

## Cholinoceptor-Blocking Drugs

### INTRODUCTION

Cholinoceptor antagonists, like agonists, are divided into muscarinic and nicotinic subgroups on the basis of their specific receptor affinities. Ganglion-blockers and neuromuscular junction blockers comprise the antinicotinic drugs. The ganglion-blocking drugs have little clinical use and are discussed at the end of this chapter. This chapter emphasizes drugs that block muscarinic cholinergic receptors.

Five subtypes of muscarinic receptors have been identified, primarily on the basis of data from ligand binding and cDNA-cloning experiments. A standard terminology ( $M_1$  through  $M_5$ ) for these subtypes is now in common use, and evidence, based mostly on selective agonists and antagonists, indicates that functional differences exist between several of these subtypes.

The  $M_1$  receptor subtype is located on central nervous system neurons, sympathetic postganglionic cell bodies, and many presynaptic sites.  $M_2$  receptors are located in the myocardium, smooth muscle organs, and some neuronal sites.  $M_3$  receptors are most common on effector cell membranes, especially glandular and smooth muscle cells.

### I. BASIC PHARMACOLOGY OF THE MUSCARINIC RECEPTOR-BLOCKING DRUGS

#### Introduction

Muscarinic antagonists are sometimes called parasympatholytic because they block the effects of parasympathetic autonomic discharge. However, they do not "lyse" parasympathetic nerves, and they have some effects that are not predictable from block of the parasympathetic nervous system. For these reasons, the term "antimuscarinic" is preferable.

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.

#### Chemistry & Pharmacokinetics

##### A. SOURCE AND CHEMISTRY

Atropine and its naturally occurring congeners are tertiary amine alkaloid esters of tropic acid. Atropine (hyoscyamine) is found in the plant *Atropa belladonna*, or deadly nightshade, and in *Datura stramonium*, also known as jimsonweed (Jamestown weed), sacred Datura, or thorn apple. Scopolamine (hyoscine) occurs in *Hyoscyamus niger*, or henbane, 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.

A variety of semisynthetic and fully synthetic molecules have antimuscarinic effects.

The tertiary members of these classes 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.

## **B. ABSORPTION**

The natural alkaloids and most tertiary antimuscarinic drugs are well absorbed from the gut and conjunctival membranes. When applied in a suitable vehicle, some (eg, scopolamine) are even absorbed across the skin (transdermal route). In contrast, only 10-30% of a dose of a quaternary antimuscarinic drug is absorbed after oral administration, reflecting the decreased lipid solubility of the charged molecule.

## **C. DISTRIBUTION**

Atropine and the other tertiary agents are widely distributed in the body. Significant levels are achieved in the central nervous system within 30 minutes to 1 hour, and this can limit the dose tolerated when the drug is taken for its peripheral effects.

Scopolamine is rapidly and fully distributed into the central nervous system where it has greater effects than most other antimuscarinic drugs. In contrast, the quaternary derivatives are poorly taken up by the brain and therefore are relatively free—at low doses—of central nervous system effects.

## **D. METABOLISM AND EXCRETION**

After administration, atropine disappears rapidly from the blood with a half-life of 2 hours. About 60% of the dose is excreted unchanged in the urine. Most of the rest appears in the urine as hydrolysis and conjugation products. The drug's effect on parasympathetic function declines rapidly in all organs except the eye. Effects on the iris and ciliary muscle persist for  $\geq 72$  hours.

## **Pharmacodynamics**

### **A. MECHANISM OF ACTION**

Atropine causes reversible (surmountable) blockade of cholinomimetic actions at muscarinic receptors—ie, blockade by a small dose of atropine can be overcome by a larger concentration of acetylcholine or equivalent muscarinic agonist. Mutation experiments suggest that aspartate in the receptor forms the characteristic bond with the nitrogen atom of acetylcholine; this amino acid is also required for binding of antimuscarinic drugs. When atropine binds to the muscarinic receptor, it prevents actions such as the release of inositol trisphosphate ( $IP_3$ ) and the inhibition of adenyl cyclase that are caused by muscarinic agonists.

The effectiveness of antimuscarinic drugs varies with the tissue and with the source of

agonist. Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands. Secretion of acid by the gastric parietal cells is the least sensitive. In most tissues, antimuscarinic agents block exogenously administered cholinergic agonists more effectively than endogenously released acetylcholine.

Atropine is highly selective for muscarinic receptors. Its potency at nicotinic receptors is much lower, and actions at nonmuscarinic receptors are generally undetectable clinically.

Atropine does not distinguish between the  $M_1$ ,  $M_2$ , and  $M_3$  subgroups of muscarinic receptors. In contrast, other antimuscarinic drugs are moderately selective for one or another of these subgroups. Most synthetic antimuscarinic drugs are considerably less selective than atropine in interactions with nonmuscarinic receptors. For example, some quaternary amine antimuscarinic agents have significant ganglion-blocking actions, and others are potent histamine receptor blockers. The antimuscarinic effects of other agents, eg, antipsychotic and antidepressant drugs, have been mentioned. Their relative selectivity for muscarinic receptor subtypes has not been defined.

## **B. ORGAN SYSTEM EFFECTS**

**1. Central nervous system**— In the doses usually used, atropine has minimal stimulant effects on the central nervous system, especially the parasympathetic medullary centers, and a slower, longer-lasting sedative effect on the brain. Scopolamine has more marked central effects, producing drowsiness when given in recommended dosages and amnesia in sensitive individuals. In toxic doses, scopolamine and to a lesser degree atropine can cause excitement, agitation, hallucinations, and coma.

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. As discussed in [Chapter 28](#), parkinsonian tremor and rigidity seem to result from a *relative* excess of cholinergic activity because of a deficiency of dopaminergic activity in the basal ganglia-striatum system. The combination of an antimuscarinic agent with a dopamine precursor drug (levodopa) can sometimes provide more effective therapy than either drug alone.

Vestibular disturbances, especially motion sickness, appear to involve muscarinic cholinergic transmission. Scopolamine is often effective in preventing or reversing these disturbances.

**2. Eye**— The pupillary constrictor muscle (see [Figure 6-9](#)) depends on muscarinic cholinergic activation. This activation is blocked by topical atropine and other tertiary antimuscarinic drugs and results in unopposed sympathetic dilator activity and mydriasis ([Figure 8-3](#)). Dilated pupils were considered cosmetically desirable during the Renaissance and account for the name belladonna (Italian, "beautiful lady") applied to the plant and its active extract because of the use of the extract as eye drops during that time.

The second important ocular effect of antimuscarinic drugs is to weaken contraction of the ciliary muscle, or **cycloplegia**. Cycloplegia results in loss of the ability to

accommodate; the fully atropinized eye cannot focus for near vision ([Figure 8-3](#)).

Both mydriasis and cycloplegia are useful in ophthalmology. They are also potentially hazardous, since acute glaucoma may be induced in patients with a narrow anterior chamber angle.

A third ocular effect of antimuscarinic drugs is to reduce lacrimal secretion. Patients occasionally complain of dry or "sandy" eyes when receiving large doses of antimuscarinic drugs.

**3. Cardiovascular system—**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 ([Figure 8-4](#)). This slowing may be due to block of prejunctional  $M_1$  receptors (autoreceptors, see [Chapter 6](#)) on vagal postganglionic fibers that normally limit acetylcholine release in the sinus node and other tissues. 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. 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.

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 (see [Chapter 6](#)). Atropine can block this vasodilation. Furthermore, almost all vessels contain endothelial muscarinic receptors that mediate vasodilation (see [Chapter 7](#)). These receptors are readily blocked by antimuscarinic drugs. At toxic doses, and in some individuals at normal doses, antimuscarinic agents cause cutaneous vasodilation, especially in the upper portion of the body. The mechanism is unknown.

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.

**4. 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  $\beta$ -adrenoceptor stimulants in the treatment of asthma (see [Chapter 20](#)). 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. Nevertheless, antimuscarinic agents are valuable in some patients with

asthma or COPD.

Antimuscarinic drugs are frequently used prior to administration of inhalant anesthetics to reduce the accumulation of secretions in the trachea and the possibility of laryngospasm.

**5. 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. As in other tissues, exogenously administered muscarinic stimulants are more effectively blocked than the effects of parasympathetic (vagal) nerve activity. The removal of autoinhibition, a negative feedback mechanism by which neural acetylcholine suppresses its own release, might explain the greater efficacy of antimuscarinic drugs against exogenous muscarinic stimulants.

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: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required. Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol. Pirenzepine and a more potent analog, telenzepine, reduce gastric acid secretion with fewer adverse effects than atropine and other less selective agents. This results from a selective blockade of presynaptic excitatory muscarinic receptors on vagal nerve endings as suggested by their high ratio of  $M_1$  to  $M_3$  affinity. Pirenzepine and telenzepine are investigational in the USA. Pancreatic and intestinal secretion are little affected by atropine; these processes are primarily under hormonal rather than vagal control.

Gastrointestinal smooth muscle motility is affected from the stomach to the colon. In general, the walls of the viscera are relaxed, and both tone and propulsive movements are diminished. Therefore, gastric emptying time is prolonged, and intestinal transit time is lengthened. Diarrhea due to overdosage with parasympathomimetic agents is readily stopped, and even that caused by nonautonomic agents can usually be temporarily controlled. However, intestinal "paralysis" induced by antimuscarinic drugs is temporary; local mechanisms within the enteric nervous system will usually reestablish at least some peristalsis after 1-3 days of antimuscarinic drug therapy.

**6. 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. The antimuscarinic drugs have no significant effect on the uterus.

**7. 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."

## **II. CLINICAL PHARMACOLOGY OF THE MUSCARINIC RECEPTOR-BLOCKING DRUGS**

### **Therapeutic Applications**

#### **A. CENTRAL NERVOUS SYSTEM DISORDERS**

**1. Parkinson's disease**— the treatment of Parkinson's disease is often an exercise in polypharmacy, since no single agent is fully effective over the course of the disease. Most antimuscarinic drugs promoted for this application were developed before levodopa became available. Their use is accompanied by all of the adverse effects described below, but the drugs remain useful as adjunctive therapy in some patients.

**2. Motion sickness**— Certain vestibular disorders respond to antimuscarinic drugs (and to antihistaminic agents with antimuscarinic effects). Scopolamine is one of the oldest remedies for seasickness and is as effective as any more recently introduced agent. It can be given by injection, by mouth, or as a transdermal patch. The patch formulation produces significant blood levels over 48-72 hours. Unfortunately, useful doses by any route usually cause significant sedation and dry mouth.

#### **B. OPHTHALMOLOGIC DISORDERS**

Accurate measurement of refractive error in uncooperative patients, eg, young children, requires ciliary paralysis. Also, ophthalmoscopic examination of the retina is greatly facilitated by mydriasis. Therefore, antimuscarinic agents, administered topically as eye drops or ointment, are very helpful in doing a complete examination. For adults and older children, the shorter-acting drugs are preferred. For younger children, the greater efficacy of atropine is sometimes necessary, but the possibility of antimuscarinic poisoning is correspondingly increased. Drug loss from the conjunctival sac via the nasolacrimal duct into the nasopharynx can be diminished by the use of the ointment form instead of drops. Formerly, ophthalmic antimuscarinic drugs were selected from the tertiary amine subgroup to ensure good penetration after conjunctival application. Recent experiments in animals, however, suggest that glycopyrrolate, a quaternary agent, is as rapid in onset and as long-lasting as atropine.

Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required. Alpha-adrenoceptor stimulant drugs, eg, phenylephrine, produce a short-lasting mydriasis that is usually sufficient for fundoscopic examination.

A second ophthalmologic use is to prevent synechia (adhesion) formation in uveitis and iritis. The longer-lasting preparations, especially homatropine, are valuable for this indication.

#### **C. RESPIRATORY DISORDERS**

The use of atropine became part of routine preoperative medication when anesthetics such as ether were used, because these irritant anesthetics markedly increased airway secretions and were associated with frequent episodes of laryngospasm. Preanesthetic injection of atropine or scopolamine could prevent these hazardous effects.

Scopolamine also produces significant amnesia for the events associated with surgery and obstetric delivery, a side effect that was considered desirable. On the other hand, urinary retention and intestinal hypomotility following surgery were often exacerbated by antimuscarinic drugs. Newer inhalational anesthetics are far less irritating to the airways.

the hyperactive neural bronchoconstrictor reflex present in most individuals with asthma is mediated by the vagus, acting on muscarinic receptors on bronchial smooth muscle cells. **Ipratropium** a synthetic analog of atropine, is used as an inhalational drug in asthma. The aerosol route of administration has the advantages of maximal concentration at the bronchial target tissue with reduced systemic effects. Ipratropium has also proved useful in COPD, a condition that occurs with higher frequency in older patients, particularly chronic smokers. Patients with COPD benefit from bronchodilators, especially antimuscarinic agents such as ipratropium and the recently approved **tiotropium**. In contrast to ipratropium, tiotropium has a longer bronchodilator action and can be given once daily. Tiotropium reduces the incidence of COPD exacerbations and is a useful adjunct to pulmonary rehabilitation in increasing exercise tolerance.

#### **D. CARDIOVASCULAR DISORDERS**

Marked reflex vagal discharge sometimes accompanies the pain of myocardial infarction (eg, vasovagal attack) and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. Parenteral atropine or a similar antimuscarinic drug is appropriate therapy in this situation. Rare individuals without other detectable cardiac disease have hyperactive carotid sinus reflexes and may experience faintness or even syncope as a result of vagal discharge in response to pressure on the neck, eg, from a tight collar. Such individuals may benefit from the judicious use of atropine or a related antimuscarinic agent.

Pathophysiology can influence muscarinic activity in other ways as well. Circulating autoantibodies against the second extracellular loop of cardiac muscarinic receptors have been detected in some patients with idiopathic dilated cardiomyopathy. These antibodies exert parasympathomimetic actions on the heart that are prevented by atropine. Although their role in the pathology of heart failure is unknown, they should provide clues to the molecular basis of receptor activation.

#### **E. GASTROINTESTINAL DISORDERS**

Antimuscarinic agents are now rarely used for peptic ulcer disease in the USA . Antimuscarinic agents can provide some relief in the treatment of common traveler's diarrhea and other mild or self-limited conditions of hypermotility. They are often combined with an opioid antidiarrheal drug, an extremely effective therapy. In this combination, however, the very low dosage of the antimuscarinic drug functions primarily to discourage abuse of the opioid agent. The classic combination of atropine with diphenoxylate, a nonanalgesic congener of meperidine, is available under many names (eg, Lomotil) in both tablet and liquid form .

#### **F. URINARY DISORDERS**

Atropine and other antimuscarinic drugs have been used to provide symptomatic relief in the treatment of urinary urgency caused by minor inflammatory bladder disorders . However, specific antimicrobial therapy is essential in bacterial cystitis. In the human



urinary bladder, M<sub>2</sub> and M<sub>3</sub> receptors are expressed predominantly with the M<sub>3</sub> subtype mediating direct activation of contraction. As in intestinal smooth muscle, the M<sub>2</sub> subtype appears to act indirectly by inhibiting relaxation by norepinephrine and epinephrine.

**Oxybutynin**, which is somewhat selective for M<sub>3</sub> receptors, is used to relieve bladder spasm after urologic surgery, eg, prostatectomy. It is also valuable in reducing involuntary voiding in patients with neurologic disease, eg, children with meningomyelocele. Oral oxybutynin or instillation of the drug by catheter into the bladder in such patients appears to improve bladder capacity and continence and to reduce infection and renal damage. **Trospium**, an unselective antagonist, has recently been approved and is comparable in efficacy and side effects with oxybutynin. **Darifenacin** and **solifenacin** are recently approved antagonists that have greater selectivity for M<sub>3</sub> receptors than oxybutynin or trospium. Their advantages include once daily dosing because of their long half-lives and a reduced incidence of xerostomia and constipation. **Tolterodine**, another M<sub>3</sub>-selective antimuscarinic, is available for use in adults with urinary incontinence. It has many of the qualities of darifenacin and solifenacin. The reason for the reduced incidence of dry mouth with these drugs as compared with oxybutynin is not known.

Imipramine, a tricyclic antidepressant drug with strong antimuscarinic actions, has long been used to reduce incontinence in institutionalized elderly patients. It is moderately effective but causes significant central nervous system toxicity. Propiverine, a newer antimuscarinic agent, has been approved for this purpose.

Antimuscarinic agents have also been used in urolithiasis to relieve the painful ureteral smooth muscle spasm caused by passage of the stone. However, their usefulness in this condition is debatable.

## **G. CHOLINERGIC POISONING**

Severe cholinergic excess is a medical emergency, especially in rural communities where cholinesterase inhibitor insecticides are commonly used and in cultures where wild mushrooms are commonly eaten. The potential use of cholinesterase inhibitors as chemical warfare "nerve gases" also requires an awareness of the methods for treating acute poisoning .

**1. Antimuscarinic therapy**— both the nicotinic and the muscarinic effects of the cholinesterase inhibitors can be life-threatening. Unfortunately, there is no effective method for directly blocking the nicotinic effects of cholinesterase inhibition, because nicotinic agonists *and* antagonists cause blockade of transmission . To reverse the muscarinic effects, a tertiary (not quaternary) amine drug must be used (preferably atropine) to treat the central nervous system effects as well as the peripheral effects of the organophosphate inhibitors. Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like parathion and chemical warfare nerve gases: 1-2 mg of atropine sulfate may be given intravenously every 5-15 minutes until signs of effect (dry mouth, reversal of miosis) appear. The drug may have to be repeated many times, since the acute effects of the anticholinesterase agent may last for 24-48 hours or longer. In this life-threatening situation, as much as 1 g of atropine per day may be required for as long as 1 month for full control of muscarinic excess.



**2. Cholinesterase regenerator compounds**—A second class of compounds, capable of regenerating active enzyme from the organophosphorus-cholinesterase complex, is also available to treat organophosphorus poisoning. These oxime agents include pralidoxime (PAM), diacetylmonoxime (DAM), and others.

The oxime group (=NOH) has a very high affinity for the phosphorus atom, and these drugs can hydrolyze the phosphorylated enzyme if the complex has not "aged" .

Pralidoxime is the most extensively studied—in humans—of the agents shown and the only one available for clinical use in the USA. It is most effective in regenerating the cholinesterase associated with skeletal muscle neuromuscular junctions.

Pralidoxime is ineffective in reversing the central effects of organophosphate poisoning because its positive charge prevents entry into the central nervous system.

Diacetylmonoxime, on the other hand, crosses the blood-brain barrier and, in experimental animals, can regenerate some of the central nervous system cholinesterase.

Pralidoxime is administered by intravenous infusion, 1-2 g given over 15-30 minutes. In spite of the likelihood of aging of the phosphate-enzyme complex, recent reports suggest that administration of multiple doses of pralidoxime over several days may be useful in severe poisoning. In excessive doses, pralidoxime can induce neuromuscular weakness and other adverse effects. Pralidoxime is *not* recommended for the reversal of inhibition of acetylcholinesterase by carbamate inhibitors

A third approach to protection against excessive AChE inhibition is *pretreatment* with reversible enzyme inhibitors to prevent binding of the irreversible organophosphate inhibitor. This prophylaxis can be achieved with pyridostigmine or physostigmine but is reserved for situations in which possibly lethal poisoning is anticipated, eg, chemical warfare. Simultaneous use of atropine is required to control muscarinic excess.

**Mushroom poisoning** has traditionally been divided into rapid-onset and delayed-onset types. The rapid-onset type is usually apparent within 15-30 minutes following ingestion of the mushrooms. It is often characterized entirely by signs of muscarinic excess: nausea, vomiting, diarrhea, urinary urgency, vasodilation, reflex tachycardia (occasionally bradycardia), sweating, salivation, and sometimes bronchoconstriction. Although *Amanita muscaria* contains muscarine (the alkaloid was named after the mushroom), numerous other alkaloids, including antimuscarinic agents, are found in this fungus. In fact, ingestion of *A muscaria* may produce signs of atropine poisoning, not muscarine excess. Other mushrooms, especially those of the *Inocybe* genus, cause rapid-onset poisoning of the muscarinic excess type. Parenteral atropine, 1-2 mg, is effective treatment in such intoxications.

Delayed-onset mushroom poisoning, usually caused by *Amanita phalloides*, *A virosa*, *Galerina autumnalis*, or *G marginata*, manifests its first symptoms 6-12 hours after ingestion. Although the initial symptoms usually include nausea and vomiting, the major toxicity involves hepatic and renal cellular injury by amatoxins that inhibit RNA polymerase. Atropine is of no value in this form of mushroom poisoning

## **H. OTHER APPLICATIONS**

Hyperhidrosis (excessive sweating) is sometimes reduced by antimuscarinic agents. However, relief is incomplete at best, probably because apocrine rather than eccrine glands are usually involved.

### **Adverse Effects**

Treatment with atropine or its congeners directed at one organ system almost always induces undesirable effects in other organ systems. Thus, mydriasis and cycloplegia are adverse effects when an antimuscarinic agent is used to reduce gastrointestinal secretion or motility, even though they are therapeutic effects when the drug is used in ophthalmology.

At higher concentrations, atropine causes block of all parasympathetic functions. However, atropine is a remarkably safe drug *in adults*. Atropine poisoning has occurred as a result of attempted suicide, but most cases are due to attempts to induce hallucinations. Poisoned individuals manifest dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as a week. Body temperature is frequently elevated. These effects are memorialized in the adage, "dry as a bone, blind as a bat, red as a beet, mad as a hatter."

Unfortunately, children, especially infants, are very sensitive to the hyperthermic effects of atropine. Although accidental administration of over 400 mg has been followed by recovery, deaths have followed doses as small as 2 mg. Therefore, atropine should be considered a highly dangerous drug when overdose occurs in infants or children.

Overdoses of atropine or its congeners are generally treated symptomatically. In the past, physostigmine or another cholinesterase inhibitor was recommended, but most poison control experts now consider physostigmine more dangerous and no more effective in most patients than symptomatic management. When physostigmine is deemed necessary, *small* doses are given *slowly* intravenously (1-4 mg in adults, 0.5-1 mg in children). Symptomatic treatment may require temperature control with cooling blankets and seizure control with diazepam.

Poisoning caused by high doses of quaternary antimuscarinic drugs is associated with all of the peripheral signs of parasympathetic blockade but few or none of the central nervous system effects of atropine. These more polar drugs may cause significant ganglionic blockade, however, with marked orthostatic hypotension (see below). Treatment of the antimuscarinic effects, if required, can be carried out with a quaternary cholinesterase inhibitor such as neostigmine. Control of hypotension may require the administration of a sympathomimetic drug such as phenylephrine.

### **Contraindications**

Contraindications to the use of antimuscarinic drugs are relative, not absolute. Obvious muscarinic excess, especially that caused by cholinesterase inhibitors, can always be treated with atropine.

Antimuscarinic drugs are contraindicated in patients with glaucoma, especially angle-

closure glaucoma. Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow anterior chambers.

In elderly men, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia.

Because the antimuscarinic drugs slow gastric emptying, they may *increase* symptoms in patients with gastric ulcer. Nonselective antimuscarinic agents should never be used to treat acid-peptic disease .

### **III. BASIC & CLINICAL PHARMACOLOGY OF THE GANGLION-BLOCKING DRUGS**

#### **Introduction**

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 cholinergic receptor. 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.

#### **Chemistry & Pharmacokinetics**

All ganglion-blocking drugs of interest are synthetic amines. **Tetraethylammonium (TEA)**, the first to be recognized as having this action, has a very short duration of action. **Hexamethonium ("C6")** was developed and was introduced clinically as the first drug effective for management of hypertension. there is an obvious relationship between the structures of the agonist acetylcholine and the nicotinic antagonists tetraethylammonium and hexamethonium. Decamethonium, the "C10" analog of hexamethonium, is a depolarizing neuromuscular blocking agent.

**Mecamylamine**, a secondary amine, was developed to improve the degree and extent of absorption from the gastrointestinal tract because the quaternary amine ganglion-blocking compounds were poorly and erratically absorbed after oral administration. **Trimethaphan**, a short-acting ganglion blocker, is inactive orally and is given by intravenous infusion.

#### **Pharmacodynamics**

##### **A. MECHANISM OF ACTION**

Ganglionic nicotinic receptors, like those of the skeletal muscle neuromuscular junction, are subject to both depolarizing and nondepolarizing . Nicotine itself, carbamoylcholine, and even acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.

Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists. However, hexamethonium actually produces most of its blockade by occupying sites in or on the nicotinic ion channel, not by occupying the cholinergic receptor itself. In contrast, trimethaphan appears to block the nicotinic receptor, not the channel. Blockade can be surmounted by increasing the concentration of an agonist, eg, acetylcholine.

## **B. ORGAN SYSTEM EFFECTS**

**1. Central nervous system—**Mecamylamine, unlike the quaternary amine agents and trimethaphan, crosses the blood-brain barrier and readily enters the central nervous system. Sedation, tremor, choreiform movements, and mental aberrations have been reported as effects of mecamylamine.

**2. Eye—**The ganglion-blocking drugs cause a predictable cycloplegia with loss of accommodation because the ciliary muscle receives innervation primarily from the parasympathetic nervous system. The effect on the pupil is not so easily predicted, since the iris receives both sympathetic innervation (mediating pupillary dilation) and parasympathetic innervation (mediating pupillary constriction). Ganglionic blockade often causes moderate dilation of the pupil because parasympathetic tone usually dominates this tissue.

**3. Cardiovascular system—**Blood vessels receive chiefly vasoconstrictor fibers from the sympathetic nervous system; therefore, ganglionic blockade causes a marked decrease in arteriolar and venomotor tone. The blood pressure may fall precipitously, because both peripheral vascular resistance and venous return are decreased. Hypotension is especially marked in the upright position (orthostatic or postural hypotension), because postural reflexes that normally prevent venous pooling are blocked.

Cardiac effects include diminished contractility and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a moderate tachycardia.

**4. Gastrointestinal tract—**Secretion is reduced, although not enough to effectively treat peptic disease. Motility is profoundly inhibited, and constipation can be marked.

**5. Other systems—**Genitourinary smooth muscle is partially dependent on autonomic innervation for normal function. Therefore, ganglionic blockade causes hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia. Sexual function is impaired in that both erection and ejaculation may be prevented by moderate doses.

Thermoregulatory sweating is reduced by the ganglion-blocking drugs. However, hyperthermia is not a problem except in very warm environments, because cutaneous vasodilation is usually sufficient to maintain a normal body temperature.

**6. Response to autonomic drugs—**Patients receiving ganglion-blocking drugs are fully responsive to autonomic drugs acting on muscarinic,  $\alpha$ -, and  $\beta$ -adrenergic receptors because these effector cell receptors are not blocked. In fact, responses may be exaggerated or even reversed (eg, norepinephrine may cause tachycardia rather

than bradycardia), because homeostatic reflexes, which normally moderate autonomic responses, are absent.

## 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 already described. For most patients, these effects are intolerable except for acute use.

## PREPARATIONS AVAILABLE

### ANTIMUSCARINIC ANTICHOLINERGIC DRUGS\*

#### **Atropine** (generic)

Oral: 0.4, 0.6 mg tablets

Parenteral: 0.05, 0.1, 0.3, 0.4, 0.5, 0.8, 1 mg/mL for injection

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% drops

#### **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 injection

#### **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% drops

#### **l-Hyoscyamine** (Anaspaz, Cystospaz-M, Levsinex)

Oral: 0.125, 0.15 mg tablets; 0.375 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

Solution for nebulizer: 0.02%

Nasal spray: 0.03, 0.06%

**Mepenzolate** (Cantil)

Oral: 25 mg tablets

**Methantheline** (Banthine)

Oral: 50 mg tablets

**Methscopolamine** (Pamine)

Oral: 2.5 mg tablets

**Oxybutynin** (generic, Ditropan)

Oral: 5 mg tablets; 5, 10, 15 mg extended release tablets; 5 mg/5 mL syrup

**Propantheline** (generic, Pro-Banthine, others)

Oral: 7.5, 15 mg tablets

**Scopolamine** (generic)

Oral: 0.25 mg tablets

Parenteral: 0.3, 0.4, 0.86, 1 mg/mL for injection

Ophthalmic (Isopto Hyoscine): 0.25% solution

Transdermal (Transderm Scop): 1.5 mg (delivers 0.5 mg) patch

**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, Mydracil Ophthalmic, others)

Ophthalmic: 0.5, 1% drops

**Trospium** (Spasmex)

Oral: 5, 15, 30 mg tablets

Suppository: 0.75, 1.0 mg

Parenteral: 0.6 mg/mL

## **GANGLION BLOCKERS**

**Mecamylamine** (Inversine)

Oral: 2.5 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