Paracetamol Poisoning
Toxicology

1 Introduction
Paracetamol is a readily available analgesic and is commonly taken in overdose. Untreated paracetamol toxicity can be fatal and is characterised by hepatotoxicity which can progress to fulminant hepatic failure. Fortunately an effective antidote is readily available and treatment within 8 hours of ingestion should prevent serious hepatic toxicity. Paracetamol is available in immediate and slow release preparations.

Toxicokinetics
• Paracetamol is rapidly absorbed with peak concentrations within 1-2h for the standard tablet formulation and within 30 min for liquid preparations. Peak concentrations are delayed over 12 hours and sometimes longer in slow release preparations.
• 20% of the ingested dose undergoes first pass metabolism.
• Volume of distribution is 0.9L/kg.
• Further metabolism occurs in the liver by biotransformation. 90% is metabolised to sulphate and glucuronide conjugates that are excreted in the urine. The remainder (less than 10%) is metabolised via cytochrome p450 (mainly 2E1 and 3A4) resulting in the highly reactive intermediary compound NAPQI. Normally this is immediately bound by intracellular glutathione and eliminated in the urine. In overdose, glutathione stores are overwhelmed and NAPQI binds to other proteins leading to toxic side effects. Any organ with P450 enzymes can suffer damage, particularly the liver and kidney, but also the heart and pancreas can be affected.
2 Risk Assessment

- An accurate history as to dose ingested and time since ingestion is crucial for risk assessment. Risk differs if there is an acute single ingestion compared to repeated supratherapeutic ingestion as illustrated in the box below.

<table>
<thead>
<tr>
<th>Table 1: Paracetamol dosing that may be associated with hepatic injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children over 6 years of age</td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>Acute single ingestion</strong></td>
</tr>
<tr>
<td>&gt; 200 mg/kg or 10 g (whichever is lower)</td>
</tr>
<tr>
<td>over a period of less than 8 hours</td>
</tr>
<tr>
<td><strong>Repeated Supratherapeutic Ingestion</strong></td>
</tr>
<tr>
<td>(RSI)</td>
</tr>
<tr>
<td>&gt; 200 mg/kg or 10 g (whichever is lower)</td>
</tr>
<tr>
<td>over a single 24-hour period</td>
</tr>
<tr>
<td>&gt; 150 mg/kg or 8 g (whichever is lower)</td>
</tr>
<tr>
<td>per 24-hour period for the preceding 48 hours</td>
</tr>
<tr>
<td>&gt; 100 mg/day or 4 g/day (whichever is lower)</td>
</tr>
<tr>
<td>per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury e.g. abdominal pain, nausea or vomiting</td>
</tr>
</tbody>
</table>

*NOTE: For obese children the weight used, should be based on an ideal body weight.*
Early presenters (within 8h)
- Perform a paracetamol level 4 hours (or as soon as possible afterwards) following ingestion.
- If a sustained release preparation has been taken, take a second level 4 hours after the initial level.
- Initial level can be taken after 2 hours for accidental liquid ingestions in children <6yo, however this will need to be repeated at the 4 hour mark if it is > 150mg/L. Please refer to MJA guideline for more detail.

Delayed presenters (after 8h or if ingestion time is unknown)
- If the dose ingested is associated with hepatic injury, or if there are clinical signs suggestive of toxicity such as vomiting, RUQ pain or tenderness, commence NAC.
- Perform a baseline ELFT and paracetamol level. Sustained release preparations will require a subsequent paracetamol level 4 hours after arrival.
- Only perform a coag profile if there are clinical signs of toxicity.
- Consider repeated supratherapeutic ingestions as a delayed presentation.
Clinical stages of Hepatotoxicity

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Symptoms</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nausea &amp; vomiting, abdominal pain, sweating, general discomfort, pale color</td>
<td>0-1</td>
</tr>
<tr>
<td>2</td>
<td>Liver injury develops, Upper right quadrant pain, Rise in liver function tests (ALT, AST, bilirubin, INR)</td>
<td>1-3</td>
</tr>
<tr>
<td>3</td>
<td>Hepatotoxicity peaks, Rapid &amp; severe hepatic failure, Encephalopathy &amp; hypoglycemia, Glucose, lactate, &amp; phosphate abnormalities</td>
<td>3-5</td>
</tr>
<tr>
<td>4</td>
<td>Recovery stage for those who survive stage 3</td>
<td>5-8</td>
</tr>
</tbody>
</table>

3 Management

Decontamination

- Single dose activated charcoal is recommended in the consenting patient who presents within 2 hours after immediate release ingestion and 4 hours following sustained release ingestion when the ingested dose may lead to hepatic injury (refer to table 1).

- If it is a massive ingestion, ie greater than 30g has been ingested, charcoal should be offered in patients presenting within 4 hours after massive immediate release ingestion and to all following massive sustained release ingestion.

Antidote

- **NAC dosing** See appendix for NAC prescribing

  - 1st bag: 200mg/kg of NAC in 500mL 5% glucose over 4 hours
  - 2nd bag: 100mg/kg of NAC in 1000mL 5% glucose over 16 hours

- In the case of massive ingestion, the 2nd bag should contain double the dose of NAC ie. 200mg/kg of NAC in 1000mL 5% glucose over 16 hours

- Given the requirement for repeated paracetamol levels in slow release preparation overdose, NAC should be commenced for potentially toxic ingestions (>200mg/kg or 10g) on arrival

Early presenters (within 8 h)

- NAC should be withheld until paracetamol level is available and risk plotted on the paracetamol nomogram
Delayed presenters (after 8h or if ingestion time is unknown)
  • if dose ingested is associated with hepatic injury, or if there are clinical signs suggestive of toxicity such as vomiting, RUQ pain or tenderness, commence NAC

Repeat paracetamol and LFTs are taken prior to the 16h NAC bag finishing to ensure the paracetamol level is falling, otherwise further NAC dosing is required. If continuation is required the 16h bag is repeated and bloods are again check prior to that bag finishing. This is particularly important for massive acute ingestions where absorption can be more variable due to pharmacobezoar formation.

Supportive Measures
  • These patients can be managed in the Short Stay Unit under the toxicology team while receiving their NAC infusion
  • Mental health review if required, should be sought during this time
  • These patients can have a full diet as tolerated
  • Antiemetics should be prescribed prn

4 Disposition

Paracetamol level below treatment line after 4 hours
Once the level is available and the patient is found to be below the treatment line, any NAC infusion can be ceased and the patient discharged from a toxicological perspective. Mental Health assessment should occur if it has not done so already. For slow release preparations you need both levels taken 4 hours apart to be beneath the nomogram line and falling.

Paracetamol level above treatment line
NAC infusion should be commenced if it has not already and the patient referred to the Toxicology Unit for a Short Stay Unit admission.

Established liver toxicity
All patients with established liver toxicity should be discussed with the toxicology unit for admission. Patients with established hepatotoxicity evidenced by;
  • INR > 3.0 at 48 hours or > 4.5 at any time
  • oliguria or creatinine > 200 mmol/L
  • persistent acidosis (pH < 7.3) or arterial lactate > 3 mmol/L
  • systolic hypotension with BP <80 mmHg, despite resuscitation
  • hypoglycaemia
  • severe thrombocytopenia
  • encephalopathy of any degree, or ALOC (GCS < 15) in the absence of sedatives.

require gastroenterology and ICU input for consideration of liver transplantation.
5 Additional Information

- Massive paracetamol ingestion (greater than 1g/kg) is associated with significant morbidity and mortality. They may be associated with early ALOC and lactic acidosis. Early discussion with the toxicology team is recommended.
- NAC is associated with a non IgE mediated anaphylaxis, manifested by rash, wheeze and mild hypotension. Temporary cessation or slowing of the infusion will resolve symptoms. Occasionally bronchodilators or antihistamines are required. Severe reactions are rare and should be treated along standard lines for anaphylaxis.
- Renotoxicity has a good prognosis and typically manifests as a reversible ATN.

6 Further reading


7 References

### Appendix A: Prescribing NAC

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose (Grams)</th>
<th>Volume to be removed from fluid bag (mls)</th>
<th>Dose (Grams)</th>
<th>Volume to be removed from fluid bag (mls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50kg or less</td>
<td>10g</td>
<td>50</td>
<td>5g</td>
<td>25</td>
</tr>
<tr>
<td>51-60kg</td>
<td>12g</td>
<td>60</td>
<td>6g</td>
<td>30</td>
</tr>
<tr>
<td>61-70kg</td>
<td>14g</td>
<td>70</td>
<td>7g</td>
<td>35</td>
</tr>
<tr>
<td>71-80kg</td>
<td>16g</td>
<td>80</td>
<td>8g</td>
<td>40</td>
</tr>
<tr>
<td>81-90kg</td>
<td>18g</td>
<td>90</td>
<td>9g</td>
<td>45</td>
</tr>
<tr>
<td>91-100kg</td>
<td>20g</td>
<td>100</td>
<td>10g</td>
<td>50</td>
</tr>
<tr>
<td>101-110kg</td>
<td>22g</td>
<td>110</td>
<td>11g</td>
<td>55</td>
</tr>
<tr>
<td>&gt;110kg</td>
<td>22g</td>
<td>110</td>
<td>11g</td>
<td>55</td>
</tr>
</tbody>
</table>

---

**Intravenous and Subcutaneous Fluid Order Form**

**Dr. Emergency**

1. **1/1/15**
   - **Volume**: 500ml N-Acetylcysteine to a total volume of 500ml in 5% glucose over 4 hours
   - **Rate**: 125 mL/hr
   - **Prescriber Signature**: Dr. Emergency

2. **1/1/15**
   - **Volume**: 100ml N-Acetylcysteine to a total volume of 100ml in 5% glucose over 16 hours
   - **Rate**: 62 mL/hr
   - **Prescriber Signature**: Dr. Emergency

---

*Note: Weight: 75 kg*