ABC of Poisoning

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ANALGESICS: II—PARACETAMOL

Paracetamol is a safe and effective mild analgesic, available over the counter and widely used as self medication. It has few adverse effects in regular use in the proper dosage, but an acute overdose can be fatal. Since the first cases of hepatic damage due to paracetamol were described in 1966, there has been an increase in the number of deaths due to poisoning with this drug and the number now runs at about 200 cases per year. Effective antidotes are available and management of patients who have taken an overdose of paracetamol requires care when the patient is first seen and on arrival in hospital, to ensure that treatment is given as soon as possible.

Paracetamol is the main cause of acute hepatic necrosis in the United Kingdom. Paracetamol is toxic to two main target organs. It can cause severe damage to the liver if there is insufficient glutathione to prevent the production of a reactive metabolite. By a similar mechanism it can also cause renal tubular necrosis. Treatment with antidotes is aimed at raising intracellular glutathione and thereby preventing cell necrosis in the liver and kidney.

Clinical features

Paracetamol poisoning—symptoms		
0- 24 hours	May be nothing Sometimes vomiting, sweating	
24- 36	May be nothing Possibly upper abdominal pain	
36- 72	Onset of liver or renal failure	
72- 120	Jaundice Bleeding Liver failure Renal failure	

In many cases there are no symptoms for many hours, and it is important not to be deceived into inactivity by the lack of symptoms. There may, however, be nausea, vomiting, abdominal pain, and sweating in the first few hours after overdosage. Metabolic acidosis or coma may very rarely follow massive overdosage but coma is much more likely to be caused by the concomitant ingestion of another drug or ethanol. As antidotal treatment can be given for paracetamol overdosage, it is important to check the plasma paracetamol concentration urgently in all unconscious patients if there is a possibility that they have taken paracetamol.

By 20-24 hours after ingestion there may be right upper quadrant pain due to early liver damage. Nausea and vomiting may be continuing or develop for the first time. Jaundice may be apparent by 36-48 hours. The manifestations of acute hepatic necrosis may then subside or steadily increase till they reach a peak by four to five days after ingestion, with death occurring in a hepatic coma. Renal failure is less common, and is usually marked by a transient rise in plasma urea and creatinine concentrations. More rarely full blown tubular necrosis may occur, sometimes with only minimal evidence of liver toxicity. The earliest biochemical signs of hepatotoxicity are a rise in prothrombin time and an increase in unconjugated bilirubin. The serum enzyme activities increase a little later.

Children—The symptoms are similar to those in adults, but serious toxicity is rare, and only two deaths have been recorded due to paracetamol poisoning in children. Whether this is because children are resistant to paracetamol toxicity or because the amount taken is lower is not known.

Management of a case of paracetamol poisoning

Paracetamol poisoning: antidotes

	Methionine	Acetylcysteine
Route	Oral	Intravenous
Dose	10g over 12h	300mg/kg over 20h
Time	Up to 12h	Up to 12 (?15)h
Problems	Patient must be conscious or drug given by tube	Complex regimen, supervision needed
Adverse effects	Vomiting	Allergic reactions
Cost	80p	Over £30

Treatment regimens in paracetamol poisoning

Methionine

Supplied as 250 mg tablets.
Give 10 tablets on history of overdose,
followed by 10 tablets 4 hourly
(total dose of 40 tablets=10 grams)

Acetylcysteine

Supplied as 10ml ampoules containing 2g (200 mg/ml) Start infusion as soon as possible: 150 mg/kg over 15 minutes, followed by 50 mg/kg in 500 ml 5% dextrose over 4 hours, followed by 100 mg/kg in 1 litre 5% dextrose over 16 hours (total 300 mg/kg over 20 1/2 hours).

Warning. Check the dose regimen carefully. Iatrogenic overdoses have occurred

-Mant TGK, et al Br Med J 1984; 289: 217-9

Patients presenting outside hospital

When a patient presents with a history of paracetamol overdose, particularly within the previous 12 hours, immediate hospital referral is essential, even though the patient may be asymptomatic.

Patients in hospital

- (1) Gastric lavage or syrup of ipecacuanha should be used for paracetamol overdose ingested within the last six hours, and an urgent plasma paracetamol concentration measured at four hours should be used to determine further treatment. Earlier samples may prove that paracetamol has been taken but are unreliable as a guide to treatment since absorption may still be occurring.
- (2) When the patient presents in hospital with a history of paracetamol ingestion in the last 12 hours, treatment should be started at once with oral methionine or intravenous acetylcysteine (see treatment chart). A blood sample should be taken for urgent plasma paracetamol assay and the course of treatment can be stopped if the level is below the line.
- (3) In cases of very large overdose or very high plasma paracetamol concentrations acetylcysteine should be given since more rapid and certain protection is provided by the intravenous route.
- (4) Estimates of vomiting in paracetamol poisoning vary. If vomiting is persistent or if the patient is comatose from any cause acetylcysteine should be used in preference to methionine.
- (5) More than one drug is often taken in overdose. In every unconscious patient presenting with a suspected drug overdose, the paracetamol concentration should be measured urgently, and treatment for paracetamol poisoning started on the basis of the result.

Other analgesics

For any analgesic agent clinical use will invariably be associated with acute overdose. Drug research and monitoring should lead to safer analgesics in the future

Analgesic drugs are all likely to be taken in overdose. The patient should be carefully monitored in suspected overdose with novel compounds. *Nefopam* (Acupan) is chemically related to orphenadrine. Its mode of action as an analgesic is unknown. Taken in overdose it has a characteristic pattern of toxicity and may cause widening of the pulse pressure, tachycardia, hyperreflexia, dilated pupils, and convulsions. Few cases have been reported including one fatal.¹ Gastric lavage is recommended. Treatment is symptomatic, and propranolol may help if cardiovascular symptoms are pronounced.

¹ Piercy DM, Cumming JA, Dawling S, Henry JA. Death due to overdose of nefopam. *Br Med J* 1981;283:1508-9.