Pharmacology I

Lecture 8

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Cholinergic Antagonist

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists. The most clinically useful of these agents are selective blockers of muscarinic receptors.

They are commonly known as anticholinergic agents (a misnomer, as they antagonize only muscarinic receptors), antimuscarinic agents (more accurate terminology), or parasympatholytics.

A second group of drugs, the ganglionic blockers, shows a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important of the cholinergic antagonists. A third family of compounds, the neuromuscular-blocking agents (mostly nicotinic antagonists), interfere with transmission of efferent impulses to skeletal muscles. These agents are used as skeletal muscle relaxant adjuvants in anesthesia during surgery, intubation, and various orthopedic procedures.

ANTIMUSCARINIC AGENTS

Commonly known as anticholinergic drugs, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors, causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. The anticholinergic drugs are beneficial in a variety of clinical situations.

A. Atropine:

Atropine is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh from binding to those sites (Figure 1a). *Atropine* acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days.

Neuroeffector organs have varying sensitivity to *atropine*. The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva (Figure 1b).

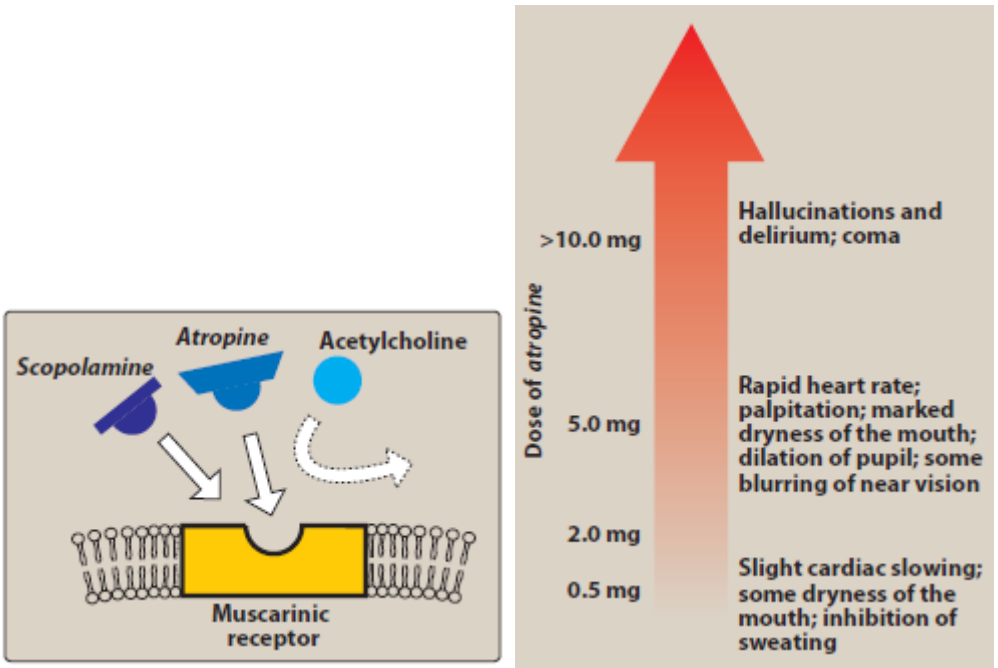

Figure 1: A. Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor. B. Dose-dependent effects of *atropine.*

1. Actions:

a. Eye: *Atropine* blocks muscarinic activity in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.

b. Gastrointestinal (GI): *Atropine* can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* are probably the most potent antispasmodic drugs available. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, *atropine* is not effective for the treatment of peptic ulcer.

Doses of *atropine* that reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with *atropine*.

c. Cardiovascular: *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 1b). At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of the M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of *atropine* cause a progressive increase in heart rate by blocking the M_2 receptors on the sinoatrial node.

d. Secretions: *Atropine* blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are similarly affected.

Therapeutic uses:

a. Ophthalmic: Topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. Shorter-acting antimuscarinics (*cyclopentolate* and *tropicamide*) have largely replaced *atropine* due to prolonged mydriasis observed with *atropine* (7 to 14 days vs. 6 to 24 hours with other agents).

b. Antispasmodic: *Atropine* is used as an antispasmodic agent to relax the GI tract.

c. Cardiovascular: The drug is used to treat bradycardia of varying etiologies.

d. Antisecretory: *Atropine* is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

e. Antidote for cholinergic agonists: *Atropine* is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as *physostigmine*, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of *atropine* may be required over a long period of time to counteract the poisons. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

3. Pharmacokinetics: *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

4. Adverse effects: Depending on the dose, *atropine* may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity.

B. Scopolamine

Scopolamine, another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamine* has greater action on the CNS (unlike *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action as compared to *atropine*.

1. Actions: *Scopolamine* is one of the most effective anti–motion sickness drugs available. It also has the unusual effect of blocking short-term memory. In contrast to *atropine*, *scopolamine* produces sedation, but at higher doses, it can produce excitement. *Scopolamine* may produce euphoria and is susceptible to abuse.

2. Therapeutic uses: The therapeutic use of *scopolamine* is limited to prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days.

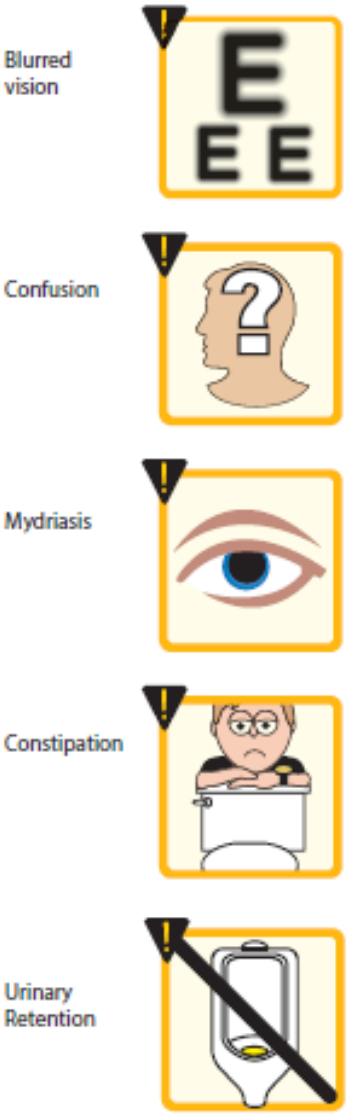

Figure 2: Adverse effects commonly observed with muscarinic antagonists.

C. Ipratropium and tiotropium

Ipratropium and *tiotropium* are quaternary derivatives of *atropine*. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). *Ipratropium* is also used in the acute management of bronchospasm in asthma. Both agents are delivered via inhalation.

Because of their positive charges, these drugs do not enter the systemic circulation or the CNS, isolating their effects to the pulmonary system. *Tiotropium* is administered once daily, a major advantage over *ipratropium*, which requires dosing up to four times daily.

D. Tropicamide and cyclopentolate

These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*. *Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

E. Benztropine and trihexyphenidyl

Benztropine and *trihexyphenidyl* are useful as adjuncts with other antiparkinsonian agents to treat Parkinson's disease and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

***F. Oxybutynin* and other antimuscarinic agents for overactive bladder**

- *Oxybutynin , darifenacin , fesoterodine, solifenacin, tolterodine,* and *trospium* are synthetic *atropine-like* drugs with antimuscarinic actions.
- Act by competitively blocking muscarinic (M3) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced.
- These agents are used for management of overactive bladder and urinary incontinence.
- Antimuscarinic actions at M3 receptors in the Gl tract, salivary glands, CNS, and eye may cause adverse effects.
- *Darifenacin* and *solifenacin* are relatively more selective M3 muscarinic receptor antagonists;
- *Oxybutynin* is also used in patients with neurogenic bladder
- Rospium is a quaternary compound that minimally crosses the blood-brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia

GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. The responses of the nondepolarizing blockers are complex and mostly unpredictable. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

Nicotine

A component of cigarette smoke, *nicotine*, is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, *nicotine* depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitters, due to effects on both sympathetic and parasympathetic ganglia. The overall response of a physiologic system is a summation of the stimulatory and inhibitory effects of *nicotine*. These include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.