Paracetamol Poisoning & Overdose

- **Epidemiology**: 135,000 cases of poisoning/overdose per year → 3000 die before they present, 100,000 are admitted and 300 die in hospital (0.3%).
- **Routes of exposure** to poisons include oral, inhaled, percutaneous, ocular, IV, rectal and transvaginal.
- Most commonly overdose presents as deliberate self-poisoning using oral drugs, for example:
  - **Paracetamol** 43%
  - **NSAIDs** 6%
  - **Opioids** 15%
  - **Neuroleptics** 4%
  - **Benzodiazepines** 15%
  - **Household** 4%
  - **Ethanol** 13%
  - **SSRIs** 4%
  - **TCAs/related** 12%
  - **Antibiotics** 3%
  - **Aspirin** 7%
  - **Antiepileptics** 2%
- Deliberate overdoses often involve a MIXTURE of drugs → complex.
- Patients who self-poison have 30% 10yr mortality: either suicide or “natural” causes like alcohol or drugs.
- **Immediate management** of patients with suspected poisoning:
  - **A**: Conscious level is commonly reduced in overdose so neurological airway support may be lost.
  - **B**: ↑ anticholinergics, TCAs → metabolic acidosis, cannabis-induced PTX ↓ opiates.
  - **C**: Collapse may follow overdose of cardiac medications e.g. beta blockers, CCBs, or recreational drugs such as amphetamines, ecstasy, pipеридине, cannabis and cocaine.
  - **Adult life support**: Cardiac arrest is common and resuscitation should be prolonged. TCAs, phenytoin and cocaine have sodium channel blocking properties → use sodium bicarbonate.

- **Initial investigations**
  - **Examination**: skin colour and temperature (↑↑ cocaine, amphetamines, ecstasy), pulse rate and rhythm (↓↓ CCBs, digoxin, foxtail), respiratory rate, BP (↑↑ cocaine), pupils (miosis: opiates, organophosphates, mydriasis: sympathomimetics, anticholinergics), GCS, muscle tone and reflexes.
  - **Needle marks** (heroin, metamfetamine, ↑↑ risk of HIV and hepatitis).
  - Bilirubin levels peak or other pesticides, industrial chemicals, long time lying collapsed on floor.
  - **Bloods**: FBC, U+E, LFT, clotting, BM, ABG, tests for specific poisons, tox screen (rarely indicated).

- **Gastric decontamination** aims to reduce absorption of poisons taken by mouth when ingested poison carries significant risk. Ideally given within 1 hour. Protect airway in unconscious/drowsy patients.
  - **Induced emesis with syrup of ipecacuanha**
    - Very effective at producing vomiting but little effect on removal of poisons and may mask Sax.
    - Only appropriate → avoid in adults and those with poor gag reflexes.
  - **Complications include persistent vomiting, diarrhoea, lethargy, aspiration, Mallory-Weiss tear, gastric herniation and foetal abortion.**
  - **Gastric lavage/aspiration**
    - Suitable for very large/life-threatening overdoses and where activated charcoal is ineffective.
    - Protect airway with cuffed ET tube if gag reflex poor.
    - Contraindicated in hydrocarbon ingestion or caustic fluid ingestion, avoid in children.
    - Complications include gut perforation, aspiration, laryngospasm, water intoxication in children, dysrhythmias, PTX, increased early drug absorption.
  - **Activated charcoal**
    - Adsoorbs poisons in GI tract by direct contact and reduces their absorption into the bloodstream.
    - Give 10x dose of poison taken (max 50g) suspended in flat cola, can be given via NGT too.
    - **Ineffective for elemental metals, insecticides, cyanide, acids/alkalis, alcohol, hydrocarbons.**
    - **Complications include aspiration pneumonitis, ↓ therapeutic drug absorption, obstruction.**
    - **Very effective for paracetamol and aspirin** but avoid in ileus, poor gag reflex, unsafe swallow.
    - **Multiple dose activated charcoal**
      - 50g activated charcoal followed by 25g every 2 hours (+ lactulose to prevent constipation).
      - Increases elimination of some drugs from blood e.g. theophylline, quinine, digoxin, phenytoin.
    - **Other methods**: haemodialysis for small molecules, charcoal haemoperfusion of bound drugs.

- **Paracetamol** is the most popular analgesic in the UK and is involved in almost half of all overdoses.
- Leading cause of poisoning mortality (100-200 per year) but overall mortality low (<1%).
- **Mechanism of action**
  - In overdose, the major route of metabolism is saturated and NAPQI production is increased.
  - Glutathione reserves eventually run out.
  - NAPQI accumulates in hepatocytes and reacts with cell constituents to cause cell death.
- **Clinical features**
  - Very non-specific.
  - Early: nausea, vomiting, abdominal pain WITHOUT impairment of conscious level.
  - Delayed features of hepatic necrosis: jaundice, liver pain, liver failure, encephalopathy.
  - Delayed features of renal failure: oliguria, loin pain, hypoglycaemia, metabolic acidosis.

- **Investigations**
  - **Paracetamol level 4hrs post-overdose** is best early predictor of prognosis and determines need for antidote through use of a nomogram.
  - If <150mg/kg is potentially toxic.
  - >250mg/kg makes severe liver damage very likely.
  - >12g total is potentially fatal.
  - Bilirubin >70, PT >100s or rising after day 3, metabolic acidosis, encephalopathy.
  - **LFTs and clotting studies** to assess liver damage and function.
  - U+E and creatinine to assess renal function (urea may remain low due to ↓hepatic synthesis).
  - **Abg** for metabolic acidosis → indicator of severe poisoning.
  - **Poor prognostic indicators**
    - High dose of paracetamol.
    - >150mg/kg is potentially toxic.
    - >250mg/kg makes severe liver damage very likely.
    - >12g total is potentially fatal.
    - Bilirubin >70, PT >100s or rising after day 3, metabolic acidosis, encephalopathy.

- **Treatment: within 1 hour of overdose**
  - **Gastric decontamination with multiple doses of activated charcoal**
  - In very large overdose (>50g) use gastric lavage alongside activated charcoal.
  - **Glutathione** acts as an antidote to NAPQI but value decreases rapidly with time.

- **Treatment: more than 4 hours after overdose**
  - **IV acetylcysteine** is a glutathione precursor which increases the availability of glutathione for binding to NAPQI and may also increase sulphate conjugation of paracetamol.
  - Given IV by three separate infusions over 20 hours.
  - Highly effective up to 8 hours after overdose: value decreases thereafter but there is some beneficial effect for up to 24 hours → basically use at any time after severe poisoning.
  - Complications include anaphylactic reaction in 10-15%, due to dose-related IgA-mediated histamine release from affected cells → reduce infusion rate and give chlorphenamine.
  - **Oral methionine** is a glutathione donor which is less effective and rarely used.
**Opiates**

- 15% of all overdoses: most common scenario is a heroin addict who used a higher than usual dose, accidentally injected concentrated solution or used heroin after a prolonged period of abstinence
- "Body packers" or "mules" pack their GI tract with bags of heroin for smuggling purposes may rupture
- "Body stuffers" ingest all the drugs on them to hide them from the police, often multiple drugs involved

**Mechanism:** respiratory depression and coma are usually complicated by hypoxia, non-cardiogenic pulmonary oedema, metastatic infections (often severe in HIV +ve patients), rhabdomyolysis, arrest

**Clinical features**
- CNS depression and coma
- Respiratory depression
- Miosis → pinpoint pupils
- Tachycardia
- Hypotension
- Complications at injection sites e.g. cellulitis, lymphadenitis, arterial damage, abscess, gangrene
- Complications due to cutting of drugs e.g. valve disease, RHF, lung abscess, talc granulomas

**Clinical features**
- Hallucinations
- Rhabdomyolysis
- Pulmonary oedema
- "Track marks"

**Treatment**
- IV naloxone is a competitive inhibitor of opioid receptors which quickly acts as an antidote: it is useful in both diagnosis and treatment of opiate overdose
  - Give enough to maintain airway and breathing but NOT to completely rouse the patient as there is significant risk of self-discharge and subsequent relapse
  - Usually 0.4-2.4mg IV for adults given in small boluses until breathing is satisfactory
  - Short ½ so give 2/3 of the dose required to rouse the patient every hour after that
  - Dangers include withdrawal, self-discharge during alert phase, unmasking of pain, hypertension, altered behaviour, fits and tachyarrhythmias
  - Supportive measures: oxygen, airway management, BBV precautions

**Tricyclic Antidepressants**

- About 12% of all overdoses, high mortality rate of 100-200 deaths per year

**Mechanism:**
- Anticholinergic effects
- Block noradrenaline uptake
- Block alpha-adrenergic receptors
- Block Na⁺ channels → cardiotoxic

**Clinical features**
- Hot, dry skin
- Dilated pupils
- Tachycardia, arrhythmias e.g. VT, VF
- Refractory hypotension

**Clinical features**
- Urinary retention
- Agitation, delirium, convulsions
- Hypertonia, hyperreflexia
- Coma

**Investigations**
- Can’t get plasma concentration of drug 😐

**Investigations**
- U+E for ↑↓K⁺
- Blood glucose
- ABG for metabolic acidosis: pH <7.4 represents ↑↑ risk of arrhythmia
- ECG is very important in diagnosis and monitoring
  - Sodium blockade causes intraventricular conduction delay → widened QRS complexes
  - QRS >160ms (>4 squares) represents high risk of arrhythmia and cardiac arrest

**Treatment**
- Gastric decontamination within 1 hour: 50g activated charcoal +/- gastric lavage
- Enhance elimination with repeated doses of activated charcoal every 2 hours
- Treat arrhythmias with sodium bicarbonate and K⁺ correction (NOT ANTIARRHYTHMICS)
- Treat fits with buccal midazolam/IV lorazepam/rectal diazepam, consider sedation/paralysis

**Aspirin/Salicylates**

- 7% of all overdoses
- Acute aspirin overdose has a mortality rate of 2%, chronic has a mortality rate of up to 25%

**Clinical features**
- Dizziness and hyperventilation
- Sweating and flushing
- Tinnitus
- Vomiting

**Investigations**
- Plasma salicylate concentration 6hrs post-overdose → repeats in case of delayed absorption
  - >125mg/kg = mild toxicity
  - >250mg/kg = moderate toxicity
  - >500mg/kg = severe, potentially fatal toxicity
- U+E, bicarbonate and ABG
  - Hypokalaemia
  - Direct respiratory stimulation → respiratory alkalosis
  - Then ↑↑ acid salicylate and lactate release 2↑ to ↓↓ tissue perfusion → metabolic acidosis

**Blood glucose**
- Reduced gluconeogenesis → hypoglycaemia

**Treatment**
- Gastric decontamination within 1 hour: 50g activated charcoal +/- gastric lavage if v large OD
- Enhance elimination:
  - repeated doses of activated charcoal every 2 hours to drive salicylate back into gut lumen
  - urinary alkalinisation with sodium bicarbonate to increase urinary excretion
  - haemodialysis is indicated in renal failure, acidosis, salicylate >700mg/L, oedema, CNS Sx.

**Theophylline**

- Overdose is uncommon but serious due to narrow therapeutic index and its use in children
- May be acute (often accidental/intentional) or chronic and precipitated by illness/drug interactions
- Most preparations are slow release

**Mechanism**
- Catecholamine excess and adenosine antagonism
- CYP450 inhibition increases plasma levels avoid use of cimetidine, erythromycin, etc…

**Clinical features**
- Sweating
- Vomiting
- Tachycardia
- Tremor
- Coma

**Clinical features**
- Agitation, fits
- Hyperventilation
- Coma
- Cardiotoxicity and arrhythmias

**Investigations**
- Plasma theophylline concentration: due to slow release of drug repeat every 2hrs until levels ↓
  - >60mg/L or >4.5g total could be fatal
- U+E for hypokalaemia, blood glucose for hyperglycaemia, ABG for acidosis
- ECG

**Treatment**
- Gastric decontamination within 1 hour: 50g activated charcoal +/- gastric lavage
- Whole bowel irrigation with polyethylene glycol solution may be indicated in large overdose
- Enhance elimination with repeated doses of activated charcoal every 2 hours
- Charcoal haemoperfusion is indicated for severe poisoning with fits, arrhythmias, coma etc…
- Supportive measures: KCI, sodium bicarbonate, ondansetron for vomiting, lorazepam for fits
Iron

- Iron overdose is one of the leading causes of death by poisoning in children under 6 years: iron tablets are commonly used and are particularly attractive to young children because they look like sweets.
- Can develop chronically in patients receiving frequent blood transfusions e.g. sickle cell, thalassaemia.

**Mechanism**
- Corrosive toxicity of ingested iron to GI tract → pain, D+V, significant fluid and blood loss
- Cellular toxicity of absorbed iron
  - Inhibition of oxidative phosphorylation → anaerobic metabolism and lactate production
  - Mitochondrial dysfunction and cell death, especially in liver
- This results in hypovolaemia and lactic acidosis

**Clinical features**
- Early (6hrs): N+V, abdominal pain, diarrhoea or black melaena stools
- Delayed (72hrs): GI symptoms deceptively seem to resolve, drowsiness/coma, CV collapse
- Late (2-4 days): fulminant liver necrosis, renal failure (gastric strictures after 2-5 weeks)

**Investigations**
- Serum iron level at 4hrs post-overdose then every 2 hours
  - >20mg/kg will cause GI toxicity
  - >60mg/kg will cause severe toxicity and could be fatal
- FBC: ↑ Hb, ↑ WCC, U+E, LFT, clotting, glucose; ↑↑ ABG; acidosis + increased anion gap, G&S

**Treatment**
- Gastric decontamination within 1 hour if large overdose
  - activated charcoal doesn’t work → gastric lavage, possibly induced emesis
- IM/IV desferrioxamine chelates iron to reduce its toxicity → ferrioxamine is excreted in urine
  - Can cause hypotension and pulmonary oedema
- Supportive measures: IV fluids, analgesia

Ethylene glycol

- Thick and syrupy with sweetish taste
- Found in antifreeze, brake fluid, radiator fluid
- Caused CNS depression, optic nerve toxicity and metabolic acidosis

**Clinical features**
- 30-12hrs: inebriation, convulsions, coma, metabolic acidosis
- 12-24hrs: ↑ HR, ↓ BP, ↑ RR, pulmonary oedema, heart failure
- 24-72hrs: renal failure and stone formation → calcium oxalate monohydrate crystalluria
- Death from MOF usually occurs within 24-36 hours

**Investigations**
- ABG + anion gap: (Na⁺ + K⁺) – (Cl⁻ + HCO₃⁻) normal anion gap is 8-12; ↑ by lactic acidosis, ketoacidosis, renal failure, acidic toxins e.g. methanol, ethylene glycol, salicylates, iron

**Treatment**
- Gastric decontamination within 1 hour: activated charcoal doesn’t work → gastric lavage
- Fomepizole competitively inhibits alcohol dehydrogenase: few side effects but expensive
- Ethanol does the usual, 7 shots! More side effects and can have unpredictable response
- Supportive measures: IV fluids, sodium bicarbonate for acidosis, may need airway support

Benzodiazepines

- Around 15% of overdoses but very low mortality rate unless part of complicated mixed overdose
- **Mechanism**: Potentiate activity of inhibitory neurotransmitter GABA to hyperpolarise membranes, inhibit cellular excitation and cause sedation, anxiety, muscle relaxation...

**Clinical features**: isolated BZD overdose classically presents as coma with normal vital signs
- Dizziness
- Confusion
- Drowsiness and coma
- Blurred vision and nystagmus
- Slurred speech
- Hypotension

**Investigations**
- Can measure serum/urine BZDs but usefulness limited as does not detect active metabolites and has no effect on immediate clinical management
- Following intentional overdose obtain FBC, U+E, glucose, LFT, clotting, paracetamol level
- ABG if evidence of respiratory depression
- ECG to rule out TCA involvement

**Treatment**
- Most important thing is to rule out other drugs first e.g. TCAs, opiates, paracetamol
  - Always worth trying naloxone in patients with CNS and respiratory depression
- Gastric decontamination within 1 hour: 50g activated charcoal +/- gastric lavage
- IV flumazenil is a competitive BZD receptor antagonist which acts as an antidote: Contraindicated in mixed overdose as may precipitate TCA seizures and arrhythmias
  - Use cautiously in chronic BZD users as may precipitate withdrawal and seizures
- Ideal situation for use is an isolated BZD overdose in BZD-naïve patients
- Supportive measures: oxygen, airway management, sodium bicarbonate for acidosis, glucose

Antifreeze

- Methanol
  - Looks like ethanol
  - Found in antifreeze, screenwash, solvents
  - Toxic by ingestion, inhalation and contact
- Very small doses are toxic
  - 10ml can lead to blindness
  - 30ml can be fatal
- Metabolised by liver alcohol dehydrogenase pathway to formaldehyde + formic acid
- Causes CNS depression, optic nerve toxicity and metabolic acidosis

**Clinical features**
- 30-12hrs: inebriation, convulsions, coma, metabolic acidosis
- 12-24hrs: ↑ HR, ↓ BP, ↑ RR, pulmonary oedema, heart failure
- 24-72hrs: renal failure and stone formation → calcium oxalate monohydrate crystalluria
- Death from MOF usually occurs within 24-36 hours

**Investigations**
- ABG + anion gap: ([Na⁺] + [K⁺]) – ([Cl⁻] + [HCO₃⁻]) normal anion gap is 8-12; ↑ by lactic acidosis, ketoacidosis, renal failure, acidic toxins e.g. methanol, ethylene glycol, salicylates, iron

**Treatment**
- Gastric decontamination within 1 hour: activated charcoal doesn’t work → gastric lavage
- Fomepizole competitively inhibits alcohol dehydrogenase: few side effects but expensive
- Ethanol does the usual, 7 shots! More side effects and can have unpredictable response
- Supportive measures: IV fluids, sodium bicarbonate for acidosis, may need airway support

Important Antidotes

- Paracetamol
  - Glutathione relepers e.g. acetylcysteine, methionine
- Opiates
  - Specific receptor antagonists e.g. naloxone
- Iron, heavy metals and cyanide
  - Chelating/fixing agents e.g. desferrioxamine, dimercaprol, sodium thiosulfate, edetate, B12
- Alcohols: methanol, ethylene glycol
  - Alcohol dehydrogenase inhibitors e.g. fomepizole, ethanol
- Benzodiazepines
  - Specific antagonists e.g. flumazenil
- Anticoagulants: warfarin
  - Vit K, prothrombin complex concentrate/FFP
- Digoxin
  - Antibody fragments e.g. Digibind
- Beta blockers
  - Atropine, glucagon bolus with 5% dextrose
- Dapsone
  - Reducing agent e.g. methylene blue
- Organophosphates
  - Cholinesterase activators e.g. pralidoxime
- Snake bites
  - IgG antivenoms e.g. Zagreb antivenom
- Carbon monoxide
  - Oxygen

IF IN DOUBT: TOXBASE
Call NPIS
# Common Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Adverse Reactions</th>
</tr>
</thead>
</table>
| **NSAIDs** | • GI ulceration and bleeding  
             • Cerebral haemorrhage  
             • Renal impairment  
             • Wheezing/exacerbation of asthma  
             • Rash |
| **Diuretics** | • Renal impairment  
               • Hypotension  
               • Electrolyte disturbances  
               • Gout |
| **ACEIs/ARBs** | • Renal impairment  
                  • Hypotension  
                  • Electrolyte disturbances |
| **Beta blockers** | • Bradycardia  
                    • Heart block  
                    • Hypotension  
                    • Wheezing/exacerbation of asthma |
| **Warfarin** | • Bleeding |
| **Clopidogrel** | • GI bleeding |
| **Digoxin** | • Toxicity |
| **Opiates** | • Constipation  
             • Vomiting  
             • Confusion  
             • Urinary retention |
| **Prednisolone** | • GI ulceration and bleeding  
                   • Hyperglycaemia  
                   • Osteoporosis and fractures |