Pharm-04A2 Outline the factors determining speed of onset of neuromuscular blocking agents.

**Background**

Neuromuscular blocking agents (NMB) are used as part of general anaesthesia to facilitate intubation and surgery

*Speed of onset* is defined as the rate of achieving a given degree of muscle relaxation (e.g. 95% suppression of T1 twitch height on train of four)

Factors that affect speed of onset of muscle relaxation include:
- Drug factors
- Patient factors
- Administration factors

**Drug factors**

(1) type of NMB

NMBs are can be divided into depolarising and non-depolarising

Depolarising NMBs (e.g. suxamethonium) activate post-synaptic nAChR → persistent depolarisation → prevents further neuromuscular transmission

Non-depolarising NMBs (e.g. rocuronium, atracurium) competitively blocks post-synaptic nAChR → prevents depolarisation by ACh → blocks neuromuscular transmission

Depolarising NMBs require only activation of ~ 20% of nAChRs to exert clinical effect ∴ faster onset

Non-depolarising NMBs require blocking of ~ 70% of nAChRs to exert clinical effect ∴ slower onset

(2) potency of NMB

More potent the non-depolarising NMBs → clinically used at lower doses → smaller concentration gradient between plasma and NMJ → slower rate of onset (Bowman principle)

e.g. cisatracurium (ED95 = 0.03 mg/kg) is more potent than rocuronium (ED95 = 0.15 mg/kg) → cisatracurium is used at lower dose (0.15 mg/kg) than rocuronium (0.6 mg/kg) for intubation → cisatracurium (5 min to reach intubation condition) rate of onset is slower than rocuronium (2 min)

(3) dose of NMB

Higher dose of NMB → greater concentration gradient between plasma and effect site → more rapid diffusion to effect site (Fick’s law) → more rapid onset of action
(4) drug-NMB interactions

Volatile anaesthetics → vasodilatation → ↑muscle blood flow → ↑rate of NMB diffusion to muscle → ↑rate of onset
Can also directly potentiate NMB activity (des > sevo > iso > halo) via:
  - central depressant effect on α-motor neurone activity
  - inhibition of post-synaptic nAChR
  - increase NMB affinity for nAChR
Mg²⁺, local anaesthetics (in large doses), aminoglycosides can all ↑rate of onset of NMB

Acetylcholinesterase inhibitors (e.g. neostigmine) → inhibit breakdown of ACh → ↑synaptic [ACh] → competes with NMB for nAChR → ↓rate of onset

Sugammadex compounds and inactivates rocuronium (and vecuronium) → ↓concentration gradient between plasma and effect site → ↓rate of onset

Some anticonvulsants can increase clearance of NMB → ↓rate of onset

(5) priming

Priming refers to administration of a small priming dose of a non-depolarising NMB (e.g. ≤10% intubation dose) five minutes prior to administration of intubating dose of non-depolarising NMB → results in ↑↑rate of onset

Mechanism:
(1) small priming dose blocks a fraction of post-synaptic nAChRs
(2) priming dose has minimal clinical effect (∵ need a large fraction of nAChR blockade to result in noticeable clinical effect)
(3) subsequent intubating dose of non-depolarising NMB → blocks remainder of nAChRs → faster rate of onset

Patient factors

(5) cardiac output
↓cardiac output → ↓muscle perfusion → ↓rate of onset
↑age → ↓cardiac output → ↓rate of onset

(6) pathology
myasthenia gravis → less nAChRs → faster onset with non-depolarising NMB but slower onset with suxamethonium

Administration factors

More rapid injection → ↑rate of onset

Injection into central line → ↑rate of onset vs distal peripheral cannula
Intravenous faster than intramuscular for suxamethonium
**Muscle groups**

Different muscle groups also have different rates of onset

Muscle with greater blood flow $\rightarrow$ reach equilibrium with plasma faster $\rightarrow$ faster onset
Larger muscle groups have more nAChR $\rightarrow$ slower onset
Balance of above factors

**Examiner’s comments** - This question had a 71% pass rate
The main factors for a pass mark were:
- **Dose of agent** noting that multiples of ED95 had faster onset of action compared to lower doses.
- **Potency of the agent** noting that more potent agents have a slower onset of action compared to equivalent doses of a less potent agent, with an explanation of this effect.
- The effect of **cardiac output** and the **perfusion to muscle groups** to distribute the agent.
- **Relevant physicochemical properties** of the agents and an explanation of their relevance.

Additional marks were awarded for identifying and explaining the differences in speed of onset between **depolarising muscle relaxants and non-depolarising neuromuscular blocking agents**, discussion of the **different speed of onset between different muscle types and groups**, the effects of **different routes** and sites of administration and the **priming principle** on speed of onset, the **effects of other drugs** and the **effects of age** and relevant **disease states**.