicity even with therapeutic doses of paracetamol. However, recent work indicates that the hepatotoxicity of paracetamol in these situations is unlikely to be increased unless, possibly, several factors combine to produce a very marked depletion of glutathione.[1]

Many cases of hepatotoxicity have been associated with the use of therapeutic doses of paracetamol, but recent critical reviews of this field indicate that overdosage is the major cause of the toxicity.[2-5] Furthermore, prospective short-term studies have not shown hepatotoxicity from paracetamol.[4] In addition, paracetamol is a widely used drug and the liver disease in some patients taking paracetamol has been unrelated to the drug.[3]

1.1 Hepatotoxicity in Children

The unknowing administration of excessive

*The full version of this manuscript is in press for publication in Drugs Safety.

doses is the probable cause of hepatoxicity in most patients.[2,3] Therefore, possible overdosage with paracetamol should be considered in children who have a prodromal illness with encephalopathy, even if the dosage has been stated to be correct for the age or weight of the child.[2] Hypoglycaemia, prolonged prothrombin time, high concentrations of aminotransaminases (>4 000 U/L) and concentrations of bilirubin less than 200 μmol/L are very suggestive of recent overdosage.[2] Toxic levels in children are unclear and they should be treated with the antidote, *N*-acetylcysteine, at lower plasma concentrations of paracetamol than would be the case in adults.

1.2 Hepatotoxicity in Adults

As is the case in children, hepatotoxicity from therapeutic doses of paracetamol has been claimed, but many cases also appear to be associated with overdosage, because of the high plasma concentrations many hours after the last dose.[3-5] Careful discussions with the patients and their relations or friends often indicate acute or chronic overdosage.

Centrilobular necrosis is the classical form of paracetamol-induced hepatotoxicity. A variety of other syndromes, including chronic active hepatitis, cholestasis and primary biliary cirrhosis have been associated with paracetamol, but are generally not proven to be caused by paracetamol treatment. Rechallenge with therapeutic doses of paracetamol has led to signs of hepatic damage in very few patients.[3]

1.3 Hepatotoxicity in Alcohol Abusers

It has been claimed widely that alcohol potentiates the hepatotoxicity of paracetamol sufficiently to make therapeutic doses potentially hepatotoxic but, again, it appears that most cases were the result of the ingestion of overdoses of paracetamol, not therapeutic doses.[4,5] Overdoses of paracetamol may very well be more common in abusers of alcohol than in the remainder of the population. This does not necessarily mean that the chronic use of alcohol potentiates the hepatotoxicity of paracetamol. Rather, this may be just one example of the high rates of suicide and self-destructive behaviour seen in alcoholics.[6] Furthermore, the memory loss often seen in severe alcoholism may make the individual unaware of having taken excessive doses. For these reasons, alcoholic patients should be instructed or supervised as far as practicable concerning safe dosage with paracetamol. Paracetamol may, however, be the best analgesic to use in compliant alcoholics, because of the adverse effects associated with aspirin and other NSAIDs.[4]

1.4 Use of Paracetamol in Patients with Liver Diseases

Paracetamol does not appear to exacerbate stable chronic liver disease, and it appears to be the optimal simple analgesic in patients with chronic liver disease. Doses up to 1g three times a day are recommended.[7] It is, however, prudent to monitor liver function in such patients, and the period of use of paracetamol should be kept as short as possible.

2. Gastrointestinal Tolerability

Paracetamol produces no significant endoscopic damage in controlled investigational studies. Paracetamol has a gastrointestinal tolerability that is in contrast to that of aspirin, which is associated with considerable risk of bleeding even when given in low doses.

Recent epidemiological studies have indicated a greater incidence of adverse gastrointestinal reactions with increasing daily dosage above 2–2.6g.[8,9] However, these studies may have been biased. The greater incidence of bleeding in patients taking the larger doses of paracetamol could occur because of the use of paracetamol in patients with possible or known gastrointestinal ulceration.[10] Protopathic bias may have resulted from the use of paracetamol for the pain or discomfort of early gastrointestinal disease.[10] Epidemiological data are corrected for risk factors, but it is difficult to remove confounding variables

completely, particularly when the reasons for the uses of drugs are not known.

3. Renal Tolerability

Unlike the non-selective NSAIDs and selective cyclo-oxygenase (COX)-2 inhibitors, paracetamol has not been associated with the precipitation of acute renal failure in patients with risk factors such as congestive cardiac failure, pre-existing renal impairment and transplanted kidneys.[11] Overdoses of paracetamol may, however, produce acute renal failure as a result of acute tubular necrosis, possibly because of the metabolism of the drug to reactive metabolites by the peroxidase function of COX-1 or COX-2.

The toxicity of paracetamol on the kidney has mainly been examined with respect to the development of chronic renal failure, particularly that resulting from analgesic nephropathy. The general conclusion is that the habitual use of paracetamol is not associated with an increased risk of chronic renal disease.[11]

4. Haemostasis

In contrast to the marked antiplatelet effects of the non-selective NSAIDs, paracetamol at therapeutic doses has no significant effect on platelet aggregation. Consequently, paracetamol is considered safe in patients with clotting disorders and in patients taking anticoagulants. However, paracetamol may increase the effect of warfarin in some patients,[12] and monitoring of the prothrombin time is recommended when regular dosage with more than 2g paracetamol daily is started or stopped.

Thrombocytopenia is also associated with hepatotoxicity of paracetamol in a small proportion of cases of overdose, but is extremely rare at therapeutic doses.

5. Hypersensitivity Reactions

Allergic skin reactions to paracetamol are extremely rare, but urticaria has been produced after oral doses of paracetamol. A small proportion of asthmatic patients have their disease exacerbated by the non-selective NSAIDs.[13] In contrast, paracetamol is well tolerated by most, but not all, asthmatic individuals; furthermore, the asthmatic reaction is milder after paracetamol than after dosage with the non-selective NSAIDs. 'Routine warnings about paracetamol use in asthma are, therefore, not warranted', although medical personnel should be aware of this problem in occasional patients.[13]

Despite the very low incidence of asthma in patients whose disease is precipitated by paracetamol, its use was associated with asthma in a controversial case-control study.[14] In this study, the avoidance of aspirin was considered, although the use of other non-selective NSAIDs was not. Because of this and other potential confounding variables, there is no definite proof that paracetamol increases the incidence of asthma.

Acknowledgement

Conflict of interest: A research project of Professor Graham has been supported by GlaxoSmithKline, and Professor Day is or has been a member of advisory boards for the companies marketing celecoxib (Pfizer), rofecoxib (Merck) and paracetamol (GlaxoSmithKline).

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