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Paracetamol Poisoning

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Paracetamol Poisoning

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Introduction

Paracetamol is the most common antipyretic analgesic in use, and is freely available over-the-counter. In India, self-poisoning is underreported. However, unintentional poisoning is increasing with availability of several unregulated formulations in the market. Paracetamol poisoning may be due to accidental ingestion or intentional overdose.

Pharmacokinetics and Pathophysiology of Poisoning

Paracetamol is rapidly absorbed from small intestine. Most of drug from syrup formulations is absorbed within 15 minutes of ingestion. For the standard tablet forms, serum level peaks within 1–2 hours. Majority undergoes hepatic biotransformation. A minor fraction gets converted to highly reactive alkylating metabolite, which readily gets inactivated by glutathione reductase antioxidant system in liver. However, with paracetamol overdose, there is saturation of this pathway, and depletion of reduced glutathione. Thus, the alkylating metabolite accumulates and causes acute hepatic necrosis. Similar mechanism may lead to acute renal tubular necrosis as well.

Toxic Dose

- ☑ In children, the recommended maximum therapeutic dose is 90 mg/kg/day (15 mg/kg/dose, q 4 hourly). Acute toxicity is known to occur with single ingestion of immediate-release paracetamol >140 mg/kg. Toxic blood levels by ingesting paracetamol syrup are rare.
- ☑ Moreover, significant hepatic injury is rare among children under 6 years of age. Patients with blood paracetamol levels above the standard treatment line on the paracetamol overdose treatment nomogram have a poor prognosis, if left untreated.
- ☑ Among infants of 6–9 weeks, even lower doses (of 60–100 mg/kg/day) may cause hepatotoxicity.
- ☑ Repeated supratherapeutic doses can also lead to severe hepatotoxicity, especially with dosage only slightly above the current maximum recommended doses (i.e., >100 mg/kg/day).

Clinical Evaluation

History

- ☑ Intentional or accidental overdose.
- ☑ *Formulation*: Syrup, immediate-release, or sustained-release tablets.
- ☑ Exact brand name and drug-content of the tablet.
- ☑ Stated or likely dose taken with exact timing (err on the side of the worst case scenario, e.g., all tablets from the empty container have been ingested, no significant spillage/vomiting, one child has taken all the drug if multiple children were present, and possibility of an earlier ingestion time).
- ☑ Calculate the maximum possible dose per kg body-weight.
- ☑ Consider possibility of coingestion of other drugs, either accidental or deliberate.
- ☑ Underlying risk factors for increased hepatotoxicity [e.g., patients on anticonvulsant therapy (phenobarbitone and carbamazepine), acute illness, fasting, malnutrition, anorexia nervosa, viral hepatitis, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), and patients with Gilbert's syndrome or Crigler–Najjar syndrome].

Clinical Course of a Poisoned Child

- ☑ Symptoms usually develop after 24 hours of ingestion, and include nausea, vomiting, pallor, and sweating.
- ☑ Subsequently, right upper quadrant tenderness develops.
- ☑ In untreated patients, signs of hepatic failure usually develop after 48–72 hours and may include hypotension and encephalopathy.
- ☑ It is followed by signs of fulminant hepatic failure and coagulopathy.

Blood Paracetamol Levels and Paracetamol Overdose Treatment Nomogram

- ☑ A paracetamol overdose treatment nomogram was developed by joining 150 mg/L at 4 hours and 20 mg/L at 15 hours on a semilogarithmic plot **(Fig. 1)**. Blood paracetamol level plotted above the line on the nomogram is the best marker to indicate potential liver damage.
- ☑ Blood paracetamol level should be obtained at 4 hours after ingestion (or as soon as possible after 4 hours). Levels obtained within 4 hours of ingestion are of no clinical utility.

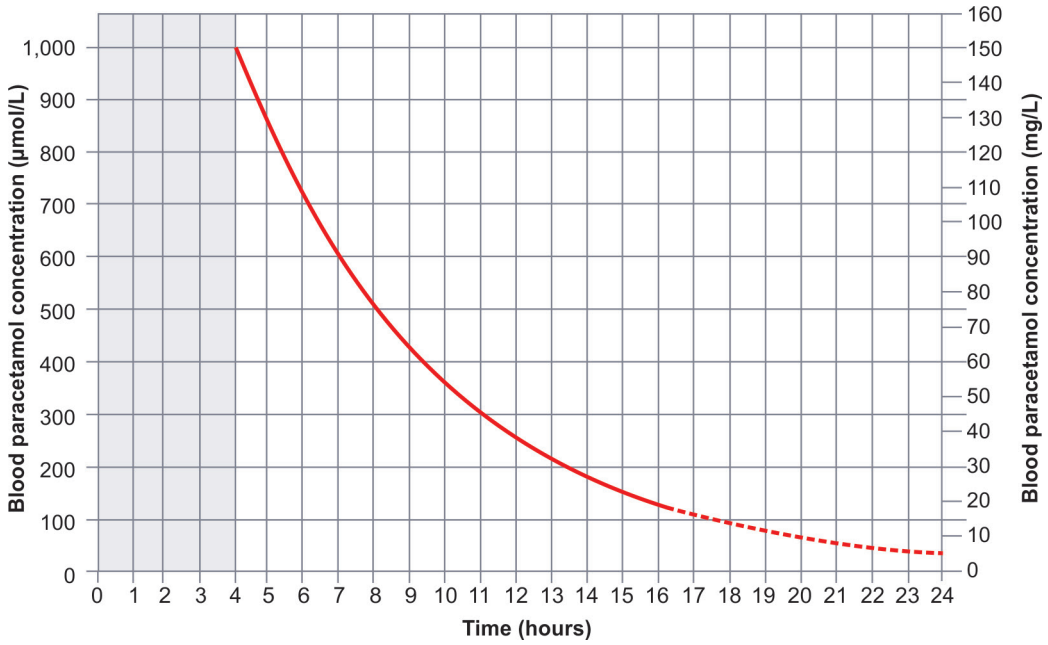


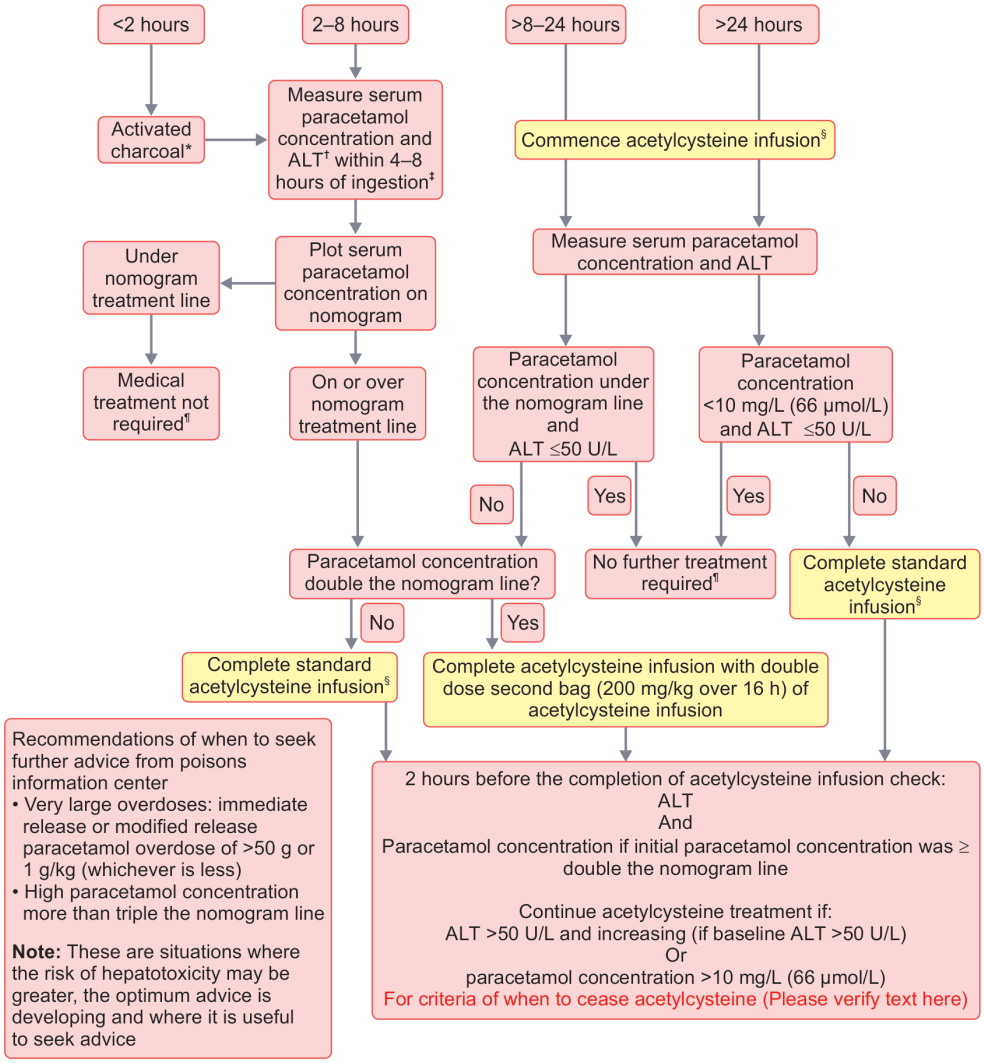
Fig. 1: Nomogram for acute single-dose immediate-release paracetamol poisoning.

Management

- ☑ *Gastric lavage* is useful within 1 hour of tablet consumption. It is of no clinical use if child has ingested syrup formulation. *Induced emesis* with ipecacuanha is not recommended.
- ☑ *Activated charcoal* may be effective within 1 hour of consumption of syrup, while within 2 hours of consumption of immediate-release tablets. Currently, this is the best available intervention to reduce gastrointestinal absorption. It should not be used if there is coingestion of a drug which may cause seizures or alteration of sensorium. Aspiration pneumonia, vomiting, loose stools, and ileus are possible side effects. There is no evidence for repeat administration.

N-acetylcysteine (NAC) infusion is used to prevent hepatotoxicity. Aim is to prevent acute liver failure, liver transplantation or death, with minimal adverse effects. Plotting blood paracetamol level obtained at or after 4 hours of ingestion on the nomogram helps in decision-making. Value above the line indicates need for NAC infusion, which is most effective when started within 8 hours of ingestion. Management algorithm is given in **Flowchart 1**.

Flowchart 1: Management algorithm for acute ingestion of immediate-release paracetamol tablets.



ALT = alanine aminotransferase.

*Cooperative adult patients who have potentially ingested ≥10 g or ≥200 mg/kg (whichever is less). For paracetamol ingestions ≥30 g, activated charcoal should be offered until 4 hours after ingestion.

†Baseline ALT measurement.

‡If paracetamol concentration will not be available until ≥8 hours after ingestion, commence acetylcysteine while awaiting paracetamol concentration.

§For acetylcysteine dosage, see Table 1.

¶Patients should be advised that if they develop abdominal pain, nausea or vomiting, further assessment is required. For patients in rural or remote regions where pathology services are not available.

Currently, a two-stage infusion of NAC over 20 hours is recommended **(Table 1)**.

1. *Stage 1*: 200 mg/kg over 4 hours, followed by
2. *Stage 2*: 100 mg/kg over 16 hours

The required dose of NAC should be diluted in 0.9/0.45% sodium chloride solution. 5% dextrose may also be used, but is not preferred due to risk of hyponatremia.

TABLE 1: Dose of N-acetylcysteine and dilution for children with different body-weights.

	Infusion Stage	***Dose of N-acetylcysteine***	***Dilute to make total volume in 0.9/0.45% sodium chloride***
1.	*For Infants with <10 kg body weight*		
	Stage–1	200 mg/kg	Total infusion volume 100 mL
	Stage–2	100 mg/kg	Total infusion volume 250 mL
2.	*For children with ≤20 kg body weight*		
	Stage–1	200 mg/kg	Total infusion volume 250 mL
	Stage–2	100 mg/kg	Total infusion volume 250 mL
3.	*For children with 20–40 kg body weight*		
	Stage–1	200 mg/kg	Total infusion volume 250 mL
	Stage–2	100 mg/kg	Total infusion volume 500 mL
4.	*Children or adolescents with >40 kg (Ceiling body weight, 110 kg)*		
	Stage–1	200 mg/kg	Total infusion volume 500 mL
	Stage–2	100 mg/kg	Total infusion volume 1000 mL

If NAC is required further, it should be continued at infusion rate of stage-2, i.e., 100 mg/kg over another 16 hours.

Massive paracetamol ingestions (more than double the height of line on the paracetamol overdose treatment nomogram following) may be treated with higher stage-2 infusion rates (i.e., 200 mg/kg over 16 hours).

For consultation, a clinical toxicologist, or the National Poison Information Center at All India Institute of medical Sciences (AIIMS), Delhi may be contacted. Contact details of the National Poison Information Center are 011-26589392, 011-26593677, 1800116117 (Toll-free).

Adverse Effects of N-acetylcysteine Infusion

Allergic reactions (flushing, urticaria, wheeze, angioedema, hypotension, and fever) are commonly reported but are rarely severe. These are dose-dependent, and usually occur during rapid administration of stage-1 infusion. Minor symptoms (flushing and urticaria) may be managed with hydrocortisone and/or promethazine and reducing the stage-1 infusion rate. However, more serious symptoms (angioedema, wheeze, and hypotension) require stoppage of infusion and symptomatic management. After an hour of subsidence of symptoms, infusion may be recommenced at half the previous rate, to be slowly increased to full rate over next 30 minutes.

Further Care

At 18 hours into the NAC infusion (2 hours before completion), blood should be sent for:

- ☑ Blood paracetamol level
- ☑ Liver and renal functions
- ☑ Electrolytes

N-acetylcysteine infusion should be stopped only if:

- ☑ Patient is clinically well
- ☑ Liver transaminases have reached their peak levels and are declining
- ☑ Renal functions and electrolytes are normal
- ☑ International normalized ratio (INR) <2, and
- ☑ Paracetamol level returned to <10 mg/L.

Liver transplantation may be considered with one or more of following:

- ☑ INR >3.0 at 48 hours OR >4.5 at any time
- ☑ Oliguria and/or creatinine >2.25 mg/dL (200 µmol/L)
- ☑ Persistent acidosis (pH <7.3) or arterial lactate >3 mmol/L
- ☑ Systolic hypotension despite resuscitation
- ☑ Encephalopathy (GCS <15), not associated with sedative coingestions
- ☑ Hypoglycemia
- ☑ Severe thrombocytopenia.

Discharge

- ☑ Majority of single pediatric accidental ingestions do not require treatment.
- ☑ Patient requiring NAC may be discharged after normalization of liver and renal functions.
- ☑ Parents should be educated about safe storage of drugs and supervision of children.
- ☑ In case of intentional overdose in an older child or adolescent, psychiatric consultation may be sought.

Further Reading

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