14.1

Pharmacology

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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NOTE: this is half of lecture 14, this sheet will include ONLY the material needed for the midterm exam. It'll be sufficient so you don't need to go back to the slides.
Enjoy :D

In the previous lecture…
We were talking about actions of muscarinic antagonists, their early derivation from natural resources (especially *Atropa belladonna),* and some of their effects on some organ systems. Today we'll continue with that and then talk about **Therapeutic applications of such drugs**.

Effects on **Genito-Urinary tract:**

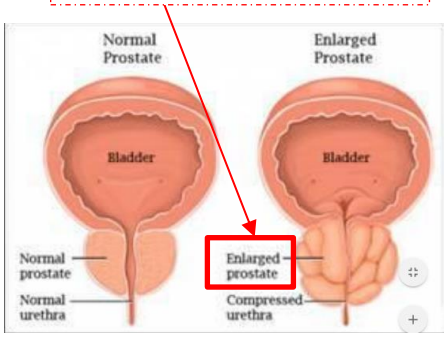
The normal **parasympathetic effect** on the GU tract is **contraction of the bladder** muscles and **relaxation of the sphincter** resulting in voiding of urine(excretion).

→If we **block parasympathetic** receptors by **antimuscarinics**, we'll observe the opposite: **relaxation** of smooth muscles of the **bladder** and **ureters**, and **contraction of sphincter**; which in turn slows voiding of urine.

What are these drugs useful for in this case?

Ans: **renal colic** cases, **spasms of ureters and bladder** that could be induced by mild inflammation, surgery, and certain neurologic conditions.

Notice how enlarged prostate nearly blocks the ureter.



Any major Bad effects on this system?

→yes, it can **precipitate urinary retention** in men who have **prostatic hyperplasia**. These individuals already have difficulty in urination, because their ureters are nearly blocked by the pressure of the enlarged prostate. Upon taking atropine these individuals suffer **acute urinary retention** which makes matters worse.

Remember sweat is a mechanism of thermo regulation.

Effects on **sweat glands**:

Sweat glands are innervated by **cholinergic sympathetic nerves**, through **muscarinic receptors**, blockade of those by atropine; causes **inhibition of sweat**.
Effects: (caused by inhibition of sweating)
In **adults**→ Increase in temperature that can occur **only** by large doses.
In **Infants**→ which are more **sensitive to Atropine**, they may have '**atropine fever'**. Even by usual therapeutic doses, infants might be presented with **fever**.

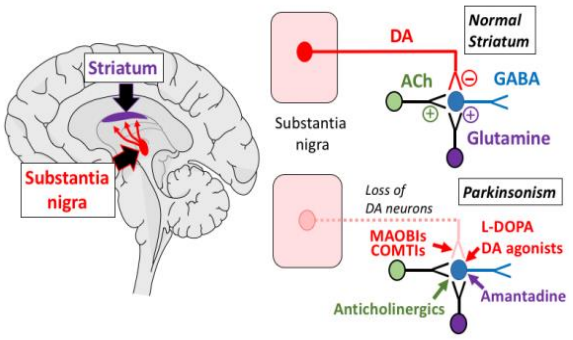
Therapeutic Applications:

CNS disorders:

To **counteract** the extra **effectiveness of cholinergic neurons** caused by DA dysfunction, **anticholinergics** can be used, but they're **not as effective as L-dopa or dopamine agonists**. Still, anti-cholinergics are better at controlling the tremor associated with the disease.

As a final solution, we **use dopamine agonists**, and for the tremor, we **give anti-cholinergics**.

Trihexyphenidyl, benztropine are useful as adjunctive therapy.



About **substantia nigra** and **Parkinson's disease**:

Substantia nigra is the place in the brain where **coordination of muscle activation** takes place, it sends out **dopaminergic inhibitory neurons** and **Ach stimulating neurons**, these two maintain balance in the fine movement by tuning muscular activity.

In Parkinson's however, there's **degeneration of the dopaminergic neuron**s, resulting in **imbalance**. Thus, **cholinergic effect becomes way higher**.

Motion sickness:

Scopolamine is as effective as any recently introduced agent.

It is given by **injection** or by **mouth** (problem here is that it has very short half-life, 2 hours only) or as a **transdermal patch**.
The patch formulation introduces significant amount of drug to the blood levels, so its effect can last for 48–72 hours, which makes it the best.

Useful doses, by any route, usually cause significant sedation and dry mouth.

Ophthalmology:

Antimuscarinic agents produce mydriasis (they block parasympathetic effect by blocking M3 receptors, so the only effector left is the sympathetic) and cycloplegia (paralysis of ciliary muscles) which is very helpful in performing a complete examination.

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

This is a comparison between **atropine** and other **synthetic drugs used in ophthalmology**, and their duration of action. This **duration lasts after a single application** to the eye. Notice how **Atropine lasts the longest**. **Homatropine,** which is a derivative of atropine and **Tropicamide**, lasts six hours. It is used in **ophthalmologic clinics to cause mydriasis**, so the doctor can examine the eye. It also causes **photophobia**.

Antimuscarinics should never be used If we **only** desire mydriasis or if we don't want prolonged effect, instead we use **Phenylephrine**, which is an α1 stimulant. **Phenylephrine** produces a **short mydriasis** sufficient for **funduscopic examination**.

Antimuscarinics are also used to prevent **synechia**. In this case, the longer-lasting preparations, especially homatropine, are preferred.

A synechia: a condition where the **iris** adheres to either the **cornea or lens**.

Respiratory Disorders:

Before, anesthetics like **Ether** were used for anesthesia. Alongside it, **Atropine** was routinely used as a **preoperative medication** to decrease airway secretions (to prevent patient's suffocation on their own mucosal secretions) and to prevent **laryngospasm.** Newer inhalational anesthetics are far less irritating to the airways, so no need to use Atropine.

Scopolamine also produces significant **amnesia** for the events associated with surgery and obstetric delivery.

Urinary retention and **intestinal hypomotility** following surgery are **exacerbated** (increased) by antimuscarinic drugs.

Bronchial Asthma:

The **release of acetylcholine** from **parasympathetic postganglionic neurons** stimulates contraction of airway smooth muscle through M3 receptors. And stimulates secretion of mucus by way of M1 muscarinic receptors.

In asthma, **reflex pathways** are thought to be **activated,** which increase vagal outflow that leads to cholinergically-mediated **bronchoconstriction**. Atropine, **wasn't** very effective here because it had many side effects, so other medications were produced:

Ipratropium, a synthetic **non selective** Muscarinic blocker, is used as an **inhalational drug** in asthma with reduced systemic effects (no systemic absorption). It is also useful in **chronic obstructive pulmonary disease** (COPD), a condition that occurs more frequently in older patients (particularly chronic smokers). Still, β-2 agonists **are more superior** in **broncho-dilation.**

Tiotropium: has a **longer bronchodilator action duration**, and can be given **once daily**.

Cardiovascular Disorders:

Sometimes, **Myocardial infarction** causes something called **vasovagal attack,** which is a **sudden increase** in **vagal activity** towards **the heart**. This causes a **drop** in: **1. heart rate** (bradycardia) and **2.** the **cardiac output**

It may depress sinoatrial or atrioventricular node function **decreasing induction sufficiently to impair cardiac output**.

In the case of myocardial infarction, we give **Atropine**, which prevents the progress of this condition.

→another rare case is that some individuals have **Hyperactive Carotid Sinus Reflexes.**

We know **carotid artery** is in the neck and it has baroreceptors. Any **pressure on this area** may activate the vagus nerve suddenly →results in **vagal discharge** → causes **drop in the heart rate** → **drop in the cardiac output** → **not enough** blood flow to the **brain** → individual **drops unconscious** for a few minutes.

Causes can be as simple as a tight collar.

Such individuals may benefit from the use of **Atropine** or a related antimuscarinic agent.

Gastrointestinal Disorders:

Antimuscarinic agents cause decrease in the peristatic movement. This characteristic can provide some relief in the treatment of common **traveler's diarrhea** and other mild hypermotility of the GIT.

Antimuscarinic drugs are often combined with an **opioid antidiarrheal drug**.

An excellent example of such combination is: **Lamotil** which is Atropine with diphenoxylate (the opioid agent). The great thing about such combination is that small doses of both drugs in the capsule, cancel out the side effects of each individual drug.

This combination is available in both tablet and liquid form.

Urinary Disorders:

Antimuscarinics Provide symptomatic relief in the treatment of **urinary urgency (continuous feeling of wanting to urinate)** caused by minor inflammatory bladder disorders.

Examples of drugs to be used for such condition:.

Oxybutynin More selective for M3 receptors, it has way less effect on other muscarinic receptors. It is used to relieve bladder spasm after urologic surgery. It produces the effect we want without the side effects.

Darifenacin Has greater **selectivity for M3 receptors** & long half-life, and is used in adults with **urinary incontinence** (they urinate involuntarily).

If these didn't work:
An **alternative treatment** for **urinary incontinence** stubborn to antimuscarinic drugs is **intrabladder injection** of a small dose of botulinum toxin A.

botulinum toxin is reported to reduce urinary incontinence for several months after a single treatment, by interfering with the **release of neuronal acetylcholine**.

NOTE: These drugs(all of them) **reduce involuntary voiding** in patients with neurologic disease

Cholinergic poisoning:

Caused by ingestion of **wild mushrooms,** and by **cholinesterase inhibitor.**

Atropine is used to reverse the muscarinic effects (it is the standard antidote), to treat the **CNS effects,** as well as **the peripheral effects** of the organophosphate inhibitors.

Large doses of atropine given for multiple times to oppose the muscarinic effects of extremely potent agents like **parathion** (from insecticides) and **chemical warfare nerve gases**.

1–2 mg of atropine sulfate may be given **IV** every **5–15** minutes until signs of effect (increase in heart rate, dry mouth, reversal of miosis) appear.

The drug is repeated many times for a span up to 2 days, since the acute effects of the anticholinesterases may last 24–48 h.

After **acute phase had passed**, 1 g of atropine per day may be required for one month for full control of muscarinic excess.

Adverse Effects:

Like any other drug, treatment with atropine or its congeners induces **undesirable effects.**
At **higher concentrations**, atropine causes block of all parasympathetic functions.
Poisoned individuals show: 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 (flushing, heart rate increase, pressure). **Deaths** have followed doses as small as 2 mg. → **Overdoses** of atropine are treated symptomatically.

Drugs For Atropine poisoning:

When physostigmine (a reversible cholinesterase inhibitor) is used, small doses are given *slowly,* intravenously and by a professional. We use it because it **can cross the blood-brain** barrier and **treat both CNS and PNS.** We don't use it systematically because it's very dangerous. (We use it only in atropine poisoning)

Symptomatic treatment:
may **require temperature control** with cooling blankets and **seizure (convulsions) 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 effects of atropine on the CNS.

quaternary antimuscarinic drugs:

their fourth N is similar to that of Ach, due to that they block autonomic ganglia in high doses.

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 (used just for peripheral effect, no central).

Control of hypotension may require the administration of a sympathomimetic drug such as phenylephrine which is an α_1 stimulant.

Orthostatic hypotension:

A state where a laying or sitting individual, falls when he stands up. Normally, when we stand up, gravity pulls the blood down, with major vessels of the legs, large enough to accommodate all the blood in the body. But baroreflex and increase in sympathetic activity causes vasoconstriction of these vessels which **prevents pooling of blood**. If sympathetic ganglia are blocked, **this reflex is gone**, and the person falls, not being able to stand.

Contraindications: (cases where we should not give the drug)

We don't give antimuscarinics to patients with the following problems, because their case will only become worse:

Glaucoma

Even systemic use of moderate doses may precipitate (cause) **angle closure** (and **acute glaucoma**) in patients with shallow anterior chambers. It could cause **increase in the intraocular pressure**.

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, because it causes urinary retention, which is a very harmful effect.

Nonselective antimuscarinic agents should **NEVER** be used to treat acid-peptic disease (peptic ulcer), because the **antimuscarinic** drugs slow gastric emptying, which may increase symptoms in patients with gastric ulcers.

This is all you need to know for the midterm exam, **study well** and

GOOD LUCK