BMJ 2016;353:i2579 doi: 10.1136/bmj.i2579 (Published 18 May 2016)

PRACTICE

THERAPEUTICS

Treatments for paracetamol poisoning

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A 24 year old woman is brought to the emergency department semi-conscious after a suspected overdose; empty packs of paracetamol (acetaminophen) and diazepam are found with her. She is also taking carbamazepine for seizures. Her paracetamol concentration at the time of admission is 100 mg/L (660 µmol/L); she probably ingested the pills four to eight hours earlier.

Effects of paracetamol poisoning

Paracetamol poisoning can cause severe hepatotoxicity owing to a minor but highly reactive metabolite produced by cytochrome P450 enzymes. At therapeutic doses, the metabolite (*N*-acetyl-p-benzoquinoneimine; NAPQI) is detoxified by glutathione. However, in paracetamol overdose, glutathione stores are depleted and hepatotoxicity ensues, starting about eight hours after the overdose and potentially leading to fulminant liver failure within a few days.

The risk of hepatotoxicity is calculated from the blood concentration of paracetamol and hours since ingestion (fig 1⇓). If the concentration is above the line on the nomogram, treatment should be considered. The risk of toxicity without treatment is low until concentrations are substantially higher than this line. The nomogram is inaccurate if presentation is very late or the overdose was taken over several hours. If a measurement cannot be obtained within eight hours, treatment decisions cannot wait for laboratory results. Risk is then based on reported ingested dose (≥200 mg/kg or 10 g in Australia, >75 mg/kg or 4 g in United Kingdom) or on evidence of hepatotoxicity if the overdose was taken >24 hours ago.

What are paracetamol poisoning antidotes?

Antidotes acetylcysteine and methionine provide a substrate for further glutathione synthesis,[1 2] thus detoxifying NAPQI and reducing hepatotoxicity. Intravenous acetylcysteine is the main antidote in many countries but is also available as an oral preparation. UK guidelines were updated in 2012, when the recommended treatment threshold was lowered, and they differ from other international ones.[3 4] This change benefits a small number of patients but results in side effects for a greater number of patients and increased costs.

Methionine, oral only, is used in some low income countries and is on the World Health Organization's essential medicines list.[5] Other treatments include early activated charcoal to reduce absorption of paracetamol and haemodialysis to increase elimination.

How well do they work?

Acetylcysteine and methionine

Original data supporting the use of these antidotes in paracetamol poisoning come from cohort studies. Paracetamol poisoning treated within eight hours with intravenous or oral acetylcysteine is consistently associated with avoidance of serious hepatotoxicity and death in cohort studies.[2-8] Data from the 1970s, before such antidotes were available, show that 3-5% of patients died.[9] Smaller cohort studies suggest similar favourable outcomes with early methionine (table 1⇓).[1]

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com.

A randomised controlled trial (RCT; n=50) found that treatment with acetylcysteine up to four days later reduces risk of death, even in those with established liver failure (number needed to treat (NNT) to prevent death 4, compared with no use of acetylcysteine).[10]

Despite treatment, hepatotoxicity (eg alanine aminotransferase >1000 U/L) still occurs, particularly with very large overdoses (>50 g) even if people receive early treatment, and in those treated >8-10 hours after the overdose and those with increased susceptibility (eg people with chronic alcohol use or malnutrition and those taking enzyme inducing drugs).

No clinical trials have compared intravenous versus oral acetylcysteine[6] or acetylcysteine with methionine.[6]

Activated charcoal

No RCTs have looked at activated charcoal specifically for paracetamol poisoning.[11] RCTs of its routine use in all poisoning in both developed and developing countries show no overall improvement in outcomes such as mortality or hospital stay.[12 13]

A cohort study of patients who ingested >10 g of paracetamol found that early (<2 h) use of charcoal was associated with reduced need for acetylcysteine.[14] If we assume that the link was causal, the NNT to obviate the need for further treatment was 7. This is biologically plausible as the duration of paracetamol absorption is prolonged with larger overdoses.

Haemodialysis

This removes a small proportion of ingested paracetamol but also removes acetylcysteine. It is not generally recommended and will not be discussed further.[15]

How safe are they?

Intravenous acetylcysteine is associated with anaphylactoid reactions such as rash, pruritis, vomiting, flushing, wheeze, and hypotension in RCTs, with numbers needed to harm (NNH) of 2-10, depending on the rate of infusion.[7 16] Anaphylactoid reactions do not reflect an allergy but seem to be related to peak acetylcysteine concentration in rapid loading doses; slower initial infusions may reduce the risk.[7 17] Other serious adverse effects arise from excessive dosing owing to errors in dose calculation[18] (eg lethal anaphylactoid reactions from 10-fold dosing errors[19]). Less serious adverse effects such as nausea and vomiting are also common.[7 16]

Oral methionine is commonly associated with vomiting, but data on its adverse effect profile are limited.[11]

Two large RCTs show that activated charcoal is very safe.[12 13]

What are the precautions?

Deliver intravenous acetylcysteine in a closely monitored area such as the emergency department, with capacity to treat anaphylactoid reactions. Ensure correct dose calculation and use an infusion pump to ensure intended infusion rates are not exceeded.

Consider avoiding activated charcoal if oral acetylcysteine or methionine is likely to be given because it impairs their absorption (although outcomes are no worse when it is given before oral acetylcysteine[20]). It also enhances elimination of anticonvulsants and oral contraceptives—advise patients of the short term increased risk of treatment failure (seizures, pregnancy) and that they should take appropriate precautions.

How cost effective are they?

Wholesale purchase costs per treatment are low (activated charcoal, <$10 (£6.9; €8.8); methionine, <$10; acetylcysteine, <$100).[5] All are cost effective if given to patients at serious risk of major morbidity or intensive care admission because they reduce the need for admission or shorten duration of stay.

The threshold for treatment and the choice of antidote and regimen determine the cost effectiveness. In the UK, the dose requiring treatment has recently been reduced (fig 1⇓). This has increased the numbers treated roughly 1.5-fold and increased the cost per life saved by about £17.4m.[4] In the UK, 40% of bed occupancy for paracetamol overdose was for intravenous acetylcysteine therapy. A new shorter regimen (not recommended in current guidelines) might save about 10 000 bed days per year[21]; outpatient oral therapy with acetylcysteine or methionine for low risk patients could save more.

In low income countries cost effectiveness analyses suggest methionine may be more cost effective than acetylcysteine, particularly in low risk patients.[5 22]

How are they given and monitored?

Acetylcysteine is often given as a three bag intravenous infusion regimen diluted in 5% dextrose—150 mg/kg over one hour, then 50 mg/kg over four hours, and finally 100 mg/kg over 16 hours. Monitor the patient for infusion reactions over the first few hours. If necessary, slow the infusion or temporarily stop it. Consider using inhaled salbutamol (for wheeze) and histamine blockers (for skin reactions). Two bag infusions with the same total dose but slower initial infusion rates are being used to reduce the rate of infusion reactions (eg 200 mg/kg over four hours then 100 mg/kg over16 hours). Such regimens are unlicensed but have shown similar efficacy in cohort studies.[23]

Towards the end of the infusion, check liver function tests and paracetamol concentrations in patients with signs of liver damage (such as nausea and right upper quadrant abdominal tenderness) and those who took large overdoses (more than double the standard nomogram line). If alanine aminotransferase is raised or paracetamol is >10 mg/L, consider longer treatment with a continuous infusion of 150 mg/kg/day.

Oral acetylcysteine is usually given as 140 mg/kg initially and then 70 mg/kg four hourly for up to 72 hours and oral methionine as four doses of 2.5 g four hourly. The durations suggested are a legacy from the first studies. Shorter (for acetylcysteine) or longer (for methionine) courses would make sense in many patients to cover the time that paracetamol concentrations remain high. Nausea and vomiting are the commonly reported adverse effects and monitoring is used to check adherence.

Oral activated charcoal is given orally as 50 g in suspension. The patient should be cooperative and alert, or intubated, to avoid the risk of aspiration. Routine blood test monitoring is not needed.

Case outcome

The patient was not fully conscious but did not require intubation so she could not safely receive activated charcoal (which might also have interfered with her carbamazepine, which was confirmed as being in the normal range). She received intravenous acetylcysteine as soon as the paracetamol result was obtained. Risk assessment with the nomogram had to use a “worst case” scenario, which assumed up to eight hours had elapsed, putting the concentration above the treatment line. She

Tips for patients

- Activated charcoal reduces the amount of paracetamol absorbed so may reduce the need for other treatments and time in hospital. It is safe but may temporarily reduce the effectiveness of other regular drugs
- Acetylcysteine is given to reduce liver damage, usually in a drip over 24 hours. Rashes, itch, nausea, and vomiting are common in the first hour or two
- In most countries life saving treatments can be given without patient consent in emergencies—for example, under a mental health act or as the treating doctor's "duty of care."[24] Acetylcysteine generally meets these criteria, but the evidence for charcoal is less clear
- No long term liver damage or adverse effects are expected after leaving hospital
- Return to hospital or seek medical help if symptoms such as nausea or abdominal pain emerge in the next few days

was also potentially at higher risk because she was taking carbamazepine (CYP450 enzyme inducer) and this also caused some baseline changes in her liver function tests.

Contributors: All authors helped draft and revise this article and have approved the final version to be published. NAB is guarantor.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

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How patients were involved in the creation of this article

We based our tips for patients on the most common questions patients ask (Why do I have to take this? Do I have to take this? Will I have any long term problems after this?) and the MHRA model patient discharge card.[3] We asked some lay people who had not taken an overdose to advise on the wording of the tips for patients.

Education into practice

- Do you consider giving activated charcoal to patients who present within two hours after a large paracetamol overdose (>10 g)?
- Do you routinely advise patients who are not treated with acetylcysteine to return if they have symptoms of liver toxicity?

What you need to know box

- Acetylcysteine or methionine is associated with reduced mortality if given within eight hours and perhaps even up to four days later
- Slower infusions of intravenous acetylcysteine reduce the risk of anaphylactoid reactions
- Consider activated charcoal for patients who present within two hours of a large overdose (>10 g) if risk of aspiration is low

Table

Table 1| Reported rates of hepatotoxicity and death when antidotes used in high risk paracetamol poisonings (concentration more than double the nomogram line)* 1258

Antidote	Hepatotoxicity		Death	
	<10 h	10-24 h	<10 h	10-24 h
Methionine[1]	6/43 (14%)	14/31 (45%)	0	2 (6%)
Oral NAC[8]	17/206 (8%)	199/578 (34%)	1 (0.5%)	9 (0.4%)
IV NAC[2]	1/33 (3%)	18/27 (67%)	0	2 (7%)

*IV=intravenous; NAC=acetylcysteine.

Figure

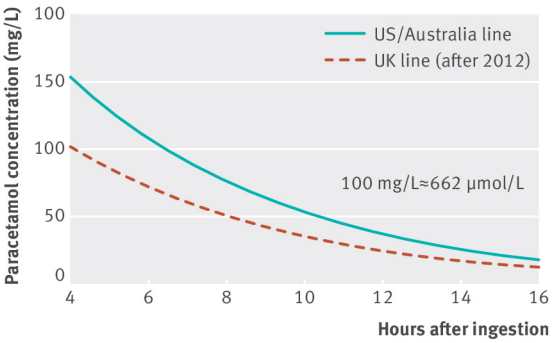

Fig 1 Nomograms for the treatment of paracetamol poisoning. Concentrations above the lines require treatment. Nomograms for clinical use usually show just one of the lines to avoid confusion. The US/Australia line is sometimes referred to as the Rumack-Matthew line and is commonly used in Canada, New Zealand, and parts of Europe and Asia