REVIEW ARTICLE

Drug Safety 2005; 28 (3): 227-240
0114-5916/05/0003-0227/$34.95/0

Tolerability of Paracetamol

Garry G. Graham,[1] *Kieran F. Scott*[2] and *Richard O. Day*[1]

1 Department of Clinical Pharmacology, St Vincent's Hospital and Department of Physiology and Pharmacology, School of Medical Sciences, Sydney, Australia
2 St Vincent's Hospital Clinical School, University of New South Wales, Sydney, Australia

Contents

Abstract . . . 227
1. Identification of Studies . . . 228
2. Metabolism of Paracetamol (Acetaminophen) Relevant to its Toxicity . . . 228
3. Hepatotoxicity of Paracetamol . . . 230
3.1 Hepatotoxicity from Overdosage . . . 230
3.2 Hepatotoxicity from Therapeutic Doses in Adults? . . . 231
3.3 Hepatotoxicity from Therapeutic Doses in Children? . . . 232
3.4 Hepatotoxicity from Therapeutic Doses in Patients Drinking Alcohol? . . . 233
3.5 Use of Paracetamol in Alcoholics and in Patients with Liver Diseases . . . 234
4. Labelling and Packaging . . . 234
5. Gastrointestinal Tolerability . . . 235
6. Renal Tolerability . . . 236
7. Haemostasis . . . 237
8. Hypersensitivity Reactions . . . 237
9. Occurrence of Cancers . . . 238
10. Tolerability During Pregnancy . . . 238
11. Conclusions . . . 238

Abstract

The excellent tolerability of therapeutic doses of paracetamol (acetaminophen) is a major factor in the very wide use of the drug. The major problem in the use of paracetamol is its hepatotoxicity after an overdose. Hepatotoxicity has also been reported after therapeutic doses, but critical analysis indicates that most patients with alleged toxicity from therapeutic doses have taken overdoses. Importantly, prospective studies indicate that therapeutic doses of paracetamol are an unlikely cause of hepatotoxicity in patients who ingest moderate to large amounts of alcohol. Controlled clinical trials have found that paracetamol is very well tolerated by the gastrointestinal tract. While variable results have been found in case control studies, most studies have shown no change or a small increase in the relative risk of perforations, ulcer or bleeding in the upper gastrointestinal tract. However, associations between the use of paracetamol and gastrointestinal toxicity, as well as with chronic renal disease and asthma, are very likely to reflect biases in some case control studies. In particular, such biases may be caused by the perceived high tolerability of paracetamol in these diseases. The consequent use of paracetamol in these diseases states then leads to an apparent association between paracetamol and the disease. Despite metabolism of paracetamol to reactive compounds, hypersensitivity reactions are rare, although urticaria occurs in occasional patients. Paracetamol appears to be well tolerated during pregnancy although prospective studies are required.

Paracetamol is a very well tolerated drug at therapeutic doses (i.e. up to 4 g/day in adults) and this excellent tolerability is a major factor in its wide usage. The aim of this review is to survey the adverse reactions to therapeutic dosages of paracetamol. In particular, we have examined the conclusions of recent reviews on these reactions and commented on the clinical significance and actual occurrence of these adverse reactions.

Hepatotoxicity after overdosage of paracetamol is well known and is the major problem with use of this drug. Conversely, hepatotoxicity after therapeutic dosages appears to be highly unusual. Although many case histories have been interpreted as indicating that therapeutic doses of paracetamol can cause hepatoxicity, recent critical reviews indicate that hepatotoxicity from therapeutic dosages of paracetamol is much less common than is widely believed. Controlled prospective studies generally indicate the safety of therapeutic doses of paracetamol to the liver as well as to the gastrointestinal tract, although mild toxicity may occur in the respiratory tract. By contrast, adverse reactions in the gastrointestinal tract have been indicated by epidemiological studies. Examination of these discordant results and conclusions is a significant aspect of the present review.

Analysis of epidemiological studies of paracetamol indicates that several studies have biases that may very well invalidate conclusions drawn from them about the incidence of adverse reactions. One bias is confounding by indication. In the case of paracetamol, this confounding may occur when paracetamol is selected by prescribers or by purchasers in preference to NSAIDs because of the perceived greater safety of paracetamol with respect to a particular organ system (e.g. the gastrointestinal tract).[1] This type of bias, although well recognised, is difficult to eliminate when full patient histories are not known to the investigators, as is often the case.

A second problem is protopathic bias.[1] With respect to adverse reactions to drugs, this term is used to describe the occurrence of disease that starts to develop before the administration of the drug. The drug is then started by the patient in an early phase of the disease that continues to develop and is then associated with use of the drug. Protopathic bias poses a problem in the evaluation of adverse reactions to analgesics and is a particular problem with paracetamol because of its widespread use.[1]

Adverse reactions to NSAIDs are largely due to their inhibition of the synthesis of prostaglandins. The non-selective NSAIDs, such as aspirin (acetylsalicylic acid) and indometacin, inhibit prostaglandin synthesis by blocking both cyclo-oxygenase (COX)-1 and COX-2. The gastrointestinal damage produced by these drugs is largely attributed to their inhibition of the production of cytoprotective prostaglandins in the gastrointestinal tract.[2] This is primarily a COX-1 dependent pathway and the COX-2 selective drugs are better tolerated by the gastrointestinal tract than are the older non-selective drugs.[2] In intact cells stimulated by cytokines, paracetamol inhibits prostaglandin synthesis when the latter is probably mediated by COX-2.[3] Thus, not surprisingly, the gastrointestinal and overall tolerability profiles of paracetamol, apart from hepatotoxicity, are similar to those of the selective COX-2 inhibitors.

1. Identification of Studies

Relevant studies and review papers for examination were mostly identified from the Medline database (1975– January 2005), using the keywords 'acetaminophen' or 'paracetamol', together with 'adverse effects', 'side effects', 'tolerability', 'gastrointestinal', 'stomach', 'hepatic', 'liver', 'glutathione', 'metabolism', 'renal', 'kidney', 'sodium', 'pregnancy', 'asthma', 'hypersensitivity', 'prostaglandin', 'cancer' or 'dose'. The reference lists of recent reviews (2000–January 2005) and research papers were also used to identify relevant papers.

2. Metabolism of Paracetamol (Acetaminophen) Relevant to its Toxicity

The bulk of the metabolism of paracetamol is by formation of the glucuronic acid and sulfate conjugates (figure 1). These two conjugates account for about 80% of the elimination of paracetamol. In addition, a small amount is excreted unchanged. None of these processes is associated with toxicity, apart from occasional thrombocytopenia possibly because of paracetamol sulfate. By contrast, it is

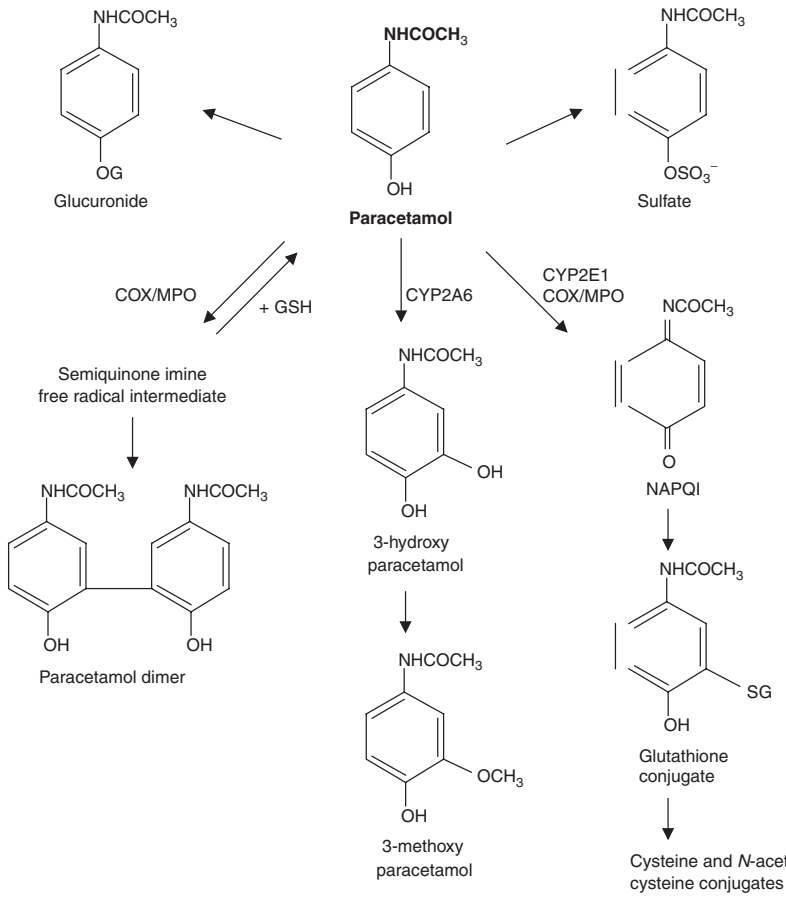

Fig. 1. Pathways of the metabolism of paracetamol (acetaminophen). The major metabolites involve non-oxidative metabolism to the glucuronide (G = glucuronyl) and sulfate conjugates that account for approximately 50% and 30% of doses of paracetamol, respectively. Cytochrome P450 (CYP) 2E1 oxidises paracetamol by a two electron oxidation process to *N*-acetyl-p-benzoquinone imine (NAPQI), which is subsequently hydrolyzed to the cysteine adduct and acetylated. CYP2A6 oxidises paracetamol to 3-hydroxy paracetamol, which is methylated. Myeloperoxidase (MPO) and the peroxidase functions of cyclo-oxygenase (COX) isoenzymes convert paracetamol by overall one electron and two electron oxidation processes. The one electron oxidation product is the semiquinone free radical intermediate that is either reduced back to paracetamol by reduced glutathione (GSH) with the simultaneous oxidation of GSH, or converted to paracetamol dimer and small amounts of higher polymers. The dimer and further polymeric products have been detected *in vitro* but have not been examined *in vivo*. NAPQI is also formed by MPO and COX isoenzymes.

well recognised that oxidative metabolism of paracetamol can lead to hepatotoxicity.[2]

The cytochrome P450 (CYP) system in the liver catalyses the production of the reactive *N*-acetyl-p-benzoquinone imine (NAPQI) that, as discussed in section 4, is the cause of the characteristic centrilobular hepatotoxicity of overdoses of paracetamol. The reactive NAPQI reacts with glutathione to form the paracetamol-glutathione conjugate. The bulk of this compound is converted to the cysteine conjugate and then to *N*-acetyl conjugate, which are both excreted in urine (figure 1).[2]

CYP2E1 is the CYP isoenzyme that oxidises paracetamol. This conclusion arises largely from the observation that disulfiram, through its active metabolite diethyldithiocarbamate, is a selective inhibitor of CYP2E1 and decreases the urinary excretion of the metabolites of NAPQI by about 70%.[4]

Paracetamol is also oxidised to NAPQI by several peroxidases, including myeloperoxidase[5,6] and

the peroxidase function of COX-1.[7,8] A free radical species is also produced by these peroxidases leading to the final production of a paracetamol dimer and further polymers of paracetamol (figure 1).

The main function of myeloperoxidase is to catalyse the formation of hypochlorous acid, an important bactericidal product of neutrophils and monocytes. By acting as a substrate for myeloperoxidase, paracetamol decreases the production of hypochlorous acid. However, the decreased formation of hypochlorous acid after therapeutic doses of paracetamol appears insufficient to produce a significant attenuation of the bactericidal activity of these cells.[9]

The conversion of paracetamol to reactive metabolites by myeloperoxidase raises the question of their potential toxicity when produced by this enzyme. The metabolism of several drugs, such as propylthiouracil and clozapine,[10,11] by myeloperoxidase in neutrophils and monocytes is associated with the development of agranulocytosis and systemic lupus. There are also claims that paracetamol very occasionally causes agranulocytosis in some patients,[12] although definitive evidence is still lacking. Furthermore, given its widespread use and the very rare reports of possible associations between agranulocytosis and the intake of paracetamol, any causation of agranulocytosis by paracetamol must be very rare.

The production of reactive metabolites through the peroxidase function of COX-1 is also of note (figure 1).[7,8] It is presumed that COX-2 metabolises paracetamol in a similar way to COX-1. Although the COX isoenzymes are known only as cyclooxygenases, both have dual functions, namely cyclo-oxygenase and peroxidase activities. The metabolism of paracetamol by the peroxidase activities of these enzymes may be highly relevant to its mechanism of action.[3] Furthermore, excessive production of reactive metabolites of paracetamol via COX enzymes could result in cellular toxicity in the kidney medulla.[13]

It should be emphasised that the extent of *in vivo* metabolism of paracetamol by myeloperoxidase and the peroxidase function of the COX isoenzymes are unknown. It is widely considered that CYP2E1 is the major source of NAPQI,[4] but the contribution of the peroxidases *in vivo* has not been determined. The dimer and further polymers are produced selectively by peroxidases but, as far as we are aware, their urinary output has not been examined. At this stage, the clinical significance of the oxidative metabolism of paracetamol by the peroxidases to reactive metabolites is unknown, but it should be kept in mind in any consideration of the toxicity of paracetamol.

3. Hepatotoxicity of Paracetamol

3.1 Hepatotoxicity from Overdosage

The hepatotoxicity of overdoses of paracetamol is well known and is the most worrisome aspect of its use. The typical pattern of toxicity is possible nausea and vomiting in the first 12–24 hours. Between 2 and 3 days after overdosage, plasma concentrations of the hepatic enzymes ALT and AST begin to rise with a subsequent increase in bilirubin concentration and prolongation of prothrombin time. In severe cases, coma and bleeding develop. Death often follows unless the patient receives a liver transplant. The toxicity results from centrilobular necrosis. Emergency treatment for this condition consists of gastric lavage and administration of *N*-acetylcysteine, which must be commenced within about the first 24 hours after overdosage, i.e. before centrilobular necrosis develops fully.[2]

A significant clinical question in acute medical units concerns the identification of patients who have, in fact, taken substantial doses of paracetamol. Patients often supply incorrect or unreliable histories of their drug intake. Paracetamol is a widely used drug and it may be present when other drugs have been taken in overdose. A nomogram relates the plasma concentrations to the time after dosage and indicates if the patient has taken a dangerous overdose.[14] However, the nomogram is often difficult to apply because the time of dosage is unknown or multiple large doses have been taken. It follows that *N*-acetylcysteine should be administered irrespective of the plasma concentrations if the biochemical features (see section 3.3) are consistent with an overdose and if an acute overdose or repeatedly very high doses have possibly been taken.

Although questions remain about the details of the mechanism of paracetamol hepatotoxicity, it is

widely accepted that the toxicity of paracetamol results from its oxidative metabolism to NAPQI. The commonly accepted mechanism is that NAPQI reacts with glutathione and, when hepatocellular glutathione is very much depleted by large amounts of NAPQI, the NAPQI reacts with the thiol groups of liver proteins, which results in centrilobular necrosis.[2] Depletion of glutathione may also provide an oxidant stress to cells or decrease the activities of enzymes for which glutathione is a cofactor.[2] Both mechanisms have been cited in suggestions that lower than average levels of glutathione in the liver or other tissues predispose to the toxicity induced by paracetamol. Thus, it has been claimed that malnourished patients or patients with hepatitis C, cirrhosis or AIDS, who possibly have low levels of glutathione, should be at great risk of hepatotoxicity, even from therapeutic doses of paracetamol.[14,15] However, recent reviewers have concluded that there is no convincing evidence that patients with these disease states have any increased incidence or severity of toxicity in the liver or other organs.[14,15] The pre-existing depletion of glutathione appears to be insufficient to potentiate hepatotoxicity from therapeutic doses of paracetamol.[15] However, it should be emphasised that depletion of glutathione leading to paracetamol-induced hepatotoxicity should be considered a kinetic phenomenon rather than a static situation. Hepatotoxicity develops when the rate of production of the reactive metabolite of paracetamol markedly exceeds the rate of supply of reduced glutathione and toxicity occurs only when the glutathione concentrations in the liver are considerably depleted.[15]

Further insight into the intracellular proteins that mediate toxicity has been gained from examining the effects of targeted gene disruption on paracetamol toxicity in mice. Such studies have confirmed *in vivo* that the CYP2E1 and CYP1A2 forms of CYP are largely responsible for mediating toxicity in this species.[16] Also, loss of the reduction/oxidation-sensitive transcription factor Nrf2 enhances paracetamol toxicity by suppressing the induction of both paracetamol-detoxifying enzymes and glutathione biosynthetic enzymes, resulting in enhanced paracetamol-mediated oxidative stress.[17]

As outlined in section 2, CYP2E1 is the major CYP responsible for oxidative hepatic metabolism of paracetamol in humans.[4] Thus, it has been suggested that the CYP2E1 inhibitor disulfiram may be useful in decreasing the hepatotoxicity of paracetamol in some patients.[4] However, at present there is no definition of patients in whom disulfiram may be any more useful than the current effective treatment, *N*-acetylcysteine. *In vivo*, *N*-acetylcysteine yields cysteine, which is then conjugated with glycine and glutamic acid to form reduced glutathione. Provided that it is administered within about 24 hours after the overdosage, *N*-acetylcysteine provides a very effective treatment for paracetamol overdose.[2]

3.2 Hepatotoxicity from Therapeutic Doses in Adults?

Following the discovery of the hepatotoxicity of overdoses of paracetamol, many cases of hepatotoxicity were reported with use of therapeutic doses of paracetamol. However, recent critical reviews in this field indicate that overdosage is the major cause of the toxicity.[18-20]

Careful reviews of hepatotoxicity in adults indicate that there are two types of liver changes associated with alleged therapeutic doses of paracetamol.[18-20] One type is consistent with overdose but the second type may not be caused by paracetamol.

In the first type, affected patients have developed centrilobular necrosis but the plasma concentrations of paracetamol during hospitalisation indicate that overdoses were taken within the 2–3 days before hospitalisation. Although therapeutic dosage has been claimed, most patients have probably taken overdoses. An example of this first type of hepatotoxicity was outlined by Bonkovsky et al.[19] A 67-year-old man with a history of chronic cardiovascular, renal and pulmonary impairment developed the classic features of paracetamol overdosage, including elevated transaminase levels, a slow increase in serum bilirubin level, and centrilobular hepatic necrosis. There was also evidence of acute renal failure. He claimed to have taken 1–3g of paracetamol daily for a short period of time, with the last dose having been taken 72 hours before hospitalisation. The plasma concentration of paracetamol, presumably measured near the time of admission, was 27.5 mg/L. After the patient had recovered from his hepatotoxicity, the elimination half-life of paracetamol was 7.9 hours. Based on this half-life, extrapo-

lation of his plasma concentrations to 68 hours before the plasma sample (allowing for 4 hours to attain peak plasma concentrations) yielded a plasma concentration of 11 g/L. This is an impossibly high value. The volume of distribution of paracetamol is approximately 50L and this body content would require a single dose of about 500g of paracetamol or accumulation after multiple dosage to a body content of this level. After recovery from the acute hepatotoxicity, this patient had a low level of hepatic glutathione and a prolonged elimination half-life of paracetamol. These factors were suggested to indicate a greater than usual hepatic sensitivity to paracetamol. However, the most likely reason for hepatotoxicity in this patient is still an acute overdose of paracetamol over the preceding 2–3 days, as Prescott[18] concluded from his survey of this and similar cases. In general, a patient's history of paracetamol dosage cannot be accepted if the clinical and biochemical changes observed, and particularly the plasma concentrations of paracetamol measured, are at great variance with the patient's statements. A number of recent reviews have emphasised this very reasonable point.[14,15,18,20,21]

The second type of hepatoxicity from alleged therapeutic dosage of paracetamol is, on examination, found not to be centrilobular necrosis, the classical hepatotoxic change seen with paracetamol. A variety of syndromes, including chronic active hepatitis, cholestasis and primary biliary cirrhosis, have developed during treatment with paracetamol but are generally not proven to be caused by paracetamol treatment. As noted by Prescott,[18] "in some cases, it is not clear why paracetamol should have been implicated as a cause of what appears to be naturally occurring liver disease".

Idiosyncratic hepatic reactions after low doses of paracetamol do occur but are extremely rare. In his survey of hepatotoxicity in non-alcoholic adults, Prescott[18] found only one case in which challenge dosage with therapeutic doses of paracetamol yielded convincing evidence of the signs of any hepatic disease. In this case, the toxic change resembled chronic active hepatitis. More recently, two patients with melanoma receiving interferon-α showed marked increases in the plasma concentrations of ALT while taking relatively low dosages of paracetamol (500–1500 mg/day).[22] Cessation of treatment with paracetamol allowed the liver enzymes to return to normal, but the enzyme concentrations in blood increased again after single doses of paracetamol.

The hepatic safety of paracetamol is also evident from recent studies. Firstly, dosage with 8 g/day (twice the currently recommended maximal daily dosage) for 3 days did not increase hepatic transaminase levels in healthy subjects.[23] This high dosage is not recommended at this stage but indicates the safety of therapeutic dosages of paracetamol. Furthermore, the incidences of adverse hepatic and renal events, which are not necessarily caused by paracetamol, are very similar at dosages of 3 g/day and 4 g/day of paracetamol in elderly patients.[24]

The overall conclusion is that hepatotoxicity from therapeutic doses of paracetamol is most uncommon.

3.3 Hepatotoxicity from Therapeutic Doses in Children?

Liver damage after paracetamol dosing for therapeutic purposes has been widely reported in children. The signs are very similar to those seen in acute overdosage.[25] Furthermore, the plasma concentrations of paracetamol, when they have been measured, generally indicate that, as in adults, administration of excessive doses is the probable cause of liver failure in most patients.[25,26] The drug may have been administered for therapeutic purposes, but the parents or guardians have, in fact, administered excessive doses. 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.[25] Investigations should include measurement of glucose levels, prothrombin time, aminotransaminase levels, bilirubin levels, acid-base status and paracetamol concentrations in plasma. As in adults, hypoglycaemia, prolonged prothrombin time, high levels of aminotransaminases (>4 000 IU/L) and levels of bilirubin (<200 μmol/L) are very suggestive of recent overdosage.[25]

Although a nomogram is available to predict the likelihood of overdosage with single overdoses of

paracetamol in adults, the potentially toxic levels of paracetamol are less clear after overdosage in children, especially after repeatedly excessive doses. Children should, therefore, be treated with *N*-acetylcysteine if biochemical indices are consistent with paracetamol-induced hepatotoxicity *and* there is any evidence of the child receiving paracetamol. Evidence of overdosage can be gathered from careful discussions with the parents or guardians and by measuring the plasma concentrations of the drug or detecting it in the urine. Paracetamol is, of course, a widely used drug and liver disease in many children will be unrelated to use of the drug. If the liver function tests remain abnormal, exclusion of other causes of liver failure is important in the long-term management of these patients. Other possible causes include hepatotoxicity from other drugs, hepatitis A, B or C viruses, Epstein-Barr virus, cytomegalovirus or inborn errors of metabolism, such as Wilson's disease and α_1-antitrypsin deficiency.[25] However, tests for these diseases are generally too slow for the emergency management of patients who have possibly taken overdoses of paracetamol and the antidote, *N*-acetylcysteine, should therefore be started before these diseases can be eliminated.

3.4 Hepatotoxicity from Therapeutic Doses in Patients Drinking Alcohol?

It has been claimed widely that alcohol potentiates the hepatotoxicity of paracetamol sufficiently to make therapeutic doses potentially hepatotoxic.[20,21,27] This claim has been formalised with the term 'alcohol-paracetamol syndrome' to describe the hepatotoxicity that is said to occur from the ingestion of therapeutic doses of paracetamol in moderate to heavy drinkers of alcohol.[27] This belief is also reflected in a ruling by the US FDA, which now requires that all packages of paracetamol sold in the US should be labelled with the warning "if you consume 3 or more alcoholic drinks every day, you should ask your doctor whether you should take acetaminophen (paracetamol) or other pain relievers/fever reducers. Acetaminophen may cause liver failure" (see section 4). However, once again, critical examination indicates that many cases of hepatoxicity in alcohol drinkers have been due to the ingestion of overdoses, not therapeutic doses, of paracetamol.[14,20,21] Indeed, Prescott[21] concluded that "although the possibility remains that chronic consumption of alcohol does increase the risk of paracetamol hepatotoxicity in man, there is insufficient evidence to support the alleged major toxic interaction".

There are two major reasons for concluding that alcohol does not potentiate the hepatotoxicity of paracetamol sufficiently to make therapeutic doses hepatotoxic. Firstly, as with cases of hepatotoxicity ascribed to therapeutic doses of paracetamol in non-alcohol drinking adults and children, extrapolation of the plasma concentrations in moderate and heavy alcohol drinkers with hepatotoxicity indicates that excessive doses have often been administered.[14,20,21] Secondly, all prospective studies indicate that therapeutic doses of paracetamol are not hepatotoxic in alcoholic patients.[14,20,21] However, a limitation in the prospective studies should be noted. This is that the dosage of paracetamol has generally been short-term (from 1 to 5 days). Although difficult, it would be useful to conduct longer term prospective studies.

The possible effect of alcohol on the hepatotoxicity of paracetamol is being investigated at the level of the metabolic interaction between the two compounds. Alcohol has variable, although generally modest, effects on the CYP2E1 pathway, which is largely responsible for production of the hepatotoxic metabolites of paracetamol.[4] Alcohol induces this enzyme, but it also inhibits CYP2E1 while the alcohol remains in the body. Alcohol may, therefore, protect the liver by inhibiting the oxidative metabolism of paracetamol. Subsequently, alcohol may make the liver more sensitive to paracetamol because hepatic concentrations of CYP2E1 appear to decline at a slower rate than the plasma concentrations of alcohol. Thus, alcohol may be removed from the body and unable to inhibit the metabolism of paracetamol while the concentrations of CYP2E1 are still elevated and capable of a higher than normal rate of conversion of paracetamol to hepatotoxic metabolites. However, alcohol appears to produce only a small increase (range from 2% to 38%) in the oxidative metabolism of paracetamol when the paracetamol is administered 8 hours after the cessation of an infusion of alcohol sufficient to produce a blood concentration of 0.1g per 100mL.[28] Nevertheless, simulations indicate that up to an approxi-

mate doubling of the rate of formation of the reactive metabolite, NAPQI, could occur after cessation of an intake of alcohol sufficient to produce a blood concentration of 0.3g per 100mL.[28] More directly, testing indicates that 1g of paracetamol four times per day does not lead to biochemical evidence of liver damage in alcoholic patients in the period just after cessation of alcohol use, the point at which they should be maximally sensitive to paracetamol.[29]

Calculations of the rate of formation of NAPQI and glutathione do not indicate that paracetamol should be markedly more toxic in alcoholics than in non-alcoholics.[14,15] Furthermore, paracetamol (4 g/day for 3 days) does not reduce glutathione levels in the plasma of alcoholics.[30] Glutathione in the liver may be depleted in chronic alcoholics, but this does not appear to increase the risk of paracetamol-induced hepatotoxicity, possibly because the oxidative metabolism of paracetamol is also inhibited in these patients.[14,15] However, the interaction between alcohol and paracetamol is still a contentious area and it is reasonable to suggest that alcoholics who have taken an overdose of paracetamol should be treated with *N*-acetylcysteine at lower plasma concentrations of paracetamol than non-alcoholics.[31]

Overdoses of paracetamol may be more common in alcoholics than in the remainder of the population,[32] but this does not necessarily mean that chronic use of alcohol potentiates the hepatotoxicity of therapeutic doses of paracetamol. Rather, the depression and other psychological and psychiatric factors associated with alcoholism may make them more likely to take an overdose of paracetamol.[33,34] Furthermore, the memory loss often associated with severe alcoholism may make affected individuals unaware of having taken excessive doses.

Overall, it appears unlikely that alcohol increases the hepatotoxicity of paracetamol sufficiently to cause toxicity during therapeutic dosages. However, the toxicity of paracetamol overdoses may be increased in alcoholics. This is an area of ongoing research.

3.5 Use of Paracetamol in Alcoholics and in Patients with Liver Diseases

Limited clinical studies indicate that paracetamol can be administered to patients with chronic liver diseases.[35-37] Paracetamol does not exacerbate stable chronic liver disease,[35] for example. Furthermore, the metabolism of paracetamol appears normal in patients with liver disease although the elimination half-life is prolonged by an average of 75% in patients with severe liver disease.[36] In an authoritative textbook, paracetamol (up to 1g three times per day) is recommended as the optimal analgesic in patients with chronic liver disease.[37] However, it is prudent to monitor liver function in such patients and use of paracetamol in patients with hepatic diseases should be kept as short as possible.

What alternative analgesics or antipyretics can be used in patients with liver disease or in alcoholics? The NSAIDs, such as aspirin or ibuprofen, are relatively contraindicated because of the morbidity and mortality resulting from gastrointestinal damage produced by NSAIDs and the risk of bleeding in patients with varices.[38] Alcohol tends to potentiate the gastric damage produced by non-selective NSAIDs[39] and initial bleeding from varices is also increased.[38] The selective COX-2 inhibitors, such as celecoxib, may ultimately prove to be useful, but clinical evidence for the safety of these drugs combined with alcohol and in liver failure is lacking at present. Opioid analgesics may be used in severe pain, but care should be taken with the dosage of these agents because of possible decreased metabolic clearance and respiratory depression.

Overall, it appears that paracetamol is a reasonable analgesic or antipyretic drug to use in alcoholics and patients with liver diseases. However, the dosage should be monitored and the number of tablets or capsules of paracetamol available for alcoholic patients should be restricted in order to reduce the chances of overdosage. In this regard, it is notable that very large packs of paracetamol tablets are marketed in the US despite the warning on the label.

4. Labelling and Packaging

No warnings about the use of paracetamol with alcohol are specified in most countries but, as outlined in section 3.4, paracetamol sold in the US is

accompanied by a warning that it must be taken with care if alcohol is also taken in moderate to excessive amounts.

What are the reasons for the FDA labelling of paracetamol? There are two possible reasons for inclusion of this warning about the potential for hepatotoxicity of paracetamol in alcoholics. The first is that critical analyses of reports of hepatotoxicity said to be produced by therapeutic doses of paracetamol in alcoholics have only recently been published. The second reason is that the FDA may have tried to err on the side of patient safety. This was a reason admitted to by the American College of Rheumatology (ACR) in relation to its 2000 Guidelines for the Medical Management of Osteoarthritis.[40] In these guidelines, the ACR recommended that paracetamol should be avoided in patients with chronic alcohol abuse and used with caution in patients with existing liver disease. Subsequent correspondence in *Arthritis and Rheumatism*[41,42] was generally critical of these statements and, in reply, the spokesman for the ACR[43] stated that it was "… better to err on the side of patient safety given that alternative treatments are available …". While statements on product labels or in information given to physicians about the possible hepatotoxicity of therapeutic dosages of paracetamol are currently being considered in countries other than the US, it is important to note that poorly justified statements are not helpful and decrease attention to well accepted warnings about other drugs.

It is also important that the correct dosage of paracetamol should be emphasised to patients. However, the potential for death from overdoses of paracetamol should still not be widely broadcast because of the danger of popularising overdosage with this drug. There is now documented evidence that imitations of suicides occur following news items, films and television dramas in which suicides are reported or depicted. Not all news reports or fictional stories have been clearly followed by suicides or attempted suicides, but many have been.[44] Judging from the occurrence of copycat suicides, the label on US packs about the hepatotoxicity of paracetamol may encourage some patients to take overdoses of the drug.

In recent years, the package size of paracetamol has been limited in many countries, although not in the US. It is very difficult to evaluate the effect of restricting the size of packages of any drug. However, preliminary evidence suggests that the numbers of paracetamol overdoses have declined since the pack size was reduced in the UK,[45] despite the fact that it is still easy to obtain several packs of paracetamol tablets or capsules.

5. Gastrointestinal Tolerability

In pharmacology texts and reviews, it is frequently stated that paracetamol has excellent gastrointestinal tolerability. These statements are based on prospective studies that show that paracetamol does not damage the gastrointestinal tract.[46-48] As discussed in the introduction, this tolerability has been related to selective inhibition of cellular prostaglandin synthesis involving COX-2 by paracetamol, although further work is required to support this hypothesis concerning its mechanism of action.[3] The favourable gastrointestinal tolerability of paracetamol is in contrast with that of aspirin, which is associated with considerable risk of bleeding even when given at low doses.[49]

The excellent gastrointestinal tolerability of paracetamol has been confirmed in recent meta-analyses of case-control studies. Lewis et al.[50] found no significant effect of paracetamol on the gastrointestinal tract at any dose. Another researcher (Henry DA, personal communication) found that paracetamol had a significantly increased relative risk of upper gastrointestinal reactions (perforations, ulcers or bleeding), but the pooled relative risk was only 1.5 (95% CI 1.21, 1.85). These figures were calculated from the results of ten studies in which some adjustment was made for potential confounding variables such as alcohol and other NSAIDs. Although statistically significant, the association is weak and very much within the area where confounding variables make the risk uncertain.

Three epidemiological studies have indicated a greater incidence of adverse gastrointestinal reactions with increasing daily doses of paracetamol.[51-53] In one of these studies, patients taking paracetamol had a higher incidence of gastrointestinal events than patients taking NSAIDs, but this was related to older age and risk factors for gastropathy in the patients taking paracetamol.[53] In the same study, dyspepsia was far more common than ulcers

or upper gastrointestinal bleeding in the groups taking the higher doses of paracetamol.[53] This was described as "somewhat reassuring", although the dyspepsia is still troublesome and often causes costly medical investigation.

The relationship between increasing dose of paracetamol and gastrointestinal events reported in these studies[51-53] may be a biased result. It has been suggested that the higher incidence of bleeding in patients taking the larger doses of paracetamol could occur because "physicians would be especially careful not to prescribe high doses of NSAIDs to those at greatest risk of GI bleeding" and would therefore use paracetamol instead.[1] The gastrointestinal safety of paracetamol is widely advertised and patients who know or suspect they have upper gastrointestinal disease may have bought over-the-counter preparations of paracetamol. Therefore, a greater incidence of gastrointestinal events overall, and particularly with high doses of paracetamol, may be expected.

Protopathic bias may also occur. For paracetamol, this can occur because this agent may be used to treat the pain or discomfort of early gastrointestinal disease.[1] Peptic ulcer is then associated with the use of paracetamol. An indication of this bias with paracetamol is that an association between the use of paracetamol and gastrointestinal bleeding was seen when paracetamol was used for indigestion but not when it was used for headaches or colds.[54] The results of case control or cohort studies are corrected for risk factors, but it is difficult to remove confounding variables completely when the reasons for the use of drugs are not known. This is a particular problem with widely available drugs, such as paracetamol.

Because of the lack of acute changes in the upper gastrointestinal tract observed with use of paracetamol, the majority view is still that this drug is free of major gastrointestinal toxicity. Nevertheless, the questions raised by epidemiological studies remain and may not be answered finally until a large scale randomised prospective clinical trial of major events, such as perforations, ulcer or bleeding, is conducted in paracetamol users. Data from such a trial might also indicate if paracetamol causes dyspepsia. At this stage, there is no clear evidence that it does.

6. Renal Tolerability

Non-selective NSAIDs and selective COX-2 inhibitors may precipitate acute renal failure in patients with risk factors such as congestive cardiac failure, pre-existing renal impairment and transplanted kidneys.[55] By contrast, exacerbation of cardiac failure has not been reported with paracetamol and acute renal failure has not been associated with therapeutic doses of the drug.[55] However, overdoses of paracetamol may produce acute renal failure as a result of acute tubular necrosis, possibly because of metabolism of the drug to reactive metabolites by the peroxidase function of COX-1 or COX-2.[13]

Possibly through their renal effects, the non-selective NSAIDs and the selective COX-2 inhibitors may decrease the efficacy of diuretics and antihypertensives.[55] No such interactions have been related to use of paracetamol although NSAIDs and paracetamol were associated with the development of hypertension in young women (aged from 25 to 42 years) in one cohort study.[56]

Studies of the effects of paracetamol on the excretion of prostaglandins and sodium have yielded inconsistent results.[55] Although the excretion of prostaglandins, their metabolites and sodium have been reduced in most studies,[55] this has not been a universal result.[55] Overall, the effects of paracetamol on the renal output of prostaglandins and sodium appear to be weaker than those of the non-selective and selective COX-2 inhibitors.[55] However, direct comparative studies are required, particularly in patients with risk factors such as cardiac failure, for the retention of sodium and water. Investigational studies of sodium clearance should also be conducted on the first day of treatment with paracetamol because it is at this time that NSAIDs show their greatest inhibitory effect on this aspect of renal function.[55]

The renal toxicity of paracetamol has mainly been examined in terms of development of chronic renal failure, particularly that resulting from analgesic nephropathy.[57] The results have been inconsistent. A recent reviewer concluded that "there is currently insufficient evidence to conclude that the habitual use of paracetamol is associated with an increased risk of chronic renal disease".[57] Despite

this conclusion, there are studies showing such an association, most recently that by Fored et al.[58] As in other settings, it is difficult to remove confounding variables in epidemiological studies of the renal effects of paracetamol. In recent years at least, paracetamol has been considered to be safer for kidneys than the non-selective NSAIDs. Therefore, as is the case with the use of paracetamol in other disease states, the prescription of paracetamol for patients with renal disease may have led to the association between paracetamol and renal disease. However, there may not be any causation underlying the association.

7. Haemostasis

Therapeutic doses of paracetamol decrease the synthesis of thromboxane A_2 by platelets (a COX-1-dependent system) after therapeutic dosage.[59] However, an almost total blockade of thromboxane A_2 synthesis is required before platelet aggregation is markedly inhibited and therapeutic doses of paracetamol therefore have no significant effect on platelet aggregation. This result contrasts with the marked anti-platelet effects of the non-selective NSAIDs at therapeutic doses.[2]

Thrombocytopenia is also associated with hepatotoxicity of paracetamol in a small proportion of overdoses[60] but is extremely rare at therapeutic doses. Nevertheless, immune thrombocytopenia has been reported in a very small number of patients.[61] This immune-induced thrombocytopenia may be induced by paracetamol sulfate, a major metabolite of paracetamol. Other hypersensitivity reactions of paracetamol are extremely rare and are discussed in section 8.

Because of its weak effect on platelets, 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.[62,63] This potentiation of the effect of warfarin is a contentious issue, but an interaction between paracetamol and warfarin is now included in standard references on drug interactions.[62,63] Paracetamol is still recommended as a reasonable analgesic and antipyretic to use with warfarin because of the weak effect of paracetamol on platelet aggregation at therapeutic dosages.[62,63] Nevertheless, monitoring of the prothrombin time is recommended in patients taking paracetamol and warfarin, particularly when regular and daily dosage with >2g paracetamol is started or stopped.[62,63]

8. Hypersensitivity Reactions

The metabolism of paracetamol to reactive compounds suggests that it may act as a hapten and lead to hypersensitivity reactions. Although the mechanisms involved are unclear, such reactions do occur with paracetamol but are very rare. For example, while allergic skin reactions to paracetamol are extremely rare, urticaria has been produced after administration of test oral doses.[64] Many patients who have skin reactions to aspirin or other NSAIDs do not react to paracetamol.[64] Conversely, paracetamol produces urticaria in a few patients who tolerate aspirin.[65] Anaphylactic shock also occurs very rarely in patients taking paracetamol,[66] although, in some cases, it is caused by an additive in the tablet and not by the paracetamol itself.[67]

Despite the very low incidence of paracetamol-precipitated asthma, use of paracetamol was associated with asthma in a controversial case control study.[68] This found that the odds ratio for the incidence of asthma increased with more frequent use of the drug. Avoidance of aspirin was considered in this study, but 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.

Of more significance is the effect of paracetamol in aspirin-induced asthma. Acute asthma is precipitated by aspirin and the non-selective NSAIDs in some asthmatics. The recorded proportion of asthmatics who are sensitive to aspirin and the non-selective NSAIDs is very variable but probably in the range of 4% to 20%.[69-71] These patients frequently develop nasal polyps before their sensitivity to aspirin and the non-selective NSAIDs manifests itself. Paracetamol is well tolerated by most, but not all, of these asthmatics.[69-71] Furthermore, the asthmatic reaction is milder after exposure to paracetamol than after dosage with the non-selective NSAIDs.[69-71] Unfortunately, detecting the few patients with cross-reactivity between paracetamol and the non-selective NSAIDs can only be achieved with provocation tests.[71] The general safety of paracetamol in asthmatics has led to the recommen-

dation that "routine warnings about paracetamol use in asthma are, therefore, not warranted",[71] although medical personnel should be aware of this occasional problem in patients in whom testing for the reaction or withdrawal of paracetamol is warranted.[70,71] The low incidence of asthmatic reactions to paracetamol may be related to some inhibition of prostaglandin synthesis by COX-1. The conclusion is reached that non-selective NSAIDs all precipitate asthma in aspirin-sensitive asthmatics, whereas the COX-2 selective asthmatics do not appear to produce this syndrome.[72]

9. Occurrence of Cancers

While elevated risks for the development of some tumours of the urinary tract with use of paracetamol have been detected in some case control studies,[73] a recent reviewer concluded that "results do not support a major role for paracetamol in the development of cancers".[73] Conversely, there are inconsistent reports of paracetamol decreasing the risk of ovarian cancer[73,74] although, again, the results are insufficient to allow any definitive conclusions.

10. Tolerability During Pregnancy

Paracetamol is preferred to the non-selective NSAIDs as an analgesic during pregnancy.[75] Studies in mice show that prostaglandins formed through the COX-2 pathway are important in the early processes of pregnancy, including ovulation, fertilisation and implantation.[76] COX-2 activity is also significant in the initiation of labour.[77] By inhibiting the COX-2 pathways in intact cells, the non-selective NSAIDs, COX-2 selective inhibitors and paracetamol could affect all of these processes. The non-selective NSAIDs and the selective COX-2 inhibitors delay labour[77,78] but, as far as we are aware, no effect of paracetamol on late pregnancy in women has been reported. A recent cohort study indicated that NSAIDs, but not paracetamol, may increase the chance of miscarriage.[79] Prospective studies of the NSAIDs and paracetamol on the early processes of pregnancy and its maintenance are clearly required.

A clear difference between the actions of paracetamol and the non-selective NSAIDs is the much weaker antiplatelet effect of paracetamol (see section 7). The non-selective NSAIDs inhibit COX-1 in platelets and may increase blood loss associated with childbirth or produce bleeding in the baby.[75] By contrast, paracetamol should not.

11. Conclusions

The major problem arising from the widespread use of paracetamol is the ability of overdoses to cause hepatotoxicity as a result of metabolism of the drug to reactive compounds. Many cases of hepatotoxicity have been claimed to be associated with therapeutic doses of paracetamol, but critical analysis indicates that many of these cases have resulted from overdoses. The dosage of paracetamol, particularly in children and alcoholics, should be controlled carefully in order to prevent hepatotoxicity. Medical practitioners, nurses and pharmacists should emphasise to patients the need to take the correct dosage of paracetamol, although discussion of the dangers of overdose in the media should be restricted because of the risk of increasing the numbers of suicides from overdoses. Adequate labelling based on critical analysis of the literature is also important.

Epidemiological reports of associations between paracetamol and chronic renal disease, gastrointestinal damage and asthma may be biased, at least in part, because of the perceived safety of paracetamol in patients with these known diseases or because of other confounding variables. However, continuing surveillance of such possible associations is warranted.

Acknowledgements

The authors gratefully acknowledge discussions with Professor David Henry, Dr Richard Robson, Dr Robert Graham and Dr Bridin Murnion in the preparation of this article. A research project of Professor Graham has been supported by GlaxoSmithKline and Professor Day is a member of advisory boards for the companies marketing celecoxib (Pfizer and Pharmacia), rofecoxib (Merck) and paracetamol (acetaminophen) [GlaxoSmithKline]. Dr Scott is supported by the National Health and Medical Research Council of Australia (Grant no. 222870).

References

1. Signorello LB, McLaughlin JK, Lipworth L, et al. Confounding by indication in epidemiological studies of commonly used analgesics. Am J Ther 2002; 9: 199-204

2. Roberts LJ, Morrow JD. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill, 2001: 687-731
3. Graham GG, Robins S-A, Bryant KJ, et al. Inhibition of prostaglandin synthesis in intact cells by paracetamol (acetaminophen). Inflammopharmacology 2001; 9: 131-42
4. Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000; 67: 275-82
5. O'Brien PJ, Khan S, Jatoe SD. Formation of biological reactive intermediates by peroxidases: halide mediated acetaminophen oxidation and cytotoxicity. Adv Exp Med Biol 1990; 283: 51-64
6. Graham GG, Milligan MK, Day RO, et al. Therapeutic considerations from pharmacokinetics and metabolism: ibuprofen and paracetamol. In: Rainsford KD, Powanda MC, editors. Safety and efficacy of non-prescription (over-the-counter) analgesics and NSAIDs. Edinburgh: Kluwer Press, 1997: 77-92
7. Potter DW, Hinson JA. The 1- and 2-electron oxidation of acetaminophen catalyzed by prostaglandin H synthase. J Biol Chem 1987; 262: 974-80
8. Harvison PJ, Egan RW, Gale RH, et al. Acetaminophen and analogs as cosubstrates and inhibitors of prostaglandin H synthase. Chem Biol Interact 1988; 64: 251-66
9. Graham GG, Day RO, Milligan MK, et al. Current concepts of the actions of paracetamol (acetaminophen) and NSAIDs. Inflammopharmacology 1999; 7: 255-64
10. Uetrecht JP. Idiosyncratic drug reactions: possible role of reactive metabolites generated by leukocytes. Pharm Res 1989; 6: 265-73
11. Uetrecht JP. Metabolism of clozapine by neutrophils: possible implications for clozapine-induced agranulocytosis. Drug Saf 1992; 7 Suppl. 1: 51-6
12. Lacotte J, Perrin C, Mosquet B, et al. Agranulocytosis from paracetamol. Therapie 1990; 45: 438-9
13. Mohandas J, Duggin GG, Horvath JS, et al. Metabolic oxidation of acetaminophen (paracetamol) mediated by cytochrome P-450 mixed-function oxidase and prostaglandin endoperoxide synthetase in rabbit kidney. Toxicol Appl Pharmacol 1981; 61: 252-9
14. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol 2002; 40: 3-20
15. Lauterburg BH. Analgesics and glutathione. Am J Ther 2002; 9: 225-33
16. Gonzalez FJ. The use of gene knockout mice to unravel the mechanisms of toxicity and chemical carcinogenesis. Toxicol Lett 2001; 120: 199-208
17. Chan K, Han X-D, Kan YW. An important function of Nrf2 in combating oxidative stress: detoxification of acetaminophen. Proc Natl Acad Sci U S A 2001; 98: 4611-6
18. Prescott LF. Therapeutic misadventure with paracetamol: fact or fiction. Am J Ther 2000; 7: 99-114
19. Bonkovsky HL, Kane RE, Jones DP, et al. Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. Hepatology 1994; 19: 1141-8
20. Dart RC, Kuffner EK, Rumack BH. Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: a systematic review. Am J Ther 2000; 7: 123-34
21. Prescott LF. Paracetamol, alcohol and the liver. Br J Clin Pharmacol 2000; 49: 291-301
22. Fabris P, Palma MD, de Lalla F. Idiosyncratic acute hepatitis caused by paracetamol in two patients with melanoma treated with high-dose interferon-α [letter]. Ann Intern Med 2001; 134: 345
23. Gelotte CK, Auiler JF, Temple AR, et al. Clinical features of a repeat-dose multiple-day pharmacokinetics trial of acetaminophen at 4, 6, and 8 g/day [abstract]. J Toxicol Clin Toxicol 2003; 41: 726
24. Ganry H, Pruvot F, Vesque D, et al. Liver and renal tolerance to paracetamol: 3 g or 4 g per day? [in French]. Presse Med 2001; 30: 724-38
25. Miles FK, Kamath R, Dorney SF, et al. Accidental paracetamol overdosing and fulminant hepatic failure in children. Med J Aust 1999; 171: 472-5
26. Penna A, Buchanan N. Paracetamol poisoning in children and hepatotoxicity. Br J Clin Pharmacol 1991; 32: 143-9
27. Draganov P, Durrence H, Cox C, et al. Alcohol-acetaminophen syndrome. Postgrad Med 2000; 107: 189-95
28. Thummel KE, Slattery JT, Ro H, et al. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. Clin Pharmacol Ther 2000; 67: 591-9
29. Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: a randomized, double-blind, placebo-controlled trial. Arch Intern Med 2001; 161: 2247-52
30. Palmer RB, Green JL, Kuffner EK, et al. Plasma reduced glutathione (GSH) in alcoholics receiving maximal therapeutic doses of acetaminophen [abstract]. J Toxicol Clin Toxicol 2003; 41: 726
31. Buckley NA, Srinivasan J. Should a lower treatment line be used when treating paracetamol poisoning in patients with chronic alcoholism?: a case for. Drug Saf 2002; 25: 619-24
32. McMahon GT, McGarry K. Deliberate self-poisoning in an Irish county hospital. Irish J Med Sci 2001; 170: 94-7
33. Hufford MR. Alcohol and suicidal behaviour. Clin Psychol Rev 2001; 21: 797-811
34. Thase ME, Salloum IM, Cornelius JD. Comorbid alcoholism and depression: treatment issues. J Clin Psychiatry 2001; 62 Suppl. 20: 32-41
35. Benson GD. Acetaminophen in chronic liver disease. Clin Pharmacol Ther 1983; 33: 95-101
36. Forrest JA, Adriaenssens P, Finlayson ND, et al. Paracetamol metabolism in chronic liver disease. Eur J Clin Pharmacol 1979; 15: 427-31
37. McIntyre N. The general management of liver disease. In: Bircher J, Benhamou J-P, McIntyre N, et al., editors. Oxford textbook of clinical hepatology. Oxford: Oxford University Press, 1999: 1917-23
38. de Ledinghen V, Heresbach D, Fourdan O, et al. Anti-inflammatory drugs and variceal bleeding: a case control study. Gut 1999; 44: 270-3
39. Lanza FL, Royer GL, Nelson RS, et al. Ethanol, aspirin, and the gastroduodenal mucosa: an endoscopic assessment. Am J Gastroenterol 1985; 80: 767-9
40. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of hip and knee osteoarthritis. 2000 update. Arthritis Rheum 2000; 43: 1905-15
41. Lynch JM, Fox TM. Use of acetaminophen in the treatment of osteoarthritis in patients with liver disease: comment on the 2000 update of the American College of Rheumatology recommendations for the management of hip and knee osteoarthritis [letter]. Arthritis Rheum 2001; 44: 2448-9
42. Dart RC, Kuffner EK. Use of acetaminophen in alcoholic patients: comment on the 2000 update of the American College of Rheumatology recommendations for the management of hip and knee osteoarthritis [letter]. Arthritis Rheum 2001; 44: 2449
43. Hochberg MC. Reply to letters. Arthritis Rheum 2001; 44: 2455-6

44. Gould MS. Suicide and the media. Ann NY Acad Sci 2001; 932: 200-24

45. Langford NJ, Aruna RS, Mutimer D, et al. The impact of pack size legislation on paracetamol (acetaminophen) poisoning in the West Midlands (United Kingdom). J Toxicol Clin Toxicol 2003; 41: 419-20

46. Ivey KJ, Settree P. Effect of paracetamol (acetaminophen) on gastric ionic fluxes and potential difference in man. Gut 1976; 17: 916-9

47. Hoftiezer JW, O'Laughlin JC, Ivey KJ. Effects of 24 hours of aspirin, Bufferin, paracetamol and placebo on normal gastroduodenal mucosa. Gut 1982; 23: 692-7

48. Lanza FL, Codispoti JR, Nelson EB. An endoscopic comparison of gastroduodenal injury with over-the-counter doses of ketoprofen and acetaminophen. Am J Gastroenterol 1998; 93: 1051-4

49. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ 1995; 310: 827-30

50. Lewis SC, Langman MJS, Laporte JR, et al. Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and on serious upper gastrointestinal bleeding: a meta analysis based on individual patient data. Br J Clin Pharmacol 2002; 54: 320-6

51. Savage RL, Moller PW, Ballantyne CL, et al. Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy. Arthritis Rheum 1993; 36: 84-90

52. Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res 2001; 3: 98-101

53. Rahme E, Pettitt D, LeLorier J. Determinants and sequelae associated with utilization of acetaminophen versus traditional nonsteroidal antiinflammatory drugs in an elderly population. Arthritis Rheum 2002; 46: 3046-54

54. Langman MJ, Coggon D, Spiegelhalter D. Analgesic intake and the risk of upper gastrointestinal bleeding. Am J Med 1983; 74: 79-82

55. Graham GG, Graham RI, Day RO. Comparative analgesia, cardiovascular and renal effects of celecoxib, rofecoxib and acetaminophen (paracetamol). Curr Pharm Des 2002; 8: 1063-75

56. Curhan GC, Willett WC, Rosner B, et al. Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med 2002; 162: 2204-8

57. Barrett BJ. Acetaminophen and adverse chronic renal outcomes: an appraisal of the epidemiological evidence. Am J Kidney Dis 1996; 28 Suppl. 1: S14-9

58. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin and chronic renal failure. N Engl J Med 2001; 345: 1801-8

59. Lages B, Weiss HJ. Inhibition of human platelet function in vitro and ex vivo by acetaminophen. Thromb Res 1989; 53: 603-13

60. Fischereder M, Jaffe JP. Thrombocytopenia following acute acetaminophen overdose. Am J Hematol 1994; 45: 258-9

61. Bougie D, Aster R. Immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen. Blood 2001; 97: 3846-50

62. Stockley IH. Drug interactions. 3rd ed. Oxford: Blackwell, 1994

63. Hansten PD, Horn JR. Drug interactions. St Louis (MO): Facts and Comparisons Publishing Group, 2003

64. Quaratino D, Romano A, Papa G, et al. Long-term tolerability of nimesulide and acetaminophen in non-steroidal anti-inflammatory drug-intolerant patients. Ann Allergy Asthma Immunol 1997; 79: 47-50

65. De Paramo BJ, Gancedo SQ, Cuevas M, et al. Paracetamol (acetaminophen) hypersensitivity. Ann Allergy Asthma Immunol 2000; 85: 508-11

66. Kvedariene V, Benchericua AM, Messaad D, et al. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial. Clin Exp Allergy 2002; 32: 1366-9

67. Ronnau AC, Wulferink M, Gleichmann E, et al. Anaphylaxis to polyvinylpyrrolidine in an analgesic preparation. Br J Dermatol 2000; 143: 1055-8

68. Shaheen SO, Sterne JA, Songhurst CE, et al. Frequent paracetamol use and asthma in adults. Thorax 2000; 55: 266-7

69. Morassut P, Yang W, Karsh J. Aspirin intolerance. Semin Arthritis Rheum 1989; 19: 22-30

70. Jenkins C. Recommending analgesics for people with asthma. Am J Ther 2000; 7: 55-61

71. Levy S, Volans G. The use of analgesics in patients with asthma. Drug Saf 2001; 24: 829-41

72. West PM, Fernandez C. Safety of COX-2 inhibitors in asthma patients with aspirin hypersensitivity. Ann Pharmacother 2003; 37: 1497-501

73. Friis S, Nielsen GL, Mellemkjaer L, et al. Cancer risk in persons receiving prescriptions for paracetamol: a Danish cohort study. Int J Cancer 2002; 97: 96-101

74. Cramer DW, Harlow BL, Titus-Ernstoff L, et al. Over-the-counter analgesics and the risk of ovarian cancer. Lancet 1998; 351: 104-7

75. Rubin PC, Rutherford JM. Drug therapy in pregnant and breast-feeding women. In: Carruthers SG, Hoffman BB, Melmon KL, et al., editors. Clinical pharmacology. 4th ed. New York: McGraw-Hill, 2000: 1117-42

76. Lim H, Paria BC, Das SK, et al. Multiple female reproductive failures in cyclooxygenase 2-deficient mice. Cell 1997; 91: 197-208

77. Ostensen M. Non-steroidal anti-inflammatory drugs during pregnancy. Scand J Rheumatol Suppl 1998; 107: 128-32

78. Stika CS, Gross GA, Leguizamon G, et al. A prospective randomized safety trial of celecoxib for treatment of preterm labour. Am J Obstet Gynecol 2002; 187: 653-60

79. Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ 2003; 327: 368-72

Correspondence and offprints: Professor *Garry G. Graham*, Department of Clinical Pharmacology, St Vincent's Hospital, Darlinghurst, NSW 2010, Australia.
E-mail: ggraham@stvincents.com.au