1. **Rocuronium** = intermediate-acting aminosteroid-type non-depolarising muscle relaxant
   a. Mechanism = competitive antagonist of nAChR at NMJ:
      i. Post-synaptic 2βδε nAChR antagonism → muscle relaxation
      ii. Pre-synaptic α1β2 nAChR antagonism → prevent facilitation of ACh release → fade
   b. Intubating dose 0.6mg/kg produces paralysis within 60-120s for ~30mins
   c. >70% receptor occupation required for paralysis

2. Recovery of neuromuscular function depends on:
   a. [Rocuronium] at NMJ
   b. Pharmacokinetic factors
   c. Pharmacodynamic factors

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**Pharmacokinetics**

**Concentration of Rocuronium at NMJ**

| Larger dose | Larger dose (e.g.) RSI dose = 3-4×ED95 = 0.9-1.2 mg/kg | Takes longer for concentration to fall below threshold for offset of action | Slower rate of recovery |

**Pharmacodynamics**

**Electrolyte Disturbance**

- Hypokalaemia: ↓ more → Emax (hyperpolarised) → potentiates rocuronium → Slower rate of recovery
- Hypocalcaemia: ↓ pre-synaptic release of ACh → Slower rate of recovery
- Hypermagnesaeamia: Mg2+ competes with Ca2+ at pre-synaptic channels → ↓ ACh release → potentiates rocuronium → Slower rate of recovery

**Hypothermia** → ↓ Hepatic metabolism → Slower rate of recovery

**Temperature**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Hypothalamic response to change in T°C:</th>
<th>Recovery 2° elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>↓ to ↓ metabolic rate of ACh synthesis</td>
<td>Slower rate of recovery</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>↑ to ↑ metabolic rate of ACh synthesis</td>
<td>Faster rate of recovery</td>
</tr>
</tbody>
</table>

**Acid/Base**

- Acidosis → ↓ Hepatic metabolism → Slower rate of recovery
- Alkalosis → ↑ Hepatic metabolism → Faster rate of recovery

**Drug Interactions**

**Volatiles:**
- Desflurane > Sevoflurane > Isoflurane > Halothane
  - Dose dependent CNS depression → inhibition of alpha-motoneurones → ↓ pre-synaptic ACh release & ↓ post-synaptic nAChR activity → potentiates muscle relaxation → Slower rate of recovery

**Antibiotics:**
- Aminoglycosides (gentamicin) & clindamycin:
  - Compete with Ca2+ for pre-synaptic channels → ↓ ACh release → Slower rate of recovery
  - ↓ Post-synaptic nAChR sensitivity to ACh → Slower rate of recovery
- Local Anaesthetics:
  - Large doses potentiate neuromuscular blockade → ↓ Pre-synaptic ACh release, stabilise post-synaptic membrane & depress skeletal muscle fibres → Slower rate of recovery

**Calcium Channel Blockers:**
- Blockade of pre-synaptic Ca2+ channels → ↓ ACh release → Slower rate of recovery

**Frusemide & Diuretics:**
- Low dose (1mg/kg) → ↓ Pre-synaptic release ACh → Slower rate of recovery
- High dose → Inhibits phosphodiesterase → ↑ cAMP → ↑ ACh release → Faster rate of recovery

**Lithium:**
- Na+ channel blockade → Slower rate of recovery

**Dantrolene:**
- Slower rate of recovery

**Anticonvulsants (phenytoin):**
- ↓ Hepatic enzyme induction → ↑ metabolism → Faster rate of recovery

**Other Physiological States**

**Elderly:**
- ↓ Muscle mass → ↓Vd ↓ need lower dose → Slower rate of recovery (if dose not adjusted)
- ↓ CO → May have ↓muscle perfusion → Slower rate of recovery

**Neonates:**
- ↑ Sensitivity to NDMRs → Slower rate of recovery

**Obesity:**
- Dose based on IBW
- ↑Vd → ↑dose required → Slower rate of recovery
- ↑ GFR → ↑ renal elimination → Faster rate of recovery

**Pregnancy:**
- Altered pharmacokinetics until gradual return to non-pregnant status
- ↓[Protein] (especially albumin) → ↑ Unbound fraction of drug → Minimal effect on NDMRs
- ↑ GFR → ↑ renal elimination → Faster rate of recovery
- Heparic enzyme induction 2° steroid hormones → ↑metabolism → Faster rate of recovery
- ↑GFR by 50% → ↑ renal elimination → Faster rate of recovery

**NMJ States**

- **Myasthenia Gravis:** ↓nAChR number → ↑ Sensitivity to rocuronium → Slower rate of recovery
- **Lambert-Eaton:** Autoantibodies to pre-synaptic Ca2+ channels → ↓ ACh release → Slower rate of recovery
- **Burns:** Uregulation of foetal (immature) nAChRs in the extra-junctional region:
  - Foetal receptors are more unstable with t1/2 = 24hrs (2wks for mature), smaller ionic conductance, longer channel opening time & ↑ sensitivity to agonists (ACh, sux)
Reversal

**Recovery**: ↑ [ACh] to compete with [rocuronium] at nAChR in NMJ until rocuronium redistributes to plasma & is metabolised/eliminated

Major determinants of speed & adequacy of reversal agents:

1. Depth of blockade when reversal administered
   - Neostigmine effect peaks at 10mins, if no adequate recovery within this time, subsequent recovery is slow & requires ongoing elimination of NMDR from plasma
2. Type of reversal agent
   - Sugammadex provides more rapid and reliable reversal than neostigmine
3. Dose of reversal agent
   - Larger dose antagonises more rapidly & completely (∃ ceiling effect with anticholinesterase)
4. Concentration of volatile

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**Examiner’s Comments**

The factors influencing the recovery from neuromuscular blockade are dependent not only on drug pharmacokinetics but also on the state of the neuromuscular junction. Candidates needed to show an understanding of the pharmacokinetics of rocuronium and how alteration of pharmacokinetic variables influence offset of action. Simply listing a pharmacokinetic variable without explaining how it affects duration of neuromuscular blockade did not gain marks. Marks were also awarded for discussing alterations in pharmacokinetics due to age, obesity and pregnancy. Many candidates omitted to state that giving repeat doses or drug infusions would affect recovery from rocuronium.

Recovery from neuromuscular blockade also depends on pharmacodynamic factors such as changes in receptor numbers or sensitivity as occurs in myasthenia gravis and burns patients. A thorough knowledge of the drugs which interfere with rocuronium induced neuromuscular blockade was required. Successful candidates not only stated the drugs but also explained how they affected neuromuscular transmission at a pre or post synaptic level. Successful candidates also included physiological variables which affect reversal from neuromuscular blockade including hypothermia, acidosis and hypokalaemia.

Although reversal agents influence the recovery of neuromuscular blockade, this question was not about reversal agents. Marks were not gained for in depth discussion about the various anticholinesterases and cyclodextrin.