Pharm-09A3 Outline the factors that determine the rate of recovery from non-depolarising neuromuscular block.

**Background**

Non-depolarising neuromuscular blockers (ND-NMBs) are competitive antagonists of the nicotinic ACh receptor at the neuromuscular junction.

Rate of recovery of neuromuscular block may be assessed in a variety of ways. For example, surrogate markers of rate of recovery may be:

1. time taken to return to 25% baseline twitch height
2. time recover to TOF ratio ≥ 0.9

Rate of recovery depends on:

1. concentration of ND-NMB at the NMJ
2. pharmacokinetic factors
3. pharmacodynamic factors – either drug or patient factors

**Concentration of ND-NMB at NMJ**

Larger dose → ↑[NMB] at NMJ → takes longer for concentration to fall below threshold to result in offset of action → ↓rate of recovery

**Pharmacokinetic Factors**

**(1) Distribution**

After single bolus → recovery from redistribution
After repeated boluses or infusion → recovery from metabolism and excretion

↑V_d → ↑recovery after single bolus (because ↑redistribution)
↑V_d → ↓recovery after infusion (because more accumulation)

↓[protein] → ↑unbound drug → ↓rate of recovery (minimal effect as most NMBDs have low protein binding)

**(2) Metabolism**

In general, hepatic dysfunction → ↓metabolism → ↓rate of recovery

↓butyrylcholinesterase → ↓metabolism of mivacurium → ↓rate of recovery
↓non-specific plasma esterase → ↓metabolism of atracurium → ↓rate of recovery

**(3) Elimination**

Hepatic disease → ↓biliary excretion (e.g. rocuronium) → ↓rate of recovery

Renal disease → ↓renal excretion → ↓rate of recovery

With ↑age → ↓hepatic function, ↓renal function ± ↓V_d → ↓rate of recovery
Pharmacodynamic Factors

**Patient factors** that slow rate of recovery
(1) acidosis → slower metabolism
(2) hypothermia → slower metabolism
(3) hypocalcaemia → ↓pre-synaptic ACh release at NMJ
(4) hypokalaemia → hyperpolarise post-synaptic membrane
(5) hypermagnesaemia → competes with Ca\(^{2+}\) → ↓pre-synaptic ACh release
(6) elderly → less muscle mass → prolonged block
(7) female → less muscle mass → prolonged block
(8) neonate → immature NMJ → prolonged block
(9) NMJ disorders: e.g. myasthenia gravis, burns, spinal cord injury

In contrast, alkalosis, hyperthermia, ↑K, ↑Ca, ↓Mg all *speed up* rate of recovery

**Drug factors** that slow rate of recovery
(1) volatile anaesthetics → via multiple mechanisms: central motor neuron inhibition, increase affinity of nAChR for NMBs, direct depression of post-synaptic nAChR (at high MAC)
(2) aminoglycoside antibiotics → ↓presynaptic ACh release and ↓nAChR sensitivity for NMBs
(3) local anaesthetics (high doses) → stabilise post-synaptic membrane and direct muscle fibre depression
(4) calcium channel blockers → ↓ACh release
(5) class I antiarrhythmics (e.g. quinidine) → ↓ACh release
(6) frusemide → ↓ACh release + causes hypokalaemia
(7) magnesium → ↓ACh release (esp. with vecuronium)
(8) lithium

**Drug factors** that increase rate of recovery
(1) anticholinesterase → ↑[ACh] at NMJ
(2) anticonvulsants (e.g. phenytoin, carbamazepine) → ↑clearance, ↑binding of NMB to \(\alpha_1\)-acid glycoprotein, upregulation of nAChR

**Examiner’s comments** - 38% of candidates passed this question.

Recovery from neuromuscular block is dependent on the competitive balance of ACh and nondepolarising blocking agent (NDBA) at the ACh receptor. After a single bolus of NDBA the offset is as a result of redistribution. Only after repeat boluses or infusion does metabolism and excretion become significant. This important point was mentioned in only one paper. Most mentioned that recovery was slower after large doses without further explanation. There was much confusion as to whether an increased volume of distribution resulted in an increased or decreased duration. This is dependent on whether the drug is administered as a single bolus. The pharmacological properties of the drugs were generally well done as were the lists of physiological and drug interactions. Candidates who were able to give correct examples scored additional marks. The use of anticholinesterase agents and their effectiveness depending of the depth of block was seldom mentioned.
The main mechanisms expected to be addressed were:

- **Overdose**
- **Pharmacokinetic; hypothermia, hepatic failure, renal failure**
- **Pharmacodynamic**
  - drug interactions (e.g. volatiles, antibiotics)
  - physiological disturbance (hypothermia, acidosis, electrolyte abnormalities)
  - neuromuscular abnormality (e.g. myaesthenia gravis)

Candidates were asked to "Explain..." the mechanisms by which the various mechanisms produced prolonged neuromuscular blockade. For example, overdosage might be produced by a dose calculation error, repeated bolus or infusion without neuromuscular monitoring, or a drug swap error with a long acting agent. The majority of candidates listed some mechanisms that could prolong neuromuscular block but frequently omitted an adequate explanation.

Few answers considered the potential for a combined effect created by the clinical context of the question. A four hour case will commonly require repeated doses of neuromuscular blockers, long exposure to volatile anaesthetic agents, and may result in patient hypothermia and acidosis.