Parasympathomimetic and parasympatholytic agents

DR T.N. CHIDUMAYO

MD, PHARMACOLOGY SPECIALISTS

General Intended learning outcomes

DESCRIBE THE PHARMACOLOGICAL EFFECTS, CLINICAL USES AND UNWANTED EFFECTS OF MUSCARINIC RECEPTOR AGONISTS AND ANTICHOLINESTERASES

EXPLAIN WHY MUSCARINIC RECEPTOR AGONISTS AND ANTICHOLINESTERASES HAVE LIMITED CLINICAL USES

PARASYMPATHOMIMETICS/ MUSCARINIC RECEPTOR AGONISTS & ANTICHOLINASTARASES

Intended Learning Outcomes Parasympathomimetics

List the receptors of the parasympathetic nervous system.

Contrast the actions and effects of direct and indirect stimulation of muscarinic cholinoreceptors.

List the therapeutic uses of parasympathomimetic agents.

List the adverse effects of parasympathomimetic agents.

DEFINITIONS

Parasympathetic nervous system: An anatomic division of the autonomic nervous system (the other is the sympathetic nervous system).

Preganglionic fibers are carried on cranial and sacral spinal nerves to synapse on ganglia that give rise to short postganglionic fibers, many of which are in the organs they innervate.

Ptosis: Drooping of the eyelids.

Diplopia: Double vision.

Cholinomimetic agents: Agents that mimic the action of ACh. They act directly or indirectly to activate cholinoreceptors.

Receptor Class

The efferent nerves of the parasympathetic autonomic nervous system release the neurotransmitter ACh at preganglionic and postganglionic nerve endings called “cholinergic”

Parasympathetic nervous system interacts at cholinoreceptors.

Receptor classification: nicotinic or muscarinic

Nicotinic cholinoreceptors: localized at all postganglionic neurons (the autonomic ganglia); adrenal medulla, skeletal muscle endplates innervated by somatic nerves (NN & NM).

Muscarinic cholinoreceptors (M1, M2, M3, M4, & M5) **:** localized at organs innervated by parasympathetic postganglionic nerve endings, on **cardiac atrial muscle, sinoatrial node cells, and atrioventricular node cells.**

Activation:	
Negative chronotropic effect and delayed atrioventricular conduction.	Bronchoconstriction, increased acid secretion, and vasodilation.

Introduction Parasympathomimetics

Directly acting agents: (**pilocarpine, bethanechol, carbachol**) act selectively on either muscarinic or nicotinic cholinoreceptors.

- **Pilocarpine** is a directly acting cholinomimetic agent acting at **muscarinic cholinoreceptors**.
- Additional selectivity of pilocarpine and other cholinomimetics in the treatment of glaucoma is achieved by the use of an ophthalmic (topical) preparation.

Indirectly acting agents: (**neostigmine, physostigmine, edrophonium, demecarium**); inhibit the enzyme AChE that is responsible for the metabolism of Ach. They can activate both muscarinic or nicotinic cholinoreceptors.

Activation of Muscarinic Cholinomimetics

Muscarinic cholinoreceptors activate inhibitory G-proteins (Gi). Which stimulate the activity of phospholipase C.

The cascade leads to mobilization of intracellular calcium

Opening smooth muscle calcium channels and influx of extracellular calcium.

Potassium flux resulting in cell hyperpolarization

Mechanism of Action of Nicotinic Cholinomimetics

The nicotinic receptor functions as a cell membrane ligand-gated ion channel pore.

↓

Undergoes conformational change result in influx of sodium

Membrane depolarization of the nerve cell or the skeletal muscle neuromuscular endplate.

↓

Indirectly acting parasympathetic cholinomimetic agents inhibit AChE

Increase ACh levels at muscarinic and nicotinic cholinoreceptors.

MUSCARINIC AGONISTS: PHARMACOLOGICAL EFFECTS

Effector	Effects
Heart	Negative chronotropic effect and decreased conduction velocity
Arterioles	Vasodilatation Blood pressure falls due to a fall in total peripheral resistance
Lacrimation	Increases
Respiratory system	Bronchoconstriction Increased bronchial secretions
GIT	Increased peristaltic activity and motility Increased salivation and GIT secretions
Urinary tract	Increased contraction of the ureter and bladder smooth muscle (detrusor) Increased trigone and sphincter relaxation (promotes micturition)
Sweat glands	Increased sweat gland secretion
Eye	Miosis and accommodation Increased outflow of aqueous humour resulting in a reduction in intraocular pressure
Other effects	Tremor, ataxia

5

Pharmacokinetics of cholinergic drugs

Directly acting muscarinic cholinomimetic agents administered topically as ophthalmic preparations (pilocarpine, carbachol), orally (bethanechol, pilocarpine), or parenterally (bethanechol).

- Pilocarpine is more lipid soluble and can be absorbed and penetrate the CNS.

Indirectly acting cholinesterase inhibitor administered topically, orally, or parenterally.

- Methacholine, carbachol and bethanechol are resistant to the action of cholinesterases.

Clinical uses of ACh and the synthetic choline esters

Treat **acute angle-closure glaucoma, urinary tract retention, postoperative ileus, xerostomia**, and the neuromuscular junction (**myasthenia gravis**).

Indirectly acting muscarinic agents inhibit metabolism of ACh, by blocking acetylcholinesterase (AChE) enzyme

- Increas availability of naturally occurring ACh in the synapse.
- AChE inhibitors used in the treatment of autonomic pathologies include physiostigmine, neostigmine, pyridostigmine, and ambedonium.

Limitations of cholinomimetics

Acetylcholine not used clinically because of numerous actions and very rapid hydrolysis by AChE and pseudocholinesterase.

The adverse effects of direct- and indirect-acting cholinomimetics result from cholinergic excess: **diarrhea, salivation, sweating, bronchial constriction, vasodilation, and bradycardia** (DUMBBELLS).

Nausea and vomiting also common.

Adverse effects of cholinesterase inhibitors

- Most often result of toxicity from pesticide exposure, eg, **organophosphates**.
- Muscle weakness, convulsions, and respiratory failure.

Therapeutic uses organophosphorus compounds :

The organophosphorus compounds have limited therapeutic uses owing to high toxicity

- Insecticides are of toxicological importance

Glaucoma: Echothiophate 0.06% reduces the intraocular tension; for 1 to 3 weeks

- Produces marked ciliary spasm, brow ache, headache and blurring

Worm infestation: Dichlorovas and trichlorophos have anthelmintic properties but are not used for this purpose

Clinical Scenario

- A 25-year-old woman has symptoms of myasthenia gravis. The edrophonium (Tensilon) test. Is performed. The test is positive and therefore the patient is started on mestinon.
  1. How does the edrophonium test aid in the diagnosis of myasthenia gravis?
  2. What are the mechanisms of action of edrophonium and mestinon?

CLINICAL CORRELATION

Myasthenia gravis: an autoimmune disorder in which the patient produces autoantibodies against the acetylcholine (ACh) receptor.

Nicotinic receptors on motor end plate of skeletal muscle; reduced(1/3 of normal or less).

Weakness and fatigability of skeletal muscle with recovery after rest.

- Ocular problems, including ptosis and diplopia
- Proximal limb muscles (hip and shoulder), and muscles of respiration

Edrophonium test and diagnosis:

This test is very specific for diagnosing myasthenia gravis.

An intramuscular or intravenous injection of edrophonium alleviates ptosis by temporarily increasing acetylcholine at the synaps

Contraction of the levator palpebrae superiorus muscle.

Mechanisms of action of edrophonium and mestinon: **acetylcholinesterase (AChE) inhibitors.**

Neostigmine in myasthenia gravis

Neostigmine & similar drugs improve muscle contraction

- Accumulation of Acetylcholine from prejunctional endings.
  - Increased Ach concentration act on receptors over a larger area
- Directly depolarizing the end plate.

Treatment is usually started with 15 mg orally 6 hourly; dose is adjusted according to response.

PARASYMPATHOLYTICS/ MUSCARINIC RECEPTOR ANTAGONISTS

Intended Learning Outcomes Parasympatholytics

Describe	Describe the mechanism of action of muscarinic cholinoreceptor antagonists.
Describe	Describe the physiologic effects of muscarinic cholinoreceptor antagonists.
List	List important therapeutic uses of muscarinic cholinoreceptor antagonists.
List	List the adverse effects and contraindications for muscarinic cholinoreceptor antagonists.

DEFINITIONS

Muscarinic cholinoceptor antagonists: Drugs that block the actions of acetylcholine.

Chronic obstructive pulmonary disease (COPD): Progressive, inflammatory lung conditions, including both chronic bronchitis and emphysema, which result in airway obstruction that is **not fully reversible**. Most COPD is due to **smoking**.

Asthma: An inflammatory lung condition characterized by **reversible** airway obstruction precipitated by irritants such as environmental allergens, cigarette smoke.

CHOLINORECEPTOR ANTAGONISTS

Cholinoreceptor antagonists: specificity for muscarinic and nicotinic cholinoreceptors.

Muscarinic cholinoreceptor antagonists block the effects of ACh at muscarinic cholinoreceptors in the parasympathetic autonomic nervous system and in the CNS.

Nicotinic cholinoreceptor antagonists block the effects of ACh at ganglia of the parasympathetic, sympathetic nervous system, medulla, and neuromuscular junction.

ADMINISTRATION & PHARMACOKINETICS

The patch formulation of scopolamine for motion sickness provides 72 hours of pharmacologic activity.

- Scopolamine can also be administered IV, IM, or PO.

Ipratropium bromide and **tiotropium** are administered topically to the airways as a metered-dose inhaler for COPD.

The **duration of action** of antimuscarinic agents ranges from less than a day (tropicamide), to 3–10 days (scopolamine, atropine).

Clinical Uses of Muscarinic Cholinoreceptor Antagonists

Muscarinic cholinoreceptor antagonists eg, **benztropine**, are used therapeutically to treat Parkinson disease.

Short-acting topical agents or ointments are used to facilitate ophthalmoscopic examination (eg, **cyclopentolate**, **tropicamide**).

Ipratropium bromide; doesnt cross the blood-brain barrier, is used to treat asthma chronic obstructive pulmonary disease (COPD).

Trospium and tolterodine are also used to treat certain bladder disorders.

Tertiary amine **atropine** is used to counter the muscarinic cholinoreceptor effects of from organophosphate insecticide poisoning because it penetrates the CNS.

Adverse Effects of Cholinoreceptor Antagonists

The adverse effects from inhibition of muscarinic cholinoreceptors in organ systems of the body.

Impairment of memory, **confusion**, **restlessness**, **hallucinations**, **drowsiness** and sedation: actions on the CNS.

- Elderly patients are sensitive to CNS effects

Sinoatrial node: results in tachycardia, may **cause arrhythmias**, especially in **heart disease**.

Adverse Effects of Cholinoreceptor Antagonists cont.

Dry mouth: reduces salivation.

Mydriasis: blocking parasympathetic tone in the muscles of the cilia and iris.

Increase intraocular pressure in angle-closure glaucoma .

Urinary retention: urinary bladder relaxation and the urinary sphincter constricted.

urinary tract obstruction eg, prostatic hypertrophy

CLINICAL SCENARIO

- A 53-year-old woman is scheduled to take a Caribbean cruise in 2 weeks but is concerned about sea sickness. Her examination is normal. You prescribe a scopolamine transdermal patch for her.
    1. What is the mechanism of action of scopolamine?
    2. What are the common side effects of this medication?
    3. What are some relative contraindications to its use?

CHOLINORECEPTOR ANTAGONISTS STRUCTURE

Scopolamine is a **tertiary amine** like atropine (prototype muscarinic cholinoreceptor antagonist).

Scopolamine has ready access to the CNS when administered parenterally

Absorbed across the skin when combined with a suitable vehicle in a transdermal patch.

Quaternary amine antimuscarinic agents, including **tiotropium bromide,** have limited access to the CNS hence used **therapeutically for their peripheral effects**.

Clinical Correlation Scopolamine

Mechanism of action of scopolamine: Competitive antagonist of muscarinic cholinoreceptors in the vestibular system and the CNS.

Overcome by increased concentrations of ACh or other muscarinic cholinoreceptor agonists.

Relatively long duration of action, given as a transdermal patch, for the treatment of motion sickness.

Common side effects: Mydriasis, dry mouth, tachycardia, urinary retention, confusion, drowsiness.

Relative contraindications: Glaucoma, urinary obstruction, heart Disease.

Organophosphorus Compound (OPC) poisoning

Poisoning with organophosphorus compounds may be occupational, accidental , or suicidal.

Acute organophosphorus pesticide poisoning has 99% of the fatal poisonings in the developing countries

The effects of acute OPP intoxication are DUMBELLS	Severe bronchospasm and pulmonary edema may be fatal	Death is usually due to paralysis of respiratory muscles and respiratory failure

The duration of effect is longest with DFP, and shorter with echothiophate and tetraethyl pyrophosphate (TEPP)

Delayed symptoms: demyelination of the nerve tracts in central & peripheral nervous systems

Principles of treatment of acute organophosphorus poisoning

- Remove soiled clothes.
- Wash soiled skin, eyes.
- Nurse in prone position.
- Clear mouth and throat.
- Insert an airway/intubate
- Gastric lavage.
- Atropine in sufficient quantities.
- Cholinesterase activator such as pralidoxime.
- Supportive measures such as oxygen, treatment of shock, prophylactic antibiotics.
- Treatment of convulsions (diazepam).
- Continued vigilance as delayed toxicity may occur as late as 2–4 weeks after apparent recovery.

"WHO" Recommends of OPP Treatment

Rapid treatment to prevent a fatal outcome

Atropine (with or without the reactivator) may be given

- Depending on severity of intoxication and response to the first dose.

Atropine antagonizes central & peripheral muscarinic effects but doesn't modify the ganglionic action and the neuromuscular paralysis.

Reactivators of cholinesterase should not be used before atropine administration (increase muscle weakness).

Atropine should not be given to a **cyanosed patient** until the cyanosis has been overcome (may cause ventricular fibrillation).

Treatment of OPP cont

In severe intoxication, 4-6 mg of atropine sulfate should be given initially, followed by repeated doses of 2 mg or as much as required to **maintain full atropinisation**

Patient's condition: respiration, convulsions, blood pressure, pulse, and salivation monitored to guide to further administration of atropine: Usually not more than 50 mg

- Tachycardia (not more than 120/min) and salivary secretion in order to prevent over-atropinisation

Reactivators are excreted rapidly if kidney function is normal (pralidoxime 80% in 2-3 hours) and repeated doses of 1 g may be needed.

- IV injection of oximes should be made slowly

Other effects of OPP

After the resolution of the initial symptoms, may develop the '**intermediate syndrome**' with flaccid, proximal paralysis.

After 2-4 weeks, a **'delayed polyneuropathy'** with sensory and motor, impairment, usually of the lower limbs

- There is no specific treatment

Blood samples taken for cholinesterase determinations before and during the continued treatment.

- Avoid working with organophosphorus until the plasma cholinesterase level exceeds 70% of normal (after several weeks)

Oximes (Cholinesterase Reactivators)

The irreversible inhibition of cholinesterase produced by the OPC due to phosphorylation of the esteratic site of the enzyme

Oximes combine with the phosphoryl groups of these phosphorylated esteratic sites forming soluble complex

- Sets free the esteratic site and reactivates the enzyme

Oximes are effective in reversing the neuromuscular paralysis where atropine is ineffective

Effects on autonomic ganglia and CNS **not significant**, except in the case of **DAM** which crosses the blood brain barrier.

- Only effective when administered within a short time after poisoning

Oximes: Late administration, Adverse reactions.

Late administration fails to produce the expected results.

- Phosphoryl bound with the enzyme gets more stabilized **(ageing of the enzyme)**

Oximes mainly metabolised in the liver

Adverse reactions: Local irritation, drowsiness, giddiness, blurred vision, diplopia, tachycardia and hypotension

Pralidoxime has weak **anti-cholinasterase activity**

- Contraindicated in the treatment of overdose with neostigmine or physostigmine
- High doses of oximes can cause neuromuscular blockade

It does not antagonise the effects of carbamate type **(Baygon/ Carbaryl**) on anticholinesterases