Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand

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Paracetamol poisoning is the commonest cause of severe acute liver injury in Western countries.1,2 It is also the most common reason for calls to Poisons Information Centres in Australia and New Zealand.3 Not only is it one of the commonest medications involved in deliberate self-poisoning, it is also involved in a large proportion of accidental paediatric exposures and in overdoses with therapeutic intent when taken for symptoms such as pain or fever (repeated supratherapeutic ingestions). Since the publication of the previous guidelines in the Medical Journal of Australia in 2015, further research has emerged, particularly regarding acetylcysteine regimens, massive paracetamol ingestions, and modified release paracetamol ingestion. These have led to a change in management of paracetamol poisoning, and the 2015 guidelines do not reflect the current practice recommended by clinical toxicologists. The key changes from the previous guidelines are acetylcysteine regimen (two-bag regimen) and dosage, management of patients taking large or massive overdoses, staggered ingestions, modified release paracetamol ingestions and repeated supratherapeutic ingestions. The full guidelines are available online in the Supporting Information.

Methods

The Treatment of Paracetamol Poisoning Writing Group was comprised of clinical toxicologists and pharmacologists from Australia and New Zealand. All members completed a detailed literature review and critically appraised existing evidence, including reviewing the relevant chapters from the newly updated Australian Therapeutic Guidelines — Toxicology and toxicology.4 Drafts of evidence-based recommendations, practice points and a background manuscript were developed. We conducted a face-to-face meeting in May 2019 to draft the guideline. Further revisions were made via email and teleconference. The summary recommendations follow the National Health and Medical Research Council levels of evidence (https://www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf) and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (www.gradeworkinggroup.org) to determine the strength of the recommendations.

Recommendations

Acute deliberate self-poisoning, accidental paediatric exposure and inadvertent repeated supratherapeutic ingestions all require specific approaches to risk assessment and management.

The initial approach focuses on risk assessment (Box 1). Key factors to consider for paracetamol poisoning are the formulation and dose ingested, time since ingestion, and serum paracetamol concentration (early), or clinical and laboratory features suggesting acute liver injury (late). Serum paracetamol concentration should be used to assess the need for acetylcysteine administration in all patients presenting with deliberate self-poisoning with paracetamol, regardless of the stated dose. The paracetamol treatment nomogram (Box 2) can only be used in acute immediate release paracetamol ingestions with a known time of ingestion.

We have summarised with flow charts the management of acute immediate release paracetamol ingestion (Box 3), acute modified release paracetamol ingestion (Box 4), repeated supratherapeutic ingestion (Box 5), and a management flow chart for rural and remote centres with limited pathology facilities (Box 6).

Acetylcysteine infusions

Acetylcysteine should be administered as a two-bag regimen (Box 7) — this has changed from previous guidelines. The standard three-bag intravenous weight-based dosage regimen (150 mg/kg body weight over 15–60 min, then 50 mg/kg over

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Immediate release paracetamol ingestion

The management of acute immediate release paracetamol ingestion — defined as any intentional or deliberate self-poisoning — is summarised in Box 3.

Recommendations on gastric decontamination have not changed since 2015. Fifty grams of activated charcoal should be administered to a cooperative, awake adult if they present within 2 hours of ingestion of a toxic dose (Box 1) of immediate release paracetamol, or within 4 hours of immediate release paracetamol overdoses greater than 30 g.13–15 GRADE: Strong; Evidence: Low.

The paracetamol treatment nomogram has been validated as an excellent predictor of risk but only for acute ingestions of immediate release paracetamol with a known time of ingestion. The current nomogram used in Australia and New Zealand has not changed (Box 3), except the units on the left and right axis have now been swapped. It is important to check the units used, with many laboratories recently changing from μmol/L (right axis) to mg/L (left axis). GRADE: Strong; Evidence: Strong.

Patients with a high initial paracetamol concentration (greater than double the nomogram line) are at increased risk of acute liver injury if given standard acetylcysteine regimens.13,16,17 Only a small percentage of paracetamol overdoses will have a paracetamol concentration greater than double the nomogram line and they typically have ingested 30 g or more of paracetamol. Those with an initial paracetamol concentration greater than double the nomogram line may benefit from an increased dose of acetylcysteine.13 The second bag in the two-bag acetylcysteine regimen should be doubled to 200 mg/kg intravenous acetylcysteine over 16 hours (instead of 100 mg/kg over 16 h). Patients with even higher concentrations (eg, ≥ triple the nomogram line) may benefit from even higher acetylcysteine doses.3,18 These patients should be discussed with a clinical toxicologist or a Poisons Information Centre. GRADE: Strong; Evidence: Low.

Near the completion of acetylcysteine (ie, 2 h before completion of the infusion), alanine aminotransferase (ALT) should be repeated in all patients. For patients with an initial paracetamol level greater than double the nomogram line, a paracetamol concentration should also be repeated. Acetylcysteine should be continued if the paracetamol concentration is greater than 10 mg/L (66 μmol/L) or ALT is elevated (> 50 U/L) and increasing (if baseline ALT > 50 U/L). The normal reference range for ALT varies between pathology laboratories and with patient age; an elevated ALT greater than 50 U/L is considered significant. Small fluctuations in ALT (eg, ± 10%) are common and do not on their own indicate the need for ongoing acetylcysteine. ALT should be repeated in all cases as there is a small (< 1%) risk of developing acute liver injury despite treatment with acetylcysteine within 8 hours.5,17,19,20 GRADE: Strong; Evidence: Low.

Multiple or staggered immediate release paracetamol ingestions

Any multiple or staggered paracetamol ingestions over more than 2 hours for the purpose of deliberate self-harm are distinct from repeated supratherapeutic ingestions, which are ingestions of excessive paracetamol for therapeutic purposes (Box 5). Staggered ingestions should be treated as per acute immediate release paracetamol ingestion (Box 3) using the earliest time of ingestion for the paracetamol nomogram. Hence, if it is more than 8 hours since the first dose of paracetamol or the paracetamol concentration cannot be obtained within 8 hours, then commence treatment with acetylcysteine. If the first paracetamol concentration was measured within 2 hours of the last ingested paracetamol dose, it should be repeated after 2 hours to ensure there is no ongoing absorption. If either concentration
3 Acute immediate release paracetamol ingestion management flow chart

**Guideline summary**

- **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 Box 7.
- 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, see Box 6.

**Flow Chart Details**

1. **< 2 hours**
   - Activated charcoal*

2. **2–8 hours**
   - Measure serum paracetamol concentration and ALT† within 4–8 hours of ingestion‡
   - Plot serum paracetamol concentration on nomogram
   - Under nomogram treatment line

3. **> 8–24 hours**
   - Commence acetylcysteine infusion§
   - Measure serum paracetamol concentration and ALT
   - Paracetamol concentration under the nomogram line and ALT ≤ 50 U/L
   - Yes
   - Paracetamol concentration <10 mg/L (66 μmol/L) and ALT ≤ 50 U/L
   - Yes
   - Paracetamol concentration double the nomogram line?
   - No
   - Yes
   - Complete standard acetylcysteine infusion
   - Complete acetylcysteine infusion with double dose second bag (200 mg/kg over 16 h) of acetylcysteine infusion

**Recommendations of when to seek further advice from Poisons Information Centre**

- Very large overdoses: immediate release or modified release paracetamol overdoses of > 50 g or 1 g/kg (whichever is less)
- High paracetamol concentration more than triple the nomogram line

**Note:** These are situations where the risk of hepatotoxicity may be greater, the optimum advice is developing and where it is useful to seek advice.

2 hours before the completion of acetylcysteine infusion check:
- ALT
- Paracetamol concentration if initial paracetamol concentration was ≥ double the nomogram line

Continue acetylcysteine treatment if:
- ALT > 50 U/L and increasing (if baseline ALT > 50 U/L)
- Or
- Paracetamol concentration > 10 mg/L (66 μmol/L)

For criteria of when to cease acetylcysteine see Box 8.
4 Acute ingestion modified release paracetamol management flow chart

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR paracetamol ingestion ≥ 10 g or ≥ 200 mg/kg (whichever is less)</td>
<td>≤ 4 hours</td>
</tr>
<tr>
<td>≥ 4 hours</td>
<td>Commence acetylcysteine infusion*</td>
</tr>
<tr>
<td></td>
<td>Measure two paracetamol concentrations at least 4 hours after ingestion and 4 hours apart</td>
</tr>
<tr>
<td></td>
<td>Either paracetamol concentration over nomogram treatment line</td>
</tr>
<tr>
<td></td>
<td>No further investigations required*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Either paracetamol concentration more than double the nomogram line?</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

ALT and paracetamol concentrations are required in all patients before ceasing acetylcysteine infusion

Continue acetylcysteine treatment if:
- Paracetamol concentration > 10 mg/L (66 μmol/L), or
- ALT > 50 U/L and increasing (if baseline ALT > 50 U/L)

For criteria of when to cease acetylcysteine, see Box 8

Recommendations of when to seek further advice from Poisons Information Centre
- Very large overdoses: modified release paracetamol overdose of > 50 g or 1 g/kg (whichever is less)
- High paracetamol concentration, more than triple the nomogram line
- Serial paracetamol concentrations remain unchanged or increasing

These are situations where the risk of hepatotoxicity may be greater, the optimum advice is developing and where it is useful to seek advice

ALT = alanine aminotransferase; MR = modified release. * Patients should be advised that if they develop abdominal pain, nausea or vomiting, further assessment is required. † If paracetamol concentration is static or rising, a repeat dose of activated charcoal may be beneficial; please seek further advice. ‡ For acetylcysteine dosage, see Box 7.
Modified release paracetamol ingestions

Modified release paracetamol contains 69% modified release and 31% immediate release paracetamol in a 665 mg tablet. In the previous guidelines, management was very similar to that for immediate release paracetamol. However, evidence from case series from Australia and Europe has shown that this approach appears inadequate. Patients developed acute liver injury despite standard treatment such as early acetylcysteine and decontamination. Therefore, the recommended management has changed considerably (Box 4). All modified release paracetamol overdoses (including mixed ingestion of immediate and modified release paracetamol) of 10 g or more or 200 mg/kg or more (whichever is less) should be offered activated charcoal up to 4 hours after ingestion. For massive modified release paracetamol overdoses (≥ 30 g or ≥ 500 mg/kg), absorption may continue up to 24 hours after ingestion; patients may benefit from activated charcoal beyond 4 hours.21

The nomogram should not be used to assess the need for treatment of potentially toxic modified release paracetamol ingestions. Paracetamol concentrations are useful to guide further management such as acetylcysteine dosage (eg, the need for increased or prolonged treatment) and the need for further decontamination (eg, further doses of activated charcoal if paracetamol concentrations remain unchanged or rise). Importantly, all patients who ingest 10 g or more or 200 mg/kg or more (whichever is less) of paracetamol should immediately commence treatment with acetylcysteine (Box 4) and receive a full 20-hour course of acetylcysteine regardless of their serum paracetamol concentration.

All patients who ingest 30 g or more or 500 mg/kg or more of modified release paracetamol or have a paracetamol concentration greater than double the nomogram line should receive an increased dose of acetylcysteine.21 The second bag in the current standard intravenous acetylcysteine regimen should be doubled to 200 mg/kg intravenous acetylcysteine over 16 hours. This is because the majority of the preparation is modified release and initial paracetamol concentrations may only reflect the immediate release component of the preparation. Hence, following large modified release paracetamol ingestions, acetylcysteine doses may be inadequate due to ongoing paracetamol absorption. Patients who report ingesting less than a toxic dose (< 10 g and < 200 mg/kg) should have two serum paracetamol concentrations 4 hours apart, starting at least 4 hours after ingestion. If either is above the nomogram line, a standard course of acetylcysteine should be given.

Acetylcysteine is often required for much longer durations. ALT and a paracetamol concentration should be checked near the completion of the second bag of acetylcysteine. Acetylcysteine should be continued if ALT is elevated (> 50 U/L) and increasing (if baseline ALT > 50 U/L) or if the paracetamol concentration is 10 mg/L or over (66 μmol/L). Higher doses of acetylcysteine may be required in subsequent infusions if the paracetamol concentration remains 100 mg/L or over (> 660 μmol/L) and further advice should be sought. GRADE: Strong; Evidence: Very low.

Rural and remote centres

Many rural and remote health care facilities do not have access to 24-hour pathology or have very limited pathology services (eg, point of care testing only). These facilities can still manage certain acute paracetamol poisoning cases, provided acetylcysteine is available and the patient is not at high risk of developing acute liver injury. Box 6 outlines the management of acute immediate release paracetamol ingestion for rural and remote facilities and

is above the nomogram line (using time from the earliest ingestion), start or continue treatment with acetylcysteine. GRADE: Weak; Evidence: Very low.
Paediatric liquid paracetamol ingestion

These recommendations are unchanged from the 2015 guidelines. In children under 6 years of age where ingestion of more than 200 mg/kg of liquid paracetamol is suspected, a serum paracetamol concentration should be measured at least 2 hours after ingestion. If the 2–4-hour concentration is below 150 mg/L (1000 μmol/L), acetylcysteine is not required. If the 2-hour paracetamol concentration is greater than 150 mg/L (1000 μmol/L), this should be repeated 4 hours after ingestion and acetylcysteine commenced if this is 150 mg/L or more (1000 μmol/L).

A 2-hour concentration should only be used in a well child under 6 years of age with isolated liquid paracetamol ingestion. In all other cases, a 4-hour concentration should be performed. Further, for children who present later than 4 hours after ingestion or in children older than 6 years of age, treatment is as per the adult acute paracetamol exposure guideline. GRADE: Strong; Evidence: Very low.

Repeated supratherapeutic ingestion

Patients who ingest excessive paracetamol for a therapeutic purpose (eg, pain, viral illness) or ingest therapeutic doses of paracetamol and have symptoms of acute liver injury (eg, abdominal pain, nausea and vomiting) are managed as per repeated supratherapeutic ingestion (Box 5). If the ingestion is deliberate or intentional, they should be managed as per acute intentional ingestion. There is little evidence to guide risk assessment for repeated ingestion of high doses of paracetamol. The margin of safety has for many years been assumed to be high. Minor subclinical elevations of serum ALT are quite common with prolonged therapy. Hepatotoxicity has been reported at doses within the therapeutic range of paracetamol (in some cases at doses less than the recommended 4 g/day). The reasons why certain individuals are at greater risk of toxicity are unclear, but toxicity could be
Cessation of acetylcysteine

Some patients will require ongoing treatment with acetylcysteine if they have a persistently high paracetamol concentration greater than 10 mg/L (66 μmol/L) or ALT greater than 50 U/L and increasing (if baseline ALT > 50 U/L) — small fluctuations in ALT (eg, ± 20 U/L or ± 10%) are common and do not on their own indicate the need for ongoing acetylcysteine. All patients with an initial ALT greater than 1000 U/L should receive at least a full 20-hour course of intravenous acetylcysteine. GRADE: Strong; Evidence: Very low.

Seeking advice from a Poisons Information Centre

It is recommended to seek advice from a Poisons Information Centre in the following situations:

- INR greater than 3.0 at 48 hours or greater than 4.5 at any time;
- oliguria or creatinine greater than 200 μmol/L;
- persistent acidosis (pH < 7.3) or arterial lactate greater than 3 mmol/L;
- systolic hypotension with blood pressure below 80 mmHg, despite resuscitation;
- hypoglycaemia, severe thrombocytopenia, or encephalopathy of any degree; or
- any alteration of consciousness (Glasgow Coma Score < 15) not associated with sedative co-ingestions.

Do not give clotting factors unless the patient is bleeding or after discussion with a liver transplant unit. GRADE: Strong; Evidence: Strong.

Hepatotoxicity and subsequent liver failure

Only a small proportion of patients develop hepatotoxicity (ALT > 1000 U/L). Early symptoms include nausea, vomiting, abdominal pain, and right upper quadrant tenderness. Of these, only a minority will develop fulminant hepatic failure, and most patients recover fully with standard treatments. Typically, in patients with paracetamol-induced acute liver injury, ALT and AST will rise for 3–4 days before recovering. Acetylcysteine is continued until the criteria in Box 8 are met. Investigations that monitor liver function and guide prognosis should be performed regularly in all patients with hepatotoxicity, including electrolytes, urea, creatinine, liver function tests, INR, blood sugar, phosphate, and venous blood gas (looking at the pH and lactate levels).

A liver transplant unit should be consulted if any of the following criteria are met:

- INR > 2.0;
- patient is clinically well

And

- For modified release ingestions and patients with an initial paracetamol concentration greater than double the nomogram line, paracetamol concentration < 10 mg/L (66 μmol/L)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalised ratio.
• very large overdoses — immediate release or modified release paracetamol overdoses of 50 g or over or 1 g/kg (whichever is less);  
• high paracetamol concentration, more than three times the nomogram line;  
• intravenous paracetamol errors or overdoses, as the treatment threshold is lower;  
• patients with hepatotoxicity (ie, ALT > 1000 IU/L); and  
• neonatal paracetamol poisonings.

These are situations where the risk of hepatotoxicity and complications is greater, where the optimum advice is potentially changing, and where it may be most useful to seek advice.

Conclusion

This is a summary of the updated guidelines for the management of paracetamol poisoning in Australia and New Zealand, for more detailed information please access the full guidelines, available in the online Supporting Information.

If there are any concerns regarding the management of paracetamol ingestion, advice can always be sought from a clinical toxicologist or a Poisons Information Centre (dialling 131126, in Australia, or 0800 764766, in New Zealand).

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This article is a summary of the full guidelines, available online in the Supporting Information.

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Supporting Information

Additional Supporting Information is included with the online version of this article.