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QUESTION 01

Outline three (3) factors that alter the pharmacodynamic response of nondepolarising neuro-muscular blocking drugs and describe the mechanism by which they may occur.

Non depolarising neuromuscular blockers
- act by non competitive binding to the nicotinic ACh receptor on the motor end plate
- this prevents the action of ACh at the motor end plate and stops muscle excitation
- aminosteroids - rocuronium, pancuronium, vecuronium
- isoquinolones - atracurium, cisatracurium
- the pharmacodynamic response is dependent on the number of receptors occupied
  - dose dependent according to the laws of mass action
  - >70% to elict a response

The factors which alter the response (number of receptors occupied) may be separated into
- pharmacodynamic factors
- pharmacokinetic factors
- pharmaceutical and drug interaction factors

Pharmacodynamic factors
- decreased pH increases the affinity of non depolarising NMB
- electrolyte disturbances
  - calcium disturbances affect the release of ACh from the presynaptic terminal (triggered by Ca)
    - hypercalcaemia results in shortened blockade from pancuronium
  - magnesium
    - stabilise membranes and decrease release and sensitivity to ACh
  - potassium
    - hypokalaemia leads to membrane hyperpolarisation (decreased drug effect)
    - hyperkalaemia has the reverse effect
- pathology
  - myasthenia gravis patients have defective nACh receptors
  - eaton-lambert syndrome patients have decreased ACh release
  - burns - leads to receptor mediated resistance to non depolarising NMBD

Pharmacokinetic factors (affect the amount of drug reaching the receptor)
- absorption
  - dose given (higher dose - more receptors occupied)
- distribution
  - lipid soluble drugs such as vecuronium may accumulate in lipid rich tissue (esp infusion)
  - women have higher lipid content which may lead to reduced effect site conc
- metabolism
  - hepatic failure may lead to decreased metabolism of a drug - pancuronium
  - deranged pH changes the metabolism of the isoquinolones which use Hoffmann elim
- excretion
  - renally excreted drugs, especially minimally metabolised vecuronium, rocuronium

Pharmaceutical/ drug interactions
- storage of the drug (isoquinolones must be stored at 4 degrees to maintain potency)
- Increase effect
  - aminoglycosides - decreased prejunctional ACh release
  - volatile anaesthetics - mechanism not well understood
  - frusemide - potassium effect, may interfere with cAMP and ACh release
- decrease effect
  - anticonvulsants - may develop resistance to pancuronium, vecuronium