VARIABILITY IN DRUG RESPONSE

(a) ***To define tachyphylaxis, tolerance, addiction, dependence and idiosyncrasy.***

(b) ***To describe mechanisms of tolerance.***

"Tachyphylaxis"
- A phenomenon where there is a rapid decrease in response to repeated doses of a drug over a short period of time (Eg. ephedrine)
- Mechanism – Due to reduction in NT stores which need to be reconstituted

"Tolerance"
- A phenomenon where chronic exposure to a drug results in a larger dose being needed to be given to produce the same effect (Eg. chronic opioids use, topical GTN)
- Mechanism:
    - (1) Cellular tolerance (most important) → involves changes in target receptor:
        - (i) ↓ receptor affinity to drug
        - (ii) ↓ receptor density (Ie. down-regulation)
        - (iii) ↓ cellular response with drug binding (Ie. ↓ activation of 2nd messenger systems)
    - (2) Depletion of intermediate substances implicated in drug effect (Eg. amphetamines deplete amine stores in nerve terminals)
    - (3) Altered drug metabolism → ↑ metabolism (Eg. EtOH, barbiturates) or ↓ metabolism (Eg. GTN)
    - (4) Physiological adaptation → homeostatic mechanisms reduce drug effects (Eg. RAAS activation with thiazide use)

> Note – "Cross-tolerance" → tolerance can occur b/t different drug classes that produce similar pharmacological effects (Eg. EtOH and GA agents)

"Dependence":
- Regular exposure to a drug leads to tolerance and cessation of the drug results in a withdrawal illness → can be either:
    - (i) Physical dependence – Abnormal physiological state a/w specific physical symptoms ("Withdrawal syndrome") occurs when a repeatedly used drug is suddenly ceased
    - (ii) Psychological dependence – Compulsion that requires continuous drug use to produce reward and avoid discomfort

> Important to note – Psychological dependence outlasts physical dependence (and withdrawal syndrome) → MAIN factor for addiction

"Addiction":
- Psychological illness characterised by continued compulsive use of a drug such that the behaviour is harmful to the individual's physical health, psychological state and/or social situation
- It involves phenomenon of "tolerance" and "dependence"

"Idiosyncrasy":
- An individual response to a drug that is infrequently observed and generally unrelated to drug dosage → it is usually explained by genetic differences

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

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

Variations in drug response can be due to:
- (1) Pharmacokinetic variations → different [drug] result at sites of drug action with same dosing due to differences in absorption, distribution, metabolism, or excretion
- (2) Pharmacodynamic variations → different drug responses occur to same [drug]

(I) **<u>Alterations to drug response in neonates</u>**:

<u>Pharmacokinetic implications of physiological changes associated with neonates</u>:

Absorption	Oral - Liquid preparations → ↑ absorption due to ↑ SA contact with intestines - ↑ gastric emptying time → ↑ gastric absorption but ↓ intestinal absorption (b/c it delays drug delivery to intestines) - ↑ intestinal transit time → ↑ absorption due to ↑ time in intestines - ↑ vomiting/regurgitation → ↓ absorption S/L – Useful for lipid-soluble drugs to avoid dermal barrier and hepatic 1st pass metabolism → but limited cooperation with neonate IM – ↑ muscle blood flow 2° to ↑ C.O. → ↑ systemic absorption SC – ↓ tissue blood flow → slower but sustained absorption → "depot effect" Transdermal – Variable absorption PR – variable absorption → ↑ pH (7-12) and varying proximity to vasculature IV – ↑ C.O. means fast onset of action → but difficult access Neuraxial – ↓ epidural fat to buffer drug uptake → ↑ systemic absorption Inhalational – Faster wash-in (FA/FI) of inhaled anaesthetic agents due to ↓ BG solubility and 2x ↑ MV (esp ↑ RR) → ↑ C.O. should retard wash-in, but it is less than magnitude cf. other factors, so net effect is still faster wash-in
Distribution	- ↓ protein binding (esp albumin and α1 acid glycoprotein) – Means ↑ free % of drugs (esp if highly protein bound) → this is exaggerated by acidosis, ↑ circulating FFA, ↑ bilirubin levels (with neonatal jaundice) → thus, need to ↓ drug dose for effect - ↑ V_D – Due to (i) ↑ TBF/ECF/BV cf. adult, and (ii) ↑ free % of drug 2° to ↓ PB → thus, ↑ loading drug dose given (esp for polar/hydrophilic drugs that stay within ECF) - Ionisation – Neonatal pH is ↓ cf. adult → ↑ ion trapping of basic drugs as they will have ↑ ionised % - ↑ C.O. – ↑ rapid distribution to and from site of action → large % of CO distributed to VRG (esp brain – 33% C.O. (50% VRG) cf. 15% C.O. (25% VRG) in adults) → thus, rapid onset/offset of drug (esp in VRG organs) - ↓ % fat/muscle per unit weight – (i) ↓ redistribution of drugs from site of action → thus, ↑ initial peak blood level and more sustained blood level of drug. (ii) ↓ apparent V_D for non-polar/lipophilic drugs → thus, ↓ dose - ↑ % brain content per unit weight – (i) acts as a reservoir for lipophilic drugs and (ii) ↓ redistribution to peripheral compartments → ↑ duration of action
Metabolism and Excretion	- Immature hepatic enzyme system (incl CYP450) – ↓ phase I (esp oxidation) and phase II (esp glucuronidation) reactions → prolonged drug t ½ - ↓ plasma cholinesterase levels (50% of adult enzyme activity)

	- ↓ renal function (↓ $C_{CREATININE}$ < 10%) → due to incomplete glomerular development, ↓ RBF/GFR, and ↓ tubular secretion → prolonged drug t ½ - Respiratory excretion of inhaled anaesthetic agents → faster wash-out for same reasons as uptake

Pharmacodynamic implications of physiological changes associated with neonates:

- Immature neonatal BBB → ↑ drug delivery to brain → ↑ CNS toxicity risk (esp sedatives, narcotics)
- Immature respiratory centre → ↑ risk of respiratory depression and apnoea (esp GA agents, narcotics, sedatives)
- Immature CVS control (heart ↓ compliant, ↓ Ca^{2+} sensitivity of myocardial fibres, immature SNS reflexes, C.O. is more rate and preload dependent) → ↑ risk of CVS depression (esp GA agents)
- ↑ sensitivity to drugs (Ie. ↓ BG solubility → ↑ MAC; NMJ has ↓ ACh → ↑ sensitivity to NMBD; respiratory muscles have ↓ % type 1 muscle fibres → ↑ resistance to NMBD)

(II) **Alterations to drug response in the elderly**:

Pharmacokinetic implications of physiological changes associated with the elderly:

Absorption	Oral – ↑ reflux, ↓ GI motility, ↓ GI blood flow and mucosal SA → ↓ absorption IM/SC/transdermal – ↓ C.O./tissue blood flow, and ↓ muscle/subcutaneous mass → ↓ absorption IV – ↓ C.O. → ↓ onset of action Neuraxial – Narrow epidural space → ↑ absorption and spread of LA Inhaled – ↓ MV → ↓ uptake; ↓ C.O. → ↑ uptake
Distribution	- Protein binding – (i) ↓ albumin → ↓ binding of acidic drugs, (ii) ↑ A1AGP → ↑ binding of basic drugs - ↓V_D – Due to ↓ TBF (a/w ↓ ICFV/BV), ↓ LBM and ↑ body fat → thus, ↓ loading drug dose given - ↓ C.O. – slower redistribution to/from site of action → slow onset/offset - ↓ % muscle content – ↓ redistribution of drugs from site of action → thus, ↑ initial peak blood level and more sustained blood level of drug - ↑ % fat content – ↑ reservoir for lipid-soluble drugs (Eg. volatiles)
Metabolism and Excretion	- ↓ hepatic metabolism (esp CYP450 and oxidative) due to ↓ HBF and ↓ liver mass (↓ # of enzymes) → prolonged drug t ½ - ↓ renal excretion (due to ↓ RBF/GFR and tubular secretion) → prolonged drug t ½

Pharmacodynamic implications of physiological changes associated with the elderly:

- ↑ sensitive to GA/sedatives (Ie. opioids, MAC-sparing for volatiles) and other drugs (Eg. vasopressors) → due to ↓ receptor sites and ↓ post-receptor signalling
- ↓ LA requirements → due to ↓ # and myelination of nerve fibres, narrower epidural spaces, and ↓ hepatic clearance
- ↑ sensitivity to NMBD → due to ↓ skeletal muscle mass
- Impaired compensatory mechanisms (cardio-respiratory) → ↓ dose to minimise acute haemodyanmic changes (esp IV anaes agents)
- Polypharmacy → ↑ potential for drug interactions
- ↓ compliance of drugs

(III) **Alterations to drug response in pregnancy**:

Pharmacokinetic implications of physiological changes associated with pregnancy:

Absorption	Oral - N/V and heartburn common → ↓ absorption - ↓ gastric emptying only during labour (due to pain, anxiety, opioids) → ↓ absorption - ↓ gastric motility 2° to intestinal compression → ↑ gastric absorption but ↓ intestinal absorption IM/SC/transdermal - ↑ skin blood flow 2° to ↑ C.O. (by 30-40%) and ↓ SVR → ↑ absorption IV - ↑ C.O. → ↑ onset of action Neuraxial - ↓ epidural space 2° to engorged epidural veins → ↓ spinal and epidural doses Inhalational - Progesterone-mediated ↑ MV (by 50-70%) 2° to ↑ TV and MV, and ↓ FRC (by 20%) → ↑ FA/FI ratio (or uptake) of inhaled anaesthetic agents - ↑ C.O. → opposes effect of ↑ MV
Distribution	- ↑ TBW/ECF (by 50%) → ↑ V_D (esp for polar/ionized drugs (Eg. NMBD)) - ↑ body fat % → ↑ V_D and ↑ sequestration of lipid soluble drugs (Eg. propofol) - ↓ plasma protein 2° to dilutional effect a/w ↑ TBW/ECF: o (i) Esp ↓ albumin → results in ↑ free % of acidic drugs (Eg. STP, propofol) → thus, ↓ dose required and ↑ transplacental transfer of drug. Note – this is further exacerbated late in pregnancy when ↑ FFA that competes with acidic drugs for binding to remaining plasma albumin o (ii) ↓ A1AGP (by 30%) → ↑ free % of basic drugs (Eg. LA, β blockers) → thus, ↓ dose required and ↑ transplacental transfer of drug - Ionisation → mild respiratory alkalosis (pH 7.42) 2° to ↑ MV → ↑ transplacental transfer of basic drugs as they will have ↑ % in unionized form → also ↑ ion trapping of drug in more acidotic foetal circulation - ↑ C.O. – ↑ rapid distribution to and from site of action → thus, rapid onset/offset of drug
Metabolism	- Progesterone:oestrogen ratio o Progesterone → induces hepatic enzymes → ↑ metabolism o Oestrogen → inhibits hepatic enzymes → ↓ metabolism - ↓ plasma cholinesterase (30%) → ↓ metabolism of SCh (Nb. but ↑ prolonged effect of SCh is offset by ↑ in its V_D) - Placenta has enzymes similar to liver → metabolises drugs also - Foetal liver have functioning CYP450 and can metabolise drugs too → but are poor conjugators (Ie. drugs pass back into maternal circulation for conjugation)
Excretion	- ↑ RBF/GFR (50%) → ↑ clearance/↓ elimination t ½ of water-soluble drugs - ↑ MV/↓ FRC → ↑ washout of volatile agents

<u>Pharmacodynamic implications of physiological changes associated with pregnancy</u>:

- MAC of inhaled anaesthetic agents ↓ 40% (due to progesterone/β-endorphins)
- ↓ induction dose of STP by 35% (due to ↑ Vd and elimination)
- ↑ sensitivity to vecuronium (as ED_{50} ↓ by 50%)
- Effect on SCh relatively unchanged (↓ metabolism 2° to ↓ plasma cholinesterase levels offset by ↑ Vd)
- ↓ LA dose (by 25-30%) required in neuraxial blocks due to → (i) ↑ spread of LA (esp at 2nd TM due to distension of EDV), (ii) ↑ sensitivity of nerve fibres to LA, and (iii) ↑ diffusion of LA to membrane receptor sites
- ↓ responsiveness to vasopressors (Eg. ephedrine)
- ↑ hypotension associated with regional blockade (due to ↑ SNS tone during pregnancy)

- ↑ dose of anti-coagulants (Eg. heparin, warfarin) due to ↑ CFs

(IV) **Alterations to drug response with cardiac disease**:

Pharmacokinetic implications of cardiac disease:

Absorption	Oral – ↓ GI blood flow 2° to ↓ C.O. and gut mucosal oedema → ↓ absorption IM/SC/transdermal – ↓ C.O./tissue blood flow and tissue oedema → ↓ absorption IV – ↓ C.O. → ↓ onset of action Inhaled – ↓ C.O. → ↑ uptake
Distribution	- ↑ V_D – Due to ↑ TBF (Ie. generalised oedema) → thus, ↑ loading drug dose - ↓ C.O. – slower redistribution to/from site of action → slow onset/offset - ↓ plasma protein 2° to dilutional effect a/w ↑ TBW/ECF: o (i) ↓ albumin → results in ↑ free % of acidic drugs (Eg. STP, propofol) o (ii) ↓ A1AGP → ↑ free % of basic drugs (Eg. LA, β blockers)
Metabolism and Excretion	- ↓ hepatic metabolism due to ↓ HBF (a/w ↓ C.O.) and ↓ liver mass (↓ # of enzymes) → prolonged drug t ½ - ↓ renal excretion (due to ↓ RBF/GFR a/w ↓ C.O.) → prolonged drug t ½

Pharmacodynamic implications of cardiac disease:
- ↑ haemodynamic sequelae with –ve inotropic agents (Eg. volatile agents, induction agents, β-blockers)

(V) **Alterations to drug response with respiratory disease**:

Pharmacokinetic implications of respiratory disease:

Absorption	- ↓ lung surface area → ↓ absorption of inhaled drugs - ↓ FRC (and ? ↑ MV) → ↑ uptake of volatile agents
Distribution	- Respiratory acidosis → ↑ ion trapping of basic drugs
Metabolism and Excretion	- ↓ excretion of volatile agents → prolonged offset

Pharmacodynamic implications of respiratory disease:
- None

(VI) **Alterations to drug response with renal disease**:

Pharmacokinetic implications of renal disease:

Absorption	Oral – Gut mucosal oedema (a/w generalised oedema), and ↑ vomiting and delayed gastric emptying (a/w uraemia) → ↓ absorption IM/SC/transdermal – Tissue oedema → ↓ absorption
Distribution	- ↑ V_D – Due to ↑ TBF (Ie. generalised oedema) → thus, ↑ loading drug dose - ↓ plasma protein (2° to dilutional effect a/w ↑ TBW or nephrotic syndrome): o (i) ↓ albumin → results in ↑ free % of acidic drugs (Eg. STP, propofol) o (ii) ↓ A1AGP → ↑ free % of basic drugs (Eg. LA, β blockers) - Ionisation – Metabolic acidosis (Ie. uraemia) → ↑ ion trapping of basic drugs
Metabolism and	- ↓ renal clearance of renally-cleared drugs (and metabolites) causing prolonged drug t ½ → depends on (i) degree of renal impairment and (ii) degree of renal

Excretion	clearance of drug - Consider dose reduction +/- extended dosing intervals of renally-cleared drugs: $\text{Reduced dose} = \frac{\text{(Usual dose) x (Pt's } C_{CREATININE})}{\text{(Expected normal } C_{CREATININE})}$

Pharmacodynamic implications of renal disease:
- Uraemic encephalopathy → ↑ sensitivity to GA agents, Bz and opioids
- ↑ K^+ → ↓ sensitive to ND NMBD; ↑ sensitive to SCh
- Metabolic acidosis → ↑ duration of NMBD; ↑ toxicity to LA's

(VII) **Alterations to drug response with hepatic disease**:

Pharmacokinetic implications of hepatic disease:

Absorption	Oral – Gut mucosal oedema (a/w generalised oedema), ↑ vomiting, delayed gastric emptying → ↓ absorption; ↑ GI blood flow 2° to ↑ C.O. → ↑ absorption IM/SC/transdermal – Tissue oedema → ↓ absorption; ↑ tissue blood flow 2° to ↑ C.O. → ↑ absorption IV – ↑ C.O. → ↑ onset of action Inhaled – ↑ C.O. → ↓ uptake; ↓ FRC (due to ascites) and ↑ MV (due respiratory compensation for acidosis) → ↑ uptake
Distribution	- ↑ V_D – Due to ↑ TBF (Ie. generalised oedema) → thus, ↑ loading drug dose - ↓ plasma protein (2° to ↓ synthesis and dilutional effect a/w ↑ TBW): o (i) ↓ albumin → results in ↑ free % of acidic drugs (Eg. STP, propofol) o (ii) ↓ A1AGP → ↑ free % of basic drugs (Eg. LA, β blockers) - Ionisation – Metabolic acidosis → ↑ ion trapping of basic drugs
Metabolism and Excretion	- ↑ bioavailability due to ↓ hepatic first-pass clearance 2° to portocaval shunts - ↓ hepatic metabolism due to ↓ liver mass (↓ # enzymes) → ↑ t ½ of hepatically-cleared drugs

Pharmacodynamic implications of hepatic disease:
- Encephalopathy → ↑ sensitivity to GA agents, Bz and opioids
- Coagulopathy → ↓ dose of anticoagulants/antiplatelet agents
- Metabolic acidosis → ↑ duration of NMBD; ↑ toxicity to LA's

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

Rawlins & Thompson classification of adverse drug effects:

Type A (Augmented) effect:
- These reactions are common and predictable from drug pharmacology → generally dose related, reversible and managed with dose adjustment
- Mechanisms:
    - (i) Extension of drug's therapeutic response at target site (Eg. Bleeding with warfarin, ↓ BGL with insulin)
    - (ii) Other effects of drug at same target site (Eg. opioids act on μ-receptors to cause analgesia, but cause sedation, respiratory depression, constipation, Etc.)
    - (iii) Effects of drug at different target site (Eg. adrenaline acts on β2 receptors to cause bronchodilation, but act on β1 and cause unwanted ↑ HR and BP)

> Note – Many have a pharmacokinetic basis (Eg. impaired organ-dependent metabolism → ↑ plasma [drug] → adverse effects)

Type B (Bizarre) effect (aka. "Idiosyncratic reaction"):
- These reacts are rare and unpredictable from drug pharmacology → generally occur in predisposed patients (Ie. rare genetic polymorphism), show little or no dose relationship, are irreversible and drug needs to be ceased
- Mechanism is poorly understood → likely immunological or involves genetic pre-disposition
- Eg. Allergic/anaphylactic reactions, hepatitis with halothane, agranulocytosis with clozapine

Type C (Chronic) effect:
- Adverse reactions occur after long term therapy
- Eg. Amiodarone and pulmonary lung disease, adrenal suppression with steroids

Type D (Delayed) effect:
- Adverse reactions occur years after a drug was used
- Eg. Tardive dyskinesia with neuroletpics

Type E (End of use) effect:
- Rebound effect after drug cessation
- Eg. Withdrawal reactions with chronic benzodiazepine use

(f) ***To classify and describe mechanisms of drug interaction.***

"Drug interactions" occur when the pharmacological action of one drug is altered by another → can lead to unwanted or therapeutically beneficial effects

Types of drug interactions:

(1) Pharmaceutical → involves delivery of drug
- (a) Physicochemical incompatibility b/t drugs → causes precipitation of drug (Eg. STP (alkaline) + SCh (acidic))
- (b) Absorption or binding to containers (Eg. GTN + PVC lines)
- (c) Degradation of drug (Eg. insulin denatures in solution of dextrose)

(2) Pharmacokinetic → one drug alters the way the body handles another, resulting in an altered plasma [drug]
- (a) Absorption
  - Mainly due to altered oral absorption a/w:
    - (i) Complex formation (Eg. tetracycline + Ca in milk/antacids)
    - (ii) Altered gastric emptying/intestinal motility (Ie. opiates ↓ intestinal motility → ↓ absorption of drugs absorbed in small intestine (Eg. paracetamol); metoclopramide ↑ intestinal motility → ↓ absorption of drugs absorbed in stomach (Eg. cimetidine))
    - (iii) Altered gastric and intestinal pH (Ie. ↑ gastric pH by antacids impairs absorption of weakly acidic drugs)
  - Altered parental absorption a/w localised vasoconstriction (Eg. adrenaline + LA)
- (b) Distribution
  - (i) Competition by drugs for plasma protein binding site → affects drugs that:
    - Are highly protein-bound drugs (Eg. warfarin, diazepam, phenytoin) → b/c displacement of such drug will lead to large ↑ unbound % in plasma
    - Have enzyme system close to saturation or zero-order kinetics (Eg. phenytoin) → b/c ↑ displacement of drug and ↑ unbound % cannot be cleared effectively, resulting in large ↑ unbound % in plasma
  - (ii) Drugs that alter C.O. impact on distribution of drugs to target, peripheral tissues (Eg. β-blockers ↓ C.O. → slow onset/offset times of drugs reliant on distribution)
- (c) Metabolism
  - (i) Inhibition/induction of microsomal enzymes (Eg. CYP450)
    - Enzyme induction – Certain drugs can induce CYP450 enzyme synthesis → ↑ enzyme activity and drug metabolism → resulting in ↓ plasma [drug]

      Examples – A/Bs (rifampicin), chronic EtOH, volatiles (halothane, enflurane), barbiturates (STP, Phenobarbital), AEDs (phenytoin, carbamazepine), cigarette smoking, hormones (steroids)

    - Enzyme inhibition – Certain drugs inhibit CYP450 enzyme by competitive inhibition → ↓ enzyme activity and drug metabolism → resulting in ↑ plasma [drug]

      Examples – A/Bs (metronidazole, isoniazid, chloramphenicol), H2RB (cimetidine), MAOis (phenelzine, tranylcypromine), amiodarone, grapefruit juice)

  - (ii) Inhibitors of non-microsomal enzymes (Eg. MAOi, COMTi)
- (d) Excretion
  - (i) ↓ urinary excretion – Competition for common tubular transport system occurs with weak organic acids (Eg. probenecid + penicillin)

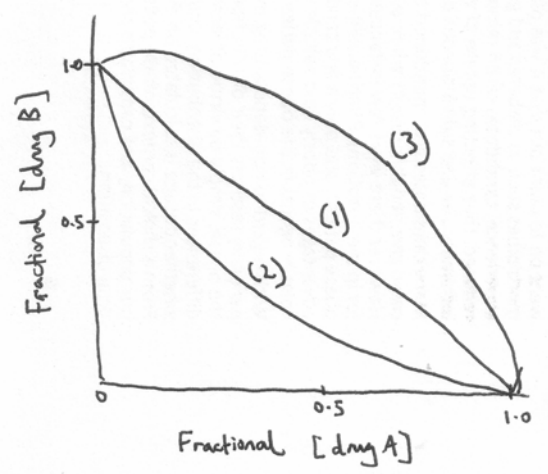
- (ii) Changes in urine pH – Alkalinising agents (Eg. $NaHCO_3$/acetazolamide) facilitate excretion of weak acids; acidic agents (Eg. NH_4Cl) do the opposite
- (iii) Changes in urine volume
- (iv) Changes in biliary excretion (Eg. Phenobarbital ↑ bile flow and biliary conjugation of drugs)

(3) <u>Pharmacodynamic</u> → one drug alters the body's response to another at a given plasma [drug] → effect can be either (i) antagonistic, (ii) additive, or (iii) synergistic

- (a) Direct interaction – Drugs act at same receptor site for effect (Eg. naloxone + opioids → direct antagonism; N_2O + volatiles → direct additivity)
- (b) Indirect interaction – Drugs act at different receptor sites for same effect (Eg. opioids + volatiles → indirect synergism; atropine + neostigmine → indirect antagonism)

Important to note – "<u>Isobologram</u>":

- A graph used to study the nature of drug interactions → describes the combined effects of two different drugs using a line to connect equipotent dose (or [ ]) of two drugs that exert a similar effect



- Isobologram can produce 3 sets of lines:
  - (1) Additivity (or Summation) – Effect of 2 drugs combined equal sum of drugs given separately (Eg. N_2O + volatile agents; midazolam + propofol)
  - (2) Supra-additivity (or Synergism) – Combined effects of two drugs is greater than would be seen from a purely additive effect → due to drugs having similar effects through different mechanisms (Eg. opioids + volatile agents)
  - (3) Intra-additivity (or Antagonism) – Combined effect of two drugs is less than would be seen from a purely additive effect (Eg. adrenaline + β-blocker)

(g) ***To outline the pathophysiology of drug abuse with particular reference to peri-operative period and potential drug interactions (specific drugs to consider include alcohol, nicotine, benzodiazepines, opioids, cannabinoids, cocaine, amphetamines and ecstasy).***

Patients with chronic drug abuse develop "tolerance" to drugs with varying degrees of "psychological dependence" and "physical dependence" (esp with opioids, EtOH, benzodiazepines and barbiturates)

<u>Anaesthetic considerations during perioperative period</u>:

(1) Anaesthetic requirements vary:
- Acute drug abuse → act in additive or synergistic manner with anaesthetic agents, thus requiring ↓ anaesthetics
- Chronic drug abuse → generally causes tolerance to most anaesthetic agents (via "cross-tolerance") – see above for definitions and mechanisms – thus needing ↑ anaesthetics

Substance	Acute use	Chronic use
Opioids	↓ requirements	↑ requirements
Barbiturates	↓ requirements	↑ requirements
EtOH	↓ requirements	↑ requirements
Cannabinoids	↓ requirements	0
Benzodiazepines	↓ requirements	↑ requirements
Cocaine	↑ requirements	0
Amphetamines	↑ requirements	↓ requirements
Phencyclidine	↓ requirements	?

(2) "Withdrawal syndrome" can occur in patients who are physically dependent
- Life-threatening complications due to SNS overactivity can occur with abstention (barbiturate withdrawal is most lethal)
- Perioperative doses of abused substances should be provided or specific agents given to prevent withdrawal → for example:
    - Opioid dependence → provide any opioid (EXCEPT those with mixed agonist-antagonist activity)
    - EtOH dependence → provide a benzodiazepine
    - Bz or barbiturate dependence → provide a Bz
- Clonidine is useful to treat post-operative withdrawal syndromes → α2 agonist that ↓ central SNS outflow a/w withdrawal syndromes

(3) Consider a regional technique, if possible

(h) ***To explain the mechanisms and significance of pharmacogenetic disorders such as malignant hyperpyrexia, porphyria, atypical cholinesterase and disturbance of cytochrome function.***

> "Pharmaco-genomics" → genetic contribution to population variability in drug responses → field for potential individualised prescribing based upon their genetic make-up

(I) Malignant Hyperpyrexia (MH):

Overview of MH:

- MH is a genetically-inherited condition whereby exposure to a triggering agent (esp SCh or volatile anaesthetic agent) triggers an acute and uncontrolled hypermetabolic state involving hyperactive muscle contraction
- Incidence – 1:40,000 (adults); 1:15,000 (children)
- It is a life-threatening emergency – It has a 80% mortality without specific treatment, and 8% mortality with appropriate treatment

Pathophysiology of MH:

- MH is a heterogenous genetic disorder:
    - Majority involve an autosomal dominant inheritance with variable penetrance pattern – Involves RYR1 (chromosome 19), which codes for the Ryanodine Ca^{2+} channel on skeletal muscle fibre. This channel controls sarcoplasmic reticulum Ca^{2+} release during muscle depolarisation
    - Other defects involve 2nd messenger systems and Na^{+} channel located on other chromosomes (1, 3, 7, 17)
    - Autosomal recessive inheritance with Ken-Denborough syndrome
- In genetically predisposed persons, the presence of a triggering agent causes an acute hypermetabolic state whereby the principle event involves massive Ca^{2+} release from skeletal muscle SR. This precipitates:
    - (i) Hyperactive muscle contraction, which leads to:
        - Uncontrolled metabolism, resulting in excessive O_2 consumption, CO_2 production, severe acidosis and hyperthermia
        - Muscle breakdown causing K^{+} efflux (and hyperkalaemia), an elevated CK and myoglobinaemia
    - (ii) Increased SNS activity
    - (iii) Organ dysfunction, such as cardiac arrest (due to acidosis, hyperkalaemia and SNS stimulation), renal failure (due to myogloburia), seizures (due to cerebral oedema), DIC and hepatic dysfunction
- Triggering agents include:
    - (1) All volatile anaesthetic agents
    - (2) Muscle relaxants – Suxamethonium, decamethonium, and curare
    - (3) Stimulants – Caffeine, xanthines, cocaine
    - (4) Carbachol (parasympathomimetic used in ocular surgery and treatment of glaucoma)
    - (5) Phenothiazine (antipsychotic)

Risk factors for MH-susceptibility:

- (1) Previous episode of MH following exposure to triggering agent

> Note – Previous exposure to an anaesthetic agent without MH does NOT rule out MH susceptibility. 33% of MH cases have had prior exposure to the trigger without complication

- (2) Diagnosed as MH-susceptible from:
    - (i) Muscle biopsy (most sensitive and specific) → obtain vastus medialus from FNB and exposing it to halothane/caffeine
    - (ii) Genetic testing for RYR1 mutations (Note: –ve test does NOT exclude MH. 30% of true MH-susceptible patients test +ve)
- (3) Previous trismus during induction of anaesthesia
- (4) Positive family history of MH (Note: 75% of cases do not have such history)
- (5) Musculoskeletal disorders (Eg. strabismus, kyphoscoliosis, clubfoot)
- (6) Central-core disease (Eg. osteogenesis imperfecta, King-Denborough syndrome, myopathies such as Duchenne's muscular dystrophy)

Features of MH:
- Clinical signs:
    - (1) Abnormal muscle contractile response and damage
        - Generalised muscle rigidity (occurs in 75% of cases)
        - Masseter spasm (often an early sign of MH; 50% of patients with this sign following induction of anaesthesia are MH-susceptible)
    - (2) Hyperthermia
        - Fever – A rise in temperature of 1°C every 5 minutes (can be a late sign)
        - Profuse sweating
    - (3) Hypermetabolism
        - Increased $ETCO_2$ (usually by 2-3X; an early and sensitive marker)
        - Decreased ETO_2
        - Tachypnoea (if not relaxed)
        - Cyanosis
    - (4) Increased SNS activity
        - Tachycardia
        - Initial hypertension, then hypotension
        - Cardiac arrhythmia (can present as sudden cardiac arrest)
    - (5) Organ dysfunction
        - ARF
        - DIC
        - Cerebral oedema with seizures
        - Liver failure
- Biochemical/laboratory signs:
    - Electrolyte imbalance – Hyperkalaemia, hypernatraemia, hyperphosphataemia
    - Elevated CK
    - Myoglobinaemia and myoglobinuria
    - Mixed respiratory and metabolic acidosis

(II) <u>Porphyria</u>:

Overview of porphyria:
- There are two forms of porphyria → (i) Hepatic (acute) and (ii) Erythropoeitic (cutaneous)
- Only the "acute hepatic" form has anaesthetic implications → it has 3 sub-types:
    - (i) Acute intermittent porphyria
    - (ii) Variegate porphyria
    - (iii) Hereditary porphyria

Pathophysiology of porphyria:
- Porphyria is an inherited disease (autosomal dominant) whereby a defect in haem synthesis leads to an accumulation of precursors that are oxidised (via δ-aminolaevulinic acid (ALA) synthetase) into porphyrins, which are toxic at high levels
- Porphyric crisis are generally occur in women in 3rd to 4th decade → precipitated by:

- (i) Drugs that induce ALA synthetase → include barbiturates, etomidate, some steroid drugs (incl aminosteroid NMBD), some benzodiazepines (midazolam is OK), enflurane, some anti-hypertensives (hydralazine, α-methyldopa), phenytoin, cephalosporins, sulphonylurea, OCP, Etc.
- (ii) EtOH
- (iii) Starvation and dehydration
- (iv) Infection
- (v) Stress
- (vi) Menstruation
- (vii) Pregnancy

Clinical features of porphyria:
- Pyrexia
- Abdominal crisis (Eg. pain and vomiting)
- Autonomic changes
- Neurological disturbances:
  - PNS – Sensory changes and motor paralysis due to demyelination of nerves
  - CNS – Mental disturbances, coma, convulsions

> Note:
> - Patients may never had an attack previously → taking a good FHx is vital!
> - Normal biochemistry can occur b/t episodes
> - Symptoms can mimic surgical pathology (Eg. acute abdomen)

Management of porphyria:
- (1) Cease triggering agent
- (2) Haem arginate (inhibitor of ALA synthetase) → 3 mg/kg IV daily for 4 days
- (3) Supportive management – Treat HTN/tachycardia (with β-blockers), convulsions (with midazolam, propofol), pain (with opioids), dehydration (with IV glucose/fluids), electrolyte imbalances and any underlying infection

(III) Atypical cholinesterase:

Overview of atypical cholinesterase:
- A single gene locus on chromosome 3 encodes plasma cholinesterase (PC), an enzyme that hydrolyses suxamethonium (SCh) into succinylmonocholine, then into succinic acid and choline
- A nucleotide alteration in this gene leads to a single amino acid substitution that can produce several variants of PC with differing levels of enzyme activity (Ie. qualitatively-abnormal enzyme) → this results in ↓ metabolism of SCh, which causes ↑ plasma [SCh] and prolonged muscle paralysis

Types of atypical cholinesterase:
- There are four alleles involved:
  - (1) Usual (normal) allele (Eu)
    - Eu/Eu (DN80/FN60) – Normal SCh response (3-5 mins) – 96% prevalence
  - (2) Atypical (dibucaine-resistant) allele (Ea)
    - Ea/Ea (DN20) – Greatly prolonged block (> 3 hrs) – 1:3200
    - Eu/Ea (DN40-60) – Slightly prolonged block (30 mins) – 1:480
  - (3) Fluoride-resistant gene
    - Ef/Ef (DN70/FN35; 1:150,000) and Ef/Ea (DN45/FN35; 1:20,000) – Greatly prolonged blocks (2-3 hrs)
    - Ef/Eu (DN75/FN50) – Slightly prolonged block – 1:200
  - (4) Silent (absent) type

- Es/Es (1:100,000) is the most severe form of mutation as the enzyme lacks activity (and reversal of SCh depends on its renal excretion!) – Causes up to 8 hours of paralysis after single dose!
- Es/Ea (1:30,000) and Es/Ef (1:150,000) produce greatly prolonged paralysis
- Eu/Es (1:90) produces a slightly prolonged block

Important to note:

"Dibucaine number" (DN):
- DN is the % inhibition of normal PC activity in metabolising benzylcholine substrate in the presence of 10^{-5} mol/L dibucaine (an amide LA)
- DN is proportional to the level of PC function in hydrolysing SCh – DN80 means normal PC, while DN20 means homozygous atypical PC variant, and DN40-60 means heterozygous atypical PC variant
- Note – DN does NOT reflect the quantity of enzyme in plasma (only its quality), thus ↓ PC levels (Ie. liver disease) will have a DN80 but prolonged SCh duration of action

"Fluoride number" (FN) is the % inhibition of normal PC in metabolising benzylcholine when 50 mM Na fluoride is added. FN60 means normal PC, while FN35 means homozygous fluoride-resistant enzyme

Management of atypical cholinesterase:
- Patients should remain anaesthetised and mechanically ventilated while the NMB naturally wears off and muscle function returns
- Administration of FFP (containing source of PC) can reverse the block BUT carries risks associated with a transfusion!

(IV) <u>Disturbance of cytochrome function</u>:

Overview of CYP450:
- CYP450 is a superfamily of membrane-bound haeme proteins that catalyses metabolism of most drugs (esp oxidation, reduction and conjugation reactions) → usually found in liver (within SER), but is also in GIT (esp small intestines), adrenal cortex, kidney, lung and brain

Examples of relevant CYP450's:
- CYP2B6: Propofol
- CYP2D6: Codeine, flecainide, metoprolol
- CYP2E1: Halogenated volatiles, paracetamol
- CYP3A4: Diazepam, temazepam, midazolam, fentanyl, vecuronium, lignocaine

Key CYP450 – CYP 3A4/3A5 (metabolise > 50% drugs) and CYP2D6 (metabolise 25% drugs)

Example of genetic CYP2D6 dysfunction:
- CYP2D6 substrates include – (i) Analgesics (codeine, dextromethorphan), (ii) Psychiatric meds (SSRI, haloperidol, TCAs), (iii) CVS drugs (metoprolol, amiodarone, flecainide)
- CYP2D6 is inactive in 1% Orientals and 6% Caucasians; ultra-rapid metabolisers (Ethiopian, Spanish)
- Genetic variants (Ie. CYP2D6 deficiency in HK Chinese) can cause defect in drug metabolism (Ie. lack analgesic effect from codeine metabolism)

(i) ***To outline the management of malignant hyperthermia with particular reference to the pharmacology of dantrolene.***

(I) Acute management of MH:

A crisis should be declared – Help should be sought immediately and the surgeon notified ASAP

The key aspects of management include:

- (1) Immediately ceasing all possible triggering agents (Ie. turn off volatile agent)
- (2) Hyperventilating with 100% O_2 (> 10 L/min) to minimise hypercapnoea and acidosis, and to cope with increased metabolic state
- (3) Administering Dantrolene sodium – IV bolus of 2.5 mg/kg until MH is controlled or up to 10 mg/kg is used (Nb. may need up to 30 mg/kg)
- (4) Actively cooling the patient if temperature > 39 °C – IV iced saline, surface cooling with ice, lavage cavities (stomach, bladder, rectum) with iced saline. Stop cooling when temperature at 38 °C
- (5) Treating acidosis by hyperventilating the patient and giving $NaHCO_3^-$
- (6) Treating hyperkalaemia by hyperventilating the patient, giving $NaHCO_3^-$, CaCl, and actrapid/dextrose infusion
- (7) Treating cardiac arrhythmia by – (i) Reversing acidosis, (ii) Treating hyperkalaemia, (iii) Using antiarrhythmic agents (Nb. do NOT use CCBs due to risk of exacerbating hyperkalaemia in presence of dantrolene)
- (8) Supporting circulation with IV fluids and inotropes, as needed
- (9) Maintaining anaesthesia with a propofol infusion until surgery is either abandoned or completely urgently
- (10) Establishing diuresis (with mannitol infusion or IV frusemide) to prevent ARF
- (11) Consider monitoring with arterial line and CVC (can be used to take bloods, such as EUC, CMP, ABG, coagulation studies), and IDC (monitor urine output)
- (12) Changing the anaesthetic machine (including tubes, bags, soda lime) to remove trace amounts of triggering agents is NOT urgent and can be done later
- (13) Admitting the patient to ICU when stable

(II) Dantrolene Sodium in treating MH:

Class: Hydantoin derivative

Preparation: Each vial has 20 mg of orange lysophillised power of active drug, 3 g of mannitol (to ↑ water solubility), and NaOH (to bring pH > 9) → an assistant is often required to prepare it in 60 mL of H_2O

Mechanism of treating MH:

- In MH, there is a genetic defect of the RYR1 gene, which is responsible for the Ryanodine Ca^{2+} channel on skeletal muscle fibre → exposure to a triggering agent causes inappropriate release of stored SR Ca^{2+}, leading to hyperactive muscle contraction
- Dantrolene binds to this defective receptor channel and prevents SR Ca^{2+} release

Pharmacokinetics:

- Metabolised in the liver to an active metabolite (5-HO-dantrolene has 50% activity), which then excreted in urine and bile
- t ½ of 6-10 hours → thus, it needs to be given every 6 hours as either an IV or PO dose

Issues:

- (i) Do NOT give with a calcium-channel blocker due to risk of accentuating hyperkalaemia and precipitating cardiac arrest
- (ii) Phlebitis and tissue necrosis with extravasation 2° to alkalinity (thus, use CVC)
- (iii) Can cause sedation, confusion and muscle weakness

- (iv) APO can occur when large volumes are given (Nb. dantrolene has no direct cardiac effects)
- (v) Dantrolene can potentiate ND NMBD blockade

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

(I) Immune mechanisms that cause drug reactions:

Type I: Immediate Anaphylactic Hypersensitivity

- Initial Ag exposure – Ag presented to T-helper cell → causes it to stimulate B-cells to produce specific antibodies (IgE) against the Ag → IgE then binds to mast cells via Fc receptor and sensitises them
- Re-exposure to Ag – Ag reaches sensitised mast cell → binds to and cross-links surface-bound IgE's on mast cell → causes mast cell degranulation in 2 phases:
    - (i) Immediate phase (15-30 mins post-Ag exposure) – Release pre-formed mediators (histamine, bradykinin, 5-HT, SRS-A, PAF) → cause ↑ vascular permeability (oedema), ↓ vascular SM tone (vasodilation), ↑ bronchial SM tone (bronchoconstriction) and ↑ mucous secretions
    - (ii) Late phase (6-12 hrs later) – Synthesis and release of mediators (esp SRS-A's, such as LTs and PGs) with progressive tissue influx of inflammatory cells (PMNL, monocytes, eosinophils)
- Clinical manifestation depend where and how Ag enters the body:
    - Local manifestations – Urticaria (hives), eczema, asthma, conjunctivitis (hay fever) → Ag contacts skin or respiratory mucous membranes in sensitised individuals
    - Systemic manifestations – Systemic anaphylaxis (hypotension/CVS collapse, bronchospasm, laryngeal oedema, skin rashes and death) → Ag administered parentally in sensitised individuals
- Drug examples – Penicillin, streptokinase

Type II: Cytotoxic Hypersensitivity

- Antibody-mediated "cytotoxic" reaction where IgG and IgM Ab are directed at cell membrane surface Ag's (Eg. Ag source may be from pathogens or drugs stuck to membrane surface) → (i) activates complement via classical pathway, causing cell lysis, and (ii) induces Ab-dependent cell cytotoxicity
- Drug cal examples – Penicillin, quinidine

Type III: Immune-Complex Hypersensitivity

- Immune complexes (or Ag-Ab complexes) are normally cleared by the reticulo-endothelial system → but when (i) there are too many complexes to clear or (ii) complexes are too small to be cleared effectively, these complexes deposit in tissues → elicits complement activation and PMNL infiltration → AIR and tissue damage
- Two types:
    - (i) Serum sickness (systemic form)
        - Serum Ag excess leads to immune complex formation in blood → complexes then deposit in tissues → cause systemic effects (Eg. fever, arthralgia, vasculitis, splenomegaly, lymphadenopathy)
        - Drug example – Tetanus/diphtheria vaccine antitoxins
    - (ii) Arthus phenomenon (localised form)
        - Repeated exposure to an Ag results in production of a ↑↑↑ [ ] of serum IgG towards that Ag → re-exposure to the Ag leads to immune complex formation within the tissue site of Ag exposure → causes local effects

Type IV: Delayed Type Hypersensitivity

- Initial Ag exposure – Ag is presented to T-cells by APCs → causes them to proliferate and form a sensitized population of CD4+ T-cells
- When Ag is represented to this sensitised CD4+ T-cell population by APCs → T-cells release cytokines (esp Il-2, Il-4 and IFN-γ) to cause:

    - (i) Activation of localised macrophages
    - (ii) Attraction of lymphocytes and macrophages to the site of drug exposure
- Drug examples – Latex allergy

(II) Anaphylaxis and Anaphylactoid reactions:

Overview of anaphylaxis:
- A life-threatening anaesthetic event involving a type I hypersensitivity reaction (IgE-mediated mast cell/basophil degranulation) that occurs in response to exposure of a triggering Ag in a patient who has been previously sensitised to the Ag
- Incidence 1:6000 to 1:20,000 – triggers include:
    - (i) Mainly NMBD (60%) – SCh > rocuronium > vecuronium > pancuronium > atracurium
    - (ii) Antibiotics (15%) – esp penicillin
    - (iii) Latex (15%)
    - (iv) Others (10%) – Gel-based colloids, LA, protamine, NSAID, contrast, Etc.

Mechanism of anaphylaxis:
- Initial Ag exposure – Ag presented to T-helper cell → causes it to stimulate B-cells to produce specific antibodies (IgE) against the Ag → IgE then binds to mast cells via Fc receptor and sensitises them
- Re-exposure to Ag – Ag reaches sensitised mast cell → binds to and cross-links surface-bound IgE's on mast cell → causes mast cell degranulation in 2 phases:
    - (i) Immediate phase (15-30 mins post-Ag exposure) – Release pre-formed mediators (histamine, bradykinin, 5-HT, SRS-A, PAF) → cause ↑ vascular permeability (oedema), ↓ vascular SM tone (vasodilation), ↑ bronchial SM tone (bronchoconstriction) and ↑ mucous secretions
    - (ii) Late phase (6-12 hrs later) – Synthesis and release of mediators (esp SRS-A's, such as LTs and PGs) with progressive tissue influx of inflammatory cells (PMNL, monocytes, eosinophils)

> Note – Anaphylaxis can occur without previous exposure to a triggering Ag → this is due to "cross-sensitisation" with Ag of similar structures in food, cosmetics, Etc.

Clinical features of anaphylaxis:
- Initial Ag exposure and sensitisation → no symptoms
- Upon re-exposure to Ag → Skin rashes, erythema, urticaria, abdominal pain/vomiting, laryngeal oedema (with AW compromise), bronchospasm, hypotension, tachycardia → profound CVS collapse → cardiac arrest and death

Management of anaphylaxis:
- (1) Cease administration of triggering agent
- (2) Call for help
- (3) Secure airway and ventilation
    - Consider securing AW (due to laryngeal oedema) with ETT if not done so → requires careful IV induction to avoid precipitating CVS collapse
    - 100% FiO_2
- (4) Adrenaline (most important therapy) → maintain C.O. (β1), ↑ BP (α1/β1), and ↓ bronchoconstriction/mucous secretions (β2)
    - IMI – 0.5-1 mg
    - IV – 1-10 ug/kg slow boluses (depending on severity of reaction) → repeated PRN (or requiring IV infusion), titrated to maintain CVS stability. 1 mg bolus every 2-3 mins with cardiac arrest
    - ETT or nebulised – 5 mL of 1:1000 for laryngeal oedema/bronchospasms
- (5) Liberal IVF resuscitation (crystalloid or colloid) → maintain C.O. and BP

- (6) Antihistamines – H1RB (promethazine 0.5-1 mg/kg IV) and H2RB (ranitidine 1 mg/kg IV) → antagonise systemic effects of histamine
- (7) Steroids – Hydrocortisone 2-6 mg/kg IV q6h → attenuate late inflammatory phase
- (8) Consider metaraminol or vasopressin infusion if resistant to adrenaline
- (9) Post-resuscitation – consider:
    - Serum tryptase → immediately and 1-3 hrs later to confirm anaphylactic reaction
    - ICU referral
    - Referral to allergy clinic 4-6 wks later for testing

Aside – Anaphylactoid reactions:

- Mechanism – Direct release of mast cell/basophil mediators by a triggering Ag
- Clinical features – Similar symptoms as anaphylaxis due to same mediators released by mast cells/basophils → clinically indistinguishable
- Differences between anaphylactoid and anaphylaxis reactions:

	Anaphylactoid	Anaphylaxis
Previous Ag exposure	Not required	Required
Reaction to Ag	Occurs with 1st exposure	Occurs with subsequent exposure
IgE mediated	No	Yes
Severity of reaction	Less severe	Severe and fatal
Response of reaction	Graded → reaction severity related to agent dose	All-or-nothing → reaction severity not related to agent dose