**Skeletal Muscle Relaxants**

### Therapeutic Overview

Drugs that relax skeletal muscle are classified according to their use and mechanisms of action. These agents include the **neuromuscular blocking agents**, which produce muscle paralysis required for surgical procedures, and the **spasmolytics**, which are used to treat muscle hyperactivity.

The introduction of the neuromuscular blockers in the early 1940s marked a new era in anesthetic and surgical practice. Today, many surgical procedures are performed more safely and rapidly with the aid of drugs that produce skeletal muscle paralysis. These drugs interrupt transmission at the skeletal neuromuscular junction and are classified according to their action as either **depolarizing** or **nondepolarizing**.

The **spasmolytics** include **antispasticity drugs**, the **antispasm drugs**, and the **motor nerve blocking drug botulinum toxin**. The antispasticity drugs include agents such as baclofen that act via the spinal cord, and dantrolene, which has a direct action on skeletal muscle and is often referred to as a **directly acting skeletal muscle relaxant**. These agents alleviate skeletal muscle hyperactivity, cramping, and tightness caused by specific neurological disorders such as multiple sclerosis, cerebral palsy, stroke, or spinal injury. Although these drugs are not curative, their ability to relieve symptoms enables patients to successfully pursue other treatments, such as physical therapy.

The **antispasm drugs**, formerly known as centrally active muscle relaxants, include agents such as cyclobenzaprine, metaxalone, and methocarbamol and are used to treat use-related muscle spasms. These compounds relax skeletal muscle by acting on the **central nervous system** (CNS) and perhaps **spinal reflexes**.

The motor nerve blocker **botulinum toxin** is used for muscle disorders of the eye (blepharospasm and strabismus), certain forms of spasticity (e.g., cerebral palsy), and elective cosmetic purposes. Botulinum toxin produces long-lasting muscle paralysis by blocking the release of **acetylcholine** (ACh) from motor nerves.

Clinical uses of these compounds are listed in the Therapeutic Overview Box.

### Mechanisms of Action

**Neuromuscular Blocking Drugs**

Skeletal muscles are innervated by somatic motor nerves, which originate in the spinal cord, terminate at muscle cells, and release ACh as their neurotransmitter (see Chapters 9 and 10). Upon arrival of an action potential, ACh is released from synaptic vesicles by exocytosis, crosses the synapse, and interacts with skeletal muscle nicotinic cholinergic receptors to depolarize the postsynaptic membrane (see Chapter 1). When the membrane reaches threshold, a muscle action potential is generated and propagates along the fiber to initiate excitation-contraction coupling. The action of ACh is terminated very rapidly by hydrolysis by **acetylcholinesterase** (AChE) located...
in the synaptic junction. Neuromuscular transmission is depicted in Figure 12-1.

Neuromuscular blocking agents interfere with neurotransmission by either: (1) occupying and activating the nicotinic receptor for a prolonged period of time, leading to blockade, which occurs with the depolarizing agents; or (2) competitively antagonizing the actions of ACh at nicotinic acetylcholine receptors, which occurs with the nondepolarizing agents. Not surprisingly, the structures of the depolarizing agents resemble that of ACh, whereas the nondepolarizing agents are bulky, rigid molecules. A comparison of the structure of ACh with prototypical depolarizing (succinylcholine) and nondepolarizing (tubocurarine and pancuronium) neuromuscular blockers is shown in Figure 12-2.

As mentioned, the nondepolarizing blockers are competitive antagonists at nicotinic receptors. They have little or no agonist activity but competitively occupy the receptor binding site. The first compound, d-tubocurarine, was extracted from plants by native South Americans to coat their darts and rapidly paralyze their prey. This led to the development of synthetic compounds including the benzylisoquinolines such as atracurium and the aminosteroids such as pancuronium.

Nondepolarizing neuromuscular blocking drugs decrease the ability of ACh to open the ligand-gated cation channels in skeletal muscle, producing flaccid paralysis. Muscle contraction is partially impaired when 75% to 80% of receptors are occupied and inhibited totally when 90% to 95% are occupied. Required concentrations vary with the drug, the muscle and its location, and the patient.

Because nondepolarizing blockers compete with ACh, the blockade can be reversed by increasing the concentration of ACh. This is done by inhibiting AChE, which hydrolyzes ACh (Chapters 9 and 10). Neostigmine, edrophonium, and pyridostigmine are AChE inhibitors used clinically to reverse neuromuscular block caused by nondepolarizing blockers. However, if the concentration of the competitive blocking agent is greater than that needed for blockade of 95% of the receptors, AChE inhibitors will be unable to increase ACh sufficiently to reverse the block.

There is only one depolarizing agent currently in clinical use, succinylcholine (see Fig. 12-2). This compound binds to and activates muscle nicotinic receptors in the same manner as ACh. However, succinylcholine is not metabolized by AChE, resulting in receptor occupation for a prolonged period. Succinylcholine is hydrolyzed primarily by butyrylcholinesterase, which is present in the plasma but not in high concentrations at the neuromuscular junction, resulting in continuing muscle depolarization. The neuromuscular block resulting from succinylcholine is characterized by two phases. The first, termed phase I block, is a consequence of prolonged depolarization, rendering the membrane unresponsive to further stimuli. It is characterized by initial muscle fasciculations followed by a flaccid paralysis that is not reversed, but intensified, by administration of AChE inhibitors. With continued exposure to succinylcholine, phase II block occurs, during which the membrane repolarizes but is still unresponsive, reflecting a desensitized state of the nicotinic cholinergic receptor. This phase progresses to a state in which the block appears similar to that produced by nondepolarizing agents, that is, it becomes responsive to high concentrations of ACh and can be reversed by AChE inhibitors.

**Spasmolytics**

**Antispasticity Drugs**

The antispasticity agents include **baclofen**, which is a structural analog of γ-aminobutyric acid (GABA). Baclofen decreases spasticity by binding to GAB<sub>B</sub> receptors on presynaptic terminals of spinal interneurons (Fig. 12-3). Binding to presynaptic GAB<sub>B</sub> receptors results in hyperpolarization of the membrane, which reduces Ca<sup>2+</sup> influx and decreases the release of the excitatory neurotransmitters, glutamate, and aspartate. Postsynaptic interactions with sensory afferent terminals cause membrane hyperpolarization via a G-protein-coupled receptor that leads to increases in K<sup>+</sup> conductance, enhancing inhibition. Baclofen may also inhibit γ-motor neuron activity.
and reduce muscle spindle sensitivity, leading to inhibition of monosynaptic and polysynaptic spinal reflexes.

Benzodiazepines such as diazepam have an antispasticity effect by acting on GABA_A receptors to increase their affinity for GABA in the brain and in the spinal cord (see Chapter 31 and Fig. 12-3).

Tizanidine is a clonidine derivative with short-acting presynaptic _a_2 adrenergic receptor agonist actions. The ability of tizanidine to affect spinal motor neurons via presynaptic inhibition is believed to mediate its antispasticity effects.

Dantrolene has direct effects on skeletal muscle to inhibit ryanodine receptor Ca++ release channels on the sarcoplasmic reticulum of skeletal muscle, thereby uncoupling motor nerve excitation and muscle contraction (see Fig. 12-3). Dantrolene may also have actions on the CNS that contribute to its antispasticity effects, although the cellular mechanisms have not been elucidated.
Antispasm Drugs

The antispasm agents do not act on motor neurons or on the muscle itself. Rather, these compounds act primarily on the brain and perhaps spinal reflexes to relax skeletal muscle by unknown mechanisms. Cyclobenzaprine, methocarbamol, and metaxalone depress the CNS and induce sedation, which may be counter-productive for the active physical therapy currently recommended to treat certain types of muscle spasms. Diazepam exerts both antispasm and antispasticity actions by enhancing the effects of GABA at GABA_A receptors in the brain (see Chapter 31) and spinal cord (see Fig. 12-3), where it may have both presynaptic and postsynaptic effects.

Motor Nerve Blocker

Botulinum neurotoxins are produced by the anaerobic bacterium Clostridium botulinum. There are seven types of the toxin (A-G), all of which block ACh release. Botulinum toxin interferes with specific synaptic proteins involved in exocytotic release of synaptic vesicles containing ACh. This results in a long-duration (3 months) flaccid paralysis of the muscle into which it is injected (see Fig. 12-3). Botulinum toxin will also block autonomic synapses in the vicinity of the injection. Botulism is a serious form of food poisoning from improperly processed foods, and outbreaks of this problem occur sporadically.

Pharmacokinetics

Neuromuscular Blocking Drugs

The neuromuscular blocking drugs differ considerably in their pharmacokinetic properties, and the choice of a particular compound is determined in part by the duration of action of the agent needed for the particular procedure (Table 12-1). Because these drugs are positively charged, they cross membranes poorly and are generally limited in distribution to the extracellular space. However, small amounts of pancuronium, vecuronium, and pipecuronium cross membranes. Pancuronium also crosses the placenta but not in sufficient amounts to cause problems in the fetus when used during a cesarean section.

The use of pancuronium or tubocurarine is discouraged in patients with impaired renal function, because appreciable fractions of these drugs are cleared by renal filtration. Atracurium is inactivated almost entirely by metabolism, two-thirds enzymatic and one-third by spontaneous nonenzymatic breakdown. Vecuronium and pancuronium undergo significant hepatic metabolism, and their 3-hydroxy metabolites have much less neuromuscular blocking activity than do the parent drugs. Succinylcholine and mivacurium are metabolized by plasma butryrylcholinesterase, with minimal hydrolysis by AChE.

Spasmolytics

Antispasticity Drugs

Baclofen is rapidly absorbed after oral administration. It has a therapeutic t_{1/2} of 3.5 hours and is excreted primarily unchanged by the kidney; 15% is metabolized in the liver. Baclofen crosses the blood-brain barrier readily.

Dantrolene is metabolized primarily in the liver and is eliminated in urine and bile. After oral administration, its t_{1/2} is 15 hours. Benefits may not be apparent for a week or more, and development of hepatotoxic effects can become a concern with continued use.

The pharmacokinetics of diazepam are discussed in Chapter 31.

Tizanidine has poor oral bioavailability because it undergoes extensive first-pass metabolism. Its t_{1/2} is approximately 3 hours, and less than 3% is excreted unchanged in the urine.

### TABLE 12-1 Selected Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Compound</th>
<th>Onset (min)</th>
<th>Duration of Action (min)*</th>
<th>Metabolism</th>
<th>Elimination</th>
<th>Protein Binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>3-6</td>
<td>Intermediate</td>
<td>Carboxylesterase and nonenzymatic</td>
<td>R 6%-10%</td>
<td>80</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>5-7</td>
<td>Intermediate</td>
<td>Carboxylesterase and nonenzymatic</td>
<td>R &lt; 10%</td>
<td>nd</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>4-6</td>
<td>Long</td>
<td>Plasma ChE (75%)</td>
<td>R 25%-50%</td>
<td>30-35</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2-4</td>
<td>Short</td>
<td>Plasma ChE (100%)</td>
<td>R &lt; 10%</td>
<td>nd</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>4-6</td>
<td>Long</td>
<td>Hepatic (35%)</td>
<td>R 40%-60%</td>
<td>85</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>3-6</td>
<td>Long</td>
<td>Hepatic (20%)</td>
<td>R 40%-60%</td>
<td>nd</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>2-4</td>
<td>Intermediate</td>
<td>Hepatic (35%)</td>
<td>R 20%-30%</td>
<td>nd</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1-2</td>
<td>Ultrashort</td>
<td>Plasma ChE (100%)</td>
<td>R &lt; 10%</td>
<td>nd</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>4-6</td>
<td>Long</td>
<td>Hepatic (50%)</td>
<td>R 45%-60%</td>
<td>35-55</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2-4</td>
<td>Intermediate</td>
<td>Hepatic (35%)</td>
<td>R 20%-30%</td>
<td>70</td>
</tr>
</tbody>
</table>

*Duration: Ultrashort ≤ 10 min; Short = 10-30; Intermediate = 30-90 min; Long ≥ 90 min.

¹Additional drug; binds to cartilage and connective tissue.

R, Renal; B, biliary; nd, not determined due to rapid metabolism in plasma.
Antispasmodic Drugs

Cyclobenzaprine is administered orally and is highly protein-bound. The onset of effect is approximately 1 hour, with a duration of action of 12 to 24 hours, and a t1/2 of approximately 18 hours. Antispasms effects may take 1 to 2 days to be fully manifest. Cyclobenzaprine is metabolized extensively in the liver and is excreted mainly as inactive metabolites in the urine.

Metocarbamol is administered orally, reaching mean peak plasma concentrations in approximately 3 hours. Its onset of action is within 1 hour, and effects last for approximately 4 to 6 hours. The terminal t1/2 is approximately 9 hours, and metaxalone is metabolized in the liver and excreted by the kidneys.

Motor Nerve Blocker

Botulinum toxin is administered by intramuscular injection. The onset of muscle weakness varies from a few days to 2 weeks, depending on the time it takes for drug to reach the inside of the nerve terminal from its intramuscular injection site. The effects of botulinum toxin last for approximately 3 months, at which time time muscle function begins to recover as a consequence of nerve terminal sprouting and the formation of new synaptic contacts.

Spasmolytics

Antispasticity Drugs

Spasticity is a common neurological problem present in patients with damage of central motor pathways. It is characterized by velocity-dependent hyperexcitability of α-motoneurons in the spinal cord because of a loss of normal inhibitory function and an imbalance of excitatory and inhibitory neurotransmitters. Antispasticity drugs alter the activity of neurotransmitters in the CNS and at peripheral neuromuscular sites.

Dantrolene is the drug of choice for the treatment of malignant hyperthermia, which is a rare and potentially lethal disorder characterized by hypermetabolism, tachycardia, hypertension, premature ventricular contractions, rigidity, cyanosis, and rapid temperature increase. The hyperthermic response is not ameliorated by typical antipyretic drugs such as aspirin or acetaminophen. Malignant hyperthermia may develop in susceptible patients exposed to halogenated anesthetic gases with or without succinylcholine (see Chapter 35).

Antispasmodic Drugs

Cyclobenzaprine, metocarbamol, and metaxalone are approved for use as adjunctive treatment with physical therapy and rest for certain types of muscle spasm. Metocarbamol is also approved for treatment of muscle spasticity associated with tetanus (toxin) poisoning.

Motor Neuron Blocker

Botulinum toxin A is approved for treatment of muscle disorders of the eye, including blepharospasm and strabismus, characterized by excessive neuromuscular contractility, and for elective cosmetic purposes. Botulinum toxin is
also injected into muscles characterized with “repetitive use” disorders such as “tennis elbow” and “violinist wrist” and to treat chronic spasticity of skeletal muscle in cerebral palsy, and cervical dystonia, primary auxillary hyperhidrosis (severe underarm sweating); it is also being investigated for the treatment of severe migraine and overactive bladder. In spasticity disorders the objective is to permit the contralateral muscle to grow while the spastic muscle is relaxed.

When botulinum toxin is injected intramuscularly, it induces partial chemical denervation and diminishes involuntary contracture without causing complete paralysis. Some patients may develop tolerance to botulinum toxin by forming neutralizing antibodies.

Because botulinum toxin inhibits ACh release from all parasympathetic and cholinergic postganglionic sympathetic neurons, it may be useful for treating patients with conditions such as hyperhidrosis and detrusor spincter dyssynergia.

**Pharmacovigilance: Side Effects, Clinical Problems, and Toxicity**

Problems associated with the use of compounds that relax skeletal muscle are summarized in the Clinical Problems Box.

**Neuromuscular Blocking Drugs**

The major side effects of the neuromuscular blocking drugs are cardiovascular effects and histamine release. Their significance varies, with the older compounds exhibiting greater effects and the newer drugs having fewer effects.

Although nondepolarizing neuromuscular blocking drugs are generally selective for nicotinic cholinergic receptors in skeletal muscle, cholinergically innervated parasympathetic and sympathetic ganglia and cardiac parasympathetic neuroeffector junctions can all be affected if drug concentrations are sufficiently high. At normal doses most agents do not exhibit these effects except for tubocurarine, which produces a significant degree of ganglionic blockade. Because of the structural similarity of succinylcholine to ACh, succinylcholine binds to ganglionic nicotinic and cardiac muscarinic receptors and stimulates cholinergic transmission. Pancuronium exerts a direct blocking effect on muscarinic M2 receptors at doses used for neuromuscular blockade, but tubocurarine and atracurium produce muscarinic blockade only at much higher concentrations. Pancuronium and succinylcholine also produce direct muscarinic effects that result in cardiac dysrhythmias. Pancuronium also causes tachycardia and hypertension by blocking norepinephrine reuptake. The reduced cardiac effects of the newer agents greatly increase their safety margins.

Histamine release is a major problem with tubocurarine and a lesser problem with succinylcholine and mivacurium. Because of its marked histamine release and ganglionic blockade leading to hypotension and reflex tachycardia, tubocurarine is now seldom used, except as a pre-curarizing agent before the administration of succinylcholine.

The main disadvantage of atracurium is histamine release, which occurs in approximately 30% of patients. Pancuronium does not release histamine or block ganglia, but it does cause moderate increases in heart rate, blood pressure, and cardiac output as a consequence of sympathomimetic and anticholinergic effects. Histamine release may also occur with cisatracurium and mivacurium, but there are no cardiovascular effects at clinical doses. Doxacurium, rocuronium, and vecuronium are essentially free of cardiovascular and histamine effects.

Long-term use of several neuromuscular blockers in the intensive care unit to maintain controlled ventilation has resulted in prolonged periods of paralysis. Indications for reversal of neuromuscular block are postoperative residual curarization—that is, the inability of the patient to breathe adequately after discontinuation of anesthesia, or when it is impossible to artificially ventilate the patient after administration of a muscle relaxant. Although many criteria, such as the ability of the patient to sustain voluntary activities (adequate swallowing, coughing, eye opening, and head lifting), are used to evaluate the return of muscle function immediately after the use of muscle relaxants, monitoring the response to electrical stimulation is one of the most accurate methods to detect residual neuromuscular blockade. Other methods include electroencephalography, electromyography, mechanomyography, and accelerography.

The K+ efflux elicited by succinylcholine is dangerous in patients with neurological diseases such as hemiplegia, paraplegia, intracranial lesion, peripheral neuropathy, and in patients with extensive soft-tissue damage such as burns. Plasma K+ concentrations ≥13 mM produce cardiac arrhythmias and arrest. In these patients a marked resistance to nondepolarizing neuromuscular agents called extrajunctional chemosensitivity is present, probably because of an increased number of extrajunctional receptors. In addition, a combination of succinylcholine and halothane or other volatile anesthetics may result in a malignant hyperthermia syndrome in patients, which is a pharmacogenic disorder of skeletal muscle that presents as a hypermetabolic response that can be fatal. This disorder involves an uncontrolled rise of muscle Ca++, which is treated with dantrolene.

Neuromuscular blocking agents must be used with caution in patients with underlying neuromuscular, hepatic, or renal disease or electrolyte imbalance. Patients with neuromuscular disorders such as myasthenia gravis may be resistant to succinylcholine because of a decrease in the number of ACh receptors; the dose of muscle relaxants must be reduced by 50% to 75% in such patients. Patients with myasthenia gravis are also more likely than healthy patients to develop a phase II block in response to succinylcholine, particularly when repeated doses have been administered. Patients with myasthenia gravis exhibit much greater sensitivity to nondepolarizing agents, and the use of long-acting muscle relaxants such as pancuronium, pipercuronium, and doxacurium must be avoided in these patients. Intermediate- and short-acting nondepolarizing drugs can be administered carefully in lower doses with close monitoring of neuromuscular transmission. Lambert-Eaton Myasthenic syndrome, an autoimmune...
presynaptic neuromuscular disorder in which the stimulated release of Ach is reduced at the neuromuscular junction, is another disease in which patients are very sensitive to muscle relaxants.

Special consideration is required for use of neuromuscular blockers in patients with renal or hepatic disease. Prolonged neuromuscular block has been reported in these patients with pancuronium, vecuronium, rocuronium, and tubocurarine. These drugs are all H₂O-soluble compounds that depend on glomerular filtration, tubular excretion, and tubular reabsorption for clearance. The larger volume of distribution in the edematous renal patient, a reduced renal clearance, and decreased plasma protein binding can cause prolonged elimination. The drug of choice in patients with renal disease is atracurium because of its unique degradation that is unaffected by renal or hepatic dysfunction.

Hepatic disease also prolongs the duration of neuromuscular blockade. The liver is especially important in the metabolism of steroid-type relaxants such as vecuronium and rocuronium. In patients with cholestasis or cirrhosis, uptake of drug into the liver is decreased; thus plasma clearance is also decreased, leading to a prolonged effect. Because butyrylcholinesterase is produced in the liver, in patients with hepatic disease a decrease in enzyme production may prolong the effect of succinylcholine. Again, because the liver is not involved in the elimination of atracurium, it is the drug of choice in patients with hepatic failure.

**Drug interactions** occur between neuromuscular blockers, anesthetics, Ca⁺⁺ channel blockers, and some antibiotics. Many volatile anesthetic agents enhance the action of the nondepolarizing neuromuscular blockers by decreasing the open time of the ACh receptor, which increases ACh binding affinity. Enflurane has the strongest effect, followed by halothane. The local anesthetic bupivacaine potentiates blockade by nondepolarizing and depolarizing agents, and lidocaine and procaine prolong the duration of action of succinylcholine by inhibiting butyrylcholinesterase.

Ca⁺⁺ channel blockers, and to a lesser extent β adrenergic blockers, potentiate neuromuscular blocking drugs. Antibiotics that interact with neuromuscular blocking agents are aminoglycosides, tetracyclines, polymyxin, and clindamycin. Aminoglycosides decrease ACh release and lower postjunctional sensitivity to ACh. Tetracyclines chelate Ca⁺⁺ and reduce ACh release. Lincomycin and clindamycin block nicotinic receptors and depress muscle contractility, enhancing neuromuscular blockade. The duration of action of vecuronium, pancuronium, doxicurium, and pimecuronium is also reduced in patients taking phenytoin or carbamazepine. These anticonvulsants decrease the affinity of nicotinic receptors for neuromuscular blockers and increase the number of receptors on muscle fibers. The duration of action of vecuronium is also prolonged in patients treated with cimetidine, and magnesium sulfate, used to treat preeclampsia, prolongs the effect of nondepolarizing relaxants and inhibits the effect of succinylcholine.

A source of acute pharmacovigilance in the use of neuromuscular blocking drugs has surfaced lately, because these drugs are widely used as adjuncts during surgery. It has been known for more than 60 years that these agents have essentially no effect on brain activity and consciousness. The patient’s respiration is often completely controlled externally during surgery. It is known that a patient could experience pain from the surgical procedures if the anesthetic level is or becomes insufficient during the procedure, but the patient is unable to communicate this because they are unable to move or speak. This can lead to unacceptable infliction of pain, which can be avoided if physiological parameters, such as electroencephalographic activity described previously, are monitored; procedures should be used to prevent this from occurring.

Genetic variations in butyrylcholinesterase activity result in either lower concentrations of normal enzyme or an abnormal enzyme. A dose of 1 to 2 mg/kg succinylcholine in healthy patients produces neuromuscular blockade lasting <15 minutes; in a patient with a variant of this enzyme with decreased effectiveness, the same dose may last much longer. This is illustrated in Figure 12-4, with block defined as the duration of apnea. Trauma, alcoholism, pregnancy, use of oral contraceptives, and other conditions in which butyrylcholinesterase activity is changed can alter the duration of neuromuscular block produced by succinylcholine.

**Spasmyotics**

**Antispasticity Drugs**

Clinical problems with the antispasticity drugs involve weakness as a major adverse effect. CNS depression including drowsiness occurs to a variable extent with these agents. Side effects of baclofen include hypotension, dizziness, drowsiness, weakness, fatigue, and depression. In addition, baclofen may interfere with attention and memory in elderly or brain-injured patients.

Adverse effects of dantrolene are muscle weakness, drowsiness, dizziness, diarrhea, and seizures; chronic use may result in hepatotoxicity.
**Antispasm Drugs**

The major pharmacovigilance issue with all antispasm drugs is sedation, and caution is required when driving or operating machinery; these agents are additive with alcohol or other sedative-hypnotics. All of these drugs can cause excessive adverse reactions, particularly on the CNS, in elderly patients.

Cyclobenzaprine is contraindicated in patients with myocardial infarction and cardiac conduction defects and in patients receiving monoamine oxidase inhibitors. Cyclobenzaprine possesses muscarinic antagonist effects and may cause constipation, increased intraocular pressure, and urinary retention.

The most frequent reactions to metaxalone include nausea, gastrointestinal upset, sedation, dizziness, headache, and anxiety or irritability.

**Motor Nerve Blocker**

All adverse effects of botulinum toxin are a consequence of its mechanism of action. If the toxin is inhaled, “botulism” results, consisting of ptosis, generalized weakness, dizziness, blurred vision and diplopia, dysarthria, and dysphagia followed by flaccid paralysis and respiratory failure. When administered by injection, side effects vary with the site of injection. For example, in patients injected in the neck for treating cervical dystonia, dysphagia may develop. Other side effects include influenza-like illness, brachial plexopathy, and gallbladder dysfunction. Botulinum toxin should not be used in patients who are pregnant or lactating, or who have a neuromuscular disease.

**New Horizons**

Neuromuscular blocking drugs are now commonly used in anesthesia during surgical procedures and on a long-term basis to allow controlled ventilation in patients in intensive care units. However, this practice is not without problems, including prolonged muscle paralysis after termination of treatment. In recent years the search for new neuromuscular relaxants has concentrated on finding drugs with a rapid onset and shorter and more predictable duration of action with minimal side effects.

Sugammadex is a novel investigational drug in clinical testing to reverse neuromuscular blockade. This agent is a modified γ-cyclodextrin, which forms H₂O-soluble complexes with steroidal neuromuscular blocking drugs (rocuronium, vecuronium, and pancuronium). Intravenous administration of sugammadex creates a concentration gradient favoring the movement of the steroidal agents from the neuromuscular junction back into the plasma, resulting in rapid recovery of neuromuscular function and reversing deep neuromuscular blockade without muscle weakness.

Succinylcholine and mivacurium are neuromuscular blocking drugs with short durations of action resulting from rapid hydrolytic degradation by plasma butyrylcholinesterase, but certain patients exhibit several variants of this enzyme, which lead to prolonged and potentially dangerous durations of neuromuscular block. Malignant hyperthermia, associated with succinylcholine and volatile anesthetic administration, is also a genetic abnormality that occurs in 1 of 3000 individuals and may be attributed to mutations in the ryanodine receptor.

**TRADE NAMES**

(In addition to generic and fixed-combination preparations, the following trade-named materials are some of the important compounds available in the United States.)

**Neuromuscular Blocking Drugs**
- Atracurium (Tracrium)
- Cisatracurium (Nimbex)
- Doxacurium (Nuromax)
- Mivacurium (Mivacron)
- Pancuronium (Pavulon)
- Rocuronium (Zemuron)
- Succinylcholine (Aneclute, Quelicin)
- Tubocurarine (Intacostrin)
- Vecuronium (Norcuron)

**Antispasticity Drugs**
- Baclofen (Lioresal)
- Dantrolene (Dantrium)
- Diazepam* (Valium)
- Tizanidine (Zanaflex)

**Antispasm Drugs**
- Cyclobenzaprine (Flexeril)
- Metaxalone (Skelaxin)
- Methocarbamol (Robaxin)
- Motor nerve blocker
- Botulinum toxin* (BoTox)

*Drug is useful as both antispasm and antispasticity agent

**CLINICAL PROBLEMS**

**Neuromuscular Blocking Drugs**
- Fasciculations and postoperative myalgias, particularly in the neck, shoulders, and chest
- Masseter muscle spasm
- Increased intraocular pressure
- Increased intra-abdominal and intracranial pressure
- Bradycardia and cardiac arrest
- Malignant hyperthermia
- Histamine release
- Tachycardia and hypertension
- Paralysis with insufficient analgesia

**Antispasticity Drugs**
- Weakness
- Sedation

**Antispasm Agents**
- Sedation
- Increase toxicity of other depressant drugs

**Motor Nerve Blocker**
- Influenza-like illness
- Brachial plexopathy
SELF-ASSESSMENT QUESTIONS

1. Which of the following neuromuscular blocking drugs cause histamine release?
   A. Vecuronium
   B. Mivacurium
   C. Tubocurarine
   D. Doxacurium
   E. Pancuronium

2. At therapeutic concentrations the primary action of doxacurium is to:
   A. Block acetylcholine release.
   B. Inhibit acetylcholinesterase.
   C. Block muscarinic receptors.
   D. Block ion channels opened by activation of nicotinic receptors.
   E. Block nicotinic receptors at motor end plates.

3. Which of the following neuromuscular blocking agents has the shortest duration of action?
   A. Doxacurium
   B. Mivacurium
   C. Succinylcholine
   D. Atracurium
   E. Vecuronium

4. Potentially devastating adverse effects of neuromuscular blockers include:
   A. Muscle paralysis but awareness of pain during surgery.
   B. Lack of paralysis with normal doses in patients with myasthenia gravis.
   C. Block of histamine receptors during surgery.
   D. Inability to reverse paralysis with nondepolarizing neuromuscular blockers.
   E. Potential induction of malignant hypothermia in patients anesthetized with certain inhalation anesthetics.

5. Potential therapeutic uses of neuromuscular blockers include:
   A. Diagnosis of myasthenia gravis.
   B. Control of ventilation during surgery.
   C. Control of spasticity of cerebral palsy.
   D. To produce high airway pressures during in intensive care.
   E. Block of pain during electroconvulsive therapy.