# Non-opioid analgesic poisoning

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In most developed countries, analgesics top the list of the most frequent causes of poisoning. Currently, paracetamol overdose remains the most frequent, whilst ibuprofen has overtaken aspirin in keeping with changes in usage.

## Paracetamol (acetaminophen)

Since the first cases of severe and fatal liver damage were reported in 1966,[1,2] overdose of paracetamol has become the cause of 100–200 deaths in the UK each year.[3] Paracetamol toxicity remains the leading cause of fulminant hepatic failure in the UK and is a common reason for liver transplantation.[4,5] Knowledge of the toxic mechanism (Fig 1) has led to effective antidotes which provide substrates for increased glutathione production. Intravenous acetylcysteine (Parvolex®) is the treatment of choice in the UK. (Methionine is an oral alternative[7] that can be considered only within the first 12 hours of overdose.) Although treatment of acute paracetamol overdose is well defined, decisions are complicated by late presentation, staggered overdoses and marked variation in individual susceptibility (Table 1).

### *Management of overdose*

Table 2 lists the expected clinical features of paracetamol overdosage, but clinical information is of little help in determining the risk of toxicity. The interpretation of the plasma paracetamol concentration using a nomogram (Fig 2) is the established method for determining diagnosis, assessing risk (see Table 3 also) and deciding on management.

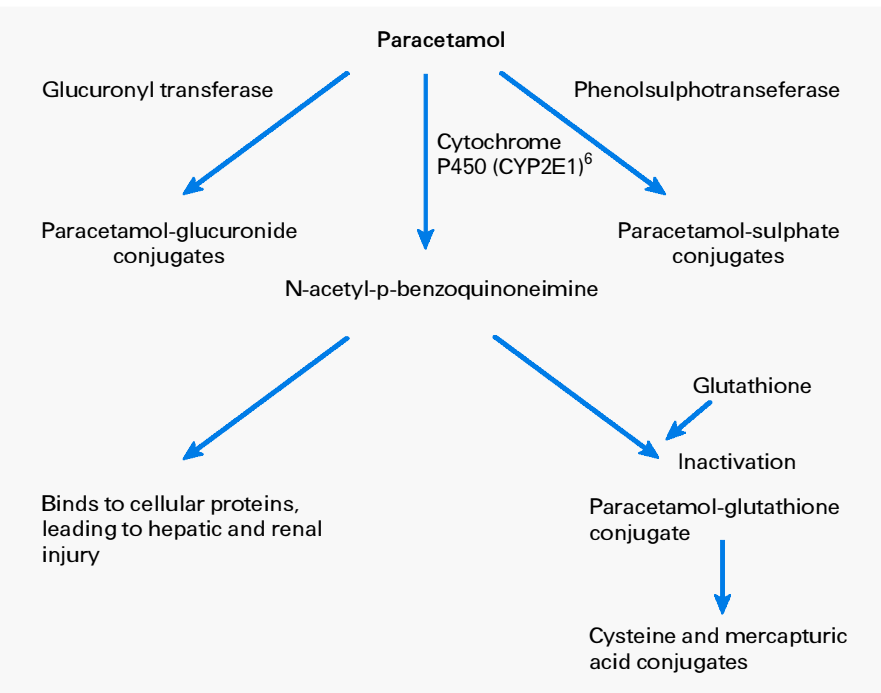


**Fig 1. Metabolism of paracetamol to non-toxic and toxic metabolites.**

Activated charcoal can be given within one hour of ingestion. This is unnecessary in most children because self-administration of paracetamol elixir by a child rarely results in toxicity. Blood should be taken no earlier than four hours post-ingestion for measurement of the plasma paracetamol concentration in any patient following a single ingestion of more than 150 mg/kg or 12 g, whichever is smaller. The risk of liver damage can then be assessed using the paracetamol nomogram. Acetylcysteine should be commenced if the concentration is above the treatment line. An alternative treatment line exists for 'high-risk' patients (those fulfilling any of the criteria listed in Table 1). Doses as low as 75 mg/kg may be hepatotoxic in such patients; although there is little evidence supporting this figure, there are reasonable empirical reasons to accept it.

The plasma paracetamol concentration provides a good diagnostic indicator, and treatment is successful in patients presenting early with an accurate history, particularly with regard to time of ingestion which is essential for interpreting a paracetamol concentration. If the time of ingestion is unknown, or paracetamol has been taken chronically or in a staggered fashion (eg >2 hours between doses), the plasma paracetamol concentration cannot be interpreted accurately. Acetylcysteine should therefore be given if the total dose in 24 hours exceeds 150 mg/kg or 12 g,

**Table 1. Some of the high-risk groups in paracetamol overdose.**

- Malnourished patients (including anorexia nervosa/bulimia)
- Patients taking enzyme-inducing drugs (eg carbamazepine, phenytoin, barbiturates, primidone, glutethimide, rifampicin and the herbal preparation, St John's Wort)
- Patients with induced liver enzymes due to chronic ethanol abuse
- HIV-positive patients

**Table 2. Clinical features of paracetamol poisoning.**

| Time post-overdose | Clinical features |
|---|---|
| Within the first 24 hours | • Often no symptoms, even following potentially fatal doses<br>• There may be:<br>– nausea<br>– vomiting<br>– abdominal pain<br>– pallor<br>– rarely, drowsiness, coma, metabolic acidosis |
| 16–24 hours | A rise in:<br>• prothrombin time<br>• bilirubin levels<br>• transaminase activity |
| Within 48 hours | If changes occur in LFTs, hepatic and/or renal tenderness may develop |
| At 3–5 days | Peak hepatotoxicity with:<br>• jaundice<br>• coagulation abnormalities<br>• hepatic failure<br>• renal failure (also in the absence of liver toxicity)<br>• hypoglycaemia<br>• encephalopathy<br>• coma |
| Also reported | • thrombocytopenia<br>• DIC<br>• hypokalaemia<br>• hypophosphataemia<br>• pancreatitis<br>• myocarditis |

DIC = disseminated intravascular coagulation; LFT = liver function test.

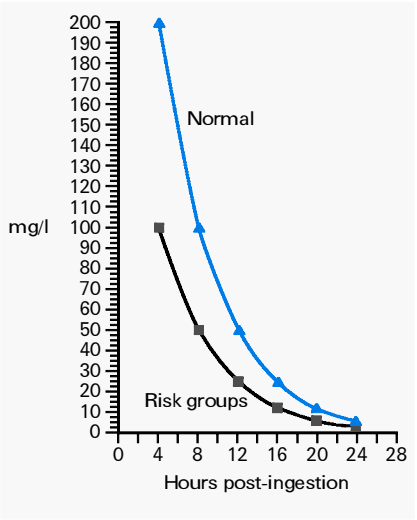


**Fig 2. Paracetamol treatment nomogram.**

whichever is the smaller (>75 mg/kg for high risk patients).

If the patient presents more than eight hours from ingestion, treatment should be commenced immediately (since the efficacy of the antidote begins to decrease at this time), but stopped if the paracetamol concentration is later found to be non-toxic. There are no data supporting the nomogram beyond 15 hours, after which time the line on the treatment graph is extrapolated (up to 24 hours post-ingestion). Results should therefore be interpreted with caution and a wider margin of error. The international normalised ratio, plasma creatinine, plasma venous bicarbonate, liver function tests and renal function are all useful markers of potential hepatotoxicity in such patients. Management of patients presenting more than 24 hours after ingestion should not be based on the paracetamol blood concentration or the paracetamol nomogram but on the results of measuring the above set of markers.

In some cases it is necessary to contact a specialist liver unit. The criteria for referral, which are all indications of severe hepatotoxicity and poor prognosis, are outlined in Table 4.

## Non-steroidal anti-inflammatory drugs

The use of NSAIDs is now wide and varied. Unsurprisingly, the pattern of usage is reflected in the circumstances and frequency of NSAID overdose.

### *Ibuprofen*

Ibuprofen overdose has become common since it was licensed for over-the-counter use, although severe poisoning is rare.[9]

In 60–80% of patients symptoms are mild or absent. In the seven reported deaths, additional factors such as co-ingestants or refusal of treatment were involved.[10] In contrast to aspirin and paracetamol, ibuprofen shows no evidence of a toxic mechanism in overdose that is different from its pharmacological mechanism. The overdose effects (Table 5) can be attributed either to inhibition of prostaglandin synthesis or to the acidic nature of the drug and its metabolites.

Toxic effects are unlikely at doses below 100 mg/kg, but may be severe above 400 mg/kg. Attempts have been made to relate blood ibuprofen concentrations to severity of poisoning, but there is no benefit in measuring blood ibuprofen.[12]

**Table 3. Risk assessment of paracetamol overdose.[8]**

| Level of overdose | Risk |
|---|---|
| <150 mg/kg (in patients not at high risk) | Liver damage unlikely |
| >150 mg/kg (or 12 g total) | Liver damage possible |
| >350 mg/kg | Severe liver damage in almost all cases |

**Table 4. Criteria for liver unit referral.**

- If the INR is >2 at 24 hours, >4 at 48 hours, or >6 at 72 hours post-ingestion

*OR*

- PT in seconds (Manchester reagent) is greater than the number of hours since overdose

*OR if any of the following are present*:

- Elevated plasma creatinine (>200 μmol/l)
- Hypoglycaemia
- Acidosis even after resuscitation
- Hypotension (mean arterial pressure <60 mmHg) even after resuscitation
- Encephalopathy

INR = international normalised ratio; PT = prothrombin time.

*Management.* The management of ibuprofen overdose is straightforward. Observation (4 hours) is required only for doses above 100 mg/kg. Oral fluids should be encouraged and renal function monitored.

**Table 5. Summary of symptoms* in ibuprofen overdose** (adapted from Ref 11).

| System | Symptoms |
|---|---|
| GI** | • Nausea, vomiting, abdominal pain<br>• No reports of ulceration, haemorrhage or strictures occurring *de novo* |
| Renal** | • Decline in function often clinically unimportant<br>• Failure occurs after large doses with acidosis or additional factors (eg infection, dehydration, binge drinking or pre-existing renaldisease) |
| Metabolic | • Rare acidosis after massive doses |
| CNS** | • Mild drowsiness to light coma<br>• Headache<br>• Dizziness<br>• Blurred vision<br>• Nystagmus<br>• Tinnitus |

* Many patients will be asymptomatic.
** Effects often dose related.
CNS = central nervous system;
GI = gastrointestinal.

### *Other non-steroidals*

NSAIDs in general (except mefenamic acid and phenylbutazone) are similar to ibuprofen in their toxic effects and management. Initial reports of overdose of the newer cyclooxygenase (Cox) II inhibitors provide no evidence of unexpected toxic effects.

*Mefenamic acid.* Mefenamic acid (Ponstan®) is used in the treatment of dysmenorrhoea, and overdoses mostly occur in young women. Symptoms are usually relatively benign and include gastrointestinal disturbance, dizziness, drowsiness and tachycardia. There is, however, a high incidence of convulsions, rarely leading to cardiac or respiratory arrest,[13] though there are no reported deaths. Management includes observation, and diazepam for recurrent convulsions.

*Phenylbutazone.* In the UK phenylbutazone is licensed only for use in hospital, but it is often prescribed to holidaymakers abroad. Clinical effects are similar to salicylate toxicity, with severe poisoning characterised by multi-organ failure. Treatment is supportive.

## Aspirin

Aspirin (acetylsalicylic acid) has analgesic, anti-inflammatory, antipyretic and thrombolytic properties. It is not licensed as a general-purpose analgesic in children because of an epidemiological association with Reyes syndrome, but is still used for treatment of juvenile arthritis. The clinical course (see Table 6) of salicylate overdose is complex: the degree of metabolic disturbance determines toxicity, not just the salicylate level. The acute fatal dose of aspirin in adults has been estimated at 500 mg/kg.[14] Young children and the elderly are most susceptible.

### *Mechanism of toxicity in overdose*

In overdose, salicylate stimulates the respiratory centre, causing hyperventilation and a respiratory alkalosis. The body compensates by excreting bicarbonate, sodium and potassium ions, and water, resulting in electrolyte

**Table 6. Clinical effects of aspirin toxicity.**

| Overdose | Clinical effects |
|---|---|
| **Mild** (>150 mg/kg) | Nausea, vomiting, epigastric pain, tinnitus, flushing |
| **Moderate** (>250 mg/kg) | Sweating, hyperventilation, dehydration, deafness, tremor, respiratory alkalosis with metabolic acidosis (acidosis predominant in children) |
| **Severe** (>500 mg/kg) | • Hypo/hyperglycaemia, hypokalaemia, hypo/hypernatraemia, hypoprothrombinaemia, pyrexia (mostly in children), confusion, drowsiness, delirium, coma, convulsions (more common in children)<br>• CNS effects are usually relieved if the acidosis is corrected<br>• Rarely, renal failure, pulmonary oedema or cardiovascular collapse<br>• Death is usually due to cardiopulmonary arrest |

CNS = central nervous system.

imbalance, dehydration and a decrease in buffering capacity. There is then an anion gap metabolic acidosis, which enhances transfer of the salicylate ion across the blood–brain barrier resulting in central nervous system (CNS) effects.

Salicylate uncouples oxidative phosphorylation, leading to:

- decreased adenosine triphosphate (ATP) production
- increased oxygen utilisation
- increased carbon dioxide production (contributing to hyperventilation), and
- increased lactate production (contributing to metabolic acidosis).

The energy that would otherwise be used to produce ATP is dissipated as heat, causing flushing, sweating and further dehydration. Fluid loss also occurs from vomiting, and nausea may diminish fluid intake.

Aspirin is insoluble in acid and may form concretions in the stomach, prolonging absorption. It is rapidly converted to salicylic acid, which is then further metabolised to five main metabolites. The early metabolic pathways involve saturable hepatic enzymes, so in overdose they quickly become overloaded. This results in a change from first-order kinetics (in which elimination is proportional to the plasma concentration) to zero-order kinetics (in which only a certain amount is eliminated, irrespective of the concentration). Thus, salicylate may accumulate following mild therapeutic overdoses, particularly in children, and prior therapeutic use may increase the toxicity of an acute overdose. Also, under zero-order kinetics the amount of salicylate excreted unchanged in the urine increases. This phenomenon is sensitive to changes in urine pH: as the pH rises, excretion of salicylate is enhanced.

### *Management of overdose*

In smaller overdoses, activated charcoal is used for initial prevention of absorption; gastric lavage may be required in large aspirin overdoses. Repeat doses of activated charcoal have been recommended for preventing delayed absorption.[15] Because of the tendency for continued absorption, salicylate concentrations must be measured every 2–3 hours until they have peaked. Rehydration is vital, with central venous pressure monitoring in moderate and severe cases, particularly in the elderly or those with cardiac disease. Renal function and metabolic status (urea and electrolytes, arterial blood gases, blood glucose, prothrombin time) should be closely monitored and corrected as necessary. Correction of a metabolic acidosis usually resolves CNS effects (since acidosis increases transfer of salicylate across the blood–brain barrier). Salicylate elimination may be further enhanced by administration of sodium bicarbonate (**not** forced diuresis) to make the urine alkaline. In severe cases, haemodialysis is useful, both to remove salicylate and to ameliorate the metabolic disturbances.

## Key Points

**Management of paracetamol overdose depends upon the number of hours post-overdose at which the patient presents**

**Paracetamol blood concentrations must be measured for patients with a history of ingestion of over 150 mg/kg or 12 g, whichever is smaller (>75 mg/kg in high-risk groups). These cannot accurately be interpreted following staggered overdosage or if the time of ingestion is unknown**

**Acetylcysteine is an effective antidote against paracetamol toxicity**

**Supportive treatment and a brief period of observation is usually all that is necessary in cases of non-steroidal anti-inflammatory drug (NSAID) overdose, with the exception of mefenamic acid and phenylbutazone**

**Blood concentrations of NSAIDs are not clinically useful**

**Aspirin management is complicated and guided by blood concentrations, measurement of which must be repeated until concentrations are decreasing, and metabolic status**

**Urinary alkalinisation and/or charcoal haemoperfusion may be necessary in severe cases of aspirin overdose**

**KEY WORDS: aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), overdose, poisoning**

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# Acute effects of drugs of abuse

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The terms 'recreational drugs' and 'drugs of abuse' are, to some extent, societal. Substances known to be toxic (eg ethanol) may be legal and culturally accepted in some countries but illegal in others. Similarly, therapeutic use of heroin (diamorphine) as an analgesic or a cannabinoid as an antiemetic is deemed legal and acceptable.

Drugs of abuse are widely available. Data from the British and Scottish crime surveys suggest that 22% of 16–29 year olds have used cannabis within the previous 12 months but that opiate use is much rarer.[1,2] Exact quantification of acute drug abuse deaths remains difficult due to the methods of classification, but several hundred people die acutely from drugs of abuse each year in England and Wales and the number is rising for heroin.[3]

## Adverse effects of drugs of abuse

The adverse effects of drugs of abuse are both acute and chronic. Adverse effects on the user include risks associated both with the drug itself and with the route of administration. Intravenous drug abusers in particular are at increased risk.[4] Drugs are often administered in secluded places where even transient respiratory depression may prove fatal. Infections associated with drug misuse include viral hepatitis, HIV, bacterial endocarditis, typically affecting the right side of the heart, and local infections at the site of injection.

Societal effects of drug abuse include those from the effect of crime undertaken to support an illegal and potentially expensive activity, and also indirectly due to the spread of infection into the wider community. Many treatment strategies for drug abusers (eg needle exchange schemes) focus upon harm reduction rather than an attempt to end misuse completely. Even these schemes are not without their own problems – methadone, prescribed as a heroin substitute, is now a regular cause of death.[5]

For overdose from drugs of abuse, the mainstay of treatment remains good supportive care. The importance of obtaining an accurate history and in maintaining airway, breathing and circulation cannot be overemphasised.

## Key Points

- **Abuse of drugs is common**
- **The diagnosis of drug abuse should be considered in patients with decreased consciousness**
- **The diagnosis of drug abuse should be considered in agitated patients**
- **Treatment is generally supportive and symptomatic**
- **Harm may arise from both the route of administration and the drug itself**
- **Street drugs are not pure products**
- **Consider associated infectious diseases**
- **Anticipate withdrawal syndromes**

**KEY WORDS: cannabis, cocaine, drugs of abuse, ecstasy, gamma hydroxybutyrate (GHB), heroin, lysergic acid diethylamide (LSD), overdose, poisoning**