Anticholinergic Drugs — Definition and Classification

The anticholinergic drugs are substances that block the effect of acetylcholine and some cholinergic agents on their receptors in cells of the nervous system. These agents are also called cholinergic antagonists or parasympatholytics. These medications are classified based on the type of receptor blocked: antimuscarinics, antinicotinics (divided into neuromuscular blocking agents and ganglionic blockers), and cholinesterase regenerators. The majority of anticholinergic drugs are antimuscarinic agents, which have been used in a variety of clinical situations, for example, to produce bronchodilatation, mydriasis, sedation, and amnesia.

Definition of Anticholinergic Drugs

Anticholinergic drugs or cholinergic antagonists are drugs that bind to cholinergic receptors (muscarinic and nicotinic) to prevent the effect of acetylcholine and other cholinergic agonists. These drugs are also called parasympatholytics. Anticholinergic drugs are classified into 3 groups: antimuscarinic drugs, antinicotinic drugs (neuromuscular blockers and ganglionic blockers), and cholinesterase regenerators.

Anticholinergics are classified according to the receptors that are affected:

Antimuscarinic agents
Antimuscarinic agents operate on the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors, or mAChRs, are acetylcholine receptors. Five subtypes of muscarinic receptors have been determined, named M1 through M5. M1, M3, and M5 receptors are coupled with Gq proteins, while M2 and M4 receptors are coupled with Gi/o proteins.

The receptors form G protein-receptor complexes in the cell membranes of certain neurons and other cells. They play several roles, including acting as the main end-receptor stimulated by acetylcholine released from postganglionic fibers in the parasympathetic nervous system. The majority of anticholinergic drugs are antimuscarinics.

**Antinicotinic agents**

Antinicotinic agents operate on the nicotinic acetylcholine receptors. The majority of these are non-depolarizing skeletal muscle relaxants for surgical use that are structurally related to curare. Several of these drugs are depolarizing agents.

**Antimuscarinic drugs**

- Atropine
- Benztropine

- Cyclopentolate
- Darifenacin
- Fesoterodine
- Ipratropium
- Oxybutynin
- Scopolamine
- Solifenacin
- Tiotropium
- Tolterodine
- Trihexyphenidyl
- Tropicamide

[Image: "Chemical structure of a benztropine analog" by Ed (Edgar181) - Own work. License: Public Domain]
Trospium chloride

These are further classified into:

**M1 selective blockers:** Pirenzepine and telenzepine

**Non-selective blockers:** Atropine

Pharmacokinetics of antimuscarinic drugs

- Atropine is a tertiary amine belladonna alkaloid. It is relatively lipid-soluble and readily crosses membrane barriers. Atropine has a high affinity for muscarinic receptors.
- Eliminated partially by metabolism in the liver and partially unchanged in the urine.
- Half-life is 2–4 hours and the duration of action is 4–8 hours. However, ocular retention is more than 72 hours.

Mechanism of action of antimuscarinic drugs

Muscarinic blocking agents bind competitively and prevent acetylcholine from binding to the sites. However, their antagonistic actions can be reduced by increasing the concentration of the muscarinic agonists.

Always remember: Their action on organ systems will always be opposite to the action of cholinergic agonists.

Effect of antimuscarinic drugs on organ systems

Central nervous system (CNS): Antimuscarinic agents produce sedation, amnesia, delirium, anti-motion sickness, and antiparkinson effects.

Scopolamine has a greater and longer duration of action on the CNS compared to atropine. It is the most effective anti-motion sickness drug available. It also has an unusual effect of blocking short-term memory. It produces sedation at a low dose and excitement at a high dose. It produces euphoria and is susceptible to abuse.

For motion sickness, it is available as a topical patch that is effective for 3 days and can be used as prophylactic medication. It is also used for postoperative nausea and vomiting.

Benztropine, biperiden, and trihexyphenidyl are used in parkinsonism as adjuncts when patients become unresponsive to levodopa.

Eye: Mechanism of action is by blockage of M3 receptors.
Antimuscarinic drugs administered topically to the eye cause mydriasis, cycloplegia, and loss of accommodation. The drugs are absorbed from the conjunctival sac into the eye.

The duration of action varies for each drug: atropine (> 72 hours), homatropine (24 hours), cyclopentolate (2–12 hours) and tropicamide (0.5–4 hours).

Important: Among the muscarinic receptor blockers, tropicamide has a shorter duration of action.

Bronchi: Mechanism of action is by blockage of the M3 receptors, thus promoting bronchodilation.

Atropine is used parenterally to decrease secretions during general anesthesia.

Ipratropium is used by inhalation to promote bronchodilation in asthma and COPD. As it is poorly absorbed and rapidly metabolized, antimuscarinic effects outside the lung, like tachycardia and arrhythmias, are less likely. It is administered 4 times daily.

Tiotropium, a newer drug, is administered once daily.

Gut: Mechanism of action is by blockade of the M1 and M3 receptors.

Atropine and scopolamine act as the most potent antispasmodic agents by decreasing gastric motility. The dose of atropine used for antispasmodic action also decreases saliva secretion, ocular accommodation, and urination. Because of these effects, compliance with atropine is decreased.

Antimuscarinic drugs like atropine, methscopolamine, and propantheline can be used in peptic ulcer because of their effect on blocking acid secretion; however, they are not used currently because they are inferior to H2 blockers and proton pump inhibitors for this indication.

Bladder: oxybutynin and tolterodine are used to reduce urgency in mild cystitis and to reduce bladder spasms after urologic surgery.

Tolterodine, darifenacin, solifenacin, and fesoterodine are used for the treatment of stress incontinence.
Oxybutynin is available as a transdermal patch, which is better tolerated due to fewer side effects.

Cardiovascular: A low dose of atropine blocks M1 receptors on presynaptic neurons and decreases the heart rate. A high dose of atropine blocks M2 receptors at the sinoatrial (SA) node and increases the heart rate.

Secretions: Atropine blocks muscarinic receptors in the salivary glands producing dryness of the mouth (xerostomia). Sweat glands and lacrimal glands are similarly affected, resulting in a decrease in secretions.

Therapeutic uses of antimuscarinic drugs

Atropine is used as an antispasmodic agent; to treat bradycardia; as an antisecretory agent to block secretions in the upper and lower respiratory tract prior to surgery, and to treat organophosphorus poisoning and overdose of anticholinesterases such as physostigmine.

Scopolamine is used for motion sickness.

Adverse effects of antimuscarinic drugs

Adverse effects or toxicity of antimuscarinic agents can be described with the mnemonics “dry as a bone, red as a beet, mad as a hatter.”

Atropine causes inhibition of secretion of the sweat glands, causing hyperthermia in children and the elderly, which is called atropine fever. Because of inhibition of sweating, salivation, and lacrimation, it is termed “dry as a bone.”

Large doses of atropine cause tachycardia and arrhythmias and also, a block in intraventricular conduction, which is difficult to treat.

In elderly patients, atropine causes angle-closure glaucoma; it can also cause urinary retention in men with prostatic hyperplasia.

Constipation and blurred vision are common adverse effects of antimuscarinic agents in all age groups.

CNS toxicity from antimuscarinic agents includes sedation, amnesia, delirium, hallucination (‘mad as a hatter’), and convulsions.

Dilatation of cutaneous vessels of the arms, head, neck, and trunk is seen in overdoses of atropine, which is called atropine flush (‘red as a beet’).
Atropine at a dose of 0.5 mg causes bradycardia, dryness of the mouth, and inhibition of sweating. At 5 mg, it causes tachycardia, palpitations, marked dryness of the mouth, mydriasis, and blurring of vision. At a dose > 10 mg, it causes hallucinations, delirium, and coma.

**Treatment of toxicity**

Treatment of toxicity is usually symptomatic.

Important: Severe tachycardia requires cutaneous administration of small doses of physostigmine.

Hyperthermia is managed with cooling blankets or evaporative cooling.

**Contraindications of antimuscarinic drugs**

Antimuscarinic agents should be used cautiously in infants because of the danger of hyperthermia.

Antimuscarinic drugs are contraindicated in individuals with closed-angle glaucoma and in men with prostatic hyperplasia.

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Image: “Photograph showing acute angle-closure glaucoma, which is a sudden elevation in intraocular pressure that occurs when the iris blocks the eye’s drainage channel—the trabecular meshwork.” by Jonathan Trobe, M.D. – The Eyes Have It. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0)

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**Antinicotinic Drugs**

Antinicotinic drugs are classified into two types:

1. Neuromuscular blocking agents
2. Ganglionic blockers

**Neuromuscular blocking agents**

These are further classified into two classes:

1. **Non-depolarizing Blockers**: Pancuronium, cisatracurium, rocuronium, vecuronium
Depolarizing Blockers: Succinylcholine

These classes of drugs act as antagonists (non-depolarizing type) and agonists (depolarizing type) at the receptors of the end plate of the neuromuscular junction.

At lower doses, they produce complete muscle relaxation, facilitating their use in tracheal intubation during surgery. They also allow fast recovery from anesthesia and decrease postoperative respiratory depression.

**Mechanism of action of non-depolarizing blockers**

These agents are also called competitive blockers. At low doses, these drugs compete with ACh at the receptor without stimulating it, thus preventing depolarization of muscle cell membrane and inhibiting muscular contraction.

This effect can be reversed by administration of cholinesterase inhibitors like neostigmine and edrophonium, which increase the concentration of ACh at neuromuscular junctions, and also by direct electrical stimulation.

At high doses, these drugs block the ion channel at the motor end plate, reducing neuromuscular transmission. This effect cannot be reversed by cholinesterase inhibitors and electrical stimulation.

Susceptibility to the drugs follows in this order: small contracting muscles of the face and eyes are paralyzed first, followed by finger, limb, neck, and trunk muscles and, lastly, the diaphragm. Recovery occurs in the reverse order.

Rocuronium has the most rapid onset of action at 60–120 sec.

**Pharmacokinetics of non-depolarizing blockers**

These drugs are administered via intravenous or intramuscular routes. These agents are not effective when administered orally.

Because of the presence of a quaternary amine in their structure, they are not absorbed through the gut. Also, they do not cross cell membranes and blood-brain barriers.

These drugs are not metabolized and are redistributed. Pancuronium, metocurine, pipecuronium, and tubocurarine are excreted unchanged in the urine and have a duration of action of less than 30 min.

Vecuronium and rocuronium are excreted unchanged in bile and have a duration of action of 10-20 min.

In addition to hepatic metabolism, atracurium is eliminated via another method called Hoffman elimination, which is rapid spontaneous breakdown resulting in the formation of laudanosine. Laudanosine in high concentration causes seizures.

Cisatracurium (a stereoisomer of atracurium) is degraded in the plasma by ester hydrolysis. Dosage adjustment is not necessary for renal failure because its elimination is not dependent on hepatic or renal function. It is one of the most commonly used muscle relaxants in clinical practice.

**Drug interactions of non-depolarizing blockers**

Cholinesterase inhibitors like edrophonium, neostigmine, pyridostigmine, and physostigmine interact with neuromuscular blocking agents and overcome their action.

Halogenated hydrocarbon anesthetics like desflurane sensitize the neuromuscular
junction to these drugs and increase the blocking effect.

Aminoglycoside antibiotics like gentamicin and tobramycin compete with calcium ions and inhibit ACh release, and thus, the effect of the blockade is synergized with pancuronium.

**Calcium channel blockers** also increase the neuromuscular blockade effect.

Elderly patients and patients with myasthenia gravis are sensitive to non-depolarizing drugs, and the dose should be decreased.

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**Mechanism of action of depolarizing agents**

These drugs act by depolarizing the plasma membrane of the muscle fibers. But their action is not reversed by anticholinesterases, and thus, the depolarization of muscle fiber persistently increases. Succinylcholine is a depolarizing muscle relaxant. The process of depolarization occurs in 2 phases.

Phase 1 starts with the opening of sodium channels attached with the nicotinic receptors, resulting in depolarization of the receptor. This causes transient twitching of the muscle.

Phase 2 includes continuous binding of the depolarizing agent to the receptor, which makes it incapable of transmitting impulses. When this continues, gradual repolarization of the sodium channel takes place, thus blocking it and resulting in resistance to depolarization and flaccid paralysis.

Administration of a non-depolarizing neuromuscular blocker prior to succinylcholine reduces the muscle soreness caused by succinylcholine. The duration of action of succinylcholine is short because of hydrolysis by pseudocholinesterase.

**Therapeutic uses of depolarizing agents**

During the induction of anesthesia in endotracheal intubation to prevent aspiration of gastric contents, succinylcholine is used because of its rapid onset of action.

It is also used during electroconvulsive shock treatment.

**Pharmacokinetics of depolarizing agents**

IV injection of succinylcholine results in redistribution of the drug and hydrolysis by pseudocholinesterase in the liver and plasma, resulting in a short duration of action. Continuous infusion of succinylcholine will produce a longer duration of action.
Adverse effects of depolarizing agents

On interaction with inhaled anesthetics, succinylcholine may cause malignant hyperthermia. Increased end-tidal CO$_2$ is the first sign noticed in this condition. Immediate cessation of anesthesia and reversal of paralysis along with cooling and large doses of dantrolene may save the patient’s life.

Muscle pain is the most common postoperative complaint when succinylcholine is administered.

In patients with deficiency of pseudocholinesterase, there will be prolonged apnea due to paralysis of the diaphragm. These patients can’t move or breathe, but they’re fully alert. It’s important to make them aware of the problem and the steps being taken to resolve it. They frequently need to be kept on a mechanical ventilator overnight, at which time tissue cholinesterase will have finally degraded succinylcholine.

In patients with electrolyte imbalance, succinylcholine causes the release of potassium, resulting in prolonged apnea.

Succinylcholine causes potassium outflow from the cells, which can be a dangerous effect in patients with burns and in patients with massive tissue damage, spinal cord injury, peripheral nerve dysfunction, and muscular dystrophy.

Ganglionic blocking agents

Ganglionic blockers act specifically on the nicotinic receptors present in the sympathetic and parasympathetic nervous systems. As these drugs show no selectivity towards the sympathetic and parasympathetic nervous systems, they are used in experimental pharmacology.

Effects of ganglionic blocking drugs

Eye: Ganglionic blockers cause mydriasis and cycloplegia.

GI tract: Reduction of motility and severe constipation.

Genitourinary tract: Impairment of ejaculation and reduced contractility of the bladder.

Heart: Moderate tachycardia and reduction in cardiac output at rest.

Glands: Reduction in salivation, lacrimation, sweating, and gastric secretion.

Blood vessels: Reduction in arterial and venous tone, causing dose-dependent reduction in blood pressure. Orthostatic hypotension is usually marked.

Hexamethonium and mecamylamine were used in the past for the treatment of hypertension but were banned later for the adverse effects.

Trimethaphan is another ganglionic blocker that previously was used intravenously to treat refractory hypertension and to produce controlled hypertension. However, due to its poor lipid solubility, short half-life, and orally inactive nature, it was banned.

Varenicline, mecamylamine, and nicotine in the form of patches are the ganglionic blockers that enter the CNS and are used in smoking cessation.

Adverse effects of ganglionic blockers include postural hypotension, dry mouth, blurred vision, constipation, and severe sexual dysfunction.
Cholinesterase Regenerators

Pralidoxime is a cholinesterase regenerator. It is used to treat organophosphate poisoning (parathion and malathion).

Important: It is only effective before the aging of the complex of ACh and the organophosphate compound.

References


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