:Muscarinic Antagonists

د.اسماء الثويني

Asist.Prof./M.B.Ch.B/M.S.C/P.h.D

Pharmacology and therapeutics

- ***Scopolamine*** (also known as ***hyoscine***)
- Similar to atropine cross BBB but cause **CNS depression**.
- well absorbed from GIT and skin so can be used as **transdermal patches** in the treatment of **motion sickness**.
- It is drug of choice for the treatment of **motion sickness**
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- ***Hyoscine-N-butyl bromide***
- Synthetic derivative of scopolamine. It is very effective in relaxing smooth muscles and used as **antispasmodic** **for** **GIT** **,** **biliary,** and **urinary tract**.
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- ***Dicycloverine (dicyclomine)***
- Is similar to atropine and used mainly as antispasmodic agent
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- ***Cyclopentolate*** and ***Tropicamide***
- Are tertiary amines developed for **ophthalmic use (as mydriatic agents).**
- Ophthalmic duration of action is much shorter than atropine and scopolamine ***(≈ 6 hours***

- **Quaternary derivatives of atropine:**

- These are **quaternary ammonium derivatives** of atropine
- Do **not cross the BBB** and have peripheral antimuscarinic actions without effect on CNS, they include :
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- ***1- Atropine methonitrate*, *Homatropine*, *Methscopolamine* and *Propantheline***
- **Poorly absorbed**
- **Lacks CNS effects**
- Mainly used for **gastrointestinal hypermotility**
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- ***2- Ipratropium* and *Tiotropium***
- Quaternary ammonium compounds similar to atropine. Used **by inhalation** as **bronchodilators for the treatment of asthma** and **COPD**
- **Tiotropium is (LAMA) that has longer duration of action than Ipratropium (SAMA) and used once daily (as dry powder inhalation) to control COPD**

- **LAMA= long-acting muscarinic antagonist**
- **SAMA= short-acting muscarinic antagonist**
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• Selective muscarinic antagonists:

- Currently used muscarinic antagonists show little subtype selectivity, but **few drugs** are selective muscarinic blockers, they include :
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- ***1- Pirenzepine* (M_1-selective)**
- Used to treat ***peptic ulcer*** disease by **suppressing gastric acid secretion**
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- ***2- Oxybutynin*and *Darifenacin* (M_3-selective)**
- They are **new drugs** that act on the bladder to inhibit micturition, and are used for treating ***urinary incontinence***.
- **S.E.** typical of muscarinic antagonists, such as dry mouth, constipation and blurred vision.

- **Centrally acting muscarinic antagonists:**
- Antimuscarinic drugs with CNS effects more than peripheral effects, they include: ***Benztropine*, *Benzhexol*, *Procyclidine*, and *Biperiden***
- They mainly affect the **extrapyramidal system**, and used to reduce tremor, involuntary movement and rigidity in patients with **Parkinson's disease** and also used to counteract the **extrapyramidal S.E.** of many **antipsychotic drugs**.

- ***Atropine poisoning:***
- Poisoning is more serious in children.
- **Dry as a bone**
- **Blind as a bat**
- **Red as a beet**
- **Mad as a hatter**

- ***Dry mouth, mydriasis, blurred vision, tachycardia, hot and flushed skin, agitation and delirium.***

- **Hyperthermia** is due to blockage thermoregulatory sweating (also called ***atropine fever***) it occur especially **in infants** which may be dangerous
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- There is cutaneous vasodilatation of the vessels **of head, neck, arms & trunk** (***atropine flush***) which is described as red as a beet, it may be diagnostic.
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- Antidote is ***physostigmine***

NEUROMUSCULAR-BLOCKING DRUGS

- Drugs that **block muscular nAChRs**. **They** produce **skeletal muscle relaxation**.
- Clinically, **used** as an adjunct to **anesthesia**, when artificial ventilation is available
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- **They fall into two categories:**
- ***Non-depolarizing blocking agents*** (the majority), which act by blocking ACh receptors (**nAChRs antagonists**)
- ***Depolarizing blocking agents***, which are **agonists** at **nAChRs**.

• Non- depolarizing blocking drugs

- ***Curare*** is a mixture of **naturally occurring alkaloids** found in various plants and used as **arrow poisons** by **South American Indians**.
- The most important component of curare is ***Tubocurarine*** which is now rarely used in clinical medicine, and replaced by compounds with fewer side effects.
- These substances are all **quaternary ammonium** compounds, which means that they are **poorly absorbed** (safe in hunting animals) and generally **rapidly excreted** and **fail to cross the placenta** (used in obstetric practice).

- **Mechanism of action :**
- all act as **competitive antagonists** at the **nAChRs** of the endplate, thus prevent the depolarization of the muscle membrane causing flaccid paralysis.
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- **Effects of non-depolarizing blocking drugs :**
- **Motor paralysis** (flaccid paralysis). The **first muscles** to be affected are the **extrinsic eye muscles** (causing double vision) and the **small muscles of the face**, **followed by the muscles of the fingers**, **then the limbs**, **then neck and trunk muscles**. **Respiratory muscles** (**intercostal muscles then the diaphragm**) are the **last** to be affected and the first to recover.

- **Pharmacokinetic aspects :**
- All of these agents are given **i.v.**
- **Differ** in their rates of **onset** and **recovery**.
- Most agents are **metabolized by the liver** or **excreted unchanged in the urine**, ***exceptions:***
- ***Atracurium*** (**hydrolyzed spontaneously in plasma**)
- ***Mivacurium*** (**hydrolyzed by plasma cholinesterase**)
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- **Duration of action** varies between about **15 minutes** and **1-2 hours**. (**depend on the route of elimination**)

Impaired renal or hepatic function can prolong the paralysis. Drugs with **spontaneous hydrolysis** like (***Atracurium***) has a short duration of action, which is unaffected by renal or hepatic function

- **Unwanted effects :**
- ***Tubocurarine*** cause:
- **Fall in arterial pressure**, chiefly due to ganglion block.
- **Release of histamine** from mast cells, which can also give rise to ***fall in arterial pressure*** and ***bronchospasm*** in sensitive individuals. This is unrelated to **nAChRs**
- ***Atracurium*** and ***Mivacurium*** **also cause release of histamine** but less than Tubocurarine.
- Other agents lack these S.E., and hence cause less hypotension.
- ***Gallamine***, and to a lesser extent ***Pancuronium***, block **mAChRs**, particularly in the heart, which results in **tachycardia**.

Classification of non-depolarizing blocking agents

Isoquinoline Derivatives :

Drug	Onset	Duration of action	Main side effects	Notes
Tubocurarine	Slow (> 5 m)	Long (1-2 h)	*Hypotension Broncho-constriction* (histamine release)	metabolized by the **liver** and excreted by the **kidney**, now rarely used
Atracurium	Interm. (2-3 m)	Interm . (< 30 m)	Transient hypotension (histamine release)	elimination by (**spontaneous degradation in plasma**); Widely used drug

Cisatracurium	Interm.	Interm . (< 30 m)	less histamine release than Atracurium	Derivative of atracurium, eliminated also by **spontaneous hydrolysis**
Doxacurium	Interm.	Long	less histamine release than Atracurium	eliminated by **kidney**
Mivacurium	Fast (~2 m)	Short (~15 m)	Transient hypotension (histamine release)	rapidly inactivated by **pseudocholinesterase** (longer effects in patients with genetic cholinesterase deficiency).

Steroid Derivatives :

Drug	Onset	Duration of action	Main side effects	Notes
Pancuronium	Interm.	Long	Slight tachycardia No hypotension	excreted by the kidney, less side effect than tubocurarine Widely used drug
Vecuronium	Interm.	Interm. (30-40 m)	Few side effects	Widely used drug, mostly metabolized by the liver ***Rocuronium*** is similar, with faster onset (has the fastest onset of all agents)

• Depolarizing blocking drugs

- ***Decamethonium*** was the first agent found to produce depolarization block of skeletal muscles. (long duration of action).
- ***Succinylcholine (Suxamethonium)*** Its action is **shorter** than that of decamethonium, because it is quickly **hydrolyzed by plasma cholinesterase**.
- **Succinylcholine** and **decamethonium** act (like ACh) as **agonists** on the receptors of the motor endplate for long enough that the depolarization causes **loss of electrical excitability**.
- **Depolarizing blocking drugs first causes the opening of Na^+ channels which results in depolarization** (**phase I**) that produce a transient twitching of skeletal muscle (***fasciculation***) which **subsides after a few seconds** as the electrical excitability of the endplate region of the fiber is lost.
- The **continued binding of the depolarizing agent** render the receptor incapable of transmitting further impulses (**Desensitization**) and results in flaccid paralysis (**phase II**) in which the membrane is repolarizes but the receptor is desensitized to the effects of acetylcholine.

• Comparison of non-depolarizing and depolarizing blocking drugs

- Non-depolarizing block is reversed by anticholinesterase drugs (like neostigmine), depolarizing block is not (phase I is augmented
- Depolarizing block produces initial fasciculations and often postoperative muscle pain, non-depolarizing block is not

- ***Succinylcholine***
- It is the **only** depolarizing blocking drug in **clinical use**
- it is used **i.v.**, has **fast onset** of action **(~2 min)** and **short duration (~10 min)** (***hydrolysis by plasma cholinesterase***)
- prolonged action in patients with **liver disease** or **genetic deficiency of plasma cholinesterase**.
- It is Used mainly for **brief procedures** (e.g. **tracheal intubation, electroconvulsive shock therapy** {*ECT*}).

- **Unwanted effects and dangers of Succinylcholine :**
- ***Bradycardia:***
- **Direct muscarinic action**. (can be prevented by atropine)
- ***Potassium release:***
- **Increase in cation permeability of the motor endplates.**
- The resulting **hyperkalaemia** can be enough to cause **ventricular dysrhythmia** or even **cardiac arrest.**
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- ***Increased intraocular pressure:***
- ***Prolonged paralysis:*** (***scoline apnea***)
- The action of succinylcholine given i.v. normally lasts for **less than 5 minutes**, because the drug is hydrolyzed by plasma cholinesterase. Its action is prolonged by various **factors** that **reduce the activity of this enzyme**:

- **Genetic variants** in which plasma cholinesterase is abnormal.
- (***scoline apnea***) occurs in only about 1 in 2000 individuals.
- **Neonates** and **patients with liver disease** may have low plasma cholinesterase activity.
- ***Malignant hyperthermia:***
- Rare **inherited condition**, due to a **mutation of the Ca^{2+} releasing channels** of the sarcoplasmic reticulum, which results in **intense muscle spasm** and a dramatic **rise in body temperature** when certain drugs are given. The most commonly implicated drugs are ***succinylcholine*** and ***halothane***. high **mortality** (about **65%**) and is treated by cooling the body and administration of ***Dantrolene***, a drug that inhibits muscle contraction by preventing Ca^{2+} release from the sarcoplasmic reticulum.


THANK YOU!