Version 2.4

Paracetamol (Acetaminophen, APAP)

8/09/2015

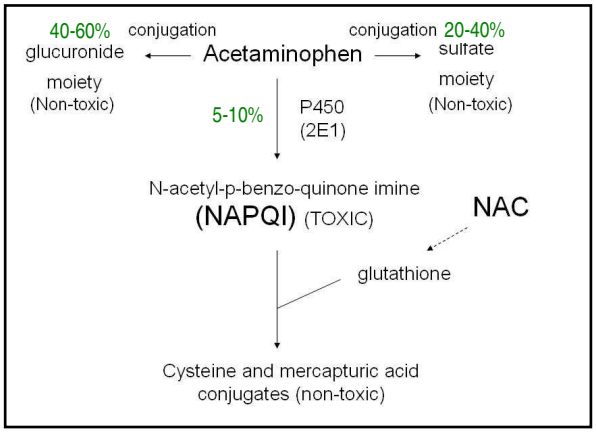
Overview/Risk assessment

Most commonly used OTC analgesic & also most common OD leading to hospital presentation & admission. Paediatric accidental overdose is also common. Hepatic failure & death are uncommon and preventable by early management with NAC. Acute, staggered, repeated supratherapeutic, paediatric and extended-release preparation ingestions all require different strategies. Risk Assessment is based on dose, time to presentation, investigation results, and clinical features.

Toxicokinetics

Rapid oral abs with peak levels at 1-2hrs for tablets (30mins for elixir). Extended release preparations may be absorbed over 12hrs or longer in OD esp if pharmacobezoars form. VD is 0.9-1L/kg. 20% is met by gut wall, rest by the liver by conjugation & cytochrome P450 (chiefly 2E1 and 3A4) [see below]. Elim. $T_{\frac{1}{2}}$=~2hrs, but may reach ≥4hrs in OD where ↑$T_{\frac{1}{2}}$ reflects saturation of conjugation & more P450 metabolism.

Toxic mechanism



In OD, SO_4^{2-} conjugation can become saturated & ↑NAPQI depletes glutathione stores. If ~<30% normal, NAPQI can bind to cell proteins → Zone 3 centrilobular liver necrosis ± renal or myocardial injury. Low levels of glutathione may expose cell to other oxidative damage. NAC is a glutathione & SO_4^{2-} source. Potential ↑toxicity if on specific CYP2E1 inducers (chronic EtOH, rifampin, isoniazid, carbamazepine but **not** phenytoin nor phenobarbital), or pre-existing low glutathione stores (genetic variation, malnutrition, HIV+ve, and EtOH-related or other liver disease) – but CYP2E1 production may also be reduced too, negating this. Young children have ↓toxicity (?↑SO_4^{2-} conjugation capacity, ↑detox of NAPQI or ↑glutathione).

Clinical features

Split into 4 clinical phases:

1. *<1 day* - Asymptomatic, anorexia, nausea, vomiting (esp. large overdose or children), malaise, pallor, diaphoresis. *(NB caution with **ondansetron** as may ↑liver injury)*
2. *1-3 days* - Resolving Phase 1 symptoms, RUQ abdominal pain, elevated transaminases/INR
3. *3-4 days* - Peak hepatic enzyme (AST>10,000, ALT>100x normal), jaundice, nausea and vomiting, oliguria, metabolic acidosis, coagulopathy, encephalopathy
4. *4-21 days* - Either resolution in 1- 3 weeks, or progressive liver +/- renal failure

Investigations

Screening: BSL & ECG should be performed.
Specific: Serum APAP level/s & LFTs. Rarely avail APAP-cysteine adduct level is marker for sev.
Other tests: INR, UEC, glucose, ABG may be indicated if toxic or presenting>24hrs post-OD.

Risk factors for acute liver failure (ALF) & referral to specialist unit:

- INR>3.0 at 48hr or >4.5 at any time
- pH<7.3 or lac>3 post resus
- BPsys<80mmHg
- Oliguria or Cr>200micromol/L
- Encephalopathy or GCS<15
- ↓↓Plts or ↓BSL

Kings College Hospital (O'Grady) Criteria for liver transplantation in paracetamol-induced ALF:

- Arterial pH <7.30 post-resus OR
- PT>100s (or INR>6.5), Cr>300micromol/L and Grade III/IV encephalopathy OR
- Arterial lactate>3.5 at 4hrs or >3.0 at 12hrs (Bernal modification)

Guidelines for the management of paracetamol overdose

Adapted from Daly FFS, Fountain JS, Murray L, Graudins A, Buckley NA. Guidelines for the management of paracetamol poisoning in Australia and New Zealand. MJA. 2008;188:296–301
And Chiew AL, Fountain JS, Graudins A, et al. Summary statement. New guidelines for the management of paracetamol poisoning in Australia and New Zealand. MJA. 7 September 2015;203(5):215-18

- In **accidental** overdose where the amount ingested is accurately known, if the dose is less than the thresholds in Table 1 below then serum paracetamol levels, LFTs or follow-up are not required.

1 Paracetamol dosing that may be associated with hepatic injury

	Adults and children > 6 years of age	Children (aged 0–6 years)*
Acute single ingestion	> 200 mg/kg or 10 g (whichever is lower) over a period of <8 hours	> 200 mg/kg over a period of < 8 hours
Repeated supratherapeutic ingestion	> 200 mg/kg or 10 g (whichever is lower) over a single 24-hour period	> 200 mg/kg over a single 24-hour period
	> 150 mg/kg or 6 g (whichever is lower) per 24-hour period for the preceding 48 hours	> 150 mg/kg per 24-hour period for the preceding 48 hours
	> 100 mg/day or 4 g/day (whichever is lower) per 24-hour period, for more than 48 hours in those who also have symptoms indicating possible liver injury (eg, abdominal pain, nausea or vomiting)	> 100 mg/kg per 24-hour period for more than 48 hours

* For obese children, the body weight used for calculations should be an ideal body weight. ◆

- Predisposing risk factors: chronic EtOH abuse, P450 inducers, low glutathione reserves, liver disease.
- All patients with **deliberate** self-poisoning, or when an accidental dose cannot be estimated, require a serum paracetamol level to refine the risk of hepatic injury and requirement for the antidote N-acetylcysteine.
- Decontamination with charcoal only indicated in patients >6 years, who present within 2h of a toxic dose of immediate-release paracetamol (4h if modified-release paracetamol, ?≥4h if >30g) and are co-operative.

Acute Ingestion

Follow flow-chart on right:

Applies to:

- All deliberate single overdoses
- All accidental single overdoses above thresholds

Staggered Overdose

If doses taken within the last 8 hours,

- Follow 1-8 hours path in flow-chart
- Interpret the level as if all doses were taken at the earliest dose time

If >8 hours since the first dose,

- Follow >8 hours path in flow-chart

Unknown Time of Overdose

If detectable paracetamol level:

- Commence NAC and treat the patient as per the end of the >8 hours scenario (i.e. at † on the flow-chart)

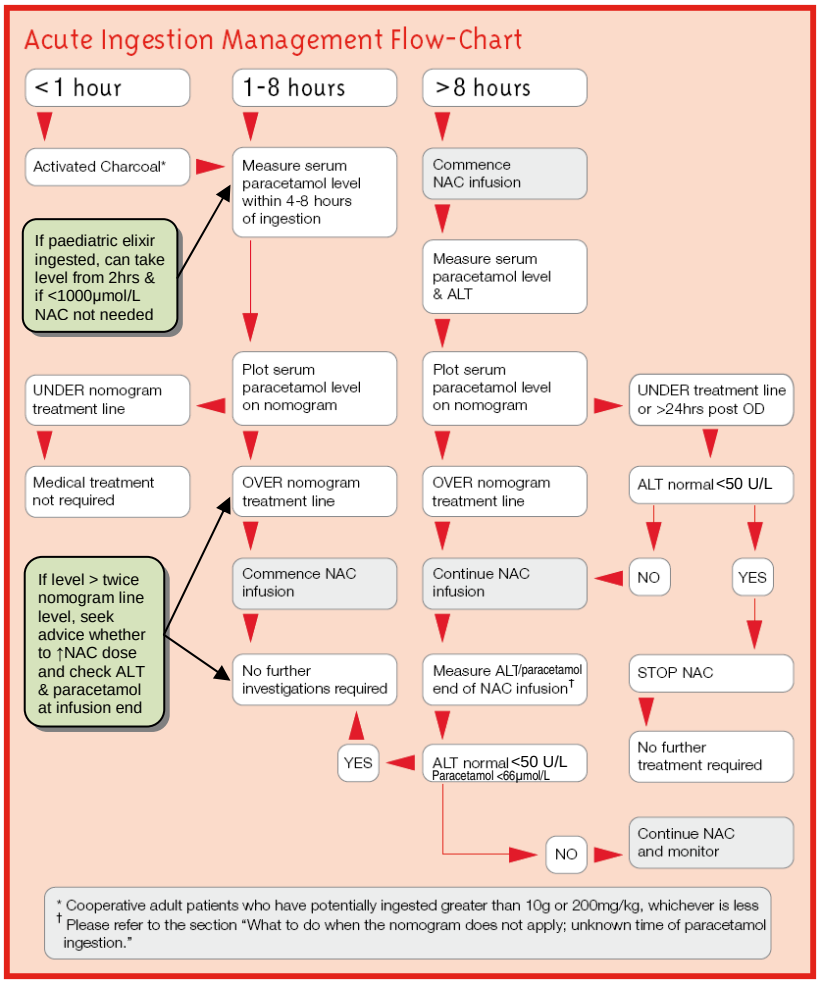
Modified-Release Paracetamol

665mg tabs (31% IR, 69% SR)

If >10g or >200mg/kg ingested start NAC.

Measure paracetamol level in all at ≥4h post-ingestion **and** at 4h later.

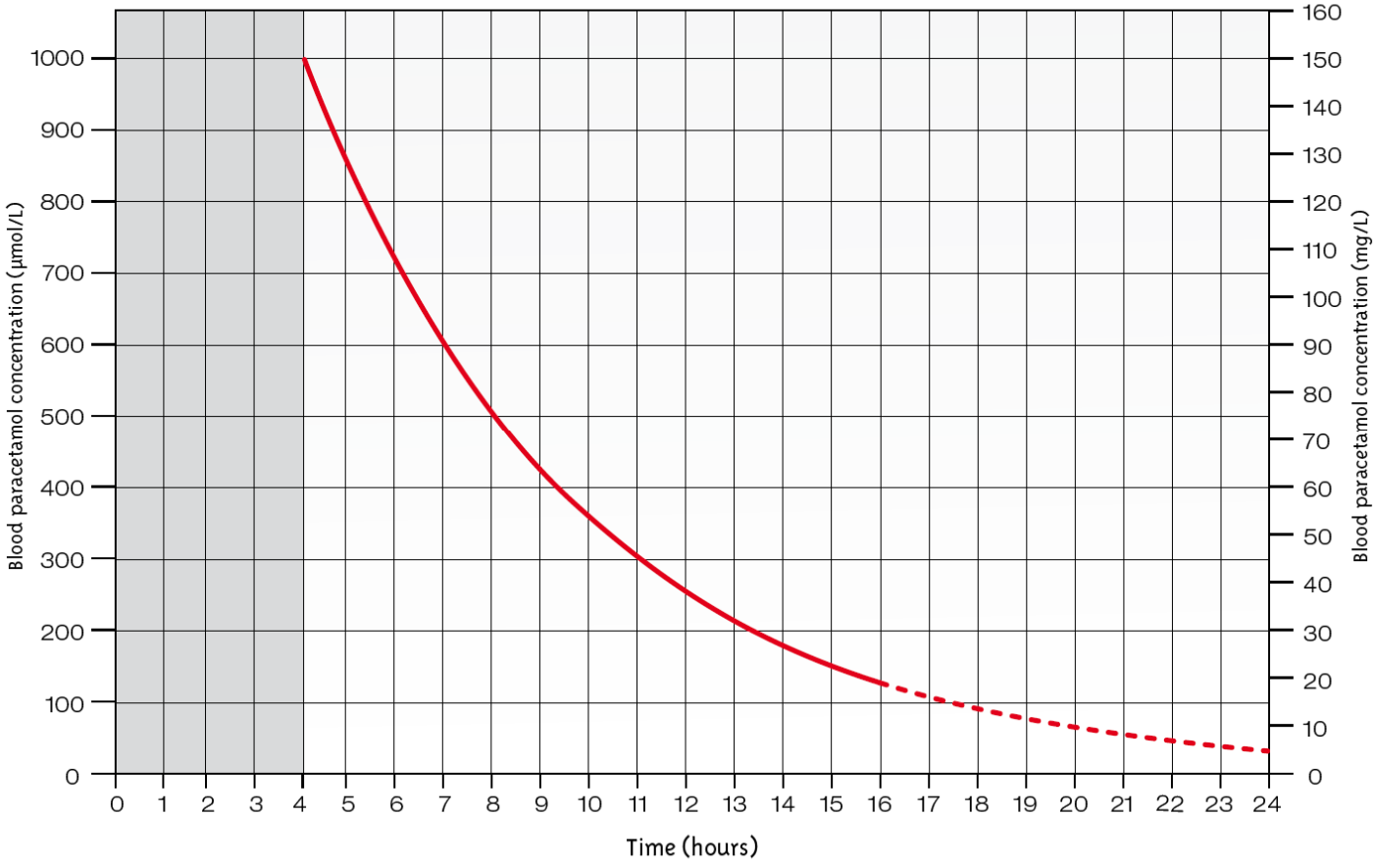
If levels not both below nomogram line and decreasing OR if the bloods 2h before end of NAC infusion show ALT is increasing (>50 U/L) or the paracetamol level >66 mmol/L then continue NAC.



IV Paracetamol (not covered in MJA article so only local guidelines available with little evidence backing)

Nomogram invalid (early peak at 100% bioavail). Suggested Mx: treat with NAC if>100mg/kg or 4h level>660µmol/L.

Paracetamol Treatment Nomogram



Adapted from Rumack and Mathew
(Smilkstein et al. Ann Emerg Med 1991; 20: 1058-63)

Repeated Supertherapeutic Ingestion

Manage as per the flow-chart on the right: Threshold criteria are in Table 1 above.

N-Acetylcysteine (NAC)

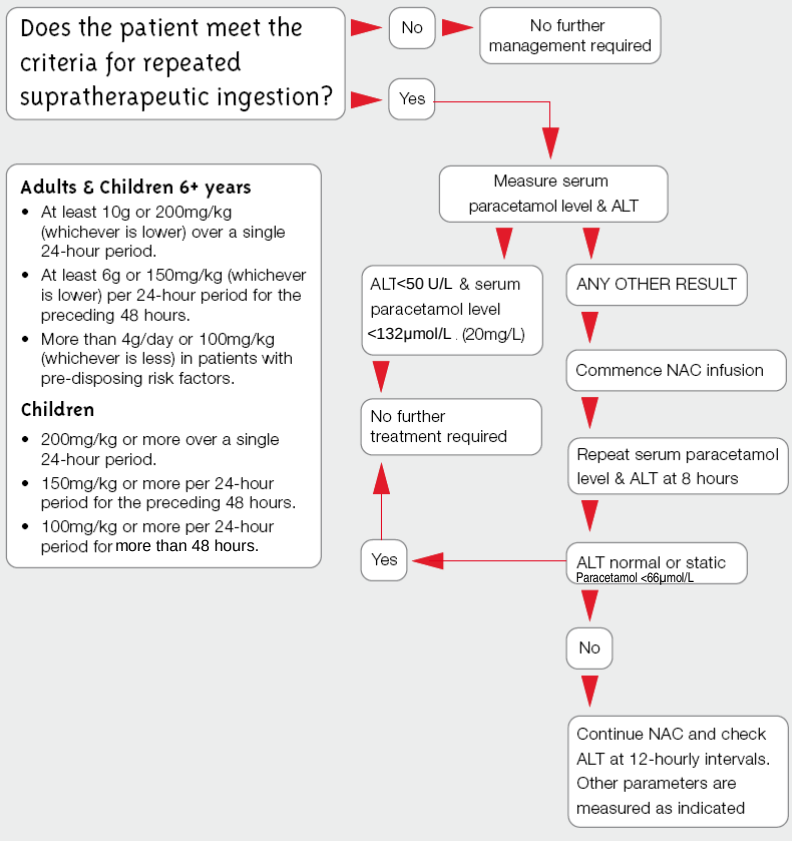
NAC (glutathione precursor & sulphydryl group source, also antioxidant) prevents mortality if given <8hrs & improves prognosis if given at any time following overdose.

If hepatotoxicity occurs do q12h bloods & continue NAC at 150mg/kg/24h (same rate as last bag) until patient improving, ALT falling, INR<2 and paracetamol<66µmmol/L.

In large OD with ↑$T_{\frac{1}{2}}$ usual IV regimen may not supply enough NAC for long enough. Doubling dose in 3rd bag & rpt suggested, but little evidence. Dialysis may be alternative in massive (>1g/kg) OD, esp if RF.

NAC is usually well tolerated but anaphylactoid reactions (rash, bronchospasm, & rarely ↓BP) can occur during the initial infusions. If this happens, stop infusion, consider antihistamines and, when resolved, restart at a reduced rate and slowly titrate back up.

Repeated Supratherapeutic Ingestion Management Flow-Chart



NAC Dosing

Give 150mg/kg over 15min, then 50mg/kg 4hr & finally 100mg/kg over 16hr. All in 5% dextrose. Volumes for children <20kg are 3ml/kg, 7ml/kg & 14ml/kg, for children >20kg are 100,250 & 500ml and for children>50kg or adults the volumes are 200, 500 & 1000ml respectively.