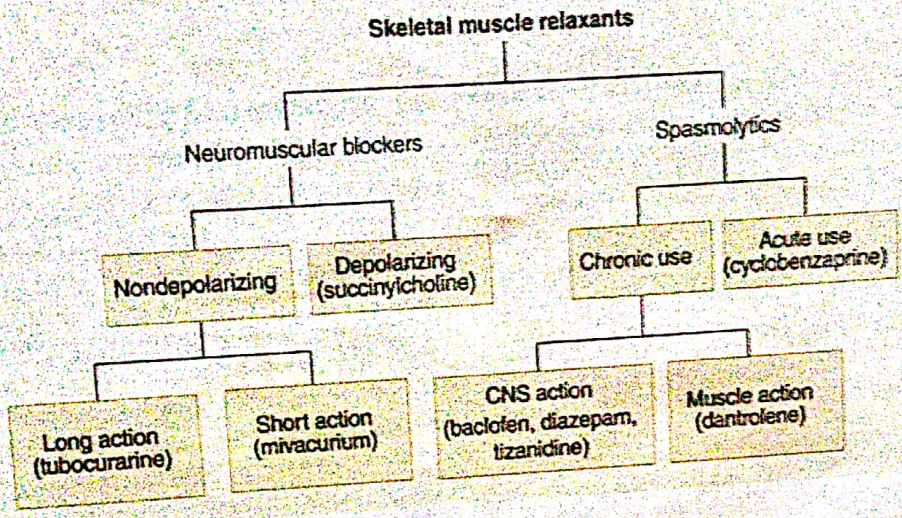
CHAPTER 27

Skeletal Muscle Relaxants

The drugs in this chapter are divided into 2 dissimilar groups. The neuromuscular blocking drugs, which act at the skeletal myoneural junction, are used to produce muscle paralysis to facilitate surgery or assisted ventilation. The spasmolytic drugs, most of which act in the CNS, are used to reduce abnormally elevated tone caused by neurologic or muscle end plate disease.



NEUROMUSCULAR BLOCKING DRUGS

A. Classification and Prototypes

Skeletal muscle contraction is evoked by a nicotinic cholinergic transmission process. Blockade of transmission at the end plate (the postsynaptic structure bearing the nicotinic receptors) is clinically useful in producing muscle relaxation, a requirement for surgical relaxation, tracheal intubation and control of ventilation. The neuromuscular blockers are quaternary amines structurally related to acetylcholine (ACh). Most are antagonists (nondepolarizing type), and the prototype is **tubocurarine.** One neuromuscular blocker used clinically, **succinylcholine,** is an agonist at the nicotinic end plate receptor (depolarizing type).

B. Nondepolarizing Neuromuscular Blocking Drugs

1. Pharmacokinetics—All agents are given parenterally. They are highly polar drugs and do not cross the blood-brain barrier. Drugs that are metabolized (eg, mivacurium, by plasma cholinesterase) or eliminated in the bile (eg, vecuronium) have shorter durations of action (10–20 min) than those eliminated by the kidney (eg, metocurine, pancuronium, pipecuronium, and tubocurarine), which usually have durations of action of less than 35 min. In addition to hepatic metabolism, atracurium clearance involves rapid spontaneous breakdown (Hofmann elimination) to form laudanosine and other products. At high blood levels, laudanosine may cause seizures. Cisatracurium, a stereoisomer of atracurium, is also inactivated spontaneously but forms less laudanosine and currently is one of the most commonly used muscle relaxants in clinical practice.

2. Mechanism of action—Nondepolarizing drugs prevent the action of ACh at the skeletal muscle end plate (Figure 27–1). They act as surmountable blockers. (That is, the blockade can be overcome by increasing the amount of agonist [ACh] in the synaptic cleft.) They behave as though they compete with ACh at the receptor, and their effect is reversed by cholinesterase inhibitors. Some drugs in this group may also act directly to plug the ion

High-Yield Terms to Learn

Depolarizing blockade	Neuromuscular paralysis that results from persistent depolarization of the end plate (eg, by succinylcholine)
Desensitization	A phase of blockade by a depolarizing blocker during which the end plate [illegible] is less than normally responsive to agonists (acetylcholine or succinylcholine)
Malignant hyperthermia	Hyperthermia that results from massive release of calcium from the sarcoplasmic reticulum, leading to uncontrolled contraction and stimulation of metabolism in skeletal muscle
Nondepolarizing blockade	Neuromuscular paralysis that results from pharmacologic antagonism at the acetylcholine receptor of the end plate (eg, by tubocurarine)
Spasmolytic	A drug that reduces abnormally elevated muscle tone (spasm) without paralysis (eg, baclofen, dantrolene)
Stabilizing blockade	Synonym for nondepolarizing blockade

channel operated by the ACh receptor. Post-tetanic potentiation is preserved in the presence of these agents, but tension during the tetanus fades rapidly. See Table 27–1 for additional details. Larger muscles (eg, abdominal, diaphragm) are more resistant to neuromuscular blockade, but they recover more rapidly than smaller muscles (eg, facial, hand). Of the available nondepolarizing drugs, rocuronium (60–120 s) has the most rapid onset time.

C. Depolarizing Neuromuscular Blocking Drugs

1. Pharmacokinetics—Succinylcholine is composed of two ACh molecules linked end to end. Succinylcholine is metabolized by cholinesterase (butyrylcholinesterase or pseudocholinesterase) in the liver and plasma. It has a duration of action of only a few minutes if given as a single dose. Blockade may be prolonged in patients [illegible]

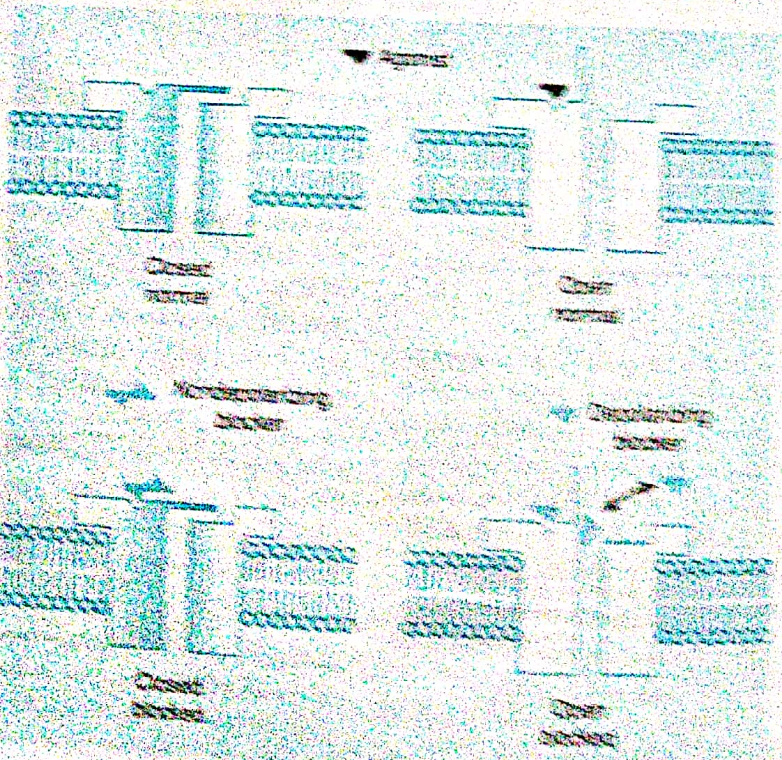


FIGURE 27–1 Drug interactions with the acetylcholine (ACh) receptor on the skeletal muscle end plate. **Top:** ACh, the normal agonist, opens the sodium channel. **Bottom left:** Nondepolarizing blockers bind to the receptor to prevent opening of the channel. **Bottom right:** Succinylcholine causes initial depolarization (fasciculation) and then persistent depolarization of the channel, which leads to muscle relaxation. (Reproduced, with permission, from Katzung BG, editor: Basic & Clinical Pharmacology, 12th ed. McGraw-Hill, 2012: Fig. 27–[illegible].)

TABLE 27–1 Comparison of a typical nondepolarizing neuromuscular blocker (tubocurarine) and a depolarizing blocker (succinylcholine).

Process	Tubocurarine	Succinylcholine	
		Phase I	Phase II
Administration of tubocurarine	Additive	Antagonistic	Augmented[a]
Administration of succinylcholine	Antagonistic	Additive	Augmented[a]
Effect of neostigmine	Antagonistic	Augmented[a]	Antagonistic
Initial excitatory effect on skeletal muscle	None	Fasciculations	None
Response to tetanic stimulus	Unsustained ("fade")	Sustained[b]	Unsustained
Post-tetanic facilitation	Yes	No	Yes

[a]It is not known whether this interaction is additive or synergistic (superadditive).

[b]The amplitude is decreased, but the response is sustained.

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genetic variants of plasma cholinesterase that metabolize succinylcholine very slowly. Such variant cholinesterases are resistant to the inhibitory action of dibucaine. Succinylcholine is not rapidly hydrolyzed by acetylcholinesterase.

2. Mechanism of action—Succinylcholine acts like a nicotinic agonist and depolarizes the neuromuscular end plate (Figure 27–1).

The initial depolarization is often accompanied by twitching and fasciculations (prevented by pretreatment with small doses of a nondepolarizing blocker). Because tension cannot be maintained in skeletal muscle without periodic repolarization and depolarization of the end plate, continuous depolarization results in muscle relaxation and paralysis. Succinylcholine may also plug the end plate channels.

When given by continuous infusion, the effect of succinylcholine changes from continuous depolarization (phase I) to gradual repolarization with resistance to depolarization (phase II) (ie, a curare-like block; see Table 27–1).

D. Reversal of Blockade

The action of nondepolarizing blockers is readily reversed by increasing the concentration of normal transmitter at the receptors. This is best accomplished by administration of cholinesterase inhibitors such as neostigmine or pyridostigmine. In contrast, the paralysis produced by the depolarizing blocker succinylcholine is *increased* by cholinesterase inhibitors during phase I. During phase II, the block produced by succinylcholine is usually reversible by cholinesterase inhibitors.

E. Toxicity

1. Respiratory paralysis—The action of full doses of neuromuscular blockers leads directly to respiratory paralysis. If mechanical ventilation is not provided, the patient will asphyxiate.

2. Autonomic effects and histamine release—Autonomic ganglia are stimulated by succinylcholine and weakly blocked by tubocurarine. Succinylcholine activates cardiac muscarinic receptors, whereas pancuronium is a moderate blocking agent and causes tachycardia. Tubocurarine and mivacurium are the most likely of these agents to cause histamine release, but it may also occur to a slight extent with atracurium and succinylcholine. Vecuronium and several newer nondepolarizing drugs (cisatracurium, doxacurium, pipecuronium, rocuronium) have no significant effects on autonomic functions or histamine release. A summary of the autonomic effects of neuromuscular drugs is shown in Table 27–2.

3. Specific effects of succinylcholine—Muscle pain is a common postoperative complaint, and muscle damage may occur. Succinylcholine may cause hyperkalemia, especially in patients with burn or spinal cord injury, peripheral nerve dysfunction, or muscular dystrophy. Increases in intragastric pressure caused by fasciculations may promote regurgitation with possible aspiration of gastric contents.

4. Drug interactions—Inhaled anesthetics, especially isoflurane, strongly potentiate and prolong neuromuscular blockade. A rare interaction of succinylcholine (and possibly tubocurarine) with inhaled anesthetics can result in malignant hyperthermia. A very early sign of this potentially life-threatening condition is contraction of the jaw muscles (trismus). Aminoglycoside antibiotics and antiarrhythmic drugs may potentiate and prolong the relaxant action of neuromuscular blockers to a lesser degree.

5. Effects of aging and diseases—Older patients (>75 years) and those with myasthenia gravis are more sensitive to the actions of the nondepolarizing blockers, and doses should be reduced in these patients. Conversely, patients with severe burns or who suffer from upper motor neuron disease are less responsive to these agents, probably as a result of proliferation of extrajunctional nicotinic receptors.

TABLE 27–2 Autonomic effects of neuromuscular drugs.

Drug	Effect on Autonomic Ganglia	Effect on Cardiac Muscarinic Receptors	Ability to Release Histamine
Nondepolarizing			
Atracurium	None	None	Slight
Cisatracurium	None	None	None
Mivacurium	None	None	Moderate
Pancuronium	None	Moderate block	None
Tubocurarine	Weak block	None	Moderate
Vecuronium	None	None	None
Depolarizing			
Succinylcholine	Stimulation	Stimulation	Slight

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SKILL KEEPER: AUTONOMIC CONTROL OF HEART RATE (SEE CHAPTER 6)

Tubocurarine can block bradycardia caused by phenylephrine but has no effect on bradycardia caused by neostigmine. Explain! The Skill Keeper Answer appears at the end of the chapter.

SPASMOLYTIC DRUGS

Certain chronic diseases of the CNS (eg, cerebral palsy, multiple sclerosis, stroke) are associated with abnormally high reflex activity in the neuronal pathways that control skeletal muscle; the result is painful spasm. Bladder control and anal sphincter control are also affected in most cases and may require autonomic drugs for management. In other circumstances, acute injury or inflammation of muscle leads to spasm and pain. Such temporary spasm can sometimes be reduced with appropriate drug therapy.

The goal of spasmolytic therapy in both chronic and acute conditions is reduction of excessive skeletal muscle tone without reduction of strength. Reduced spasm results in reduction of pain and improved mobility.

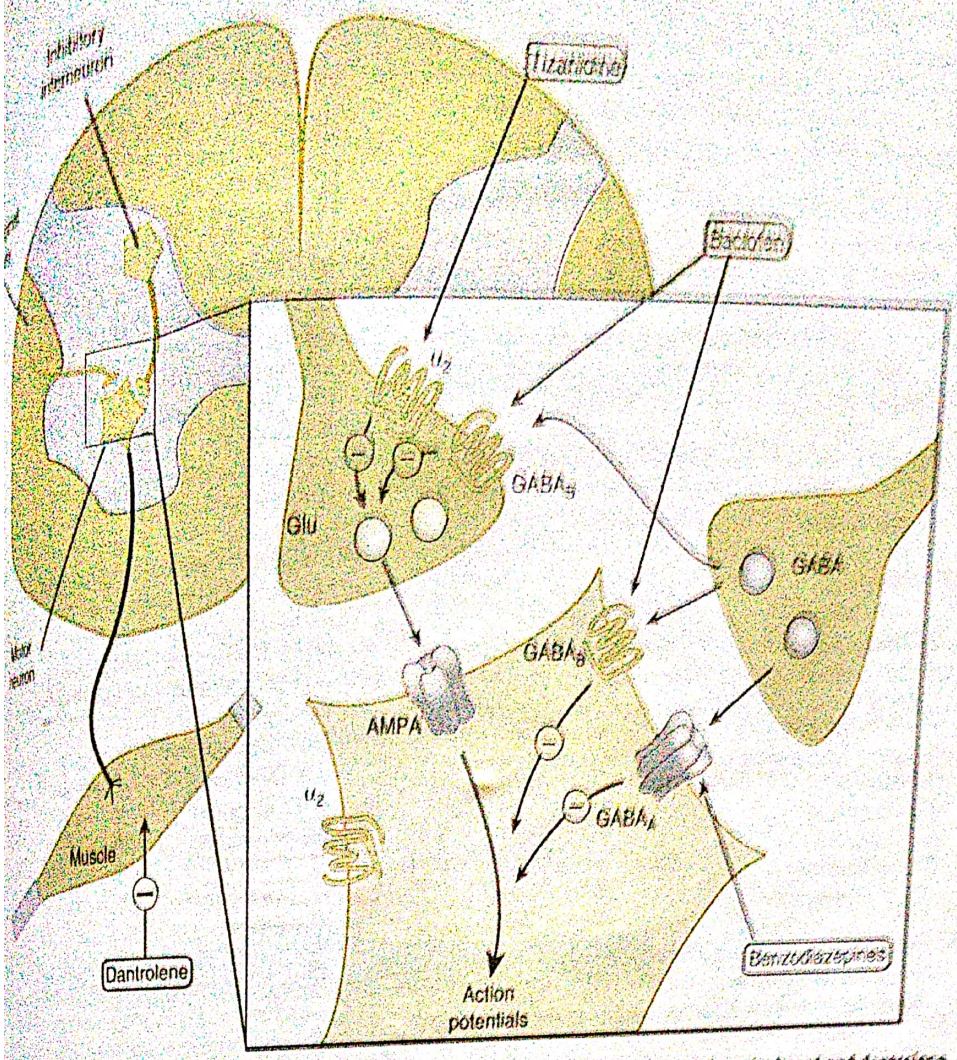
A. Drugs for Chronic Spasm

1. Classification—The spasmolytic drugs do not resemble ACh in structure or effect. They act in the CNS and in one case in the skeletal muscle cell rather than at the neuromuscular end plate. The spasmolytic drugs used in treatment of the chronic conditions mentioned previously include **diazepam,** a benzodiazepine (see Chapter 22); **baclofen,** a γ-aminobutyric acid (GABA) agonist; **tizanidine,** a congener of clonidine; and **dantrolene,** an agent that acts on the sarcoplasmic reticulum of skeletal muscle. These agents are usually administered by the oral route. Refractory cases may respond to chronic intrathecal administration of baclofen. **Botulinum toxin** injected into selected muscles can reduce pain caused by severe spasm (see Chapter 6) and also has applications for ophthalmic purposes and in more generalized spastic disorders (eg, cerebral palsy). **Gabapentin** and **pregabalin,** anticonvulsant drugs, have been shown to be effective spasmolytics in patients with multiple sclerosis.

2. Mechanisms of action—The spasmolytic drugs act by several mechanisms. Three of the drugs (baclofen, diazepam, and tizanidine) act in the spinal cord (Figure 27–2).

Baclofen acts as a $GABA_B$ agonist at both presynaptic and postsynaptic receptors, causing membrane hyperpolarization. Presynaptically, baclofen, by reducing calcium influx, decreases the release of the excitatory transmitter glutamic acid; at postsynaptic receptors, baclofen facilitates the inhibitory action of GABA. Diazepam facilitates GABA-mediated inhibition via its interaction with $GABA_A$ receptors (see Chapter 22). Tizanidine, an imidazoline related to clonidine with significant α_2 agonist activity, reinforces presynaptic inhibition in the spinal cord. All 3 drugs reduce the tonic output of the primary spinal motoneurons.

Dantrolene acts in the skeletal muscle cell to reduce the release of activator calcium from the sarcoplasmic reticulum via interaction with the ryanodine receptor (RyR1) channel. Cardiac muscle and smooth muscle are minimally depressed. Dantrolene is also effective in the treatment of **malignant hyperthermia,** a disorder characterized by massive calcium release from the sarcoplasmic reticulum of skeletal muscle. Though rare, malignant hyperthermia can be triggered by general anesthesia protocols that include succinylcholine or tubocurarine (see Chapter 25). In this emergency condition, dantrolene is given intravenously to block calcium release.



Sites of spasmolytic action of benzodiazepines (GABA$_A$), baclofen (GABA$_B$), tizanidine (α_2) in the spinal cord and dantrolene at AMPA, amino-hydroxyl-methyl-isosoxazole-proprionic acid, a ligand for a glutamate receptor subtype; Glu, glutamatergic duced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 27–11.)

The sedation produced by diazepam is significant than that produced by other sedative-hypnotic drugs duce equivalent muscle relaxation. Baclofen causes n sedation than diazepam, and tolerance occurs e withdrawal should be accomplished slowly. cause asthenia, drowsiness, dry mouth, and hypo- tance causes significant muscle weakness but less than diazepam or baclofen.

for Acute Muscle Spasm

The cyclobenzaprine, metaxalone, methocarba- mol) are promoted for the treatment of acute from muscle injury. Most of these drugs act in the brain stem. **Cyclobenzaprine,** a of this group, is believed to act in the brain by interfering with polysynaptic reflexes that ased muscle tone. The drug is active by the oral route and has marked sedative and antimuscarinic actions. Cyclobenzaprine may cause confusion and visual hallucinations in some patients. None of these drugs used for acute spasm is effective in muscle spasm resulting from cerebral palsy or spinal cord injury.

Patients with renal failure often have decreased levels of plasma cholinesterase, thus prolonging the duration of action of mivacurium or succinylcholine.

QUESTIONS

1. Characteristics of phase I depolarizing neuromuscular blockade due to succinylcholine include
   (A) Easy reversibility with nicotinic receptor antagonists
   (B) Marked muscarinic blockade
   (C) Muscle fasciculations only in the later stages of block
   (D) Reversibility by acetylcholinesterase (AChE) inhibitors
   (E) Sustained tension during a period of tetanic stimulation