CHAPTER 13

Anticholinergic Drugs

KEY CONCEPTS

1. The ester linkage is essential for effective binding of the anticholinergics to the acetylcholine receptors. This competitively blocks binding by acetylcholine and prevents receptor activation. The cellular effects of acetylcholine, which are mediated through second messengers, are inhibited.
2. Anticholinergics relax the bronchial smooth musculature, which reduces airway resistance and increases anatomic dead space.
3. Atropine has particularly potent effects on the heart and bronchial smooth muscle and is the most efficacious anticholinergic for treating bradyarrhythmias.
4. Ipratropium solution (0.5 mg in 2.5 mL) seems to be particularly effective in the treatment of acute chronic obstructive pulmonary disease when combined with a β-agonist drug (eg, albuterol).
5. Scopolamine is a more potent antisialagogue than atropine and causes greater central nervous system effects.
6. Because of its quaternary structure, glycopyrrolate cannot cross the blood–brain barrier and is almost devoid of central nervous system and ophthalmic activity.

One group of cholinergic antagonists has already been discussed: the nondepolarizing neuromuscular-blocking agents. These drugs act primarily at the nicotinic receptors in skeletal muscle. This chapter presents the pharmacology of drugs that block muscarinic receptors. Although the classification *anticholinergic* usually refers to this latter group, a more precise term would be *antimuscarinic*.

In this chapter, the mechanism of action and clinical pharmacology are introduced for three common anticholinergics: atropine, scopolamine, and glycopyrrolate. The clinical uses of these drugs in anesthesia relate to their effect on the cardiovascular, respiratory, cerebral, gastrointestinal, and other organ systems (Table 13–1).

MECHANISMS OF ACTION

Anticholinergics are esters of an aromatic acid combined with an organic base (Figure 13–1). The ester linkage is essential for effective binding of the anticholinergics to the acetylcholine receptors. **This competitively blocks binding by acetylcholine and prevents receptor activation.** The cellular effects of acetylcholine, which are mediated through second messengers, are inhibited. The tissue receptors vary in their sensitivity to blockade. In fact, muscarinic receptors are not homogeneous, and receptor subgroups have been identified including: neuronal (M_1), cardiac (M_2), and glandular (M_3) receptors.

TABLE 13–1 Pharmacological characteristics of anticholinergic drugs.[1]

	Atropine	Scopolamine	Glycopyrrolate
Tachycardia	+++	+	++
Bronchodilatation	++	+	++
Sedation	+	+++	0
Antisialagogue effect	++	+++	+++

[1]0, no effect; +, minimal effect; ++, moderate effect; +++, marked effect.

CLINICAL PHARMACOLOGY

General Pharmacological Characteristics

In normal clinical doses, only muscarinic receptors are blocked by the anticholinergic drugs discussed in this chapter. The extent of the anticholinergic effect depends on the degree of baseline vagal tone. Several organ systems are affected.

A. Cardiovascular

Blockade of muscarinic receptors in the sinoatrial node produces tachycardia. This effect is especially useful in reversing bradycardia due to vagal reflexes (eg, baroreceptor reflex, peritoneal traction, or oculocardiac reflex). A transient slowing of heart rate in response to smaller intravenous doses of atropine (<0.4 mg) has been reported. The mechanism of this paradoxical response is unclear. Facilitation of

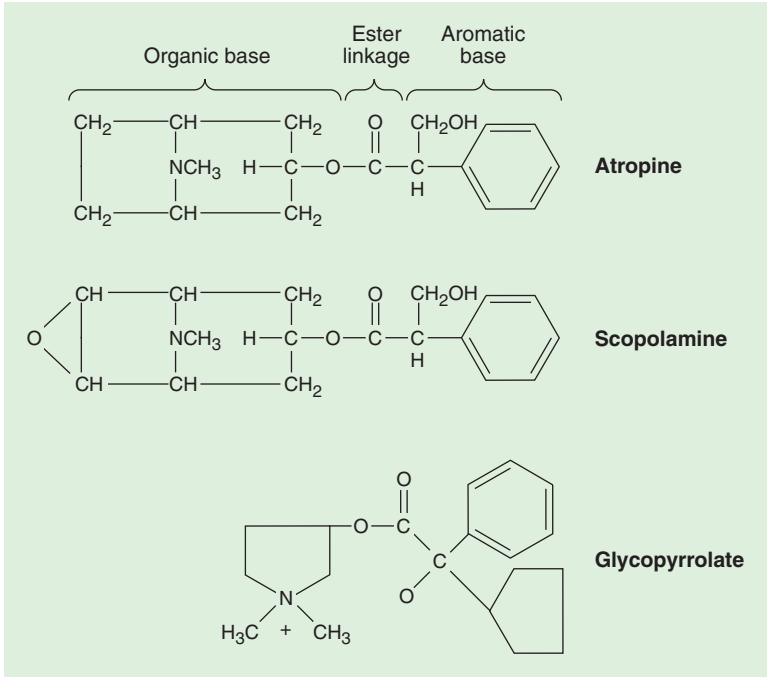

FIGURE 13–1 Physical structures of anticholinergic drugs.

conduction through the atrioventricular node shortens the P–R interval on the electrocardiogram and often decreases heart block caused by vagal activity. Atrial arrhythmias and nodal (junctional) rhythms occasionally occur. Anticholinergics generally have little effect on ventricular function or peripheral vasculature because of the paucity of direct cholinergic innervation of these areas despite the presence of cholinergic receptors. Presynaptic muscarinic receptors on adrenergic nerve terminals are known to inhibit norepinephrine release, so muscarinic antagonists may modestly enhance sympathetic activity. Large doses of anticholinergic agents can result in dilation of cutaneous blood vessels (atropine flush).

B. Respiratory

The anticholinergics inhibit the secretions of the respiratory tract mucosa, from the nose to the bronchi, a valuable property during airway endoscopic or surgical procedures. Relaxation of the bronchial smooth musculature reduces airway resistance and increases anatomic dead space. These effects are particularly pronounced in patients with chronic obstructive pulmonary disease or asthma.

C. Cerebral

Anticholinergic medications can cause a spectrum of central nervous system effects ranging from stimulation to depression, depending on drug choice and dosage. Cerebral stimulation may present as excitation, restlessness, or hallucinations. Cerebral depression, including sedation and amnesia, are prominent after scopolamine. Physostigmine, a cholinesterase inhibitor that crosses the blood–brain barrier, promptly reverses anticholinergic actions on the brain.

D. Gastrointestinal

Salivary secretions are markedly reduced by anticholinergic drugs. Gastric secretions are also decreased, but larger doses are necessary. Decreased intestinal motility and peristalsis prolong gastric emptying time. Lower esophageal sphincter pressure is reduced. Overall, the anticholinergic drugs do not prevent aspiration pneumonia.

E. Ophthalmic

Anticholinergics cause mydriasis (pupillary dilation) and cycloplegia (an inability to accommodate to near vision); acute angle-closure glaucoma is unlikely following systemic administration of most anticholinergic drugs.

F. Genitourinary

Anticholinergics may decrease ureter and bladder tone as a result of smooth muscle relaxation and lead to urinary retention, particularly in elderly men with prostatic hypertrophy.

G. Thermoregulation

Inhibition of sweat glands may lead to a rise in body temperature (atropine fever).

Specific Anticholinergic Drugs

ATROPINE

Physical Structure

Atropine is a tertiary amine. The naturally occurring levorotatory form is active, but the commercial mixture is racemic (Figure 13–1).

Dosage & Packaging

As a premedication, atropine is administered intravenously or intramuscularly in a range of 0.01–0.02 mg/kg, up to the usual adult dose of 0.4–0.6 mg. Larger intravenous doses up to 2 mg may be required to completely block the cardiac vagal nerves in treating severe bradycardia. Atropine sulfate is available in a multitude of concentrations.

Clinical Considerations

Atropine has particularly potent effects on the heart and bronchial smooth muscle and is the most efficacious anticholinergic for treating bradyarrhythmias. Patients with coronary artery disease may not tolerate the increased myocardial oxygen demand and decreased oxygen supply associated with the tachycardia caused by atropine. A derivative of atropine, ipratropium bromide, is available in a metered-dose inhaler for the treatment of bronchospasm. Its quaternary ammonium structure significantly limits systemic absorption. Ipratropium solution (0.5 mg in 2.5 mL) seems to be particularly effective in the treatment of acute chronic obstructive pulmonary disease when combined with a β-agonist drug (eg, albuterol). The central nervous

system effects of atropine are minimal after the usual doses, even though this tertiary amine can rapidly cross the blood–brain barrier. Atropine has been associated with mild postoperative memory deficits, and toxic doses are usually associated with excitatory reactions. An intramuscular dose of 0.01–0.02 mg/kg reliably provides an antisialagogue effect. Atropine should be used cautiously in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder-neck obstruction.

SCOPOLAMINE

Physical Structure

Scopolamine, a tertiary amine, differs from atropine by the addition of an epoxide to the heterocyclic ring.

Dosage & Packaging

The premedication dose of scopolamine is the same as that of atropine, and it is usually given intramuscularly. Scopolamine hydrobromide is available as solutions containing 0.3, 0.4, and 1 mg/mL.

Clinical Considerations

5 Scopolamine is a more potent antisialagogue than atropine and causes greater central nervous system effects. Clinical dosages usually result in drowsiness and amnesia, although restlessness, dizziness, and delirium are possible. The sedative effects may be desirable for premedication but can interfere with awakening following short procedures. Scopolamine has the added virtue of preventing motion sickness. The lipid solubility allows transdermal absorption, and transdermal scopolamine has been used to prevent postoperative nausea and vomiting. Because of its pronounced ocular effects, scopolamine is best avoided in patients with closed-angle glaucoma.

GLYCOPYRROLATE

Physical Structure

Glycopyrrolate is a synthetic product that differs from atropine in being a quaternary amine and having both cyclopentane and a pyridine moieties in the compound.

Dosage & Packaging

The usual dose of glycopyrrolate is one-half that of atropine. For instance, the premedication dose is 0.005–0.01 mg/kg up to 0.2–0.3 mg in adults. Glycopyrrolate for injection is packaged as a solution of 0.2 mg/mL.

Clinical Considerations

6 Because of its quaternary structure, glycopyrrolate cannot cross the blood–brain barrier and is almost devoid of central nervous system and ophthalmic activity. Potent inhibition of salivary gland and respiratory tract secretions is the primary rationale for using glycopyrrolate as a premedication. Heart rate usually increases after intravenous—but not intramuscular—administration. Glycopyrrolate has a longer duration of action than atropine (2–4 h vs 30 min after intravenous administration).

CASE DISCUSSION

Central Anticholinergic Syndrome

An elderly patient is scheduled for enucleation of a blind, painful eye. Scopolamine, 0.4 mg intramuscularly, is administered as premedication. In the preoperative holding area, the patient becomes agitated and disoriented. The only other medication the patient has received is 1% atropine eye drops.

How many milligrams of atropine are in one drop of a 1% solution?

A 1% solution contains 1 g dissolved in 100 mL, or 10 mg/mL. Eyedroppers vary in the number of drops formed per milliliter of solution, but average 20 drops/mL. Therefore, one drop usually contains 0.5 mg of atropine.

How are ophthalmic drops systemically absorbed?

Absorption by vessels in the conjunctival sac is similar to subcutaneous injection. More rapid absorption is possible by the nasolacrimal duct mucosa.

What are the signs and symptoms of anticholinergic poisoning?

Reactions from an overdose of anticholinergic medication involve several organ systems. The central anticholinergic syndrome refers to central nervous system changes that range from unconsciousness to hallucinations. Agitation and delirium are not unusual in elderly patients. Other systemic manifestations include dry mouth, tachycardia, atropine flush, atropine fever, and impaired vision.

What other drugs possess anticholinergic activity that could predispose patients to the central anticholinergic syndrome?

Tricyclic antidepressants, antihistamines, and antipsychotics have antimuscarinic properties that could potentiate the side effects of anticholinergic drugs.

What drug is an effective antidote to anticholinergic overdosage?

Cholinesterase inhibitors indirectly increase the amount of acetylcholine available to compete with anticholinergic drugs at the muscarinic receptor. Neostigmine, pyridostigmine, and edrophonium possess a quaternary ammonium group that prevents penetration of the blood–brain barrier. Physostigmine, a tertiary amine, is lipid soluble and effectively reverses central anticholinergic toxicity. An initial dose of 0.01–0.03 mg/kg may have to be repeated after 15–30 min.

Should this case be canceled or allowed to proceed?

Enucleation to relieve a painful eye is clearly an elective procedure. The most important question that must be addressed for elective cases is whether the patient is optimally medically managed. In other words, would canceling surgery allow further fine-tuning of any medical problems? For example, if this anticholinergic overdose were accompanied by tachycardia, it would probably be prudent to postpone surgery in this elderly patient. On the other hand, if the patient's mental status responds to physostigmine and there seems to be no other significant anticholinergic side effects, surgery could proceed.

SUGGESTED READING

Brown JH: Muscarinic receptor agonists and antagonists. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 12th ed. Brunton LL (editor). McGraw-Hill, 2011.

Katzung BG (editor): Cholinoceptor-blocking drugs. In: *Basic and Clinical Pharmacology*, 11th ed. McGraw-Hill, 2009.