

# CLINICAL REVIEW

## Management of paracetamol poisoning

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Paracetamol (acetaminophen) is an effective oral analgesic, with few adverse effects when used at the recommended dose. Nevertheless, paracetamol poisoning is common and potentially fatal.<sup>1</sup> It is a leading cause of acute liver failure in the United Kingdom<sup>2</sup> and the United States.<sup>3</sup> Potential liver damage, predicted from blood paracetamol concentration and time from ingestion, can be prevented by prompt treatment with antidote. However, young and otherwise healthy patients still risk serious liver injury, especially if they present more than a few hours after overdose or take staggered overdoses over hours or days.<sup>4</sup>

### How does paracetamol cause damage and who is at risk?

The recommended therapeutic dosage of paracetamol depends on age (table 1). Therapeutic doses of paracetamol are mainly metabolised by conjugation to inactive metabolites. Paracetamol predominantly damages the liver.<sup>6</sup> The reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), formed when paracetamol is oxidised by the cytochrome P450 enzyme family, is the key to hepatic injury. NAPQI binds covalently to sulphhydryl groups, which can be provided by glutathione; but when glutathione stores are depleted NAPQI binds to cellular proteins (fig 1). Toxicity is therefore affected by the rate of enzyme catalysed formation of NAPQI, which can be induced by several drugs and chronic alcoholism, and by the availability of glutathione, which depends crucially on nutritional status. Thus, some patients are more susceptible than others to liver injury from paracetamol ingestion—box 1 lists the risk factors. After covalent binding of NAPQI to cellular proteins, cell injury is mediated by free radicals. An inflammatory response follows cell death and may determine the outcome once liver injury is established.<sup>7</sup>

Serious liver damage after a single 75 mg/kg body weight dose of paracetamol is rare, even in patients at increased risk. In patients without risk factors, a dose less than 150 mg/kg body weight is unlikely to cause serious liver damage.<sup>5</sup>

Severe paracetamol induced liver injury can be associated with renal failure.<sup>8</sup> Isolated renal dysfunction occurs only rarely, and

mostly in patients with glutathione depletion, or those who have taken nephrotoxic compounds as well, become dehydrated, or have pre-existing renal insufficiency.<sup>4</sup>

### How do patients with paracetamol overdose present?

Many patients who present do so within a few hours of taking an overdose, when symptoms and signs are absent or confined to nausea and vomiting. Lactic acidosis and coma can, exceptionally, occur soon after ingestion of massive amounts of paracetamol.<sup>9</sup> Their presence usually implies mixed overdose. Right upper quadrant tenderness is common in patients presenting with established liver damage. Patients who present after 24 hours may already have signs of liver failure—hepatic tenderness, jaundice, impaired consciousness, asterixis, foetor hepaticus, and haemorrhage. Overt liver failure can, however, be delayed for two or three days. It is important not to overlook paracetamol in those who have signs suggesting overdose with another agent.

### How should the patient with suspected paracetamol poisoning be investigated?

The history is crucial in patients who do not yet have liver failure because it determines the risk of serious liver damage, and hence treatment strategy. Ascertain the dose and timing of ingestion, and whether a patient may be more susceptible than average to the toxic effects of paracetamol (box 1).

### Dose of paracetamol

After a single overdose, the patient may be able to say how many tablets have been taken. Difficulties arise if the tablets have been taken over a period, or if the patient is unable or unwilling to give the relevant information.

**Summary points**

Patients still die from paracetamol poisoning because they are not recognised to be at risk of harm or present too late for effective treatment

Patients who are malnourished, have been fasting, take enzyme inducing drugs, or regularly drink alcohol to excess are at higher risk of liver damage

Treat patients who have ingested too much paracetamol within eight hours of ingestion whenever possible

If the time of ingestion is known, treatment can be based on blood tests taken after four hours

If the timing is uncertain or unknown, treatment should be started immediately in all patients who are at potential risk

Treat patients as high risk unless factors that increase risk of harm are known to be absent

**Sources and selection criteria**

We based our review on a PubMed search for articles on paracetamol (or acetaminophen) and acetylcysteine or (*N*-acetylcysteine) published between 1 January 1990 and 31 December 2010, without language limits. The search was limited to human clinical trials, meta-analyses, randomised controlled trials, reviews, and case reports. We also searched a newspaper database for reports published after 1988 of coroners' inquests and procurators' fiscal inquiries into fatal cases of paracetamol poisoning. In addition, we used a bibliography and our own collections of relevant references.<sup>5</sup>

**Box 1 Factors that increase the risk of liver injury after an overdose of paracetamol**

High chance of glutathione depletion:

- Malnourished (for example, not eating because of dental pain or fasting for more than a day)
- Eating disorders (anorexia or bulimia)
- Failure to thrive or cystic fibrosis in children
- AIDS
- Cachexia
- Alcoholism

Clinical clues: history, low body mass index, urinalysis positive for ketones, low serum urea concentration

Hepatic enzyme induction:

- Long term treatment with enzyme inducing drugs, such as carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, rifabutin, efavirenz, nevirapine, and St John's wort
- Regular consumption of ethanol in excess of recommended amounts

Clinical clues: history, abnormal liver function tests, increased international normalised ratio, increased  $\gamma$ -glutamyl transpeptidase

Abnormal renal or hepatic function at presentation

**Time of ingestion**

Knowing the time of tablet ingestion is crucial for calculating whether treatment with antidote is needed. Because it takes some time to swallow a substantial number of tablets, take the start of ingestion as the relevant time if all tablets were taken during a period shorter than one hour, otherwise treat as a staggered overdose. In cases of staggered overdose, more than one supratherapeutic dose, or if the patient has been poisoned with an intravenous or modified release formulation,<sup>10</sup> decisions regarding treatment are more difficult.

**Physical examination**

As well as eliciting signs of liver damage from paracetamol, the examination may indicate that the patient is more susceptible to developing such damage (see box 1)—for example, because the patient is malnourished.<sup>11</sup> It may also identify an antecedent liver disorder.

**Investigation**

The crucial investigations are the timed serum paracetamol concentration, to determine risk of liver damage, and tests of liver function (including prothrombin time or international

normalised ratio) and kidney function. These tests are needed to assess risk and monitor progress. Prognosis is worse if they are abnormal at presentation.<sup>4 12</sup> Paracetamol concentration in venous blood should be measured between four and 16 hours after ingestion of a single dose to allow the patient's risk to be determined from the standard nomograms (discussed below). Values obtained earlier than four hours cannot be interpreted because absorption is not yet complete. Values taken after 16 hours may be high because of acute liver injury that delays paracetamol metabolism,<sup>13</sup> or falsely reassuring, even though irreversible liver damage has already occurred. In untreated patients with negative tests for paracetamol and normal hepatic and renal function 24 hours after exposure, serious harm is unlikely.

Ketones on urinalysis and low blood urea concentration can indicate starvation or poor nutrition, which increases the risk of liver damage. Raised  $\gamma$ -glutamyl transpeptidase activity is a potentially useful indicator of hepatic enzyme induction.

## What is the initial approach to treatment?

### Out of hospital treatment

Treatment depends on adequate assessment, first aid measures, and transfer of at risk patients for antidotal treatment. Activated charcoal taken soon after overdose should reduce absorption of paracetamol.<sup>14</sup> It is unlikely to help more than an hour after overdose.<sup>15</sup>

### Acetylcysteine

The mainstay of treatment for patients who have taken a potentially toxic dose of paracetamol is the antidote acetylcysteine, which is a sulphhydryl donor.<sup>16</sup> It is given intravenously in three sequential infusions, each containing a different dose of antidote, and is based on the patient's body weight (up to a maximum dose equivalent to a weight of 110 kg) (table 2).

Acetylcysteine replenishes glutathione stores, which at least partly explains its antidotal efficacy. A large multicentre study of efficacy published in 1988 found that the antidote is uniformly effective if given within eight hours of a single overdose, but subsequently its efficacy falls.<sup>18</sup> A controlled trial provided evidence that acetylcysteine can improve outcome even in patients with encephalopathy,<sup>19</sup> so those who present more than eight hours after overdose are still treated with the antidote if they are deemed at risk of liver damage or if liver function is already abnormal.

A retrospective cohort study of more than 4000 patients showed that intravenous treatment is at least as effective as oral treatment but takes less time to administer.<sup>20</sup> Intravenous treatment can be administered reliably even if the patient is vomiting.

Findings from animal studies suggest that the alternative sulphhydryl donor methionine is less effective than acetylcysteine.<sup>21</sup>

### The treatment nomogram

Decisions to treat paracetamol overdose with acetylcysteine are based on an assessment of the risk of serious liver damage. The treatment nomogram, originally derived from a study of just 32 patients, separates those who will develop serious hepatotoxicity (transaminase activity >1000 U/L) from those who will not on the basis of a graph of paracetamol concentration against time from ingestion as it falls from 200 mg/L at four hours (the "200" line) (fig 2).<sup>13</sup> Healthcare professionals can consult their poisons information service (in the UK and Ireland: [www.toxbase.org/](http://www.toxbase.org/)) for treatment recommendations.

In the US, Australia, and New Zealand a similar semi-logarithmic plot at paracetamol concentrations 25% lower (the "150" line) is used to permit a wider margin of error.<sup>22 23</sup> Some patients reportedly come to harm even if the paracetamol concentration falls below the 200 or 150 lines.<sup>24</sup> An appreciation of the factors that increased the risk of liver damage led to the introduction in the UK of a second (high risk) line, running from 100 mg/L at four hours after ingestion (fig 2). We strongly advise that all patients be treated according to the high risk line unless factors that increase the risk of harm (box 1) are known to be absent.

The risk assessment nomogram requires the time from ingestion to be known with reasonable accuracy (fig 2). The efficacy of the antidote declines from about eight hours after overdose, so it is important not to delay treatment of potentially poisoned patients beyond eight hours even if the paracetamol concentration is not known. The nomogram is misleading or

unhelpful if the overdose was repeated or staggered, if the exact timing is unclear, or if the patient received an intravenous preparation, because the pharmacokinetics of such preparations are different. In these circumstances, the initial treatment decision has to be based on the total dose, taking any risk factors into account; subsequently, abnormalities in renal and hepatic function tests will guide treatment.

### Treating adverse events related to acetylcysteine

Acetylcysteine is sulphurous and commonly causes vomiting when given by mouth or nausea when given intravenously. It can also provoke an anaphylactoid reaction, which is mediated by histamine and depends on blood acetylcysteine concentrations. Such reactions may be more common in patients with asthma, those with a family history of drug allergy, and women.<sup>25</sup> Almost all reactions can be treated effectively by interrupting the acetylcysteine infusion and providing symptomatic relief with an antihistamine such as chlorphenamine and nebulised salbutamol if needed. In severe reactions where the patient becomes haemodynamically unstable resuscitation may be needed. Once the reaction has subsided, however, ensure that the entire dose of acetylcysteine is given in due course, possibly at a slower rate of infusion (for example, at a rate of 50 mg/kg/h).

Acetylcysteine has, very rarely, been associated with fatal adverse reactions; some reported cases have been caused by miscalculation of the dose, which has led to overdose with the antidote.<sup>26</sup>

The risk of an anaphylactoid reaction is higher in patients with lower plasma concentrations of paracetamol<sup>27</sup>; this suggests that treating patients who are unlikely to benefit from the antidote may increase the frequency of adverse reactions. Neither cost-benefit analysis,<sup>28</sup> nor experience in Denmark,<sup>29</sup> supports a policy of universal treatment with acetylcysteine.

### What supportive treatment should be given?

Fluid replacement and symptomatic treatment for nausea and vomiting are often needed. When acute liver failure has already occurred, or seems likely, intensive supportive treatment and—in the appropriate circumstances—liver transplantation will be needed. A transplant is most likely to be successful if the need for one is identified early, so swift referral is important (box 2).

### How to manage the patient after administering the antidote

Liver damage can be detected by measuring international normalised ratio, serum creatinine concentration, and liver function at the end of acetylcysteine treatment; some units also measure paracetamol concentration because appreciable concentrations can indicate a risk of continuing damage. UK guidelines, which have extrapolated from the study of acetylcysteine in encephalopathy,<sup>16</sup> suggest that if the international normalised ratio exceeds 1.3, or transaminases have increased to more than double baseline values, then the antidote should continue to be infused at a dose of 100 mg/kg over 16 hours until results are acceptable. Patients with renal dysfunction after paracetamol poisoning require ongoing monitoring and may need renal support.

**Box 2 Criteria for possible liver transplantation\*<sup>30</sup>**

- Arterial pH less than 7.3
- Hepatic encephalopathy grade III or IV and serum creatinine concentration >300 µmol/L and prothrombin time >100 seconds
- Arterial lactate concentration >3.5 mmol/L on admission or >3.0 mol/L 24 hours after paracetamol ingestion or after fluid resuscitation

It is best to discuss transplantation with a liver transplant unit as soon as the possible need is identified

## Why do patients still die from paracetamol poisoning?

Most deaths in the UK occur because patients present to hospital too late for the antidote to be effective. The diagnosis of paracetamol poisoning may be missed in patients who take a dose only slightly higher than therapeutic but have one or several factors that increase the risk of hepatotoxicity (box 3), when drug errors occur,<sup>9</sup> and in patients who have inadvertently taken more than the recommended dose of paracetamol in two or more different preparations containing paracetamol (box 4; fig 3). Paracetamol poisoning may also be missed in patients who have taken a mixed overdose and are unconscious, because unconsciousness is rare in paracetamol poisoning.

Mistakes can be made when estimating the risk of hepatic damage after paracetamol overdose.<sup>31</sup> Whenever risk assessment is difficult or uncertain, we recommend that the patient is assumed to be at high risk.

Treatment errors can occur when paracetamol concentrations are misunderstood. The cardinal measurement in ascertaining risk is the timed plasma paracetamol concentration. Patients have died when doctors have thought that results quoted in mmol/L are actually in mg/L (151 mg=1 mmol) and have therefore withheld acetylcysteine.<sup>32</sup> The acetylcysteine regimen is complex, and errors are common.<sup>33</sup> Errors also arise when absorption of paracetamol is delayed because co-ingestion of a drug such as codeine or an anticholinergic antihistamine has slowed gastric emptying and thus delayed absorption of paracetamol, or a modified release formulation has been taken. In such circumstances, toxic paracetamol concentrations may be reached much longer than four hours after overdose.<sup>34</sup>

Patients also come to harm when non-immunological adverse reactions to acetylcysteine are interpreted as anaphylaxis and the antidote is withheld.

## Areas of uncertainty

The optimal dosage of acetylcysteine and the appropriate dose adjustment for body weight remain unclear and are difficult to study in patients. Because the initial rapid infusion seems to cause most adverse effects, some people advocate giving the loading dose over one hour, although this is of no confirmed benefit.<sup>35</sup>

Better indicators of prognosis both at presentation and as a warning of impending liver failure, and more secure criteria for liver transplantation, are needed.<sup>30</sup>

Drugs that prevent mitochondrial injury<sup>36</sup> and drugs that target key inflammatory mediators<sup>7</sup> have been shown to prevent injury from paracetamol in experimental models and represent potential new therapeutic targets.

Contributors: The article was originally conceived by REF and DNB. All authors helped search the literature, structure the article, and draft the

article. All have seen and approved the final manuscript. REF and DNB are guarantors.

Competing interests: All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; REF and DNB are members of the Pharmacovigilance Expert Advisory Group of the Commission for Human Medicines, and JWD and DNB are consultants to the National Poisons Information Service.

Provenance and peer review: Not commissioned; externally peer reviewed.

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**Box 3 Case scenario 1**

A 19 year old woman with a rare syndrome, which meant she weighed just five and a half stone (35 kg) and was only four feet tall, was admitted to a neurology ward. She was prescribed intravenous paracetamol 1 g, when the correct (weight adjusted) dose was 525 mg. She received a total of 20 doses. When she developed fatal liver failure as a result, this was initially ascribed to Reye's syndrome. (*Evening Times (Glasgow)* 2010 September 17; <http://news.stv.tv/scotland/west-central/186253-doctor-tells-court-of-battle-to-save-danielle-welsh/>)

**Box 4 Case scenarios 2 and 3**

A 72 year old woman died after taking capsules of Lemsip Max cold relief as well as her prescribed paracetamol. She was taking the daily dose of paracetamol for pain and had been mixing it with the Lemsip Max for about a week—almost doubling her normal dose. After the court hearing, her husband urged people to read the labels carefully and called for large warnings about the dangers of paracetamol overdose to be printed on the front of packets. "[My wife] knew too much paracetamol was dangerous but she did not realise there was paracetamol in Lemsip. If you go into a chemist and ask for something the first thing they ask is if you are taking any medication. But if you go into a supermarket there is no proper dispensary counter and the people at the check-out don't know anything about it." (This is Bradford 2004 July 21.)

A 43 year old woman with a history of polymyositis was prescribed a paracetamol based painkiller known as Kapake by her general practitioner for a dental abscess, but she was also taking standard paracetamol tablets. She was admitted to hospital with a suspected recurrence of the polymyositis, but tests showed she had serious liver damage, from which she later died. (This is Lancashire 2004 November 23.)

**Additional educational resources***Resources for healthcare professionals*

TOXBASE e-learning site ([www.toxbase.co.uk/](http://www.toxbase.co.uk/))—An e-learning resource for NHS and public health staff on Toxbase and the clinical management of poisoned patients

BMJ Learning (<http://learning.bmj.com/learning/channel-home.html>)—Includes an update of the management of paracetamol overdose

WiKi Tox (<http://curriculum.toxicology.wikispaces.net/>)—Provides a set of resources that can be used as tools to learn or teach clinical toxicology

National Institute for Health and Clinical Excellence ([www.nice.org.uk/Guidance/CG16](http://www.nice.org.uk/Guidance/CG16))—National UK guideline on self harm

*Resources for patients*

X-PIL. (<http://xpil.medicines.org.uk/>)—Product information leaflets: give advice on quantities of paracetamol in over the counter preparations

Samaritans ([www.samaritans.org/](http://www.samaritans.org/)) and MIND ([www.mind.org.uk/](http://www.mind.org.uk/))—Both organisations provide information to patients and relatives on self harm

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**Accepted: 23 March 2011**

## Tables

Table 1 | Recommended maximum doses of paracetamol

Patients	Maximum single dose	Minimum dosing interval (hours)	Maximum dose in 24 hours
Adults	1 g	4	4 g
Children 6-12 years	500 mg	4	2 g
Children 1-5 years	240 mg	4	960 mg
Infants 3-12 months	120 mg	4	480 mg

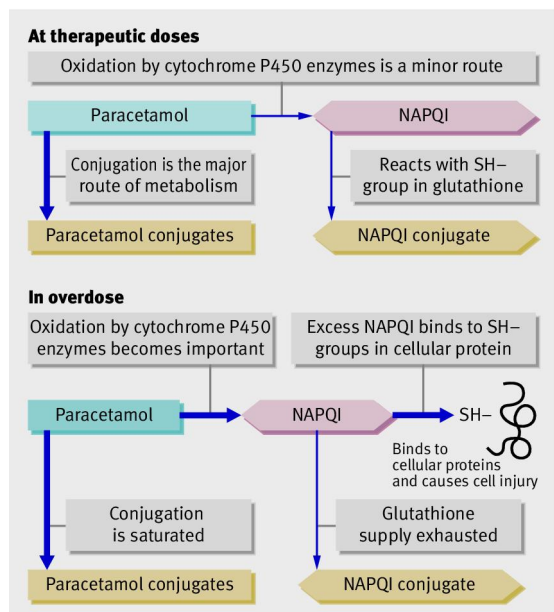
**Table 2| Recommended doses of acetylcysteine as antidote to paracetamol poisoning in adults. Adapted from the summary of product characteristics for Parvolex17**

Recommended sequential doses*	Dose according to patient's weight		
	70 kg	110 kg	140 kg†
150 mg/kg in 200 mL over first 0.25 hours	10.5 g	16.5 g	16.5 g
50 mg/kg over next 4 hours in 500 mL	3.5 g	5.5 g	5.5 g
100 mg/kg over next 16 hours in 1000 mL	7 g	11 g	11 g
Total dose (300 mg/kg in 20 hours)	21 g	33 g	33 g

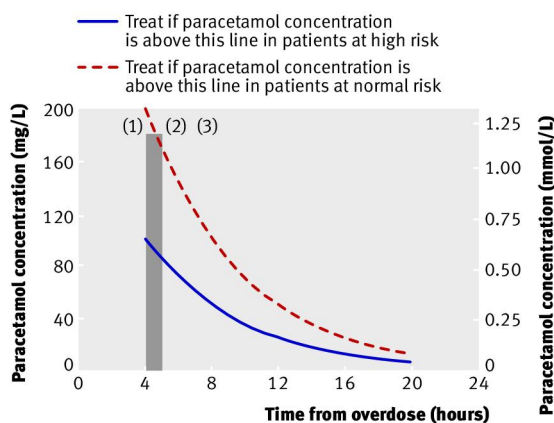
\*Acetylcysteine in glucose 5% solution.

†A ceiling weight of 110 kg is recommended when calculating the dosage for obese patients.

## Figures



**Fig 1** At therapeutic doses, paracetamol is mainly metabolised by conjugation to inactive metabolites. A reactive metabolite, *N*-acetyl-*p*-benzoquinoneimine (NAPQI), is formed by oxidation. When a large dose of paracetamol is taken, more NAPQI is formed, sulphation conjugation pathways are saturated, and NAPQI binds covalently to sulphhydryl (SH-) groups. These can be provided by glutathione, but when hepatic glutathione stores are depleted, NAPQI binds to cellular proteins and causes cell injury



**Fig 2** The graph shows how a relatively small inaccuracy in timing could result in the wrong course of action. Paracetamol concentration is shown on the y axes (as both mg/L (left hand axis) and mmol/L (right hand axis)) and time from overdose on the x axis for patients at high risk (lower line) and normal risk (upper line). In this example, the sample is thought to have been taken at four hours (1) after overdose, in which case no treatment would be needed (in a patient at normal risk). If, however, the wrong time had been given and the sample had actually been taken at five hours (2) it would require treatment and more clearly if had been taken at eight hours (3)—it would require treatment