

Neuromuscular blocking agents

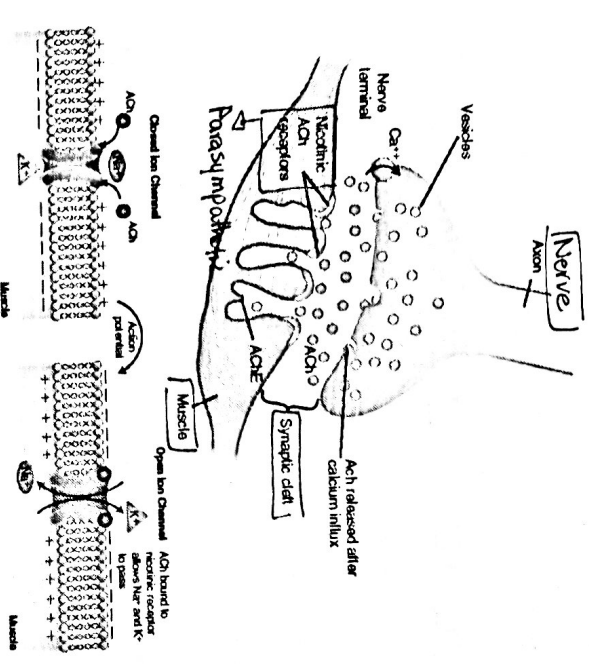
Introduction

- Induce state of pharmacologic paralysis by interfering with normal processes of neurotransmitter—receptor interaction at neuromuscular junction (NMJ)

Introduction

- One of the primary anesthetic goals is akinesia abd. & pelvis → enhance surgical exposure & ↓ total anesthetic dose
- Muscle relaxants = neuromuscular relaxants = neuromuscular blockers (NMB)

Neuromuscular junction



Classification of muscle relaxants

- Two main types:

- Depolarizing
- Nondepolarizing

Depolarizing / Succinylcholine

(Scoline)

- Physically resemble Ach

- Two Ach molecules joined

* Short acting

10% reach NMJ

90% metabolism in circulation
by pseudocholinesterase.

Cause activation of Nicotinic receptors

Mechanism of action

- Depolarization of skeletal muscle membrane & muscle contraction (fasciculations) followed by flaccid paralysis
- Higher affinity for Ach receptor as compared with Ach
- Remains bound & blocks subsequent stimulation

Metabolism

- Rapidly cleared by nonspecific plasma esterases
- Only small fraction of administered dose reaches NMJ
- Hypothermia & medications affect plasma cholinesterase activity prolong duration
- Deficiency of pseudocholinesterase prolonged paralysis (Heterozygous or homozygous)
↳ block 1/2 hr ↳ block 2hr
- Treated with mechanical ventilation & ? FFP

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Dosage & uses

- Adult 0.5-1.5 mg/kg
- Pediatric 2.0 mg/kg
- Muscle paresis occurs within 45 seconds → 30 sec بعد بدأ فقدان العضلات
- Ideal drug for rapid sequence induction (RSI) → 45 sec بعد بدء intubation
- Duration of action 5-10 min
- Short case
- Difficult airways
- Patients prone to hypoxia
- Electroconvulsive therapy
- Emergent intramuscular administration
- Laryngospasm rescue

* Rocuronium

- 60 sec by inhibitory cur
- 0.6-0.8 mg/kg
- 1-1.2 mg/kg for rapid sequence induction

Contraindications

- Severe burns : destruction of receptor as compensatory mechanism
- Myopathy extra junctional receptors note هذا يزيد Hyper K+
- Extensive degenerative neuropathy
- Hyperkalemia
- Prolonged paralysis with previous use → ↑ no. of receptors.
- Family history of malignant hyperthermia

Side effects

- ↑ Potassium (0.5 to 1 mEq/L) receptors في العضلات → scoline لرفع receptors في العضلات
- Myalgias / to prevent give predose of non depolarizing
- Transient ↑ ICP, ↑ ICP & ↑ IOP
- ↓ by pretreatment with "defasciculating dose = 1/10 intubating dose" of nondepolarizing agent & intravenous lidocaine
- Masseter muscle spasms → لا يستطيع فتح الفم
- Malignant hyperthermia
- Anaphylaxis
- Bradycardia (pediatric) adults any type of arrhythmia
- but first dose → لا يحدث
- but sec. cause arrhythmia
- Scoline لا يمنع muscle spasm
- Scoline لا يمنع malignant hyperthermia
- Scoline لا يمنع Non depolarizing

Nondepolarizing

- Competitive antagonists of Ach at postsynaptic membrane
- Several nondepolarizing muscle relaxants
- Subclassified by:
 - Chemical structure
 - Duration of action
 - Potency

Chemical structure

- Aminosteroid
 - Vagolytic $\rightarrow \uparrow$ HR, $\uparrow$ MAP & $\uparrow$ CO $\uparrow$ BP
- Benzylisoquinolines
 - Stimulate release of histamine $\rightarrow$ hypotension, tachycardia, bronchospasm & facial flushing

Chemical structure

Aminosteroid		Benzylisoquinolines	
Rocuronium		Atracurium	$\rightarrow$ histamine release
Vecuronium		Cisatracurium	
Pancuronium		Mivacurium	$\rightarrow$ histamine release

$\rightarrow$ histamine release

$\rightarrow$ histamine release

Duration of action

Ultra-Short	Short	Intermediate	Long
Succinylcholine	Mivacurium	Vecuronium	Pancuronium
5-10 sec	50 m	Cis-atracurium	60-90 m
		Rocuronium	

$\frac{1}{2}$ - $\frac{3}{4}$ hr

Rocuronium

- Intubating dose 0.6–1 mg/kg.
- RSI 0.6–1.2 mg/kg.
- Rapid onset of 0.9–1.7 min
- Alternative to succinylcholine in RSI
- Duration of action is 36–73 min
- Minimal cardiovascular effects
- Hypersensitivity reactions & anaphylaxis
- Excreted through biliary system & in urine minimally
- Duration prolonged in hepatic impairment

Vecuronium

drug of choice
in trauma

- Intubating dose 0.08–0.1 mg/kg
- Onset 2–3 min
- Duration of action is 40–45 min
- Hypersensitivity
- Minimal cardiovascular effects
- ICU patients paralyzed → higher incidence of prolonged blockade & critical illness polynuropathy
- Metabolized in liver & excreted through biliary system
- Hepatic disease & severe renal impairment prolong duration of action

Pancuronium

long acting.

- Intubating dose 0.06–0.1 mg/kg
- Onset 3–4 min
- Duration of action is 85–100 min
- Vagolytic effects
- hypersensitivity reactions
- Metabolized in liver
- Avoided in renal impairment excreted by kidney

Atracurium

- Intubation Dose 0.2–0.3 mg/kg
- Onset 3 mins
- Duration of action 45 mins
- Metabolized by Hoffman elimination & plasma esterases
 - Hoffman elimination is enzyme-independent hydrolysis relies on physiologic pH & temperature
- Laudanosine is byproduct → cross BBB → convulsion
- Histamine release → avoided in bronchial asthma.

Cisatracurium

does not release histamin.

- Intubating dose 0.15–0.2 mg/kg
- Onset of 2–8 mins
- Duration of action of 45–90 min
- Hoffman elimination
- Amount of laudanosine produced from cisatracurium < atracurium
- Does not release histamine

Mivacurium

- Metabolized by plasma pseudocholinesterase
- Duration of action prolonged in renal & liver failure
- Histamine release the most
- No longer available in the United States

Local anesthetic (LA)

Definition

- Drug reversibly prevents transmission of nerve impulse without affecting consciousness

Structural classification

- Amides
- Esters

Amides

- Bupivacaine *in vivo*
- Prilocaine
- Lidocaine
- Ropivacaine
- Etidocaine
- Mepivacaine

Metabolism of esters results in production of para-aminobenzoate (PABA) which is associated with allergic reaction

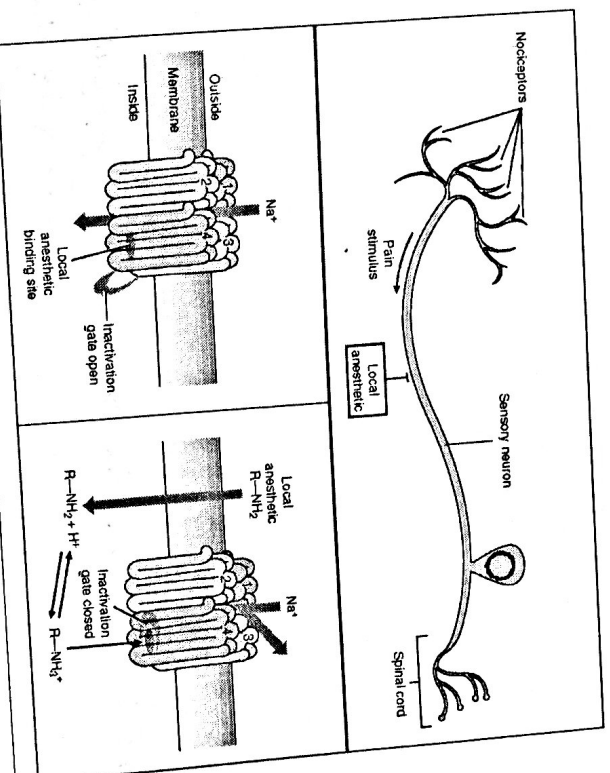
- Amides very rarely cause allergic phenomena
- Amides more commonly used than esters

Esters

- Cocaine
- Amethocaine
- Chlorprocaine
- Procaine
- Tetracaine

metabolism of esters result in production of Para amino benzoic acid

Mechanism of action



Mechanism of action

• Block voltage-gated sodium channels from inside the cell ^{should cross the cell membrane} → interfering with sodium influx associated with ^{not fixed lipid soluble}

membrane depolarization → impulse conduction

slows until action potential no longer generated &

impulse propagation abolished

* stenotic valvular heart disease with fixed CO is contraindication for local anesthesia.

Comparative Pharmacology of Local Anesthetics

Classification	Potency	Onset	Duration after Infiltration (min)	Maximum Single Dose for Infiltration (mg)	Toxic Plasma Concentration (μg/mL)	pK	Protein Binding (%)
Esters							
Procaine	1	Slow	45-60	500		8.9	6
Chlorprocaine	4	Rapid	30-45	600		8.7	
Tetracaine	16	Slow	60-180	100 (topical)		8.5	76
Amides							
Lidocaine	1	Rapid	60-120	300	>5	7.9	70
Prilocaine	1	Slow	60-120	400	>5	7.9	55
Mepivacaine	1	Slow	90-180	300	>5	7.6	77
Bupivacaine	4	Slow	240-480	175	>3	8.1	95
Levobupivacaine	4	Slow	240-480	175	>4	8.1	>97
Ropivacaine	4	Slow	240-480	200		8.1	94

* Epidural anesthesia → Pain لا يفسد في الوريد
لأنه يمتص في الوريد

Sympathetic ٢١ ٢٢ ٢٣ ٢٤ ٢٥

- Loss of nerve function proceeds as pain, temperature, touch, proprioception then skeletal muscle

- This is why people may still feel touch but not pain when using LA any nerve block is associated with vasodilation.
can cause hypotension.

Onset of action

- Onset of action depends on relative concentration of non-ionized lipid-soluble form & ionized water-soluble form, expressed by pKa
- LA with pKa closest to physiological pH will have higher concentration of non-ionized that can pass through nerve cell membrane & more rapid onset
- PKa: pH at which 50% ionized, 50% non-ionized.

Potency

- Potency correlates with lipid solubility $\rightarrow$ $\text{C}_{12}\text{H}_{25}\text{O}_2$
- The higher the lipid solubility, the higher the potency

Total body wt $\leftarrow$ water soluble drug $\xrightarrow{\text{excretion}}$ $\frac{\text{water}}{\text{total body wt}}$: obese $\rightarrow$ $\frac{\text{water}}{\text{total body wt}}$ *

lean body mass $\leftarrow$ fat soluble drug $\rightarrow$ $\text{conc} \rightarrow$ 1d
~~ideal~~ ideal body wt: male = height - 100

lean body mass = total body weight - 105
Absorption

Absorption

- Rate of systemic absorption is proportionate to the vascularity of the site of injection:
- IV > tracheal > intercostal > caudal > paracervical > epidural > brachial plexus > sciatic > subcutaneous

Duration

- The greater the protein binding, the longer the duration

to increase duration of action of LH
use vasoconstrictors.

LA + vasoconstrictors

reabsorption $\rightarrow$ in circulation

- Epinephrine is added LA in dilute concentrations
- This causes local tissue vasoconstriction → limiting up taking of LA into the vasculature → prolonging its effect & reducing its toxic potential

potential

*leucocain	without Adrenaline	5 mg/kg
* N	with "	7 mg/kg

* prepralane without 2 mda
with 3 mda

Contraindication of additives vasoconstrictors

- Unstable angina pectoris
- Cardiac dysrhythmias
- Peripheral nerve blocks to fingers, toes, penis
- Uncontrolled hypertension
- Intravenous regional anaesthesia

Metabolism

- Ester LA metabolized by non-specific plasma esterase
- Amide LA metabolized by P-450 enzymes in liver

Toxicity

- overdose*
- CNS is the site of premonitory signs of overdose in awake patients
 - *lethargy*
 - *myoclonus*
 - *purpura*
 - *cardiac*
 - Symptoms
 - Circumoral numbness & tongue paresthesia
 - Dizziness
 - Tinnitus
 - Blurred vision
 - Restlessness
 - Agitation
 - Nervousness
 - Tonic-clonic seizures
- * how to manage:*
- ABC
 - *midazolam*
 - *propofol*
 - *midazolam*
 - *with local*

- Unintentional IV injection of bupivacaine during regional anaesthesia produces severe cardiotoxic reactions

- Hypotension
- Atrioventricular heart block
- Ventricular tachycardia & fibrillation

Management of LA toxicity

- Oxygenation
- Fluids
- Hypotension → ephedrine 10-30mg bolus
- Convulsions → diazepam 5-10mg bolus

... pharmacology over clinical
doses case

Thanks