Pharm-07B6 Describe how suxamethonium produces neuromuscular blockade.
What is the mechanism of recovery of neuromuscular function and what mechanisms may be involved in Phase II block?

Background

Suxamethonium (sux) is a depolarising muscle relaxant
C–C dimer of acetylcholine
Rapid onset of action → intubation condition within 60 seconds → commonly used for rapid sequence induction
Dose = 1 mg/kg

Mechanism of action

(1) sux enters intravascular space
(2) fraction of sux metabolised by plasma butyrylcholinesterase
(3) remaining fraction reaches neuromuscular junction (NMJ)
(4) sux binds to α-subunits of NMJ post-synaptic nicotinic acetylcholine receptors (nAChR)
(5) nAChR activated → opens central ligand gated cation channel → myocyte membrane depolarisation → contraction → clinically observed fasciculation
(6) unlike ACh, sux is not broken down by NMJ acetylcholinesterase → persistent binding to nAChR → persistent depolarisation
(7) local currents render nearby voltage gated Na+ channels to remain inactivated → prevent further transmission of muscle action potentials → muscle relaxation (Phase I block)
(8) further sux given → phase II block (discussed below)

Characteristics of Phase I block:
- effect requires > 20% nAChR occupancy with sux
- ↓ twitch amplitude
- no fade (sux does not block pre-synaptic nAChRs)
- no post-tetanic potentiation
- TOF ratio > 0.7
- block enhanced by cholinesterase inhibitors

Mechanism of recovery

Recovery of blockade when
(1) plasma [sux] falls due to metabolism by tissue butyrylcholinesterase:

suxamethonium → succinylmonocholine + choline
succinylmonocholine → succinic acid + choline

(2) concentration gradient established → sux diffuses from NMJ into plasma
(3) sux released from nAChR → block recovery

ke0 ≈ 2 min
duration of block ≈ 8 ~ 10 min (with typical butyrylcholinesterases)
**Mechanism of phase II block**

Phase II block refers to the pattern of muscle relaxation after administration of high doses of sux (> 2 mg/kg)
Block pattern similar to that seen with non-depolarising muscle relaxants

Characteristics:
(1) ↓ twitch amplitude
(2) fade phenomenon
(3) TOF < 0.7
(4) post-tetanic potentiation
(5) block reversed by cholinesterase inhibitors

Exact mechanism uncertain
Multiple proposed mechanisms:

? prolonged binding of sux of nAChR → desensitisation of nAChR to ACh after sux offset

**Examiner’s comments** - 75% of candidates passed this question.

In general this question was well answered. In order to gain maximum marks it was important that candidates specifically answered the three parts of the question i.e. mode of action, mechanism of termination of effect and the mechanism of Phase II block.

Most candidates explained the salient features of the ion channel comprising the Ach receptor at the neuromuscular junction (NMJ) and the role of the alpha sub-units.

There was some confusion as to why the post-junctional membrane remained resistant to further depolarization by Ach, but most correctly stated that this is because it remains in a continual state of suxamethonium induced inactivation. With regard to termination of action the main error was to suggest metabolism of suxamethonium by pseudocholinesterase at the NMJ. Pseudocholinesterase is not found at the NMJ - the main route of termination of action is simple diffusion away from the NMJ into the plasma following its concentration gradient. With regard to the mechanism of Phase II block it is acknowledged that this can’t be stated with certainty. However, the recommended texts suggest at least four mechanisms that could be involved and points were awarded for mentioning any of these. Unfortunately many candidates spent a great deal of time writing about how a Phase II block can be produced clinically and the means by which it can be identified using the nerve stimulator.