

# Poisoning: focus on paracetamol

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**ABSTRACT** Presentations with acute self harm are a worldwide problem. In developed countries drug overdose is a common form of self harm, and in the UK the most frequently involved agent is paracetamol, implicated in around one-third of presentations. Risk factors for paracetamol hepatotoxicity include starvation, eating disorders, and enzyme induction from drugs and alcohol. Treatment is based on assessment of these and time since ingestion. Antidotal therapy is with acetylcysteine. Assessment of treatment efficacy is based on measurement of liver function tests and serum creatinine. Adverse reactions to the antidote acetylcysteine are frequent, thus understanding their mechanisms and treatment is important. Treatment of patients presenting after 20 hours is aimed at preventing hepatic encephalopathy. Patients presenting with severe liver damage should be considered for referral to a specialised centre.

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**LIST OF ABBREVIATIONS** British National Formulary (BNF), central nervous system (CNS), electrocardiogram (ECG), gamma glutamyl transferase (GGT), international normalised ratio (INR), National Poisons Information Service (NPIS)

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CME

## INTRODUCTION

All physicians working in acute medical areas will see patients with suspected poisoning. This is one of the most frequent diagnoses in acutely presenting medical patients. The majority of cases are due to deliberate self-harm, although accidental poisoning is also seen. Accidental poisoning in the home is a common problem in children below the age of five. Deliberate self harm begins to feature as a major problem in adolescence, with incidence peaking between the ages of 15 and 30. Mortality is more frequent in the elderly who are more likely to have planned their actions and also have more toxic prescription medicines available. An increasing proportion of patients are admitted with the adverse effects of drugs of abuse.

In the UK, Europe and North America the most frequent presentations include paracetamol and other simple analgesics, opioids including prescription drugs, benzodiazepines, antidepressants, antipsychotics, and drugs of abuse.

In this article I will concentrate on the most frequent causes of poisoning seen in Scotland, and on one that continues to cause problems in management, namely paracetamol.

## WHERE TO FIND INFORMATION

Information on the management of poisoning is available free to NHS staff from the NPIS on their dedicated online system TOXBASE ([www.toxbase.org](http://www.toxbase.org)) or via its dedicated 24-hour telephone line (0844 892 0111). This telephone line is manned by clinical scientists who are supported by a 24-hour rota of consultant clinical toxicologists within the UK who also provide a service to Ireland. There is also a dedicated e-learning website to help those unfamiliar with TOXBASE to learn how to use the database ([www.toxbase.co.uk](http://www.toxbase.co.uk)).

## GENERAL MANAGEMENT

As in all acute medicine careful patient assessment is necessary. Many patients ingest multiple agents so features from these may be present. Assessment should therefore include examination for specific 'toxidromes' (e.g. opioid, anticholinergic). Regular monitoring of level of consciousness, cardiovascular status, and oxygenation are important in the first few hours after ingestion of any potential CNS depressant. Appropriate first-aid management procedures should be instituted. 12-lead ECGs are required for patients who have taken cardioactive medicines, and these recordings need to be repeated at appropriate intervals if patients are becoming clinically more intoxicated. ECG machines with automated read-outs, particularly of QRS and QT intervals, are extremely useful for this purpose.

A clear history is an important component of management. Safe-keeping of tablet packets and identification of container labels may be crucial. Patients who present early (within one hour) after drug ingestion may benefit from administration of activated charcoal, which will bind drugs non-specifically in the stomach and prevent absorption.

## PARACETAMOL

Paracetamol is involved in between 30 and 40% of acute presentations with poisoning. A small proportion of these are due to accidental ingestion in the context of pain relief. The toxicity of paracetamol is well understood, but there remains significant ignorance among the general public, many of whom believe it is sedative and thus do not consult the hospital if they are asymptomatic after ingestion.

As little as 10–15 g (20–30 tablets) or 150 mg/kg paracetamol taken within 24 hours may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis.

## MECHANISM OF TOXICITY

Paracetamol is toxic to the liver as a result of conversion to a benzoquinonimine metabolite which is normally conjugated with the amino acid glutathione. The metabolism of paracetamol via this route is inducible, and therefore more rapid in patients on inducing drugs (e.g. phenytoin, carbamazepine, barbiturates, rifampicin, St John's Wort) or who are chronic alcoholics. Alcoholics who have recently stopped drinking are at greatest risk.

Supplies of glutathione in the liver depend on the patient's diet and there is suspicion that acute starvation may therefore represent an additional risk factor to the known ones of eating disorders and chronic malnutrition.

### Assessment of risk

Assessment of these risk factors is therefore necessary in determining whether to administer the antidote to paracetamol, acetylcysteine. It is generally acknowledged that patients should be treated in accordance with plasma concentration measurements as read from the paracetamol treatment nomogram, published in the BNF and available on TOXBASE. Patients who are below treatment lines based on (i) history of ingestion, (ii) an appropriate clinical assessment of nutritional state, and (iii) drug and alcohol history, do not require treatment.

## TREATMENT

Treatment is generally divided into four phases.

- 1 Before four hours have elapsed after ingestion, blood levels are not interpretable. It is unnecessary and inappropriate to administer acetylcysteine.

- 2 Between four and eight hours after exposure there is time to obtain a plasma concentration to decide if treatment is necessary.
- 3 After eight hours: only after this time should 'blind' treatment with acetylcysteine be commenced, and only then if the patient has ingested more than a potentially toxic amount: >150 mg/kg in a normal patient, less in an 'at risk' patient. Treatment can be stopped if the paracetamol level is below threshold.
- 4 Beyond 24 hours: acetylcysteine is most effective when given early in preventing liver damage. Its effect declines from about 12 hours and management approaches therefore change for presentations 24 hours or more after ingestion. Acetylcysteine is used at this time to treat acute liver failure, and not act as a specific paracetamol antidote. In patients who present late, it is reasonable to obtain blood results and determine treatment based on these. Samples should include liver function tests (ALT or AST (alanine or aspartate aminotransferase)), prothrombin time, serum electrolytes, and a paracetamol level, which may be undetectable even in severe liver failure.

### Acetylcysteine use

Acetylcysteine is normally administered for 20 hours. Pseudo-allergic reactions are relatively common (5–10%) and should be treated with antihistamines. A larger proportion of patients (~25%) suffer nausea or vomiting. True anaphylaxis has not been observed and a history of previous reactions is not a reason not to treat. Liver function tests (ALT or AST), prothrombin time, and serum electrolytes (creatinine) should be checked prior to discharge.

A small proportion of patients develop renal damage from paracetamol, in the absence of any major liver damage. Renal damage is a common complication of acute liver failure and an important index of its severity.

Patients who develop significant hepatic dysfunction (ALT >1,000 or INR >2) after acetylcysteine should be discussed either with the NPIS or a liver unit. Approximately 40 to 50 patients a year are referred into the Scottish liver unit with paracetamol-related acute liver injury, and around 20 patients die of hepatic failure from paracetamol per annum in Scotland.

## POTENTIAL PROBLEMS IN ASSESSMENT

In patients who are unconscious, or who have CNS depression from other ingested drugs, the exact timing of ingestion of paracetamol may be difficult to determine. In such circumstances treatment should not be delayed to obtain a clear history, but be based on a worst-case scenario with respect to timing of paracetamol ingestion. Acetylcysteine treatment can always be discontinued should a patient subsequently wake and change their story.

In patients in whom there is uncertainty about regularity of ethanol ingestion, the evidence suggests that patients with an elevated GGT are much more likely to develop hepatotoxicity, and therefore it is this group in whom particular care should be taken, and who should be treated as high risk.

Minor changes in prothrombin time may be caused by acetylcysteine. A patient who has a normal transaminase at admission, and no rise in transaminase over the period of admission, and a mildly abnormal INR (1.3 or less) after treatment may generally be regarded as not at risk of major liver injury.

Assessing nutritional status may be problematic and, in any patient who has a low blood urea, a detailed dietary history should be examined. Clinical experience also suggests that acute starvation, for example in patients with severe dental pain, may potentially contribute to a risk of hepatic damage. There are no formal studies in this area, but an interventionist approach to treatment is advisable.

Patients with chronic liver disease often have elevated transaminases. An elevated transaminase which does not rise further in the context of a patient with normal clotting after acetylcysteine should not be thought to be an indicator of liver damage.

The time course of renal damage is delayed after that of hepatic damage. Minor rises in serum creatinine after acetylcysteine should therefore be viewed with caution, and a repeat serum creatinine measured 6–12 hours later. Further rises in creatinine at this time indicate the likelihood of acute renal injury secondary to paracetamol.

Falls in serum potassium are routinely observed in paracetamol poisoning, and may be as much as 0.5 mmol/l. In the acute phase of poisoning these are due to renal potassium leak. In patients presenting later who develop hepatic injury a rising serum potassium is associated with renal failure.

### FURTHER READING

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In patients who have had a full course of acetylcysteine and who require further treatment with the agent as prophylaxis against hepatic encephalopathy there is no need to give a further loading dose of acetylcysteine. Such a loading dose is more likely to induce adverse effects as paracetamol levels will be low or absent. Genealogical data suggests that paracetamol itself is protective against adverse reactions to the antidote.

Patients who have had acetylcysteine therapy on a previous occasion, and suffered adverse effects previously, should (as stressed above) be given treatment if they re-present with paracetamol poisoning. Patients with asthma are more likely to develop symptoms, and although there really is no evidence to support its efficacy, most clinical toxicologists treating patients with this history would consider use of a prophylactic antihistamine and have a bronchodilator nebuliser available in the event of any asthmatic response. Pragmatically it is reasonable to stop infusion in a patient who is having a severe reaction but then recommence at a lower infusion rate as soon as is practicable. The reactions seem to be predominantly related to the plasma concentrations of acetylcysteine in that they occur early after the infusion is commenced. Studies show that delayed onset reactions of this nature are not generally seen.

### KEYPOINTS

- Paracetamol is involved in approximately one-third of overdoses in Scotland.
- Risk factors for hepatic damage include enzyme induction and dietary deficiency affecting hepatic glutathione levels.
- Treatment is based on a well-proven nomogram.
- Management is tailored upon time of presentation and risk factors.
- It is unnecessary to treat all patients who have ingested paracetamol as adverse reactions to the antidote are common.

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