13 Muscarinic Blocking Drugs

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DRUG LIST

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Atropine	136	Oxybutynin	137
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Muscarinic blocking drugs are compounds that selectively antagonize the responses to acetylcholine (ACh) and other parasympathomimetics that are mediated by activation of muscarinic receptors. These agents are also referred to as *muscarinic antagonists, antimuscarinic drugs,* and *anticholinergics.* The belladonna alkaloids, such as atropine, are the oldest known muscarinic blocking compounds, and their medicinal use preceded the concept of neurochemical transmission.

CHEMISTRY

The best known of the muscarinic blocking drugs are the belladonna alkaloids, atropine (*Atropine*) and scopolamine (*Scopolamine*). They are tertiary amines that contain an ester linkage. Atropine is a racemic mixture of DL-hyoscyamine, of which only the levorotatory isomer is pharmacologically active. Atropine and scopolamine are parent compounds for several semisynthetic derivatives, and some synthetic compounds with little structural similarity to the belladonna alkaloids are also in use. All of the antimuscarinic compounds are amino alcohol esters with a tertiary amine or quaternary ammonium group. The control of access to muscarinic receptors in the central nervous system (CNS) by a tertiary amine versus quaternary ammonium group is fundamentally important in selecting among antimuscarinic agents.

MECHANISM OF ACTION

Antimuscarinic drugs are competitive antagonists of the binding of ACh to muscarinic receptors. The seven transmembrane helices of these receptors have a ringlike organization in the cell membrane that forms a narrow central cleft where ACh binds. At least seven amino acids from four transmembrane helices have been implicated in agonist binding to the muscarinic receptors. Some of these residues, particularly a negatively charged aspartate, interact electrostatically with the positively charged quaternary ammonium moiety of ACh, whereas other residues are required for binding to the ester moiety. Although the tertiary amine and quaternary ammonium groups of antimuscarinic drugs bind to the same anionic site on the receptor that agonists occupy, these drugs do not fit into the narrow cleft and consequently cannot activate the receptor.

Dicyclomine (*Bentyl*), oxybutynin (*Ditropan*), and tolterodine (*Detrol*) are nonselective smooth muscle relaxants that produce relatively little antagonism of muscarinic receptors at therapeutic concentrations. The mechanism of relaxation is not known. Finally, some other classes of drugs can act in part as muscarinic antagonists. For example, the antipsychotics and antidepressants produce antimuscarinic side effects (e.g., dry mouth).

PHARMACOLOGICAL ACTIONS

Muscarinic antagonists have no intrinsic activity, and they can produce effects only by blocking the activation of muscarinic receptors by muscarinic agonists or by neuronally released ACh. Therefore, the magnitude of the response produced by muscarinic antagonists depends on the existing level of cholinergic activity or on the presence of muscarinic agonists. Also, the nature of the response of an organ to the administration of a muscarinic antagonist will depend on the organ's pattern of innervation; for example, some organs receive dual innervation from adrenergic and cholinergic pathways. At these locations, block of the activation of muscarinic receptors can increase the tone provided by the adrenergic input.

The effects of muscarinic blocking drugs on various human organ systems are summarized in Table 13.1. The tissues or systems affected will depend on the dose administered, the drug's pharmacokinetic properties (e.g., increased entry into the CNS at higher concentrations), and the differential sensitivity of muscarinic receptors in various organs to individual blocking agents. Although muscarinic *agonists* typically do not exhibit selectivity among muscarinic receptors (see Chapter 12), some muscarinic *antagonists* are selective in their ability to block subtypes of muscarinic receptors.

TABLE 13.1 Effects of Muscarinic Blocking Drugs in Humans

Tissue or system	Effects
Skin	Inhibition of sweating (hyperpyrexia may result); flushing
Visual	Cycloplegia (relaxation of ciliary muscle); mydriasis (relaxation of sphincter pupillae muscle); increase in aqueous outflow resistance (increases intraocular pressure in many cases of glaucoma)
Digestive	Decreased salivation; reduced tone and motility in the gastrointestinal tract; decrease in vagus-stimulated gastric, pancreatic, intestinal, and biliary secretions
Urinary	Urinary retention (relaxation of the detrusor muscle); relaxation of ureter
Respiratory	Bronchial dilation and decreased secretions
Cardiovascular	Bradycardia at low doses (may be a CNS effect) and tachycardia at higher doses (peripheral effect); increased cardiac output if patient is recumbent
Central nervous system	Decreased concentration and memory; drowsiness; sedation; excitation; ataxia; asynergia; decrease in alpha EEG and increase in low-voltage slow waves (as in drowsy state); hallucinations; coma

Heart

Intravenous administration of low doses of atropine or scopolamine often produces slight bradycardia, whereas higher doses produce tachycardia by directly blocking the parasympathetic input to the sinoatrial node. Although it has been suggested that the bradycardia results from an effect of the drugs on the CNS (thought to be central vagal stimulation), this appears unlikely, since methylatropine (a quaternary ammonium derivative of atropine) produces a similar response. One plausible explanation for the *paradoxical bradycardia* produced by low doses of muscarinic blockers is that they block presynaptic muscarinic receptors that normally provide feedback inhibition of the release of ACh. Antagonism of these presynaptic muscarinic receptors prevents feedback inhibition and increases the release of ACh, and this effect may dominate postsynaptic muscarinic receptor blockade produced by low doses of antagonist. Atropine can also facilitate atrioventricular (A-V) conduction and block parasympathetic effects on the cardiac conduction system and on myocardial contractility.

Blood Vessels

Atropine and other muscarinic antagonists produce minimal effects on the circulation in the absence of circulating muscarinic agonists. This reflects the relatively minor role of cholinergic innervation in determining vascular smooth muscle tone. Atropine can produce flushing in the blush area owing to vasodilation. It is not known whether this is a direct effect or a response to the hyperthermia induced by the drug's ability to inhibit sweating.

Gastrointestinal Tract

Muscarinic antagonists have numerous effects on the digestive system (see Chapter 40). The inhibition of salivation by low doses of atropine results in a dry mouth and difficulty in swallowing. Antimuscarinic

drugs also inhibit gastric acid secretion and gastrointestinal motility, because both processes are partly under the control of the vagus nerve. Relatively large doses of atropine are required to inhibit acid secretion, and side effects such as dry mouth, tachycardia, ocular disturbances, and urinary retention are drawbacks to the use of muscarinic antagonists in the treatment of peptic ulcers.

Bladder

Muscarinic antagonists can cause urinary retention by blocking the excitatory effect of ACh on the detrusor muscle of the bladder. During urination, cholinergic input to this smooth muscle is activated by a stretch reflex.

Central Nervous System

Although atropine and scopolamine share many properties, an important difference is the easier entry of scopolamine into the CNS. Typical doses of atropine (0.2–2 mg) have minimal central effects, while larger doses can produce a constellation of responses collectively termed the *central anticholinergic syndrome*. At intermediate doses (2–10 mg), memory and concentration may be impaired, and the patient may be drowsy. If doses of 10 mg or more are used, the patient may exhibit confusion, excitement, hallucinations, ataxia, asynergia, and possibly coma.

Even low doses of scopolamine have central effects. Sedation, amnesia, and drowsiness are common during the clinical use of this drug. Large doses of scopolamine can produce all of the responses seen with atropine. Other tertiary amine compounds with muscarinic receptor blocking activity have similar central effects.

Eye

Antimuscarinic drugs block contraction of the iris sphincter and ciliary muscles of the eye produced by ACh. This results in dilation of the pupil (*mydriasis*) and paralysis of accommodation (*cycloplegia*), responses that cause photophobia and inability to focus on nearby objects. Ocular effects are produced only after higher parenteral doses. Atropine and scopolamine produce responses lasting several days when applied directly to the eyes.

Lung

Muscarinic antagonists inhibit secretions and relax smooth muscle in the respiratory system. The parasympathetic innervation of respiratory smooth muscle is most abundant in large airways, where it exerts a dominant constrictor action. In agreement with this innervation pattern, muscarinic antagonists produce their greatest bronchodilator effect at large-caliber airways. By this mechanism they can block reflex laryngospasm during surgery. In addition, these drugs are potent inhibitors of secretions throughout the respiratory system, from the nose to the bronchioles.

Nicotinic Receptors

Although the antimuscarinic drugs are normally selective for muscarinic cholinergic receptors, high concentrations of agents with a quaternary ammonium group (e.g., propantheline) can block nicotinic receptors on autonomic ganglia and skeletal muscles. However, these effects are generally not clinically important at usual therapeutic doses.

ABSORPTION, METABOLISM, AND EXCRETION

Both atropine and scopolamine are tertiary amines that cross biological membranes readily. They are well absorbed from the gastrointestinal tract and conjunctiva and can cross the blood-brain barrier. After the intravenous injection of atropine (DL-hyoscyamine), the biologically inactive isomer, D-hyoscyamine, is excreted unchanged in the urine. The active isomer, however, can undergo dealkylation, oxidation, and hydrolysis.

The quaternary ammonium derivatives of the belladonna alkaloids, as well as the synthetic quaternary ammonium compounds, are incompletely absorbed from the gastrointestinal tract. Consequently, greater amounts of these compounds are eliminated in the feces following oral administration. The blood-brain barrier prevents quaternary ammonium muscarinic blockers from gaining significant access to the CNS.

CLINICAL USES

Cardiovascular Uses

Atropine can be useful in patients with *carotid sinus syncope*. This condition results from excessive activity of afferent neurons whose stretch receptors are in the carotid sinus. By reflex mechanisms, this excessive afferent input to the medulla oblongata causes pronounced bradycardia, which is reversible by atropine.

Atropine can be used in the differential diagnosis of S-A node dysfunction. If sinus bradycardia is due to extracardiac causes, atropine can generally elicit a tachycardic response, whereas it cannot elicit tachycardia if the bradycardia results from intrinsic causes. Under certain conditions, atropine may be useful in the treatment of acute myocardial infarction. Bradycardia frequently occurs after acute myocardial infarction, especially in the first few hours, and this probably results from excessive vagal tone. The increased tone and bradycardia

facilitate the development of ventricular ectopy. Although atropine sulfate has proved beneficial in patients whose bradycardia is accompanied by hypotension or ventricular ectopy, it *is generally not otherwise recommended in this condition.* Use of atropine is not without hazard, because cardiac work can be increased without improved perfusion, and ventricular arrhythmias may occur. Atropine can also be used to induce positive chronotropy during cardiopulmonary resuscitation.

Uses in Anesthesiology

At one time, atropine or scopolamine was routinely administered before the induction of general anesthesia to block excessive salivary and respiratory secretions induced by certain inhalation anesthetics (e.g., diethyl ether). With the newer, less irritating anesthetics, antimuscarinic premedication is not routinely required as an *antisialagogue* (i.e., to counteract the formation of saliva). Sedation can occur following scopolamine administration, and preanesthetic or postoperative agitation has been observed in some patients. High serum levels of drugs with antimuscarinic activity can produce postoperative delirium. Glycopyrrolate bromide (*Robinul*) has also been given intramuscularly as a preanesthetic medication with satisfactory results. This agent is a quaternary ammonium compound and therefore produces no central effects.

Use With Cholinesterase Inhibitors

During reversal of competitive neuromuscular blockade with neostigmine or other anticholinesterase agents and in the management of myasthenia gravis with cholinesterase inhibitors, atropine or another muscarinic antagonist should be given to prevent the stimulation of muscarinic receptors that accompanies excessive inhibition of AChE. However, extra care must be exercised because the prevention of muscarinic receptor stimulation eliminates an important early sign of cholinergic crisis (see Chapter 12).

Uses in Ophthalmology

Antimuscarinic drugs are widely used in ophthalmology to produce mydriasis and cycloplegia. These actions permit an accurate determination of the refractive state of the eye, and the antimuscarinics are also useful in treating specific ocular diseases and for the treatment of patients following iridectomy.

Atropine, scopolamine, cyclopentolate (*Cyclogyl, AK-Pentolate,* and others) and tropicamide (*Mydriacyl, Tropicacyl,* and others) are among the antimuscarinic drugs used in ophthalmology. All of these agents are tertiary amines that reach the iris and ciliary body after topical application to the eye. Systemic absorption of these drugs from the conjunctival sac is minimal, but significant absorption and toxicity can occur if the antimuscarinic drugs come into contact with the nasal and pharyngeal mucosa via the nasolacrimal duct. To minimize this possibility, pressure should be applied to the lacrimal sac for a few minutes after topical application of muscarinic blockers.

The mydriatic and cycloplegic actions of atropine and scopolamine can persist for a week after topical application to the eye. Shorter-acting drugs, such as cyclopentolate and tropicamide, are now favored for this application because complete recovery of accommodation occurs within 6 to 24 hours and 2 to 6 hours, respectively.

Uses in Disorders of the Digestive System

Nonselective antimuscarinic drugs have been employed in the therapy of peptic ulcers (see Chapter 40) because they can reduce gastric acid secretion; they also have been used as adjunctive therapy in the treatment of *irritable bowel syndrome.* Antimuscarinic drugs can decrease the pain associated with postprandial spasm of intestinal smooth muscle by blocking contractile responses to ACh. Some of the agents used for this disorder have only antimuscarinic activity (e.g., propantheline), while other drugs have additional properties that contribute to their antispasmodic action. Dicyclomine (*Bentyl*) and oxybutynin (*Ditropan*) at therapeutic concentrations primarily have a direct smooth muscle relaxant effect with little antimuscarinic action.

Uses in Urology

Propantheline (*Pro-Banthine*), oxybutynin, dicyclomine, and several other agents have been used for uninhibited bladder syndrome, bladder spasm, enuresis, and urge incontinence. Tolterodine (*Detrol*), a nonselective muscarinic antagonist, exhibits functional specificity for blocking muscarinic receptors in the bladder, with fewer side effects than oxybutynin. However, total prevention of involuntary bladder contractions is difficult to achieve. The participation of noncholinergic, nonadrenergic nerves in bladder contraction may explain this apparent resistance to muscarinic blocking agents.

Uses in Respiratory Disorders

For a long time, muscarinic receptor–blocking drugs occupied a major place in the therapy of asthma, but they have been largely displaced by the adrenergic drugs (see Chapter 41). The problems associated with the use of antimuscarinic alkaloids in respiratory disorders are low therapeutic index and impaired expectoration. The

latter is a consequence of their inhibition of mucous secretion, ciliary activity, and mucous transport.

Ipratropium bromide (*Atrovent*), in contrast, is a synthetic muscarinic blocking drug that has gained widespread use in recent years for the treatment of respiratory disorders. The drug is a quaternary ammonium compound, and it is applied topically to the airways through the use of a metered-dose inhaler. A substantial portion of the dose is swallowed, but absorption from the airways and gastrointestinal tract is negligible and most of the drug is eliminated in the feces. Consequently, systemic antimuscarinic effects are not observed with ipratropium. Dryness of the mouth, cough, and a bad taste have been reported by some patients, but the drug appears to have no other significant adverse effects. Ipratropium does not affect mucociliary transport or the volume and viscosity of sputum.

Clinical studies have demonstrated the effectiveness of ipratropium in chronic obstructive lung disease, for which it is equal or better in effectiveness than β_2-adrenergic agonists. Maximum bronchodilator responses to ipratropium develop in 1.5 to 2 hours. Consequently, it would be less suitable than a rapidly acting β-adrenergic agonist in emergencies. Ipratropium is less effective than the β_2-receptor agonists in asthma, but it may be useful when combined with other bronchodilators.

Uses in Parkinsonism

Antimuscarinic agents can have beneficial effects in the treatment of parkinsonism, since there is an apparent excess of cholinergic activity in the striatum of patients suffering from this disorder. Although therapy of Parkinson's disease is directed toward replacement of the dopaminergic deficiency rather than blocking the cholinergic excess, antimuscarinics are sometimes employed for mild cases and in combination with other agents (e.g., levodopa) for treatment of advanced cases. Side effects due to peripheral muscarinic blockade are common, and CNS side effects (e.g., confusion and hallucinations) can occasionally limit their use (see Chapter 31 for a more detailed discussion of the use of antimuscarinic drugs in extrapyramidal disorders).

Uses in Motion Sickness

Scopolamine is useful for prevention of motion sickness when the motion is very stressful and of short duration. A transdermal preparation (*Transderm-Scop*) with a 72-hour duration of action has been marketed for this purpose. Blockade of cholinergic sites in the vestibular nuclei and reticular formation may account for the effectiveness of this agent. When the motion is less stressful and lasts longer, the antihistamines (H_1-antagonists) are probably preferable to the antimuscarinic drugs, especially for the prophylactic treatment of motion sickness.

Uses as Antidotes for Cholinomimetic Poisoning

Atropine is used as an antidote in poisoning by an overdose of a cholinesterase inhibitor (see Chapter 14). It also is used in cases of poisoning from species of mushroom that contain high concentrations of muscarine and related alkaloids (e.g., *Clitocybe dealbata*).

ANTIMUSCARINIC POISONING

Antimuscarinic poisoning can result from the intake of excessive doses of belladonna alkaloids, synthetic antimuscarinic drugs, and drugs from other pharmacological groups that have significant antimuscarinic activity (Table 13.2).

Signs of peripheral muscarinic blockade (e.g., speech disturbances, swallowing difficulties, cardioacceleration, and pupillary dilation) are most common at lower doses, whereas CNS effects (e.g., headache, restlessness, ataxia, and hallucinations) are more apparent after large doses. Antimuscarinic drugs can produce atrial arrhythmias, A-V dissociation, and ventricular tachycardia and fibrillation. Many cases of antimuscarinic poisoning can be managed by removing unab-

TABLE 13.2 Sources of Anticholinergic Poisoning

Group	Examples
Antihistamines (H_1-receptor antagonists)	Diphenhydramine Chlorpheniramine Dimenhydrinate
Antiparkinsonian drugs	Benztropine Trihexyphenidyl
Antipsychotics	Chlorpromazine Thioridazine Loxapine
Antispasmodics	Dicyclomine Propantheline
Belladonna alkaloids and related drugs	Atropine Scopolamine
Belladonna alkaloid-containing plants	Deadly nightshade Angel's trumpet Jimsonweed
Cyclic antidepressants	Amitriptyline Doxepin Fluoxetine
Cycloplegics and mydriatics	Cyclopentolate Tropicamide
Muscle relaxants	Orphenadrine Cyclobenzaprine

Source: Modified from L. Goldfrank, *Goldfrank's Toxicologic Emergencies.* East Norwalk, CT: Appleton & Lange, 1990.

sorbed drug, treating symptoms, and providing supportive therapy. However, any life-threatening effects (i.e., seizures, severe hypertension, hallucinations, or life-threatening arrhythmias) would justify the use of specific antidotal therapy with the cholinesterase-inhibiting compound physostigmine. Special caution should be employed if the patient has any disorder that might be aggravated by the cholinergic stimulation resulting from the use of physostigmine.

CONTRAINDICATIONS AND CAUTIONS

Muscarinic blocking agents are contraindicated in angle-closure glaucoma. Caution also should be used in individuals with untreated open-angle glaucoma, cardiac disease, hyperthyroidism, or prostatic hypertrophy. Muscarinic antagonists can aggravate reflux esophagitis by decreasing the tone of the lower esophageal sphincter. Infants and children are especially sensitive to the hyperthermic action of muscarinic blockers. Elderly patients are especially sensitive to antimuscarinic effects in the CNS, such as impairment of memory. Phenothiazines and tricyclic antidepressants have antimuscarinic activity and can produce effects that are additive to those of the muscarinic blocking drugs. Antimuscarinics should not be given to patients with gastrointestinal infections because the drug will slow gastric motility and cause the patient to retain the infectious organisms in the gastrointestinal tract.

Study Questions

1. Which of the responses to atropine listed below is most likely to be different in an elderly versus a young patient?
(A) Inhibition of sweating
(B) Tachycardia
(C) Mydriasis
(D) Drowsiness

2. You have successfully prescribed neostigmine to a young patient with myasthenia gravis, and her muscle strength has improved markedly. However, she also exhibits cardiovascular and gastrointestinal signs of excessive vagal tone, which you would like to block with atropine. Which of the following risk factors in prescribing atropine is most important to you?
(A) Dry mouth
(B) Ocular disturbances
(C) Paralysis of the respiratory muscles
(D) Tachycardia

3. Antimuscarinic mydriatics, such as tropicamide, are useful in ophthalmological examinations. Prior to administering tropicamide, it would be most important to know
(A) If the patient has angle-closure glaucoma
(B) If the patient has open-angle glaucoma
(C) If the patient is taking a cholinomimetic miotic drug

4. In which of the following conditions would atropine be the *least* likely to increase blood pressure?
(A) A healthy young medical student
(B) A patient being treated with an AChE inhibitor
(C) A patient being treated with bethanechol

5. A patient has come to you complaining of feeling drowsy and finding it hard to concentrate. The patient tells you that he is taking a medication, but he cannot remember the name of the medication. You proceed to ask questions that might provide a clue to the source of his problems. Which of the following questions would be *least* likely to be helpful?
(A) Has the patient had problems with hay fever and stuffiness?
(B) Is the patient being treated for glaucoma?
(C) Has the patient had back spasms?
(D) Is the patient being treated for mood disorders?

ANSWERS

1. B. The resting level of vagal stimulation of the heart decreases with age, which is typically accompanied by a gradual increase in heart rate with age. Therefore, the tachycardia produced by atropine is greater in young patients with strong vagal tone, and the response decreases with age in parallel with the decrease in vagal tone.

2 C. Atropine will not directly paralyze the respiratory muscles. However, it can prevent the detection of early signs of an overdose of neostigmine, which can quickly progress to a depolarizing block of skeletal muscle and paralysis of the respiratory muscles. Dry mouth, ocular disturbances, and tachycardia are common side effects of atropine given alone, but these effects are less likely to occur with competition between atropine and the increase in the synaptic ACh produced by inhibition of AChE by neostigmine.

3 A. Application of tropicamide to the eye of a patient with narrow-angle (angle-closure) glaucoma is a very serious risk, because the peripheral movement of the relaxed iris can block the outflow of fluid and trigger a rapid rise in intraocular pressure. Open-angle glaucoma does not present the same

risk for the application of a short-acting mydriatic such as tropicamide. If the patient is taking a cholinomimetic miotic for open-angle glaucoma, there is even less risk of applying tropicamide, although potential competition between the miotic and the antagonist may have to be considered.

4 **A.** Atropine has little effect on blood pressure in the absence of a circulating muscarinic agonist because the muscarinic receptors on endothelial cells do not receive synaptic input. Therefore, the blood pressure of a healthy patient will not change with treatment with atropine. In contrast, patients being treated with an AChE inhibitor may have slightly elevated plasma ACh levels, and patients being treated with bethanechol may be hypotensive because of its direct actions on the muscarinic receptors on endothelial cells.

5 **B.** The symptoms are suggestive of central antimuscarinic effects of a drug. Glaucoma is treated with muscarinic agonists or noncholinergic drugs. Although the entry of pilocarpine into the CNS can disturb CNS function, it is not as likely as an antimuscarinic drug to produce drowsiness and loss of concentration. The other questions would all be useful. A patient who has hay fever or stuffiness may be taking an antihistamine. A patient with back spasms may be taking a muscle relaxant, such as cyclobenzaprine. One who is being treated for mood disorders may be taking antipsychotic medication. All of these treatments can produce significant central antimuscarinic side effects.

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CASE Study The Risks of Treating Peptic Ulcers with Antimuscarinic Drugs

A 55-year-old man who works in the furnace room at a steel foundry has developed chronic peptic ulcer disease that has not responded to treatment with antibiotics and H_2 receptor blockers. You are considering giving him an antimuscarinic drug to block gastric acid secretion as adjunctive therapy. What are your concerns regarding the suitability of this treatment for this worker?

ANSWER: Antimuscarinics are not frequently used for peptic ulcer disease today because of their many side effects, but they still can play a useful role as adjunctive therapy. Unfortunately, high concentrations are required to block gastric acid secretion, which means that many side effects are difficult to avoid. This man works in a dangerous environment, and his concentration cannot be compromised. Although CNS depression and loss of concentration is a concern with tertiary amine muscarinic antagonists, quaternary ammonium muscarinic antagonists that do not enter the CNS, such as glycopyrrolate, can be prescribed for blocking gastric acid secretion, thereby avoiding central side effects. Probably the most important risk factor for this worker is his exposure to a hot workplace. Antimuscarinics prevent sweating, which can impair temperature regulation and produce hyperthermia. Hyperthermia alone is a health risk, and it is aggravated by the fact that heart rate increases steeply in proportion to increased body temperature. This worker is probably required to do heavy physical labor, which will add to the hyperthermia and cardiac stimulation. Compensatory feedback via the vagus nerve to slow the heart rate will be blocked by a peripherally acting muscarinic antagonist, and this could lead to very dangerous tachycardia and arrhythmia. Overall, antimuscarinic therapy would not be a good choice for this worker unless he can be moved to a safer work environment.