PHARMACOLOGICAL BASIS OF POISOINING

(a) ***To outline methods which decrease absorption and enhance drug elimination such as activated charcoal, emetic agents, gastric lavage, haemodialysis and charcoal haemoperfusion.***

(I) Activated charcoal:

Mechanism	Activated charcoal has a large SA and porous molecular configuration → adsorbs a large number of organic and inorganic compounds → prevents their absorption from GI tract
Clinical uses	- Used when multiple or unknown substances given (BUT ineffective for caustic agents, alcohols and simple ions (Eg. Fe, CN, Li)) - Given as a slurry in H_2O either orally or via gastric tube (but risk of oesophageal perforation and pulmonary aspiration) → dose given needs to be 5-10x amount of toxin ingested (up to 1-2 g/kg max.)
Issues	Poor taste → minimal risks (except if pt vomiting or aspiration risk)

(II) Emetic agents (Eg. syrup of Ipecac):

Mechanism	Induces emesis of poison out of GI tract → ↓ systemic absorption
Clinical uses	Given orally → induces emesis within 30 mins
Issues	- Contraindicated when risk of (i) oesophageal/gastric perforation (Ie. ingestion of corrosive agents, such as acids/alkali), (ii) pulmonary aspiration (Ie. unconscious patient), or (iii) emesis-induced seizures (Ie. ingestion of CNS stimulants) - Can cause prolonged vomiting and become an issue when substantial amounts of poisons have been ingested

(III) Gastric lavage:

Mechanism	Poison is sequentially removed from GI tract (and thus ↓ systemic absorption) by pumping the stomach with a fluid (usually saline) then withdrawing it through a gastric tube
Clinical uses	Must be performed within 1 hr of poisoning → rarely done as time of poisoning unclear or > 1 hr since poisoning
Issues	- Risk of (i) pulmonary aspiration → requires airway protection with ETT and (ii) pharyngeal/oesophageal injury with gastric tube insertion - Time of poisoning commonly unclear or > 1 hr - Contraindicated if poison ingested is caustic

(IV) Dialysis:

Mechanism	- (i) Haemodialysis → blood flows in opposite direct to dialysate fluid separated by a semipermeable membrane in a dialysis machine → toxic substances are cleared down their [ ] gradient via passive diffusion - (ii) Peritoneal dialysis → dialysate fluid is placed into peritoneum to allow toxic substances to diffuse passively down their [ ] gradient from peritoneal capillary bed → fluid then removed - (iii) Charcoal haemoperfusion → large volumes of blood are passed over adsorbent substance (usually resins and activated carbon) → due to large SA and porous molecular confirugation, large number of poisons are adsorbed
Clinical uses	Reserved for extreme and life-threatening poisoning (esp alcohols, ethylene glycol, lithium, theophylline, aspirin, and CNS-active drugs)
Issues	- Not useful for poisons that are (i) large or charged (polar) molecule (Ie. cannot cross membrane), (ii) ↑↑↑ V_D (esp lipophilic), or (iii) highly protein-bound (Eg. digoxin, NSAIDs, TCA) - Carries risk of invasive procedures (Ie. CVC insertion)

(V) Others:

- (1) Alkaline diuresis

    - Enhance elimination of weak acids (Eg. aspirin, phenobarbital, TCA) by IV administration of $NaHCO_3$ to keep urine pH > 8
    - Issues with ↑ Na^+, metabolic alkalosis and fluid overload
- (2) <u>Whole bowel irrigation</u>
    - Used for drug packets, poisoning by sustained-released drugs, toxins not adsorbed by charcoal (Eg. heavy metals) → flush GI tract with a nonabsorbable solution (Eg. polyethylene glycol) given via a gastric tube to shorten GI transit time of poisons and ↓ systemic absorption
    - Issues → Not shown to ↓ morbidity/mortality, carries risk of gastric tube insertion, and takes long time (hours to days)
- (3) <u>Topical decontamination</u>
    - Flush body part exposed to poison with large amounts of saline or H_2O

(b) ***To describe the physiological effects and management of overdose of agents such as paracetamol, aspirin, tricyclic anti-depressants, sedatives, cyanide, digoxin, and organophosphates.***

(I) Paracetamol toxicity:

Toxic daily dose > 4-6 g (while lethal dose occurs at > 10-15 g (or > 300 mg/kg LBM)) → but the toxic and lethal doses are lower in "at-risk" groups:

- (i) EtOH abuse (due to CYP450 induction (↑ toxic metabolite produced) and ↓ glutathione stores)
- (ii) Malnutrition (due to ↓ glutathione stores)
- (iii) Elderly (due to ↓ glutathione stores)
- (iv) Preexisting liver dysfunction

Mechanism:

- At therapeutic doses – "N-acetyl-p-amino-benzoquinoneimine" (highly toxic metabolite) is produced in small amounts, but is rapidly conjugated with hepatic glutathione (anti-oxidant) into a harmless metabolite
- BUT with toxic doses – Hepatic conjugation pathway is saturated and ↑↑↑ N-acetyl-p-amino-benzoquinoneimine is produced → this depletes hepatic glutathione stores, causing remaining N-acetyl-p-amino-benzoquinoneimine to then forms covalent bonds with sulphydryl groups on hepatocytes → results in centrilobular hepatic necrosis

Clinical features:

- Generally conscious and c/o N/V, epigastric pain, erythema, sweating → later developing:
    - Acute haemolytic anaemia
    - Develop hepatic failure (Ie. jaundice and cholestasis) after 48 hrs
    - LFT/INR derangements at 3-5 days
    - Fulminant hepatic failure at 3-7 days
- With severe OD, can present with hypotension/shock

Diagnosis – Serum paracetamol levels → correlate with "nomogram" to predict likelihood of liver damage → used as a guide to dictate therapy

Treatment:

- (i) Activated charcoal/gastric lavage→ limit paracetamol absorption
- (ii) Replace hepatic glutathione store within 12 hrs of OD → permits glucuronidation of toxic metabolite
    - (a) Oral methionine → ↑ glutathione synthesis
    - (b) IV N-acetylcysteine → hydrolysed to cysteine (which is a glutathione precursor)
    - Nb. IV NAC is preferred b/c of N/V a/w toxicity (Ie. ↓ oral methionine absorption)
- (iii) IV glucose → due to risk of ↓ BGL with liver dysfunction
- (iv) Serial monitoring of LFTs and coagulation studies
- (v) Referral to a specialist centre

Important to note → Paracetamol toxicity also causes "Analgesic-induced nephropathy":

- Paracetamol metabolites (esp p-aminophenol) concentrate in hypertonic renal papillae → they are oxidised into metabolites that form covalent bonds with sulphydryl groups on tissues → cause papillary necrosis

(II) Aspirin toxicity:

Pathophysiology of aspirin toxicity:

- Aspirin uncouples [O] phosphorylation → ↑ O_2 consumption and CO_2 production → hypermetabolic state (Ie. ↑ BGL, hyperthermia, hyperventilation, ↑ HR, Etc.)
- Respiratory alkalosis occurs due to hyperventilation → caused by (i) direct aspirin stimulation of medullary ventilatory centres and (ii) hypermetabolic state
- In late stages, mixed respiratory and metabolic acidosis occur → due to (i) respiratory depression 2° to aspirin and (ii) accumulation of metabolic acids 2° to renal dysfunction (Ie. accumulate strong acids) and ↑ CHO metabolism (Ie. lactic acid)

> Note – Mixed respiratory/metabolic acidosis occurs 1°ly in children → rare in adults

Clinical features of aspirin toxicity:

- Conscious (unless with massive OD)
- Tinnitus → an early sign of OD
- Pyrexia and sweating
- Blurred vision
- Tachycardia
- Hyperventilation
- Respiratory alkalosis (later complicated by metabolic acidosis)
- Hyperglycaemia

Treatment of aspirin toxicity:

- (1) Activated charcoal/gastric lavage → ↓ aspirin absorption
- (2) Forced-alkaline diuresis (diuretic + IV $NaHCO_3$)
    - (i) Treat metabolic acidosis → ↓ transfer of salicylate from plasma to CNS
    - (ii) ↑ trapping of salicylate within renal tubule → ↑ urinary excretion
- (3) Haemofiltration/haemodialysis

(III) <u>Tricyclic antidepressant toxicity</u>:

TCAs have a narrow therapeutic index → risk factors that ↑ toxicity include:

- (i) ↑ age
- (ii) Preexisting cardiac conditions (Ie. arrhythmias)
- (iii) Concurrent drug use (Ie. other antidepressants, anti-arrhythmic agents)

Pathophysiology of TCA toxicity → due to:

- (i) Anticholinergic effects
- (ii) Inhibition of NAd uptake at preganglionic synapse
- (iii) Direct α-adrenoceptor blockade
- (iv) Inhibition of VG Na^+ channels (esp in myocardium and neurons)

Clinical features of TCA toxicity

- CVS effects – Tachycardia, hypotension, arrhythmias

> Note – ECG → sinus tachycardia, prolonged QRS complex and PR/QT intervals (due to delayed intraventricular conduction)

- CNS effects – Drowsiness, confusion, agitation, hallucinations, seizures
- Respiratory effects – Apnoea (in severe cases)
- GI/GU effects – Urinary retention, dry mouth, N/V

Management of TCA toxicity:

- (1) ↓ GI absorption of TCA by activated charcoal within 1-2 hrs of ingestion → other means (such as emesis, gastric lavage, whole bowel irrigation) are NOT recommended

- (2) Admit to ICU → Monitor airway/breathing, haemodynamics, arterial pH, and ECG. Provide supportive therapy as required
- (3) Metabolic acidosis → consider IV $NaHCO_3$
- (4) Cardiovascular complications → anti-arrhythmics (esp phenytoin and Mg^{2+}; but NOT lignocaine), IVF and vasopressors/inotropes
- (5) CNS complications → seizures resolve spontaneously but Bz can be used

Note – Dialysis cannot be used to treat TCA toxicity due to its ↑ V_D and protein-binding!

(IV) Sedative toxicity:

Sedative overdose (esp opioid or benzodiazepine-related) is characterised by respiratory depression (hypopnoea/apnoea), UAW obstruction (due to muscle flaccidity), sedation (leading to coma)

Managed with mechanical ventilation with O_2 and careful administration of naloxone or flumazenil (while preventing withdrawal). Support haemodynamics as necessary with IVF and/or vasopressors/inotropes

Important to note → Naloxone therapy:
- IV bolus 1-4 ug/kg for opioid overdose → onset of effect within 2 minutes 2° to its ↑ lipid solubility (Ie. crosses BBB rapidly)
- May need supplementary IV boluses or IV infusion (at 5 ug/kg/hr) when used to treat overdoses of longer acting opioids (esp morphine or high-doses of fentanyl) → b/c it has a short duration of action (30-45 mins) 2° to ↑ clearance rate and short elimination t ½

Important to note → Flumazenil therapy:
- IV 0.1-0.2 mg IV given with effect evident within 1-2 minutes (Eg. reverse CNS effects of Bz). Further 0.1 mg IV can be given minutely (to a max of 1 mg IV)
- Usually 0.3-0.6 mg is needed to reverse sedation with Bz (while up to 1 mg may be needed to completely abolish the effects of Bz). Unconsciousness due to OD of Bz may need up to 5 mg!
- Short t ½ β means that the duration of action is only 30-60 minutes – Thus, repeated doses or continuous infusion (0.1-0.4 mg/hr) is needed to maintain level of consciousness

(V) Cyanide toxicity:

CN^- toxicity generally occurs with SNP therapy → risk factors include:
- (i) Dose > 2 ug/kg/min (esp in young children/adults due to active BRR) → this is b/c liver can clear CN^- at SNP dose < 2 ug/kg/min only
- (ii) ↓ CN^- clearance by conversion to SCN by liver (severe hepatic failure, hypothermia, malnutrition, children), renal excretion (severe renal failure), or sequestration to hydroxycobalamine (vitamin B12 deficiency) or metHb

Mechanism of CN toxicity:
- Free CN^- binds tissue cytochrome oxidase c → tissue anoxia due to impaired aerobic metabolism via oxidative phosphorylation OP → metabolic acidosis due to lactate produced from anaerobic metabolism

Suspect CN^- toxicity if:

- (i) Resistant to hypotensive effects of SNP despite maximal infusion rates or tachyphylaxis (Ie. previously responsive pt is now unresponsive to effects of SNP)
- (ii) Increased PvO_2 (as tissues cannot utilise O_2)
- (iii) Metabolic acidosis a/w ↑ lactate (due to anaerobic metabolism)
- (iv) Symptoms of altered mental status tachycardia, arrhythmias, hyperventilation, sweating, and seizures
- (v) Plasma $[CN^-]$ > 8 ug/mL → but use of assay is limited by delay in results, and inaccuracies due to photodecomposition of CN^- during analysis

Management:

- (i) Cease SNP infusion
- (ii) Provide supportive therapy (Ie. 100% FiO_2, correct acidosis with $NaHCO_3$, Etc.)
- (iii) Clear CN^- from circulation
    - Dicobalt edetate → chelates CN^-
    - Na thiosulphate → provides additional sulphydryl groups to convert CN^- to SCN
    - Na nitrite or amyl nitrite → convert Hb-O_2 to met-Hb, which has a higher affinity for CN^- than cytochrome oxidase
    - Vitamin B12 → complex CN^- to cyanocobalamin

Prevention:

- Dose-dependent CN^- toxicity occurs at SNP rates > 2 ug/kg/min
- Toxicity is minimised by – (i) Combining SNP with other anti-hypertensive agents (Eg. CCB, β-blockers, volatiles) to reduce its dose < 2 ug/kg/min, or (ii) Giving prophylactic thiosulphate or hydroxycobalamin when rates > 2 ug/kg/min need to be given
- Foetal CN toxicity in pregnant patients is prevented by using SNP cautiously → use modest doses for short durations only

(VI) <u>Digoxin toxicity</u>:

Digoxin has a very narrow therapeutic index → toxicity occurs in 20% of patients

Risk factors:

- (i) Renal dysfunction (as it is cleared renally)
- (ii) ↓ K^+ (esp with diuretics or ↓ $PaCO_2$ with hyperventilation) → ↑ affinity of digoxin binding to cardiac myocytes
- (iii) Other electrolyte disturbances – ↑ Na^+, ↑ Ca^{2+}, ↓ Mg^{2+}
- (iv) pH disturbances
- (v) ↑ SNS activity (esp by arterial hypoxaemia)
- (vi) ↓ skeletal mass (loss of inactive store)

Features:

- GI symptoms – Anorexia, N/V, diarrhoea, abdominal pain
- CNS symptoms – Visual disturbances (deranged red-green colour perception), headaches, confusion, drowsiness, muscle weakness
- CVS symptoms – Any arrhythmia can occur, although atrial tachycardia with block is more common, while death is usually a/w VF
    - ↑ automaticity – PVBs, atrial and ventricular tachycardias, bigemini, Etc.
    - Delayed AVN conduction – Junctional rhythm and AV heart block
    - Sinus arrest (at high doses) due to SAN block by vagal tone
- Others: Skin rash and gynaecomastia are rare

> Note – Plasma digoxin levels usually 0.5-2.5 ng/mL → toxic if > 3 ng/mL (BUT symptoms can occur below this toxic levels, esp when risk factors are present)

Treatment:

- (i) Correct risk factor (Ie. ↓ K^+, ↓ Mg^{2+}, hypoxaemia, Etc.)
- (ii) Phenytoin, lignocaine, propranolol → treat cardiac arrhythmias
- (iii) Atropine and temporary pacemarker → treat bradycardia and AV heart block
- (iv) Supplement K^+ (assuming normal serum [K^+]) to ↓ digoxin binding to cardiac myocytes
- (v) Digoxin-specific Fab (IgG antibodies)
    - Indicated when – Life-threatening arrhythmias, uncontrolled ↑ K^+, plasma digoxin levels > 20 ng/mL
    - Mechanism – Avidly binds digoxin to form a Fab-digitalis complex → removed from circulation via renal excretion
    - Issues – Hypersensitivity and anaphylaxis with subsequent use of Fab

(VII) Organophosphate toxicity:

Organophosphate-type AChEi (Eg. Insecticides) are a common cause of AChEi overdose as they are easily absorbed via the lungs, skin and GIT due to their high lipid-solubility (due to tertiary amine structure). Moreover, they also cause more CNS symptoms as they can cross the BBB

Symptoms of AChEi overdose symptoms are due to excessive:

- (i) Muscarinic effects – Difficult to focus vision, excess salivation, bronchoconstriction, respiratory secretions, bradycardia, abdominal cramps, N/V, sweating, and loss of bladder/rectal control
- (ii) Nicotinic effects – Muscle weakness leading to paralysis with apnoea, fasciculations, hypertension and tachycardia
- (iii) CNS effects (esp if AChEi is lipid-soluble agent, such as OP's) – Confusion, ataxia, seizures, coma, and respiratory depression

Management includes:

- (1) Atropine – Treats muscarinic symptoms by antagonising effect of ACh on mAChR. Requires repeated dosing until symptoms disappear
- (2) Pralidoxime
    - "AChE reactivator" that promotes hydrolysis of the covalent bond that the drug has with the enzyme (esp drugs that phosphorylate AChE, rather than those that carbamylate it)
    - Treats both muscarinic and nicotinic symptoms by reducing synaptic levels of ACh through reactivation of AChE
    - Ineffective unless given within minutes of exposure to AChEi. Requires repeated dosing until symptoms disappear
- (3) Supportive therapy (Eg. ETT/mechanical ventilation, seizure control, circulatory management with IVF, Etc.)