Cholinergic Antagonists

5

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I. OVERVIEW

Cholinergic antagonist is a general term for agents that bind to cholinoceptors (muscarinic or nicotinic) and prevent the effects of acetylcholine (ACh) and other cholinergic agonists. The most clinically useful of these agents are selective blockers of muscarinic receptors. They are commonly known as anticholinergic agents (a misnomer, as they antagonize only muscarinic receptors), antimuscarinic agents (more accurate terminology), or parasympatholytics. The effects of parasympathetic innervation are thus, interrupted by these agents, and the actions of sympathetic innervation are left unopposed. A second group of drugs, the ganglionic blockers, shows a preference for nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important cholinergic antagonists. A third family of compounds, the neuromuscular blocking agents (mostly nicotinic antagonists), interfere with transmission of efferent impulses to skeletal muscles. These drugs are used as skeletal muscle relaxants in surgical anesthesia and as agents to facilitate intubation in surgical and critical care patients. Figure 5.1 summarizes the cholinergic antagonists discussed in this chapter.

ANTIMUSCARINIC AGENTS

Aclidinium TUDORZA
Atropine GENERIC ONLY
Benztropine COGENTIN
Cyclopentolate AKPENTOLATE, CYCLOGYL
Darifenacin ENABLEX
Fesoterodine TOVIAZ
Glycopyrrolate ROBINUL, SEEBRI
Hyoscyamine LEVSIN, OSCIMIN, SYMAX
Ipratropium ATROVENT HFA
Oxybutynin DITROPAN, GELNIQUE, OXYTROL
Scopolamine TRANSDERM SCŌP
Solifenacin VESICARE
Tiotropium SPIRIVA RESPIMAT
Tolterodine DETROL
Trihexyphenidyl GENERIC ONLY
Tropicamide MYDRIACYL, TROPICACYL
Trospium GENERIC ONLY

GANGLIONIC BLOCKERS

Nicotine NICODERM, NICORETTE, NICOTROL

NEUROMUSCULAR BLOCKERS

Cisatracurium NIMBEX
Mivacurium MIVACRON
Pancuronium GENERIC ONLY
Rocuronium GENERIC ONLY
Succinylcholine ANECTINE, QUELICIN
Vecuronium GENERIC ONLY

Figure 5.1
Summary of selected cholinergic antagonists.

II. ANTIMUSCARINIC AGENTS

Commonly known as anticholinergic drugs, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors (Figure 5.2), causing inhibition of muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating the salivary and sweat glands. Because they do not block nicotinic receptors, the anticholinergic drugs (more precisely, antimuscarinic drugs) have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. The anticholinergic drugs are beneficial in a variety of clinical situations. [Note: A number of antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity.]

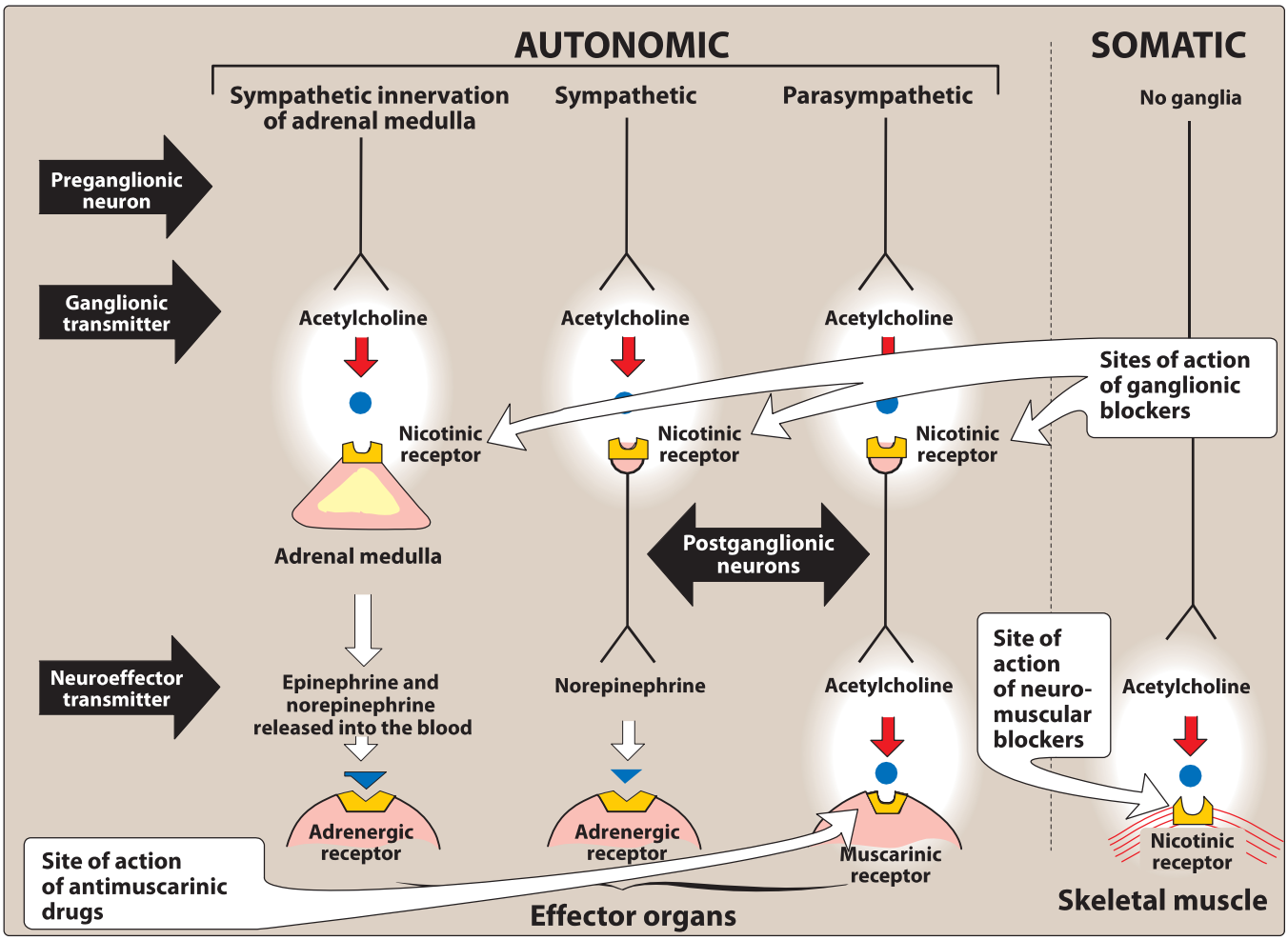

Figure 5.2
Sites of action of cholinergic antagonists.

A. Atropine

Atropine [A-troe-peen] is a tertiary amine extracted from belladonna alkaloid. It has a high affinity for muscarinic receptors and binds competitively to prevent ACh from binding (Figure 5.3). *Atropine* acts both centrally and peripherally. General actions last about 4 hours; however, effects of topical administration in the eye may persist for days. Neuroeffector organs have varying sensitivity to *atropine*. The greatest inhibitory effects are seen in bronchial tissue, salivary and sweat glands, and the heart.

1. *Actions*

a. Eye: *Atropine* blocks muscarinic activity in the eye, resulting in mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with angle-closure glaucoma, intraocular pressure may rise dangerously.

b. Gastrointestinal (GI): *Atropine* (as the active isomer, *L-hyoscyamine* [hi-oh-SYE-uh-meen]) can be used as an antispasmodic to reduce activity of the GI tract. *Atropine*

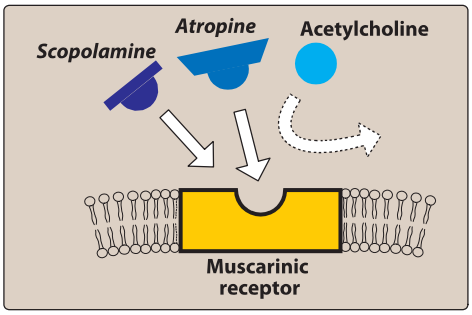

Figure 5.3
Competition of *atropine* and *scopolamine* with *acetylcholine* for the muscarinic receptor.

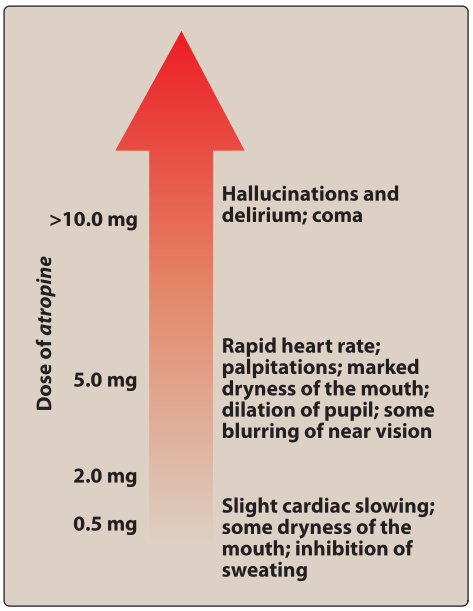

Figure 5.4
Dose-dependent effects of *atropine*.

and *scopolamine* (discussed below) are probably the most potent antispasmodic drugs available. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, *atropine* is not effective for the treatment of ulcers. Doses of *atropine* that reduce spasms also reduce saliva secretion, ocular accommodation, and urination. These effects decrease compliance with *atropine*.

c. **Cardiovascular:** *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 5.4). At low doses, the predominant effect is a slight decrease in heart rate. This effect results from blockade of M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. Higher doses of *atropine* cause a progressive increase in heart rate by blocking M_2 receptors on the sinoatrial node.

d. **Secretions:** *Atropine* blocks muscarinic receptors in the salivary glands, producing dryness of the mouth (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are similarly affected. [Note: Inhibition of secretions of sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]

2. **Therapeutic uses**

a. **Ophthalmic:** Topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. Shorter-acting antimuscarinics (*cyclopentolate* [sye-kloe-PEN-toe-late] and *tropicamide* [troe-PIK-a-mide]) have largely replaced *atropine* due to prolonged mydriasis observed with *atropine* (7 to 14 days vs. 6 to 24 hours with other agents). [Note: *Phenylephrine* or similar α-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required.]

b. **Antispasmodic:** *Atropine* is used as an antispasmodic agent to relax the GI tract.

c. **Cardiovascular:** Injectable *atropine* is used to treat bradycardia of varying etiologies.

d. **Antisecretory:** *Atropine* is sometimes used as an antisecretory agent to block secretions in the respiratory tract prior to surgery. [Note: *Glycopyrrolate* (see below) is also used for this indication.]

e. **Antidote for cholinergic agonists:** *Atropine* is used for the treatment of organophosphate (insecticides, nerve gases) poisoning, of overdose of clinically used anticholinesterases such as *physostigmine*, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of injectable *atropine* may be required over a long period to counteract the poisons. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

3. **Pharmacokinetics:** *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

4. **Adverse effects:** Depending on the dose, *atropine* may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity. *Atropine* may also induce troublesome urinary retention. The drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature.

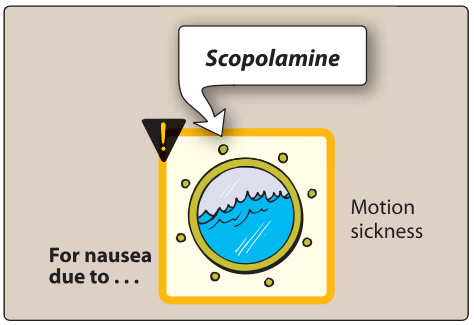

Figure 5.5
Scopolamine is an effective agent for motion sickness.

B. *Scopolamine*

Scopolamine [skoe-POL-a-meen], another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamine* has greater action on the CNS (unlike *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action as compared to *atropine*. It has some special actions as indicated below.

1. **Actions:** *Scopolamine* is one of the most effective drugs available for motion sickness (Figure 5.5). It also has the unusual effect of blocking short-term memory. In contrast to *atropine*, *scopolamine* produces sedation, but at higher doses, it can produce excitement. *Scopolamine* may produce euphoria and is susceptible to abuse.

2. **Therapeutic uses:** *Scopolamine* is used for the prevention of motion sickness and postoperative nausea and vomiting. For motion sickness, it is available as a topical patch that provides effects for up to 3 days. [Note: As with all drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs.]

3. **Pharmacokinetics and adverse effects:** These aspects are similar to those of *atropine*, with the exception of longer half-life.

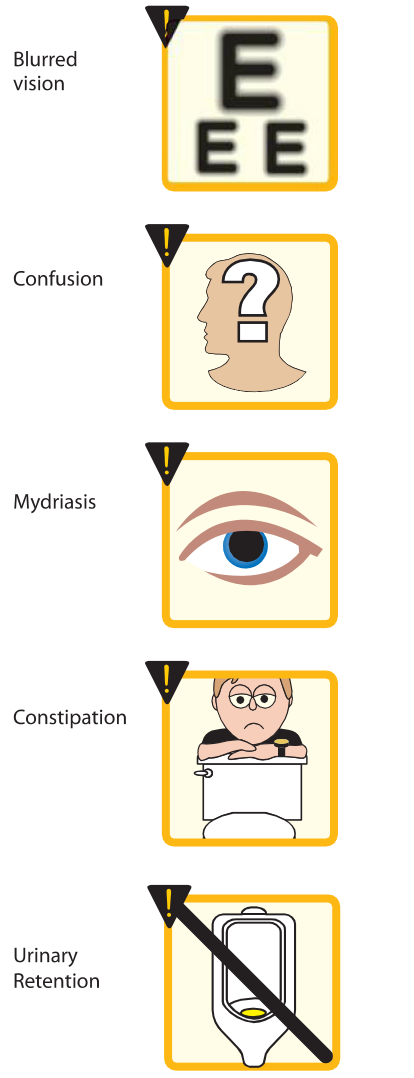

Figure 5.6
Adverse effects commonly observed with muscarinic antagonists.

C. *Aclidinium*, *glycopyrrolate*, *ipratropium*, and *tiotropium*

Ipratropium [i-pra-TROE-pee-um] and *tiotropium* [TYE-oh-TROE-pee-um] are quaternary derivatives of *atropine*, and *glycopyrrolate* [glye-koe-PYE-roe-late] and *aclidinium* [a-kli-DIN-ee-um] are synthetic quaternary compounds. *Ipratropium* is classified as a short-acting muscarinic antagonist (SAMA), while *glycopyrrolate*, *tiotropium*, and *aclidinium* are classified as long-acting muscarinic antagonists (LAMAs) based on the duration of action. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). *Ipratropium* and *tiotropium* are also used in the acute management of bronchospasm in asthma and chronic management of asthma, respectively (see Chapter 39). All of these agents are delivered via inhalation. Because of the positive charge, these drugs do not enter the systemic circulation or the CNS, restricting effects to the pulmonary system.

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl *Benztropine*	● Treatment of Parkinson disease ● Management of antipsychotic-induced extrapyramidal effects
Darifenacin *Fesoterodine* *Oxybutynin* *Solifenacin* *Tolterodine* *Trospium*	● Treatment of overactive urinary bladder
Cyclopentolate *Tropicamide* *Atropine**	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
*Atropine**	● To treat spastic disorders of the GI tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery ● To treat bradycardia
Scopolamine	● To prevent motion sickness
Aclidinium *Glycopyrrolate* *Ipratropium* *Tiotropium*	● Treatment of COPD
Ganglionic blockers	
Nicotine	● Smoking cessation

Figure 5.7
Summary of cholinergic antagonists. *Contraindicated in angle-closure glaucoma. GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.

D. *Tropicamide* and *cyclopentolate*

These agents are used as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*. *Tropicamide* produces mydriasis for 6 hours and *cyclopentolate* for 24 hours.

E. *Benztropine* and *trihexyphenidyl*

Benztropine and *trihexyphenidyl* are useful as adjuncts with other antiparkinson agents to treat Parkinson disease (see Chapter 8) and other types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms.

F. *Oxybutynin* and other antimuscarinic agents for overactive bladder

Oxybutynin [ox-i-BYOO-ti-nin], *darifenacin* [dar-e-FEN-a-sin], *fesoterodine* [fes-oh-TER-oh-deen], *solifenacin* [sol-ee-FEN-a-sin], *tolterodine* [tol-TER-oh-deen], and *trospium* [TROSE-pee-um] are synthetic *atropine*-like drugs with antimuscarinic actions.

1. **Actions:** By competitively blocking muscarinic (M_3) receptors in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Antimuscarinic actions at M_3 receptors in the GI tract, salivary glands, CNS, and eye may cause adverse effects. *Darifenacin* and *solifenacin* are relatively more selective M_3 muscarinic receptor antagonists; however, the other drugs are mainly nonselective muscarinic antagonists, and binding to other muscarinic receptor subtypes may contribute to adverse effects.

2. **Therapeutic uses:** These agents are used for management of overactive bladder and urinary incontinence. *Oxybutynin* is also used in patients with neurogenic bladder.

3. **Pharmacokinetics:** All of the agents are available in oral dosage forms. Most agents have a long half-life, which allows once-daily administration. [Note: Immediate-release *oxybutynin* and *tolterodine* must be dosed two or more times daily; however, extended-release formulations of these agents allow for once-daily dosing.] *Oxybutynin* is also available in a transdermal patch and topical gel formulation. These drugs are hepatically metabolized by the cytochrome P450 system (primarily CYP 3A4 and 2D6), with the exception of *trospium*, which is thought to undergo ester hydrolysis.

4. **Adverse effects:** Side effects include dry mouth, constipation, and blurred vision, which limit tolerability of these agents. Extended-release formulations and the transdermal patch have a lower incidence of adverse effects and may be better tolerated. *Trospium* is a quaternary compound that minimally crosses the blood–brain barrier and has fewer CNS effects than do other agents, making it a preferred choice in treating overactive bladder in patients with dementia. Important characteristics of the muscarinic antagonists are summarized in Figures 5.6 and 5.7.

III. GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. Except for *nicotine*, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses of the nondepolarizing blockers are complex and mostly unpredictable. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

A. *Nicotine*

A component of cigarette smoke, *nicotine* [NIK-oh-teen] is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, *nicotine* depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitters (Figure 5.8), due to effects on both sympathetic and parasympathetic ganglia (see Chapter 15 for a full discussion of *nicotine*).

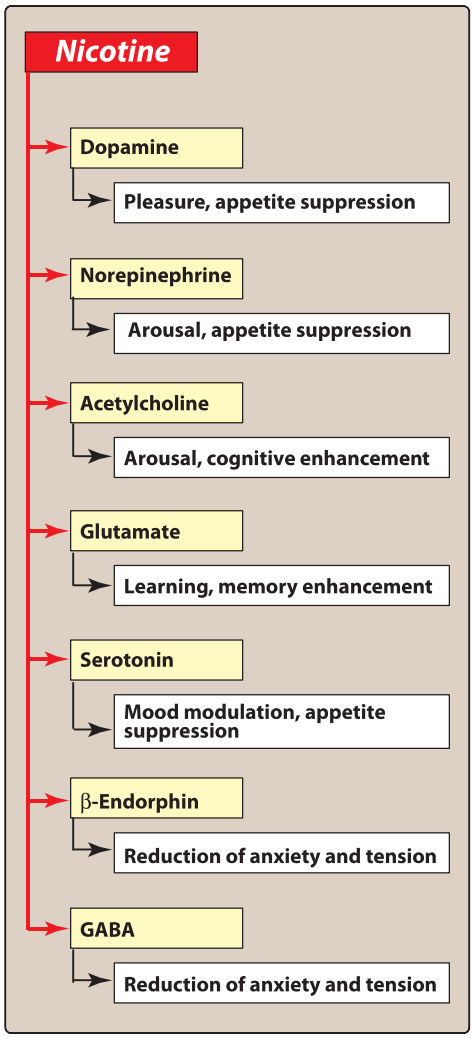

Figure 5.8
Neurochemical effects of *nicotine*. GABA = γ-aminobutyric acid.

IV. NEUROMUSCULAR BLOCKING AGENTS

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on skeletal muscle (Figure 5.2). They possess some chemical similarities to ACh and act either as antagonists (nondepolarizing) or as agonists (depolarizing) at the receptors on the endplate of the NMJ. Neuromuscular blockers (NMBs) are clinically useful to facilitate rapid intubation when needed due to respiratory failure (rapid sequence intubation). During surgery, they are used to facilitate endotracheal intubation and provide complete muscle relaxation at lower anesthetic doses. This increases the safety of anesthesia by allowing patients to recover quickly and completely. NMBs should not substitute for inadequate anesthesia. NMBs are also used in the intensive care unit (ICU) as adjuvant therapy to facilitate intubation and mechanical ventilation in critically ill patients.

A. Nondepolarizing (competitive) blockers

The first known NMB was *curare* [kyoo-RAH-ree], which Amazon hunters used to paralyze prey. The development of *tubocurarine* [too-boe-kyoo-AR-een] followed, but it has been replaced by agents with fewer adverse effects, such as *cisatracurium* [cis-a-trah-CURE-ih-um], *mivacurium* [mi-vah-KYOO-ree-um], *pancuronium* [pan-kure-OH-nee-um], *rocuronium* [roe-kyoor-OH-nee-um], and *vecuronium* [ve-KYOO-roe-nee-um].

1. Mechanism of action

a. At low doses: NMBs competitively block ACh at the nicotinic receptors (Figure 5.9). They compete with ACh at the receptor without stimulating it, thus preventing depolarization of the

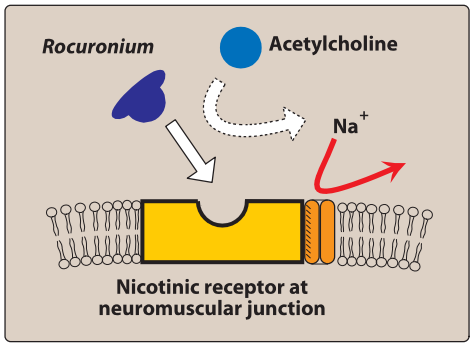

Figure 5.9
Mechanism of action of competitive neuromuscular blocking drugs.

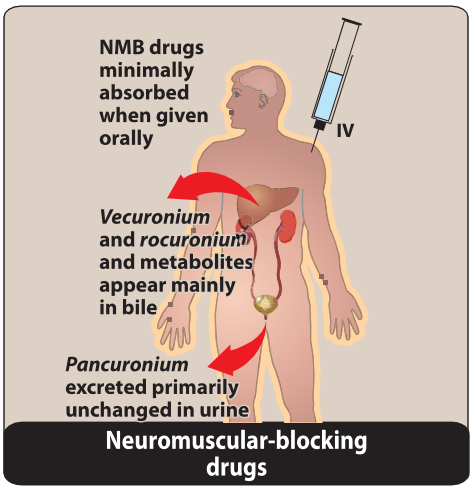

Figure 5.10
Pharmacokinetics of the neuromuscular blocking drugs. *Cisatracurium* undergoes organ-independent elimination. *Mivacurium* and *succinylcholine* are metabolized by plasma cholinesterase. IV = intravenous.

muscle cell membrane and inhibiting muscular contraction. Their competitive action can be overcome by administration of cholinesterase inhibitors, such as *neostigmine* and *edrophonium*, which increase the concentration of ACh in the NMJ. Clinicians employ this strategy to shorten the duration of neuromuscular blockade. In addition, at low doses the muscle responds to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, allowing for monitoring of the extent of neuromuscular blockade.

   b. **At high doses:** Nondepolarizing agents can block the ion channels of the motor end plate. This leads to further weakening of neuromuscular transmission, reducing the ability of cholinesterase inhibitors to reverse the actions of the nondepolarizing blockers. With complete blockade, the muscle does not respond to direct electrical stimulation.

2. **Actions:** Muscles have differing sensitivity to blockade by competitive agents. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers, limbs, neck, and trunk muscles. Next, the intercostal muscles are affected and, lastly, the diaphragm. The muscles recover in the reverse manner. [Note: *Sugammadex* is a selective relaxant-binding agent that terminates the action of both *rocuronium* and *vecuronium* and can be used to speed recovery (see Chapter 13).]

3. **Pharmacokinetics:** All NMBs are injected intravenously or occasionally intramuscularly. These agents possess two or more quaternary amines in their bulky ring structure that prevent absorption from the gut. They penetrate membranes very poorly and do not enter cells or cross the blood–brain barrier. Drug action is terminated in a variety of ways (Figure 5.10). *Pancuronium* is excreted unchanged in urine. *Cisatracurium* undergoes organ-independent metabolism (via Hofmann elimination) to laudanosine, which is further metabolized and renally excreted. The amino steroid drugs *vecuronium* and *rocuronium* are deacetylated in the liver and excreted unchanged in bile. *Mivacurium* is eliminated by plasma cholinesterase. The choice of agent depends on the desired onset and duration of muscle relaxation and the route of elimination. Characteristics of the neuromuscular-blocking drugs are shown in Figure 5.11.

4. **Adverse effects:** In general, these agents are safe with minimal side effects. The adverse effects of the specific NMBs are shown in Figure 5.11.

5. **Drug interactions**

   a. **Cholinesterase inhibitors:** Drugs such as *neostigmine*, *physostigmine*, *pyridostigmine*, and *edrophonium* can overcome the action of nondepolarizing NMBs. However, with increased dosage, cholinesterase inhibitors can cause a

depolarizing block due to elevated ACh concentrations at the end plate membrane. If the NMB has entered the ion channel (is bound to the receptor), cholinesterase inhibitors are not as effective in overcoming blockade.

b. Halogenated hydrocarbon anesthetics: Drugs such as *desflurane* act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of NMBs.

c. Aminoglycoside antibiotics: Drugs such as *gentamicin* and *tobramycin* inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with competitive blockers, enhancing neuromuscular blockade.

d. Calcium channel blockers: These agents may increase the neuromuscular blockade of competitive blockers.

B. Depolarizing agents

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by acetylcholinesterase (AChE) and can more persistently depolarize the muscle fibers. *Succinylcholine* [suk-sin-il-KOE-leen] is the only depolarizing muscle relaxant in use today.

1. **Mechanism of action:** *Succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarize the junction (Figure 5.12). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a longer time and providing sustained depolarization of the muscle cell. [Note: The duration of action is dependent on diffusion from the motor end plate and hydrolysis by plasma cholinesterase (also called butyrylcholinesterase or pseudocholinesterase). Genetic variants in which plasma cholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.] The depolarizing agent first causes opening of the sodium channel associated with nicotinic receptors, which results in depolarization of the receptor (phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (phase II) and flaccid paralysis.

2. **Actions:** As with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces brief muscle fasciculations that cause muscle soreness. This may be prevented by administering a small dose of nondepolarizing NMB prior to *succinylcholine*. Normally, the duration of action of *succinylcholine* is extremely short, due to rapid hydrolysis by plasma

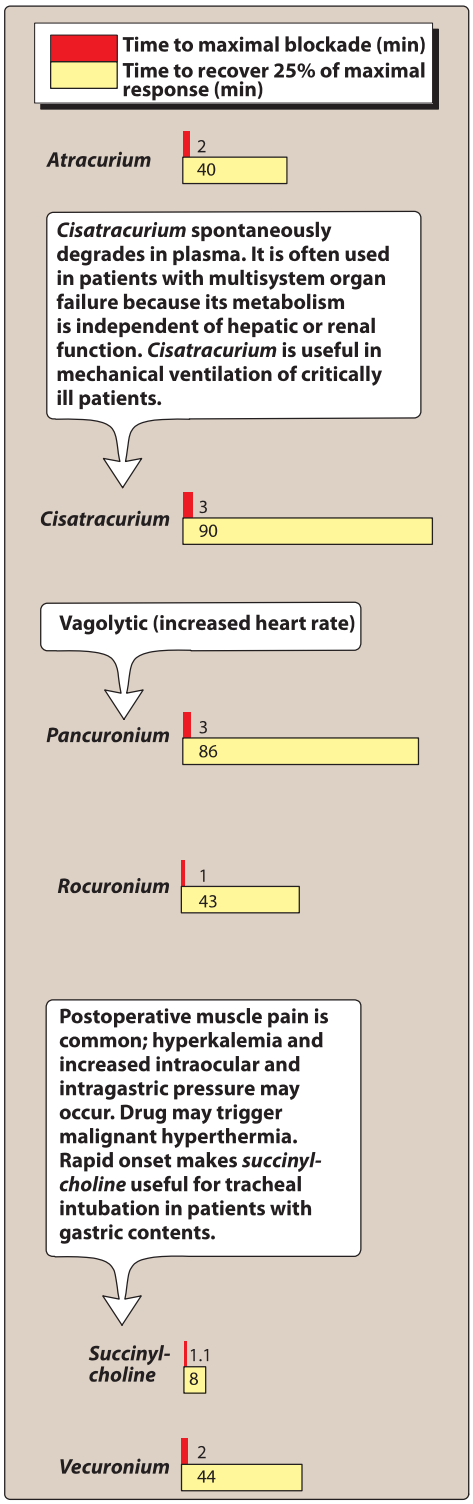

Figure 5.11
Characteristics of neuromuscular blocking drugs.

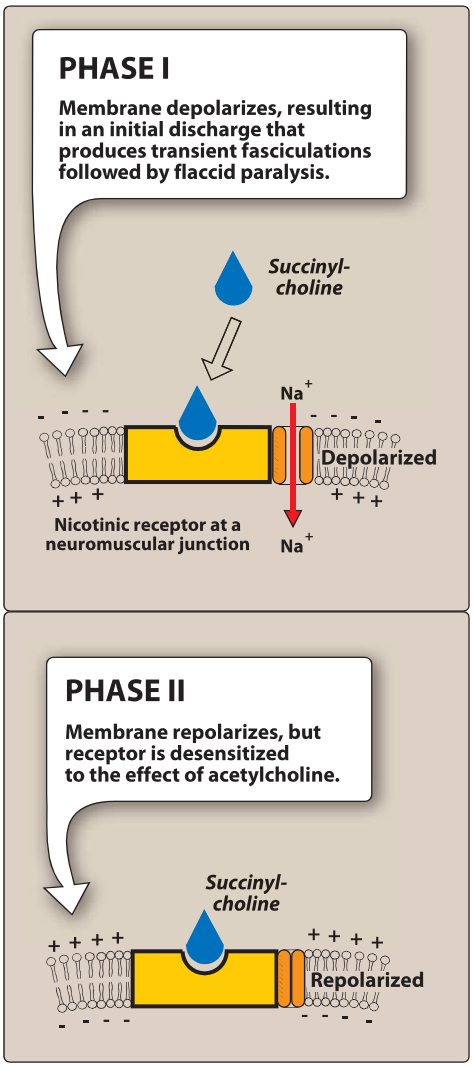

Figure 5.12
Mechanism of action of depolarizing neuromuscular blocking drugs.

cholinesterase. However, *succinylcholine* that reaches the NMJ is not metabolized, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism.

3. **Therapeutic uses:** Because of its rapid onset of action, *succinylcholine* is useful when rapid endotracheal intubation is required. It is also used during electroconvulsive shock treatment.

4. **Pharmacokinetics:** *Succinylcholine* is injected intravenously. Its brief duration of action results from redistribution and rapid hydrolysis by plasma cholinesterase. Drug effects rapidly disappear upon discontinuation.

5. **Adverse effects**

   a. **Hyperthermia:** S*uccinylcholine* can potentially induce malignant hyperthermia in susceptible patients (see Chapter 13).

   b. **Apnea:** Administration of *succinylcholine* to a patient who is deficient in plasma cholinesterase or has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm. The rapid release of potassium may also contribute to prolonged apnea in patients with electrolyte imbalances. In patients with electrolyte imbalances receiving *digoxin* or diuretics (such as heart failure patients) *succinylcholine* should be used cautiously or not at all.

   c. **Hyperkalemia:** *Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost or in patients with renal failure.

Study Questions

Choose the ONE best answer.

5.1 During an ophthalmic surgical procedure, the surgeon wanted to constrict the pupil using a miotic drug. However, he accidentally used another drug that caused dilation of the pupil (mydriasis). Which drug was most likely used?

A. Acetylcholine
B. Pilocarpine
C. Tropicamide
D. Bethanechol

Correct answer = C. Muscarinic agonists such as ACh, pilocarpine, and bethanechol contract the circular muscles of iris sphincter and cause constriction of the pupil (miosis), whereas muscarinic antagonists such as tropicamide prevent contraction of the circular muscles of the iris and cause dilation of the pupil (mydriasis).

5.2 Sarin is a nerve gas that is an organophosphate cholinesterase inhibitor. Which agent could be used as an antidote to sarin poisoning?

A. Pilocarpine
B. Carbachol
C. Atropine
D. Physostigmine

Correct answer = C. Sarin is an organophosphate cholinesterase inhibitor. It causes an increase in ACh levels in tissues that leads to cholinergic crisis through activation of muscarinic and nicotinic receptors. Most symptoms of cholinergic crisis are mediated by muscarinic receptors and, therefore, the muscarinic antagonist atropine is used as an antidote for sarin poisoning. Cholinergic agonists such as pilocarpine, carbachol, and physostigmine (indirect agonists) worsen symptoms of sarin poisoning.

5.3 A patient with Alzheimer disease needs treatment for overactive bladder (OAB). Which drug is the best choice for this patient?

A. Darifenacin
B. Solifenacin
C. Tolterodine
D. Trospium

Correct answer = D. All of agents for OAB except trospium cross the blood–brain barrier to various degrees and could worsen dementia symptoms in Alzheimer disease. Trospium is a quaternary ammonium compound that minimally crosses the blood–brain barrier.

5.4 A patient with asthma was prescribed a β_2 agonist for acute relief of bronchospasm, but did not respond to treatment. Which drug is the most likely next option for this patient?

A. Benztropine
B. Ipratropium
C. Oxybutynin
D. Physostigmine

Correct answer = B. Major receptors present in the bronchial tissues are muscarinic and adrenergic β_2 receptors. Muscarinic activation causes bronchoconstriction, and β_2 receptor activation causes bronchodilation. Therefore, direct or indirect (physostigmine) muscarinic agonists worsen bronchospasm. Ipratropium is a muscarinic antagonist that can relax bronchial smooth muscles and relieve bronchospasm in patients who are not responsive to β_2 agonists. Benztropine is used in the treatment of Parkinson disease or relief of extrapyramidal symptoms from antipsychotics. Oxybutynin is used for overactive bladder.

5.5 A 50-year-old male who is noncompliant with medications was recently diagnosed with chronic obstructive pulmonary disease (COPD). His physician would like to prescribe an inhaled anticholinergic that is dosed once or twice daily. Which drug is most appropriate for this patient?

A. Atropine
B. Ipratropium
C. Tiotropium
D. Trospium

Correct answer = C. The physician should prescribe a long-acting muscarinic antagonist (LAMA) so that the patient has to inhale the medication only 1 or 2 times daily. Tiotropium is a LAMA, whereas ipratropium is a short-acting muscarinic antagonist (SAMA). Atropine and trospium are muscarinic antagonists, but are not indicated for pulmonary conditions such as asthma or COPD and are not available as inhaled formulations.

5.6 Which is the most effective drug for motion sickness for a person planning to go on a cruise?

A. Atropine
B. Fesoterodine
C. Scopolamine
D. Tropicamide

Correct answer = C. All muscarinic antagonists (anticholinergic drugs) listed are theoretically useful as antimotion sickness drugs; however, scopolamine is the most effective in preventing motion sickness. Tropicamide mostly has ophthalmic uses, and fesoterodine is used for overactive bladder.

5.7 Which is correct regarding ganglion-blocking drugs?

A. Blockade of sympathetic ganglia could result in reduced blood pressure.
B. Blockade of parasympathetic ganglia could result in reduced heart rate.
C. Nicotine is a nondepolarizing ganglion blocker.
D. Atropine is a nondepolarizing ganglion blocker.

Correct answer = A. Selective blockade (in theory) of the sympathetic ganglion causes reduction in norepinephrine release and, therefore, reduction in heart rate and blood pressure. Selective blockade (in theory) of the parasympathetic ganglion causes reduction in ACh release and an increase in heart rate. Receptors at both sympathetic and parasympathetic ganglia are of the nicotinic type. Nicotine is an agonist at nicotinic receptors and produces a depolarizing block in the ganglia. Atropine is a muscarinic antagonist and has no effect on the nicotinic receptors found in the ganglia.

5.8 Which drug is useful in treating sinus bradycardia?

A. Atropine
B. Cisatracurium
C. Neostigmine
D. Succinylcholine

Correct answer = A. Sinus bradycardia is a condition where the heart rate is below normal and most often caused by increased vagal tone (increased release of ACh in the sinoatrial [SA] node that acts on muscarinic receptors to reduce heart rate). A muscarinic antagonist such as atropine is useful in this situation to bring the heart rate back to normal. Succinylcholine and cisatracurium are nicotinic antagonists and have no effect on muscarinic receptors in the SA node. Neostigmine is a cholinesterase inhibitor and can worsen bradycardia by increasing the level of ACh in the SA node.

5.9 An ICU patient with severe lung injury requires a neuromuscular blocking agent to assist in his ventilator management. He has liver disease and is currently in renal failure. Which neuromuscular blocker is the best choice for this patient?

A. Cisatracurium
B. Pancuronium
C. Vecuronium
D. Rocuronium

Correct answer = A. Pancuronium is renally eliminated and the patient has renal failure. Vecuronium and rocuronium are hepatically metabolized and the patient has liver disease. Cisatracurium is cleared by organ-independent metabolism (Hofmann elimination).

5.10 Where would you expect to see the first return of function in skeletal muscles following discontinuation of a nondepolarizing neuromuscular blocking agent?

A. Arms
B. Diaphragm
C. Fingers
D. Pupils

Correct answer = B. Following administration of a neuromuscular blocker, the facial muscles are impacted first, but the pupils are not controlled by skeletal muscle and are not affected. The fingers and arms would be next, with the diaphragm function lost last. Function returns in the opposite order, so function of the diaphragm returns first.