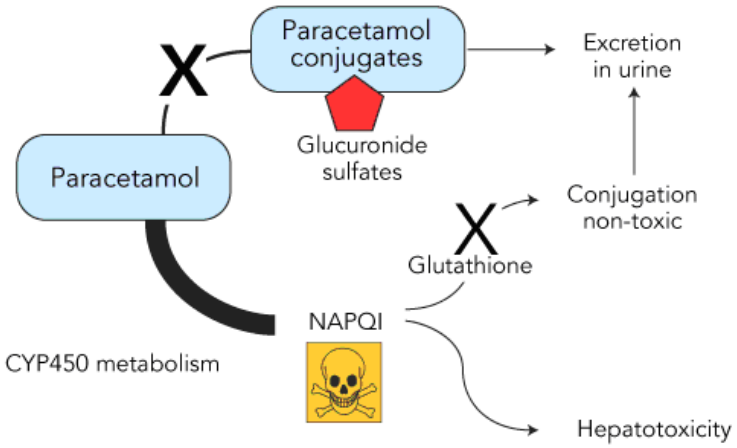
# TOXICOLOGY

## PARACETAMOL POISONING

### Pharmacokinetics and Mechanism of Toxicity




Peak serum concentration: 4 hours.

Half life: 2-4 hours but longer in overdose.

90% conjugated with sulphate or glucuronide and excreted in urine.

2% excreted unchanged in urine.

The remainder is metabolised to NAPQI by cytochrome P450 enzymes.

**N-acetyl-p-benzoquinoneimine** (NAPQI) is a metabolite of paracetamol which irreversibly binds to cysteine groups on hepatic molecules and causes **hepatocellular centrilobular necrosis** through oxidative injury. Normally NAPQI is quickly bound to hepatic **glutathione** to form non-toxic compounds which are then excreted in the urine.

In overdose the sulphation and glucuronidation pathways become saturated and more paracetamol is metabolised by the cytochrome P450 enzymes. This produces more NAPQI and **glutathione becomes depleted**. Unbound NAPQI then causes acute hepatic injury.

### Clinical Features

| Clinical Features | Stage I (0-24 hours) | Stage II (1-3 days) | Stage III (3-4 days) | Stage IV (4 days - 6 weeks) |
|---|---|---|---|---|
| **Symptoms** | N&V, lethargy or asymptomatic | RUQ pain | Confusion | Recovery (4-7 days usually) |
| **Signs** | | Hepatomegaly and RUQ tenderness | Jaundice, encephalopathy | |
| **LFTs** | Normal/abnormal (ALT rises first) | Abnormal (50% by 24 hours, 100% by 36 hours) | Bilirubin , AST and ALT elevated +++ | Recovery over weeks |
| **Other** | | | Hypoglycaemia, lactic acidosis, coagulopathy, AKI, death | Histologic recovery over months. |

**AKI** is caused by either **acute tubular necrosis** or **hepatorenal syndrome.** The risk of AKI increases with the severity of poisoning. N-acetylcysteine has not been shown to treat AKI.

**Toxic Doses**

- **<75mg/kg over 24 hours** – serious toxicity unlikely.
- **75-150mg/kg over 24 hours** – toxicity uncommon but possible.
- **>150mg/kg over 24 hours** – serious toxicity may occur.

**Pregnancy:** use the pre-pregnancy weight for calculating the toxic dose. However, the current weight should be used for calculating the NAC dose.

**Obesity:** if the patient is heavier than 110kg, use 110kg as the upper limit for calculating the toxic dose and NAC dose.

## N-acetylcysteine (NAC)

- NAC is an effective antidote to paracetamol.
- It **repletes glutathione stores**. Acetylcysteine is a prodrug to L-cysteine which in turn is a precursor to glutathione.
- It is most effective if given **within 8 hours of ingestion** (before hepatic injury occurs).
- It also reduces mortality and improves cerebral function in those who already have evidence of hepatic failure.
- **Anaphylaxis** is the most serious adverse effect of NAC. 10-20% of patients develop hypersensitivity reactions, though most are non-severe. After the hypersensitivity reaction is treated, NAC may be restarted in some patients.
- Advice should be sought from the poisons centre on whether to restart NAC in a critical care setting (oral NAC may be an alternative).

## Indications for N-acetylcysteine:

- Paracetamol concentration above the nomogram line (usually 4 hours post ingestion).
- Paracetamol dose >150mg/kg if the paracetamol level is unavailable within 8 hours of ingestion or will be unreliable (staggered overdose or unknown time of ingestion).
- Biochemical evidence of liver injury.
- Clinical evidence of liver failure.