SKELTAL MUSCLE RELAXANTS (SKMRs)

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SKELETAL MUSCLE RELAXANTS
(I) Centrally Acting Muscle Relaxants
(II) Peripherally Acting Muscle Relaxants
(III) Directly Acting Muscle Relaxant (Dantrolene)
Skeletal Muscle Relaxants -
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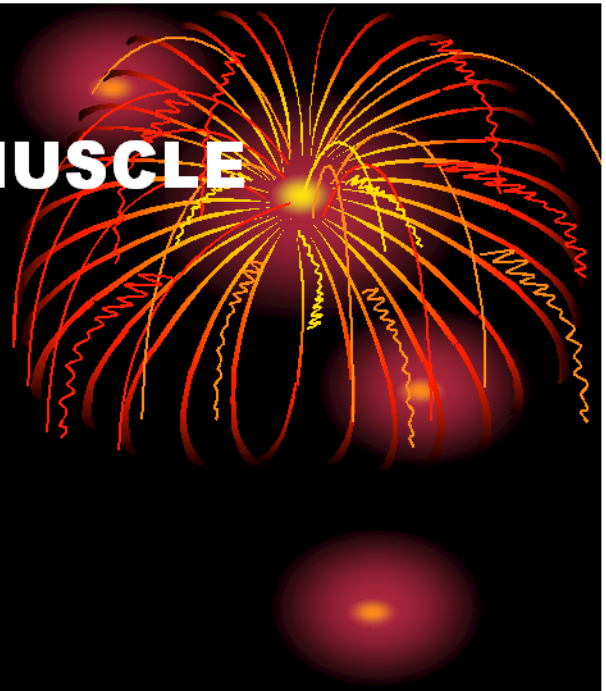
CLASSIFICATION OF SKELETAL MUSCLE RELAXANTS



- **(I) Centrally Acting :-**
- **Methocarbamol**
- **Chlorzoxazone**
- **Chlormezanone**
- **Tizanidine**
- **Diazepam,Gabapentin**
- **Thiocholchicoside**
- **Tolperidone Hcl**
- **Baclofen**

CLASSIFICATION OF SKELETAL MUSCLE RELAXANTS

- **(II) Peripherally Acting at NMJ :-**

- **(a) Depolarizing NM Blockers:-**
- **Succinylcholine**
- **Dexamethonium**

- **(b) Non-Depolarizing NM Blockers :-**
- **D-Tubocurarine (d-TC) ; Pancuronium**
- **Vecuronium ; Atracurium**
- **Mivacurium**

- **(c) Others :-**
- **Botulinium Toxin A**

CLASSIFICATION OF SKELETAL MUSCLE RELAXANTS

- **(III) Directly Acting SkMRs :-**
- **Dantrolene**

SKELETAL MUSCLE RELAXANTS (Differences)

C-SKMRs	P-SKMRs
Oral, Parenteral	Parenteral only
CNS depression	No CNS depression
Selectively block Polysynaptic reflexes	Blocks N-M trans
Spastic,tetanus , Sk.M spasm	Surgical procedure

SKELETAL MUSCLE RELAXANTS (Differences) (contd..)

C-SKMRs	P-SKMRs
Eg. Chlormezanone, Chloroxazone, Methocarbamol, Diazepam.	Eg. Succinylcholine, Pancuronium, d-TC
↓ Muscle tone without affecting muscle power.	Cause muscle Paralysis, loss of voluntary work.

PHYSIOLOGY OF SKELETAL MUSCLE CONTRACTION

Motor nerve impulse

↓

Release of Acetylcholine

↓

Binds with NM receptors at NMJ

↓

Depolarization and Development of End-plate potential (EPP) at motor end plate (Due to Na+ influx)

↓

Muscle – action potential (MAP) -

Contraction of Skeletal Muscle

↓

Action is rapidly inactivated by cholinesterase leading to repolarization

↓

Muscle ready for a fresh nerve impulse

DISORDERS OF SKELETAL MUSCLES

- **(i) Acute Skeletal Muscle Disorders :-**
- **Sprain; Strain; Fracture; Dislocation**
- **Torticollis; Lumbago ; Tendinitis**
- **Ligament rupture**
- **(ii) Spastic Neurological Disorders :-**
- **Tetanus**
- **Multiple sclerosis**
- **Amyotrophic Lateral Sclerosis (ALS)**
- **Malignant Hyperthermia**

CENTRALLY ACTING SKMRs

PROPERTIES:

- Effective C-SKMRs
- Reduces unwanted spasm, spasticity, rigidity and hyperflexia
- Does not alter consciousness
- No effect on voluntary movements , N-M transmission

MECHANISM OF ACTION
C-SKMRs)

Selective action of cerebrospinal axis

↓

Depresses spinal & supraspinal polysynaptic reflexes

↓

Depresses polysynaptic pathway in ascending reticular system

↓

Produces sedation.

CHLORMEZANONE

- Anti-anxiety, Hypnotic
- OOA : 15-20 mins. DOA: 4-6 Hrs.
- S/Es : Dizziness, Drowsiness,Skin Rashes
- Indications :-
  - * Painful Skeletal muscle spasm
  - * Premenstrual syndrome
  - * Tension headache
  - * Dysmenorrhoea
  - * Neuromuscular vasomotor pain.

Dose :- 100 - 200 mg TDS

Available :- Tab. 100mg.

CHLORZOXAZONE

- Longer DOA, Better tolerability orally
- OOA : 30 mins. DOA : 6 – 8 Hrs.
- S/Es : Lethargy , Headache
- Indications :-
  - * Painful SK.M. spasms
  - * Trauma, Sprains, Strains
  - * Sports injury, Lumbago (Low Backache)
- Dose : 250 mg – 750 mg QID (Adults)
  125 mg – 250 mg TID (Children).

TIZANIDINE

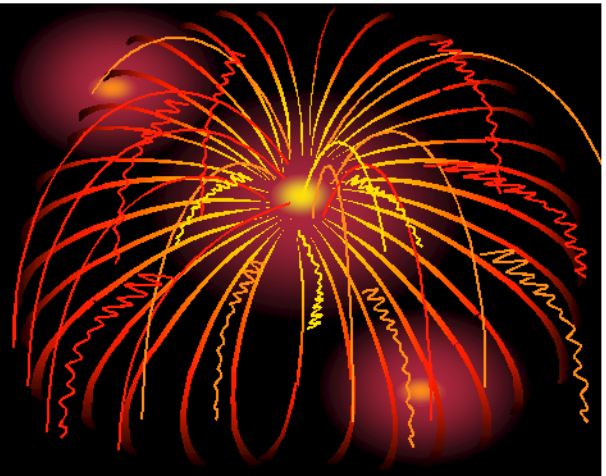
- Clonidine derivative
- C-SKMRs – Central alpha-2 receptor agonist
- Inhibits release of excitatory amino acids in spinal interneurones
- Facilitates inhibitory transmitter – Glycine
- Inhibits polysynaptic reflexes – reduces muscle tone and frequency of muscle spasm– improves mobility, flexibility, Quality of Life (QOL).
- **Half-Life :** 2 – 3 Hrs.
- **Dose :** 2mg TDS Maximum 24 mg/day.

TIZANIDINE (Contd..)

- **Indications :-**
  - * Painful SK.M spasm of spinal origin
  - * Multiple sclerosis, spinal injury (with Baclofen, Diazepam)
  - * Dysmenorrhoea

* **S/Es :-** Drowsiness, Night – time insomnia, Hallucinations, Dry mouth, ↑Antihypertensive effect of clonidine, ↑Liver transaminases levels.

DIAZEPAM



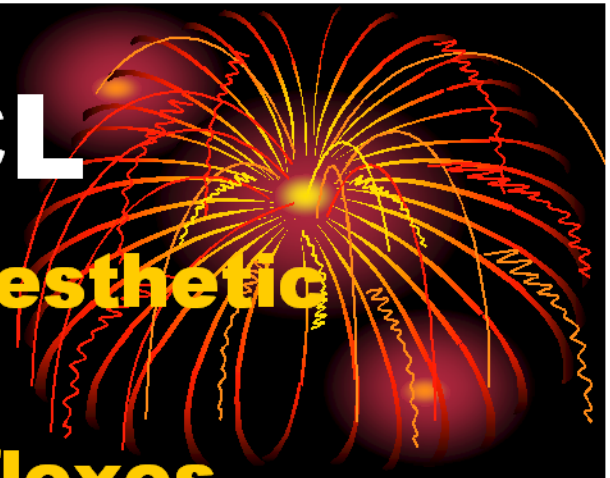
- Benzodiazepine
- Has sedative, muscle relaxant, anticonvulsant effect
- Acts on SP. Receptor in brain
- Enhance GABA – nergic transmission

- Reduces muscle tone by supra-spinal action
- Less GIT S/Es
- Valuable in Spinal injuries and Tetanus
- Combined with analgesics in rheumatoid disorders with spasm
- I.V. (10 – 100 mg) in Tetanus
- Oral :- 5 mg TDS.

THIOCHOLCHICOSIDE

- Chemically related to Colchicine
- Acts by :- GABAmimetic & Glycinergic action
- Used in :- Painfull muscle spasm, degenerative & vertibral disorder, torticollis,sprain
- S/Es :- Photosensitivity
- Dose : 4mg BD 0r 8mg OD orally

TOLPERISONE HCL



- Central SKMR + Local Anaesthetic action
- Inhibits Reticulo-spinal reflexes without affecting cortical functions
- Improves peripheral blood flowdue to peripheral effect
- Reduces rigidity, Hypertonia
- Uses :-Elevated SK M tone & Tension
- Circulatory problems of extremities,
- Dose : 150 mg TDS + NSAIDs
- C/I : My. Gravis, CABG surgery, Ulcer

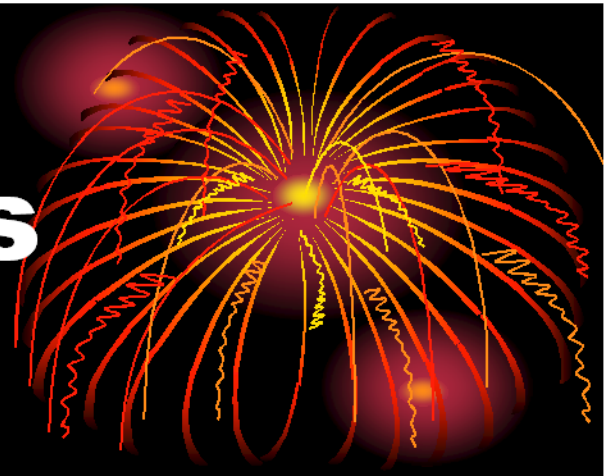
RILUZOLE

- Amyotrophic Lateral Sclerosis
- 50 mg BD before meals
- Decrease Glutaminergic transmission in CNS
- Blocks Polysynaptic NMDA Glutamate receptor
- Inhibits voltage dependent Na-channel

IDROCILAMIDE

- Inhibits release of Ca2+ from sarcoplasmic reticulum
- Uses : ALS

USES OF C-SKMRs



- (1) **Acute Muscle Spasms :-**
  - * Sprain, strain, dislocation, fractures, tearing of ligaments/tendons , fibrositis, rheumatic disorders.
    (Chlormezanone+Diazepam+NSAIDs)

(2) **Torticollis, Lumbago, Neuralgias :-**

(3) **Anxiety and Tension :-**
(Diazepam + Chlormezanone)

USES OF C-SKMRs (Contd..)

(4) **Spastic Neurological Diseases :-**

* Muscle spasticity, Spinal injuries, multiple sclerosis, hemiplegia, paraplegia , multiple sclerosis, cerebral palsy, ALS.

(Baclofen + Diazepam + Tizanidine) / (Dantrolene)

(5) Tetanus : (I.V. infusion of diazepam)

(6) **Electroconvulsive Therapy (ECT) :-**

(Diazepam + Succinylcholine)

(7) **Orthopaedic Manipulation:-**

(Diazepam / Methocarbamol ....I.V.)

PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS (P-SKMRs)

- **Neuromuscular blocking agents**
- **(I) Non-Depolarising Agents :**

  (a) D-Tubocurarine (d-TC), Mivacurium, Atracurium

  (b) Steroidal derivatives :-

  Pancuronium, Rocuronium, Rapacuronium, Vecuronium

  (c) Others :- Gallamine

P-SKMRs..(Contd..)

- **(II) Depolarising Agents :-**

  (a) Succinylcholine (6-8 min)

(III) Others :-

(a) Botulinum toxin

PSKMRs- Classification According to Duration of Action

Ultra Short acting	**Succinylcholine**	**6-8 mins**
Short acting	**Mivacurium, Rapacuronium**	**10-20 mins**
Intermediate acting	**Atracurium, Vecuronium, Rocuronium**	**30-40 mins**
Long acting	**Pancuronium, D-Tubocuronium (d-TC)**	**80 – 180 mins**

P-SKMRs..(Contd..)

D-NMB agents	ND-NMB agents
• Succinylcholine	d-TC
• Phase I,II block	Competitive Nicotinic receptor block
• AntiCHE prolongs block	Reverses block

P-SKMRs..(Contd..)

- **D-NMB agents** **ND-NMB agents**
- **S/Es :-**
  - * Malignant hyperthermia — Hypotension
  - * Bradycardia — Bronchospasm
  - * P.O Muscle soreness — No P.O. Muscle soreness.

MOA- ND-NMB agents :

(d-TC, Pancuronium)

D-tubocurarine

↓

Small doses of d-TC

↓

Acts on Nicotinic (N_M) receptor

↓

Compete with Acetylcholine(Ach)

↓

Produces surmountable(competitive) antagonism

MOA- ND-NMB Agents :

(d-TC, Pancuronium) (contd...)

D-tubocurarine

↓

High doses of d-TC

↓

Enter the pore of Na- ion channel

↓

Causes blockade of Na- ion channel

↓

No Depolarization – No Sk. M contraction

MOA- ND-NMB Agents :

(d-TC, Pancuronium) contd.

D-tubocurarine

↓

At much Higher doses of d-TC

↓

Blocks Pre-synaptic Sodium channel

↓

Inhibit Acetylcholine (Ach) release

MOA- D-NMB Agents :

(Succinylcholine)

PHASE – I BLOCK

Succinylcholine

↓

Acts like Acetylcholine (Ach)

↓

Acts on Nicotinic (N_M) Receptors

↓

Opens up Na-ionic channel

↓

Causes Depolarization of SKM end plate

MOA- D-NMB agents :

(Succinylcholine) (Contd..)

PHASE – I BLOCK (Contd..)

Spreading of Depolarisation

↓

Produces disorganize contraction of muscle motor units

(Twitching and Fasciculations)

↓

Membrane remain depolarized

↓

Unresponsive to further impulses

↓

Inhibition of re-polarization causing Flaccid Paralysis

MOA- D-NMB agents :

(Succinylcholine) (Contd..)

PHASE – II BLOCK

With Continuous exposure of SCh

↓

Appearance of Na – Channel & Desensitization Blockade

↓

Slow in onset due to desensitization of receptors to Ach

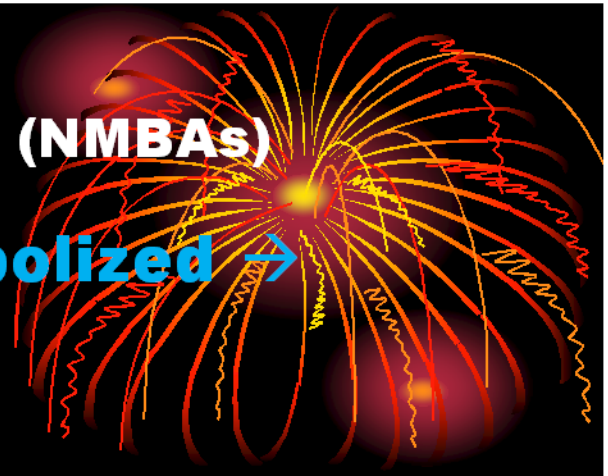
↓

Resembles block produced by d-TC.

Pharmacokinetic Properties of PSKMRs (NMBAs)

- Not absorbed orally → given I.V.
- Do not cross BBB → no CNS toxicity
- Do not cross placental membrane → No foetal abnormality → safe during C.S.
- Some are metabolized to active metabolites; excreted through kidneys

Pharmacokinetic Properties of PSKMRs (NMBAs)



- D-TC, Gallamine are not metabolized → have long duration of action
- Steroidal drugs are metabolized in liver to active 3-hydroxy metabolite → accumulate on prolonged administration in ICU
- Intermediate acting vecuronium, rocuronium are excreted through bile
- Atracuronium is inactivated by spontaneous breakdown – (Hofmann reaction) to inactive metabolite Laudanosine which can cross BBB → precipitates Seizures

USES OF NMB AGENTS

(1) Adjuvants to G.A. for all major surgeries

(2) Employed for short diagnostic procedures :-

Laryngo / broncho / endoscopy, Endotracheal intubation

(3) In orthopedic procedures :- Reduction of fractures, Dislocations,

(4) d-TC , Gallamine, Pancuronium for ocular surgery

USES OF NMB AGENTS (Contd..)

(5) Sch in ECT with Diazepam

(6) In spastic disorders :- Severe cases of Tetanus

(7) In refractory cases of status epilepticus (D-TC / Pancuronium + respiration)

(8) In ICU with Ventilators

(9) For provocative diagnostic test in Myaesthenia gravis

(d-TC - 0.5-2mg I.V.) = Muscle weakness → Confirm My. Gravis)

S/Es OF NMB AGENTS

(I) NDP – Agents (d-TC, Pancuronium) :-

(a) Hypoxia, respiratory paralysis
(Neostigmine+Atropine+ Resp)

(b) Hypotension (Antihist +IV fluids), Bronchospasm (dTC)

(c) Tachycardia (Gallamine)

(d) Regurgitation, constipation.

S/Es OF NMB AGENTS (Contd..)

(II) DP - Agents (Succinylcholine)

(a) Cardiac arrest, arrhythmia, bradycardia

(b) Malignant hyperthermia (Sch + Halothane)

(c) Hyperkalaemia, Emesis

(d) Increase IOP (Intraocular pressure)

Drug Interactions of PSKMRs

- 1) G.A + PSKMRs → Augment action of PSKMRs
- 2) AntiCHEs (Neostigmine) + d-TC → Reverses the action of competitive NMBAs – d-TC
- 3) Aminoglycosides, CCBs + PSKMRs → potentiate the action of PSKMRs → C/I

BOTULINUM TOXIN

- Is obtained from a Gram Positive Anaerobic Bacterium Clostridium Botulinum

- It prevents release of Acetylcholine into synaptic cleft by inhibiting necessary proteins for the release of Ach → normalizes the tone in hyperactive or spastic muscles when given locally → inhibition lasts for 3-4 months

- S/Es are myalgia, muscle paralysis , rashes

Botulinum Toxin (Contd...)

- Therapeutic Uses :-
- 1) In Cosmetic surgery – I.M.; I.D
- ** For removal of facial lines
- ** To give wrinkle - free face
- ** To prevent ageing process
- 2) For spasticity or Dystonia → given in muscles in multiple doses
- 3) For strabismus, blepharospasm, hemifacial spasms, LES spasm
- 4) For hyper-hydrosis of palms and axillae

Malignant Hyperthermia

- **Caused by co-administration of halogenated inhalational anaesthesia and depolarizing NMBA**

  (Halothane + succinylcholine)

- **Occurs in genetically susceptible individuals deficient of Raynodine (RyR1) receptors on calcium channel of sarcoplasmic reticulum of skeletal muscles.**

→Hence, impairment of the ability to sequester calcium from the sarcoplasmic reticulum → ↑ in iCa^{++} concentrations.

Malignant Hyperthermia

- **Clinical features :-** Severe rise in body temperature, hyper-reflexes, hypertonia, hyperventilation, tachycardia, palpitations, rigidity and metabolic acidosis → a life threatening condition.
- **Treatment :-**
- 1) 1mg/Kg Dantrolene i.v. inj
- 2) Rapid cooling by cool sponging
- 3) Ventilation, 100% oxygen inhalation
- 4) Treatment of acidosis

FAQs :-

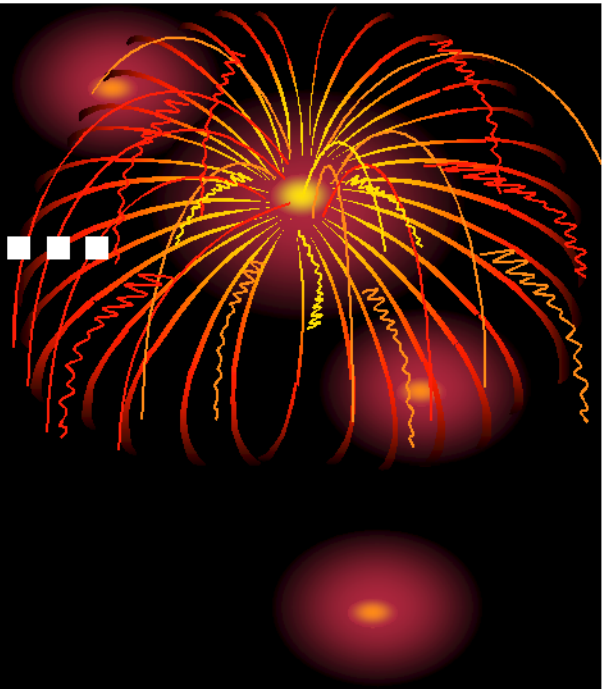
- **1) Classify NMBAs. Describe pharmacological actions, therapeutic uses, Important adverse effects , drug-Interactions of Depolarizing or Non-depolarizing agents.**

- **2) Compare & contrast D-NMBAs & ND-NMBAs**

FAQs :-

- 3) What is Hofmann Reaction? Which drug produces it?
- 4) What is malignant Hyperthermia? How to treat it?
- 5) What is Botulinum Toxin? What are its uses?

SKMRs AGENTS.....



THANK YOU

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