CLINICAL PRACTICE

Paracetamol poisoning

Paracetamol is one of the most widely used analgesic/antipyretic agents because of its overall efficacy and safety. However, paracetamol overdose is the most important cause of acute liver failure in the UK and is not uncommon in South Africa.[1]

Liver damage usually occurs with ingestion of approximately 7,5 g paracetamol, and doses of 12 - 16 g commonly result in fatal acute liver failure. Prior long-term use of enzyme-inducing agents such as alcohol, anticonvulsant drugs (phenytoin) and antituberculosis therapy may enhance paracetamol toxicity so that doses of 6 - 8 g may be fatal.[2] If alcohol and paracetamol are taken together in an overdose, then alcohol may decrease metabolism of paracetamol to reactive metabolites either by direct competition for cytochrome P-450 or as a result of indirect inhibition of cytochrome P-450 by depletion of cytosolic-reduced NADPH.

Clinical picture

The initial onset of gastro-intestinal liver damage is rapid, with anorexia, nausea and vomiting occurring within a few hours of ingestion of a hepatotoxic dose. These are followed by abdominal pain and liver tenderness which may persist for 36 - 72 hours.

Liver failure may then worsen, particularly if the initial prothrombin international normalised ratio (INR) values are in excess of 2,2 and if bilirubin levels increase to more than 68 μmol/l.

Overall mortality rates are about 2 - 13%; fulminant liver failure tends to occur between days 3 and 6. If patients recover, results of liver tests usually return to normal within 7 - 20 days and there is no residual hepatic damage. Renal failure secondary to acute tubular necrosis is common and patients may require dialysis.[3]

Metabolism of paracetamol

Paracetamol is modified via several routes, some of which are detoxifying, while others lead to the production of toxic metabolites. Usually about 70 - 80% of the parent drug is conjugated to form non-toxic sulphates and glucuronides which are then excreted in the urine; 5 - 10% of paracetamol is excreted as glutathione-derived conjugates (3-cysteinyl, 3-mercapturate and 3-methyl conjugates). These thio-ethers are the detoxification products of the reactive and toxic metabolite of paracetamol, *N*-acetyl-*p*-benzo-quinone-imine (NAPQI).

Approximately 5 - 10% of the dose is excreted as 3-hydroxy- and 3-methoxyacetaminophen metabolites. Like the thio-ethers, their formation clearances decrease with increasing doses and they are found in large amounts in urine taken from overdosed patients.[4]

Mechanisms of NAPQI toxicity

NAPQI thus appears to be the major toxic metabolite. In overdose, larger amounts of paracetamol are metabolised by oxidation as a result of saturation of the sulphate/glucuronide conjugate pathway. Hepatotoxicity occurs when hepatic glutathione stores become depleted and the liver is no longer able to detoxify NAPQI. Hepatocellular injury may occur as a result of covalent binding of NAPQI to hepatocyte proteins, particularly mitochondrial proteins, resulting in cell injury. NAPQI is a powerful oxidant, particularly of cellular thiols and pyridine nucleotides, and this results in extreme oxidative stress and lipid peroxidation with the generation of superoxide anions. Finally, NAPQI depletes cellular protein and non-protein thiols; arylation (covalent binding) of thiols appears to be more damaging than s-thiolation. Depletion of cellular thiols results in inhibition of calcium ATPase and loss of the ability of mitochondrial proteins to sequestrate Ca^{2+}. This results in sequential increases in cytosolic Ca^{2+} concentrations, mitochondrial Ca^{2+} cycling, activation of proteases and endonucleases with consequent hepatocellular injury.[4]

Use of *N*-acetylcysteine

N-acetylcysteine is the antidote of choice in the treatment of paracetamol overdose. It protects against hepatotoxicity by replenishing intracellular glutathione stores and decreasing covalent binding of paracetamol to hepatic proteins.[5] Late administration of *N*-acetylcysteine potentially still offers some protection against hepatotoxicity, as glutathione generated from cysteine releases covalently bound NAPQI from arylated proteins and restores s-thiolated proteins to their reduced state. There are further mechanisms influencing microvascular integrity which may facilitate recovery of end-organ function.[6] In view of the potentially fatal outcome of paracetamol intoxication, we have proposed the following management scheme which should be both clinically effective and safe. It is hoped that the application of this protocol will prevent avoidable deaths from this mode of poisoning.

Protocol for the management of acute paracetamol poisoning

1. Suspected significant paracetamol overdose presenting less than 24 hours after ingestion.

(a) If a significant ingestion of paracetamol is suspected or if the patient is unconscious and neither the dose nor the time of ingestion are known, *or* if a delay in obtaining paracetamol blood levels is anticipated, then intravenous *N*-acetylcysteine therapy must be commenced immediately. Paracetamol levels must be estimated as an emergency investigation whenever possible, and the result plotted on the accompanying graph (Fig. 1). If the paracetamol level is well below the treatment line, liver damage is unlikely, and *N*-acetylcysteine should be stopped. If the paracetamol level is just below or above the treatment line, the intravenous infusion of *N*-acetylcysteine must be continued as liver damage is highly likely.

(b) A patient with a high level of paracetamol in the blood less than 4 hours after ingestion must receive N-acetylcysteine. However, sub-toxic levels less than 4 hours after ingestion of the overdose may be misleading because absorption is incomplete. Levels should therefore be checked again at 4 hours.

(c) Patients who have taken an overdose within 2 hours (8 - 12 hours if in coma or when there has been concomitant ingestion of other drugs which delay gastric emptying) of presentation to hospital must undergo gastric lavage and should receive activated charcoal, particularly if there is suspicion of ingestion of other drugs which may delay gastro-intestinal transit time and may be toxic in their own right (viz. opioids and tricyclics).

2. Delayed presentation after paracetamol overdose. Patients presenting after more than 24 hours should have liver enzymes, prothrombin, INR and blood paracetamol levels tested. If any paracetamol is detected, or if liver function test results are abnormal, or if ingestion of a toxic dose is suspected, the patient should be admitted to hospital for observation and management.

CLINICAL PRACTICE

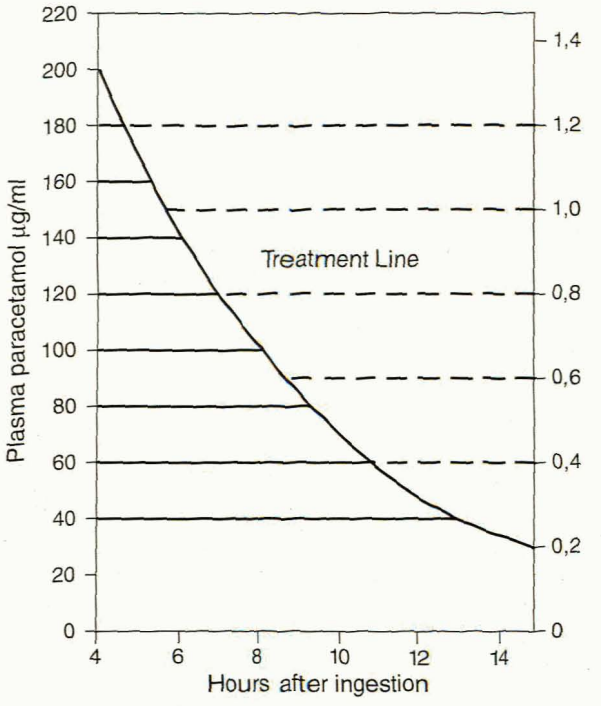

FIG. 1.
Graph on which estimated paracetamol levels should be plotted.

This patient may be reviewed by pharmacologists and physicians experienced in the management of liver failure and drug intoxication, and must receive early supportive therapy in hospital.

The use of *N*-acetylcysteine in these circumstances is controversial, but it should probably be given if paracetamol is still detectable in the blood.

3. Probable non-significant paracetamol overdose. If it is reasonably certain that less than 7,5 g have been taken, liver damage is unlikely. Activated charcoal should be administered to bind the drug in the gastrointestinal tract. If, however, blood levels show potentially toxic paracetamol levels, intravenous *N*-acetylcysteine must be administered.

4. Specific antidote. The dose of *N*-acetylcysteine (Parvolex), which is available in 10 ml ampoules containing 2 g (200 mg/ml), is administered as an infusion as follows: 150 mg/kg in 200 ml 5% dextrose water over 15 minutes. Then 50 mg/kg in 500 ml 5% dextrose water over 4 hours, then 100 mg/kg in 1 litre of 5% dextrose water over 16 hours. A total of 300 mg/kg Parvolex is therefore administered over approximately 20 hours. The serious side-effects from this infusion are uncommon but include allergic manifestations, anaphylactic reactions, ECG changes and electrolyte disturbances. Careful monitoring is indicated, particularly in patients with asthma. It should also be stressed that ECG and electrolyte changes may in any event be seen in paracetamol overdose.

Oral methionine, another precursor for hepatic glutathione, is inferior to *N*-acetylcysteine because of the risks of vomiting and impaired conversion to glutathione in the setting of liver dysfunction.

5. Supportive therapy. This is important and includes adequate fluid, electrolyte and vitamin replacement. Antihistamine anti-emetics are recommended if required. Conventional anti-liver failure treatment should be initiated if the coagulation disturbances are pronounced (INR 2,5 on the second or third day after overdose), or if liver enzyme levels are extraordinarily high (AST greater than 5 000 U/l). At this point a specialist centre with intensive care facilities should be contacted.

Conclusions

These recommendations are guidelines only, as clinical judgement is most important. If in doubt, it is better to err on the side of caution and to administer *N*-acetylcysteine intravenously while awaiting drug levels. A significant paracetamol overdose is a true medical emergency as the development of acute established liver failure has a high mortality rate.

C. W. SPEARMAN
S. C. ROBSON
R. E. KIRSCH
P. PILLANS

MRC/UCT Liver Research Centre, Emergency Unit
Departments of Medicine and Pharmacology
University of Cape Town

1. Hift RJ, Robson SC, Kirsch RE. Drug-induced liver disease. *CME/VMO* 1992; **10:** 1567-1578.
2. Bray GP, Harrison PM, O'Grady JG, Tredger JM, Williams R. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. *Hum Exp Toxicol* 1992; **11:** 265-270.
3. Davidson DGD, Eastham WN. Acute liver necrosis following overdose of paracetamol. *BMJ* 1966; **2:** 497-499.
4. Nelson SD. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. *Semin Liver Dis* 1990; **10:** 267-278.
5. Keays R, Harrison PM, Wendon JA, *et al.* Intravenous acetylcysteine in paracetamol-induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991; **303:** 1026-1029.
6. Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990; **335:** 1572-1573.