2. SKELETAL MUSCLE RELAXANTS

(PERIPHERAL: NON-DEPOLARIZING)

+ CENTRALLY ACTING

DR SHAMS SULEMAN

LEARNING OBJECTIVES

- Classify skeletal muscle relaxants.
- Describe the mechanism of action of Non depolarizing and depolarizing neuromuscular blockers.
- Discuss the differences between depolarizing and non depolarizing skeletal muscle relaxants
- Describe the therapeutic uses and adverse effects of skeletal muscle relaxants
- Describe centrally acting skeletal muscle relaxants (Spasmolytics)

LEARNING OBJECTIVES

- Name drugs causing malignant hyperthermia
- Discuss the rationale for use of Dantrolene in the treatment of malignant hyperthermia
- Discuss succinylcholine apnea and its management

PERIPHERALLY ACTING…….

NEUROMUSCULAR BLOCKING AGENTS

Non depolarizing agents

- ✓ **Isoquinolone derivatives (IQ)**
- ✓ **Steroid derivatives (SD)**

PERIPHERALLY ACTING…….

Non depolarizing agents ……..

a):- ***LONG ACTING:*** 30 to 100 minutes

- D Tubocurarine; also ganglion blocker
- Gallamine; anticholinergic
- Pancuronium (SD)
- Doxacarium (ID)
- Pipecuronium (SD)
- Metocurine (ID)

PERIPHERALLY ACTING…….

***Non depolarizing agents*……..**

b):- **INTERMEDIATE ACTING**; 20 to 60 minutes

- Vecuronium (SD)
- Atracurium (ID)
- Cisatracurium (ID)
- Rocuronium (SD); fastest onset of action

PERIPHERALLY ACTING…….

***Non depolarizing agents*……..**

c):- **SHORT ACTING;** 10 to 20 minutes

- Mivacurium (ID)

CENTRALLY ACTING

SELETAL MUSCLE RELAXANTS

- Benzodiazepines (**GABAergic**)
  - Diazepam
  - Clonazepam
  - Chlorodiazepoxide
- GABA derivatives
  - Baclofen (**GABA.B agonist)**
  - Gabapentin
- Central α2 agonists
  - Tizanidine

CENTRALLY ACTING

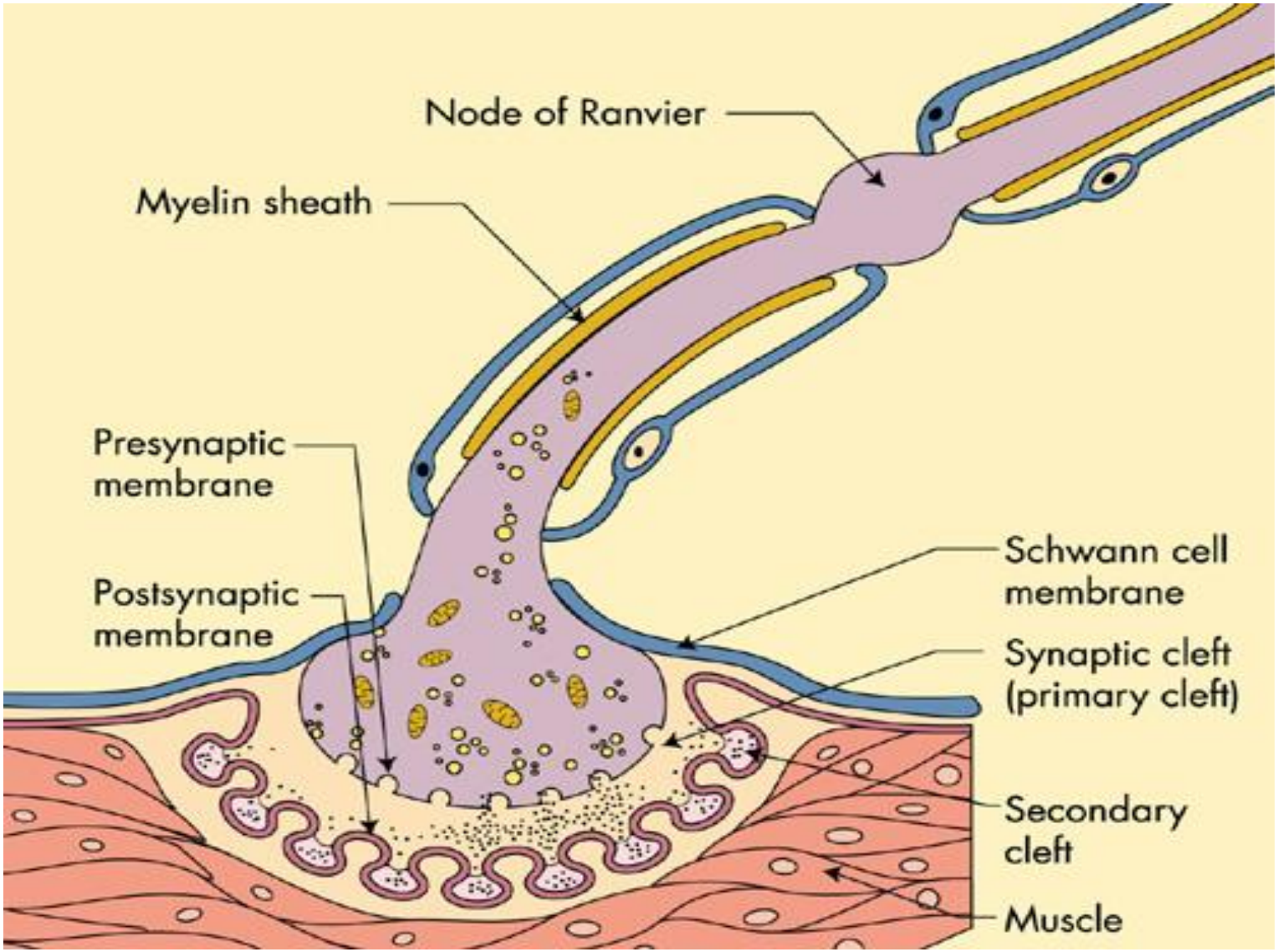
SELETAL MUSCLE RELAXANTS

- Mephenesin derivatives…….
  - Chlorozoxazone
  - Chlormezanone
  - Methocarbamol
  - Mephenenisine
  - Carisoprodol
- Ethanolamine Group
  - Orphenadine citrate

CENTRALLY ACTING

SELETAL MUSCLE RELAXANTS

- **Miscellaneous**
  - Cyclobezaprine
  - Metoxalone
  - Progabide
  - Glycine
  - Idrocilamide, riluzole (for ALS)


Node of Ranvier
Myelin sheath
Presynaptic membrane
Postsynaptic membrane
Schwann cell membrane
Synaptic cleft (primary cleft)
Secondary cleft
Muscle

SKELETAL MUSCLE RELAXATION AND PARALYSIS

By interruption of function at several sites

- Along the pathway from the central nervous system (CNS) to myelinated somatic nerves
- Unmyelinated motor nerve terminals
- Nicotinic acetylcholine receptors
- Motor end plate
- Muscle membrane
- Intracellular muscular contractile

NON-DEPOLARIZING

BENZYL-ISOQUINOLINES

- Natural
  - d-Tubocurarine
- Synthetic
  - Mivacurium
  - Atracurium
  - Doxacurium
  - Gantacurium

AMMONIO-STEROIDS

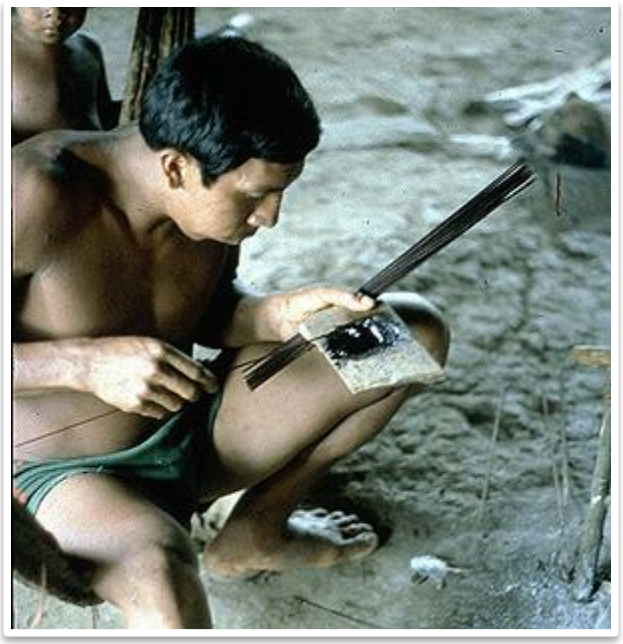
- Rapacuronium
- Rocuronium
- Vecuronium
- Pancuronium
- Pipecuronium

Mixed-onium chlorofumarates

- Gantacurium

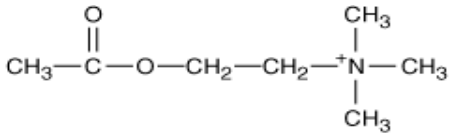
HISTORY

- Curare - arrow poison
- *Strychnos* species
- *Strychnos toxifera*
- *Quarternary neuromuscular - blocking alkaloids*

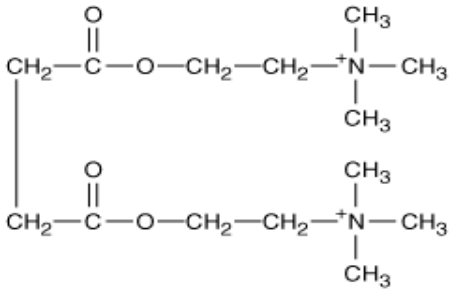


Chemistry

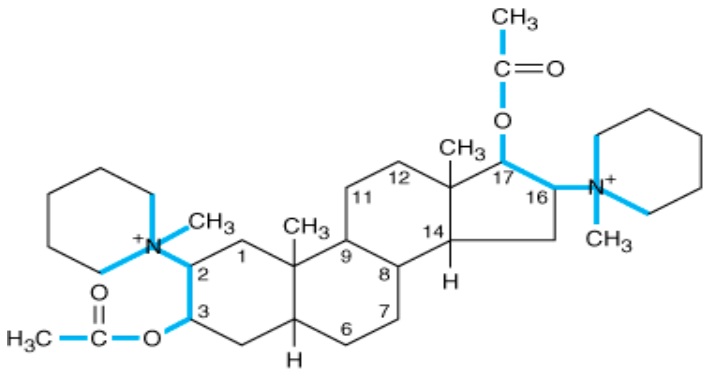
- Structural resemblance to acetylcholine
- Succinylcholine 2 acetylcholine molecules linked end-to-end
- Nondepolarizing agents conceal the "double-acetylcholine" structure in bulky, semi-rigid ring systems
- Presence of one or two quaternary nitrogens - makes them poorly lipid soluble and limits entry into the CNS



Acetylcholine



Succinylcholine



Pancuronium

PHARMACOKINETICS

- Drugs excreted by kidney
  - - longer half-lives
  - longer durations of action (> 35 minutes)

- Drugs eliminated by the liver (Ammonio-steroids)
  - Shorter half-lives
  - Shorter durations of action

PHARMACOKINETICS

- **intermediate-acting steroid** (eg, **vecuronium and rocuronium**)
- More dependent on biliary excretion/ hepatic metabolism for their elimination
- These muscle relaxants are more commonly used clinically than the long-acting steroid-based drugs (eg, pancuronium)

Pharmacokinetics

ROUTES OF ELIMINATION AND DURATION OF ACTION

- Plasma Pseudocholinesterase (Butyrylcholinesterase) (10 mins)
  - Succinylcholine, Mivacurium
- Spontaneous (Non-enzymatic) (20 – 40 mins)
  - Atracurium, Cisatracurium
- Liver (20 – 35 mins)
  - Rocuronium, Vecuronium
- Kidneys (35 – 60 min)
  - Tubocurarine, Doxacurium, Pancuronium, Pipecuronium

BENZYLISOQUINOLINES

DRUG	ELIMINATION MECHANISM	DURATION OF ACTION (min)
Atracurium	Enzymatic & nonenzymatic ester hydrolysis	45
Cisatracurium	Spontaneous	45
Mivacurium	Plasma pseudocholinesterase	15
Tubocurarine	Renal (40%)	80

AMMONIOSTEROIDS

DRUG	ELIMINATION MECHANISM	DURATION OF ACTION (min)
Pancuronium	Enzymatic & nonenzymatic ester hydrolysis	90
Rocuronium	Hepatic (80%) and renal	30
Vecuronium	Hepatic (80%) and renal	45

Pharmacokinetics

- Highly ionized
- Do not readily cross cell membranes
- Not strongly bound in peripheral tissues –---- so larger volume of distribution than blood volume
- The duration of neuromuscular blockade produced by nondepolarizing relaxants is strongly correlated with the elimination half-life

PHARMACOKINETICS

POTENCY

- Tubocurarine _ 1.0 (taken as standard)
- Succinylcholine _ 0.4
- Rocuronium – 0.8
- Atracurium – 1.4
- Cis-atracurium – 1.4
- Mivacurium – 4.0
- Doxacurium _ 6.0
- Pancuronium _ 6.0
- Pipecuronium _ 6.0

PHARMACOKINETICS

ONSET OF ACTION

- Mivacurium = Shortest duration of action
- Rocuronium = fastest onset, least potent
- Gantacuriun = phase 3 trial (rapid, short)

Pharmacokinetics

- Atracurium = Duration of action 20 – 40 minutes
- Cis-atracurium
  - Spontaneous non-enzymatic breakdown in plasma (Hofmann elimination)
- **Laudanosine** ==
  - Main metabolite of Atracurium
  - Slowly metabolized by the liver
  - longer elimination half-life (i.e. 150 minutes)
  - Readily crosses BBB
  - May cause seizures

PHARMACOKINETICS: METABOLISM

- Vd =80- 140mL/kg
- Highly polar; little peripheral tissue binding
- Metabolized by kidneys = longer half life
- Metabolized by liver = shorter half life
- Contains Quaternary Ammonium
- Rapid initial distribution, slow elimination

PHARMACOKINETICS: METABOLISM

- Steroids derivatives = 3OH, 17OH, 3,17 OH
- 3OH = 40 to 80% potent
- cumulates in ICU use
- **Atracurium** = Hoffman degradation, hepatic, its laudanosine derivative = 150 hours == Epileptogenic
- Cis atracurium = safe

The Adult Nicotinic Acetylcholine Receptor

- Composed of **five peptides**:

- **Two** alpha peptides
- **One** beta
- **One** gamma, and
- **One** delta peptide

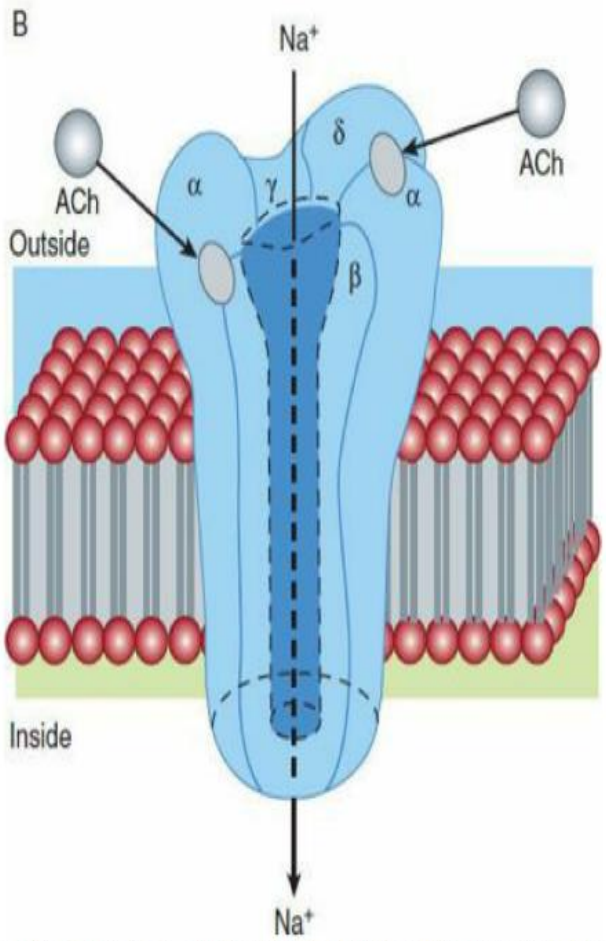


FIGURE 27–1 The adult nicotinic acetylcholine receptor (nAChR) is an intrinsic membrane protein with five distinct subunits (α_2 β δ γ). **A:** Cartoon of the one of five subunits of the AChR in the end plate surface of adult mammalian muscle. Each subunit contains four

MECHANISM OF ACTION

- Site of action: motor end plate
- **Competes** with acetylcholine for nicotinic receptors
- Blockade is
- **Competitive** and
- ***Surmountable***
- Decrease frequency of Na channel opening
- Not preceded by fasciculation

MECHANISM OF ACTION

- Enter the pores of channels
- Also block pre-junctional sodium channels

- → interfere with the mobilization of Ach at the nerve ending

- → cause fade of evoked nerve twitch contractions
- Weak blockade of cardiac muscarinic receptors (Tubocurarine)

MECHANISM OF ACTION

- **Consequence of the surmountable nature of the postsynaptic blockade :**
  - Tetanic stimulation (rapid delivery of electrical stimuli to a peripheral nerve) releases a large quantity of Ach,
  - Followed by transient post-tetanic facilitation of the twitch strength (i.e. relief of blockade)
  - An important clinical consequence of this principle is the reversal of residual blockade by cholinesterase inhibitors

MECHANISM OF ACTION

REVERSED

- Neostigmine

POTENTIATED

- **Ether**
- **Halothane**
- **Aminoglycosides**
- **Chlorpromazine**
- **Acidosis**
- **Hypokalaemia**
- **raised temperature**

PHARMACOLOGICAL ACTIONS

- Release of systemic histamine:
  - Tubocurarine
  - Atracurium = lesser extent
  - Mivacurium = lesser extent

  Results in

  - ✓ Hypotension

    (*Premedication with an antihistamines prevent hypotension)*
  - ✓ Bronchospasm
- Ganglionic blockade – hypotension
  - Tubocurarine = At large dose,
  - Metocurine

PHARMACOLOGICAL ACTIONS

CARDIOVASCULAR EFFECTS

- More with Pancuronium, minimal with Atracurium
  - Moderate tachycardia
  - Increased cardiac output

(Due to a vagolytic action, and increased release of NE from nerve endings

and blockade of neuronal uptake of NE)

- Minimal cardiovascular effects
  - Vecuronium
  - Pipecuronium
  - Doxacurium
  - Cis-atracurium
  - Rocuronium

HYPOTENSION

- **Tubocurarine**
- **Atracurium**
- **Mecuronium**
  - Systemic histamine release
  - Ganglionic blockade, with larger doses Tubocurarine

- Premedication with an antihistaminic compound attenuates **tubocurarine-induced hypotension**

HISTAMINE RELEASING POTENTIAL

Significant		Insignificant	
Tubocurarine	+ + +	Rocuronium bromide	±
Metocurine	++	Vecuronium bromide	±
Atracurium besylate	+	Pancuronium bromide	±
Mivacurium chloride	+	Pipecuronium bromide	±
Succinylcholine chloride	+	Doxacurium chloride	±

PHARMACOLOGICAL ACTIONS : SUMMARY

- Flaccid paralysis (T>P>A>Mi>Me)
- Hypotension; histamine release
- Ganglion blockade = higher doses

  (T> Me)
- Bronchoconstriction = (T> Mi)
- Vagal block = (Pan: > Gall:)
- Increased IOP, intragastric pressure, muscular

DRUG INTERACTIONS

- Potentiation == General Anesthesia
- Competitive blockade == Ketamine
- Blockade of calcium ***(specific P type)*** channels ==
  - Aminoglycosides
  - Tetracycline
  - Polypeptides
  - Lincosamides
- Blockade of twitching ==Calcium channel blockers
- Diminished response == Alkalosis & hyperkalemia =
- increased response == Acidosis & hypokalemia

DRUG INTERACTIONS

- **Inhaled anesthetics**
- → Potentiate the neuromuscular blockade
- In a dose dependent manner in the following order
  - Isoflurane
  - Sevoflurane
  - Desflurane
  - Halothane
  - Nitrous oxide

CLINICAL PHARMACOLOGY

- **The most important factors involved in interaction b/w Neuromuscular blockers x Inhaled anesthetics**:
- (1) nervous system depression at sites proximal to the neuromuscular junction (i.e. CNS);
- (2) increased muscle blood flow (i.e. due to peripheral vasodilation produced by volatile anesthetics), which allows a larger fraction of the injected muscle relaxant to reach the neuromuscular junction
- (3) decreased sensitivity of the post junctional membrane to depolarization.

DRUG INTERACTIONS

LOCAL ANESTHETICS

- **In small doses**, local anesthetics can depress post-tetanic potentiation via a pre-junctional neural effect

- **In large doses**, local anesthetics can block neuromuscular transmission
  - → as a result of blockade of the nicotinic receptor ion channels rather than typical Na channel blockade by Local anesthetics
  - Bupivacaine

    (Higher doses are associated with cardiac arrhythmias)

DRUG INTERACTIONS

ANTIARRHYTHMIC DRUGS:

- Quinidine == sodium channel blocking drug
  - Effects similar to local anesthetics

ADVERSE EFFECTS

- PROLONGED APNEA
- Hypotension,
- CV collapse (histamine release , anaphylaxis)
- Bronchospasm
- Bradycardia---cardiac arrest

PROLONGED APNEA

- Decreased elimination:
  - ✓ Hepatic dysfunction
    - Cis-atracurium
    - Rocuronium
    - Vecuronium
  - ✓ Renal dysfunction (Pancuronium)
- Airway obstruction
- Hyperventilation due to decreased PCO2
- Neuromuscular depressant effect of excessive neostigmine
- Alteration in body temp, electrolyte imbalance
- Presence of latent myasthenia gravis or SCLC (Eaton Lambert myasthenic syndrome)

D TUBOCURARINE

Prototype:

Mono-quarternary ammonium alkaloid

- Highly polar
- Not absorbed from GUT
- Vd is only slightly larger than the blood volume
- NOT metabolised in liver
- Excreted unchanged

ATRACURIUM

- An intermediate-acting
- Elimination
  - Hepatic
  - Hofmann elimination, a form of spontaneous breakdown
- Causes histamine release
- **Cis-atracurium – a potent isomer of Atracurium:** with even lesser dependence on hepatic inactivation
- Safe in patients with hepatic and renal dysfunction

MIVACURIUM

- - shortest duration of action
- Onset of action is significantly slower than that of succinylcholine
- Use of a larger dose to speed the onset can be associated with profound histamine release leading to hypotension, flushing, and bronchospasm
- Clearance by plasma cholinesterase

GANTACURIUM

- (investigational phase 3)-
- Ultra-short acting
- Degraded non-enzymatically by adduction of the amino acid cysteine & ester bond hydrolysis
- Rapid onset
- Predictable duration of action
- Reversed with edrophonium or cysteine
- Cardiovascular adverse effects due to histamine release
- No bronchospasm or pulmonary vasoconstriction has been reported at these

Non-depolarizing Drugs

- Gallamine
  - Less potent than curare
  - Tachycardia
- D-Tubocurarine
  - 1-2 hr duration of action
  - Histamine releaser (Brochospasm, hypotension)
  - Blocks autonomic ganglia (Hypotension)
- Atracurium
  - Rapid recovery
  - Safe in hepatic & renal impairment
  - Spontaneous inactivation to laudanosine (seizures)

Non-depolarizing Drugs

- Mivacurium
  - Metabolized by pseudocholinesterase
  - Fast onset and short duration
- Pencuronium
  - Long duration of action
  - Tachycardia
- Vecuronium
  - Intermediate duration of action
  - Fewer side effects (no histamine release, no ganglion blockade, no antimuscarinic action)

Effects of Aging on the Neuromuscular Response

ADVANCED AGE

- → associated with a prolonged duration of action from these drugs
  - Due to decreased clearance of the drugs by the liver and kidneys –
  - needs dose reduction in old patients
- .

Effects of Diseases on the Neuromuscular Response

- **MYASTHENIA GRAVIS**
- → enhances the neuromuscular blockade produced by non-depolarizing muscle relaxants

- **SEVERE BURNS**
- **UPPER MOTOR NEURON DISEASE**
  - Resistant to these drugs
    - Due to proliferation of extra-junctional receptors
    - → so increased dose requirement for the non-depolarizing relaxant to block a sufficient number of receptors

Table 3 - Characteristics of the neuromuscular blocking agents most frequently used in children

Drug	Action	Dose (mg/kg)	Onset (minutes)	Length (minutes)	Advantages	Comments
Succinylcholine	Depolarizing	1-2 Not recommended for INF	Immediate	3-5	Short action (intubation)	Hyperpotassemia Fasciculations
Vecuronium	Non-depolarizing	Initial bolus: 0.08-0.2 INF: 0.08-0.2 mg/k/h	2-4	20	No cardiovascular effects	Muscle weakness
Pancuronium	Non-depolarizing	Initial bolus: 0.1 INF: 0.1 mg/k/h	2-4	30-45	Longer action	Tachycardia, hypertension Increase in ICH
Atracurium	Non-depolarizing	Initial bolus: 0.3-0.6 INF: 0.3-0.6 mg/k/h	2-3	25-30	Not metabolized by the liver and kidney	Bronchospasm Bradycardia
Rocuronium	Non-depolarizing	Initial bolus: 0.6-1.2 INF: 5-15 µg/k/min	1-2	30-40	No cardiovascular effects	Tachycardia at high doses
Mivacurium	Non-depolarizing	Initial bolus: 0.1-0.2 INF: 10-14 µg/k/min	2-4	12-18	Short action	Bronchospasm Coughing
Cisatracurium	Non-depolarizing	Initial bolus: 0.15 INF: 1.5 µg/k/min	3-4	30	Not metabolized by the liver and kidney	No cardiovascular effects

ICH = intracranial hypertension; INF = continuous infusion.

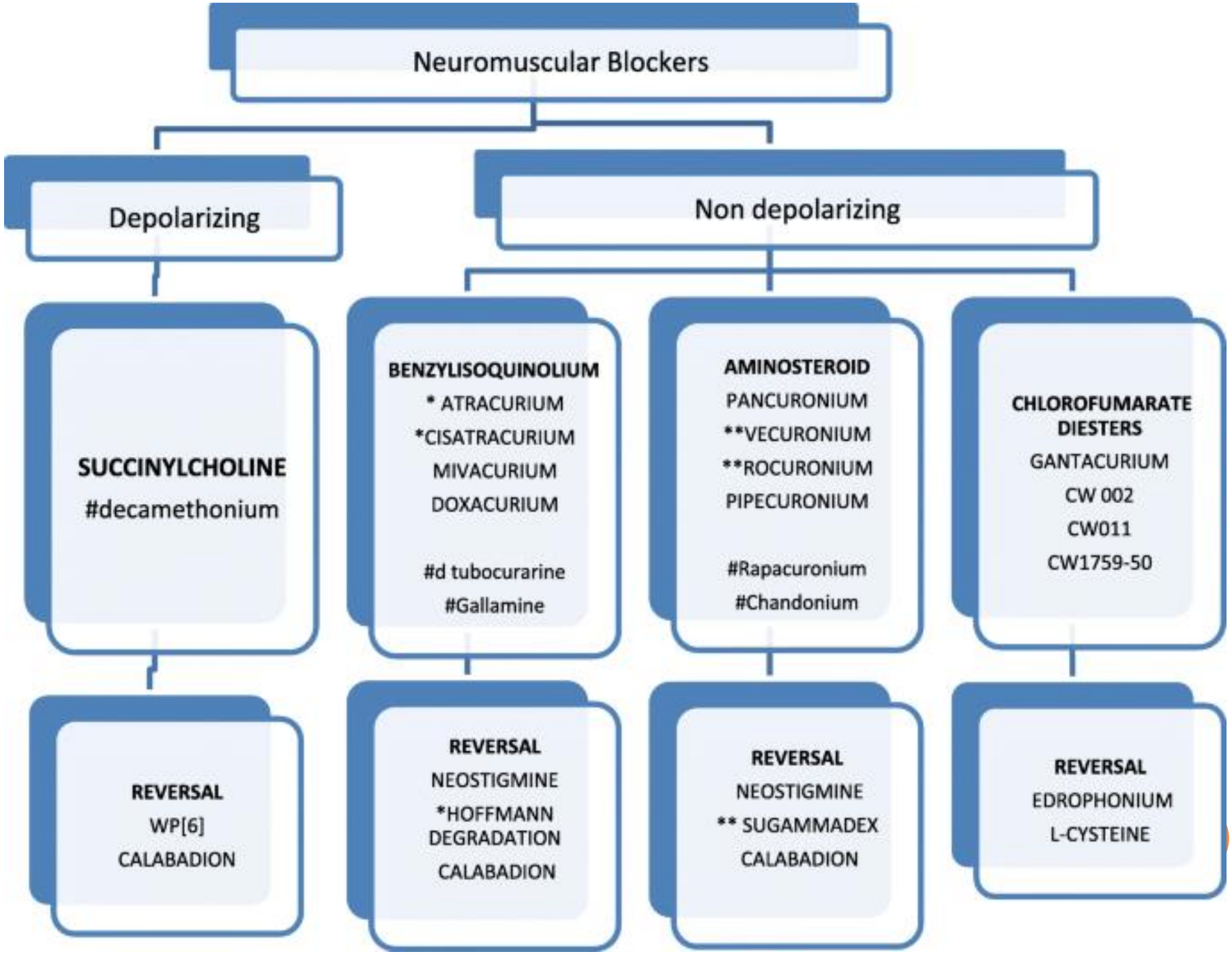
Reversal of Nondepolarizing Neuromuscular Blockade

- **Neostigmine**
- **Pyridostigmine**
- **Edrophonium**
  - Antagonize non-depolarizing neuromuscular blockade
  - Increase the availability of acetylcholine at the motor end plate
  - mainly by inhibition of acetylcholinesterase
  - Also increase the release of this NMJ blocker from the motor nerve terminal == lesser extent
  - Edrophonium, not favored due to its very short life

Reversal of Nondepolarizing Neuromuscular Blockade

- **Sugammadex:** novel reversal agent

  - Beta cyclodextrin
  - Approved in Europe
  - Selective and rapid reversal
  - NO action on NMJ
  - Action is in the plasma by chelation by binding preferably to steroidal neuromuscular blockers such as rocuronium and vecuronium
  - The blockers diffuse from NMJ to plasma under concentration gradient


Neuromuscular Blockers
Depolarizing
Non depolarizing
SUCCINYLCHOLINE
#decamethonium
BENZYLISOQUINOLIUM
* ATRACURIUM
*CISATRACURIUM
MIVACURIUM
DOXACURIUM
#d tubocurarine
#Gallamine
AMINOSTEROID
PANCURONIUM
**VECURONIUM
**ROCURONIUM
PIPECURONIUM
#Rapacuronium
#Chandonium
CHLOROFUMARATE DIESTERS
GANTACURIUM
CW 002
CW011
CW1759-50
REVERSAL
WP[6]
CALABADION
REVERSAL
NEOSTIGMINE
*HOFFMANN DEGRADATION
CALABADION
REVERSAL
NEOSTIGMINE
** SUGAMMADEX
CALABADION
REVERSAL
EDROPHONIUM
L-CYSTEINE

PROTOTYPICAL CHARACTERISTICS OF TWO GROUPS

D-tubocurarine	Succinylcholine
Uses: 1. Adjuvant to provide skeletal muscle relaxation during longer surgeries/ procedures 2. Tetanus 3. Status epilepticus 4. To reduce the chest wall resistance to inflation – in critically ill patients in the ICU who are on ventilatory support	Uses: 1. Endrotracheal intubation 2. Short procedures: Laryngoscopy, bronchoscopy, esophagoscopy, fracture reduction/dislocation 3. To prevent trauma during ECT

PROTOTYPICAL CHARACTERISTICS OF TWO GROUPS

D-tubocurarine	Succinylcholine
ADVERSE EFFECTS 1. Hypotension 2. Flushing 3. Bbronchospasm 4. Malignant hyperthermia	ADVERSE EFFECTS 1. Hyperkalemia 2. Post-operative muscle soreness 3. Arrhythmias /Cardiac arrest 4. Malignant hyperthermia 5. Succinylcholine apnea (pseudocholinesterase deficiency)
Treatment of overdose Neostigmine/Edrophonium plus atropine	Treatment of toxicity: Artificial respiration, fresh blood transfusion

	Competitive Non-depolarizing	Non-Competitive Depolarizing
Paralysis	Flaccid	Fasciculations---› Flaccid
Neostigmine	Antagonizes	Exaggerate / no effect.
Examples	Pancuronium	Succinylcholine

Difference between the competitive and depolarisinng muscle blocker

parameter	D tubocurarine	Succinylcholine
Blockade type	Competitive blockade	Depolarising blockade
Type of relaxation	Flaccid paralysis	Fasciculation followed by paralysis
Neostigmine addition +	antagonism	Potentiation
Effect of other neuromuscular blocking drug	Decreased effect	Increases effect
Histamine release	++ release	negligible
Serum k+ level	No change	Hyperkalemia
Pharmocogenetic variation	nil	pesudocholinesterase
Cardiac M2 receptor	No effect	stimulate (bradycardia)

MCMP 407

Spasmolytics

- Chronic neurologic diseases
  - Cerebral Palsy, Multiple Sclerosis
- Acute Injury
  - Spinal cord damage, muscle inflamation

Goal of therapy: Reduce spasticity and pain, while retaining function

DIAZEPAM

- Facilitates GABA (inhibitory) transmission in the CNS
- MAIN action == Sedation mediated by
  - $GABA_A$ == hyperpolarization due to opening of chloride channels
- At $GABA_B$ == lesser extent
  - Spasmolytic effect

BACLOFEN

- GABA $_B$ agonist at both presynaptic and postsynaptic receptors, causing membrane hyperpolarization
  - **Pre synaptically**
    - Reduces calcium influx
    - Decreases the release of the excitatory transmitter glutamic acid
  - **Post synaptically**

    facilitates the inhibitory action of GABA

BACLOFEN

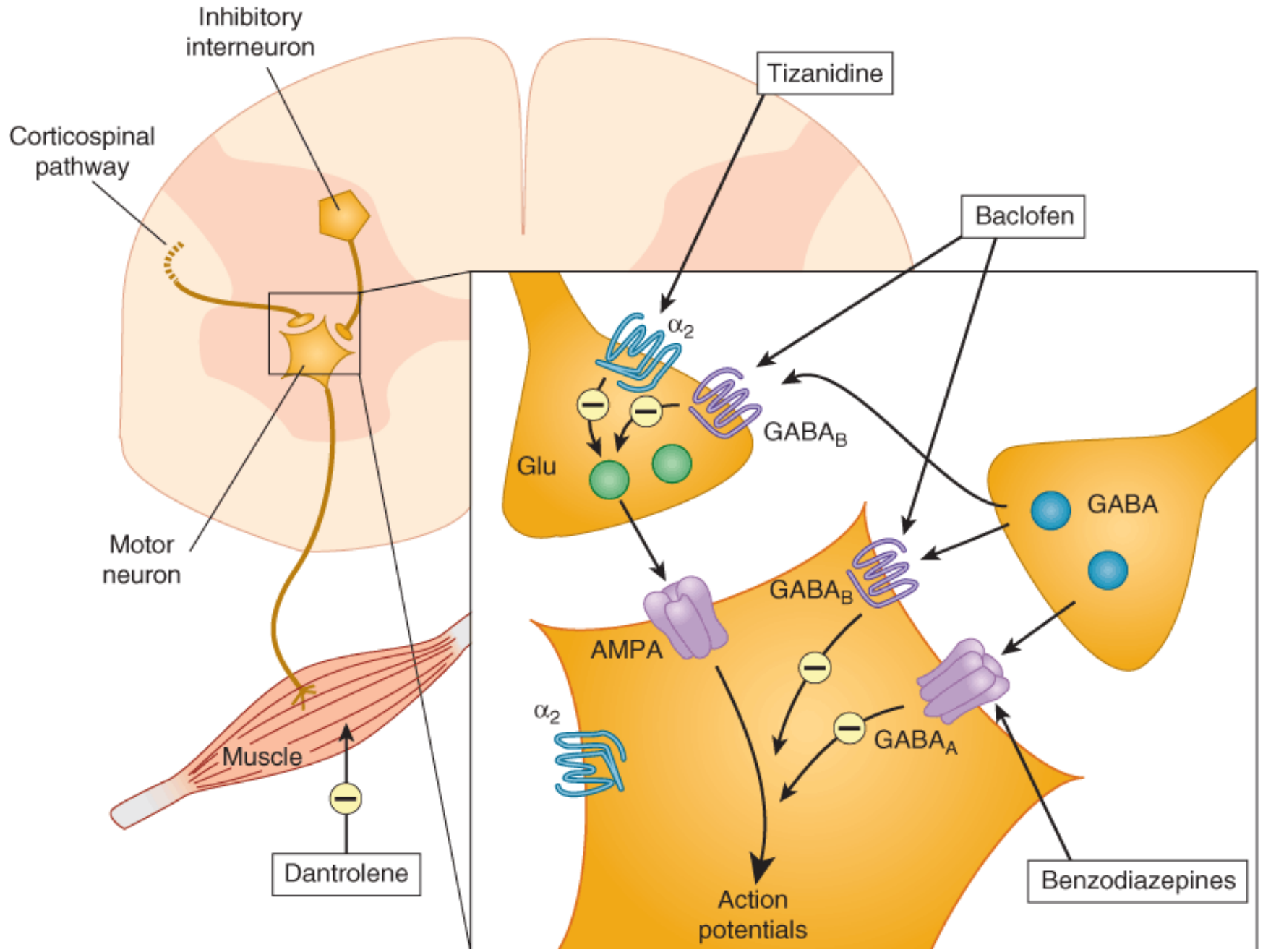
- Orally effective
- p-chlorophenyl-GABA
- Decrease the release of substance P in both the brain & SC
- Less sedation & Less muscular weakness
  - Effective as Diazepam ➔ causes less sedation
  - Dose not reduce general muscle strength like with Dantrolene
- Can be given intrathecally in severe spasms
- Off label use

TIZANIDINE

- Congener of clonidine
- **α_2 agonist = related to clonidine**
- Reinforces mainly PRE synaptic & minimal postsynaptic inhibition in spinal cord
- **Inhibits the excitatory Aspartate and stimulates the inhibitory Glycine in the spinal interneurons**

ADVERSE EFFECTS

Hypotension, Asthenia, Sedation and Dry


Inhibitory interneuron
Tizanidine
Corticospinal pathway
Baclofen
α_2
$GABA_B$
Glu
GABA
Motor neuron
$GABA_B$
AMPA
α_2
$GABA_A$
Muscle
Dantrolene
Action potentials
Benzodiazepines

DRUGS USED IN ACUTE LOCAL MUSCLE SPASM

- Cyclobenzaprine (prototype)
  Anti muscarinic effects – sedation, transient visual hallucinations
- Carisoprodol
- Chlorphenesin
- Chlorzoxazone
- Metaxalone
- Methocarbamol
- Orphenadrine

Types of skeletal muscle relaxants: 2 groups

Neuromuscular blockers

- Relax normal muscles (surgery and assistance of ventilation)
- Interfere with transmission at the motor end plate
- No central nervous system activity.
- Used primarily as a part of general anesthesia

Spasmolytics

- Reduce spasticity
- Centrally acting (except dantrolene which act on the skeletal muscle)
- Used in a variety of neurologic conditions

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Email address for queries on the topic

drshams11@hotmail.com