Autonomic Pharmacology: Cholinergic Antagonists

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Classification of Anticholinergics

Antimuscarinics

- Tertiary amines: e.g. atropine
- Quarternery amines: e.g. propantheline
- M_1 selectives: e.g pirenzepine
- M_3 selectives: e.g oxybutynin

Ganglion blockers: e.g hexamethonium

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Basic Pharmacology of Antimuscarinics

- Naturally occurring compounds with antimuscarinic effects have been known and used for millennia as medicines, poisons, and cosmetics.
- Atropine is the prototype of these drugs. Many similar plant alkaloids are known, and hundreds of synthetic antimuscarinic compounds have been prepared.

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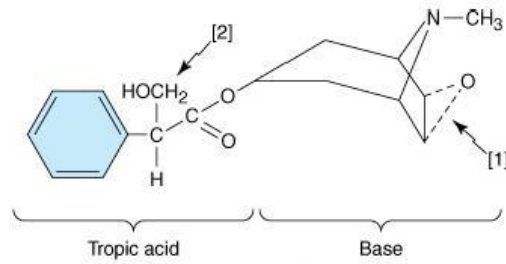
Atropine



The structure of atropine (oxygen at *[1]* is missing) or scopolamine (oxygen present). In homatropine, the hydroxymethyl at *[2]* is replaced by a hydroxyl group, and the oxygen at *[1]* is absent.

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Atropine

- Atropine and its naturally occurring congeners are tertiary amine alkaloid esters of tropic acid.
- Atropine (hyoscyamine) is found in the plant *Atropa belladonna*. Scopolamine (hyoscine) occurs in *Hyoscyamus niger* as the *l*(–) stereoisomer.
- Naturally occurring atropine is *l*(–)-hyoscyamine, but the compound readily racemizes, so the commercial material is racemic *d,l*-hyoscyamine.
- The *l*(–) isomers of both alkaloids are at least 100 times more potent than the *d*(+) isomers.

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Tertiary versus quaternary amines

- The tertiary antimuscarinics are often used for their effects on the eye or the central nervous system.
- Many antihistaminic, antipsychotic, and antidepressant drugs have similar structures and, predictably, significant antimuscarinic effects.
- Quaternary amine antimuscarinic agents have been developed to produce more peripheral effects with reduced central nervous system effects.

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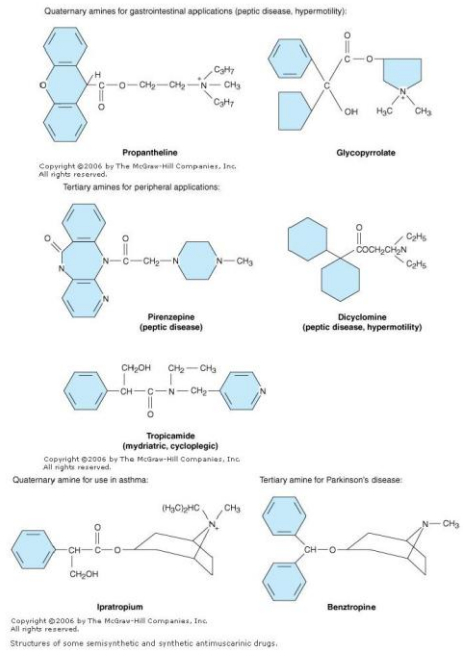

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Quaternary amines

- Anisotropine
- Clidinium
- Glycopyrrolate
- Isopropamide
- Mepenzolate
- Methantheline
- Methscopolamine
- Oxyphenonium
- Propantheline
- Tridihexethyl
- Trospium

Tertiary amines

- Atropine
- Darifenacin
- Dicyclomine
- Oxybutynin
- Oxyphencyclimine
- Propiverine
- Scopolamine
- Solifenacin
- Tolterodine

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Effects of Antimuscarinics

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Eye

- The pupillary constrictor muscle depends on muscarinic cholinoceptor activation which is blocked by topical atropine and results in unopposed sympathetic dilator activity and mydriasis.
- Antimuscarinic drugs weaken contraction of the ciliary muscle, or **cycloplegia** which results in loss of the ability to accommodate.
- Antimuscarinic drugs reduce lacrimal secretion. Patients occasionally complain of dry or "sandy" eyes when receiving large doses of antimuscarinic drugs.

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Antimuscarinic Drugs Used in Ophthalmology

- Atropine
- Scopolamine
- Homatropine
- Cyclopentolate
- Tropicamide

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Heart (1/2)

- The sinoatrial node is very sensitive to muscarinic receptor blockade. Moderate to high therapeutic doses of atropine cause tachycardia in the innervated and spontaneously beating heart by blockade of vagal slowing.
- However, lower doses often result in initial bradycardia before the effects of peripheral vagal block become manifest.
- The same mechanisms operate in the atrioventricular node; in the presence of high vagal tone, atropine can significantly reduce the PR interval of the electrocardiogram by blocking muscarinic receptors in the atrioventricular node.

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Heart (2/2)

- Muscarinic effects on atrial muscle are similarly blocked, but these effects are of no clinical significance except in atrial flutter and fibrillation.
- The ventricles are less affected by antimuscarinic drugs at therapeutic levels because of a lesser degree of muscarinic control.
- In toxic concentrations, the drugs can cause intraventricular conduction block that has been attributed to a local anesthetic action.

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Vessels

- Most blood vessels receive no direct innervation from the parasympathetic system. However, parasympathetic nerve stimulation dilates coronary arteries, and sympathetic cholinergic nerves cause vasodilation in the skeletal muscle vascular bed.
- Atropine can block this vasodilation. Furthermore, almost all vessels contain endothelial muscarinic receptors that mediate vasodilation that are readily blocked by antimuscarinic drugs.
- The net cardiovascular effects of atropine in patients with normal hemodynamics are not dramatic: tachycardia may occur, but there is little effect on blood pressure. However, the cardiovascular effects of administered direct-acting muscarinic agonists are easily prevented.

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Respiratory System

- Both smooth muscle and secretory glands of the airway receive vagal innervation and contain muscarinic receptors. Even in normal individuals, administration of atropine can cause some bronchodilation and reduce secretion. The effect is more significant in patients with airway disease, although the antimuscarinic drugs are not as useful as the β-adrenoceptor stimulants in the treatment of asthma.
- The effectiveness of unselective antimuscarinic drugs in treating chronic obstructive pulmonary disease (COPD) is limited because block of autoinhibitory M_2 receptors on postganglionic parasympathetic nerves can oppose the bronchodilation caused by block of M_3 receptors on airway smooth muscle.

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Gastrointestinal Tract

- Blockade of muscarinic receptors has dramatic effects on motility and some of the secretory functions of the gut.
- However, even complete muscarinic block cannot totally abolish activity in this organ system since local hormones and noncholinergic neurons in the enteric nervous system also modulate gastrointestinal function.
- Antimuscarinic drugs have marked effects on salivary secretion; dry mouth occurs frequently in patients taking antimuscarinic drugs for Parkinson's disease or urinary conditions.
- Gastric secretion is blocked less effectively.

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Genitourinary Tract

- The antimuscarinic action of atropine and its analogs relaxes smooth muscle of the ureters and bladder wall and slows voiding.
- This action is 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.

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Sweat Glands

- Atropine suppresses thermoregulatory sweating. Sympathetic cholinergic fibers innervate eccrine sweat glands, and their muscarinic receptors are readily accessible to antimuscarinic drugs.
- In adults, body temperature is elevated by this effect only if large doses are administered, but in infants and children even ordinary doses may cause "atropine fever."

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Indications of Cholinergic Antagonists

- AV blockage (due to parasympathetic stimulation)
- Smooth muscle relaxation
- Intoxications (cholinergic agonist or acetylcholine esterase inhibitor)
- *Enuresis nocturna*
- Hypermotility and spasm in gastrointestinal system
- Iridocyclitis, keratis, uveitis
- Promoting mydriasis (e.g. for eye test)
- Neurogenic bladder, hyperactive bladder
- For reducing the side effects of neuroleptic drugs
- Parkinson's disease
- Peptic ulcer
- Preanesthetic medication
- Stress incontinence
- Motion sickness

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General Contraindications of Cholinergic Antagonists

- Achalasia
- Disease causing fever
- Narrow angle glaucoma
- Gastrointestinal system atonia
- Ileus
- Pyloric stenosis
- Prostate hypertrophy

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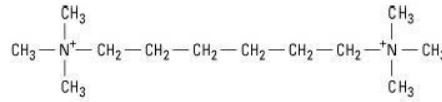
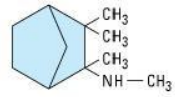
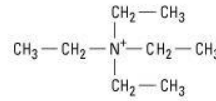
Ganglione Blockers



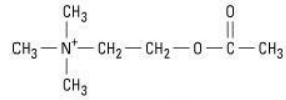
Hexamethonium



Mecamylamine



Tetraethylammonium



Acetylcholine

Some ganglion-blocking drugs. Acetylcholine is shown for reference.

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Ganglione Blockers

- These agents competitively block the action of acetylcholine and similar agonists at nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.
- Some members of the group also block the ion channel that is gated by the nicotinic cholinoceptor.
- The ganglion-blocking drugs are important and used in pharmacologic and physiologic research because they can block all autonomic outflow. However, their lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use.

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Clinical Applications & Toxicity

- Use of the ganglion blockers is infrequent because more selective autonomic blocking agents are available.
- Mecamylamine is being studied for possible use in reducing nicotine craving in patients attempting to quit smoking and for some other central indications.
- Trimethaphan is occasionally used in the treatment of hypertensive emergencies and dissecting aortic aneurysm; to produce controlled hypotension, which can be of value in neurosurgery to reduce bleeding in the operative field; and in patients undergoing electroconvulsive therapy.
- The toxicity of the ganglion-blocking drugs is limited to the autonomic effects. For most patients, these effects are intolerable except for acute use.

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PREPARATIONS AVAILABLE

ANTIMUSCARINIC ANTICHOLINERGIC DRUGS*

Atropine (generic)
Oral: 0.4, 0.6 mg tablets
Parenteral: 0.05, 0.1, 0.4, 0.5, 1 mg/mL for injection; Atropen: 0.25, 0.5, 2 mg pen injectors
Ophthalmic (generic, Isopto Atropine): 0.5, 1, 2% drops; 0.5, 1% ointments

Belladonna alkaloids, extract or tincture (generic)
Oral: 0.27–0.33 mg/mL liquid

Clidinium (generic, Quarzan, others)
Oral: 2.5, 5 mg capsules

Cyclopentolate (generic, Cyclogyl, others)
Ophthalmic: 0.5, 1, 2% solution

Darifenacin (Enablex)
Oral: 7.5, 15 mg tablets (extended release)

Dicyclomine (generic, Bentyl, others)
Oral: 10, 20 mg capsules; 20 mg tablets; 10 mg/5 mL syrup
Parenteral: 10 mg/mL for intramuscular injection

Fesoterodine (Toviaz)
Oral: 4, 8 mg extended-release tablets

Flavoxate (Urispas)
Oral: 100 mg tablets

Glycopyrrolate (generic, Robinul)
Oral: 1, 2 mg tablets
Parenteral: 0.2 mg/mL for injection

Homatropine (generic, Isopto Homatropine, others)
Ophthalmic: 2, 5% solution

l-Hyoscyamine (Anaspaz, Cystospaz-M, Levsin, others)
Oral: 0.125, 0.25 mg tablets; 0.375, 0.75 mg timed-release capsules; 0.125 mg/5 mL oral elixir and solution
Parenteral: 0.5 mg/mL for injection

Ipratropium (generic, Atrovent)
Aerosol: 200 dose metered-dose inhaler (0.17 mg/dose)
Solution for nebulizer: 0.02%
Nasal spray: 0.03, 0.06%

Mepenzolate (Cantil)
Oral: 25 mg tablets

Methantheline (Banthine)
Oral: 50 mg tablets

Methscopolamine (generic, Pamine)
Oral: 2.5, 5 mg tablets

Oxybutynin (generic, Ditropan)
Oral: 5 mg tablets; 5, 10 mg extended-release tablets; patch (3.9 mg/day); 5 mg/5 mL syrup
Topical: 10% gel

Propantheline (generic, Pro-Banthine, others)
Oral: 7.5, 15 mg tablets

Scopolamine (generic)
Oral: 0.4 mg tablets
Parenteral: 0.4 mg/mL for injection
Ophthalmic (Isopto Hyoscine): 0.25% solution
Transdermal (Transderm Scop): 1.5 mg (delivers 0.5 mg/24 h)patch; extended-release patch (delivers 0.33 mg/24 h)

Solifenacin (Vesicare)
Oral: 5, 10 mg tablets

Tiotropium (Spiriva)
Aerosol: 18 mcg tablet for inhaler

Tolterodine (Detrol)
Oral: 1, 2 mg tablets; 2, 4 mg extended-release capsules

Tridihexethyl (Pathilon)
Oral: 25 mg tablets

Tropicamide (generic, Mydriacyl Ophthalmic, others)
Ophthalmic: 0.5, 1% drops

Trospium (Spasmex, Sanctura)
Oral: 20 mg tablets; 60 mg extended-release capsule
Suppository: 0.75, 1.0 mg
Parenteral: 0.6 mg/mL

GANGLION BLOCKERS

Mecamylamine (Inversine)
Oral: 2.5, 10 mg tablets

Trimethaphan (Arfonad)
Parenteral: 50 mg/mL

CHOLINESTERASE REGENERATOR

Pralidoxime (generic, Protopam)
Parenteral: 1 g vial with 20 mL diluent for IV administration; 600 mg in 2 mL autoinjector

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Study questions

1. Comment on dose dependent effects of systemically applied atropine.
2. Compare the effects of atropine and scopolamine.
3. Make a table showing the indications of available preparations.

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Thank you...

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