Doctor 021

PHARMACOLOGY

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Cholinoceptor -Blocking Drugs

Drugs that block muscarinic cholinoceptors. Some times called antimuscarinic or muscarinic blocker.

Absorption:

- Naturalalkaloids :

They come from the plants of the **Solanaceae species** , **the most famous one is atropa belladona**, there are other plants from the same family , like Mandragora. All these Solanaceae species contain natural alkaloids and tertiary amines , **and the most tertiary antimuscarinic drugs are well absorbed**.

-This agent contain atropine and hyoscine or Scopolamine , **scopolamine (hyposcine) is absorbed across the skin (transdermal)** and it could be given by various ways but also it given as transdermal patches and absorbed cross the skin.

-while also we have number of quaternary synthetic antimuscarinic drugs cause **quaternary amines drugs** that are not fat soluble, not lipid soluble therefore **all 10–30% of the dose is absorbed after oral administration.**

Distribution :

1- **Atropine and the other tertiary agents** because of there lipid solubility is high **are widely distributed,** and they cross the blood brain barrier **and reach the CNS within 30 minutes to an 1 hour.**
2- **Scopolamine is rapidly and fully distributed into the CNS where it has greater effects than most other antimuscarinic drugs.**

In contrast, the quaternary derivatives that are poorly absorbed **, are poorly taken up by the brain** and eventually they don't have central effect.

Metabolism and Excretion :

Elimination of atropine occurs in two phases:
(the t1/2 of the rapid phase of 2 hours , and a slow phase of 13 hours) .

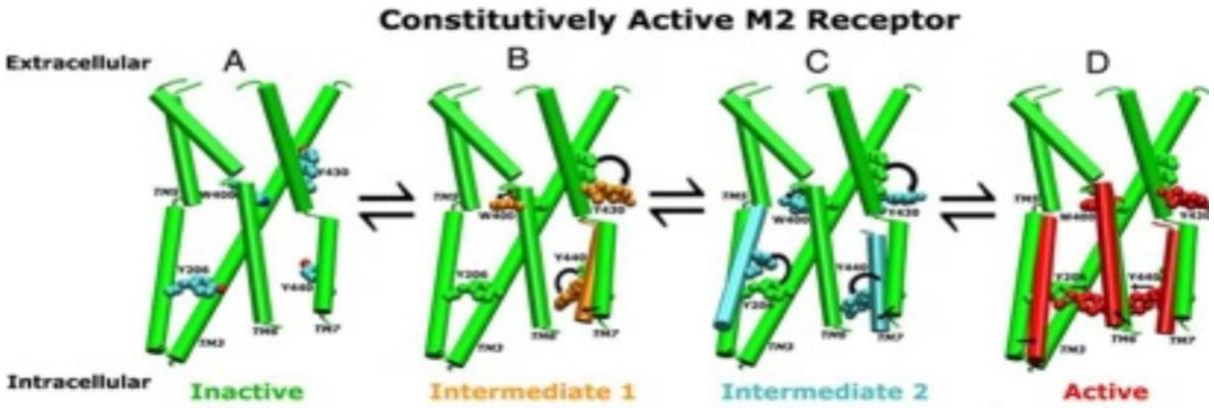
Why do we have these two phases ?

Because actually atropine access does not exist in the plants,in the plants there is levo hyoscyamine , and when we extract this levo hyoscyamine from the plant, 50% of it converted to the dextro form (D) , so atropine is a mixture of dextro and levo hyoscyamine , so metabolism takes place only in the levo form , and the dextro form is excreted unchanged in the urine (the dextro form, levo isomer is hyoscyamine).

3- **Most of the rest appears in the urine as hydrolysis and conjugation products.**
4- **The drug's (atropine) effect on parasympathetic function declines rapidly in all organs except the eye.**
5- **Effects on the iris & ciliary muscle persist for 72 hours,** and if we apply atropine locally to the eye it's affect might last up to 10 days or even two weeks.

MECHANISM OF ACTION

1) **Atropine causes reversible blockade of all muscarinic (M) receptors,** it's a non-selective muscarinic blocker.
2) But **muscarinic receptors are constitutively active** (it means that these receptors occur in different formats) **and muscarinic blockers are inverse agonists that shift the equilibrium to the inactive state of the receptor .**
3) As we can see (in the picture below) , we have the inactive form (A), intermediate 1 (B) , intermediate 2 (C) and then the active form(D) , and there is equilibrium between these forms .
4) What atropine dose is : shifting this equilibrium from the active form towards the inactive form so it's called an inverse agonist.



5) **Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands ,** at small doses they have obvious affect in this without affecting other organs.
6) **Secretion of acid by the gastric parietal cells is the least sensitive** and requires high doses of atropine.
7) **Antimuscarinic agents block exogenous cholinoceptor agonists more effectively than endogenously released** acetylcholine.

Organ System Effects :

❖ Central Nervous System :

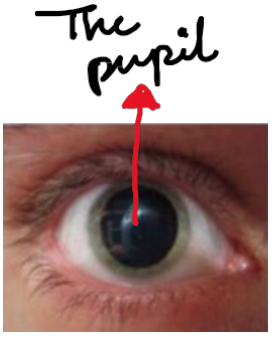
Atropine has minimal stimulant effects on CNS when is given interevent doses , we don't have central side effect or very little central side effect.

But **Scopolamine has more marked central effects, producing drowsiness and amnesia.**

In toxic doses , both scopolamine and atropine, can cause CNS stimulation causing **excitement, agitation, hallucinations**, even convulsions followed by **coma** and death , so they are poisonous .

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.

Vestibular disturbances
(such as motion sickness)



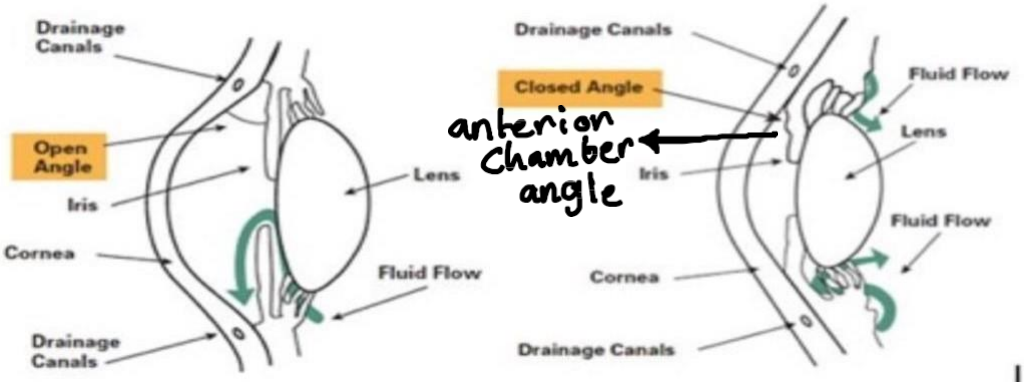
❖ Scopolamine is effective in preventing or reversing these disturbances.

❖ Eye: Atropine and other tertiary antimuscarinics cause an unopposed sympathetic dilator activity & cause mydriasis , the pupil is wide open .

why does mydriasis happen?

Because the iris has two opposite tones , Sympathetic that causes mydriasis and parasympathetic that causes miosis , atropine removes the parasympathetic tone leaving the sympathetic tone alone , so that's why it causes mydriasis.

In the same time the ciliary muscle that has (M3)receptors , atropine cause **Paralysis of the ciliary muscle** and **this cause cycloplegia** and then there is no tension on the lens , and this **results in loss of accommodation and the fully atropinized eye cannot focus for near vision** , and only can see far objects

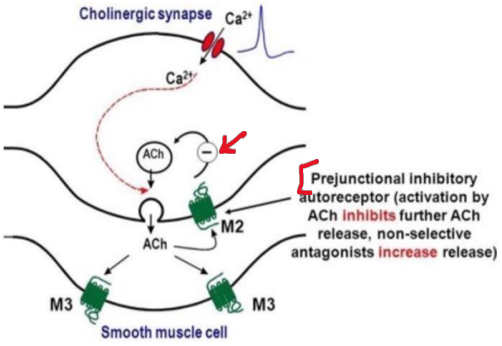


- They can cause acute glaucoma , that causes a rise in the intraocular pressure of the eye and this happens in patients with a narrow anterior chamber angle.
- (Look at the picture above), when the anterior chamber angle is narrow in some patients any mydriasis will pull the eyes towards the upward and downward directions , and this can block the angle and prevent the outflow of the aqueous humour into Schlemm's canal (SC) , this causes the rise in intraocular pressure (glaucoma) , so you have to be very cautious about give atropine or **similar drugs to people with glaucoma or patients with narrow anterior chamber angle.**
- **Antimuscarinic drugs also reduce** lacrimation **(lacrimal secretion) -tears-causing dry or "sandy" eyes.**

❖ Cardiovascular System :

1) **Atropine causes tachycardia by vagal blocking,** by blocking the muscarinic receptors at the end of the vagus nerve in the heart **.**
2) **But lower doses often result in initial bradycardia before the effects of peripheral vagal block is seen.** why?
3) Because we have M1 autoreceptors , which are presynaptic receptors , their function is to inhibit the release of acetylcholine when stimulated , so atropine blocks these M1 autoreceptors , which result in increase acetylcholine release, this increase in the acetylcholine causes this initial bradycardia , but then the postsynaptic M2 receptor are blocked and then we have the tachycardia.
4) **This slowing may be due to block of M1 autoreceptors on vagal postganglionic fibers.**
5) **The ventricles are less affected .**
6) **In toxic concentrations, it can cause intraventricular conduction block due to a local anesthetic action not due to any antimuscarinic effect.**
7) **All blood vessels contain endothelial M3 receptors that mediate vasodilation by causing the release of nitric oxide .**
8) **So these receptors are blocked by antimuscarinic drugs.**
9) **At toxic doses, antimuscarinic agents cause cutaneous vasodilation, especially in the the blush area (as you see in the picture , red cheeks and neck) , and the mechanism is unknown** but there is a theory that because atropine prevent sweating, so the body temperature rises and the body in order to get rid of the excess heat it cause this cutaneous vasodilation so that the body can radiate heat outside.

❖ Respiratory System :



Atropine causes some bronchodilation & reduce bronchial secretion but is not very effective in treating bronchial asthma , so it's effect is limited, why? Because if we look at the picture the stimulation of these M3 receptor causes bronchoconstriction , so atropine blocks the M3 receptor , and this should produce bronchodilation ,but at the same time atropine blocks these presynaptic or prejunctional autoreceptors (the function of these receptors is to inhibit the release of acetylcholine , and these block atropine then more acetylcholine is released and then acetylcholine competing with atropine on this M3 receptor , and this decreases its bronchodilator affect.

--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 :

1) **Complete muscarinic block cannot totally abolish activity of GIT, since local hormones in the enteric nervous system also modulate GI functions.**
2) **However , antimuscarinic drugs have marked effects on salivary secretion causing dry mouth** that is characteristic , even in very low doses of atropine.
3) **Gastric secretion is the least affected ,(blocked less effectively) : the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required .**
4) **Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.**

❖ Pirenzepine and telenzepine

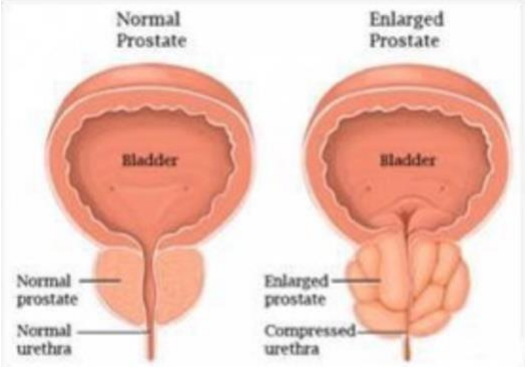
** Both are new drugs and selective **M1 blockers** , the acidity in the stomach increase when M1 receptors are stimulated , so these drug **reduce gastric acid secretion with fewer adverse effects than atropine.**

**** 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 this is bad if we are given other drugs then atropine might interfere with absorption of other drug because of delaying gastric emptying time , **and intestinal transit time is lengthened).**

** **Diarrhea due to overdosage with antimuscarinic agents are readily stopped by atropine , and also diarrhea caused by nonautonomic agents can be temporarily controlled** by atropine and similar drugs drug.

❖ **Genitourinary Tract :**

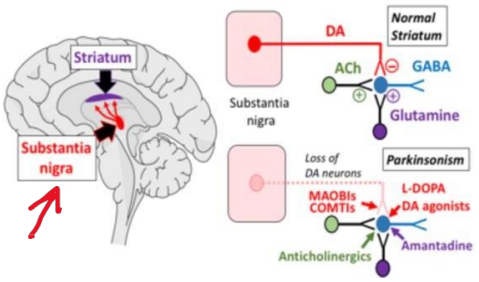


** Atropine **relaxes smooth muscle of the ureters and bladder wall and slows voiding**.
** **Useful in the treatment of spasm induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have prostatic hyperplasia**(as we see in the picture)
, we mustn't give atropine to those who have prostatic hyperplasia because in this case they have urinary retention and they have to go to the hospital in order to empty the bladder.

❖ **Sweet Glands :**

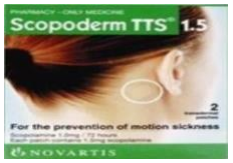
Atropine suppresses sweating.
In adults, body temperature is elevated only with large doses, but in infants and children even ordinary doses may cause "atropine fever" and the whole body becomes red.

Therapeutic Applications :



- **CNS Disorders.**
- We mentioned before that in **Parkinson's Disease** we can use antimuscurinics .
- In Parkinson (we have substantia nigra and dopamine neurones and cholinergic neurons in our brain) , and in pathogen disease there is a degeneration in dopamenargic or loss of dopamine neurones therefore the balance between the acetylcholine and dopamine is disturbed so there is more cholinergic affect than dopamine effect , acetylcholine is excitatory , dopamine is inhibitory.
- The loss of balance causes the muscles to become rigid , and we have the symptoms of Parkinson disease , like tremor , slow movement , etc .
- In the past they used to give atropine in order to block these

acetylcholine receptor , it solve the balance but it's not very effective, the most effective gives now is dopaminergic drugs like levodopa , **but Trihexyphenidyl, benztropine are still useful as adjunctive therapy** with dopamenergic drugs like levodopa. (They are the most effective drug nowadays. **Anticholinergics are reserved for the treatment of tremor that is not adequately controlled with dopaminergic medications**) .



Motion Sickness :

1) **Scopolamine is as effective as any more recently introduced agent.** For people who travel by sea, they are going to be sick, it is **given by injection or by mouth , but the most convenient way give by transdermal patch**.(the most effective and common is the transdermal path).

2) **The patch formulation produces significant blood levels over 48–72 hours.**

3) **Useful doses by any route usually cause significant sedation and dry mouth as side effects .**

Antimuscarinic Drugs Used in Ophthalmology :

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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 = 6 hour	0.5–1

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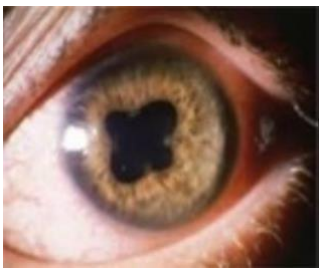
The shortest in duration is Tropicamide .

Ophthalmologic Disorders ::



1. **Antimuscarinic agents, as eye drops or ointment, produce mydriasis and cycloplegia are very helpful in doing a complete examination.**
2. **But shorter-acting drugs are preferred .**
3. **Should never be used for mydriasis unless cycloplegia or prolonged action is required.**
4. If we only need to produce mydriasis in order for the ophthalmologist

to test the fondus of the eye , the patient doesn't have to take anticholinergic drug . Instead , phenylephrine is used.

5. **Phenylephrine, is an Alpha 1stimulant, produces a short mydriasis (without causing accommodation problem - cycloplegia -) , so it's sufficient for funduscopic examination.**
6. Antimuscarinics are also used to prevent synechia.
7. **A synechia : happens when the iris adheres to either the cornea or lens**, and then with mydriasis it breaks the adhesion in this case.
8. **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** (atropine no longer needed in this case, but it used in cardiac surgery to prevent sudden vagal stimulation which can cause death during cardiac surgery).
- **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.**
- **The release of acetylcholine from parasympathetic postganglionic neurons stimulates contraction of airway smooth muscle through M3-receptors and secretion of mucus by the way of M1-muscarinic receptors , so the parasympathetic system has a role asthma.**
- In asthma, reflex pathways are thought to be activated, which increase vagal outflow that leads to cholinergically-mediated bronchoconstriction , so this is part of the problem with the bronchial asthma but as we mentioned before the use of non-selective muscurinic blocker , like atropine was not very useful , but we have a newer drugs like ; **Ipratropium and Tiotropium** .
- **Ipratropium : the synthetic non selective M blocker, not absorbed , they used as an inhalation drug in asthma , so they are delivered to the lung , and aren't absorbed , so they don't have systemic effect.**
- **It is also useful in chronic obstructive pulmonary disease (COPD) a condition that occurs more frequently in older patients, particularly chronic smokers.**
- **That the same in Tiotropium but it has a longer bronchodilator action**

and can be given once daily.

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** , in this case **atropine is used and it can solve this situation**.
- **Rare individuals have hyperactive carotid sinus reflexes** (remember that carotid arteries in the neck have a baroreceptors, so if you have a pressure on them this might activate the baroreceptors reflex and this can increase activity of vagus nerve and causes bradycardia.
- So these people **may experience faintness or even syncope as a result of vagal discharge in response to pressure on the neck , sometimes come from a tight collar.**
- **Such individuals may benefit from the use of atropine or a related antimuscarinic agent to prevent these reflexes.**

Gastrointestinal Disorders :

1. **Antimuscarinic agents can provide some relief in the treatment of common traveler's diarrhea and other mild hypermotility.**
2. **They are often combined with an opioid antidiarrheal drug.**
3. We have a very useful combination which is **atropine with diphenoxylate, the name of this combination is (Lomotil) , it is available in both tablet and liquid form** and can stop any type of diarrhea.

Urinary Disorders:

- **Provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders.**
- **Oxybutynin has more selective for M3 receptors(it's useful with less side effects), it is used to relieve bladder spasm after urologic surgery.**
- **It reduce involuntary voiding in patients with a neurologic disease .**
- **Darifenacin is the same but has greater selectivity for M3 receptors & long half-life and used in adults with urinary incontinence** that can pass urine , and can't control their urination.
- **An alternative treatment for urinary incontinence when they try drugs and they aren't effective is the 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.

1. **Atropine is used to reverse the muscarinic effects, and to treat the CNS effects as well as the peripheral effects of the organophosphate inhibitors.**
2. **Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like parathion and chemical warfare nerve gases.**
3. **1–2 mg of atropine sulfate may be given IV (intravenously) every 5–15 minutes and we continue this injection procedures until we see signs of effect of atropine (dry mouth, reversal of miosis and some tachycardia start to appear) ,** then we know that we reached the best dose , this has to be repeated many times, because when we give the atropine this way and the patient recover, we stop giving atropine **, then when the effect of atropine wears out , the enzyme is phosphorylated , so the drug is given many times, since the acute effects of the anticholinesterases may last 24–48 h.**
4. **1 g of atropine per day may be required for one month for full control of muscarinic excess.**

Adverse Effects :

1. **Treatment with atropine or its congeners induces undesirable effects.**
2. **At higher concentrations, atropine causes block of all parasympathetic functions.**
3. **Poisoned individuals manifest:**

dry mouth, mydriasis, tachycardia, hot and flushed skin, and sense effect such as agitation, and delirium for as long as 1 week (remember that one of the Solanaceae plants is called Mandragora, who eat it become crazy)

4. **Children, especially infants, are very sensitive to the hyperthermic effects of atropine. Deaths have followed doses as small as 2 mg**
5. **Overdoses of atropine are treated symptomatically.**
6. So we use Physostigmine because it is the only reversible acetylcholine inhibitor that can reach the CNS , so it can oppose the action of atropine both centrally and peripherally, but Physostigmine is toxic itself , so **when physostigmine is used, small doses are given slowly intravenously**.
7. So physostigmine is the antidote for atropine poisoning

8. 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).

9. Symptomatic treatment may require temperature control if there is fever with cooling blankets , and seizure control with diazepam.

10. 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.

11. They may cause ganglionic blockade . because quaternary pathogens resemble Ach so they can block the ganglia cause ganglionic blockade with marked orthostatic hypotension.

12. Orthostatic hypotension : happens when you stand up (when you change your position) and your blood pressure goes down .

13. Treatment of the antimuscarinic effects can be carried out with a quaternary cholinesterase inhibitor such as neostigmine.

14. Control of hypotension may require the administration of a sympathomimetic drug such as phenylephrine which is alfa 1 agonist, that causes vasoconstriction and prevent orthostatic hypotension**.**

Contraindications :

a. Glaucoma :

Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow or narrow anterior chambers , so you have to be careful not to give atropine or related drugs to those people**.**

b. Prostatic hyperplasia:

- Very common **in elderly men, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia** , because these people have already difficulty in urination, and giving them atropine or similar drugs that causes also slow or decrease urination , both conditions can cause urinary retention that requires hospital and emergency.
- **Nonselective antimuscarinic agents should never be used to treat acid- peptic disease**, actually there is no need for anticholenergic to treat acid-peptic disease , because excellent and more effective drugs (like , proton pump inhibitors and H2 antagonist) are used right now .
- **Because the antimuscarinic drugs are slow gastric emptying , they may increase symptoms in patients with gastric ulcer.**

THE END.

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