Muscle relaxants

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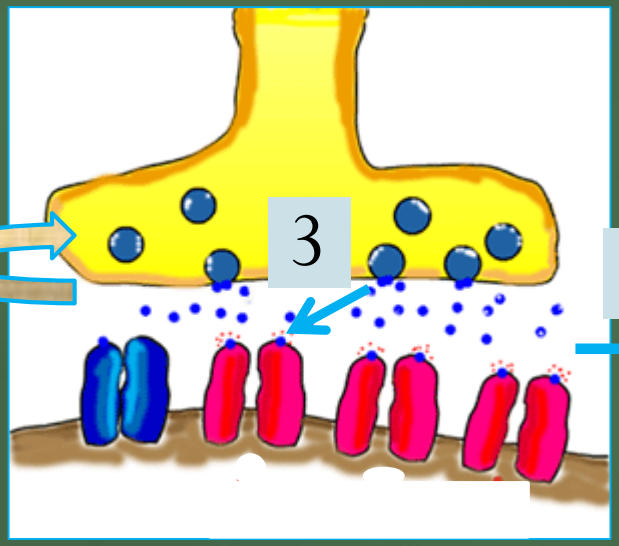
Physiology of muscle contraction

- Brain -> Spinal cord -> Nerve ending on NMJ -> Ach vesicles release Ach into cleft -> Ach:
    1. Binds NMJ pre-synaptic membrane -> + feedback
    2. Broken down by AchE in cleft
    3. Binds NMJ post-synaptic membrane NAchR
- NAchR = Na^+/K^+ channel; when Ach binds -> Na^+ in -> endplate potential
- Endplate potentials add up -> voltage across muscle membrane
- Voltage-dependent Na^+ channels open -> depolarization->Action potential (AP)
- AP reaches sarcoplasmic reticulum (SR) where Ca^{2+} is stored

Ca^{2+} released from SR into cytoplasm -> binds troponin C -> Actin/myosin binds -> muscle contraction

Ca^{2+} is pumped back into SR (ATP is used; energy consuming process)

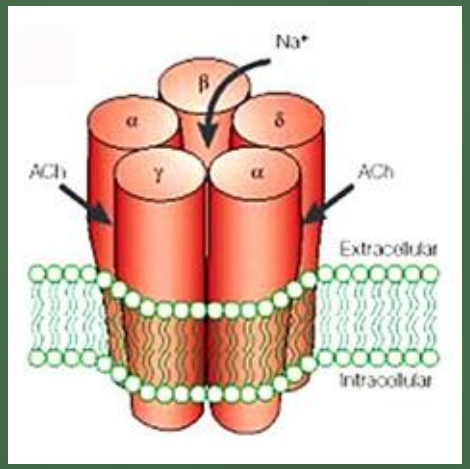
2

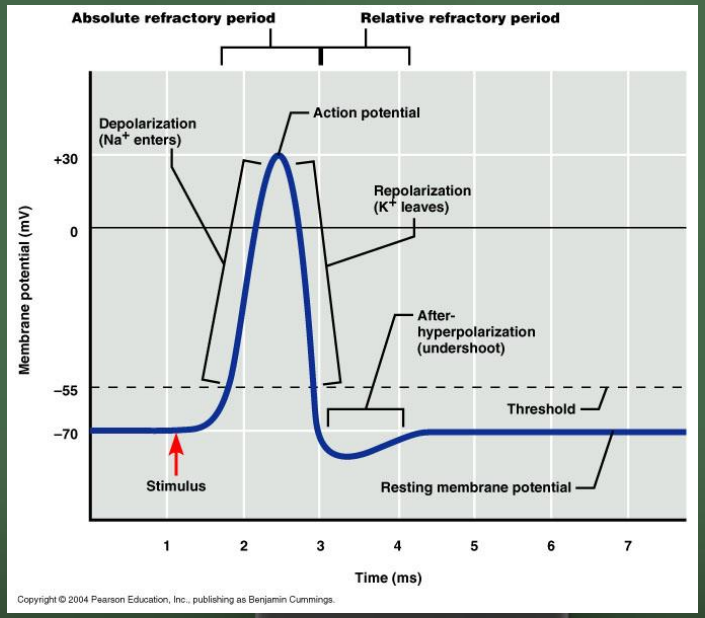


3

1

AchE


Na+
β
α
δ
γ
α
ACh
ACh
Extracellular
Intracellular


Absolute refractory period
Relative refractory period
Depolarization (Na+ enters)
Action potential
Repolarization (K+ leaves)
After-hyperpolarization (undershoot)
Threshold
Stimulus
Resting membrane potential
+30
0
–55
–70
Membrane potential (mV)
1
2
3
4
5
6
7
Time (ms)
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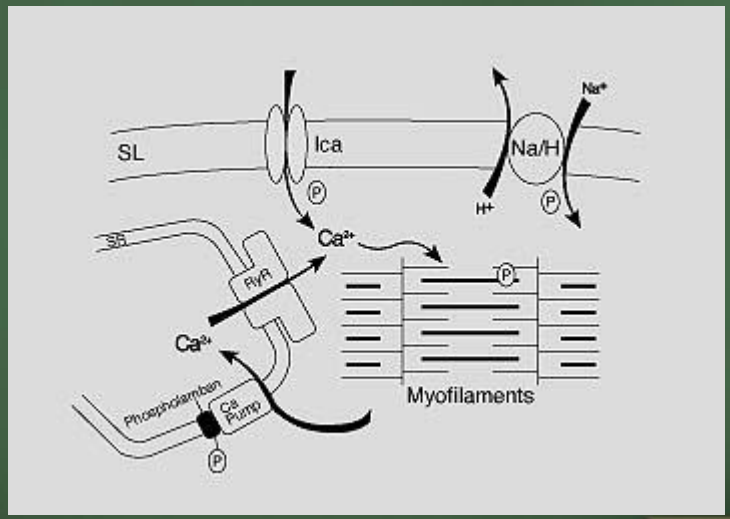
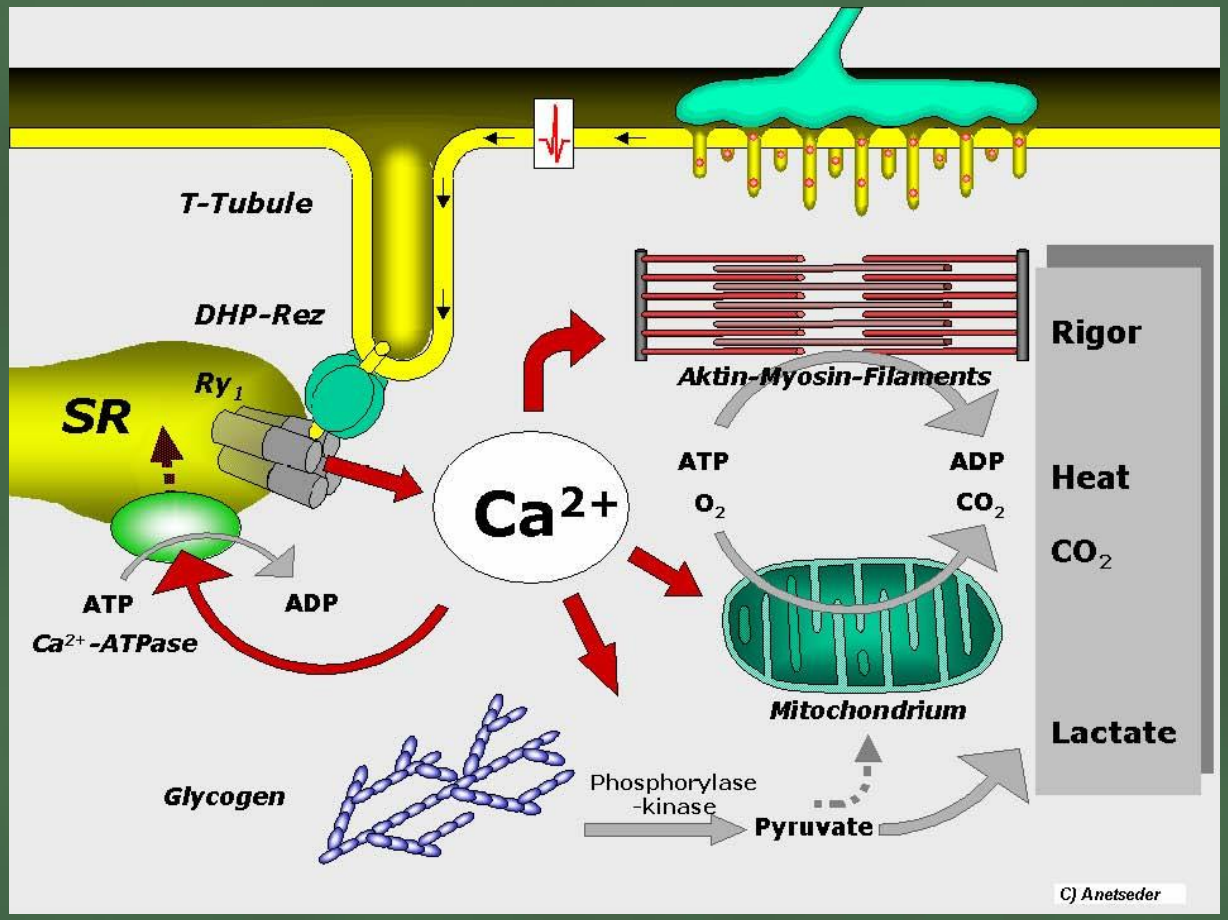
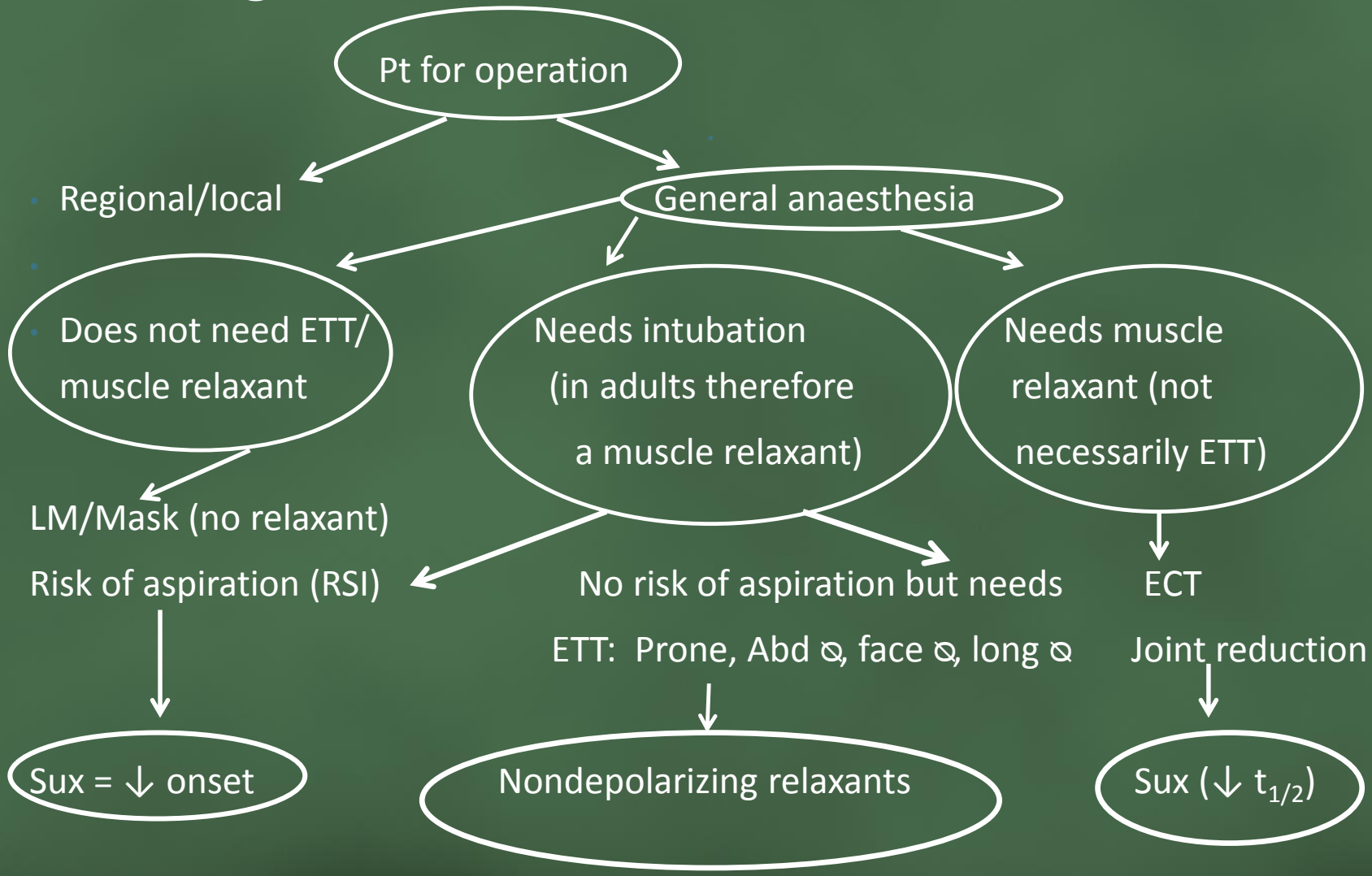

SL
Ica
Na/H
Na+
H+
P
Ca2+
SR
RyR
Ca2+
Phospholamban
Ca Pump
Myofilaments


T-Tubule
DHP-Rez
SR
Ry 1
Ca2+
ATP
Ca2+ -ATPase
ADP
Aktin-Myosin-Filaments
ATP
O2
ADP
CO2
Mitochondrium
Rigor
Heat
CO2
Lactate
Glycogen
Phosphorylase
-kinase
Pyruvate
C) Anetseder

When to give a muscle relaxant and which one?



Muscle relaxants - classification

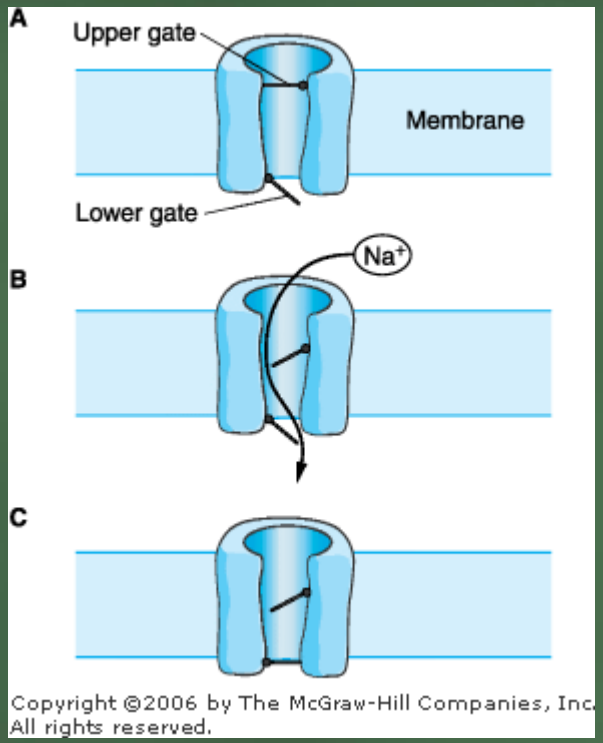
		Muscle relaxants	
	Depolarizing		Non-depolarizing
		Benzylisoquinolines	Steroids
Ultra short acting	Suxamethonium		
Short acting		Mivacurium	
Intermediate acting		Atracurium Cys-atracurium	Vecuronium Rocuronium
Long acting			Pancuronium

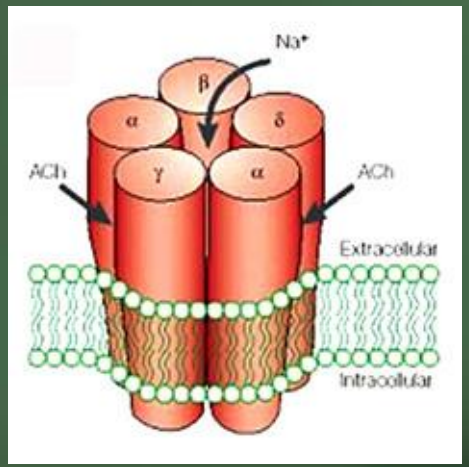
Mechanism of action

1. Suxamethonium (sux):

- Structure = 2 Ach molecules
- Sux binds 2 subunits of NAChR
- Sux = agonist; mimics action of Ach
- BUT: not broken down by AChE
- Therefore cause prolonged depolarization
- No further stimuli possible until repolarization occurs (lower gate still closed)

Termination of action: sux diffuses away from NAChR and is broken down in plasma by pCE (No pharmacological reversal agent available)





2. Non-depolarizing muscle relaxants:

Competitive antagonists of Ach at NAChR

Prevent Ach to bind -> no depolarization possible -> muscle relaxation

Termination of action:

Metabolized in body. If concentration has sufficiently decreased, reversal is possible with neostigmine

Neostigmine = AChE inhibitor; thus prevents breakdown of Ach, effectively increasing [Ach] which is the antagonist of non-depolarizing muscle relaxants.

NB: Neostigmine = non-selective, also blocking muscarinic AchR's -> side-effects include bradycardia, bronchoconstriction, diarroea, vomiting, secretions etc

Therefore anti-muscarinic agents (atropine/glycopyrrolate) given with neostigmine

Individual agents:

- 1. Suxamethonium:
- + effects: very fast onset of action (can place ETT in 30-60s)
- ultra-shortacting (effect lasts <10 min)
- Q: Why not always sux for intubation?
- A: SIDE-EFFECTS
- Fasciculations -> myalgia, fractures, $\uparrow P_{IO} \uparrow P_{IC} \uparrow P_{IG}$
- Muscarinic side effects -> bradycardia, secretions
- $\uparrow K^+$ (normal pt's - $K^+ \uparrow$ by 0.5meq/l)
- Masseter muscle spasm, Malignant hyperthermia, scoline apnoea
- Allergic reactions, histamine release (bronchospasm)

- **Indications for suxamethonium:**

1. Rapid sequence induction (patients at risk of aspiration)

2. Very short procedures needing muscle relaxation:
   - Electro-convulsive therapy (ECT)
   - Reductions of dislocated joints

3. Emergency drug to treat laryngospasm

Non-depolarizing muscle relaxants:

Muscle Relaxant	Metabolism	Excretion	Side-effects	Special characteristics
Mivacurium	pCE	Renal if ↓pCE	-Prolonged apnoea if ↓pCE	
Atracurium	Hoffman elim & ester hydrolysis	Nil, choose in renal and liver function impairment	Releases histamine, avoid asthmatics	Stored in fridge
Cis-atracurium	Hoffman elim & ester hydrolysis		Nil	No histamine release Stored in fridge
Vecuronium	40% liver	Renal: 40% metabolites 20% unchanged	Nil	Powder to be reconstituted
Rocuronium	Hepatic: minimal	Renal: 30-40% Biliary: 60%	Can release histamine	Stored in fridge
Pancuronium	Hepatic: 10-20%	Renal: 60-80% Biliary: 10%	Vagolytic – causes ↑HR; avoid in IHD	Stored in fridge

- **Prolonged action of muscle relaxants:**

Suxamethonium	Non-depolarizing agents
Lithium Ecothiopate eye drops Cyclophosphamide Metoclopramide	Metabolic acidosis Hypothermia ↓K^+ ↑ Mg^{2+} Antibiotics (especially aminoglycosides) Myasthenia Gravis, Myasthenic syndrome (Lambert Eaton), Muscular dystrophies

Foetal type NAchR's

- Immature isoform of NAchR
- Has a prolonged open channel time exaggerating the K+ efflux!
- Expressed everywhere on muscle membrane, not only on neuromuscular junction like adult type NAchR's

Therefore: 1. More receptors (entire muscle)
2. Foetal type → prolonged open time

↑K+ after succinylcholine
Resistant to nondepolarizers

- **Upregulation of NAchR's**

Found in states of functional denervation
Is characterized by the spreading of foetal type receptors at extra-junctional sites

Conditions predisposing	Consequence
1. Upper motor neuron lesions 2. Lower motor neuron lesions 3. Muscle injury 4. Burn injury 5. Immobilization 6. Sepsis/infection 7. Prolonged exposure to neuromuscular blockers 8. Multiple sclerosis 9. Guillain-Barre syndrome	1. Increased requirements for nondepolarizing muscle relaxants (resistance) 2. Hyperkalaemia after suxamethonium administration

- **Down regulation of NAchR's**
  - 1. Myasthenia Gravis
  - 2. Organophosphate poisoning

Consequence:

Decreased requirement of nondepolarizing muscle relaxants (increased sensitivity)

Anticholinergic agents:

Neostigmine = AchE inhibitor

BUT non-selective → ↑ Ach @ Nicotinic AchR AND Muscarinic AchR

Reverses non-depolarizing muscle relaxants (NAchR)
BUT also causes muscarinic side-effects (M-AchR):

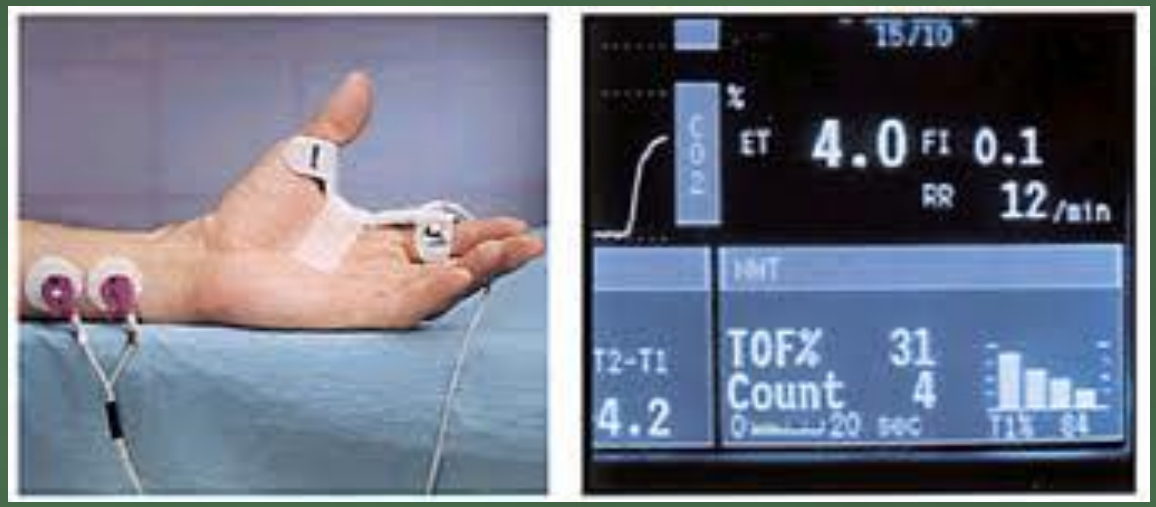
1. Bronchospasm
2. Secretions
3. Bradycardia
4. Diarrhoea
5. Hypersalivation

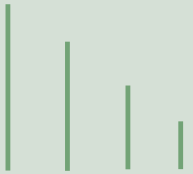
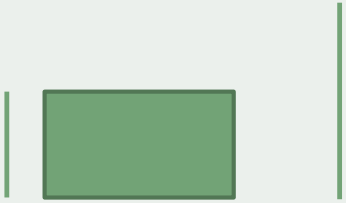
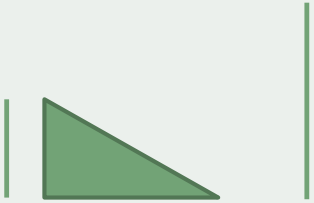
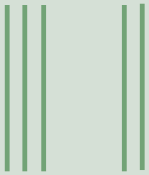
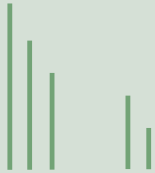
Prevention of these side-effects:
When administering neostigmine, add anti-cholinergic agent – atropine or glycopyrrolate

Atropine vs glycopyrrolate:

	Atropine	Glycopyrrolate	Implication
Structure	Tertiary amine	Quaternary amine	
Blood-brain barrier (BBB)	Crosses BBB	Does not cross BBB	Atropine causes CNS s/effects
Central effects	Yes (confusion etc)	No	Avoid atropine in elderly
Oral absorption	Yes	No	Atropine po as premed if antipsialogogue required
Onset	Fast	Slower	Emergency bradycardia treated with atropine
Duration	Shorter	Longer	
Antisialogogue	Effective	4x more effective	Choose glyco IV prior to fibre-optic intubation
Tachycardia	↑↑↑	↑	Avoid atropine in IHD or fixed CO pt's
Cost	Cheap	More expensive	

- **Monitoring of muscle relaxants:**



	Normal	Depolarising	Non-depolarising
Single twitch			
Tetanic stimulus			
Train-of-four (TOF)			
Posttetanic potentiation			
Double burst ($DBS_{3,2}$)			

Interpretation of TOF mode:

- TOF count: how many stimuli visible
- TOF percentage: All 4 visible, describes ratio of height of stimulus 4: height of stimulus 1

Examples:

TOF count = 4
TOF ratio = 30%

TOF count = 3
TOF ratio = /

NB:

- If TOF count <4, no TOF ratio can be described, since the ratio refers to the relationship of the 4th stimulus to the 1st
- No TOF ratio can be described for suxamethonium, since it will always be 1 (no fade)

TOF count/TOF ratio	Interpretation
0	Deep block, can intubate, do neurosurgery etc
Count 0-3	Can perform abdominal surgery Cannot administer neostigmine yet
Count 4	Needs more muscle relaxant to perform abdominal surgery
Count 3-4	Can now administer neostigmine to reverse block
Count 4/Ratio <90%	Patient should not yet be extubated
Count 4/Ratio >90%	Patient can now be extubated

Signs of adequate reversal:

1. Normal tidal volume
2. Effective cough
3. Strong grip with hand
4. Ability to keep eyes open (no ptosis)
5. Ability to lift head off pillow for 5 seconds
6. Presence of masseter muscle tone
7. Satisfying response measured with the nerve stimulator

Signs of inadequate reversal:

1. Tracheal tug –this is a very reliable sign
2. Jerky movements of limbs “floppy fish”
3. Ineffective cough
4. Ptosis
5. Paradoxical breathing

Sugammadex (Cyclodextrin)

- Large carbohydrate molecule (complex of sugars)
- Hydrophobic outside & Hydrophilic core
- Encapsulates steroid-like molecules
- Reverses especially rocuronium immediately
- Not yet on SA market

- ED_{95}
  - Dose required to decrease the amplitude of a single twitch (with a nerve stimulator) by 95%
  - Indicates the potency of a muscle relaxant

- **Response of muscle disease to muscle relaxants:**

	Depolarizer	Nondepolarizers
Myasthenia Gravis	Small dose: resistant Large dose: phase II block	Overly sensitive ++++
Myasthenic syndrome (Lambert-Eaton)	Overly sensitive ++++	Overly sensitive ++++
Burns	↑↑↑↑ K^+	Resistant
Myotonia	Myotonic response	Reduce dose (muscle wasting)
Muscle dystrophies	Hyperkalaemia Hyperthermia (not MH)	Overly sensitive (if myopathy)