## BIII - Variability in Drug Response

### (a) To define tachyphylaxis, tolerance, addiction, dependence & idiosyncrasy.

**Tachyphylaxis** = responsiveness to a drug dminishes **rapidly** after repeated administration, requiring higher doses to get same effect.

**Tolerance** = responsiveness to the same drug dose **gradually** decreases as a consequence of continued drug administration > 24hr. Can develop with drugs that do not cause dependence.

**Addiction** = a chronic state of physical or psychic dependence (adaptation & craving to avoid negative effects of withdrawal) on the effects of a drug beyond that required to achieve a recognised theraputic outcome.

- compulsion to self administer more than the recommended amount with excessive frequency outside the theraputc guidelines, despite detrimental consequences to the individual & society.

**Dependence** = the state of being dependent on a medication/drug. The physical parallel to acquired physical tolerance.

**Idiosyncrasy** = patient exhibiting an unusual drug response.

### (b) To describe the mechanisms of tolerance

*(1) change in receptors*

- can be rapid in receptors directly coupled to ion channels.
- in NMJ slow conformational changes can take place in the receptor -> tight binding of the agonist without opening the ionic channel.
- phosphorylation of intracellular regions of receptor proteins -> ion channel desensitization (Beta receptors) -> interfers with its ability to activate second messenger cascade.

*(2) loss of receptors*

- prolonged exposure to agonists often results in a gradual decreases in the number of receptors expressed on the cell surface (down regulation
- receptors are taken into cell by endocytosis

*(4) exhaustion of mediators*

- ie. amphetamine use -> release of amines from nerve terminals -> depletion -> tachyphylaxis

*(5) increased metabolic degradation*

- ie. barbiturates & ethanol
- same doses -> induction of metabolic pathway -> progressively lower plasma concentration.

*(6) physiological adaptation*

- diminution of a drugs effect may occur because it is nullifed by a homeostatic response
- ie. BP lowering by thiazide diuretics limited by the activation of the renin-AG-ALD system.

**(c) To describe alterations to drug response due to physiological change with special reference to neonates, the elderly & pregnancy.**

**Neonates**

- there are a number of important enzymes important for drug metabolism: hepatic microsomal oxidase, glucuronyltransferase, acetyltransferase & plasma esterases.
- these have low activity in neonates -> take 8 weeks to develop
- kernicterus -> neonatal inability to conjugate bilirubin
- morphine not used in labour -> neonates can't conjugate it -> increased half-life.

**Elderly**

- no change in receptor responsiveness

(1) decreased Q

(2) enlarged fat compartment -> increase Vd -> increased duration

(3) decreased protein binding

(4) decreased renal function

(5) decreased hepatic blood flow -> decreased delivery -> decreased metabolism

(6) decreased ability to hepatically metabolise.

**Pregnancy**

*Absorption*

- little effect on gastric emptying & absorption from GI tract
- increased in MV & reduced FRC -> rapid uptake of inhalational agents.

*Distribution*

- TBW may increase 8L
- plasma volume increases by 20% (mid) & 50% (term)
- increased extravascular volume by 5L
- increased body fat by 4kg
- decreased plasma concentration of albumin

-> increased Vd
-> free drug fraction

*Elimination*

- induction of hepatic enzymes by progesterone
- oestrogen has opposite effect
- serum choline esterase decreases at by 25% at term (slower metabolism of sux)
- increased renal blood flow & GFR -> clearance increased.

**(d) To describe the alterations in drug response due to pathological disturbance with special reference to cardiac, respiratory, renal & hepatic disease.**

- cause important changes in PK & PD parameters

*Cardiac*

(1) decreased tissue perfusion -> redistribution of Q -> heart & brain -> smaller Vd & higher concentration in plasma.

(2) decreased perfusion of kidney & liver -> impair clearance by these organs.

(3) acute cardiac failure -> increase in alpha 1 acid glycoprotein -> increase binding of basic drugs (lignocaine, bupivocaine, fentanyl)

(4) increased sensitivity to CNS depressants

*Respiratory*

- important for metabolism of some drugs (fentanyl) -> prolong duration of action.

*Renal*

(1) decreased drug clearance - use the Cockroft-Gault equation

(2) increased fluid volumes -> increased Vd

(3) acid-base changes alter ionised fraction & protein binding.

(4) increased urea leads to osmotic changes

(5) electrolyte and haematological abnormalities.

*Hepatic*

(1) decreased intrinsic enzyme clearance -> predisposes to toxicity & increased duration of action

(2) portacaval shunting -> reduces hepatic blood flow.

- important from drugs with a high extraction ratio where clearance is a function of hepatic blood flow.

(3) decreased in plasma protein production -> decrease protein binding.

(4) decreased coagulation may affect drug Vd & binding.

(5) metabolites accumlate & compete for protein binding sites -> increased free drug concentration.

(6) in sepsis -> increased Vd from leaky capillaries -> increased dose for theraputic concentration.

(7) acidosis -> decrease affinity of catecholamines for their receptor -> ionotrope tolerance.

*GI*

- slowed drug absorption

*Endocrine*

- hyperthyroidism -> increased sensitivity to certain drugs (pethidine)
- changes in receptor function (ie. nephrogenic diabeters inspidous)
- changes in signal transduction (pseudohypoparathyroidism)

**(e) To classify & describe adverse drug effects.**

- polypharmacy allows the potential for drug interactions.
- prescibed drugs can also interact with dietary consitiutents & herbal or OTC medication.

*3 mechanisms*

(1) modification of the pharmacological effects of B without altering its concentration in the tissue fluid (PD interaction).
(2) alteration of the concentration of B that reaches its site of action (PK interaction)
(3) pharmaceutical incompatibility or interactions

- for these to occur it is necessary for the theraputic range of B to be narrow (small change in effect -> loss of efficacy or toxicity)

*(1) PD interactions*

- additive or synergestic effects when drugs administed (ie. fentanyl & morphine)
- agonist + antagonists -> NDNMBD + anticholinesterase (ie. roc & neostigmine)
- combined toxicity -> renal impairment (ie. frusemide + gentamycin + ACE inhibitors + NSAIDS)
- interactions due to alteration in fluids & electrolyte (ie. sux + digoxin -> VF)

*(2) PK interactions*

Absorption - one drug:

- has large surface area for absorption
- binds or chelates
- alters gastric pH
- alters GI motility

- ie. propanolol (weak base) decreases pulmonary uptake of fentanyl

Distribution

- competition for plasma proteins
- displacement from tissue binding sites

- ie. volatile increase distribution of NMBD

Metabolism

Induction of hepatic microsomal enzymes:

- barbiturates
- carbamazepine
- glucocorticoids
- rifampicin
- ethanol
- smoking
- phenytoin

Inhibition of hepatic microsomal enzymes:

- allopurinol
- chloramphenicol
- cimetidine
- cirpro
- clarithromycin
- haloperidol

- diltiazem
- erythromycin
- fluconazole, itraconazole, ketoconazole, miconazole
- isoniazid
- omeprazole
- sulphonamides
- verapamil

- esmolol, remifentanil, etomidate & atracurium compete for same plasma esterases.
- sux, mivacurium & procaine compete for plasma cholinesterase.

Elimination

- renal excretion of weak acids or bases -> may be influenced by drugs that alter urinary pH (change of ionisation & lipi solubility)
- some drugs decrease excretion of others (ie. probencid decrease excretion of penicillin)

*(3) Pharmaceutical interactions*

- mixing drugs with differing pH -> precipitation (barbiturates (acid) + opioid (base))
- warm, dry soda lime + enflurane, isoflurane & desflurane -> carbon monoxide in circle system.
- differing osmolarities -> blood & 5% dextrose = lysis of blood.

**(f) To classify & describe the mechanisms of drug interaction**

See above

**(g) To explain the mechanisms & significance of pharmacogenetic disorders such as MH, porphyria, atypical cholinesterase and disturbance of cytochrome function.**

**MH**

- incidence 1:5,000 -> 1:65,000 anaesthetics (suspected)

- mutation in the gene coding for the **ryanodine receptor**.
- autosomal dominant
- gene on chromosome 6
- thymidine instead of cytosine
- produces a cysteine for arginine substitution at position 615 of the receptor.

- pig model = soft exudative pig disorder

*Triggers*

- stress (in pigs)
- all volatile agents (except N2O)
- sux

-> these all either enhance Ca2+ influx or slowing its efflux.
- some may have tolerated the same agents previously
- rare in barbiturate-N2O-opiate-tranquiliser-non-depolarising muscle relaxant anaesthesia.

- sux potent trigger (first exposure)
- volatiles (median exposure till fulminant -> 3)

-> excess Ca2+ release during muscle contraction -> increased musle metabolism + heat production.
- prolonged and intensified interation between actin and myosin.
- enhanced aerobic metabolism -> lactic acidosis -> accumulation of intramitochondrial calicum -> deconjugation of oxidative phosphorylation -> cytolysis.

*Clinically*

- in lower north island trigger names = Harvey, Harwere & Cook
- history of Central Core Disease
- muscular dystrophy

(1) increased ETCO2
(2) tachycardia
(3) tachypnoea
(4) masseter spasm
(5) muscle rigidity
(6) temp increase (late) - 1 C\15min

- intra-op & 4\24 post op
- tachyarrhythmias
- difficulty ventilation
- hypertension
- sweating
- cardiac arrest

*Investigations*

- PaCO2 >60mmHg
- PvCO2 >90mmHg and increasing
- BE -5 and falling

- metabolic acidiosis
- CK >50,000 IU/L
- K+ increases
- Na+ increases
- myoglobinuria

*Treatment*

- call for help
- discontinue all anesthetic agents
- maintain anaesthesia with hypnotics and opioids.
- muscle relaxation with NDNMBD
- terminate surgery
- hyperventilate
- 100% O2
- cool (N/S stomach lavage)
- maintain urine output
- inotropes as needed
- HCO3 2-4mEq/kg
- Dantrolene 2.5mg/kg every 5min (total dose 10mg/kg/day - continuous infusion **or** treat recrendences (25%))
- cardiac arrhythmias -> beta blockers & lignocaine.
- high K+ -> glucose-insulin & frusimide
- watch for DIC
- CK Q6hrly

*Prognosis*

- mortaility without dantrolene = 70%
- mortaility with dantrolene = 5%

*Prophylactic treatment*

- take history
- decrease anxiety with midazolam
- machine -> remove vapourisers, flush with O2 @ 10 L\min for 20min
- ETCO2 monitoring
- nasal temp probe
- dantrolene available

**Dantrolene**

Chemical

- hydrated 1-(((5-(4-nitrophenyl)-methylene)amino)-2,4-imidazolidinedione sodium salt)
- skeletal muscle relaxant

Uses:

- MH
- neuroleptic malignant syndrome
- spasticity
- ectasy intoxification

Structure - See diagram

Physiochemical:

- orange
- highly lipoliphillic (poor water solubility)
- in brown ampoules
- needs to be reconstituted in H2O
- has 3g of mannitol (increases solubility)
- 20mg in one amp (must be dissolved in 60mL of H20)
- final concentration = 0.33mg/mL
- pH 9.5
- needs to injected into large vein or fast running infusion.

Route - IV, PO

Dose - 2.5mg\kg to whenever responds

PK

*Absorption*

- bioavailability PO = 70%
- 2.4mg/kg -> blocks up to 75% of skeletal muscle contraction

*Distribution*

- because of poor water solubility total paralysis cannot be obtained
- levels remain therapeutic for 5 hrs
- Vd = 0.6L/kg

*Metabolism*

- hepatic
- by microsomes to 5-hydroxydantrolene = a skeletal muscle relaxant -> aminodantrolene -> reduced to acetylated derivative of dantrolene.

*Excretion*

- excreted in urine and bile
- elimination t1/2 = 12hr (adults), 10hr (children)
- clearance = 2mg/kg/min

PD

*Main action* - skeletal muscle relaxation

*Mechanism of action*

- depresses the intrinsic mechanisms of excitation-contraction coupling in skeletal muscle.
- ryanodine receptor = binding site
- exact mechanism unknown yet
- direct or indirect inhibition of the ryanodine receptor, the major Ca2+ release channel in sk muscle sarcoplasmic reticulum -> decreasing intracellular Ca2+ concentration.
- may act via the dihydropridine receptor to block electrical transmision to the ryanodine receptor.

*Musculoskeletal*

- weakness

*CVS*

- phlebitis
- no myocardial effects

*RESP*

- respiratory failure

*CNS*

- drowiness
- sleepiness
- confusion

*GI*

- dyspepsia
- N & V
- diarrhoea (PO)
- chronic liver dysfunction (PO)

New developments:

Azumolene

- 30 fold more H2O soluble
- equipotent

**Porphyria**

- drugs that increase the activity of enzymes proximal to a deficient enzyme in the haem biosynthetic pathway of porphyrins -> increase in the quantity of porphyrin precursors -> accumulation.

(1) hepatic ALA-dehdratase deficiency - autosomal recessive
(2) hepatic HMB synthase (acute intermittent porphria) - autosomal dominant
(3) hepatic URO decarboxylase (porphyria cutanea tarda) - autosomal dominant
(4) COPRO oxdiase (hereditary coproporphyria) - autosomal dominant
(5) PROTO oxidase (variegate porphyria)
(6) erythroid ALA synthetase - x-linked sideroblastic anaemia
(7) ferrochelatase (erythropoietic protoporphyria)

Drugs that increase the activities of enzymes prior to these deficiencies are:

- barbiturates
- chlordiazepoxides
- chlorproamide
- estrogens
- glutethimide
- griseofulvin
- meprobamate
- OCP
- phenytoin
- riampicin
- sulfonamide antibiotics
- Et-OH
- carbamazepine
- ergots

Classified into **hepatic** & **erythropoietic** depending on site of overproduction & accumulation of porphyrin precursor.

*Hepatic*

Symptoms are neurologic

- abdo pain
- neuropathy
- mental disturbance

*Erythropoietic*

Symptoms are cutanous photosensitivity

- excitiation of excess prophyrins in skin by long wave UV light -> cell damage -> scaring and deformation.

Diagnosis =

urinary metabolites:
- zeta-aminolevulinic acid (ALA)
- prophobilinogen (PBG)

definitively by genetics

Safe drugs to use:

- narcotics
- aspirin
- paracetamol
- phenothiazindes
- penicillins
- insulin
- atropine

**Atypical cholinesterases**

- plasma cholinesterase (pseudocholinesterase) = produced by liver and has no known function besides drug metabolism.

- ? helps body metabolize esters
- ? detoxification of plants

- all over body except at NMJ

- genetic polymorphism -> decreased availability or inhibition of cholinesterase.
- this can result in sux having a prolonged effect.

4 allelomorphic genes identified on chromosme 3 producing normal pseudocholinesterase.

(1) E1u (N)
(2) E1a (D)
(3) E1f (F)
(4) E1s (S)

- Heterozyte (4% of population) -> sux acts for 20min (dibucaine number = 30-80)

- Homozygote (0.04% of population) -> sux acts for hours (dibucaine number = 20)

*Dibucaine number*

= % inhibition of plasma cholinesterase by dibucaine (LA)
- normal = 80
- looks at activity of the enzyme
- the extent to which the enzyme can be inhibited

- mutations in these genes -> prolonged response to sux.
- total incidence = 1:2000

*Causes of Decreased plasma cholinesterase*

Decreased synthesis

- liver failure
- hereditry deficiency
- pregnancy
- neonates\elderly
- burns
- hypoproteinaemia
- malnutrition
- chronic or severe infections
- hypothyroidism

Dilute it

- heart failure
- pregnancy
- plasma pheresis

Poison it

- organophosphate poisoning
- ecothiopate
- cyclophosphamide
- phenelzine
- uraemia
- OCP
- bambuterol
- esmolol
- metclopramide
- MAOIs
- pancuronium

*Other drugs metabolised by plasma cholinesterase*

- aspirin
- ester LA
- sux
- probenacid
- mivacurium
- some Ach
- diamorphine

-> not a life threatening emergency

**Disturbances in cytochrome function**

Cytochrome P450 isoenzymes:

- superfamily of haemoproteins that are the terminal oxidases of the mixed function oxidase system found on the membrane of the cytoplasmic reticulum.

- absorption peak on spectrophotometry - 450nm when bond and reduced by CO.
- CYP450 = cytochrome P450
- last letters & numbers = designated family, individual enzyme & gene
- each consists of a single protein & a haem group as a prosthetic moiety.
- they are saturable
- they need co-factors to function

They catalyse reactions:

Phase I

- epoxidation
- N-dealkylation
- O-dealkylation
- S-oxidaiton
- hydroxylation of aliphatic & aromatic residues

Phase II

- conjugation with glucuronic acid

-> if CYP450 enzyme have defective gene origins then these reactions will be unable to be carried out -> build of substrates, prolonged action of substrate if are metabolically active or decreased/no potency if enzyme function required to change drug into an active form.

**(h) To outline the management of MH with particular reference to the phamacology of dantrolene.**

See above

**(i) To describe immune mechanisms which may result in reactions to drugs, intravenous fluids & latex. To describe the management of anaphylactic & anaphylactoid reactions.**

Hypersensitivity reaction = immune systems response to drug antigen produces tissue damage.

**Four types**

See diagram - types of hypersensitivity reactions

**Type I - IMMEDIATE (ie. anaphylaxis)**

- IgE bound antibody attached to a previously sensitised mast cell and basophil binds to antigen -> release of inflammatory mediators.

(1) increase vascular permeability & contraction of smooth muscle (histamine, platelet activating factor)

(2) chemotactic for other inflammatory cells (ECF-A, NCF, leukotriene B4)

(3) modulating the release of other mediators (BK-A, platelet activating factor)

**Type II - CYTOTOXIC (ie. ABO incompatibility)**

- when immunoglobulins bind to cell surface binding drug antigens.
- results in activation of complement lysis or phagocytosis.
- ie. halothane hepatits or ABO incompatibility

**Type III - IMMUNE COMPLEX (ie. nephritis)**

- precipitation of antigen-antibody complexes in target tissues.
- ie. glomerulonephritis, polyarteritis nodosa & RA.

**Type IV - DELAYED (ie. latex allergy)**

- extension of T lymphocyte response & interaction with macrophages that result in tissue damage.
- requires 24hr to reach maximal intensity
- ie. tuberculin skin test & contact dermatitis

**Anaphylaxis**

- type I hypersensitivity reaction
- occurs within minutes of exposure
- can be generalised or localised
- requires prior exposure
- severe & not related to dose (all or nothing)

*Mediators*

(1) histamine

- constrics GI tract & coronary smooth muscle
- bronchospasm
- increased vascualr permeability
- vasodilation via H1 receptor
- stimulation of gastric acid secretion

(2) 5-HT

- increased capillary permeability
- dilation of sk muscle capillaries
- vasoconstriciton else where
- platelet aggregation

(3) kinins

- smooth muscle contraction
- increased vascular permeability

(4) leukotrienes

- prolonged bronchospasm

(5) tissue prostglandins

- thromboxane -> contracts smooth muscle
- prostacyclin -> relaxes smooth muscle

(6) platelet activating factor & chemotactic factor

*Clinically*

- most common offenders = sux, cephalosporins
- uriticarial rash

- swelling of soft tissues
- wheeze
- hypotension

*Treatment*

- stop all potential agents
- head down
- IVF
- big IV access
- adrenaline
- histamine antagonism (ranitidine)
- corticosteroids (hydrocortisone)
- O2
- ETT
- salbutamol

**Anapylactoid reaction**

= release of mediators (histamine) from mast cells through non-immune mechanisms
- ie. morpine, pethidine, mivacurium & atracurium, synthetic colloids, midazolam.
- not mediated by IgE & doesn't not require prior sensitizations.
- less severe than anaphylaxis
- do a serum tryptase within 12 hrs
- manage in same way as anaphylaxis