PARASYMPATHOMIMETIC AGENTS

Parasympathomimetic" is used specifically to describe an ACh-like effect on effector cells innervated by postganglionic neurons of the parasympathetic nervous system. Based on mechanism of action, drugs that cause parasympathomimetic effects can be divided into two major groups: direct-acting agents, which like ACh activate cholinergic receptors of the effector cells, and cholinesterase inhibitors, which allow endogenous ACh to accumulate and thereby intensify and prolong its action.

DIRECT-ACTING PARASYMPATHOMIMETIC AGENTS

Direct-acting parasympathomimetic agents consist of esters of choline and naturally occurring cholinomimetic alkaloids.

Choline Esters. Choline, a member of the B vitamin group, possesses the characteristic depressor action of a cholinergic drug when injected intravenously in large unphysiologic amounts; however, its potency is multiplied thousands of times when it is esterified with acetic acid to yield ACh.

ACh, although essential for maintenance of body homeostasis, is not used therapeutically for two important reasons. First, it acts simultaneously at various tissue sites and no selective therapeutic response can be achieved. Second, its duration of action is quite brief because it is rapidly inactivated by the cholinesterases. Several derivatives of ACh are more resistant to hydrolysis by cholinesterase and have a somewhat greater selectivity in their sites of action. Of several hundred choline derivatives that have been synthesized, carbachol, bethanechol, and methacholine have proved effective for certain clinical uses.

MECHANISM or ACTION. Pharmacologic effects of ACh and related choline esters are mediated by activation of specific ACh-responsive sites (i.e., cholinergic receptors or cholinoceptors) located on cells innervated by cholinergic nerves and, in some cases, on cells that lack cholinergic innervation. Choline esters act directly on postsynaptic receptors and do not depend upon endogenous ACh for their effects. Based on differential responsiveness to cholinergic agonists and antagonists, two basic types of cholinoceptors have been identified within the peripheral efferent pathways of the mammalian autonomic nervous system

- Muscarinic receptor
- Postganglionic neuron

MUSCARINIC RECEPTOR: Muscarinic receptors are G protein-coupled receptors and mediate their responses by activating a cascade of intracellular pathways Muscarinic responses are slower, may produce excitation or inhibition and involve second messenger systems, rather than the direct opening of an ion channel.. Muscarine is the prototypical muscarinic agonist and derives from the fly agaric mushroom Amanita muscaria.
Muscarinic receptors are found in the parasympathetic nervous system. Muscarinic receptors in smooth muscle regulate cardiac contractions, gut motility and bronchial constriction. Muscarinic receptors in exocrine glands stimulate gastric acid secretion, salivation and lacrimation. Muscarinic receptors also are found in the superior cervical ganglion where they can produce at least two physiologically distinct responses. In addition, muscarinic receptors are found throughout the brain, including the cerebral cortex, the striatum, the hippocampus, thalamus and brainstem.

<table>
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<tr>
<th>Distribution</th>
<th>M₁</th>
<th>M₂</th>
<th>M₃</th>
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<td>AF-DX 116</td>
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<td>Phospholipase Cβ inhibition</td>
<td>Adenylyl cyclase inhibition</td>
<td>Phospholipase Cβ inhibition</td>
<td>Adenylyl cyclase inhibition</td>
<td>Phospholipase Cβ</td>
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**NICOTINIC CHOLINERGIC RECEPTORS**

Nicotinic responses are of fast onset, short duration and excitatory in nature. Nicotinic receptors are found in a variety of tissues, including the autonomic nervous system, the neuromuscular junction and the brain in vertebrates. They also are found in high quantities in the electric organs of various electric eels and rays. The high quantities of receptors in these tissues and the use of neurotoxins from snake venom (e.g., cobra venom) that bind specifically to the nicotinic receptor aided the purification of the receptor protein. Nicotinic receptors at ganglia are different subtypes from those localized to voluntary skeletal muscle.
Receptor | Skeletal muscle | Autonomic ganglion | CNS | CNS
--- | --- | --- | --- | ---
Subunits | α1,β1,δ,γ(ε) | α3,α5,α7,β2,β4 | α3,α4,β2,β4 | α7,α8,α9
α-Bungarotoxin | + | +/- | - | +
Antagonists | α-Bungarotoxin | Hexamethonium | Dihydro-β-erythroidine | α-Bungarotoxin
| | | Mecamylamine | Mecamylamine
Agonists | Epibatidine | Epibatidine | Epibatidine | ABT-418

**STRUCTURE-ACTIVITY RELATIONSHIPS**

ACh is the prototypical cholinergic agent; it acts at all cholinceptor sites and therefore evokes both nicotinic and muscarinic effects. Acetyl-β-methylcholine (methacholine) is identical in structure to ACh except for the substitution of a methyl group on the β-carbon atom of the choline group. This structural change yields a compound that is primarily a muscarinic receptor agonist lacking significant nicotinic effects when given in usual dosages. Further, it is more active on the cardiovascular system than on the GI tract. Duration of action of methacholine is considerably longer than that of ACh because the former drug is hydrolyzed by acetylcholinesterase (AChE) at a much slower rate than is ACh and methacholine is almost totally resistant to breakdown by pseudocholinesterase.

Carbachol and bethanechol each have a carbamyl (NH₂COO-) group substituted for the acetic moiety of ACh, and bethanechol also has a β-methyl group. Both of these agents are almost completely resistant to inactivation by the cholinesterases. Their duration of action is therefore considerably longer than that of ACh. Carbachol is active at both muscarinic and nicotinic receptor sites (therefore it is cholinomimetic and not just parasympathomimetic), whereas bethanechol is primarily a muscarinic agonist. Unlike methacholine, both these drugs are somewhat more active on smooth muscles of the GI tract and urinary bladder than on cardiovascular function. Chemical structures of these choline esters and their related pharmacologic characteristics are shown in following table.

| | Susceptibility to cholinesterase | Muscarinic receptors : Agonistic Properties |
| --- | --- | --- | --- |
| | True | Pseudo | Cardio | Gastro | Urinary | Eye | Nicotinic |
| Choline | | | Vascular | Intestinal | Bladder | |
| Acetylcholine | +++ | +++ | +++ | +++ | + | + | +++ |
| Methacholine | - | _ | +++ | + | + | + | ± |
| Carbachol | - | - | + | +++ | +++ | + | + |
| Bethanechol | - | - | + | +++ | + -f+ | + | - |


**ACETYLCHOLINE.** Although ACh is not used clinically, it is the prototypical cholinergic agonist, and an understanding of its activity is imperative for a comprehension of the pharmacologic effects of other cholinomimetic drugs. Since ACh is a mixed nicotinic-muscarinic agonist, different effects can be produced by administration of this agent, depending upon the relative dominance of muscarinic (parasympathomimetic) or nicotinic actions. These effects can be differentiated by use of small and large doses of ACh and by using selective cholinergic blocking drugs.

**Cardiovascular Effects of Small Doses** of Intravenous (IV) administration of small amounts of ACh (5-10 mg/kg) produces a brief but rapid fall in systolic and diastolic blood pressures. This is due to a decrease in peripheral resistance resulting from dilatation of blood vessels.

Somewhat larger doses of ACh 10-30 (mg/kg) produce pronounced muscarinic effects; therefore, a pronounced decrease in peripheral resistance and blood pressure is produced. In addition to the hypotension response, a slowing of the heart rate occurs after administration of ACh. In the atria, cholinergic activation slows conduction velocity but shortens action potential duration and the effective refractory period. These actions reinforce atrial dysrythmias and lead to atrial flutter and fibrillation.

**Smooth Muscle:** GI motility and secretions are enhanced by ACh in a manner identical to that seen upon, stimulation of the parasympathetic innervation to the alimentary tract. ACh stimulates smooth muscle of the urinary bladder and uterus to contract. Bronchiolar smooth muscle is also contracted by ACh, resulting in decreased diameter of airways. The smooth muscle effects of ACh are blocked by atropine and therefore are due to muscarinic receptor activation.

**Central Nervous System:** Because of its highly charged quaternary nitrogen group, Ach poorly penetrates cell membranes and the blood-brain barrier. Thus CNS effects are not observed when usual dosages are administered.

**Adrenal Medulla:** The adrenal medulla is functionally analogous to autonomic ganglia, and nicotinic receptors of adrenal medullary chromaffin cells are innervated by typical preganglionic cholinergic fibers. These receptors are stimulated by ACh to cause release of epinephrine and norepinephrine from chromaffin cells into the circulation. This effect contributes to the overall nicotinic-mediated sympathomimetic effect evoked by large doses of ACh in the presence of muscarinic blockade.

**Skeletal Muscle:** Intra-arterial injection of significant quantities of ACh will produce skeletal muscle fasciculations caused by penetration of some of the agent to motor end-plates and resulting activation of nicotinic receptors of skeletal muscle cells.

**METHACHOLINE, CARBACHOL, AND BETHANECHOL.**

Methacholine (acetyl-β-methylcholine) is a synthetic choline ester used occasionally in human therapeutics but infrequently employed in veterinary medicine. Methacholine causes muscarinic effects on cardiovascular function similar to those produced by ACh, but it is considerably less active on the GI system and has few agonist properties at nicotinic receptors.
Carbachol is an extremely potent choline ester that is active at both muscarinic and nicotinic receptors and therefore causes pharmacologic effects similar to changes evoked by ACh. These are particularly prominent on the nicotinic receptors of autonomic ganglia; however, this drug is also very potent at muscarinic sites. Differences between the parasympathomimetic actions of these choline esters are primarily quantitative and vary principally in relative selectivity for one organ system or another.

Bethanechol (Urecholine, carbamylmethylcholine) is somewhat similar to methacholine and carbachol in scope of pharmacologic activity. Unlike carbachol, however, it is primarily a muscarinic agonist and has little stimulant effects on nicotinic receptors.

**PHARMACOLOGIC EFFECTS**

**Cardiovascular Effects.** Methacholine is more active on the cardiovascular system than on the GI or urinary tracts. The opposite selectivity is seen with carbachol and bethanechol. IV administration of methacholine, like ACh, produces a depressor response and slowing of heart rate. Cardiac rhythm is altered by methacholine, and the AV node is particularly sensitive to this agent. Conduction velocity through the AV node is decreased. Carbachol evokes blood pressure changes similar to those seen with methacholine except relatively less pronounced, whereas bethanechol is considerably less active on cardiovascular function.

**GI Tract.** Carbachol and bethanechol are relatively more active on the GI and urinary tracts than on the cardiovascular system. Carbachol is a potent GI stimulant. It evokes profuse salivation and an increase in peristaltic movements of the gut resulting in increased fluidity of feces and defecation. These responses are due to activation of muscarinic receptors.

**Other Smooth Muscle.** Carbachol should not be used during pregnancy, because abortion or uterine rupture might result because of contraction. Carbachol causes contraction of bronchiolar smooth muscle, resulting in a decreased airway. The urinary bladder is contracted by carbachol and bethanechol, and frequent urination results. Effects of carbachol and bethanechol on these as on other smooth muscles are muscarinic and blocked by atropine.

**Skeletal Muscle.** Carbachol does not discernibly affect skeletal muscle when usual dosages are employed.

**Sweating.** Profuse sweating in the horse is evoked by carbachol. It is not known if this is due to a direct effect on sweat glands, a ganglionic stimulating effect, an increase in circulating catecholamines, or local release of catecholamines from adrenergic neurons. Because sweat gland mechanisms in the horse seem to be 3-adrenergic (Bijman and Quinton 1984), either of the latter two mechanisms could be involved.

**Other Effects.** Carbachol, like ACh, is a mixed nico-tinic-muscarinic agonist. It therefore has a potent stimulating effect on autonomic ganglia and the chromaffin cells of the adrenal medulla. Nicotinic effects of carbachol on autonomic ganglia can be demonstrated by the hypertensive response obtained with large doses after the postganglionic muscarinic receptors have been blocked with atropine.
CLINICAL USES. Methacholine and bethanechol are not used frequently in clinical veterinary medicine. Methacholine has been used in humans and animals to produce peripheral vasodilation in treating different vascular disorders such as Raynaud's disease and ergot poisoning respectively. Carbachol is a potent drug, and care should be taken to avoid overstimulation of the GI tract and uterus during its clinical use. It has been used for treatment of colic and impactions of the intestinal tract; however, its use in such cases should be closely monitored. If excessive peristaltic movements are induced in a patient suffering from intestinal obstruction, rupture or intussusception may occur. Repeated small subcutaneous (SC) doses of 1-2 mg carbachol at 30 to 60 minute intervals have been used in treating colic in mature horses after treatment with oils and saline cathartics had been instituted. When administered during the middle of farrowing, carbachol (2 mg subcutaneously) has been reported to decrease the incidence of stillbirths in litters from sows and gilts by increasing uterine contractions. Carbachol should not be given by IV or, probably, intramuscular (IM) injection because of its potency. It is given by the SC route; however, the dosage is still critical. Fatalities have occurred in human patients after IM injection of carbachol.

NATURALLY OCCURRING CHOLINOMIRAETIC ALKALOIDS

Pilocarpine, muscarine, and arecoline are plant alkaloids that exert parasympathomimetic effects with minimal activity at nicotinic sites. Although all three agents are used in research, only pilocarpine has been used frequently in clinical medicine.

Pilocarpine nitrate is the water-soluble salt of the alkaloid pilocarpine, obtained from leaves of the Brazilian shrubs *Pilocarpus jaborandi* and *P. microphyilus*. Arecoline is an alkaloid found in the betel nut, the seed of the betel palm (*Areca catechu*). Muscarine is found in the poisonous mushrooms *Amanita muscaria*.

PHARMACOLOGIC MECHANISMS AND EFFECTS. Pilocarpine, arecoline, and muscarine are rather selective parasympathomimetic agents; i.e., their cholinomimetic activity is exerted primarily at muscarinic sites with minimal nicotinic effects. These cholinomimetic alkaloids evoke their parasympathomimetic effects by direct stimulation of the muscarinic receptors of cells innervated by postganglionic cholinergic nerves. They do not inhibit cholinesterase. Also, because their effects are produced in chronically denervated tissue, they are not dependent upon release of endogenous ACh.

Pilocarpine is particularly effective in stimulating flow of secretions from exocrine glands, including salivary, mucous, gastric, and digestive pancreatic secretions. As with ACh it causes contraction of GI smooth muscle, thereby increasing smooth muscle tone and peristaltic activity. Pilocarpine has a potent constrictor effect on the pupil.

Arecoline activates muscarinic receptors of cholinergically innervated effector cells of glands, smooth muscles, and myocardium and therefore produces the usual parasympathomimetic effects. It is similar to pilocarpine in scope of activity but is considerably
more potent. Arecoline depresses heart rate and blood pressure and may produce dyspnea by constricting the bronchioles. Dyspnea generally is not marked except in cases where the dose is toxic or the animal has previously been affected with a respiratory ailment such as acute pulmonary emphysema. Arecoline stimulates secretion of the glands of the digestive tract and increases peristaltic movements of the gut.

**CLINICAL USES.** Pupillary constriction (miosis) occurs when pilocarpine is administered systemically or applied topically to the eye. Clinically, solutions of 0.5-2% are used for instillation into the conjunctiva sac for treatment of glaucoma. Pilocarpine stimulates the sphincter muscle of the iris and the ciliary muscle of the lens, causing pupillary constriction and spasm of accommodation. Pilocarpine is also used alternately with mydriatics to prevent synechiation, but it is contraindicated in patients with iridocyclitis.

**TOXICOLOGY.** Toxic doses of the cholinomiraetic alkaloids evoke severe colic and diarrhea and exocrine gland secretions. The pupil is markedly constricted. Dyspnea occurs because of constriction of the bronchioles and accumulation of mucus in the airways. Hypotension and extreme cardiac slowing, complicated by excessive bronchoconstriction and bronchial secretions, lead to death. Arecoline or systemic exposure to pilocarpine is contraindicated in animals with heart failure, depression or disease of the respiratory tract, and spasmodic colic and during gestation. Atropine is a specific antidote to toxic doses of arecoline, pilocarpine, and muscarine.

**CHOLINESTERASE INHIBITORS.** Cholinesterase inhibitors (anticholinesterase agents) inactivate or inhibit AChE and pseudocholinesterase and thereby intensify activity of endogenous ACh. In addition, the activity of drugs that are biotransformed by cholinesterase (e.g., succinylcholine) is also prolonged by cholinesterase inhibitors. Because these drugs magnify the actions of endogenous ACh at all cholinergic receptors, their scope of activity is not limited to parasympathomimetic effects but includes cholinomimetic actions throughout the body.

Physostigmine, neostigmine, and edrophonium are examples of the type of anticholinesterase agent that produces a reversible inhibition of cholinesterase, whereas organophosphate compounds such as diisopropyl fluorophosphate (DFP) produce an irreversible inhibition.

**Pharmacologic Considerations**

**MECHANISM OF ACTION.** Due to inhibition of AChE, released ACh and intensification of its action at cholinergic receptors decrease. Neostigmine and other quaternary nitrogen
anticholinesterase agents exert some direct effects (either agonistic or antagonistic) on cholinergic receptors in addition to inhibition of cholinesterase.

Neostigmine, physostigmine, and other carbamate derivatives interact with the anionic and esteratic sites of the enzyme, thereby preventing ACh from affixing to the enzyme. Edrophonium and tetraethylammonium ions are complex and simple quaternary nitrogen compounds respectively that interact with the anionic site of cholinesterase. Therefore, they are not hydrolyzed but act as simple competitive reversible inhibitors. Accordingly, the duration of action of edrophonium is much shorter than that of neostigmine or physostigmine.

Organophosphate compounds interact with AChE at the esteratic site and form an extremely stable enzyme-inhibitor complex that does not undergo significant spontaneous disassociation. The esteratic site is persistently phosphorylated, and recovery of cholinesterase activity is dependent upon *de nova* synthesis of new enzyme. Because cholinesterase synthesis requires days, organophosphates cause an irreversible inhibition. As discussed below, however, certain oxime compounds exhibit such high affinity for the organophosphate that they can actually cause detachment of the inhibitor from the esteratic site, resulting in cholinesterase reactivation.

**PHARMACOLOGIC EFFECTS.** Effects of cholinesterase inhibitors can be reliably predicted by considering the anatomic location of cholinergic nerves and the respective physiologic processes they modulate in their innervated cells. Cholinesterase inhibitors also cause intensification of ACh activity at nicotinic sites. Neostigmine and other quaternary nitrogen compounds do not easily penetrate the blood brain barrier and therefore exert little CNS activity. These compounds are relatively more active at nicotinic receptors of the skeletal neuromuscular junction than at muscarinic sites of autonomic effector cells.

**Reversible Inhibitors.**

*Physostigmine* is an alkaloid extracted from the dried ripe seed of a vine, *Physosiigma venenosum.*

*Neostigmine Bromide,* is the salt of a synthetically produced substance discovered in a research investigation of compounds structurally related to physostigmine. It is used primarily as an anticurare agent. *Pyridostigmine Bromide* and *Ambenonium Chloride* are moderately long acting, chemically synthesized cholinesterase inhibitors.

**MECHANISM OF ACTION.** These agents produce their effects by combining with cholinesterase and thereby preventing the enzyme from hydrolyzing ACh. The interaction with cholinesterase is reversible, so as the inhibitor-enzyme complex breaks down, the enzyme is reactivated and it will now hydrolyze ACh and terminate its activity. At certain sites, neostigmine may act directly on receptors and evoke release of ACh from nerve endings; however, these are considered to be secondary actions.
PHARMACOLOGIC EFFECTS

DIGESTIVE TRACT. Physostigmine and neostigmine cause contraction of smooth muscle, thereby increasing motility and peristaltic movements of the gut. Excessive peristalsis leading to intestinal spasm and colic complicates use for this purpose. Physostigmine is given by SC or IM injection; its action after oral administration is unreliable. Neostigmine is not absorbed effectively after oral administration because of its quaternary nitrogen structure.

OCULAR EFFECTS. Physostigmine causes pupillary constriction and spasm of accommodation when applied locally to the eye or when injected for systemic effect. Intraocular pressure decreases, and physostigmine has been used in treating glaucoma to relieve elevated intraocular pressure.

SKELETAL MUSCLE. Neostigmine is believed to directly stimulate nicotinic receptors of skeletal muscle fibers. Physostigmine is not active in denervated muscle. Twitching of skeletal muscles may be observed when a large dose of physostigmine or neostigmine is injected. Physostigmine, neostigmine, pyridostigmine, and edrophonium are anticholinesterase agents.

OTHER EFFECTS. A therapeutic dose of physostigmine or neostigmine does not produce pronounced effects on cardiovascular function. Effects of higher doses are complicated by concurrent ganglionic stimulation and muscarinic effects on the heart and blood vessels. Usually, hypotension and a bradycardia leading to arrhythmias are produced. Smooth muscle of the bladder is cholinergically innervated and therefore is contracted by cholinesterase inhibitors. Bronchiolar smooth muscle is also contracted by these agents.

CLINICAL USES. Physostigmine Salicylate, or Physostigmine Sulfate can be used in the treatment of glaucoma. A solution of 0.5-1% physostigmine salicylate can be applied topically three times a day. Physostigmine – to break down synechia horses. Physostigmine SC dose of 30-45 mg in cattle to stimulate ruminal activity. Edrophonium can be used to overcome the effects of true curare-like drugs in voluntary muscles. Impaction or other obstructions of the alimentary tract constitute a contraindication to the systemic use of cholinesterase inhibitors. Violent peristalsis produced by these drugs can cause rupture or intussusception of the gut. These drugs should not be used during pregnancy, particularly late in term, because of the danger of producing abortion.

TOXICOLOGY.
CNS Depression, marked skeletal muscle weakness, nausea, vomiting, bradycardia, colic, and diarrhea. Atropine is the most effective pharmacologic antagonist for physostigmine or neostigmine toxicity.

Organophosphorus Compounds.
Various organophosphates are found having effect on CNS like Parathion, Malathion, Sarin, Tetraethyl Pyrophosphate.

TOXICITY. These compounds irreversibly phosphorylate the esteratic site of both AChE and the nonspecific or pseudocholinesterase throughout the body. Endogenous ACh is not inactivated,
and the resulting effects are due to the excessive preservation and accumulation of endogenous
ACh. Organophosphate poisoning produces diffuse cholinomimetic effects: profuse salivation,
vomiting, defecation, hypermotility of the GI tract, urination, bradycardia, hypotension, severe
bron-choconstriction, and excess bronchial secretions.

In addition to the muscarinic effects, skeletal muscle fasciculations. twitching, and.
subsequently, muscle paralysis occur. Convulsions and frequently death are seen in
organophosphate poisoning, caused by penetration of the agent into the CNS and subsequent
intensification of the activity of ACh at CNS sites.

ANTAGONISTS AND ANTIDOTES
ATROPINE. Because atropine blocks muscarinic receptors, it not only lessens severity of the
parasympathomimetic effects but also increases the quantity of organophosphate required to produce
death.

CHOLINESTERASE REACTIVATORS. Although phosphorylation of the esteratic site of
cholinesterase by organophosphates yields a normally irreversible complex, certain compounds cause a
disassociation of the enzyme bondage. This compound causes an effective removal of the phosphate
group from the enzyme, so the enzyme is reactivated. In dogs. 10-20 mg/kg 2-PAM administered by
slow IV injection is usually effective; this dose may have to be repeated. In horses and cattle, 20
mg/kg and 10-40 mg/kg respectively are used. Since 2-PAM significantly reverses the combination of
organophosphate with cholinesterase, the reactivated enzyme can then perform its normal function.
Atropine should always be used first to block muscarinic receptor sites.Various other reactivator oximes
such as pyridine-2-aldoxime dodecaiodide (designed for CNS effects), monoisonitrosoacetone, and
diacetylmonoxime have also been investigated.

PARASYMPATHOLYTIC AGENTS.

Atropine and Scopolamine: Atropine, the prototypical muscarinic blocking agent, is an alkaloid
extracted from the belladonna plants that belong to the Solanaceae (potato family) and include Atropa
belladonna (deadly nightshade), Datura stramonium (jim sonweed), and Hyoscyamus niger (henbane).
Chemically, the atropine molecule consists of two components joined through an ester linkage: tropine,
which is an organic base, and tropic acid. Other related alkaloids also contain the aromatic tropic acid
moiety combined by ester linkage to either tropine or another organic base, scopine.

MECHANISM OF ACTION. Atropine Sulfate, Scopolamine Hydrobromide, and other related alkaloids
interact with muscarinic receptors of effector cells and by occupying these sites prevent ACh from
affixing to the receptor area. Physiologic responses to parasympathetic nerve impulses are thereby
attenuated. Pharmacologic effects of exogenously administered ACh and other muscarinic agonists are
similarly blocked by atropine and scopolamine.
PHARMACOLOGICAL ACTIONS

CARDIOVASCULAR SYSTEM. The usual therapeutic doses of atropine do not markedly affect blood pressure; however, pulse rate is altered. Tachycardia is the dominant effect, and large doses of atropine invariably produce an increased heart rate. Because atropine blocks transmission of vagal impulses to the heart, animals with a preexisting high vagal tone would show a relatively greater tachycardia than those with low vagal tone. Because atropine blocks the cardiac vagus, it markedly reduces or abolishes cardiac inhibitory effects of drugs acting through a vagal mechanism and will attenuate vagal-mediated reflex responses.

GI tract. Atropine causes relaxation of GI smooth muscle by inhibiting contractile effects of cholinergic nerve impulses. Secretions of the GI tract are also blocked by atropine.

BRONCHIOLES. Atropine and other drugs of the belladonna group block effects of cholinergic impulses and thereby decrease secretions and increase luminal diameter of the bronchioles.

OCULAR EFFECTS. Because atropine blocks cholinergic effects, adrenergic nerve impulses dominate and the pupil actively dilates.

URINARY SYSTEM. Atropine relaxes smooth muscle of the urinary tract. Atropine tends to cause urine retention because it inhibits smooth muscle tone.

SWEAT GLANDS. Therapeutic doses of atropine produce minimal effects on the CNS.

TOXICITY Signs of atropine poisoning are similar in all mammalian species. Dry mouth, thirst, dysphagia, constipation, mydriasis, tachycardia, hyperpnea, restlessness, delirium, ataxia, and muscle trembling may be observed; convulsions, respiratory depression, and respiratory failure lead to death. A drop of urine obtained from a patient suspected of atropine toxicosis causes mydriasis when placed in the eye of a cat. Also, the tested pupil will not constrict when exposed to light. While the untreated eye will. This simple procedure may prove helpful in the differential diagnosis of belladonna intoxication.

CLINICAL USES. Atropine is used routinely as an adjunct to general anesthesia, particularly with inhalant anesthetics, to decrease salivary and airway secretions. When used prior to anesthesia, the dose of atropine in dogs is 0.045 mg/kg, administered subcutaneously. Because of the incidence or potential for anesthesia-associated tachyarrhythmias with atropine, glycopyrrolate has been advocated as an alternative to atropine for muscarinic blockade in routine preanesthetic medication. Atropine is an essential antidote to anti-cholinesterase overdosage or poisoning.

Synthetic Muscarinic Blocking Agents.

GLYCOPYRROLATE. Glycopyrrolate is a quaternary nitrogen anticholinergic agent that has received attention for preanesthetic use in veterinary medicine. It exerts potent antimuscarinic activity but reportedly has some benefits when compared to atropine. Glycopyrrolate penetrates the blood-brain barrier less effectively than atropine, with less propensity for unwanted CNS side effects. The muscarinic blocking action of glycopyrrolate is evident within minutes after IV injection. After SC or IM administration, maximal effects generally develop within 30-45 minutes. The glycopyrrolate dose is
approximately 10 mg/kg by SC, IM, or IV routes, administered 15 minutes or so prior to anesthetic induction.

HOMATROPINE is similar in structure to atropine except that it is an ester of mandelic acid rather than of tropic acid. Homatropine closely resembles atropine in most of its pharmacologic actions, particularly the ocular effects. Mydriasis and cycloplegia are produced in the eye by topical application of a 2-5% solution of homatropine, but these effects last for a shorter duration than those resulting from atropine. Homatropine produces fewer side effects on cardiovascular and GI functions than atropine and is considerably less toxic than the parent drug.

METHANTHELINE, PROPANTHELINE, AND METHYL-ATROPINE are quaternary amines used primarily as smooth muscle relaxants. Because of the charged quaternary group, these compounds do not cross the blood-brain barrier to an appreciable extent. Accordingly, they are considerably less effective than atropine as antagonists to organophosphates, since the CNS effects of the latter agents would not be blocked. In addition to muscarinic blocking effects, these drugs act as autonomic ganglionic blockers, which most likely contributes to their antispasmodic effect on GI smooth muscle.