A. 4 Variability in drug response

a. Define tachyphylaxis, idiosyncrasy, tolerance, addiction and habituation.

Tachyphylaxis is a rapid diminution in responsiveness following administration of a drug. e.g GTN

An idiosyncratic reaction is an unusual adverse reaction, sensitivity or resistance to a drug, usually genetically determined. An example is suxamethonium apnoea in pseudocholinesterase deficiency.

Tolerance is a reduced effect or increased dose requirement after repeated administration of a drug. It may be due to receptor down-regulation or increased metabolism. e.g. opiates, barbiturates

Addiction is a state of physical or psychological dependence on a drug. Physical dependence is manifest as pathological signs or symptoms on withdrawal of a drug. Psychological dependence is manifest as compulsive drug-seeking behaviour which compromises physical wellbeing or social function.

Habituation is the neural mechanism by which a response is gradually reduced or eliminated following repeated stimuli.

b. Explain alteration in drug response due to the physiological consequences of age pregnancy and other factors including obesity, altered total body water, hypoproteinaemia and various other disease states.

Elderly

Absorption is unchanged with age except by intercurrent disease and concurrent use of multiple medications.

Distribution is affected by reduced lean body mass, reduced total body water and increased fat percentage. Binding is altered by a decrease in plasma albumin and increase in α-acid glycoprotein (which increases the V_d of basic drugs).

Metabolism is slowed for most drugs, partly by a reduced hepatic blood flow and reduced capacity of the microsomal enzyme system. The ability to conjugate compounds (phase II reactions) is substantially unchanged with age. Hepatic function tends also to be diminished by other illnesses such as CCF or malnutrition. The reduction of hepatic oxidation of drugs is most apparent in drugs such as diazepam which have a long half-life and active metabolites.

Elimination by renal clearance is slowed by a progressive reduction in creatinine clearance with age. The Cockcroft-Gault equation relates clearance to age in males, the female result being multiplied by 0.85:

$$\text{creatinine clearance (ml/min)} = \frac{(140\text{-age}) \times \text{weight (kg)}}{72 \times \text{creatinine (in mg/dl)}}$$

(creatinine in mg/dl is 11 times the level in mmol/l)

Absorption and elimination of drugs via the lungs is also impaired in the elderly because of progressive reduction in FVC and DLCO as well as more damage from prolonged smoking.

Pharmacodynamic changes in the elderly are less important than pharmacokinetic ones. There is an increased responsiveness to some sedatives and hypnotics which may be receptor-mediated and a decrease in responsiveness to β-adrenoceptor agonists and antagonists. Many homeostatic mechanisms are impaired in the elderly: functional reserve in cardiac output to maintain blood pressure is limited with increased incidence of hypotension, glucose tolerance is often impaired and temperature regulation may also be impaired, with particular susceptibility to hypothermia.

Specific examples of common drugs:

Benzodiazepines have increased volume of distribution (if lipid soluble), reduced metabolism and clearance and possibly increased receptor sensitivity. Motor functions may be particularly impaired in the elderly.

Narcotics show variable changes in pharmacokinetics. The major concern is that physiological reduction in respiratory capacity makes patients more susceptible to hypoventilation.

Drugs with anticholinergic effects (including phenothiazines, butyrophenones and most antihistamines) are more likely to cause confusion or acute brain syndrome in the elderly, especially in those with dementia.

Foetus

Pharmacokinetic factors

Lipid solubility increases placental penetration; ionized drugs do not cross the placenta easily.

Molecules larger than 1000 Dalton cross poorly except for immunoglobulins and some hormones.

Protein binding affects transfer. Some drugs are bound with different affinities to maternal and foetal proteins.

Metabolism in the placenta is limited to a few oxidation reactions. The foetal liver has a reduced metabolic capacity.

Pharmacokinetic factors

Effects on the mother are substantially the same in pregnancy, except for effects of greater circulating volume, and sometimes impaired glucose tolerance and susceptibility to cardiac failure.

Some drug effects are specific for foetal life: steroids to accelerate lung maturation and folate to prevent neural tube defects.

Some drug toxicities are predictable in foetal life: ACE inhibitors causing renal impairment and opiates causing dependence.

Teratogenic effects are usually specific to a drug and a time of gestation: thalidomide causing phocomelia when exposure occurs in weeks 4 to 7.

Paediatric

Absorption

Intramuscular administration is made unpredictable in neonates by small muscle mass and variable blood flow if cold.

Oral absorption is altered by the absence of gastric acid in premature babies for several days.

Gut motility is unpredictable in neonates, with gastric emptying commonly delayed.

Pancreatic enzymes and bile salts are present in reduced amounts up to 4 months of age.

Distribution

Total body water is 75% and ECF 40% of bodyweight in neonates. Diuresis in the first few days reduces the ECF compartment substantially.

Body fat is low in premature infants, rising to 15% at term.

Plasma protein binding is reduced in the neonate. With neonatal jaundice this effect is increased by competition of bilirubin for albumin binding sites.

Metabolism

Hepatic metabolism of drugs by both P450 and conjugation reactions is reduced in the neonate unless enzyme-inducing drugs have been given antenatally. They reach adult levels (per kg) by about three years.

Elimination

GFR/SA in the neonate is about 35% of adult values, rising to 50% at three weeks and 100% at 6 to 12 months. This substantially alters the dose requirement of drugs such as penicillins and aminoglycosides which are renally cleared.

Pharmacodynamics

Some drugs have specific effects in neonates, particularly indomethacin for closing and PGE_1 for maintaining patency of the ductus arteriosus.

Dosing

Dosage calculations are often based on weight or surface area. Doses in adolescents should not exceed the adult dose except in some isolated cases such as theophylline where metabolism in children may be more rapid than in adults.

Equations for scaling doses include Young's rule: age/(age+12) and Clarks' rule: weight/70 kg, but in infants and adolescents these rules are not useful.

Obesity, dehydration, hypoproteinaemia

c. Classify drug interactions and the principles involved.

Physicochemical
- in vitro incompatibility
  - binding
  - precipitation

Pharmacokinetic
- Absorption (affecting extent and rate of absorption)
  - adsorption (cholestyramine, charcoal)
  - chelation or binding (resonium)
  - alter gastric pH (ranitidine)
  - alter motility (narcotics)
  - second gas effect (NO_2, volatile agents)
- Distribution
  - competition for protein binding (phenytoin)
  - competition for tissue binding (digoxin & quinidine)
  - direct binding (heparin & protamine)
- Metabolism
  - induction of microsomal enzymes (rifampicin, phenytoin)
  - inhibition of microsomal enzymes (cimetidine, allopurinol)
- Excretion
  - urinary pH
  - renal function in tubular secretion
  - second gas effect

Pharmacodynamic
- potentiation
  - additive or synergistic effect
  - same or different receptors or multiple points in one pathway
- antagonism
  - direct antagonism (naloxone) or partial agonism (pentazocine)
- combined toxicity
  - predictable combination of adverse effects (NSAID & gentamicin → renal impairment)
  - potentiation of adverse effects by otherwise safe drugs (ketoconazole & terfenadine → prolonged QT interval)

d. Explain the mechanisms and significance of malignant hyperpyrexia, porphyria, atypical cholinesterase, slow acetylators and G6P-D deficiency.

Malignant hyperpyrexia is a genetically determined condition (1 in 20000, AD, long arm of chromosome 19) involving an abnormality of the ryanodine Ca^{2+} channel. In the presence of a triggering agent, commonly halothane or suxamethonium, Ca^{2+} is not taken up by the sarcoplasmic reticulum after release, resulting in persistent contraction and thus lactic acidosis and hyperthermia (a late sign). Prevention is by taking a detailed history of

anaesthetic complications, including a family history. Detection in by muscle biopsy for halothane/caffeine contraction testing or by chromosome analysis. Specific treatment is by elimination of the trigger agent: a clean anaesthetic machine, chilled intravenous fluids, and by intravenous use of dantrolene 1 mg/kg up to 10 mg/kg which inhibits Ca^{2+} release.

dantrolene
- lipid soluble hydantoin

pharmacokinetics
- low water solubility
- 20% oral bioavailability
- V_d 0.5 l/kg
- clearance 0.6 ml/min/kg
- $t^1/_2$ß 12h
- therapeutic concentration >3 μg/ml
- metabolized to 5-OH dantrolene (50% potency)

pharmacodynamics
- inhibits Ca^{2+} release from sarcoplasmic reticulum
- limits excitation-contraction coupling in skeletal muscle

adverse effects
- muscle weakness
- negative inotrope
- ↑ $[K^+]$
- electrolyte and volume disturbance due to water and mannitol load

indications
- malignant hyperpyrexia
- also used in
  - neuroleptic malignant syndrome
  - MDMA overdose, serotonin syndrome with hyperpyrexia
  - muscle cramps

clinical use
- ampoules of 20 mg with 3 g mannitol, pH 9.5
- dissolved in 60 ml water → 1 mg/3 ml
- dose 1 mg/kg up to 10 mg/kg
  - = up to 30 ml/kg free water, 1.5 g/kg mannitol

Hepatic porphyria is an AD condition resulting from a defect in the HMB synthase gene. Symptoms are triggered by exposure to agents causing an increase in porphyrin synthesis, resulting in acute crampy abdominal pain, nausea, hypertension and neurological symptoms including axonal degeneration causing sensory loss peripherally and proximal motor weakness. Surgery itself can be a trigger, but many drugs are identified as precipitating attacks. These include: barbiturates, sulfonamides, phenytoin, carbamazepine, valproate, ergots, sex steroids and alcohol. Prevention is by history taking and avoidance of precipitating drugs. Between attacks, excretion of porphobilinogen and δ-amino laevulinic aci is normal, but erythrocyte HMB synthase is low. Treatment of attacks is initially symptomatic: narcotics, phenothiazines, and benzodiazepines. Intravenous haem therapy reduces the duration of an attack.

Atypical (plasma) cholinesterase is an AR condition. The genes has been well-characterized and comes in one normal and three atypical variants: dibucaine-resistant, fluoride-resistant and silent. Patients who have neither gene normal show markedly increase duration of action of suxamethonium as it is not effectively metabolized. This results in prolonged apnoea. Some heterozygous “normal” patients also have mildly prolonged duration of apnoea. Activity is also depressed by many other chronic illnesses, burns and in neonates. There is a rare C5 variant which results in increased plasma cholinesterase. Prevention is by history taking and avoiding suxamethonium. Treatment is by mechanical ventilation until the paralysis ceases (often up to 5 hours). The incidence of significant suxamethonium

apnoea is 1:2800.

N-acetylation of isoniazid and hydralazine varies in the normal population with a bimodal distribution. Slow acetylation is an AR condition with an incidence variable by race (rare in Asians and Inuit, more common in Northern Europeans). Slow acetylators metabolize these drugs much more slowly due to low levels of normal enzyme. There are no anaesthetic consequences of this condition.

Similar conditions have been described in metabolism of other drugs, much less commonly.

Glucose-6-Phosphate Dehydrogenase deficiency is an X-linked enzyme deficiency. There are many gene defects described, the common ones being A- in 11% of blacks and variants in Eastern Mediterranean (Favism) and Chinese populations. G6PD activity falls in red cells with age, and cells with very low activity will haemolyse in the presence of an oxidan drug. Drugs inducing haemolysis include: antimalarials, sulfonamides, nitrofurantoin and many others. An acute drop in haematocrit with a rise in plasma haemoglobin and unconjugated bilirubin results from haemolysis. Because younger red cells are less susceptible, the haemolysis is usually self-limiting, even with continued exposure. Prevention is by history taking and screening for red cell G6PD (which may not be low immediately after a crisis) and avoidance of oxidant drugs. Treatment is focussed primarily on avoiding renal damage; transfusion is usually not necessary.

e. Describe immune mechanisms in anaphylactoid and anaphylactic drug reactions in general and as applied to anaesthetic drugs.

Anaphylactic (type I) hypersensitivity reactions require an initial sensitizing exposure to the allergen. This causes the synthesis of IgE which binds to the surface of mast cells and basophils by its Fc region. On re-exposure to the allergen, the Fab regions of the IgE molecules bind the allergen and become cross-linked, triggering the degranulation of mast cells (mediated by phospholipase c and Ca^{2+}), releasing histamine, heparin, chemotactic factors and PAF and the synthesis of leukotrienes B_4, C_4 and D_4, prostaglandins and thromboxane. These are collectively known as SRSA.

The immediate effects include vasodilatation, bronchoconstriction and an increase in capillary permeability. If localized, these effects may lead to rhinorrhoea, asthma, rash with urticaria, localized oedema or diarrhoea. If generalized, these effects lead to circulatory collapse and respiratory compromise, requiring immediate treatment, initially with adrenaline.

Type I hypersensitivity can occur with any anaesthetic drugs, but is most common with large molecules which patients are likely to have been exposed to before, especially β-lactams and cephalosporins and some anaesthetic agents, notably thiopentone and suxamethonium. A history of a localized type I reaction to a drug is a contraindication to its use. Patients with a serum IgE > 1 μg/ml are at a high risk of atopy.

Anaphylactoid reactions occur as a result of complement activation and subsequent mast cell degranulation on first exposure to the antigen. They are similar to but generally not as severe or long-lasting as anaphylactic reactions. Cremaphor (polyoxyethylated castor oil), a solubilizing agent, is noted for causing these reactions.

f. Explain alteration in drug response due to due to consequences of pathological changes such as liver disease, cardiac failure or renal failure.