Pharm-11A8 How may drugs enhance the action of non-depolarising neuromuscular blocking drugs at the neuromuscular junction?

**Background**

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

Drugs can enhance the action of non-depolarising NMBs via either pre-synaptic or post-synaptic mechanism.

**Pre-Synaptic Mechanisms**

Drugs can reduce pre-synaptic release of ACh → enhance action of non-depolarising NMBs.

1. Block pre-synaptic ACh receptors → prevent positive feedback → ↓ACh release
   - volatile anaesthetics
2. Reduce cAMP synthesis → ↓ACh release
   - frusemide
3. Block pre-synaptic Ca\(^{2+}\) channels → ↓ACh release
   - volatile anaesthetics
   - aminoglycosides
   - Ca\(^{2+}\) channel blockers: probably minor clinical significance
   - magnesium

**Post-Synaptic Mechanism**

Drugs can interfere with ion flux through post-synaptic nicotinic receptors → enhance action of non-depolarising NMBs.

1. Direct blockade of post-synaptic ACh receptors
   - other non-depolarising neuromuscular blockers: same class = additive effect; different class = synergistic effect
   - volatile anaesthetics: direct nAChR inhibition + ↓affinity of NMB for nAChR
2. Binding to non-receptor sites
   - local anaesthetics (large doses): block fast Na\(^+\) channels → ↓Na\(^+\) conductance
   → ↓membrane excitability
   - magnesium (large doses): inhibits postjunctional membrane potential generation
   → ↓membrane excitability
   - lithium: ↓membrane excitability
   - dantrolene: prevent release of Ca\(^{2+}\) from SR → ↓mechanical response of muscle to stimulation → indirect potentiation of non-depolarising NMBs
   - antiestrogen drugs (e.g. tamoxifen): ? mechanism
**Potentiation of NMB action by volatile anaesthetic**

Rank order of potentiation:

Desflurane > sevoflurane > isoflurane > halothane > nitrous oxide (Stoelting 5th p332)

**Examiner’s comments** - This question was passed by 57% of candidates.

The following answer would have gained a very high mark:

Drug interactions are relevant as there is a risk of failure to reverse neuromuscular blockade and residual paralysis. Drugs may interact either at the nerve terminal or the receptor to reduce the effect of acetylcholine (ACh) in competitively overcoming the block. 

**Presynaptically** there are at least three mechanisms that might reduce the release of acetylcholine (ACh):

1. Reduced AMP/ATP synthesis – frusemide
2. Blockade of presynaptic ACh receptors – volatiles
3. Blockade of calcium channels – calcium channel blockers, magnesium, aminoglycosides, volatiles

**Postsynaptically** there are several mechanisms that interfere with ion flux through the nicotinic receptor:

1. Direct blockade of the ACh receptor – volatiles, aminoglycosides, quinidine, other neuromuscular blockers
2. Desensitization block (binding to non-receptor sites) – volatiles, barbiturates, local anaesthetics

The most common error was irrelevance: detailed descriptions of the physiology of neuromuscular transmission and a classification of non-depolarizing relaxants.