**Pharm-03A8** – Describe the onset and offset of neuromuscular block at the diaphragm, larynx and adductor pollicis after administration of 2.5 x ED$_{95}$ dose of vecuronium. Comment on the differences observed. What are the clinical implications of these differences?

**Onset**

- **Mechanism:** vec onset of action depends on their ability to diffuse from circulation to NMJ (move down concentration gradient) → Competitive antagonism of nAChR at pre & post-synaptic receptors
- **Speed of onset** dependent on:
  1. **Muscle blood flow:**
     - High blood flow → Delivery of vec to effect site allowing more rapid equilibrium
  2. **Muscle size:**
     - Small fine muscles blocked before larger ones → Larynx > Diaphragm
  3. **Muscle type:**
     - Slow ‘oxidative’ twitch fibres have less density of nAChR → more quickly reach threshold receptor occupancy → Faster onset
     - Larynx & diaphragm fast ‘glycolytic’ twitch fibres with ↑ # nAChR → require more vec to be paralysed
- **ONSET:** Larynx > Diaphragm > Adductor Pollicis

**Offset**

- **Mechanism:** After 2×ED$_{95}$ vec bolus, offset depends on redistribution of vec from NMJ into plasma.
- **Offset** depends on:
  1. **Muscle blood flow:**
     - Greater muscle BF → faster redistribution of vec out of NMJ → faster offset
  2. **Muscle type:**
     - Fast twitch muscles recover more quickly than slow as they have more nAChR
- **OFFSET:** Diaphragm > Larynx > Adductor Pollicis

**Clinical Implications**

- **Time to ideal intubating or recovery conditions not easily measurable as muscles (usu. adductor pollicis) used with peripheral nerve stimulator have slowest onset and offset of neuromuscular blockade**
- **Correlation must be made:**
  - **Onset:** Larynx & diaphragm have FASTER ONSET OF ACTION than adductor pollicis therefore may have started to recover at time of maximal adductor pollicis paralysis
  - **Offset:** Diaphragm & larynx have already started to recover by the time adductor pollicis has recovered due to faster offset, this can be safely assumed from TOF
  - **Orbicularis oculi** activity may better correlate with diaphragm activity

**Examiner’s comments** - Pass rate was 50%.

In this question the candidate was expected to address the issues of the kinetics of onset and offset of neuromuscular block (NMB) and the known different levels of sensitivity of the muscles mentioned. It was important to mention that although the diaphragm (D) and larynx (Lx) are relatively resistant to competitive NMB with respect to the adductor pollicis (AP), the major determinant of onset under these circumstances is blood flow. Thus onset is more rapid in the Lx and D and slowest in the AP. Candidates needed to define ED$_{95}$ and that the ED$_{95}$ referred to is that for the AP. At the time of AP twitch disappearance both the D and Lx may have been maximally blocked and may be beginning to recover. Thus it is also critical to mention that the order of recovery is D, Lx and then AP. Clinical implications that should have been discussed included onset of block and intubating conditions, offset of block and adequacy of recovery and monitoring of block at AP, orbicularis oculi and prediction of block at AP, Lx and D. Useful diagrams (as are found in both Miller and Stoelting) to explain these phenomena were used by some candidates to their advantage.