Paracetamol Poisoning

Synonyms: acetaminophen poisoning

Background
Paracetamol is widely available and has been around since the 1950s. It is widely prescribed and cheap to buy over the counter, making it a common drug taken in overdose. It is a very useful analgesic (alone or in combination) and also is an antipyretic. It is normally found as a 500 mg tablet but it is often combined with other active ingredients in various preparations.

In the UK it is one of the most common agents of intentional self-harm. In England and Wales, there were 219 deaths from poisoning by paracetamol and its compounds in 2016[1]. This represents an 11% increase from the previous year. In an English GP study, it featured as the most common agent of self-harm among 10- to 24-year-olds[2]. Paracetamol poisoning is the most common cause of acute liver failure (ALF).

To reduce the incidence of paracetamol overdose, legislation was passed in the UK in 1998 to limit the number of tablets that could be bought in one purchase: 16 tablets at present (up to 32 tablets in pharmacies). Furthermore, paracetamol was supplied in blister packs making obtaining the actual tablets take longer.

Limiting pack size has reduced sizes of overdoses and numbers of deaths and liver transplantations in England and Wales but not in Scotland[3]. Some authors, however, have disputed the decline[4].

It is important to remember that, when used at therapeutic levels, paracetamol is usually safe and effective. However, taking >100mg/kg or >4 g per day for a few days has been known to result in hepatotoxicity.

Paracetamol overdose may occur intentionally and accidentally - the latter due to the high number of combination products available over the counter. There are also frequent cases of accidental poisoning in children.

Toxicity

Risk of severe liver damage (ie a peak ALT more than 1000 IU/L)

Based on the dose of paracetamol ingested (mg/kg body weight):
- Less than 150 mg/kg - unlikely.
- More than 250 mg/kg - likely.
- More than 12 g total - potentially fatal.

Yet paracetamol can cause serious or fatal adverse effects at around 150 mg/kg for many adults. There is considerable inter-patient variability which depends on age, health and substances taken with the paracetamol.

The level is higher for young children.

There is a theoretical argument for increased risk with enzyme induction or low glutathione reserves. There are case reports of those with chronic alcoholism taking relatively small overdoses or even therapeutic doses of paracetamol who develop liver failure. However, close examination of these case reports shows up some inconsistencies and suggests that it is unclear that these all provide any substantial evidence supporting the hypothesis. One literature review concluded that there was little good-quality clinical evidence to suggest that any groups of people were at greater risk of liver injury than others[5].

Pathophysiology

After taken orally, paracetamol is well absorbed from the stomach and small intestine. It reaches a peak plasma concentration in one hour but this may be 30 minutes if taken in liquid or rapidly absorbed form. It is mainly inactivated by the liver by conjugation leading to two metabolites; glucuronide or sulfate. It is then renally excreted through urine.

- When taken in overdose the liver conjugation becomes inundated, causing paracetamol to be metabolised by an alternative pathway.
- This results in a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is itself inactivated by glutathione, rapidly preventing any harm.
When glutathione stores are depleted to less than approximately 30%, NAPQI reacts with nucleophilic aspects of the cell, leading to necrosis. Necrosis occurs in the liver and in the kidney tubules.

Toxicity has been thought to be increased in patients with induction of the P450 system through drugs such as rifampicin, phenobarbital, phenytoin, carbamazepine and alcohol. This may occur in patients with low glutathione reserves, as a product of:

- Genetic variation.
- HIV-positive status.
- Malnutrition.
- Alcohol-related or other liver disease.

However, recent work has shed doubt on whether the induction of the P450 system has any effect on paracetamol toxicity[5].

Paediatric patients (under the age of 5 years) seem to fare better after paracetamol poisoning, perhaps due to a greater capacity to conjugate with sulfate, enhanced detoxification of NAPQI or greater glutathione stores. However, it should not be assumed that treatment in children should be different than for adults, since no controlled studies have supported any alternative paediatric therapy.

Clinical features

- Commonly, patients are asymptomatic for the first 24 hours or have nonspecific abdominal symptoms (such as nausea and vomiting).
- Hepatic necrosis begins to develop after 24 hours (elevated transaminases, right upper quadrant pain and jaundice) and can progress to acute liver failure.
- Patients may also develop:
  - Encephalopathy.
  - Oliguria.
  - Hypoglycaemia.
  - Renal failure - usually occurs around day three.
  - Lactic acidosis.

Assessment

History

- Number of tablets, formulation, any concomitant tablets (include herbal remedies as substances, such as St John's wort - an enzyme inducer).
- Time of overdose.
- Suicide risk - was a note left?
- Any alcohol taken. Acute alcohol ingestion may inhibit liver enzymes and may reduce the production of the toxin NAPQI, whereas chronic alcoholism may increase it (although the evidence base supporting these concerns is theoretical rather than based on experience).

Examination

- Usually there is very little to find, until the patient develops ALF.
- If ALF develops, the following may be seen: jaundice, hepatic flap, encephalopathy and tender hepatomegaly.

Investigations

- Paracetamol level: take paracetamol level four hours post-ingestion, or as soon as the patient arrives if:
  - Time of overdose is greater than four hours.
  - Staggered overdose (in staggered overdoses, the level is not interpretable except to confirm ingestion).

- U&E, creatinine - to look for renal failure and have a baseline.
- LFTs: may be normal if the patient presents early but may rise to ALT >1000 IU/L. This is the enzyme level taken to indicate hepatotoxicity.
- Glucose: hypoglycaemia is common in hepatic necrosis - capillary blood glucose should be checked hourly.
- Clotting screen: prothrombin time is the best indicator of severity of liver failure and the INR should be checked 12-hourly.
- Arterial blood gas; acidosis can occur at a very early stage, even when the patient is asymptomatic. It is seen in up to 10% of patients with ALF.
- FBC and salicylate levels are not routinely required.

Ongoing studies are examining the use of toxicity biomarkers to make a more accurate prediction about paracetamol overdose, to overcome the reliance on information about time since ingestion and initial dose (which is often obtained from the patient or third parties and may be highly inaccurate)[6].
Management

Immediate management of a person who has taken a potentially toxic dose of a substance within the previous hour, is covered in the separate Acute Poisoning - General Measures article.

The Medicines and Healthcare products Regulatory Agency (MHRA) changed the guidelines on management of paracetamol overdose in September 2012[7]. These are much simplified and include an updated, single line nomogram.

It should be noted that this nomogram is ultra-conservative and that there is lack of consensus internationally on the management of paracetamol overdose.

All patients who have a timed plasma paracetamol level plotted on or above the line drawn between 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion, should receive acetylcysteine. This is regardless of any risk factors they may have for hepatotoxicity.

If there is any doubt about the timing of the ingestion (including a staggered overdose over one hour or more), acetylcysteine should be given without delay. There is no need to refer to the treatment nomogram.

Paracetamol poisoning linked to modified-release paracetamol, intravenous paracetamol, massive paracetamol doses (>1 g/kg) and multiple drug overdose should be discussed with a toxicology expert whenever possible.

Refer to ICU if there is fulminant liver failure - those treated with N-acetylcysteine (NAC) to the medical team and all para-suicides to the psychiatric team.

N-acetylcysteine treatment

NAC is believed to work by a number of protective mechanisms. It acts as a precursor for glutathione, promoting normal conjugation of any remaining paracetamol, and also supplies thiols that function as antioxidants. It is virtually 100% effective in preventing liver damage when given within eight hours of ingestion[7]. After eight hours, efficacy decreases sharply.

Three consecutive intravenous infusions should be given, as follows[8]:

- First infusion: initial loading dose of 150 mg/kg body weight over 1 hour.
- Second infusion: 50 mg/kg over the next 4 hours.
- Third infusion: 100 mg/kg over the next 16 hours.
- The patient should receive a total dose of 300 mg/kg body weight over a 21-hour period. A ceiling weight of 110 kg should be used when calculating the dose for obese patients.
- Continued treatment with NAC (given at the dose and rate as used in the third infusion) may be necessary, depending on the clinical evaluation of the individual patient.

There are now no specific contra-indications to acetylcysteine use. Even if there is a previously reported reaction, the benefits of treatment outweigh the risks.

Specific weight-related dosing tables are available to guide the health professional[9]. Children receive the same doses and treatment as adults but with a reduced quantity of intravenous fluid, as fluid overload is a potential risk.

A full treatment course comprises three consecutive doses, administered sequentially, with no break between infusions.

Treatment usually continues for the duration once NAC is started, regardless of any plasma levels. This usually takes 24 hours. NAC may be stopped if started before an appropriate paracetamol level is done, if the level is below the treatment line (when the nomogram is valid) and the patient has normal LFTs and is asymptomatic. NAC is usually continued if blood tests are still significantly abnormal after the first course. The dose depends on local protocols but is often at the rate of the third (last given) bag.

Prior to discharge it is sensible to re-check the INR, renal tests and LFTs. Patients should be advised to return if vomiting occurs after discharge.

Late presentation

The treatment of patients presenting more than 24 hours after ingestion is controversial. Management is detailed on Toxbase® and is similar to presentation between 8 and 24 hours after the overdose.

- Measure INR, creatinine, ALT and venous blood acid/base balance or bicarbonate.
- If any of these is abnormal discuss with your nearest National Poisons Information Centre (0870 600 6266).
Until concerns about the evidence base are resolved, it makes sense to beware if:

- The patient is on long-term treatment with enzyme inducers - eg, carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John’s wort.
- The patient regularly consumes alcohol in excess.
- The patient has pre-existing liver disease.
- The patient is likely to be glutathione-depleted - eg, eating disorders, cystic fibrosis, HIV infection.

**NB:** the plasma paracetamol concentration >24 hours after overdose is likely to be below the limit of detection, even after substantial overdose. A measurable paracetamol concentration more than 24 hours after ingestion either indicates a very large overdose, or suggests a mistake in time of ingestion, or a staggered overdose. A full course of antidotal therapy should normally be given to patients in whom paracetamol is detected.

**Paracetamol overdose during pregnancy**

Paracetamol is the most common drug taken in overdose during pregnancy\(^{[10]}\). The resulting toxic metabolites can cross the placenta and lead to hepatocellular necrosis of maternal and fetal liver cells.

NAC can bind the toxic metabolites in the mother and fetal circulation as it crosses the placenta. NAC appears to be safe during pregnancy and therefore should be administered.

**Criteria for referral to a specialist unit**

- Encephalopathy or raised intracranial pressure (ICP). Signs of CNS oedema include BP >160/90 mm Hg (sustained) or brief rises (systolic >200 mm Hg), bradycardia, decerebrate posture, extensor spasms, and poor pupil responses. ICP monitoring can help.
- INR >2.0 at or before 48 hours or >3.5 at or before 72 hours (so measure INR every 12 hours). Peak elevation occurs around 72-96 hours. LFTs are not good markers of hepatocyte death.
- Renal impairment (creatinine >200 μmol/L). Monitor urine flow and daily U&E and serum creatinine (use haemodialysis if >400 μmol/L).
- Blood pH <7.3 (lactic acidosis results in tissue hypoxia).
- Systolic BP <80 mm Hg despite adequate fluid resuscitation.
- Hypoglycaemia.
- Metabolic acidosis (pH <7.3 or bicarbonate <18 mmol/L).

**King's College Hospital criteria for liver transplantation in paracetamol-induced acute liver failure**

The original criteria, dating from 1989, were as follows:

**List for transplantation if**\(^{[11]}\):

- Arterial pH <7.3 or arterial lactate >3.0 mmol/L after adequate fluid resuscitation; OR
- If all three of the following occur in a 24-hour period:
  - Creatinine >300 μmol/L.
  - PT >100 seconds (INR >6.5).
  - Grade III/IV encephalopathy.

**Strongly consider transplantation if:**

- Arterial lactate >3.5 mmol/L after early fluid resuscitation.

More recently, a dynamic online prediction model has been made available, based on prospective data including analysis of more than 20 daily variables sequentially assessed for three days after ICU admission\(^{[6]}\).

**Prognosis**

The mortality from severe liver failure is <5% with good supportive care.

Although liver transplantation only has a limited application, patients must be identified as early as possible, preferably on the second day\(^{[12]}\). Current data indicate a poor prognosis if:

- An arterial pH <7.30 (hydrogen ion concentration >50 nmol/L) on or after day two following overdose (found in ~70% of cases with a poor prognosis).
- A combination of a prothrombin time of more than 100 seconds (INR >6.5), plasma creatinine >300 μmol/L and grade 3 or 4 hepatic encephalopathy (only a 17% survival rate).
- An increase in prothrombin time between day three and day four after overdose.

Liver transplantation is probably contra-indicated in patients with severe hypotension, severe cerebral oedema and serious infection.
Further reading & references

- Deaths related to drug poisoning in England and Wales: 2016 registrations; Office for National Statistics
- Treating paracetamol overdose with intravenous acetylcysteine: new guidance; Medicines and Healthcare products Regulatory Agency (Sept 2012)
- Intravenous N-acetylcysteine (NAC) for paracetamol overdose: reminder of authorised dose regimen; possible need for continued treatment with NAC, GOV.UK, 2017
- Acetylcysteine 200 mg/ml injection for infusion; Medicines and Healthcare products Regulatory Agency (archived content)

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