



PHARMACOLOGY



Sheets



Slides

Number: 12

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Subject: Anti-muscarinic drugs

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Organ System Effects

1. On the Central Nervous System:

- **Atropine** has minimal stimulant effects on CNS.
- **Scopolamine** has more marked central effects, producing drowsiness and amnesia.
- In toxic doses, scopolamine, and to a lesser degree atropine, can cause excitement, agitation, hallucinations, and coma.
- The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine – in the form of belladonna extract – was one of the first drugs used in the therapy of this disease.

Parkinson disease

Parkinson disease: It is a disease in the basal ganglia in the brain

In the basal ganglia of the brain we have two transmitters which are: cholinergic transmission and dopaminergic transmission.

In Parkinson disease usually there is atrophy or destruction in the dopaminergic neurons, so the balance between the cholinergic system and the dopaminergic system is disturbed. So the symptoms of Parkinson disease will appear.

In order to restore the balance between the cholinergic and dopaminergic systems we have to either increase dopamine activity or decrease cholinergic activity.

Vestibular disturbances

Scopolamine is effective in preventing or reversing these disturbances.

Eye

- Atropine and other tertiary antimuscarinics cause an unopposed sympathetic dilator activity & **mydriasis**
- Also atropine could cause cycloplegia by paralysing the ciliary muscles of the eye which leads to make the eye focusing on the far vision only so the patient can see well the far objects but he can't read a book for example.
- They may cause **acute glaucoma** in patients with a narrow anterior chamber angle.
- Antimuscarinic drugs **reduce lacrimal secretion** causing dry or "sandy" eyes.

Cardiovascular System

- Atropine causes tachycardia by vagal block.
- Lower doses often result in initial bradycardia before the effects of peripheral vagal block is seen.
- This slowing may be due to block of M1 autoreceptors on vagal postganglionic fibers. Recent studies indicate that it is centrally mediated.

- The ventricles are less affected
- In toxic concentrations, it can cause intraventricular conduction block due to a local anesthetic action.
- All blood vessels contain endothelial muscarinic receptors that mediate vasodilation .
- These receptors are blocked by antimuscarinic drugs.
- At toxic doses, antimuscarinic agents cause **cutaneous vasodilation**, especially in the upper portion of the body (the blush area) "the face and the neck". The mechanism of this vasodilation is unknown but maybe it is due to sweat inhibition which leads to increase the body temperature so we will have vasodilation in that area in order to decrease the temperature.

Respiratory System

- Atropine causes some bronchodilation & reduce secretions.
- The effectiveness of nonselective antimuscarinic drugs in treating **bronchial asthma** is limited because block of **autoinhibitory M2** oppose the bronchodilation caused by block of **M3** receptors on airway.
- Antimuscarinic drugs are frequently used before the administration of **inhalant anesthetics** to reduce the accumulation of secretions in the trachea.

Gastrointestinal Tract

- Complete muscarinic block cannot totally abolish activity of GIT, since local hormones in the enteric nervous system also modulate GI functions.
- Antimuscarinic drugs have marked effects on salivary secretion causing **dry mouth**
- Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required which will cause a lot of side effects of course.
- Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.

Pirenzepin, telenzepine

- ❖ They are M1 blockers
- ❖ They Reduce gastric acid secretion with fewer adverse effects than atropine.
- ❖ GI smooth muscle **motility** is affected from the stomach to the colon and both tone and propulsive movements are diminished.
- ❖ **Gastric emptying time is prolonged**, and **intestinal transit time is lengthened**.
- ❖ Diarrhea due to over dosage with muscarinic agents is readily stopped.
- ❖ Diarrhea caused by nonautonomic agents can usually be temporarily controlled.

Genitourinary Tract

- Relaxes smooth muscle of the ureters and bladder wall and slows voiding.
- Useful in the **treatment of spasm** induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have **prostatic hyperplasia**

Sweat Glands

- Atropine suppresses **sweating**.
- In adults, body temperature is elevated only with large doses, but in infants and children even ordinary doses may cause "**atropine fever**."

Therapeutic Applications of the anti-muscarinic agents:

1. Central Nervous System Disorders, "Parkinson's Disease"

Usually the treatment if Parkinson disease is by giving dopaminergic drugs like L-dopa that is converted in the brain into dopamine. But sometimes they add an **adjunctive** therapy in some patients but with all of the adverse effects.

2. **Motion Sickness** "nausea and vomiting caused by over stimulation of the Body Balance Center"
 - **Scopolamine** is one of the oldest remedies & is as effective as any more recently introduced agent.
 - Given by injection or by mouth or as a transdermal patch.
 - The **patch formulation** produces significant blood levels over 48-72 hours.
 - Useful doses by any route usually cause significant sedation and dry mouth.

Antimuscarinic Drugs Used in Ophthalmology.		
Drug	Duration (days)	Usual Concentration(%)
Atropine	7-10	0.5-1
Scopolamine	3-7	0.25
Homatropine	1-3	2-5
Cyclopentolate	1	0.5-2
Tropicamide	0.25	0.5-1

Ophthalmologic Disorders

- Antimuscarinic agents, as eye drops or ointment, produce mydriasis and cycloplegia are very helpful in doing a complete examination.
- The shorter-acting drugs are preferred

- Should never be used for mydriasis unless cycloplegia or prolonged action is required.
- Alpha- adrenoceptor stimulant drugs, **phenylephrine**, produce a short mydriasis sufficient
- For fundusoscopic examination.
- Antimuscarinics also used to prevent **synechia**.
- A **synechia** is an eye condition where the iris adheres to either the cornea or lens. The longer-lasting preparations, especially homatropine, are preferred.

Respiratory Disorders

- Atropine was routinely used as a **preoperative** medication when anesthetics such as ether were used to decrease airway secretions and to prevent laryngospasm. Newer inhalational anesthetics are far less irritating to the airways.
- **Scopolamine** also produces significant amnesia for the events associated with surgery and **obstetric delivery**.
- Urinary retention and intestinal hypomotility following surgery are exacerbated by antimuscarinic drugs.

Ipratropium:

A synthetic analog of atropine, is used as an inhalational drug in **asthma** with reduced systemic effects. "Causes bronchodilation"

Ipratropium is also useful in COPD, a condition that occurs more frequently in older patients, particularly chronic smokers.

Tiotropium

Has a longer bronchodilator action and can be given once daily.

Drugs work on the lungs

Cardiovascular Disorders

- Marked reflex vagal discharge sometimes accompanies the pain of **myocardial infarction** (e.g., vasovagal attack) and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. **Atropine** is used in this situation.
- Rare individuals have **hyperactive carotid sinus reflexes** and may experience faintness or even syncope as a result of vagal discharge in response to pressure on the neck, e.g., from a tight collar. Such individuals may benefit from the use of **atropine** or a related antimuscarinic agent.

Gastrointestinal Disorders

- Antimuscarinic agents can provide some relief in the treatment of common **traveler's diarrhea** and other mild hypermotility.
- They are often combined with an **opioid antidiarrheal drug**.
- **Atropine** with **diphenoxylate**, (**Lomotil**) is available in both tablet and liquid form.

Urinary Disorders

- Provide symptomatic relief in the treatment of **urinary urgency** caused by minor inflammatory bladder disorders.

Oxybutynin

- More selective for M3 receptors, is used to relieve bladder spasm after urologic surgery.
- It reduce involuntary voiding in patients with neurologic disease.

Darifenacin

- Has greater selectivity for M3 receptors & long half-life
- Used in adults with urinary incontinence.
- ✓ There is also An alternative treatment for urinary incontinence refractory to antimuscarinic drugs is intrabladder injection of **botulinum toxin A**.
- ✓ By interfering with the release of neuronal acetylcholine, botulinum toxin is reported to reduce urinary incontinence for several months after a single treatment.

Cholinergic Poisoning

- Caused by cholinesterase inhibitor & wild mushrooms
- **Atropine** is used to reverse the muscarinic effects, to treat the CNS effects as well as the peripheral effects of the organophosphate inhibitors.
- Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like **parathion** and chemical warfare nerve gases.
- 1-2 mg of atropine sulfate may be given **IV** every 5-15 minutes until signs of effect (**dry mouth, reversal of miosis**) appear.
- The drug is **repeated many times**, since the acute effects of the anticholinesterases may last 24-48 h.

- 1 g of atropine per day may be required for **one month** for full control of muscarinic excess.

Adverse Effects

- Treatment with atropine or its congeners induces undesirable effects.
- At higher concentrations, atropine causes block of **all** parasympathetic functions.
- Poisoned individuals manifest:
Dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as 1 week.
- **Children, especially infants**, are **very sensitive** to the **hyperthermic** effects of atropine.
- Deaths have followed doses as small as 2 mg.
- **Overdoses of atropine** are treated **symptomatically**
- When **physostigmine** is used, *small* doses are given *slowly* intravenously.
- Symptomatic treatment may require temperature control with cooling blankets and **seizure** control with **diazepam**.
- Poisoning by high doses of **quaternary antimuscarinic** drugs is associated with all of the peripheral signs but few or none of the CNS effects of atropine.
- They may cause **ganglionic blockade** with marked orthostatic hypotension
- Treatment of the antimuscarinic effects can be carried out with a quaternary cholinesterase inhibitor such as **neostigmine**.
- Control of hypotension may require the administration of a sympathomimetic drug such as **phenylephrine**.

Contraindications:

1. Glaucoma

Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow anterior chambers.

2. Prostatic hyperplasia

- In **elderly men**, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia.
- Nonselective antimuscarinic agents should never be used to treat acid-peptic disease.
- Because the antimuscarinic drugs slow gastric emptying, they may *increase* symptoms in patients with gastric ulcer.

The End ..