B25 - Pharmacological Basis of Poisoning

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

Activated charcoal

- odourless, tasteless
- fine black powder
- chemically inert form of carbon

Preparation

- prepared by pyrolysis of carbonaceous matter (coconut, pulverised peat or sawdust) @ 600-900 C in a kiln without air.
- then concentrated with zinc chloride solution -> washed off with dilute acid & water -> exposed to steam or CO2 at 600-700 C -> forms an internal maze of pores.

Action

- absorbing molecules of drug on its surface -> inhibiting their absorption by as much as 50% -> excretion in faeces
- absorptive area = 3,000m2/g

Dose

- 50g in 100mL
- charcoal:toxin dose = 10:1
- should be given within 1 hr
- can be given later OD drug not lipid soluble, slow passage to intestine, sustained release preparation or ingested with anti-cholinertics

Effective in OD's from

- aspirin
- paracetamol
- barbiturates
- TCA's
- digoxin
- amphetamines
- morphine
- cocaine
- phenothiazines

Emetic agents

- Ipecacuanha (Brazil root)
- efficacy disputed

Dose - 10 to 30mL (lasts 15min)

Action = direct gastric irritation

Problems

- decreased airway protection
- increased aspiration

Gastric lavage

- efficacy disputed unless performed within 1 hr of drug ingestion
- intubation essential

Mode

- head down on left side
- 30FG tube with large side holes passed into stomach
- aspirated
- then warm H2O instilled
- aim for volumes of >1mL/kg

Haemodialysis

- effectively removes compounds of:

- low MW
- low protein binding
- small Vd
- low spontaneous clearance

- useful in OD from:

- metanol
- ethylene glycol
- salicylates
- lithium

Charcoal haemoperfusion

- removes lipid soluble drugs (theophylline & phenobarbitone)

(b) To describe the physiological effects and management of OD of agents such as paracetamol, aspirin, TCA's, sedatives, cyanide, digoxin & organophospates.

Paracetamol

Chemical

- acetaminophen
- widely used analgesic & antipyretic
- not true NSAID as it lacks significant antinflammatory effects.
- weak COX 1 & 2 inhibitor in peripheral tissues
- reduces prostaglandin production in the CNS

Uses

(1) analgesic
(2) anti-pyretic
(3) weak anti-inflammatory

Route - IV, PO, PR

Dose

- 325 to 650mg Q4-6hrs
- max = 90mg/kg/day

Onset: 30-60min

PK

Absorption - complete

Distribution

- no significant binding to plasma proteins
- Vd = 1 L/kg
- non-ionised, lipid soluble -> penetrates BBB

Metabolism

- hepatic
- conjugation & hydroxylation -> inactive compounds

Elimination

- 5% excreted in urine unchanged
- rest secreted in renal tubules
- Cl = 5mL/min/kg
- t1/2 = 2hrs

PD

Main action - analgesic & anti-pyretic

Mechanism of action

- ?
- potent inhibitor of prostaglandin synthesis within the CNS
- inhibits the synthesis of the E series of prostaglandins produced by hypothalamus in response to pyrogens.

- peripherally acts by blocking impulses generation within the bradykinin-sensitive chemoreceptors -> afferent nociceptive impulses.

CNS

- analgesic

GI

- no effect on liver unless taken in OD quantities
- doesn't cause gastric ulcerations

GU

- papillary necrosis from hypertonicity cause by metabolites

Metabolic

- potentiates the effect of ADH
- doesn't effect normal homeostatic mechanisms

Toxicity

- GI disturbance
- skin reactions
- idiosyncratic haemopoietic disorders (thrombocytopenia)
- pancreatitis

- risk of hepatic damage in first 24hrs can be calculated from a nomogram (x-axis = hrs, y-axis = serum paracetamol (mcg/mL)).
- high risk = >100mcg/miL at 8hrs

- hepatic risk increased with glutathione depletion:

- alcoholism
- malnutrition
- HIV

- hepatic damage takes place with > 150mg/kg
- supply of glutathione becomes depleted (metabolism pathway saturated) -> highly reactive intermediate metabolite (N-acetyl-p-benzoquinone) combines with hepatic cell membranes -> centrilobular necrosis

Treatment

- **N-acetylcysteine** and **methionine** act as alternative supplies of glutathione & protect against liver damage if administered withing 10hrs.
- loading dose = 150mg/kg in 200mL of 5% dextrose over 15min
- infusion dose = 50mg/kg in 500mL of 5% dextrose Q4hrly -> 100mg/kg in 1L of 5% dextrose over 16hrs.

Aspirin

Chemical - aromatic ester of acetic acid

Uses

(1) analgesia
(2) anti-inflammatory
(3) anti-pyretic
(4) prevention of MI
(5) prevention of graft occlusion post bypass/stent
(6) pre-eclampsia
(7) prevention of TIAs/CVA
(8) DVT prophylaxis post joint replacement or NOF #

Presentation - 75 to 600mg tablets

Routes - PO, PR

Dose

- 300 to 900mg 8hrly
- theraputic serum concentration = 150 to 300mg/L

- toxic concentraton = 500 to 700mg/L

PK

Absorption - bioavailability = 70%

Distribution

- rapidly hydrolysed to salicyclic acid
- 90% protein bound
- Vd = 10 L/kg
- limited ability to cross BBB

Metabolism

- 50% -> salicylurate in liver (saturable)
- 20% -> salicylphenolic glucuronide (saturable)
- 10% -> salicylacyl glucuronide
- 5% -> gentisic acid

Elimination

- t1/2 varies with dose given

PD

Main action - anti-pyretic, analgesic & anti-inflammatory

Mechanism of action

- inhibition of cyclo-oxygenase enzyme -> decreased conversion of arachidonic acid to cyclic endoperoxides -> decreased production of thromboxane & prostaglandins

- prostaglandins are involved in the sensitisation of peripheral nerve endings to pain

- also irreversibly inhibits cyclo-oxygenase in platelets (but not on endothelium)

CVS

- platelet aggregation inhibited
- bleeding time prolonged

RESP

- increase O2 consumption, increase CO2 production -> uncoupling oxidative phosphorylation

- bronchospasm

- OD: hyperventilation -> respiratory failure

CNS

- analgesic effect is centrally & peripherally mediated
- anti-pyretic action is inhibition of hypothalamic prostaglandin synthesis

GI

- increases gastic acid production
- GI haemorrhage
- gastric ulceration
- large doses -> hepatic failure

GU

- proteinuria
- increased number of renal tubular casts
- large doses -> renal failure

Metabolism

- BSL decreases
- increase in serum urea
- elevated LFTs
- lipogenesis decreased
- large doses -> steroid secretion

Other adverse effects

- aplastic anaemia

Drug interactions

- anti-coagulants -> increased effect

Toxicity

- aspirin rapidly hydrolysed to salicylate -> bind to albumin
- once albumin saturated -> free saliculate accumulates -> decreased pH -> tachypnoea and decreased PaCO2 via stimulation of respiratory centre in medulla (respiratory alkalosis)
- impaired oxidative phosphorylation -> increased lactic acid & deceased ATP

Clinically

- tinnitis -> deafness
- tachypnoea
- diaphoresis
- pyrexia
- hypoglycaemia
- haematemesis
- hypokalaemia
- increased INR

Treatment

- activated charcoal
- fluids with Na+, K+ & glucose
- vitamin K & glucose used to correct hypoprothrombinaemia & hypoglycaemia.
- hyperventilation or increased HCO3- -> decreased non-ionised drug availability & increased urinary excretion
- haemodialysis

TCA's

- surplanted as the first line anti-depressants because of unfavourable side-effects (anti-cholinergic, anti-adrenergic & anti-histaminergic)
- have a narrow theraputic index -> lethal in OD (inhibition of Na+ channels -> slowing of cardiac impulses -> arrhythmia)
- structure resembles that of a LA (hydrophobic portion linked to an amide via a linear moiety).
- tricyclic = three ringed structure

Mechanism

- block reuptake of 5-HT & norad @ presynaptic terminals -> increasing their availability.

Amitriptylline

Chemical - a dibenzocycloheptadiene derivative

Uses

(1) depression
(2) nocturnal enuresis
(3) adjunct to treatment of chronic pain syndromes:

- chronic tension headache
- post-herpetic neuralgia
- painful neuropathies
- chronic spinal syndromes

Presentation

- tablets: 10, 25, 50mg
- injection: clear, colourless 10mg/mL
- syrup: 2mg/mL

Route - PO, IV

Dose

- PO: 75-150mg/day -> decrease to 50-100mg maintenance
- IV: 10-20mg Q6hrly

- takes: 2-3wks to become effective

PK

Absorption - bioavailability 40%

Distribution

- 95% protein bound
- Vd 20 L/kg

Metabolism

- N-demethylation & hydroxylation -> conjugation to glucuronide & sulphate

Elimination

- urinary
- Cl = 12mL/min/kg
- t1/2 = 24hrs

PD

Main action

- anti-depressant
- sedative
- analgesic

Mechanism of action

- potentiation the action of biological amines within the CNS by preventing reuptake
- antagonise muscarinic, alpha 1 adrenergic & histamine receptors.

CVS

- postural hypotension
- sinus tachycardia
- dysrhythmias
- increased conduction time through the AV node
- QT & PR interval may be prolonged

RESP

- respiratory depression (in toxic doses)

CNS

- anti-depression
- sedation
- weakness
- fatigue
- blurred vision
- fine tremor in 10%

GI

- constipation
- dry mouth

GU

- urinary retension

Drug interactions

(1) sympathomimetics

- blood pressure response is unpredictable (exaggerated pressor response from increased circulating norad)
- start low, go slow

(2) inhaled anaesthetics

- increased incidence of dysrhythmias

(3) anti-cholinergics

- increased risk of post-op delirium & confusion
- use glycopyrrolate

(4) anti-hypertensives

- rebound hypertension after discontinuation of clonidine

(5) opioids

- in animals this interaction -> increase analgesic & ventilatory depressant effects.

Toxicity

- 20mg/kg is potentially fatal
- agitation -> seizures -> coma
- delirium
- depression of ventilation
- hypotension
- hypothermia
- anticholinergic effects: mydriasis, flushed dry skin, urinary retension, tachycardia

ECG changes

- QRS >100ms -> seizures
- QRS > 160ms -> arrhythmias
- R wave in aVR (SA node) > 3mm (maybe more sensitive for cardiotoxicity
- R\S ratio > 0.7 in aVR
- QT prolongation
- Sinus tachycardia
- Arrhythmias

Treatment:

- may need phytostigmine for treatment of anti-cholinergic symptoms
- diazepam then phenobarbitone for seizures
- alkalization of plasma (pH>7.45) using NaHCO3 or hyperventilation
- lignocaine & phenytoin for cardiac dysrhythmias.
- ionotropes as needed

Sedatives

Barbiturates

- CNS, CVS & RESP depression
- treatment = supportive, activated charcoal

Non-barbiturates

- treatment = gastric lavage, antidote
- benzodiazepine -> flumazenil 0.2mg/min (max 3mg)

Cyanide

Causes

- pest removalists
- ore refiners
- metallurgists
- synthetic rubber makers
- excessive apricot, preaches or apple eaters
- Na+ nitroprusside toxicity (>8mcg/kg/min for over 3 hrs with plasma concentrations over 110mcg/mL)
- levels > 150mcg/mL -> death

- risk increased by hypothermia, malnutrition, vitamin B12 deficiency, hepatic or renal impairment

- related to rate of infusion rather than total dose.

- cyanide ion combines with cytochrome C -> impairment of aerobic metabolism -> metabolic lactic acidosis

Signs

- tachycardia
- dysrhythmias
- hyperventilation
- sweating
- metabolic acidosis (lactate)
- increased venous O2 tension -> paralysis of cytochrome oxidase & electron transport -> inability of tissues to use O2

Treatment

- stop Na+ nitroprusside infusion
- supportive measures

(1) **sodium thiosulphate** (300mg IV Q15min) -> sulphur donor facilitates conversion to less toxic, readily excreted thiocyanate

(2) or **dicobalt edentate** -> enables chelation of cyanide ions.

(3) or **nitrite** by inhalation can induce formation of metHb which has a greater affinity for cyanide than the cellular cytochrome oxidases.

(4) or **hydroxycobalamin** combines with cyanide to form non-toxic cyanocobalamin

Digoxin

Chemical - glycoside (sterol lactone + a sugar)

Uses

(1) AF
(2) heart failure
(3) prevention of supraventricular dysrrhythmia

Presentation

- tablets: 0.0625mcg to 2.5mg
- elixir: 0.05mg/mL
- solution: 0.25mg/mL

Routes - PO, IV

Dose

- loading dose: 1mg over 24hrs
- maintenance: 10-20mcg/kg/day in divided doses

PK

Absorption - bioavailability = 60 to 90%

Distribution

- 30% protein bound
- Vd = 10 Lkg

Metabolism

- <10% hepatically metabolised by cleavage o sugar moieties

Elimination

- 60% excreted unchanged in urine
- Cl = calculated by formula

PD

Main action - +ve ionotrope + slowing of ventricular response

Mechanism of action

- direct: inhibition of Na+/K+ ATPase within sarcolemma -> increase in intracellular Na+ -> displaces Ca2+ from proteins -> +ve ionotropism also slowing of AV conduction with decreased K+ concentration.

- indirect: modifies automoic activty (increases vagal activity)

CVS

- increase contractility
- HR slowed
- ECG changes: prolongation of PR interval, ST segment depression, T wave flattening, shortened QT

CNS

- headache
- drowiness
- confusion
- visual disturbance
- weakness

GI

- anorexia
- n & v
- diarrhoea
- abdominal pain

GU

- mild intrinsic diuretic effect

Drug interactions

- sux, pancuronium or beta-agonists -> dyrhythmia
- co-administration of: verapmil, nifedipine, amiodarone & diazepam

Toxicity

- serum concentration > 2.5ng/mL ->

- anorexia
- nausea

- vomiting
- headache
- fatigue
- visual disturbances
- skin rashes
- gynaecomastia
- ventricular extrasystoles (elevation of RMP & re-entry conduction)
- VT
- AV block

- may be worsened by:

- hypokalamia
- hypomagnesaemia
- hypercalcaemia
- hypoxia
- renal impairment

Treatment

- WH digoxin
- correct tachyarrhythmias by giving K+, phenytoin, beta-blockade or lignocaine.
- charcoal (if within 1 hr)
- correct electrolyte abnormalities
- consider electrical pacing if bradycardia & heart block
- if level > 5ng/mL -> digoxin specific Fab fragment antibodies to IgG raised in sheep (can neutralise 0.6mg of digoxin)

Organophosphates

- binding of organophosphate to AchE is via covalent bond -> required synthesis of new enzyme (takes days)
- absorbed through skin, GIT and by inhalation

History

- exposure via agricultural, industrial or transport accidents.
- exposure in war with chemical agents

Examination

Acutely

CVS - bradycardia

RESP

- bronchorrhoea
- bronchoconstriction
- cough
- wheeze
- dyspnoea
- respiratory failure

CNS

- miosis
- anxiety
- headache
- convulsions

GI

- salivation
- vomiting
- abdominal cramps
- diarrhoea
- involuntary defaecation
- interssuseption

GU

- involuntary micturition

Skin - sweating

Musculoskeletal

- weakness
- twitching

1-4 days

- proximal flaccidd limb paralysis (muscle necrosis)

2-4 weeks

- delayed polyneuropathy -> mixed usually involving lower limbs

Chronic

- subtle cognitive defects
- peripheral neuropathy

Treatment

- ICU admission
- ventilate if necessary
- atropine (muscarinic) 0.5 to 2mg IM or IV asap -> give every 30min until dryness of mouth & heart rate > 70/min
- pralidoxime (antagonises nicotinic & muscarinic effects by reactiving enzyme to hasten its destruction) 1g IV Q4hrly by slow infusion
- diazepam of seizures
- atropine eyedrops for headache caused by miosis