Neuromuscular transmission involves the events leading from the liberation of acetylcholine (ACh) at the motor nerve terminal to the generation of end plate currents (EPCs) at the postjunctional site. Release of ACh is initiated by membrane depolarization and influx of Ca\(^{2+}\) at the nerve terminal (Fig. 28.1). This leads to a complex process involving docking and fusion of synaptic vesicles with active sites at the presynaptic membrane. Because ACh is released by exocytosis, functional transmitter release takes place in a quantal fashion. Each quantum corresponds to the contents of one synaptic vesicle (about 10,000 ACh molecules), and about 200 quanta are released with each nerve action potential.

ACh diffusing across the synaptic cleft may bind to ACh receptors (AChRs) to produce an electrical response, interact with acetylcholinesterase (AChE) and be hydrolyzed, or diffuse into the systemic circulation. AChRs are located primarily at the peaks of the subsynaptic folds, whereas AChE is distributed uniformly in the basal lamina at the subsynaptic membrane (Fig. 28.1).

The AChR consists of five subunits surrounding an ion-conducting channel (Fig. 28.2). Activation of the binding sites on the two \(\alpha\)-subunits results in a conformational change. This allows the simultaneous inflow of Na\(^{+}\) and Ca\(^{2+}\) and outflow of K\(^{+}\), with a net inflow of positive charge. The response to a spontaneously secreted quantum of ACh (that is, activation of several thousand AChRs) is seen as a miniature EPC. With nerve stimulation, many quanta are released synchronously to produce a full-sized EPC, which is the summed response of the 200 or so individual miniature EPCs. The EPC is a local graded current that in normal conditions triggers an action potential in the adjacent muscle membrane (Fig. 28.1).
**FIGURE 28.1**
Neuromuscular transmission. Transmitter release at the motor nerve terminal occurs by exocytosis of synaptic vesicles that contain acetylcholine (ACh). The process is enhanced by an action potential that depolarizes the membrane and allows Ca$^{2+}$ entry through channels at the active sites. ACh may be hydrolyzed by acetylcholinesterase (AChE) or bind to receptors (AChRs) located at the peaks of the subsynaptic folds. Simultaneous activation of many AChRs produces an end plate current, which generates an action potential in the adjacent muscle membrane.

**FIGURE 28.2**
Nicotinic ACh receptor (AChR) at the muscle end plate. A. The AChR is a pentameric complex made up of five subunits surrounding a central conducting channel. Embryonic AChR, containing the γ-subunit as shown, is a low-conducting channel. Adult AChR has instead an ε-subunit and is a high-conducting channel. B. Cooperative binding of two ACh (ACh) molecules produces a conformational change that results in channel opening. C. The open channel allows Na$^+$ and Ca$^{2+}$ to enter and K$^+$ to exit simultaneously. The result is a net inflow of positive charge and a membrane depolarization.
Drugs may modify transmission by affecting either the release of transmitter or the interaction of ACh with its receptor. An increase in transmitter release is produced by substances that induce repetitive firing in the motor nerve, prolong the nerve action potential, or promote Ca\(^{2+}\) influx at the nerve terminal. An increase in the postjunctional response is produced by drugs that inhibit AChE (and thereby increase the synaptic concentration of ACh), whereas a decrease in response is produced by drugs that block the binding sites or ion-conducting channel of the AChR.

Changes in miniature EPC frequency, amplitude, and duration can be used to identify the sites of drug action. In general, a change in frequency indicates a prejunctional action, while a change in amplitude reflects a postjunctional effect. Drugs that inhibit AChE give rise to a larger and more prolonged miniature EPC, whereas those that block the AChR binding site produce a decrease in miniature EPC amplitude. Agents that obstruct the open channel of the AChR cause a reduction in miniature EPC amplitude and duration.

**ENHANCEMENT OF ACETYLCOLINCHOLENE RELEASE**

**Aminopyridines**

The aminopyridines (4-aminopyridine; 3,4-diaminopyridine) accelerate spontaneous exocytosis at central and peripheral synapses. There is also an increase in the number of transmitter quanta released by a nerve action potential. This is probably the result of increased Ca\(^{2+}\) inflow at the terminals due to a reduction of K\(^{+}\) conductance and prolongation of the nerve action potential. Muscle strength is increased in patients with the Lambert-Eaton myasthenic syndrome and in others poisoned with botulinum E toxin (discussed later). Improvement in uncontrolled spasms, muscle tone, and pulmonary function is noted in patients with multiple sclerosis or long-standing spinal cord damage. Side effects that limit clinical utility include convulsions, restlessness, insomnia, and elevated blood pressure. Of the two agents, 3,4-diaminopyridine is the more potent and crosses the blood-brain barrier less readily.

**Guanidine**

Guanidine hydrochloride is the drug of choice in the management of patients with myasthenic syndrome and may be of use in the treatment of botulinum intoxication. Its ability to enhance transmitter release may involve a block of K\(^{+}\) channels and prolongation of the nerve action potential.

**DEPRESSION OF ACETYLCOLINE RELEASE**

**Botulinum Toxin**

Botulism is most commonly caused by ingestion of a neurotoxin produced by *Clostridium botulinum* in improperly canned food. Poisoning may also occur after wound contamination with the organism. Infant botulism may occur when spores of the organism germinate and manufacture the toxin in the intestinal tract of infants. *Botulinum toxin works by inhibiting ACh release at all cholinergic synapses.*

Botulinum toxins are classified into seven antigenically distinct types, A through G. Each consists of a polypeptide chain of about 150,000 daltons. All but one is nicked by trypsin-type enzymes to yield a light and heavy chain linked by a disulfide bridge. One end of the heavy chain mediates binding to the nerve terminal, and the other initiates internalization of the toxin. The light chain produces the intracellular inhibition of ACh release. This involves a Zn\(^{2+}\)-dependent endopeptidase action to cleave synaptic target proteins that control vesicle docking and fusion with the prejunctional membrane.

Neuromuscular paralysis occurs 12 to 36 hours after ingestion of the toxin. Early symptoms include diplopia, dysphagia, and dysarthria. Paralysis may descend to include proximal and limb muscles and result in dyspnea and respiratory depression. The toxins do not cross the placental barrier but do enter the central nervous system (CNS). Pupil size may or may not be normal, but mental and sensory functions are not impaired. Recovery from paralysis requires days to weeks.

Reliable antidotes for botulism are not available. In some cases, anticholinesterase drugs may improve muscle strength, albeit temporarily. Guanidine and 4-aminopyridine also have limited usefulness. Management depends initially on supportive measures, such as administering antitoxin and maintaining respiration.

Botulinum toxin is used clinically in the treatment of blepharospasm, writer’s cramp, spasticities of various origins, and rigidity due to extrapyramidal disorders. It is also used to treat gustatory sweating and cosmetically to decrease facial wrinkles. Botulinum toxin A (*Botox, Oculinum*) injected intramuscularly produces functional denervation that lasts about 3 months. Clinical benefit is seen within 1 to 3 days. Adverse effects range from diplopia and irritation with blepharospasm to muscle weakness with dystonias.

Botulinum toxin is the most toxic substance known. One gram of crystalline toxin adequately dispersed can kill a population of a million people, so its use in bioterrorism is a possibility. The toxin can be introduced through inhalation or ingestion but not through dermal
exposure. The threat of mass inhalation poisoning is limited by the ability or inability to aerosolize the toxin for widespread dispersion. Contaminating the water or food supply is also a possibility, although the toxin is degraded by standard water treatment and by heating of foods to 85°C (185°F) for 5 minutes. Prior immunization with toxoid vaccine is advisable for personnel at risk, but prophylactic administration of trivalent equine antitoxin is not recommended.

**Lambert-Eaton Myasthenic Syndrome**

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disease that is often associated with small-cell lung carcinoma. It is characterized by fatigability, hyporeflexia, and autonomic dysfunction. The neuromuscular junction appears normal in morphology, and postjunctional receptor function is unchanged. However, particles at the active zones of nerve terminals that correspond to Ca\(^{++}\) channels are reduced in number and disorganized, and patients with LEMS have high titers of antibodies against the prejunctional P/Q-type Ca\(^{++}\) channel. Thus, muscle weakness results from impaired influx of Ca\(^{++}\) and diminished release of ACh.

Diagnosis is confirmed by an incremental increase in electromyographic recordings upon repetitive stimulation.

Treatment with guanidine may produce clinical improvement within 3 to 4 days. Side effects include paresthesia, gastrointestinal distress, renal tubular necrosis, and hyperirritability. The most serious effect is bone marrow depression, which is dose-related and potentially fatal. Aminopyridines have been used in clinical studies with some positive results. Corticosteroids and plasmapheresis may also be of some benefit, whereas anticholinesterase agents are only marginally effective.

**Myasthenia Gravis**

The “acquired” form of myasthenia gravis (MG) is an autoimmune disease with an incidence approaching 1 in 10,000. It involves an antibody response against part of the α-subunit of the AChR in muscle. This leads to degradation of AChRs, reduction of synaptic infoldings, and weakness due to diminished postjunctional response. Because anti-AChR antibodies are found in nearly 90% of MG patients, serum testing can serve as a diagnostic tool. MG is often found associated with abnormalities of the thymus, which contains a protein that is immunologically related to muscle AChR.

**Standard treatment consists of anti-AChE agents such as pyridostigmine, whose effect is long-lasting and predictable.** A short acting anti-AChE, such as edrophonium, can be used to differentiate between a myasthenic crisis (insufficient treatment) and a cholinergic crisis (overtreatment with anti-AChEs). Thymectomy is a good option for patients under 50 years of age. Immunosuppressive agents, such as corticosteroids and possibly azathioprine or cyclosporine A, are also effective. Plasmapheresis is beneficial, but the effect is transient.

**NEUROMUSCULAR BLOCKING AGENTS**

**Depolarizing Blocker (Succinylcholine)**

Succinylcholine chloride (AneCTine) is the only depolarizing-type blocker that is in widespread clinical use. *It produces neuromuscular block by overstimulation, so that the end plate is unable to respond to further stimulation.* Structurally, succinylcholine is equivalent to two ACh molecules joined back to back. The resulting 10-carbon atom spacing between the two quaternary ammonium heads is important for activation of the two binding sites on the AChR. Because the succinylcholine molecule is “thin,” binding to the two sites does not stercially occlude the open channel, and cations are allowed to flow and depolarize the end plate.

Neuromuscular block with succinylcholine occurs by two sequential events. An initial depolarization of the end plate produces muscle action potentials and fascilitation. Maintained depolarization past the
threshold for firing produces Na\(^+\) channel inactivation, so that muscle action potentials cannot be generated. This is called \textit{phase I}, or \textit{depolarization block}. In the continued presence of succinylcholine, the membrane becomes repolarized, Na\(^+\) channel inactivation is reversed, and muscle membrane excitability is restored. Nonetheless, the neuromuscular block persists because of desensitization of the AChR. This is known as \textit{phase II}, or \textit{desensitization block}.

Although the mechanism for phase II block is not completely understood, a series of allosteric transitions in the AChR is suspected. One model to describe this has the AChR in equilibrium among four conformations: resting, active, inactive, and desensitized. Agonists stabilize the active and desensitized states, whereas antagonists tend to stabilize the resting and possibly the desensitized state.

### Absorption, Metabolism, and Excretion

Succinylcholine is given systemically because the molecule is charged and does not easily cross membranes. It is rapidly hydrolyzed by plasma cholinesterase to succinylmonocholine, which is pharmacologically inactive. Because plasma cholinesterase is synthesized in the liver, neuromuscular block may be prolonged in patients with liver disease. About 10% of succinylcholine is excreted unchanged in the urine. The response to succinylcholine may also be prolonged in individuals with a genetic defect leading to atypical plasma cholinesterase (homozygous incidence of about 1 in 2,500). In this case, the enzyme has a decreased affinity for substrates such as succinylcholine that can be measured by the dibucaine test.

### Pharmacological Actions

Succinylcholine acts primarily at the skeletal neuromuscular junction and has little effect at autonomic ganglia or at postganglionic cholinergic (muscarnic) junctions. Actions at these sites attributed to succinylcholine may arise from the effects of choline. Succinylcholine has no direct action on the uterus or other smooth muscle structures. It does not enter the CNS and does not cross the placental barrier. It may, however, release histamine from mast cells. Because succinylcholine works by stimulating rather than blocking end plate receptors, \textit{anti-AChEs will not reverse muscle paralysis and may actually prolong the block}.

### Clinical Uses

The principal advantage of succinylcholine is its rapid and ultra-short action. With intravenous (IV) administration, succinylcholine produces flaccid paralysis that occurs in less than 1 minute and lasts about 10 minutes. This makes it suitable for short-term procedures, such as endotracheal intubation, setting of fractures, and prevention of injury during electroconvulsive therapy. Apart from its rapid onset and brief action, succinylcholine has few benefits and many disadvantages.

### Adverse Effects and Contraindications

Succinylcholine produces muscle fasciculation, which may result in myoglobinuria and postoperative muscle pain. The amount produced depends on the level of physical fitness. Succinylcholine causes contractions of extraocular muscles, posing the danger of transient elevated intraocular pressure. Succinylcholine may produce hyperkalemia in patients with large masses of traumatized or denervated muscle (e.g., spinal cord injury). Denervated muscle is especially sensitive to depolarizing drugs because of the increased number of AChRs on the sarcolemma (denervation supersensitivity). Succinylcholine also causes prolonged contraction of the diseased muscles of patients with myotonia or amyotrophic lateral sclerosis.

Succinylcholine-induced hyperkalemia may lead to cardiac arrhythmia and arrest when plasma K\(^+\) reaches 7 and 10 mM, respectively. The drug also may precipitate a fulminant attack of malignant hyperthermia in susceptible individuals (not to be confused with neuroleptic malignant hyperpyrexia, which involves dopamine and the CNS). Treatment in either case consists of cooling the body and administering oxygen and dantrolene sodium (discussed later).

### Nondepolarizing Blockers: \textit{d}-Tubocurarine, Atracurium, Mivacurium, Pancuronium, Vecuronium, Rocuronium, and Rapacuronium

#### Mechanism of Action

With the exception of succinylcholine, all neuromuscular blocking agents are nondepolarizing. These agents prevent excitation of end plate AChRs by acting as reversible competitive antagonists at the binding sites. The prototype for this group is \textit{d}-tubocurarine, an alkaloid used as a South American arrow poison. In general, these compounds have two charged heads (e.g., quaternary ammonium) separated by a “thick” organic moiety (e.g., steroid nucleus). These heads enable attachment of the drug to the two AChR binding sites. However, because of the large intervening moiety, the channel is occluded such that the flow of cations is prevented. Because of the competitive nature of this blockade, the effect of nondepolarizing blockers can be reversed by \textit{anti-AChE agents} and other procedures that increase the synaptic concentration of ACh.

### Pharmacological Actions

\textit{d}-Tubocurarine blocks nicotinic AChRs in muscle end plates and autonomic ganglia but has no effect on mus-
carinic AChRs. It does not affect nerve or muscle excitability or conduction of action potentials. Because it is charged, it penetrates cells poorly and does not enter the CNS. However, if applied directly to brain or spinal cord, it will block nicotinic AChR in those tissues. In humans, \(d\)-tubocurarine has a moderate onset of action (3-4 minutes) followed by progressive flaccid paralysis. The head and neck muscles are affected initially, then the limb muscles, and finally the muscles of respiration. Recovery from paralysis is in the reverse order.

**Clinical Uses**

Nondepolarizing blockers are used to relax skeletal muscle for surgical procedures, to prevent dislocations and fractures associated with electroconvulsive therapy, and to control muscle spasms in tetanus. They do not produce anesthesia or analgesia.

The degree of blockade can be influenced by body pH and electrolyte balance. Hypokalemia due to diarrhea, renal disease, or use of potassium-depleting diuretics potentiates the effect of nondepolarizing blockers. By contrast, hyperkalemia may oppose the actions of \(d\)-tubocurarine but enhance the end plate response to succinylcholine. The effectiveness of \(d\)-tubocurarine is reduced by alkalosis.

Newborn children are extremely sensitive to nondepolarizing muscle relaxants but may require three times as much depolarizing agent as an adult for an equivalent degree of block. Like newborn children, patients with myasthenia gravis are very sensitive to paralysis by \(d\)-tubocurarine but are resistant to succinylcholine. This altered responsiveness is probably due to the fewer number of functional AChRs at the end plate. Since neonates are very sensitive to \(d\)-tubocurarine, the dosage must be reduced and the degree of block closely monitored.

**Adverse Effects and Precautions**

\(d\)-Tubocurarine may cause bronchospasms and hypotension by release of histamine from mast cells. This may be counteracted by prior treatment with antihistamines. \(d\)-Tubocurarine produces partial block of sympathetic ganglia and the adrenal medulla, which may also contribute to hypotension.

Inhalation anesthetics, such as isoflurane, enflurane, halothane, and nitrous oxide, potentiate the action of nondepolarizing blockers, either through modification of end plate responsiveness or by alteration of local blood flow. The extent of potentiation depends on the anesthetic and the depth of anesthesia. The dose of muscle relaxant should be reduced when used with these anesthetics.

Certain antibiotics (e.g., aminoglycosides, macrolides, polymyxins, lincomycin) enhance neuromuscular blockade by either decreasing ACh release or blocking the postjunctional response. Procainamide and phenytoin also increase the effects of \(d\)-tubocurarine-like drugs. The amount of neuromuscular blocker should be decreased accordingly.

**Other Nondepolarizing Blockers of Importance**

Atracurium besylate (Tracrium) is a benzylisoquinolinium compound like \(d\)-tubocurarine. Its actions are similar to those of \(d\)-tubocurarine, but its duration of action is shorter (45 minutes) because of spontaneous degradation of the molecule (Hofmann elimination). Because of this, atracurium is useful in patients with low or atypical plasma cholinesterase and in patients with renal or hepatic impairment.

Mivacurium chloride (Mivacron) is a newer agent that is chemically related to atracurium. The primary mechanism of inactivation is hydrolysis by plasma cholinesterase. Although it is useful for patients with renal or hepatic disease, some caution is warranted, since these individuals may have reduced plasma cholinesterase as a result of the disease. Mivacurium has an onset of action (1.8 minutes) and duration of effect (20 minutes) only twice that of succinylcholine, and in this respect, it is the most similar to succinylcholine of all of the nondepolarizing agents.

Pancuronium bromide (Pavulon) is a synthetic bisquaternary agent containing a steroid nucleus (amino steroid), as denoted by the -curonium suffix. It is five times as potent as \(d\)-tubocurarine. Unlike \(d\)-tubocurarine, it does not release histamine or block ganglionic transmission. Like \(d\)-tubocurarine, it has a moderately long onset (2.9 minutes) and duration of action (110 minutes). Pancuronium and its metabolite are eliminated in the urine.

Vecuronium bromide (Norcuron) is chemically identical to pancuronium except for a tertiary amine in place of a quaternary nitrogen. However, some of the drug will exist as the bisquaternary compound, depending on body pH. Vecuronium has a moderate onset of action (2.4 minutes) and a duration of effect of about 50 minutes. Like pancuronium, it does not block ganglia or vagal neuroeffector junctions, does not release histamine, and is eliminated by urinary excretion.

Rocuronium bromide (Zemuron) is a recently approved amino steroid neuromuscular blocking agent. It has a rapid onset of action (1 minute), but its duration of action is intermediate (55 minutes), about that of vecuronium. On rare occasions, it may release histamine and cause cardiac irregularities. Rapacuronium bromide (Raplon) is the most recent neuromuscular blocking agent approved by the United States Food and Drug Administration (FDA). It is an analogue of vecuronium and is thus categorized as an amino steroid. It has a rapid onset of action (1.5 minutes) and a short to intermediate
duration of action (20 minutes). This makes it a suitable alternative to mivacurium or succinylcholine for short procedures. It is eliminated mainly by the liver. Adverse effects are dose dependent; they include tachycardia, hypotension, and bronchospasm. These effects may be related to the ability of the drug to release a small amount of histamine.

PHARMACOLOGY OF ANTISPASTICITY AGENTS

Muscle relaxants have some value for relief of spastic muscle disorders, that is, a state of increased muscle tone that results from an imbalance between central and spinal control of muscle tone. Spasticity is the result of a general release from supraspinal control and is characterized by heightened excitability of α- and γ-motor systems and the appearance of primitive spinal cord reflexes. Treatment is difficult, since relief often can be achieved only at the price of increased muscle weakness.

Baclofen

Baclofen (Lioresal) is the parachlorophenol analogue of the naturally occurring neurotransmitter γ-aminobutyric acid (GABA).

Mechanism of Action

Baclofen appears to affect the neuromuscular axis by acting directly on sensory afferents, γ-motor neurons, and collateral neurons in the spinal cord to inhibit both monosynaptic and polysynaptic reflexes. The principal effect is to reduce the release of excitatory neurotransmitters by activation of presynaptic GABA_{A} receptors. This seems to involve a G protein and second-messenger link that either increases K+ conductance or decreases Ca^{2+} conductance.

Absorption, Metabolism, and Excretion

Baclofen is rapidly and effectively absorbed after oral administration. It is lipophilic and able to penetrate the blood-brain barrier. Approximately 35% of the drug is excreted unchanged in the urine and feces.

Clinical Uses

Baclofen is an agent of choice for treating spinal spasticity and spasticity associated with multiple sclerosis. It is not useful for treating spasticity of supraspinal origin. Doses should be increased gradually to a maximum of 100 to 150 mg per day, divided into four doses.

Adverse Effects

Side effects are not a major problem, and they can be minimized by graduated dosage increases. They include lassitude, slight nausea, and mental disturbances (including confusion, euphoria, and depression). The drowsiness is less pronounced than that produced by diazepam—an important therapeutic advantage. Hypotension has been noted, particularly following overdose. Elderly patients and patients with multiple sclerosis may require lower doses and may display increased sensitivity to the central side effects. Baclofen may increase the frequency of seizures in epileptics.

Benzodiazepines

Benzodiazepines also possess muscle relaxant activity. Their pharmacology is discussed in Chapter 30. Diazepam (Valium) has been used for control of flexor and extensor spasms, spinal spasticity, and multiple sclerosis. The muscle relaxant effect of the benzodiazepines may be mediated by an action on the primary afferents in the spinal cord, resulting in an increased level of presynaptic inhibition of muscle tone. Polysynaptic reflexes are inhibited. The most troublesome side effect is drowsiness, which is dose dependent. Tolerance to both the therapeutic effects and the side effects develops.

Dantrolene Sodium

Dantrolene sodium (Dantrium) is used in the treatment of spasticity due to stroke, spinal injury, multiple sclerosis, or cerebral palsy. It is also the drug of choice in prophylaxis or treatment of malignant hyperthermia. Susceptibility to malignant hyperthermia is due to a rare genetic defect that allows Ca^{2+} release from the sarcoplasmic reticulum to open more easily and close less readily than normal. This leads to a high level of Ca^{2+} in the sarcoplasm, which produces muscle rigidity, oxygen consumption, and heat. Dantrolene acts by blocking Ca^{2+} release from the sarcoplasmic reticulum and uncoupling excitation from contraction.

Dantrolene is active orally, although its absorption is slow and incomplete. Its biological half-life (t_{1/2}) is 8.7 hours in adults. The drug is metabolized by liver microsomal enzymes and is eliminated in the urine and bile. It is given IV when treating an attack of malignant hyperthermia.

The most prominent and often limiting feature of dantrolene administration is dose-dependent muscle weakness. Other side effects are drowsiness, dizziness, malaise, fatigue, and diarrhea. Symptomatic hepatitis is reported in 0.5% of patients receiving it and fatal hepatitis in up to 0.2%. Contraindications include respiratory muscle weakness and liver disease. It is suggested that patients on dantrolene therapy be given regular liver function tests.

Central Skeletal Muscle Relaxants

The central skeletal muscle relaxants are a chemically diverse group of compounds that have limited utility in
relieving the signs and symptoms of local muscle spasm. None has been shown to be superior to analgesic–antiinflammatory agents for the relief of acute or chronic muscle spasm, although all are superior to placebo. Most of these drugs have mild sedative properties, and their muscle relaxant activity may be a direct result of sedation. Experimentally, all centrally active skeletal muscle relaxants preferentially depress spinal polysynaptic reflexes over monosynaptic reflexes.

Most of the agents have similar actions, and therefore, the same adverse reactions are seen. These consist most commonly of drowsiness, dizziness, and light-headedness. One agent, cyclobenzaprine (Flexeril), has a prominent anticholinergic component and frequently causes dryness of the mouth along with sedation and dizziness.

In addition to being employed alone, many of these compounds are available in combination with a nonopioid analgesic, caffeine, or both. Because of their limited utility, they are not be considered individually. Some of the approved agents are listed in Table 28.1.

### Table 28.1 Some Centrally Acting Skeletal Muscle Relaxants

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
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</thead>
<tbody>
<tr>
<td>Carisoprodol</td>
<td>Rela, Soma</td>
</tr>
<tr>
<td>Chlorzoxazone</td>
<td>Paraflex</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Flexeril</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>Robaxin, Delaxin</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Norflex</td>
</tr>
</tbody>
</table>

**Study Questions**

1. Which of the following agents produces its therapeutic action by causing a nondepolarizing block of end plate receptors at the skeletal neuromuscular junction?
   - (A) Hexamethonium
   - (B) Nicotine
   - (C) Rapacuronium
   - (D) Scopolamine
   - (E) Succinylcholine

2. A 50-year-old white man is found to have 90% blockage of his coronary arteries and is prepared for bypass surgery. For preanesthetic medication, he is given atropine to block secretions and a mild sedative to reduce anxiety and induce sedation. He is then given an IV bolus of succinylcholine to facilitate endotracheal intubation. Induction of general anesthesia with enflurane is begun with no major complications. However, shortly thereafter, the patient displays muscle rigidity and a rapid increase in temperature. He is quickly cooled with ice packs, switched to 100% oxygen, and then given an IV bolus of which of the following?
   - (A) Atropine
   - (B) Baclofen
   - (C) Dantrolene
   - (D) Diazepam
   - (E) Neostigmine

3. A former respiratory therapist who once called himself the Angel of Death was charged in the deaths of six elderly nursing home patients. Their exhumed bodies all contained a drug that halts breathing, even though the drug was not part of their therapeutic regimen. Toxicological tests identified the drug as a muscle relaxant. Which of the following is the most likely agent used?
   - (A) Baclofen
   - (B) Mecamylamine
   - (C) Pancuronium
   - (D) Pyridostigmine
   - (E) Succinylcholine

4. Which of the following adjuvants to anesthesia has the potential to cause hyperkalemia, postoperative muscle pain, muscle fasciculation, and prolonged apnea and paralysis in genetically sensitive patients?
   - (A) Atracurium
   - (B) Diazepam
   - (C) Edrophonium
   - (D) Rocuronium
   - (E) Succinylcholine

5. A 45-year-old man in otherwise good health complains of muscle weakness early in the morning but says it is less of a problem as the day goes on. The neurologist performs electromyography and notes no alteration in nerve conduction velocity but does observe facilitation in the compound action potential with repetitive 50-Hz stimulation. This indicates a defect at the prejunctional side of the neuromuscular junction. Which of the following is a possible cause?
   - (A) Autonomic hyperreflexia
   - (B) Atypical plasma cholinesterase
   - (C) Lambert-Eaton myasthenic syndrome
   - (D) Malignant hyperthermia
   - (E) Myasthenia gravis

6. Which of the following agents blocks the release of neurotransmitter from all cholinergic nerve endings?
   - (A) Atracurium
   - (B) Baclofen
2. C. The patient has a rare genetic defect that results in a resulting improvement in muscle strength. Several months later, she felt a loss of strength and increased her dose of pyridostigmine. She now complains of significant muscle weakness. The neurologist administers edrophonium, which produces no significant improvement, and the diagnosis is cholinergic crisis. Treatment should consist of which of the following options? (A) Replacing pyridostigmine with pancuronium (B) Replacing pyridostigmine with neostigmine (C) Giving dantrolene to decrease sarcoplasmic release of calcium (D) Adding succinylcholine to her regimen (E) Allowing pyridostigmine to be eliminated

ANSWERS

1. C. Rapacuronium is a skeletal muscle relaxant that works by competing with ACh for receptors at the postjunctional membrane. Nicotine and succinylcholine also act at the end plate receptors but cause depolarization. Hexamethonium is a ganglion blocker that has essentially no activity at the end plate receptors, and scopolamine blocks cholinergic muscarinic receptors and thus does not act at the end plate receptors.

2. C. The patient has a rare genetic defect that results in susceptibility to malignant hyperthermia. Acute attacks are manifested by heat generation, muscle rigidity, and high oxygen consumption, all of which can lead to lactic acidosis. It has a fatality rate in excess of 70% if left untreated. Attacks can be precipitated by stress or infection but are generally a result of using succinylcholine and certain gaseous anesthetics. These appear to trigger excessive release of Ca$^{++}$ from the sarcoplasmic reticulum due to a defect in the calcium release channels. Dantrolene acts by blocking the release of Ca$^{++}$ and is the standard treatment for this reaction.

3. C. Pancuronium is a nondepolarizing neuromuscular blocking agent. The depolarizing neuromuscular blocking agent succinylcholine may also appear to be a viable possibility. However, it can be excluded, since it is rapidly broken down to natural products by plasma cholinesterase and would not have been detected by the toxicological tests. Because of this, succinylcholine and potassium chloride can be used to kill without leaving evidence of a foreign substance. Pyridostigmine is an anticholinesterase that can be used to reverse the effect of nondepolarizing blockers. Mecamylamine is a ganglion blocker that has no effect at the neuromuscular junction, and b--; clofen is a centrally acting relaxant that would not be effective in causing respiratory paralysis.

4. E. Succinylcholine is the only depolarizing neuromuscular blocking in widespread clinical use, particularly as an aid for intubation. Its administration may produce muscle fasciculation and postoperative muscle pain. It can produce hyperkalemia in patients with muscle damage or prolonged paralysis in patients with atypical plasma cholinesterase.

5. C. Lambert-Eaton myasthenic syndrome is a rare disorder of autoimmune attack against calcium channels of the presynaptic motor nerve ending. The result is diminished release of ACh manifested as muscle weakness. In these patients, repetitive stimulation promotes facilitation of transmitter release, and this is seen clinically as an improvement in muscle strength with increased physical activity. This is the opposite of myasthenia gravis, the autoimmune attack against postjunctional ACh receptors, in which muscle strength decreases with increased physical activity. Autonomic hyperreflexia is a syndrome found in patients with spinal cord damage in which central inhibition of reflexes is impaired. Atypical plasma cholinesterase does not affect neuromuscular transmission except with regard to breakdown of succinylcholine. Malignant hyperthermia is due to a defect in the contractile apparatus of skeletal muscle and not in neuromuscular transmission.

6. C. Botulinum toxin works by preventing exocytosis of ACh from all cholinergic nerve endings. Atracurium and rocuronium are nondepolarizing neuromuscular blockers that act specifically at the postjunctional receptors of the skeletal neuromuscular junction. Baclofen and diazepam are centrally acting muscle relaxants that stimulate presynaptic GABA$_B$ receptors and benzodiazepine sites on postsynaptic GABA$_A$ receptors, respectively.

7. E. Cholinergic crisis occurs when patients are overtreated with anticholinesterases, that is, when acetylcholinesterase at the neuromuscular junction is inhibited and ACh levels increase in the synaptic cleft. An extreme example is seen with organophosphate poisoning, that is, exposure to nerve gases or industrial insecticides such as parathion. This can lead to depolarization and desensitization of the end plate receptors so that they cannot respond to further stimulation by ACh. Unlike the irreversible organophosphates, pyridostigmine has a short to intermediate duration of action, and treatment should be to allow pyridostigmine to be eliminated by normal pathways.

SUPPLEMENTAL READING


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**CASE STUDY** Generalized Muscle Weakness

A 30-year-old white woman is referred to a neurologist after complaining of a general loss of strength at the end of the day and drooping eyelids that make reading difficult. Electromyography on the adductor pollicis using train-of-four 50-Hz stimulation reveals a progressive decrease in the compound muscle action potential. After establishing the patient’s baseline strength with a tonometer, she is given one-sixth the normal paralytic dose of mivacurium IV, which results in a decrease in measured strength. Subsequent administration of edrophonium results in an improvement in muscle strength to above baseline values. The neurologist prescribes oral pyridostigmine and prednisone, which lead to clinical improvement over the next few weeks. Further laboratory tests disclose that the patient has a thymoma and increased titers of antinuclear antibodies. Following removal of the thymoma, the patient no longer shows signs of muscle weakness and appears to be in remission. What is your diagnosis?

**ANSWER:** The patient shows classic signs of myasthenia gravis, an autoimmune disease that results from antibody attack against the end plate receptors of skeletal muscle and leads to muscle weakness. The disease may be triggered by disorders of the thymus, which contains a protein antigenically related to skeletal muscle receptors. The train-of-four stimulation is used to differentiate between a prejunctional cause of weakness (such as Lambert-Eaton myasthenic syndrome, which normally shows facilitation in the action potentials) and a postjunctional cause (such as myasthenia gravis). Use of a short-acting nondepolarizing neuromuscular blocker (mivacurium) followed by a short-acting acetylcholinesterase inhibitor (edrophonium) is an almost conclusive test for myasthenia gravis. In many instances, edrophonium alone may be used (the Tensilon test). Pyridostigmine is a long-acting cholinesterase inhibitor that can provide palliative relief, whereas prednisone is used to suppress the autoimmune process. The finding of a thymoma presents the possibility that removal may eliminate the source of the autoimmunity and lead to remission.