The management of paracetamol poisoning

Khairun Nain Bin Nor Aripin
Imti Choonara

Abstract

Paracetamol poisoning is a common presentation in paediatrics. Toxicity may cause hepatocellular injury, in certain cases progressing to fulminant liver failure. Young children appear less at risk of hepatotoxicity due to an increased metabolic capacity for paracetamol. A single dose of 150 mg/kg can cause hepatocellular damage. Children who ingest multiple supratherapeutic doses can accumulate significant concentrations and may suffer worse outcomes. Older children who intentionally overdose may also suffer worse outcomes, especially those who present late. The risk of hepatotoxicity after a single overdose can be predicted using a widely used nomogram, although it was derived from adult data. The cornerstone of management is administering the antidote N-acetylcysteine when hepatotoxicity is likely to occur. The National Poisons Information Service is available to be consulted at all hours. When severe poisoning is suspected, the child may require referral to a liver unit in view of possible liver transplantation.

Keywords children; drug metabolism; paracetamol; toxicity

Introduction

The analgesic and antipyretic properties of paracetamol were first described in 1893. It was shown to be an effective antipyretic in children in 1956 and since the 1960s, it has been widely available as a non-prescription drug, with a therapeutic profile that reflects widespread safety and efficacy. Following the discovery of an association between aspirin and Reye's syndrome in the 1980s, paracetamol became the most widely used analgesic and antipyretic in children. It is the most frequently used over-the-counter medicine in young children and is nearly universally used in infants. The drug is used by millions of children every day.

Epidemiology

On the other hand, paracetamol is one of the most common causes of poisoning in the developed world. Paracetamol poisoning is the leading subject of inquiries to poison centres in the US, UK and Australasia. It is the single most commonly taken drug in overdose in the UK, accounting for half of all admissions for poisoning and an estimated 100–200 deaths per year.

Khairun Nain Bin Nor Aripin *MBChB MSc is Postgraduate Student at University of Nottingham, Derbyshire Children's Hospital, Derby, UK.*

Imti Choonara *MBChB MD is Professor of Child Health at University of Nottingham, Derbyshire Children's Hospital, Derby, UK.*

In the US, the FDA reports that there are about 112,000 poisoning calls, 56,000 emergency department (ED) visits, 26,000 hospitalisations and over 450 deaths annually associated with paracetamol poisoning. FDA statistics also show that children aged 16 years or younger account for about 33% of ED visits, 24% of hospitalisations but only between 1–3% of mortality related to paracetamol overdose.

Paracetamol toxicity primarily manifests in the liver, and paracetamol overdose is the most common apparent cause of acute liver failure in the UK and Western countries.

Paracetamol poisoning in the paediatric age group can be divided into three major groups with differing demographic and clinical characteristics. These are intentional self-poisoning, accidental paediatric ingestion and poisoning due to repeated supratherapeutic dosings of paracetamol.

Rumack and Matthew's landmark review in 1975 brought attention to paracetamol poisoning in children. In 1984, Rumack described a cohort of 417 children, aged 5 years or younger, who had ingested potentially toxic amounts of paracetamol. Only three children had altered liver enzymes and all recovered with treatment with no fatalities in the cohort. Thus, it was accepted that in general, young children with accidental single exposures to paracetamol overdoses were less at risk of developing toxic reactions and subsequent morbidity and mortality than adolescents or adults.

A study of 140 children admitted to a hospital in Scotland reported only one case (a 13 year old girl) of hepatotoxicity. The majority of the children were less than 5 years old (Table 1).

Following early case reports, there has been growing concern regarding children developing toxicity after receiving *repeated* supratherapeutic doses of paracetamol. A Californian case series of 73 overdoses included 63 cases of intentional poisoning. The remaining 10 cases where the overdoses were unintentional were in children under 10 years of age who had been given multiple supratherapeutic doses. Eight out of the 10 developed hepatotoxicity and encephalopathy resulting in one death and three liver transplants.

Another American study of children under the age of 10 years described 24 deaths occurring in a cohort of 47 young children. The vast majority of these children experienced repeated paracetamol overdoses and these findings are in contrast to the cohort originally described by Rumack in the same country.

In an Australian review of 18 children with fulminant hepatic failure, unintentional recurrent overdose was presumed to have caused the liver failure in 11 children, aged below 11 years of age.

Alander et al. reviewed all presentations of paracetamol poisoning to two regional children's hospitals in the US over a 10 year period. They found that out of 322 paediatric paracetamol overdoses, intentional and unintentional overdoses occurred with a similar frequency. Intentional overdoses occurred in older children and adolescents ranging between 11 to 17 years old (median age, 14 years), while unintentional overdoses occurred in children with a median age of 2 years old. Only one out of the 172 young children who unintentionally ingested an overdose of paracetamol developed hepatotoxicity. 10 children presented after ingesting repeated supratherapeutic doses and one of the 10 developed hepatotoxicity. In this case series, all four cases of liver failure and one death occurred in older children who intentionally overdosed on paracetamol.

Studies describing children with paracetamol poisoning

First author, year	Age and number of children described	Setting	Type of overdose	Outcome
Rumack 1984	<5 years, $N = 417$	Poison center, Denver, USA	Acute, short term ingestion	3 developed hepatotoxicity (all less than 5 years old) No deaths
Kumar 1990	1–4 years, $N = 108$ ≥5 years, $N = 32$	Children's hospital, Glasgow, Scotland	130 accidental 10 intentional (>10 years)	1 developed hepatic failure (13 year old) Full recovery with supportive treatment
Rivera-Penera 1997	≤10 years, $N = 14$ >10 years, $N = 59$	California, USA	10 multiple overdoses (≤10 years group)	In multiple group, 8/10 had hepatoxicity, 3/10 had transplant, 1/10 died. (All less than 10 years old) In the other group, 3/63 had transplant, 1/63 died. (age not described)
Heubi 1998	≤5 years, $N = 35$ 6–10 years, $N = 12$	USA	Multiple overdoses	5 had transplant (ages 7 months, 3,6,6,8 years) 24 died (ages 1 month to 10 years)
Miles 1999	0.5–11 years, $N = 11$	Liver transplant centre, Australia	Multiple overdoses	6 recovered with supportive treatment, 1 brain damage (age 31 months) 4 died (ages 5,6,10,11 years)
Alander 2000	0–17 years, $N = 322$	2 regional children's hospitals, USA	140 intentional 172 unintentional 10 multiple overdoses	4 had liver failure and 1 died, all from intentional group (all 11 years or older)
James 2002	1.5–17 years, $N = 41$	Children's hospital, Arkansas, USA	Acute single overdoses	16/41 had hepatotoxicity 1 had transplant (age not described) No deaths
Ranganathan 2006	$N = 25$	Children's hospital, Colombo, Sri Lanka	All 25 had multiple supratherapeutic doses	3 died
Mahadevan 2006	0.8–16 years, $N = 51$	National liver unit, United Kingdom	6 multiple overdoses (<7 years) 45 single overdose	3/6 In multiple group died (all under 7 years old) 6/45 in single group died (age not described)

Table 1

James et al. described 95 children who were admitted to Arkansas Children's Hospital in the US with paracetamol poisoning between 1991 and 2001. 41 had taken a single acute overdose of paracetamol. 16 of these children between 8 to 17 years old developed hepatotoxicity; five had severe hepatotoxicity and one required a liver transplant. There were six children who had taken multiple overdoses but they were not described further in the study.

Mahadevan et al. recently reviewed 51 children admitted to the national liver unit in Birmingham (UK) with significant hepatotoxicity induced by paracetamol overdose between 1992 and 2002. There were six children less than 7 years old who developed toxicity following multiple dosing. All six were listed for transplantation, two died after transplantation while one died awaiting transplant. The other 45 children were adolescents, 43 were female. All had taken the paracetamol overdose intentionally.

Ranganathan et al. performed a case control study on 25 cases of children with fulminant hepatic failure with age matched controls in Sri Lanka. They found that all 25 cases were administered supratherapeutic doses of paracetamol (mean 145 mg/kg/day). Cases had higher mean paracetamol plasma concentrations and longer durations of dosing. All the children had acute viral infections with a fever.

In summary, younger children who accidentally ingest a single dose of paracetamol are less at risk of hepatotoxicity and other serious complications of paracetamol poisoning. On the other hand, older children who self-harm with paracetamol overdoses and young children who ingest repeated overdosings of paracetamol may suffer severe morbidity and mortality.

Pathophysiology

Paracetamol is rapidly absorbed from the small intestine and has a high bioavailability of around 80% after first-pass metabolism. The pathophysiology of paracetamol poisoning is closely related to its metabolism. Paracetamol is predominantly metabolised in the liver by conjugation with sulphate (around 30%) and glucuronide (60%). A smaller amount is eliminated unchanged

in urine. However, approximately 5–10% of paracetamol is metabolised to N-acetyl-P-benzoquinoneimine (NAPQI), a toxic metabolite via CYP450-dependent pathways. NAPQI is then detoxified by glutathione and is eliminated in urine or bile.

At toxic levels, sulphate and glucuronide conjugation can be saturated. This leads to glutathione depletion as more paracetamol is metabolised through the CYP450 pathways, and NAPQI may accumulate. NAPQI that is not detoxified then reacts with sulphydryl groups on hepatocytes and causes hepatocellular necrosis.

In infants and young children, the dominant pathway of metabolism appears to be sulphate conjugation while glucuronide conjugation matures slowly. Children are also thought to have a more active oxidative pathway, resulting in an increased rate of glutathione production, thereby conferring a protective effect from hepatotoxicity in young children.

The greater capacity for sulphation in young children alongside an increased incidence of vomiting may also explain why young children appear less susceptible to hepatotoxicity compared to adults.

Despite these apparent protective mechanisms paracetamol may accumulate significantly in children after repeated therapeutic doses. Although no children developed hepatotoxicity after repeated doses of between 66–81 mg/kg/day, increases in AUC of 14–33% were seen. Significant accumulation may explain why children who had ingested multiple supratherapeutic overdoses appear to have worse outcomes.

Minimum toxic dose

Although Rumack and Matthew did not specify a minimum level of toxicity, it was generally agreed following their work that a minimum single dose of 150 mg/kg may be associated with hepatocellular damage. Other studies have supported this dose as being the threshold for toxicity. Hepatocellular injury was associated with reported doses *in excess* of 150 mg/kg/day at an odds ratio of 18 compared to doses *below* 150 mg/kg/day (95% CI, 2–139).

However, a minimum toxic dose level of paracetamol has not been conclusively established. Firstly, it is difficult to accurately document the ingested dose as well as the time of ingestion in many cases, especially in young children due to recall issues and numerous different formulations. Secondly, the dosing picture may be complicated by repeated ingestions rather than a single overdosing as discussed earlier. Thirdly, alterations in the individual metabolism of patients can interfere with efforts to determine dose-response relationships. Fasting and malnutrition, alcohol ingestion, drug interactions or concomitant medical disorders such as viral illnesses, hepatic disease or surgery can all influence drug metabolism.

Plasma levels

In 1975, based in part from work by Prescott et al, Rumack and Matthew proposed a nomogram to determine the likelihood of developing hepatotoxicity based upon plasma paracetamol levels (Figure 1).

This nomogram has been extensively used in the following years. It is important to note that the nomogram was developed based on adult pharmacokinetic data and that the nomogram cannot be applied if the exact time of ingestion is unknown. Furthermore, the nomogram was based on actual data only up to

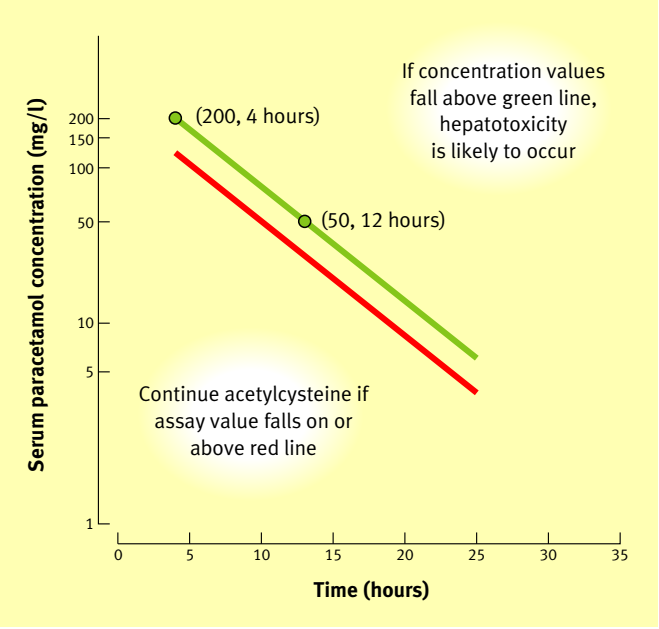

Figure 1 Plasma or serum acetaminophen concentration vs time post-acetaminophen ingestion. (Adapted from Rumack and Matthews, Pediatrics 1975; **55:** 871–876).

15 hours after ingestion. Beyond that period up to 24 hours post-ingestion, the nomogram was extrapolated. Another important consideration is that the nomogram is only valid for cases of acute ingestion and is not helpful for cases of repeated overdosages.

Nevertheless, there is evidence supporting the use of the nomogram to stratify hepatotoxic risk and guide treatment decisions. A study of more than 11,000 patients with paracetamol poisoning found that all deaths related to toxicity occurred in patients with plasma concentrations above the lower study protocol line although paediatric data or deaths were not specifically reported.

Clinical features

Paracetamol toxicity typically includes four phases of presentation.

Phase I

In the first 24 hours, the patient may be asymptomatic or experience anorexia, nausea, vomiting, malaise, pallor and diaphoresis. These symptoms may prompt further ingestion or administration of paracetamol.

Phase II

In phase II (24–48 hours after ingestion), the patient may be asymptomatic or may complain of right upper quadrant pain or tenderness. The patient may also exhibit liver enlargement and oliguria. Liver enzymes and bilirubin may be elevated and prothrombin time prolonged.

Phase III

Usually three to five days into the course of toxicity, anorexia, nausea, vomiting and malaise may appear. Signs of hepatic failure may now become prominent for example jaundice, hypoglycaemia, coagulopathy and encephalopathy. The patient can also develop renal failure and cardiac injury.

The National Poisons Information Service (Tel: 0844 892 0111) provides specialist advice on all aspects of poisoning day and night.

Phase IV

Between six days to two weeks into the presentation, the patient may recover or progressively deteriorate until death occurs usually from complete liver failure.

Toxicity may also present with other symptoms and signs such as central nervous system depression, shock, hypothermia, metabolic acidosis, hypoglycaemia, convulsions or pulmonary oedema. Rarely, acute renal failure may occur in the absence of fulminant hepatotoxicity.

Management

For a very common type of poisoning, evidence for how to treat patients with paracetamol poisoning is surprisingly weak. Furthermore, the great majority of available evidence has been obtained from research performed on adult patients.

In young children, the key risk assessment that is determining the actual dose or doses and time of dosing is difficult. This difficulty impacts heavily on treatment decisions. Nonetheless, the mainstay of treatment is using the antidote N-acetylcysteine when plasma levels exceed toxic levels as indicated by the nomogram. In remote areas, methionine by mouth can be given only when N-acetylcysteine is not available.

Several algorithms have been developed to guide treatment of patients presenting with paracetamol poisoning. The main guidelines are summarised here.

General

Resuscitation

In an isolated paracetamol overdose, immediate threats to the airway, breathing and circulation are rare. However, as mentioned earlier, massive overdosing, multiple supratherapeutic administration or poisoning complicated by coingestion or concominant disorders may present with altered level of consciousness or metabolic acidosis. Appropriate resuscitative and supportive measures should be undertaken. Altered level of consciousness would require prompt detection and correction of hypoglycaemia.

Investigations

Recommended investigations vary according to the time that has elapsed from ingestion of the paracetamol overdose. If ingestion was determined to have occurred within the previous four hours, a blood sample to determine the serum paracetamol concentration should be taken at four hours. If ingestion took place more than four hours prior to presentation, then a blood sample for the determination of the serum paracetamol concentration should be taken immediately. It is also suggested that plasma transaminase levels (ALT/AST) are obtained at this time although they are unlikely to be elevated.

If more than 24 hours have elapsed after ingestion or the time of ingestion could not be determined, serum paracetamol should be obtained as soon as possible. In addition, ALT/AST, INR/prothrombin time, creatinine and urea and blood glucose should be taken. Furthermore, if there are ominous signs such as altered consciousness, or when metabolic acidosis is suspected, an arterial blood gas may be required.

Specific measures

Prevention of absorption

Measures to prevent absorption only apply to adolescents and older children above 6 years of age if it can be determined that ingestion took place within one hour of presentation. Activated charcoal is typically used at a dose of 1 g/kg in adolescents. However, evidence on the efficacy of charcoal is weak. Furthermore it has not been determined that preventing absorption may translate into clinical benefit. Gastric lavage and syrup of ipecac are also sometimes used. All three agents, however, carry a risk of aspiration pneumonia. Some evidence suggests that serious adverse events are fewer with activated charcoal.

Significant hepatic injury after a single paracetamol overdose is extremely rare for children under 6 years of age, and plasma concentrations that require N-acetylcysteine treatment are very uncommon (Figure 2). Therefore, measures to prevent absorption are not indicated in them.

Antidotes

N-acetylcysteine N-acetylcysteine is a molecule composed of the amino acid L-cysteine with an acetyl molecule attached. L-cysteine is required for the production of glutathione in cells and controls the production rate. N-acetylcysteine therefore augments the production of glutathione and acts together with glutathione to directly bind with NAPQI.

No randomised trial has assessed the effect of N-acetylcysteine in the treatment of acute paracetamol overdose. The only randomised controlled trial that has shown N-acetylcysteine to be effective is in the setting of paracetamol-induced fulminant hepatic failure.

Nevertheless, pooled analysis of historical evidence has shown an overall decrease of mortality (from 6% to 0.7%) and hepatotoxicity (from 58% to 18%) in paracetamol poisoning since N-acetylcysteine was introduced.

N-acetylcysteine is administered by intravenous infusion in a dose of 150 mg/kg over 15 minutes. This is followed by 50 mg/kg over four hours and then subsequently 100 mg/kg over a 16 hour period. The dilution of N-acetylcysteine within specific amounts of 5% glucose solution is given in formularies such as the BNF for Children.

N-acetylcysteine carries the risk of anaphylactoid reactions and adverse events. Management is supportive with temporary halting or slowing of the infusion, and with anti-histamines.

Methionine Methionine is an essential amino acid and an intermediate in the biosynthesis of cysteine. It is thought to promote glutathione synthesis, thereby preventing hepatocellular damage by NAPQI.

As with N-acetylcysteine, there is little evidence for the efficacy of methionine in paracetamol poisoning. Two trials and one observational study suggest a hepatoprotective effect. Methionine is also thought to have a favourable adverse effect profile.

In the UK, methionine is only used in remote areas where N-acetylcysteine is not available, before the patient is transferred to a hospital for further assessment and treatment with N-acetylcysteine

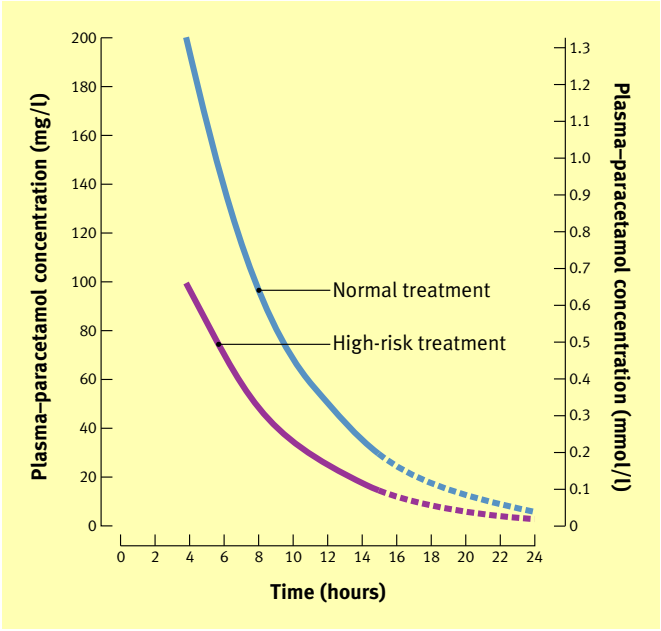

Figure 2 Patients whose plasma paracetamol concentrations are above the normal treatment line should be treated with acetylcysteine by intravenous infusion (or, if acetylcysteine cannot be used, with methionine by mouth, provided the overdose has been taken **within 10—12 hours** and the patient is not vomiting). Patients on enzyme-inducing drugs (e.g. carbamazepine, Phenobarbital, phenytoin, primidone, rifampicin, alcohol, and St John's wort), or who are malnourished (e.g. in anorexia, in alcoholism, or those who are HIV-positive), or underweight due to failure to thrive should be treated if their plasma-paracetamol concentration is above the **high-risk treatment line**. The prognostic accuracy after 15 hours is uncertain but a plasma paracetamol concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage. Graph reproduced courtesy of University of Wales College of Medicine Therapeutics and Toxicology Centre.

if required. The dose of methionine is 1 g four hourly´ four for children under the age of 6 years and 2.5 g four hourly´ four in children aged 6—18 years.

Acute ingestion The primary goal of treatment is to prevent or minimise hepatocellular injury. As previously mentioned the risk of this occurring is determined by the dose ingested and time elapsed before presentation. Any dose in excess of 150 mg/kg or where the ingested quantity is unknown should be treated as potentially toxic.

Ingestion within 1 hour of presentation: Activated charcoal can be administered for cooperative children older than 6 years. Serum paracetamol should then be measured at four hours after ingestion and plotted on the nomogram (Figure 2). N-acetylcysteine treatment is to be given if serum paracetamol is above the normal treatment line on the nomogram.

Ingestion less than 8 hours prior to presentation: Serum paracetamol at four hours of ingestion, or as soon thereafter, should be plotted on the nomogram (Figure 2). N-acetylcysteine treatment is to be given if serum paracetamol is above the normal treatment line on the nomogram.

Ingestion more than 8 hours prior to presentation N-acetylcysteine treatment should be started immediately, as its effectiveness declines sharply after eight hours. Once a serum paracetamol is obtained, it should be plotted on the nomogram. If the serum paracetamol level is below the treatment line *and* serum transaminases are normal, N-acetylcysteine can be stopped. Otherwise, N-acetylcysteine infusion should be continued.

Late presentation, especially 24 hours or more after ingestion is associated with a higher risk of hepatotoxicity. In this case, advice should be sought from the National Poisons Information Service or a specialist liver unit.

High-risk treatment line Children taking enzyme-inducing drugs (for example isoniazid, carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol and St John's Wort), who are malnourished (for example in anorexia, failure to thrive, HIV-positive, prolonged vomiting and diarrhoea, poorly controlled-diabetes) or who have existing hepatic disease may develop toxicity at lower serum paracetamol concentrations. These children should be treated with N-acetylcyteine if serum paracetamol is above the high-risk treatment line as seen on the nomograph.

Repeated supratherapeutic ingestion or when timing of ingestion is uncertain The criteria for repeated supratherapeutic ingestion is as follows:

Children under 6 years of age who have ingested:

- 200 mg/kg or more over a single 24-hour period
- 150 mg/kg or more per 24-hour period for the preceding 48 hours
- 100 mg/kg or more per 24-hour period for the preceding 72 hours or longer

Children over 6 years of age or older who have ingested:

- at least 10 g or 200 mg/kg (whichever is less) over a single 24-hour period
- at least 6 g or 150 mg/kg (whichever is less) per 24-hour period for the preceding 48 hours or longer.

For these cases, advice should be sought from the National Poisons Information Service or a specialist liver unit. Serum paracetamol levels are difficult to interpret in these cases and if there is any doubt, N-acetylcysteine treatment should be given.

Hepatotoxicity and when to refer

A specialist liver unit should be consulted when there are indicators of severe paracetamol poisoning or hepatotoxicity and liver failure. These indicators are as follows:

1. Prothrombin time more than 25 secs
2. Any grade of encephalopathy
3. Blood sugar less than 2.6 mmol/l
4. Creatinine more than 100 μmol/l
5. pH less than 7.35 in arterial blood.

Conclusions

Paracetamol poisoning is the most common poisoning presenting to health services. Young children with an acute ingestion appear less susceptible to toxicity. Older children who intentionally take overdoses, late presenters, children who have ingested multiple supratherapeutic doses, as well as children with comorbidities,

taking enzyme-inducers or are malnourished are more at risk of hepatocellular damage. Treatment with N-acetylcysteine aims to prevent or minimise hepatocellular damage and is given according to the nomogram in most cases. Advice is available at all hours from The National Poisons Information Service. ◆

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Clinical practice points

- Paracetamol poisoning is a common paediatric presentation
- Accurate history-taking is essential especially accurate times and sizes of overdoses
- Identify risk factors for hepatotoxicity eg any single dose exceeding 150 mg/kg, multiple supratherapeutic doses, intentional overdosing in older children, and late presentation
- The nomogram can be used to assess risk of hepatotoxicity after a single overdose
- The National Poisons Information Service is available at all hours to physicians
- Activated charcoal can be given to older children and adolescents to prevent absorption
- When hepatotoxicity is expected, IV N-acetylcysteine should be administered to minimise hepatocellular damage
- In remote areas where N-acetylcysteine is not available, oral methionine can be used for its hepatoprotective effect before transfer to a suitable hospital
- Severe cases may need referral to a liver unit for possible transplantation