Pharm-11B4 Describe the pathogenesis and management of paracetamol toxicity.

**Background**

Paracetamol = *N*-acetyl *p*-aminophenol
It is used as an antipyretic and analgesic; minimal anti-inflammatory properties

In excess, *N*-acetyl-*p*-benzoquinoneimine (NAPQI, one of the metabolites of paracetamol) can cause hepatotoxicity ± fulminant hepatic failure

As paracetamol is (1) readily available over the counter and (2) has good oral bioavailability (~ 70%), unintentional and intentional paracetamol overdose is the leading cause of acute hepatic failure (USA data, Stoelting 5th)

**Paracetamol Metabolism and Toxicity**

(1) Paracetamol → hepatic CYP2E1 (± CYP3A4) oxidation (*phase I*) → NAPQI

(2) NAPQI → hepatic glutathione conjugation (*phase II*) → 3-glutathionyl-NAPQI

NAPQI is a **potent oxidant** and extremely toxic to liver → causes hepatotoxicity via:

1. depletion of liver glutathione stores
2. increase formation of reactive oxygen and nitrogen species
3. oxidative stress on hepatocytes
4. loss of mitochondrial membrane potential → unable to synthesise ATP
5. hepatocyte necrosis

Normally, NAPQI is made in small quantities and rapidly eliminated via phase II metabolism

However, toxicity may result if:

- **excess paracetamol dose**
  usually, toxic oral paracetamol dose in a healthy patient is
  > 200 mg/kg stat
  > 150 mg/kg/day over 48 hours
  > 100 mg/kg/day over 72 hours
  usu. more than 10 ~ 15g PO in adult = **lethal**
- **Rapid Phase I**
  Patients with induction of the CYP2E1 or CYP3A4 pathways can produce NAPQI at high rates, which may overwhelm phase II detoxification. 
  e.g. patients taking liver enzyme inducers, esp. acute EtOH intoxication → lower maximum safe doses

- **Slow Phase II**
  Patients with slow phase II take longer to eliminate NAPQI → possible accumulation → toxicity.
  e.g. patients with depleted glutathione store (starvation, sepsis and other catabolic states) or damage to glutathione transfer enzymes (chronic liver disease, etc) → lower maximum safe doses

### Management of Paracetamol Toxicity

Unfortunately, there is no specific antidote for paracetamol toxicity → management is largely supportive.

1. **Reduce ongoing paracetamol absorption**
   - Cease paracetamol infusion
   - Gastric lavage *(if recent ingestion)*
   - Decontaminate GIT with activated charcoal *(if recent ingestion)*

2. **Increase hepatic glutathione stores**
   - Intravenous N-acetylcysteine (following local policies) up to 300 mg/kg
   - NAC acts as an antioxidant and thiol donor → replenishes hepatic glutathione stores

3. **Monitor hepatic function**
   - Serial LFT *(reflects hepatocellular necrosis)* and INR *(reflects synthetic fn)*

4. **Early referral for liver transplantation**
   - With fulminant hepatic failure, may require liver transplantation as definitive life-saving treatment

### Examiner’s comments
- 50.7% of candidates passed this question.

This question was phrased in 2 parts. Equal marks were allocated for each half of the question.

The pathogenesis of paracetamol toxicity requires a detailed discussion of the metabolism of paracetamol and how it changes when toxic doses of paracetamol are ingested. Mechanisms of toxicity primarily involving the liver and N-acetyl-p-benzoquinone imine (NAPQI) were also important.

Mention of typical doses of paracetamol that could cause toxicity and subpopulations at increased risk of toxicity with lower doses of paracetamol also attracted marks. Candidates who described paracetamol metabolism in overdose using applied principles of pharmacokinetics generally scored well.
Discussion of management of paracetamol toxicity needed to be balanced and mention general measures such as resuscitation and early consideration for liver transplantation as well as the specific therapies such as N-acetyl cysteine and methionine and the specific principles relating to their use. Candidates who were able to discuss these aspects of the question in sufficient detail achieved a pass mark.