Pharm-99A12 Explain the phenomena known as fade and post tetanic facilitation associated with the use of neuromuscular blocking agents.

**Background**

Both fade and post-tetanic facilitation are phenomena associated with the action of non-depolarising neuromuscular blockers at the neuromuscular junction.

**Fade**

Fade = repeated stimuli of same intensity (e.g. train-of-four) results in gradual reduction of twitch height

**Post-tetanic facilitation** = after tetanic stimulation followed by delay, there is potentiation of twitch height with subsequent supramaximal stimuli

**Mechanism of neuromuscular transmission:**

- Action potential arrive at pre-synaptic membrane $\rightarrow$ Ca$^{2+}$ influx $\rightarrow$ release of ACh vesicles into NMJ $\rightarrow$ acts on post-synaptic nAChR causing MEPP
- ACh also acts on pre-synaptic AChR $\rightarrow$ positive feedback $\rightarrow$↑release of ACh

Non-depolarising NMB antagonises pre-synaptic ACh $\rightarrow$ prevents positive feedback associated with repeated stimuli $\rightarrow$ this is the mechanism of **fade**

**Measurement of fade via train-of-four stimulation:**

Four supramaximal stimuli, each lasting 0.2 msec, delivered at frequency of 2Hz $\rightarrow$ measure number and height of twitches

Height of fourth relative to first twitch ($T_4:T_1$) = train-of-four ratio $\rightarrow$ reflects fade

**Post-Tetanic Facilitation**

Tetanic stimulus $\rightarrow$ mobilise ACh into vesicles ready for release into NMJ $\rightarrow$ stimulus after delay results in release of $\uparrow$amounts of ACh vesicles into NMJ $\rightarrow$ $\uparrow$twitch height after stimulus $\rightarrow$ this is the mechanism of **post-tetanic facilitation**

**Examiner’s comments** - The overall pass rate for this question was about 43%

Most candidates seemed to appreciate that this question required an explanation of the mechanism of Fade and Post Tetanic Facilitation (PTF) as seen with the non-depolarising class of neuromuscular blocking drugs. The question clearly did not call for any discussion about how these phenomena are elicited in clinical practice nor the clinical relevance or usefulness of the elicitation of these phenomena. A few
candidates indicated that Fade and PTF are restricted to the adductor pollicis muscle alone. Quite a few candidates ignored the term PTF and wrote entirely on Post Tetanic Count. The two are different and candidates must be careful to answer the question.

Most candidates furnished a definition of Fade and PTF and whilst this was not explicitly called for, it did appear to provide a good starting point to their answers. **Fade exists when, during a partial non-depolarising block, administration of frequent repeated stimuli e.g. Train of Four, results in a reduction in twitch height with each of the subsequent stimuli.**

**Post Tetanic Facilitation is seen during partial non-depolarising blockade when after a tetanic stimulation is applied to a nerve-muscle until there is seen after a delay, of classically three seconds, a potentiation of twitch height with a subsequently applied single supra-maximal stimulus.**

The explanation of Fade should have included discussion of pre-junction nicotinic receptors involved in a positive feedback loop with Acetylcholine (ACh) being blocked by the non-depolarising neuromuscular blocking agent resulting in reduced production of ACh vesicles and therefore less vesicles available for release. The explanation of Post Tetanic Facilitation required some discussion of temporarily increased mobilisation of ACh vesicles into the pre-junctional area for ready release as a result of tetanus.