CHAPTER 145

Anticholinergics

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PRINCIPLES OF TOXICOLOGY

Overview

Anticholinergic agents cause toxicity through inhibition of muscarinic, nicotinic, parasympathetic, or sympathetic acetylcholine receptors. Nicotinic receptor inhibition and ganglionic acetylcholine inhibition at parasympathetic and sympathetic locations is covered in Chapter 157. This chapter focuses on antimuscarinic effects and toxicity. The terms *anticholinergic* and *antimuscarinic* are commonly used synonymously, but the mechanism of toxicity is more accurately described by the term *antimuscarinic,* and thus that term is used in this chapter.

Antimuscarinic effects are due to inhibition of acetylcholine at muscarinic receptors. Muscarinic receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle (intestinal, bronchial, and cardiac), the secretory glands (salivary and sweat), the ciliary body of the eye, and the central nervous system (CNS).

Antimuscarinic agents have been used medicinally from antiquity to present day. Mandrake plant remains were found in the casket of Tutankhamen, the Old Testament of the Bible references use as an aphrodisiac, and antimuscarinic plants were used as anesthetics in Greek and Roman settlements in the first century. Atropine, hyoscyamine, and scopolamine are naturally occurring tertiary amine antimuscarinic agents that remain in wide clinical use today. The tertiary amine structure allows the agent to cross the blood-brain barrier; and therefore, these agents may precipitate CNS toxicity. Quaternary amine antimuscarinic agents, such as glycopyrrolate, have been developed to mitigate CNS side effects due to their limited ability to cross the blood-brain barrier, although mild delirium may occur in the setting of a large overdose.

Clinical Features

Over 600 compounds contain antimuscarinic activity, including prescription drugs, over-the-counter medications, and plants. The effects of muscarinic receptor blockade are used for clinical purposes including pupillary dilation, antispasmodics, treatment of motion sickness, drying of airway secretions, reactive airways disease, treatment of bradycardia, treatment of Parkinsonism, and the management of urinary incontinence and bladder spasm. The agents that most commonly precipitate antimuscarinic toxicity, such as H1 antihistamines and some antipsychotics, often affect several neurotransmitters and receptor systems in addition to antagonism at muscarinic receptors. This may complicate the clinical presentation, and some clinical symptoms may be unique to the specific etiologic agent (Table 145.1).

Antimuscarinic toxicity has central and peripheral manifestations (Fig. 145.1 and Box 145.1). Peripheral muscarinic antagonism causes tachycardia, hypertension, hyperthermia, mydriasis, dry mouth, dry skin (lack of sweating), skin flushing, decreased bowel motility, and urinary retention. CNS blockade of muscarinic receptors may produce delirium characterized by confusion, mumbling speech, agitation, hallucinations, picking gestures, myoclonus, tremor, and coma. Seizures are not expected from pure muscarinic receptor antagonism but many antimuscarinic medications have activity at other receptors that may precipitate seizures. Diphenhydramine toxicity is a classic example of this; it causes significant antimuscarinic symptoms and may also cause seizures through sodium channel blockade. Manifestations of the toxidrome are frequently incomplete and either peripheral or central components may predominate depending upon the antimuscarinic agent, the dose, and the individual patient (see Table 145.1). Only about one-third of patients will manifest all three classic autonomic findings: tachycardia, dry skin/axilla, and mydriasis. Patients may demonstrate delirium as their only manifestation of toxicity. The duration of toxicity is dependent on the dose and is difficult to predict but is often prolonged (18 to 72 hours) due to delayed gastric emptying.

DIFFERENTIAL DIAGNOSES

The diagnosis of antimuscarinic poisoning is most often made by obtaining a history of exposure, either from the patient or someone who was present with the patient at the time. Antimuscarinic toxicity is an important consideration when there is altered mental status with a history of exposure or if physical examination is consistent with toxicity (Box 145.2). Altered mental status, mydriasis, and tachycardia are common antimuscarinic effects that are also seen with multiple conditions (eg, sympathomimetic toxicity, serotonin syndrome, alcohol withdrawal). However, dry axilla, decreased bowel sounds, and urinary retention are less common with adrenergic toxicity and more likely to be associated with antimuscarinic causes. Agitation occurs both with sympathomimetic and antimuscarinic toxicity, but severe agitation and combativeness are more likely to represent the sympathomimetic than antimuscarinic agents—the latter generally cause only mild to moderate agitation. Major medical emergencies should be considered early in the course to ensure timely management. Intracranial hemorrhage (ICH) may lead to altered mental status, hypertension, and dilated pupils, although unilateral pupillary dilation is more likely due to tonsillar herniation when ICH is the etiology of altered mental status. CNS infections or hyperthyroidism may similarly lead to altered mental status, hyperthermia, and hypertension. Failure of physostigmine to reverse the altered mental status should prompt evaluation for meningitis, encephalitis, and thyrotoxicosis.

DIAGNOSTIC TESTING

Laboratory

Patients with mild toxicity, a reliable history of exposure, and symptoms consistent with antimuscarinic toxicity do not require specific laboratory testing. Patients with an unclear history of exposure, other potential etiologies, moderate to severe toxicity, or hyperthermia should be evaluated for causes of altered mental status and end-organ toxicity, including serum glucose,

TABLE 145.1

Specific Antimuscarinic Agents and Their Unique Clinical Manifestations

ANTIMUSCARINIC AGENT	TOXIC DOSE	UNIQUE CLINICAL MANIFESTATIONS AND RECEPTORS ANTAGONIZED
Datura spp.	Seeds contain high concentrations of hyoscyamine and scopolamine. The toxic dose depends upon the species and the mode of ingestion. In general 5 to 10 seeds may be toxic.	Classic peripheral and central antimuscarinic features M_1
Diphenhydramine	2.5 mg/kg; >10 mg/kg may result in cardiovascular and neurologic toxicity.	CNS depression, QRS prolongation and ventricular dysrhythmias, seizures* M_1, H_1, Na^+ channels
Doxylamine	>20 mg/kg associated with rhabdomyolysis.	CNS depression, seizures, rhabdomyolysis† M_1, H_1
Tricyclic antidepressants (TCAs)	2.5 mg/kg, >10 mg/kg may result in cardiovascular and neurologic toxicity.	CNS depression, QRS prolongation, ventricular dysrhythmias, seizures, hypotension, antimuscarinic symptoms may manifest late in the course. M_1, H_1, α_1, Na^+ channels
Atypical antipsychotics	Varies depending upon agent.	CNS depression, hypotension, antimuscarinic symptoms may manifest late in the course.‡ M_1, H_1, α_1, D_2, 5-HT_{2A}

5-HT_{2A}, Serotonin; α_1, alpha adrenergic; *CNS*, central nervous system; D_2, Dopamine; H_1, histamine; M_1, muscarinic.
*Jang DH, Manini AF, Trueger NS, et al: Status epilepticus and wide-complex tachycardia secondary to diphenhydramine overdose. Clin Toxicol (Phila) 48:945-948, 2010.
†Kim HJ, Oh SH, Youn CS, et al: The associative factors of delayed-onset rhabdomyolysis in patients with doxylamine overdose. Am J Emerg Med 29:903-907, 2011.
‡Levine M, Ruha AM: Overdose of atypical antipsychotics: clinical presentation, mechanisms of toxicity and management. CNS Drugs 26:601-611, 2012.

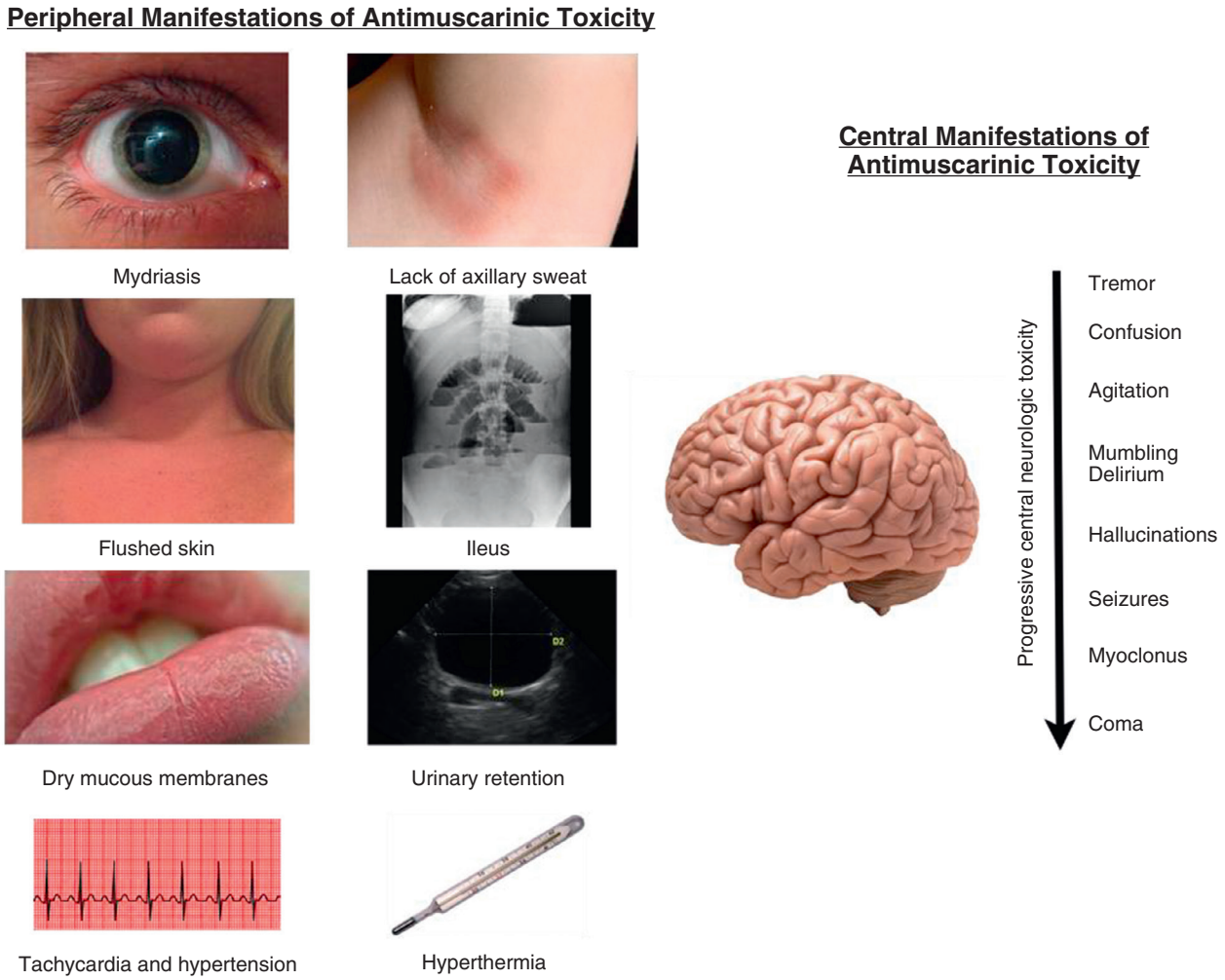

Fig. 145.1. Signs and symptoms of antimuscarinic toxicity.

BOX 145.1

Clinical Presentation of Antimuscarinic Toxicity

Mydriasis: "Blind as a bat"
Altered mental status: "Mad as a hatter"
Dry mucous membranes: "Dry as a bone"
Dry, flushed skin: "Red as a beet"
Hyperthermia: "Hot as Hades"
Urinary retention: "Full as a flask"
Decreased bowel sounds/ileus
Tachycardia

BOX 145.2

Common Differential Diagnosis Considerations With Overlapping Signs and Symptoms of Antimuscarinic Toxicity

DIFFERENTIAL DIAGNOSIS CONSIDERATIONS

Toxicological
Sympathomimetic toxicity
Serotonin toxicity
Neuroleptic malignant syndrome
Lithium toxicity
Antidepressant toxicity
Antipsychotic toxicity

Central Nervous System
Intracranial hemorrhage (ICH)
Seizure

Metabolic
Hyperthyroid
Encephalopathy

Infectious
Sepsis
Central nervous system (CNS) infections

electrolytes, cardiac biomarkers, renal function, and creatinine kinase (for rhabdomyolysis). Patients with an overdose of unclear history should be evaluated for co-ingestion, because antimuscarinic agents are often formulated with other potentially toxic agents. Acetaminophen and salicylate levels should be measured. Physostigmine may be used as a diagnostic test in some cases (see the Management section).

Electrocardiogram

An electrocardiogram (ECG) should be obtained in cases of suspected tricyclic antidepressant (TCA) or diphenhydramine toxicity to assess for possible sodium channel blockade (widened QRS interval or terminal R wave in lead AvR >3 mm). Presence of bradycardia or atrioventricular (AV) block contraindicates the use of physostigmine.

MANAGEMENT

Stabilization

Initial management should focus on evaluation and stabilization of cardiovascular and neurologic toxicity. An intravenous (IV) sodium bicarbonate bolus (50 mEq) should be given for evidence

BOX 145.3

Antimuscarinic Reversal Agent: Physostigmine

PHYSOSTIGMINE SALICYLATE
Indications: Diagnosis and treatment of antimuscarinic toxicity.
Contraindications: Narrow angle glaucoma, first degree atrioventricular (AV) blockade, bradycardia, and seizures due to current overdose.
Adverse effects: Bradycardia, seizure, vomiting.
Route: Intravenous (IV) or intramuscular (IM).
Kinetics/dynamics: Time of onset within 5 minutes following IV administration; 20 to 30 minutes following IM administration. Half-life: 16 ±3 minutes. Plasma cholinesterase inhibition 84 ±5 minutes.
Dosing: 1 to 2 mg bolus slowly (no faster than 1 mg/min). A drip (gtt) may be used. Start gtt at 1 mg/hour titrated every 30 minutes to effect.

of sodium channel blockade with a QRS interval of more than 120 msec, and it may be repeated with a goal of QRS duration of less than 110 msec. Patients with recurrent seizures or agitation that place the patient or staff at risk should be treated with lorazepam (0.05 to 0.1 mg/kg), midazolam (0.05 to 0.1 mg/kg), or diazepam (0.1 to 0.2 mg/kg) boluses. These doses may be repeated every 5 to 15 minutes as needed to halt seizures and provide adequate sedation. When seizures are not present and agitation requires intervention, physostigmine treatment, which is both diagnostic and therapeutic, is preferred (see later discussion). Patients with drug-induced hyperthermia should be promptly treated to prevent progressive acidosis and subsequent organ failure. If evaporative cooling measures and sedation fail, progression to paralysis, ventilation, and airway control is necessary. The target temperature is 36° to 38° C.

Decontamination

Most patients with antimuscarinic poisoning do well with symptomatic care alone. There is no role for gastric lavage, whole bowel irrigation, or hemodialysis. Oral activated charcoal, similarly, is not indicated for the vast majority of antimuscarinic poisoned patients. However, oral activated charcoal may be used for symptomatic patients who have ingested a highly toxic quantity of antimuscarinic plant seeds only if the patient presents early after ingestion (<2 hours) and is anticipated to remain cooperative. Administering AC after antidote treatment with physostigmine has reversed delirium is a complex decision and is best made in consultation with a medical toxicologist or regional poison center.

Pharmacologic Intervention and Antidote Treatment

Control of delirium is the most common reason for emergency intervention in antimuscarinic poisoned patients. Sedation or antidotal treatment is indicated for patients whose delirium places them at risk of harming themselves or staff, requiring ongoing physical restraint, or interfering with effective treatment (eg, pulling out IV lines). Physostigmine is the preferred for treatment for antimuscarinic toxicity if no contraindications are present.

Physostigmine salicylate is a specific antidote for antimuscarinic toxicity (Box 145.3).

Physostigmine is safe and highly effective in reversing both agitation and delirium when used as treatment of delirium caused by antimuscarinic poisoning. In this specific setting, physostigmine is several-fold more effective than benzodiazepines, which control agitation in only about one-quarter of patients and have

no effect on delirium. Physostigmine use also seems to hasten recovery from the manifestations of antimuscarinic toxicity. Therefore physostigmine should be used early in the course of suspected antimuscarinic poisoning, because it is a more effective treatment of agitation and delirium and may limit additional unnecessary diagnostic testing and sedative requirements.

The drug is a tertiary amine carbamate that reversibly inhibits cholinesterases in the both peripheral nervous system and CNS. This allows for acetylcholine accumulation and subsequent competition with the antimuscarinic blocking agent occupying the receptor. Physostigmine has a short half-life, approximately 20 minutes. Although inhibition of the esterase, which yields the pharmacodynamic effects, last considerably longer with a half-life of 80 minutes. Accordingly, the clinical duration of physostigmine is 3 to 6 hours.

Physostigmine should be used to control symptoms of agitation or delirium potentially attributable to antimuscarinic toxicity. The initial dose of physostigmine is 1 to 2 mg IV over 5 minutes (see Box 145.3). If only a partial response is observed (the delirium is not completely reversed) at 10 minutes post administration, the same dose may be repeated. If agitation or delirium symptoms recur within 3 hours and the patient is again a risk to themselves or staff, repeat dosing of 1 to 2 mg IV over 5 minutes should be given.[4] If three or more administrations are necessary over a 6-hour period to control agitation or delirium, then an infusion should be started. A bolus of 1 to 2 mg IV should be given and the infusion started at 1 mg/hour.[5,6] If symptoms recur while on the infusion, the drip can be increased by 0.5 mg/hour every hour to maintain a normal mental status. The patient should be placed on a cardiac monitor to monitor for bradycardia during physostigmine administration. The infusion should be stopped every 12 hours to determine if the toxidrome has resolved. If symptoms recur during observation off physostigmine, the same bolus and infusion rate should be given. Patients may be considered medically cleared from antimuscarinic toxicity if symptoms do not recur within 6 hours of the last antidote dose.[4] If the patient develops side effects (vomiting, diarrhea, or bradycardia), the infusion should be stopped. Extended observation with repeated dosing and/or infusions may be required in very large overdoses or in antimuscarinic plant seed ingestions because ongoing absorption leads to prolonged symptoms.

When used diagnostically, near complete reversal of delirium over a matter of minutes is specific for antimuscarinic poisoning and may be used to defer additional testing, such as lumbar puncture or neuroimaging.

We do not recommend use of physostigmine in the treatment of acutely TCA poisoned patients with cardiovascular toxicity, specifically bradycardia or AV block. Physostigmine use in this context has been associated with ventricular tachycardia and cardiac arrest. TCAs have inherent cardiac toxicity, so it is not clear that physostigmine actually causes these adverse cardiac events. Many patients who received physostigmine without adverse effects were subsequently found to have ingested a TCA.[4] Further considerations regarding the use of physostigmine in patients with TCA toxicity are discussed in Chapter 146.

When physostigmine is contraindicated, sedation can be accomplished with IV benzodiazepines, as described earlier in this chapter.

Overall, physostigmine should be given as a diagnostic and therapeutic intervention, if the antimuscarinic-induced delirium places the patient or staff at risk, in patients without overdose-induced seizure, AV blockade, or bradycardia.

DISPOSITION

Most patients do well with supportive care (sedation, hydration, temperature control, and observation). Length of observation and need for admission depend on the agent, the dose, the intent, and the patient. Antimuscarinic agents slow gut motility, which increases the time to peak symptoms. As such, long-acting agents, plant seeds, or large ingestions should have extended observation up to 24 hours even if asymptomatic. Patients at extremes of age are at increased risk for toxicity and should be considered for observation. Patients with an unreliable history or concern for self-harm should have extended observation and psychiatric consultation.

Observation at Home

Asymptomatic, accidental exposures to a known, low dose, in patients with normal mental status and normal vital signs four hours after ingestion are safe to be observed at home by a trustworthy adult.

Emergency Department Observation

Patients with mild toxicity (normal mental status or slight drowsiness, normal vital signs, no ECG changes) and small ingestions should be observed in the ED until symptoms are clearly resolving (typically less than 6 hours). Patients treated with physostigmine who are asymptomatic 6 hours following physostigmine administration are considered clear of antimuscarinic toxicity and can be medically cleared.[1]

Hospital Admission

Patients with self-harm attempts and moderate to severe toxicity (abnormal vital signs, altered mental status) should have an extended observation period for progression of toxicity or until symptoms improve. Ingestion of large amounts of pills or plant seeds should be expected to require prolonged observation (24 to 48 hours) due to decreased gastrointestinal motility. Patients requiring more than three doses of physostigmine within 6 hours or who require an infusion of physostigmine should be admitted to a monitored setting, because the clinical course is likely to be prolonged.

Intensive Care Unit Admission

Patients with agitated delirium requiring physostigmine infusion, hyperthermia, dysrhythmia, or seizures will benefit from intensive care unit (ICU) admission for monitoring, frequent medications, and airway control if high doses of sedatives or additional physostigmine administration are necessary.

Consultations

Medical toxicology or poison center consultation should be considered when there are questions about exposure, diagnosis, or the appropriateness of antidotal therapy.

KEY CONCEPTS

- Symptoms of muscarinic receptor blockade may include delirium, mydriasis, a lack of sweating, dry mucous membranes, ileus, urinary retention, hyperthermia, tachycardia, and hypertension.
- Delirium may be the sole manifestation of toxicity and only one-third of patients manifest all of the classic autonomic findings of tachycardia, dry skin and axilla, and mydriasis.
- Physostigmine should be given to control severe agitation and delirium precipitated by muscarinic receptor antagonism.
- Physostigmine is relatively contraindicated in patients with bradycardia or AV block in the setting of possible TCA toxicity.
- Benzodiazepines should be used for symptom control when seizures occur or when physostigmine is contraindicated.
- Patients who develop hyperthermia despite treatment with evaporative cooling should be paralyzed, intubated, and cooled.
- Symptomatic patients should be observed until symptoms are clearly resolving. Accidental ingestion with mild symptoms can be expected to improve in less than 6 hours. Purposeful ingestions with mild to moderate symptoms will require admission to the hospital for extended observation (24 to 48 hours).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

REFERENCES

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CHAPTER 145: QUESTIONS & ANSWERS

145.1. A 21-year-old man presents after drinking an "herbal tea" with some friends. He reports visual hallucinations. He has a resting tachycardia and a mildly elevated temperature. On physical examination, he is noted to have dry mucous membranes, dry and flushed skin, and absent bowel sounds. In addition to certain plants, which of the following medications can also cause these symptoms?

A. Amiodarone
B. Clonidine
C. Diphenhydramine
D. Lidocaine
E. Morphine

Answer: C. This patient is experiencing the antimuscarinic toxidrome. In addition to the signs and symptoms described here, patients may also have mydriasis and bladder distention. Mental status can be agitated or depressed. Myoclonus or choreoathetoid movements can also be seen. Amiodarone can cause hypothyroidism or hyperthyroidism and skin discoloration, as well as several other long-term effects. Clonidine can cause dry mouth, drowsiness, bradycardia, and hypotension. Lidocaine can cause headaches, dizziness, confusion, tinnitus, and tremor, as well as bradycardia and hypotension. Morphine can cause respiratory cerebral depression, as well as miosis, bradycardia, and hypotension.

145.2. Many signs and symptoms of the antimuscarinic syndrome are similar to those of other syndromes, including the sympathomimetic syndrome, serotonin syndrome, and neuroleptic malignant syndrome. Which of the following antimuscarinic findings is most likely to distinguish the antimuscarinic syndrome from the other syndromes listed?

A. Altered mental status
B. Altered movements
C. Dry skin
D. Fever
E. Mydriasis

Answer: C. All the other syndromes often have some degree of diaphoresis. Fever, altered mental status, and mydriasis can occur in all the named syndromes. Myoclonus can occur in the antimuscarinic syndrome, tremor in the serotonin syndrome, and rigidity in the neuroleptic malignant syndrome.

145.3. A 31-year-old woman presents with altered mental status after ingesting an unknown quantity of an unknown medication. Her vital signs are significant for tachycardia and fever. Her physical examination reveals mydriasis, dry mucous membranes, dry skin, decreased bowel sounds, and hypotension. Her electrocardiogram (ECG) reveals a wide QRS complex and prolonged QT interval. Which of the following medications is associated with this toxidrome?

A. Amitriptyline
B. Dextroamphetamine
C. Diphenhydramine
D. Fluoxetine
E. Lithium

Answer: A. This patient is experiencing many of the signs and symptoms of antimuscarinic syndrome. However, pure antimuscarinic rarely if ever cause cardiac dysrhythmias (other than sinus tachycardia). Tricyclic antidepressants (TCAs) frequently cause antimuscarinic signs and symptoms but also cause dysrhythmias. Although selective serotonin reuptake inhibitors, stimulants, and lithium can all cause similar signs and symptoms, electrocardiographic abnormalities such as those described here are rare.

145.4. Which diagnostic test should be performed in almost all patients presenting with the antimuscarinic syndrome?

A. Arterial blood gas analysis
B. Computed tomography (CT) scan of the brain
C. Electrocardiography
D. Electroencephalography
E. Urine drug screen

Answer: C. Patients with a clear presentation and mild symptoms do not necessarily require any diagnostic evaluation. However, patients with more severe symptoms should have measurements of serum electrolytes, renal function, creatine kinase, and glucose concentration performed. Electrocardiography is most helpful because cyclic antidepressants are a common cause of antimuscarinic symptoms and can cause fatal cardiac dysrhythmias. Arterial blood gas analysis might be helpful if the patient has respiratory depression. Head CT might be indicated in patients with altered mental status of unknown cause. Electroencephalography would be indicated only if there is a suspicion of unrecognized seizures. Urine drug screens are almost never helpful in determining treatment, especially in the case of antimuscarinic syndrome because they will not detect most of the medications responsible for this syndrome.

145.5. What is the best initial treatment of hyperthermia in patients with antimuscarinic syndrome?

A. Acetaminophen
B. Cooling blankets
C. Dantrolene
D. Evaporative cooling
E. Physical restraints

Answer: D. Evaporative cooling is the most effective and noninvasive way to decrease temperature. Death has occurred because of untreated hyperthermia in patients with antimuscarinic syndrome. Antipyretics such as acetaminophen are ineffective at reducing temperature because hyperthermia is not "fever." Dantrolene is useful in malignant hyperthermia but has no role in hyperthermia of other causes. Cooling blankets are ineffective. Physical restraints are likely to worsen the problem and to increase the risk of rhabdomyolysis and myoglobinuric renal failure. If a patient is dangerously agitated, physostigmine are the agents of choice to decrease agitation, muscle activity, and related metabolic activity that contribute to hyperthermia.

145.6. Which of the following medications crosses the blood-brain barrier and is potentially useful in the treatment of antimuscarinic syndrome?
A. Edrophonium
B. Metoclopramide
C. Neostigmine
D. Physostigmine
E. Pyridostigmine

Answer: D. Metoclopramide is an antiemetic and prokinetic medication that has no role in antimuscarinic syndrome. All of the other agents are acetylcholinesterase inhibitors, but only physostigmine crosses the blood-brain barrier and so it is the only drug that can reverse the central and peripheral effects of antimuscarinic medications. However, physostigmine can cause serious side effects and thus should be used carefully in patients with bradycardia and A-V block.

145.7. Which of the following is a contraindication to physostigmine use in a patient with antimuscarinic syndrome?
A. Altered mental status
B. Bradycardia and atrioventricular (AV) blockade
C. Coexisting myasthenia gravis
D. Hyperthermia
E. Seizure

Answer: B. Physostigmine is an acetylcholinesterase inhibitor that is useful to reverse the effects of antimuscarinic medications. However, it is contradicted with narrow angle glaucoma, AV blockade, bradycardia, and seizures due to the causal overdose. The main benefit of physostigmine is to reverse the altered mental status and agitation caused by the antimuscarinic medication. Physostigmine is occasionally used to treat myasthenia gravis. Hyperthermia and seizures can occur as part of the antimuscarinic syndrome, and although neither is directly treated with physostigmine, they are not contraindications to its use.