Management of paracetamol overdose

Girish L Gupte

Abstract

Paracetamol is a widely available as an 'over-the-counter medication' for children in the UK and overdose is one of the commonest reasons for contacting the UK Toxic Poisons Centre. The severity of presentation with paracetamol overdose may vary from no effect on liver function to severely deranged liver function tests causing liver failure and being rescued by liver transplantation or leading to death. *N*-Acetyl cysteine is highly effective therapy and the implementation of appropriate management in the early period of presentation to prevent the toxicity related to the liver and kidneys cannot be overemphasized. The article will aim to answer some key clinical questions facing the clinicians in the early management of paracetamol overdose.

Keywords acetaminophen; hepatotoxicity; *N*-acetyl cysteine; NAC; paracetamol; poisoning; staggered overdose; supra-therapeutic ingestion; toxicity

How big is the problem?

Paracetamol overdose was one of the commonest causes of liver failure necessitating liver transplantation in the UK in the 1990's until regulations were introduced whereby the paracetamol pack size was limited. This has resulted in a dramatic reduction in the morbidity and mortality of adults and children from paracetamol overdose. The risks were diminished further in 2005 when paracetamol/dextropropoxyphene combination (co-proxamol) was withdrawn as an over-the-counter medication and this is now only available on prescription within the UK.

An audit of drug-related deaths in England and Wales from 2000 to 2011 confirmed an overall decline in the number of deaths related to poisoning (from all drugs and chemicals) in the first decade of the 21st century. However, the exact number of children dying from paracetamol poisoning was not reported. The number is likely to be small though as from personal experience in working in a busy tertiary liver unit (Birmingham Children's Hospital), no mortality secondary to paracetamol poisoning as the sole cause of death has been documented within our records from 2005 to 2016. However, deliberate paracetamol ingestion remains a common problem and one which is frequently encountered by paediatricians. Optimum management in the acute phase is crucial if deaths are to be minimized.

Not all cases of paracetamol poisoning are deliberate. A proportion occurs after prescribing or administration errors which are compounded by the range of products containing paracetamol available and the number of routes for administration. Since the availability of IV paracetamol as an analgesic, sporadic cases of iatrogenic overdose have been reported.

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What are the toxic doses of paracetamol in children that clinicians should be worried about?

To determine whether a single dose of paracetamol is likely to be toxic it is important to consider the age of the child and how much has been taken over how long. Total doses of paracetamol more than 150 mg/kg over any 8 hour period for children under six and total doses of 200 mg/kg or 10 g (whichever is lower) are considered toxic for children 6 years and older. For repeated supra-therapeutic ingestion (staggered overdose) of paracetamol, different cut-offs exist for levels which should be considered hazardous depending on the duration of overdose:

- Less than 24 hours – same as acute single ingestion
- 24–48 hour period of overdosage: more than 150 mg/kg or more than 6 g whichever is lower per 24 hour period
- more than 48 hours: more than 100 mg/kg or more than 4 g whichever is lower per 24 hour period

Smaller doses of paracetamol may be toxic in the following circumstances:

- Chronic alcohol use
- Malnutrition (prolonged fasting, anorexia, cystic fibrosis, HIV infection etc.)
- Co-ingestion with alcohol
- Co-ingestion with drugs that delay gastric emptying
- Co-ingestion with medications that induce Cytochrome P oxidative enzymes i.e. isoniazid, rifampicin, phenytoin, phenobarbitone, carbamazepine

It is important to take a good history documenting the exact dose of paracetamol and co-morbidities as well as co-ingestion with other drugs to plan appropriate management. It is particularly important to ask for the formulation as modified release paracetamol may have been ingested. Delayed measurement of paracetamol levels may be needed in these circumstances.

Is history reliable in the assessment of paracetamol overdose?

The short answer is 'probably'. The question is pertinent as the clinicians rely on history to make a diagnosis and decision regarding management in cases of suspected poisoning. In a meta-analysis of the reliability of history in all cases of suspected poisoning, history in cases of paracetamol poisoning is moderately reliable as compared to history of street drugs due to the legal implications. In clinical practice they act as a guide only and it is always helpful to confirm the likely veracity of any history with blood paracetamol levels. If in doubt, err on the side of caution, treat first and ask further questions later.

Why and how does paracetamol toxicity occur?

Oral paracetamol is absorbed from the small intestine (but not the stomach) with a peak plasma level that reaches within 4 hours after ingestion. Delayed peak levels in children may occur if paracetamol is co-ingested with other agents that delay gastric emptying (e.g. alcohol) and in children with hepatic dysfunction where there is poor metabolism of paracetamol. The accompanying diagram (Figure 1) demonstrates the metabolism of

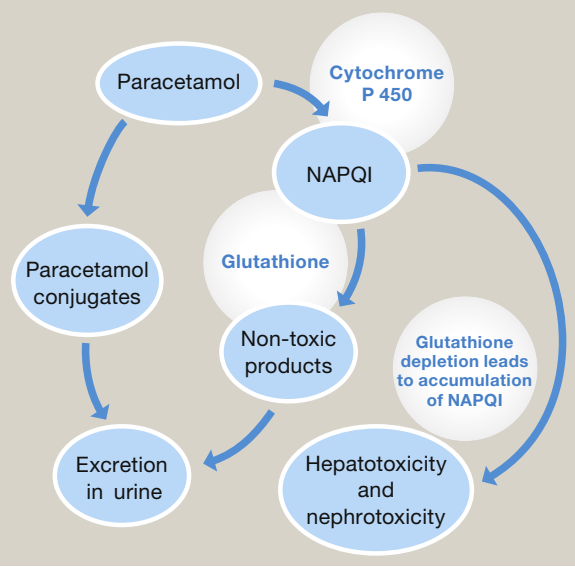

Figure 1 Metabolism of paracetamol and generation of toxic products.

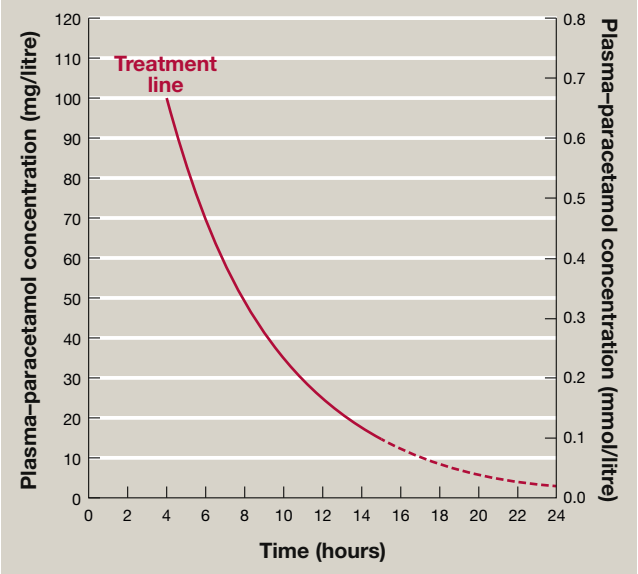

Figure 2 Modified Rumack-Mathew nomogram based on serum paracetamol level.

paracetamol and the reactions that occur in case of paracetamol overdose.

Under normal circumstances 90–95% of the paracetamol ingested will be converted to non-toxic products after conjugation with glucuronides and excreted in the urine. Around 5% is metabolized via the cytochrome P 450 enzymes to the toxic product NAPQI (*N*-acetyl benzaminoquinone). NAPQI is then conjugated with glutathione and excreted as a non-toxic product in the urine. Glutathione is therefore required to de-toxify the NAPQI. Thus conditions that result in depletion of glutathione stores (chronic alcohol ingestion, malnutrition due to various causes) or drugs that induce cytochrome P 450 (as outlined above) can result in excess production of NAPQI which can result in toxic side effects to the liver and kidneys.

What are the symptoms and signs at presentation?

The majority of children and young people are asymptomatic at the time of presentation as the symptoms do not manifest until 24–48 hours after ingestion. Some children may report anorexia, nausea or vomiting and in the later stages complain of upper quadrant pain. In children ingesting toxic doses of paracetamol resulting in hepatotoxicity and hepatic necrosis, jaundice and oliguria may rarely be the presenting feature.

How is the diagnosis made?

The diagnosis is made on the basis of measurement of paracetamol levels 4 hours after ingestion. The levels obtained are plotted on the modified Rumack-Matthew nomogram (Figure 2), which helps in planning the management of patients. The rationale for treatment is probabilistic. Not all children will develop hepatotoxicity following overdose. However, 60% of the patients with values above the 'probable' line do develop hepatotoxicity. Different countries and continents have different cut-off values for the threshold of treating paracetamol overdose, which is explained in the section below.

What investigations should be done in the initial presentation?

The initial investigations required are summarized in Box 1. There is lack of agreement about the frequency and the blood tests that need to be repeated after the initial tests and the decision can be nuanced. Discussions with the local liver unit can be helpful.

If children require a further infusion of *N*-acetyl cysteine beyond 21 hours, then blood tests (Serum AST or ALT, prothrombin time (or INR), electrolytes, urea, creatinine, venous pH, and lactate) should be repeated at least 12 hourly or more frequently depending on the clinical scenario. The monitoring should be continued for 12 hours after stopping *N*-acetyl cysteine to ensure that the risks of long term hepatotoxicity can be ascertained.

High doses of paracetamol can elevate the INR in the absence of hepatotoxicity, due to the inhibition of Vitamin K dependent activation of clotting factors. Hence a modest elevation of INR (1.1–2.0) should be interpreted with caution and management

Investigations to be undertaken following paracetamol overdose

- Serum paracetamol level at least 4 hours after ingestion.
- FBC, urea, serum sodium, serum potassium, creatinine, glucose, liver function tests (bilirubin, alkaline phosphatase, ALT, AST, GGT, albumin, total protein), clotting screen, venous blood gas and lactate to check for acidosis.
- Serum AST or ALT, prothrombin time (or INR), electrolytes, urea, creatinine, venous pH, and lactate should be repeated at the end of intravenous therapy. This helps to determine if subsequent infusion of *N*-acetyl cysteine is necessary.

Box 1