Pharm-09B5 Describe the factors that may decrease the clinical response to non-depolarising neuromuscular blocking agents.

**Background**

Non-depolarising neuromuscular blockers (NMBs) act as competitive antagonists at nicotinic ACh receptors → disrupt transmission at the neuromuscular junction

Often used to facilitate intubation, ventilation and surgery

Clinical responses to NMB include:

1. Speed of onset → e.g. measurable by time to 95% reduction in TOF1 twitch height
2. Depth of block → e.g. measurable by maximal reduction in TOF ratio
3. Duration of action → e.g. measurable by time to recover to TOF ratio of 0.9

*Train of four (TOF)* = stimulation of target nerve (e.g. ulnar nerve at the wrist) using specified electric current (e.g. 60 mA) at 2 Hz repeated 4 times and measuring the motor response elicited (e.g. contraction of adductor pollicis)

Factors that decrease NMB clinical response could be classified into:

- patient factors → either physiological or pathological
- drug factors → either NMB *per se* or interaction with other drugs

**Patient factors**

*Physiological factors*

Male sex: males have relatively more muscle mass → slower onset

Hyperthermia: faster metabolism (esp. Hoffman degradation) → slower onset

Muscle groups:

Larger muscle size → more ACh receptors needed to be blocked → slower onset

Lower muscle blood flow → slower onset

Onset → small muscles *faster than* trunk muscles *faster than* diaphragm

Offset → diaphragm *faster than* trunk muscles *faster than* small muscles

**Pathological factors**

Electrolyte abnormalities

- hyperkalaemia
- hypercalcaemia
- hypomagnesaemia
- alkalosis

Low cardiac output → ↓ muscle blood flow → slower onset

Burns: large TBSA burn → alteration to nAChR subunits → more resistant to non-depolarising NMB → slower onset, ↓ depth and ↓ duration
**Drug factors**

*NMB*

↓ dose → slower onset, ↓ duration and ↓ depth

NMB with higher potency → lower doses used → smaller concentration gradient between plasma and effect site (muscle) → slower onset

**Drug interactions**

Absence of volatiles: volatiles facilitate NMB action via multiple mechanisms. It’s absence (e.g. in ICU patients or TIVA) → slower onset, ↓ duration and ↓ depth

Reversal agents:
- acetylcholinesterase inhibitors → ↑ synaptic ACh → slower onset + ↓ depth
- sugammadex → inactivates rocuronium (and vecuronium) → ↓ plasma concentration → slower onset + ↓ depth + ↓ duration

Anticonvulsants: can upregulate hepatic enzymes → ↑ clearance → slower onset

**Examiner’s comments** - 36% of candidates passed this question.

Candidates were expected to briefly mention the important measurable clinical responses (e.g. onset, depth and duration of neuromuscular blockade), and briefly mention how these might be measured. Candidates who classified factors into such groups as physiological, pathological, drug factors and drug interactions, with multiple examples usually scored well.

Extra marks were awarded for noting that the clinical response depends on which muscle group is monitored, and that the clinical response is less intense and briefer in patients anaesthetised without volatile or sedated in critical care.

Some candidates mistakenly listed factors that contribute to prolongation of neuromuscular blockade (such as atypical plasmacholinesterase, aminoglycosides).

Marks were not awarded for arguing that absence of these factors leads to a (relative) decrease in clinical response. Nonspecific pharmacokinetic statements ("clinical response is determined by differences in absorption, volume of distribution, protein binding and clearance") without clinical examples and explanation were not awarded high marks. There was general confusion about the effect of various muscle disorders on neuromuscular blockade.