Muscle Relaxants

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Muscle Relaxants

Muscle relaxants are used when you need to have the patient NOT MOVE, and to have NO MUSCLE ACTIVITY.

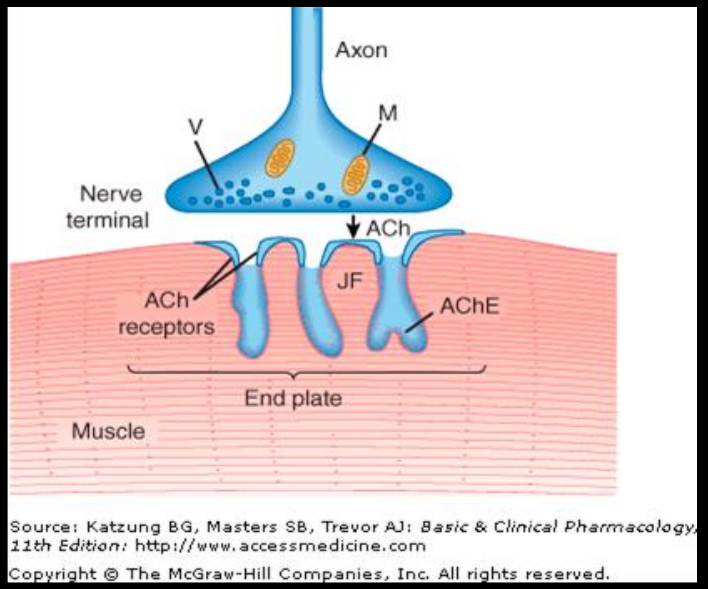
They provide ZERO sedation or analgesia.

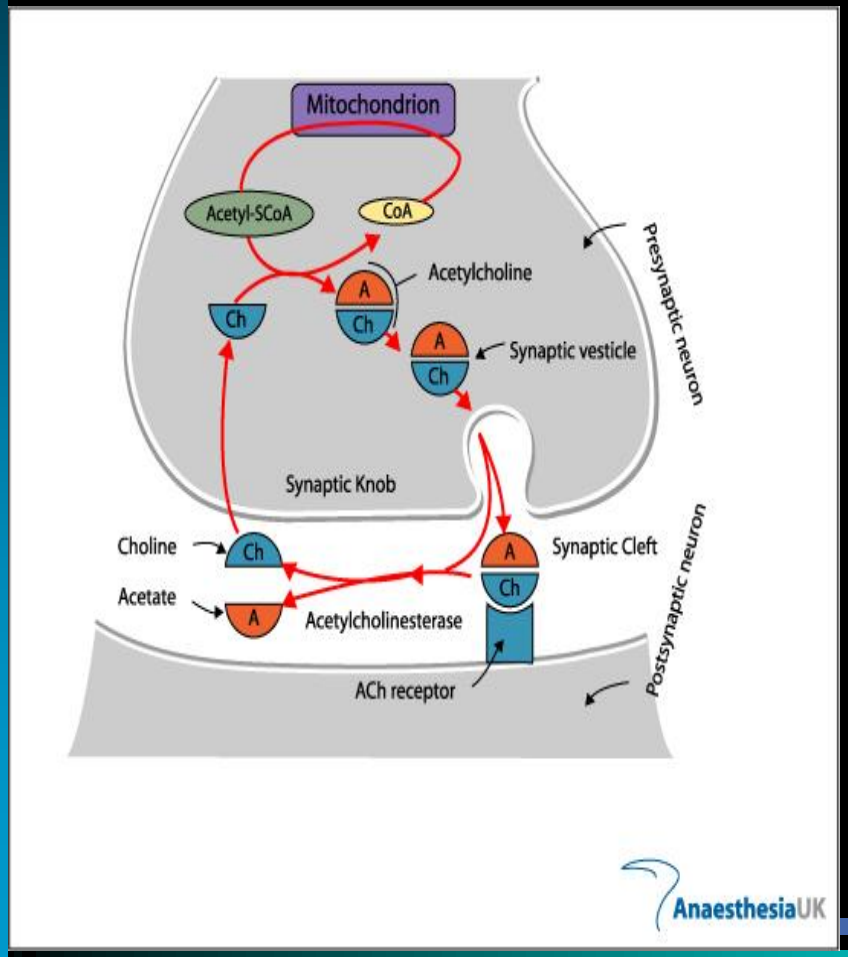
Once more, ZERO sedation or analgesia.

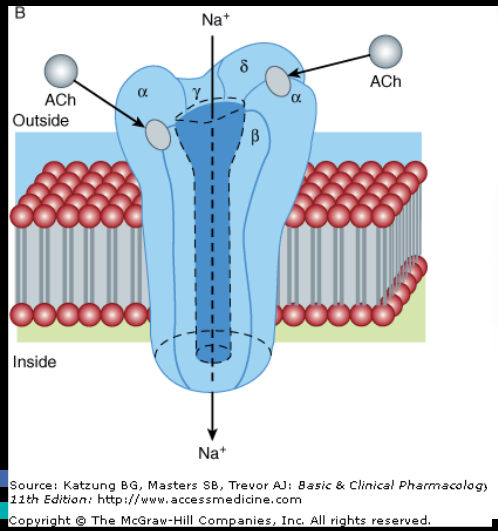
DO NOT FORGET!!

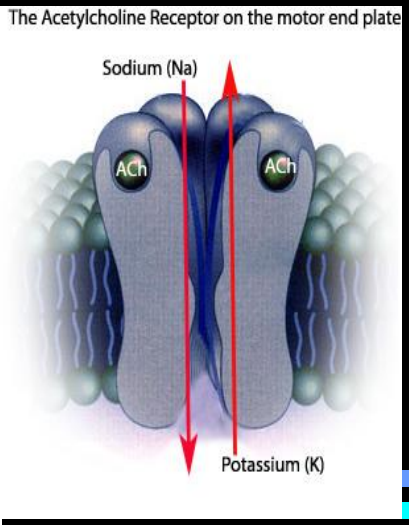
NMJ

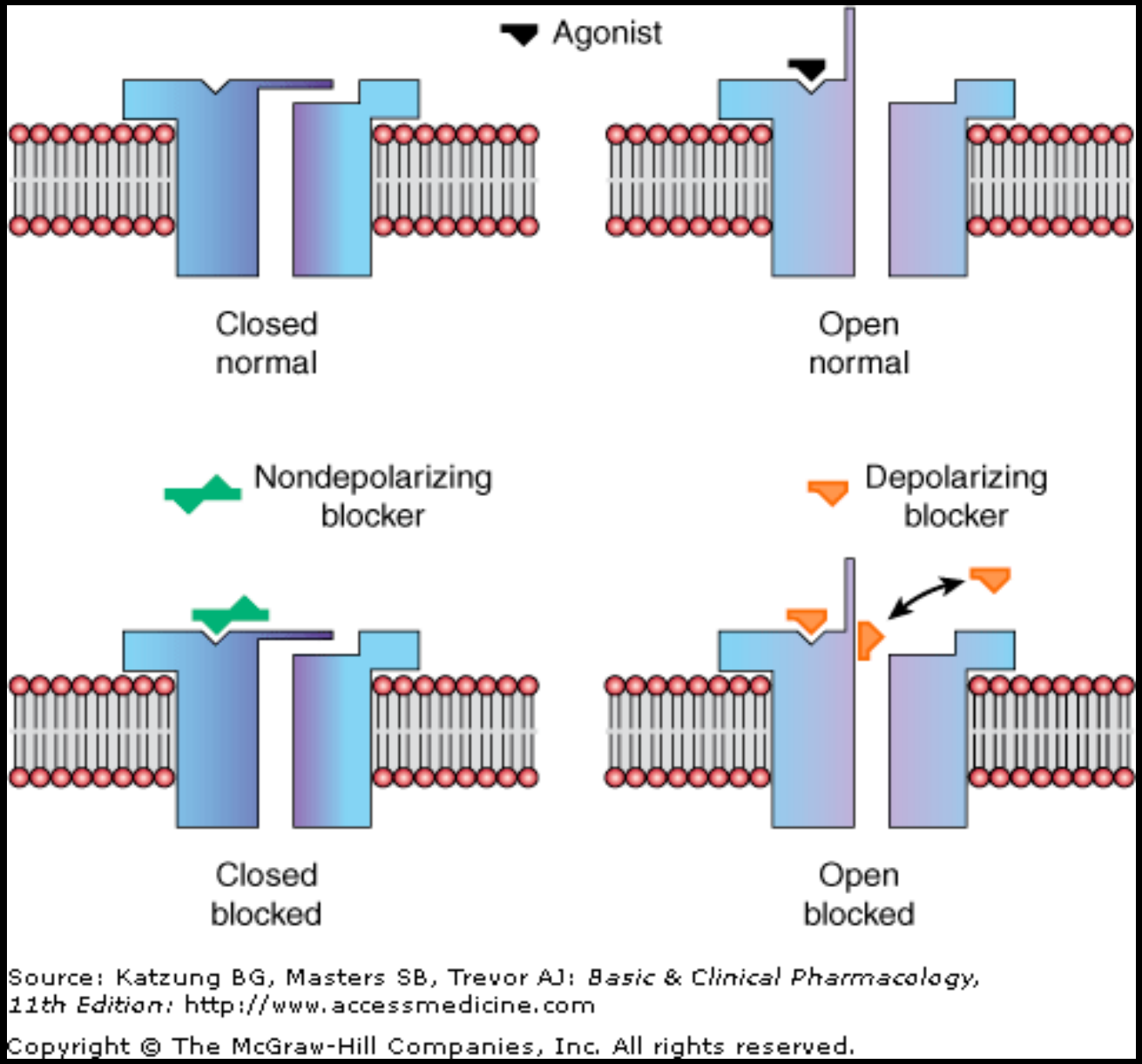
- The neuromuscular junction (NMJ) is the synapse between the presynaptic motor neuron and the postsynaptic muscle membrane.











Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Nicotinic cholinergic receptor:

- **The nicotinic receptor at the NMJ contains 5 subunits, which surround the sodium channel. Ach binds to two of these subunits; (alpha) binding of Ach results in opening of the sodium channel for 1 millisecond.**

Methods to alter transmission at the NMJ:

- **Decrease Ach at NMJ**

  Inhibit Ach synthesis or release (e.g. hemicholinium blocks the uptake of choline into the nerve terminal, which results in depletion of Ach).

- **Increase Ach or Ach effect at NMJ**

  Results in nicotinic effect, and thus depolarisation.

- **Block nicotinic cholinergic receptors at NMJ by competitive blockade (mechanism of action of most therapeutic NMJ blockers)**

MUSCLE RELAXANTS (NMJ blockers) General mechanism of action:

Block transmission through the neuromuscular junction (NMJ) at nicotinic receptors, thus decreasing skeletal muscle tone.

- Depolarizing Neuromuscular Blocker—

Succinlycholine

2. Depolarising NMJ Blockers:

Produce what appears to be a "persistent" depolarisation of the NMJ

- Cause depolarisation by mimicking the effect of Ach but without being rapidly hydrolysed by acetylcholinesterase

- Propagation of an action potential is prevented by the area of inexcitability that occurs around the Ach receptors

Examples include suxamethonium (1951) and decamethonium (1948)
Model = succinylcholine

Adverse drug reaction:

- **Histamine release**

  This is a feature of tubocurare and succinylcholine (others to lesser extent)

  Effects of histamine release:

  bronchospasm
  dilatation of peripheral blood vessels
  (decreased blood pressure)
  excessive secretions
  anticoagulant effect

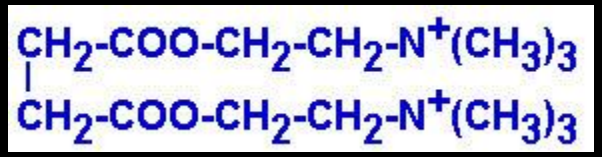
Suxamethonium (succinylcholine)

- **Uses**

  Suxamethonium is a short-acting muscle relaxant. The main uses in anaesthesia are:

- **1. to allow rapid intubation of the trachea and short periods of neuromuscular blockade**

- **2. for the modification of fits after electroconvulsive therapy.**



Succinylcholine Adverse effects

Cardiovascular: Bradycardia
This can be prevented by the prior administration of atropine.

Metabolic: the potassium level in the serum will rise (HYPERKALEMIA)

Raised intracranial and intraocular pressure:
there is a transient rise in intracranial and intraocular pressure after suxamethonium.

Prolonged paralysis:
this can occur in patients with abnormal plasma cholinesterases; if suxamethonium is given in excessive doses, e.g. by repeat injections or infusion; in patients receiving certain drugs, e.g. some antibiotics.

Anaphylaxis

Malignant hyperthermia:
suxamethonium can trigger the onset of malignant hyperthermia in those patients who have this genetic muscle disorder.

Muscle pains: Fasciculations

Non-depolarizing neuromuscular blockers

- Pancuronium
- vecuronium
- Atracurium
- cis-atracurium
- Doxacurium
- Rocuronium

	Dose (mg/kg)	onset	Duration	Side Effects	Metablism
Pancuronium	0.1	2 min	4-6 min	tachycardia with bolus use	Renal (60-80%) and biliary excretion
Vecuronium	0.1-0.3	1.5-2 min	20-30 (children) 60-80 (infants)		hepatic metabolism, biliary (80%) and renal (20%) excretion
Atracurium	0.3-0.6	2-3 min	15 min	histamine release (mild)	Hoffman degradation
Rocuronium	0.6-1.2	60sec	60 min		

. 1. Non-depolarising **NMJ blockers :**

Bind to receptors and prevent acetylcholine (Ach) from stimulating receptors
Model = Curare

Effect: compete with Ach for nicotinic receptor binding sites. The blockade is competitive, hence muscle paralysis occurs gradually.

Examples include tubocurarine, gallamine, atracurium, vecuronium, mivacurium, rocuronium and cisatracurium.

These drugs are highly ionised at body pH and contain two quaternary ammonium groups.

They are poorly lipid soluble and poorly protein bound.

Non-depalarizing Neuromuscular Blockers

- These drugs have a longer onset of action and longer duration of action than succinlcholine.
- They act as competitive antogonists of Ach at the neuromuscular junction.
- They do not effect potassium and are not MH triggering agents.
- They differ in their chemical structure, route of metabolism and elimination, onset and duration of action.

Pharmacology of the non-depolarising muscle relaxants

Mechanism of action

- Non-depolarising muscle relaxant drugs compete with acetylcholine (ACh) molecules released at the neuromuscular junction to bind with the ACh receptors on the post-synaptic membrane of the motor endplate
- They therefore block the action of ACh and prevent depolarisation.

- Non-depolarising muscle relaxant drugs also act on presynaptic receptors interfering with the entry of calcium, which causes an inhibition of the release of ACh.

- None of the drugs cross the blood-brain barrier

- All non-depolarising drugs should be used with care in patients suspected to be suffering with myasthenia gravis or myasthenic syndrome, as patients with these conditions are extremely sensitive to their effects.

Atracurium

It is a **short-acting relaxant** which is rapidly broken down by the body. This makes atracurium very predictable, as it wears off rapidly compared with the longer-acting relaxants.

Cardiovascular effects

Although atracurium produces few direct circulatory effects, the absence of vagal blocking activity makes the patient vulnerable to bradycardias during anaesthesia.

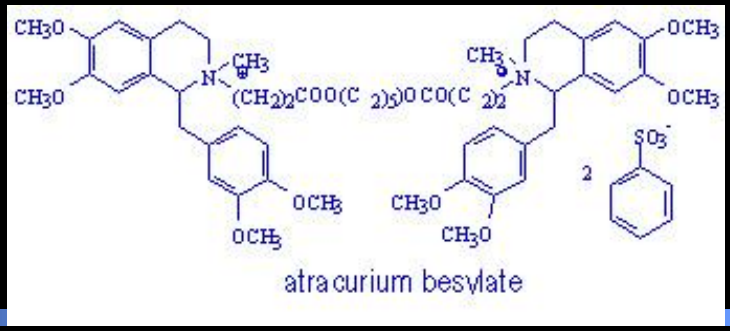
Histamine release may occur with doses of atracurium greater than 0.6 mg/kg.

Respiratory effects

In standard doses, atracurium rarely causes problems with bronchospasm.

Bronchospasm can occasionally occur secondary to histamine release.

Placental transfer is insignificant
and the drug is widely used in obstetrics.



atracurium besylate

- **Interactions of NMJ blockers**

  Blockade is potentiated with general inhalational anaesthetics; antibiotics, e.g. gentamycin (decrease Ach release) and tetracyclines (chelate calcium and decrease Ach release).

  Blockade is reduced with anticholinesterase agents (Neostigmine and pyridostigmine).

  Results in increased Ach levels at the NMJ, thus antagonising the effects of competitive agents.

Drug	Elimination	Clearance (mL/kg/min)	Approximate Duration of Action (minutes)	Approximate Potency Relative to Tubocurarine
Isoquinoline derivatives				
Atracurium	Spontaneous[1]	6.6	20–35	1.5
Cisatracurium	Mostly spontaneous	5–6	25–44	1.5
Doxacurium	Kidney	2.7	> 35	6
Metocurine	Kidney (40%)	1.2	> 35	4
Mivacurium	Plasma ChE[2]	70–95	10–20	4
Tubocurarine	Kidney (40%)	2.3–2.4	> 50	1
Steroid derivatives				
Pancuronium	Kidney (80%)	1.7–1.8	> 35	6
Pipecuronium	Kidney (60%) and liver	2.5–3.0	> 35	6
Rocuronium	Liver (75–90%) and kidney	2.9	20–35	0.8
Vecuronium	Liver (75–90%) and kidney	3–5.3	20–35	6
Depolarizing agent				
Succinylcholine	Plasma ChE[2] (100%)	>100	< 8	0.4

[1]Nonenzymatic and enzymatic hydrolysis of ester bonds.

[2]Butyrylcholinesterase (pseudocholinesterase).

TABLE VI

Drug	Intubating dose ($mg \cdot kg^{-1}$)	Intermittent dose[a] ($mg \cdot kg^{-1}$ q1–3hr)	Continuous infusion[a] ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Clinical duration[b] (min)	Duration of action[c] (min)	Relative cost[d]
Short-acting						
Succinylcholine	1.0–1.5	–	60	5–10	12	1
Mivacurium	0.15–0.20	–	6–7	17	24	N/A[e]
Intermediate acting						
Atracurium	0.5–0.6	0.6–1.2	5–6	30	64	80:1
Vecuronium	0.1–0.15	0.15–0.3	100–200	30	45	70:1
Long-acting						
Pancuronium	0.1–0.15	0.05–0.1	20–40	60	160	35:1
Pipecuronium	0.07–0.08	N/A	N/A	70	N/A	N/A
Doxacurium	0.05–0.06	0.005–0.01	N/A	83	N/A	N/A

[a]Requires continuous neuromuscular monitoring due to patient variability.
[b]Time from injection to 25% twitch recovery.
[c]Time from injection to 90% twitch recovery.
[d]Relative cost of intubating dose ($2 \times ED_{95}$) compared to succinylcholine.
[e]Data not available.

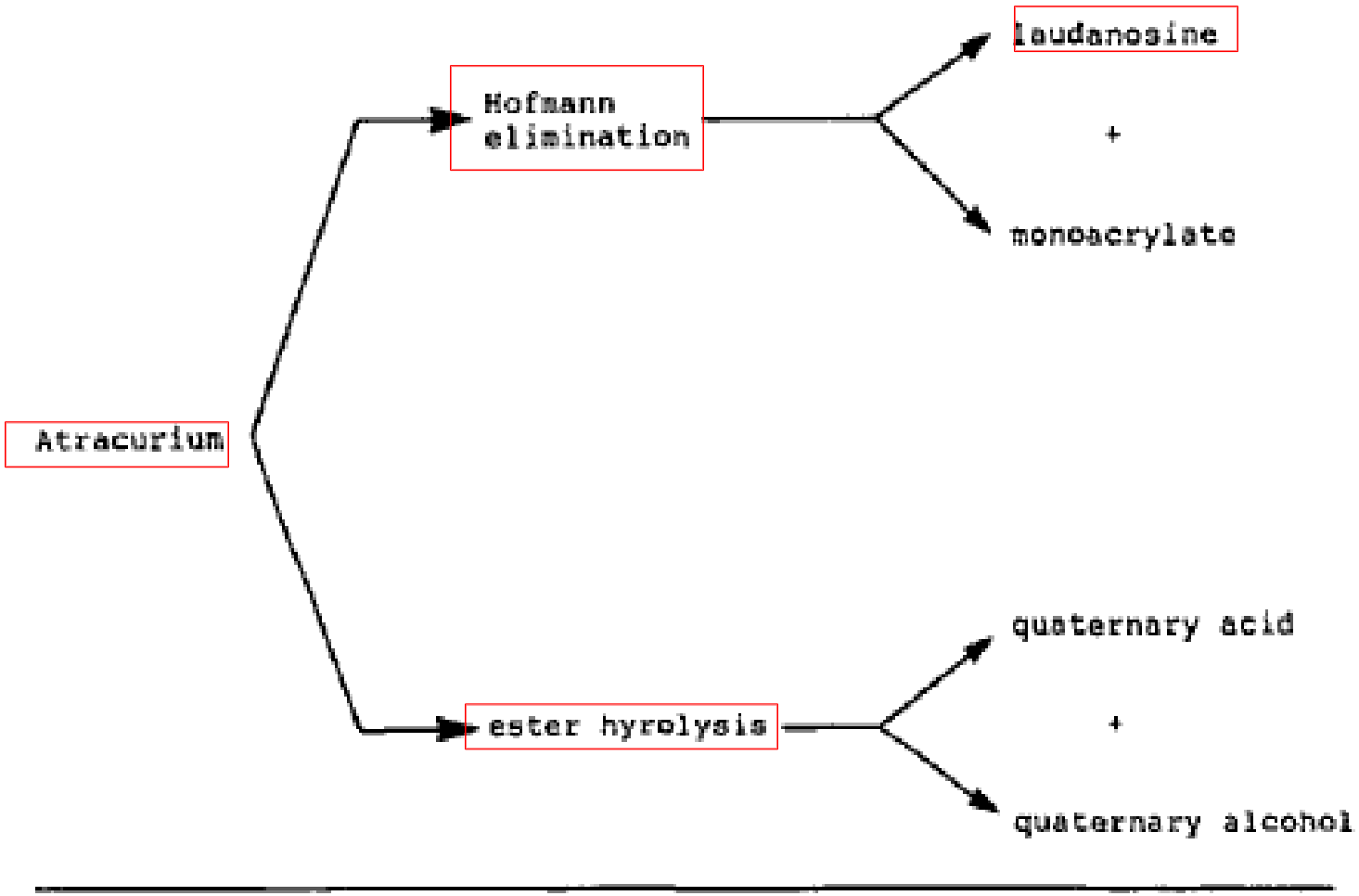


FIGURE Pathways of atracurium metabolism and the metabolic byproducts.

TABLE I Indications for continuous muscle paralysis in the critically ill patient

Decreased pulmonary/chest wall compliance with coexisting high ventilatory pressures, e.g., ARDS.
Patient/ventilator non-compliance.
Raised intracranial pressure.
Central neurogenic hyperventilation.
Tetanus.
Status epilepticus.
To reduce metabolic demands/work of breathing.
To prevent shivering during therapeutic cooling.

TABLE II Potential complications of muscle paralysis in the critically ill patient

Unrecognized patient-ventilator disconnection.
Suppression of cough reflex.
Secretion retention and atelectasis.
Pulmonary infection.
Patient immobility causing
– deep vein thrombosis and pulmonary emboli
– peripheral nerve injuries
– skin breakdown/stasis ulcers.
Inability to spontaneously perform a neurological examination.
Inadequate sedation in the paralyzed patient.
Subluxation of unstable spinal fractures.
Side effects of the muscle relaxant.

TABLE III Characteristics to consider when choosing a neuromuscular blocking agent

Speed of onset.
Potential for cardiovascular stability.
Dependency on renal/hepatic function for metabolism.
Potential for histamine release.
Potential for "cumulative" effect.
Ease and rapidity of antagonism.
Predictable action.
Intermittent or continuous infusion administration capability.
Potential for induction or inhibition of hepatic enzymes.
Potential formation of toxic or active metabolites.
Interactions with other drugs.
Cost.

TABLE VII Causes of prolonged neuromuscular blockade

1 Excessive drug administration.
2 "Cumulative" drug effect, e.g., pancuronium, vecuronium.
3 ↓ Metabolism/excretion of muscle relaxant, e.g., renal/hepatic dysfunction.
4 Accumulation of active metabolites.
5 Electrolyte imbalances: hypokalaemia, hypocalcaemia, hypermagnesaemia, hypernatraemia.
6 Hypothermia.
7 Drug interactions
   - inhalational anaesthetics
   - local anaesthetics
   - calcium-channel blockers
   - antiarrythmics, i.e., quinidine, procainamide
   - antibiotics, i.e., aminoglycosides
      - tetracyclines
      - vancomycin, lincomycin
      - clindamycin
   - immunosuppressives: cyclosporin
8 Increased sensitivity to muscle relaxants: i.e., neuromuscular disorders; myasthenia gravis, polymyositis.

NEUROMUSCULAR BLOCKING AGENTS FOR INTUBATION

AGENT	INTUBATION DOSE	INFUSION	DURATION RATE	ELIMINATION OF ACTION	ADVERSE EFFECTS
NONDEPOLARIZING					
Long Duration					
Pancuronium	0.1 mg/kg	N/A	50 - 60 min	renal	vagolytic (increased HR and BP) histamine release
Pipecuronium	85 mcg/kg	N/A	60 - 70 min	renal	N/A
Doxacurium	50 mcg/kg	N/A	80 min	renal	N/A
Intermediate Duration					
Vecuronium	0.1 - 0.2 mg/kg	0.05 - 0.2 mg/kg/hr	25 - 40 min	hepatic	N/A
Atracurium	0.5 mg/kg	0.3 - 0.6 mg/kg/hr	25 - 35 min	Hofmann Elimination	histamine release
Rocuronium	0.6 - 1.0 mg/kg	0.5 - 0.7 mg/kg/hr	30 - 40 min	hepatic	increased HR with high dose
Cisatracurium	0.1 - 0.15 mg/kg	3 - 10 mcg/kg/min	25 - 40 min	Hofmann Elimination	N/A
Short Duration					
Mivacurium	0.15 - 0.2 mg/kg	12 - 20 mcg/kg/min	15 - 20 min	plasma cholinesterase	histamine release
DEPOLARIZING					
Ultra Short Duration					
Succinylcholine	1.0 - 2.0 mg/kg	N/A	4 - 6 min	plasma cholinesterase	bradycardia, hyperkalemia, malignant hyperthermia, increased intragastric pressure, histamine release