CHAPTER 11

Neuromuscular Blocking Agents

KEY CONCEPTS

1. It is important to realize that muscle relaxation does not ensure unconsciousness, amnesia, or analgesia.
2. Depolarizing muscle relaxants act as acetylcholine (ACh) receptor agonists, whereas nondepolarizing muscle relaxants function as competitive antagonists.
3. Because depolarizing muscle relaxants are not metabolized by acetylcholinesterase, they diffuse away from the neuromuscular junction and are hydrolyzed in the plasma and liver by another enzyme, pseudocholinesterase (nonspecific cholinesterase, plasma cholinesterase, or butyrylcholinesterase).
4. With the exception of mivacurium, nondepolarizing agents are not significantly metabolized by either acetylcholinesterase or pseudocholinesterase. Reversal of their blockade depends on redistribution, gradual metabolism, and excretion of the relaxant by the body, or administration of specific reversal agents (eg, cholinesterase inhibitors) that inhibit acetylcholinesterase enzyme activity.
5. Muscle relaxants owe their paralytic properties to mimicry of ACh. For example, succinylcholine consists of two joined ACh molecules.
6. Compared with patients with low enzyme levels or heterozygous atypical enzyme in whom blockade duration is doubled or tripled, patients with homozygous atypical enzyme will have a very long blockade (eg, 4–8 h) following succinylcholine administration.
7. Succinylcholine is considered contraindicated in the routine management of children and adolescents because of the risk of hyperkalemia, rhabdomyolysis, and cardiac arrest in children with undiagnosed myopathies.
8. Normal muscle releases enough potassium during succinylcholine-induced depolarization to raise serum potassium by 0.5 mEq/L. Although this is usually insignificant in patients with normal baseline potassium levels, a life-threatening potassium elevation is possible in patients with burn injury, massive trauma, neurological disorders, and several other conditions.
9. Doxacurium, pancuronium, vecuronium, and pipecuronium are partially excreted by the kidneys, and their action is prolonged in patients with renal failure.
10. Cirrhotic liver disease and chronic renal failure often result in an increased volume of distribution and a lower plasma concentration for a given dose of water-soluble drugs, such as muscle relaxants. On the other hand, drugs dependent on hepatic or renal excretion may demonstrate prolonged clearance. Thus, depending on

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the drug, a greater initial dose—but smaller maintenance doses—might be required in these diseases.

11 Atracurium and cisatracurium undergo degradation in plasma at physiological pH and temperature by organ-independent Hofmann elimination. The resulting metabolites (a monoquaternary acrylate and laudanosine) have no intrinsic neuromuscular blocking effects.

12 Hypertension and tachycardia may occur in patients given pancuronium. These cardiovascular effects are caused by the combination of vagal blockade and catecholamine release from adrenergic nerve endings.

13 Long-term administration of vecuronium to patients in intensive care units has resulted in prolonged neuromuscular blockade (up to several days), possibly from accumulation of its active 3-hydroxy metabolite, changing drug clearance, or the development of a polyneuropathy.

14 Rocuronium (0.9–1.2 mg/kg) has an onset of action that approaches succinylcholine (60–90 s), making it a suitable alternative for rapid-sequence inductions, but at the cost of a much longer duration of action.

Skeletal muscle relaxation can be produced by deep inhalational anesthesia, regional nerve block, or neuromuscular blocking agents (commonly called *muscle relaxants*). In 1942, Harold Griffith published the results of a study using an extract of curare (a South American arrow poison) during anesthesia. Following the introduction of succinylcholine as a "new approach to muscular relaxation," these agents rapidly became a routine part of the anesthesiologist's drug arsenal. However, as noted by Beecher and Todd in 1954: "[m]uscle relaxants given inappropriately may provide the surgeon with optimal [operating] conditions in . . . a patient [who] is paralyzed but not anesthetized—a state [that] is wholly unacceptable for the patient." [1] In other words, muscle relaxation does not ensure unconsciousness, amnesia, or analgesia. This chapter reviews the principles of neuromuscular transmission and presents the mechanisms of action, physical structures, routes of elimination, recommended dosages, and side effects of several muscle relaxants.

Neuromuscular Transmission

Association between a motor neuron and a muscle cell occurs at the neuromuscular junction (Figure 11–1). The cell membranes of the neuron and muscle fiber are separated by a narrow (20-nm) gap, the synaptic cleft. As a nerve's action potential depolarizes its terminal, an influx of calcium ions through voltage-gated calcium channels into the nerve cytoplasm allows storage vesicles to fuse with the terminal plasma membrane and release their contents

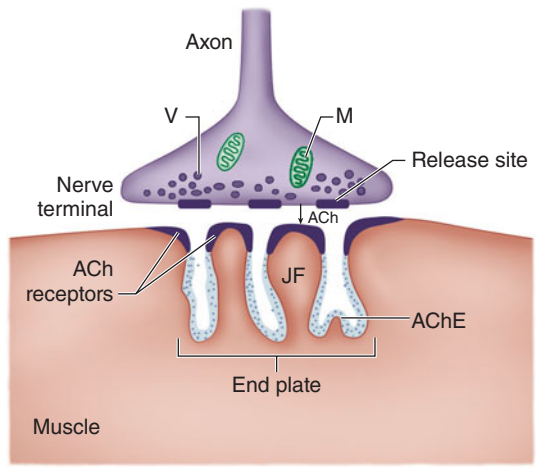

FIGURE 11–1 The neuromuscular junction. V, transmitter vesicle; M, mitochondrion; ACh, acetylcholine; AChE, acetylcholinesterase; JF, junctional folds. (Reproduced, with permission, from Drachman DB: Myasthenia gravis. N Engl J Med 1978;298:135.)

(acetylcholine [ACh]). The ACh molecules diffuse across the synaptic cleft to bind with nicotinic cholinergic receptors on a specialized portion of the muscle membrane, the motor end-plate. Each neuromuscular junction contains approximately 5 million of these receptors, but activation of only about 500,000 receptors is required for normal muscle contraction.

The structure of ACh receptors varies in different tissues and at different times in development. Each ACh receptor in the neuromuscular junction normally consists of five protein subunits; two α subunits; and single β, δ, and ε subunits. Only the two identical α subunits are capable of binding ACh molecules. If both binding sites are occupied by ACh, a conformational change in the subunits briefly (1 ms) opens an ion channel in the core of the receptor (**Figure 11–2**). The channel will not open if ACh binds on only one site. In contrast to the normal (or mature) junctional ACh receptor, another isoform contains a γ subunit instead of the ε subunit. This isoform is referred to as the fetal or immature receptor because it is in the form initially expressed in fetal muscle. It is also often referred to as extrajunctional because, unlike the mature isoform, it may be located anywhere in the muscle membrane, inside or outside the neuromuscular junction when expressed in adults.

Cations flow through the open ACh receptor channel (sodium and calcium in; potassium out), generating an **end-plate potential**. The contents of a single vesicle, a quantum of ACh (10^4 molecules per quantum), produce a miniature end-plate potential. The number of quanta released by each nerve impulse, normally at least 200, is very sensitive to extracellular ionized calcium concentration; increasing calcium concentration increases the

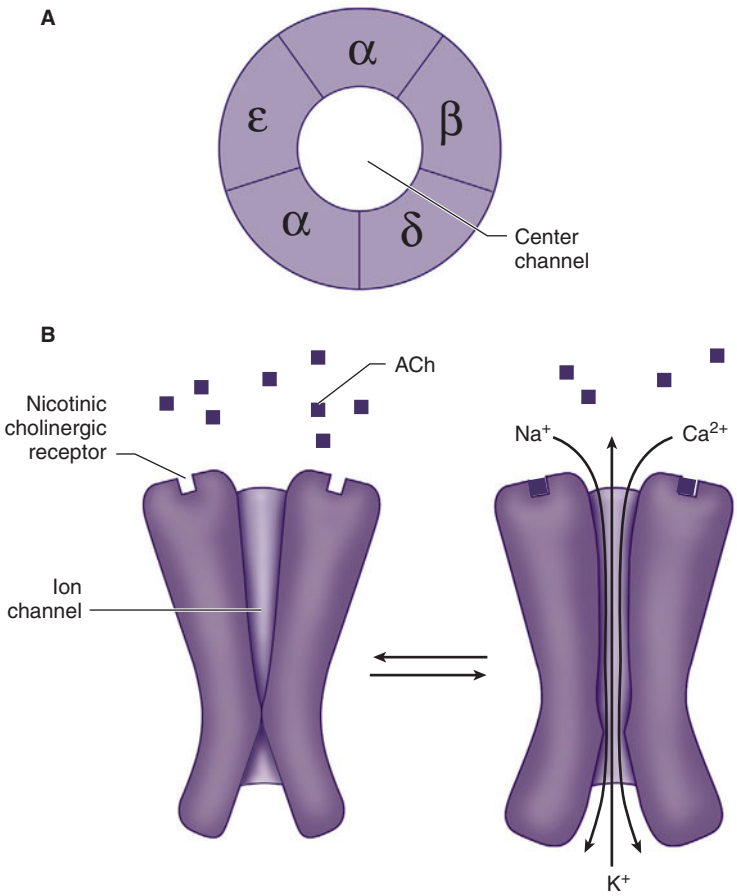

FIGURE 11–2 **A**: Structure of the ACh receptor. Note the two α subunits that actually bind ACh and the center channel. **B**: Binding of ACh to receptors on muscle end-plate causes channel opening and ion flux.

number of quanta released. When enough receptors are occupied by ACh, the end-plate potential will be sufficiently strong to depolarize the perijunctional membrane. Voltage-gated sodium channels within this portion of the muscle membrane open when a threshold voltage is developed across them, as opposed to end-plate receptors that open when ACh is applied (Figure 11–3). Perijunctional areas of muscle membrane have a higher density of these sodium channels than other parts of the membrane. The resulting action potential propagates along the muscle membrane and T-tubule system, opening sodium channels and releasing calcium from the sarcoplasmic reticulum. This intracellular calcium allows the contractile proteins actin and myosin to interact, bringing about muscle contraction. The amount of ACh released and the number of receptors subsequently activated will normally far exceed the minimum required for the initiation of an action potential. The nearly 10-fold margin of safety is lost in Eaton–Lambert myasthenic syndrome (decreased release of ACh) and myasthenia gravis (decreased number of receptors).

ACh is rapidly hydrolyzed into acetate and choline by the substrate-specific enzyme **acetylcholinesterase**. This enzyme (also called specific cholinesterase or true cholinesterase) is embedded into the motor end-plate membrane immediately adjacent to the ACh receptors. After unbinding ACh, the receptors' ion channels close, permitting the end-plate to repolarize. Calcium is resequestered in the sarcoplasmic reticulum, and the muscle cell relaxes.

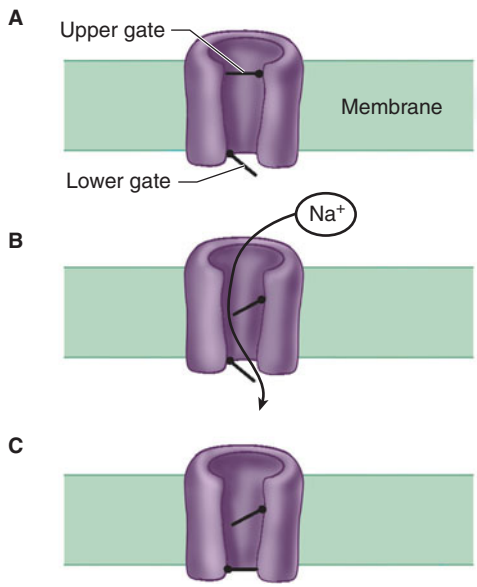

FIGURE 11–3 Schematic of the sodium channel. The sodium channel is a transmembrane protein that can be conceptualized as having two gates. Sodium ions pass only when both gates are open. Opening of the gates is time dependent and voltage dependent. The channel therefore possesses three functional states. At rest, the lower gate is open but the upper gate is closed (**A**). When the muscle membrane reaches threshold voltage depolarization, the upper gate opens and sodium can pass (**B**). Shortly after the upper gate opens the time-dependent lower gate closes (**C**). When the membrane repolarizes to its resting voltage, the upper gate closes and the lower gate opens (A).

Distinctions Between Depolarizing & Nondepolarizing Blockade

Neuromuscular blocking agents are divided into two classes: depolarizing and nondepolarizing (Table 11–1). This division reflects distinct differences in the mechanism of action, response to peripheral nerve stimulation, and reversal of block.

MECHANISM OF ACTION

Similar to ACh, all neuromuscular blocking agents are quaternary ammonium compounds whose positively charged nitrogen imparts an affinity to

TABLE 11–1 Depolarizing and nondepolarizing muscle relaxants.

Depolarizing	Nondepolarizing
Short-acting Succinylcholine	Short-acting Gantacurium[1] Intermediate-acting Atracurium Cisatracurium Vecuronium Rocuronium Long-acting Pancuronium

[1]Not yet commercially available in the United States.

nicotinic ACh receptors. Whereas most agents have two quaternary ammonium atoms, a few have one quaternary ammonium cation and one tertiary amine that is protonated at physiological pH.

Depolarizing muscle relaxants very closely resemble ACh and readily bind to ACh receptors, generating a muscle action potential. Unlike ACh, however, these drugs are *not* metabolized by acetylcholinesterase, and their concentration in the synaptic cleft does not fall as rapidly, resulting in a prolonged depolarization of the muscle end-plate.

Continuous end-plate depolarization causes muscle relaxation because opening of perijunctional sodium channels is time limited (sodium channels rapidly "inactivate" with continuing depolarization) (Figure 11–3). After the initial excitation and opening (Figure 11–3B), these sodium channels inactivate (Figure 11–3C) and cannot reopen until the end-plate repolarizes. The end-plate cannot repolarize as long as the depolarizing muscle relaxant continues to bind to ACh receptors; this is called a phase I block. After a period of time, prolonged end-plate depolarization can cause poorly understood changes in the ACh receptor that result in a phase II block, which clinically resembles that of nondepolarizing muscle relaxants.

Nondepolarizing muscle relaxants bind ACh receptors but are incapable of inducing the conformational change necessary for ion channel opening. Because ACh is prevented from binding to its receptors, no end-plate potential develops. Neuromuscular blockade occurs even if only one α subunit is blocked.

2 Thus, depolarizing muscle relaxants act as ACh receptor agonists, whereas nondepolarizing muscle relaxants function as competitive antagonists. This basic difference in mechanism of action explains their varying effects in certain disease states. For example, conditions associated with a chronic decrease in ACh release (eg, muscle denervation injuries) stimulate a compensatory increase in the number of ACh receptors within muscle membranes. These states also promote the expression of the immature (extrajunctional) isoform of the ACh receptor, which displays low channel conductance properties and prolonged open-channel time. This up-regulation causes an exaggerated response to depolarizing muscle relaxants (with more receptors being depolarized), but a resistance to nondepolarizing relaxants (more receptors that must be blocked). In contrast, conditions associated with fewer ACh receptors (eg, down-regulation in myasthenia gravis) demonstrate a resistance to depolarizing relaxants and an increased sensitivity to nondepolarizing relaxants.

OTHER MECHANISMS OF NEUROMUSCULAR BLOCKADE

Some drugs may interfere with the function of the ACh receptor without acting as an agonist or antagonist. They interfere with normal functioning of the ACh receptor binding site or with the opening and closing of the receptor channel. These may include inhaled anesthetic agents, local anesthetics, and ketamine. The ACh receptor–lipid membrane interface may be an important site of action.

Drugs may also cause either closed or open channel blockade. During closed channel blockade, the drug physically plugs up the channel, preventing passage of cations whether or not ACh has activated the receptor. Open channel blockade is use dependent, because the drug enters and obstructs the ACh receptor channel only after it is opened by ACh binding. The clinical relevance of open channel blockade is unknown. Based on laboratory experiments, one would expect that increasing the concentration of ACh with a cholinesterase inhibitor would not overcome this form of neuromuscular blockade. Drugs that may cause channel block in the laboratory include neostigmine, some antibiotics, cocaine, and quinidine. Other drugs may impair the presynaptic release of ACh. Prejunctional receptors play a role in mobilizing ACh to maintain muscle contraction. Blocking these receptors can lead to a fading of the train-of-four response.

REVERSAL OF NEUROMUSCULAR BLOCKADE

3 Because succinylcholine is not metabolized by acetylcholinesterase, it unbinds the receptor and diffuses away from the neuromuscular junction

to be hydrolyzed in the plasma and liver by another enzyme, pseudocholinesterase (nonspecific cholinesterase, plasma cholinesterase, or butyrylcholinesterase). Fortunately, this is a fairly rapid process, because no specific agent to reverse a depolarizing blockade is available.

4 With the exception of the discontinued drug mivacurium, nondepolarizing agents are not metabolized by either acetylcholinesterase or pseudocholinesterase. Reversal of their blockade depends on unbinding the receptor, redistribution, metabolism, and excretion of the relaxant by the body, or administration of specific reversal agents (eg, cholinesterase inhibitors) that inhibit acetylcholinesterase enzyme activity. Because this inhibition increases the amount of ACh that is available at the neuromuscular junction and can compete with the nondepolarizing agent, clearly, the reversal agents are of no benefit in reversing a depolarizing block. In fact, by increasing neuromuscular junction ACh concentration and inhibiting pseudocholinesterase-induced metabolism of succinylcholine, *cholinesterase inhibitors can prolong neuromuscular blockade produced by succinylcholine*. The ONLY time neostigmine reverses neuromuscular block after succinylcholine is when there is a phase II block (fade of the train-of-four) AND sufficient time has passed for the circulating concentration of succinylcholine to be negligible.

Sugammadex, a cyclodextrin, is the first selective relaxant-binding agent; it exerts its reversal effect by forming tight complexes in a 1:1 ratio with steroidal nondepolarizing agents (vecuronium, rocuronium,). This drug has been in use in the European Union for the past few years, but is not yet commercially available in the United States.

The newer neuromuscular blocking agents, such as gantacurium, which are still under investigation, show promise as ultrashort-acting nondepolarizing agents; they undergo chemical degradation by rapid adduction with L-cysteine.

RESPONSE TO PERIPHERAL NERVE STIMULATION

The use of peripheral nerve stimulators to monitor neuromuscular function is discussed in Chapter 6. Four patterns of electrical stimulation with supramaximal square-wave pulses are considered:

Tetany: A sustained stimulus of 50–100 Hz, usually lasting 5 sec.

Single twitch: A single pulse 0.2 ms in duration.

Train-of-four: A series of four twitches in 2 s (2-Hz frequency), each 0.2 ms long.

Double-burst stimulation (DBS): Three short (0.2 ms) high-frequency stimulations separated by a 20-ms interval (50 Hz) and followed 750 ms later by two ($DBS_{3,2}$) or three ($DBS_{3,3}$) additional impulses.

The occurrence of fade, a gradual diminution of evoked response during prolonged or repeated nerve stimulation, is indicative of a nondepolarizing block (**Table 11–2**), or of a phase II block if only succinylcholine has been administered. Fade may be due to a prejunctional effect of nondepolarizing relaxants that reduces the amount of ACh in the nerve terminal available for release during stimulation (blockade of ACh mobilization). Adequate clinical recovery correlates well with the absence of fade. Because fade is more obvious during sustained tetanic stimulation or double-burst stimulation than following a train-of-four pattern or repeated twitches, the first two patterns are the preferred methods for determining adequacy of recovery from a nondepolarizing block.

The ability of tetanic stimulation during a partial nondepolarizing block to increase the evoked response to a subsequent twitch is termed posttetanic potentiation. This phenomenon may relate to a transient increase in ACh mobilization following tetanic stimulation.

In contrast, a phase I depolarization block from succinylcholine does not exhibit fade during tetanus or train-of-four; neither does it demonstrate posttetanic potentiation. With longer infusions of succinylcholine, however, the quality of the block will sometimes change to resemble a nondepolarizing block (phase II block).

Newer quantitative methods of assessment of neuromuscular blockade, such as acceleromyography, permit determination of exact train-of-four ratios, as opposed to subjective interpretations. Acceleromyography may reduce the incidence of

TABLE 11–2 Evoked responses during depolarizing (phase I and phase II) and nondepolarizing block.

Normal Evoked Stimulus	Depolarizing Block: Phase I	Depolarizing Block: Phase II	Nondepolarizing Block
Train-of-four	Constant but diminished	Fade	Fade
Tetany	Constant but diminished	Fade	Fade
Double-burst stimulation ($DBS_{3,2}$)	Constant but diminished	Fade	Fade
Posttetanic potentiation	Absent	Present	Present

unexpected postoperative residual neuromuscular blockade.

Depolarizing Muscle Relaxants

SUCCINYLCHOLINE

The only depolarizing muscle relaxant in clinical use today is succinylcholine.

Physical Structure

5 Succinylcholine—also called diacetylcholine or suxamethonium—consists of two joined ACh molecules (Figure 11–4). This structure underlies succinylcholine's mechanism of action, side effects, and metabolism.

Metabolism & Excretion

The popularity of succinylcholine is due to its rapid onset of action (30–60 s) and short duration

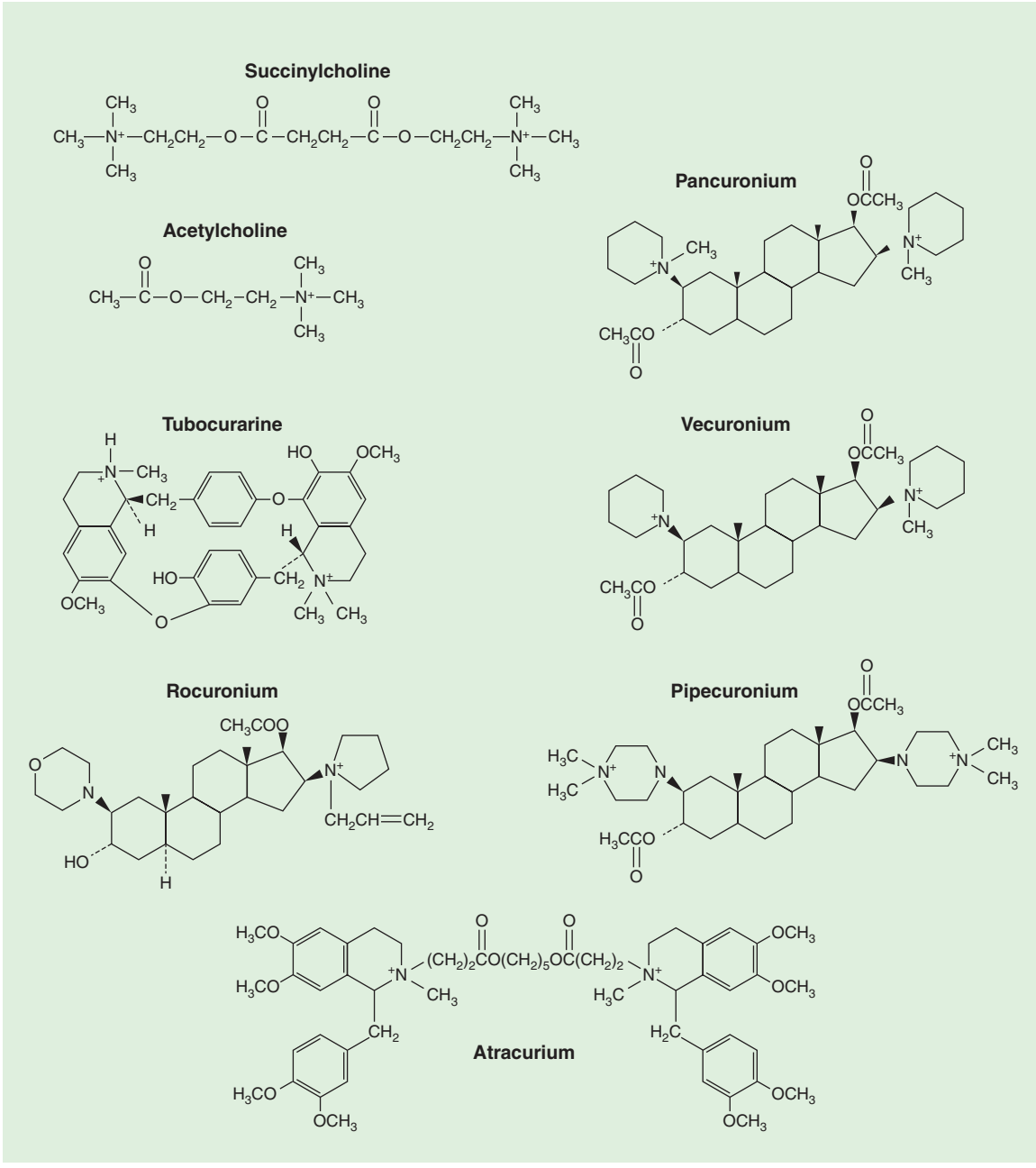

FIGURE 11–4 Chemical structures of neuromuscular blocking agents.

of action (typically less than 10 min). Its rapid onset of action relative to other neuromuscular blockers is largely due to the relative overdose that is usually administered. Succinylcholine, like all neuromuscular blockers, has a small volume of distribution due to its very low lipid solubility, and this also underlies a rapid onset of action. As succinylcholine enters the circulation, most of it is

rapidly metabolized by pseudocholinesterase into succinylmonocholine. This process is so efficient that only a small fraction of the injected dose ever reaches the neuromuscular junction. As drug levels fall in blood, succinylcholine molecules diffuse away from the neuromuscular junction, limiting the duration of action. However, this duration of action can be prolonged by high doses, infusion of succinylcholine, or abnormal metabolism. The latter may result from hypothermia, reduced pseudocholinesterase levels, or a genetically aberrant enzyme. Hypothermia decreases the rate of hydrolysis. Reduced levels of pseudocholinesterase (measured as units per liter) accompany pregnancy, liver disease, renal failure, and certain drug therapies (Table 11–3). Reduced pseudocholinesterase levels generally produce only modest prolongation of succinylcholine's actions (2–20 min).

One in 25-30 patients of European extraction is a heterozygote with one normal and one abnormal (atypical) pseudocholinesterase gene, resulting in a slightly prolonged block (20–30 min). Even fewer (1 in 3000) patients have two copies of the most prevalent abnormal gene (homozygous atypical) that produce an enzyme with little or no affinity for succinylcholine. In contrast to the doubling or tripling of blockade duration seen in patients with low enzyme levels or heterozygous atypical enzyme, patients with homozygous atypical enzyme will have a *very* long blockade (eg, 4–8 h) following administration of succinylcholine. Of the recognized abnormal pseudocholinesterase genes, the dibucaine-resistant (variant) allele, which produces an enzyme with 1/100 of normal affinity for succinylcholine, is the most common. Other variants include fluoride-resistant and silent (no activity) alleles.

Dibucaine, a local anesthetic, inhibits normal pseudocholinesterase activity by 80%, but inhibits atypical enzyme activity by only 20%. Serum from an individual who is heterozygous for the atypical enzyme is characterized by an intermediate 40% to 60% inhibition. The percentage of inhibition of pseudocholinesterase activity is termed the **dibucaine number**. A patient with normal pseudocholinesterase has a dibucaine number of 80; a homozygote for the most common abnormal allele will have a dibucaine number of 20. The dibucaine number measures pseudocholinesterase function, not the amount of enzyme. Therefore, adequacy of pseudocholinesterase can be determined in the laboratory quantitatively in units per liter (a minor factor) and qualitatively by dibucaine number (the major factor). **Prolonged paralysis from succinylcholine caused by abnormal pseudocholinesterase (atypical cholinesterase) should be treated with continued mechanical ventilation and sedation until muscle function returns to normal by clinical signs. Such unsedated patients do NOT appreciate unnecessary, repetitive use of nerve stimulation when all members of a department come by to confirm the diagnosis**.

TABLE 11–3 Drugs known to decrease pseudocholinesterase activity.

Drug	Description
Echothiophate	Organophosphate use for glaucoma
Neostigmine Pyridostigmine	Cholinesterase inhibitors
Phenelzine	Monoamine oxidase inhibitor
Cyclophosphamide	Antineoplastic agent
Metoclopramide	Antiemetic/prokinetic agent
Esmolol	β-Blocker
Pancuronium	Nondepolarizing muscle relaxant
Oral contraceptives	Various agents

Drug Interactions

The effects of muscle relaxants can be modified by concurrent drug therapy (Table 11–4). Succinylcholine is involved in two interactions deserving special comment.

A. Cholinesterase Inhibitors

Although cholinesterase inhibitors reverse nondepolarizing paralysis, they markedly prolong a depolarizing phase I block by two mechanisms. By inhibiting acetylcholinesterase, they lead to a

TABLE 11–4 Potentiation (+) and resistance (–) of neuromuscular blocking agents by other drugs.

Drug	Effect on Depolarizing Blockade	Effect on Nondepolarizing Blockade	Comments
Antibiotics	+	+	Streptomycin, aminoglycosides, kanamycin, neomycin, colistin, polymyxin, tetracycline, lincomycin, clindamycin
Anticonvulsants	?	–	Phenytoin, carbamazepine, primidone, sodium valproate
Antiarrhythmics	+	+	Quinidine, calcium channel blockers
Cholinesterase inhibitors	+	–	Neostigmine, pyridostigmine
Dantrolene	?	+	Used in treatment of malignant hyperthermia (has quaternary ammonium group)
Inhalational anesthetics	+	+	Volatile anesthetics
Ketamine	?	+	
Local anesthetics	+	+	High doses only
Lithium carbonate	+	?	Prolongs onset and duration of succinylcholine
Magnesium sulfate	+	+	Doses used to treat preeclampsia and eclampsia of pregnancy

higher ACh concentration at the nerve terminal, which intensifies depolarization. They also reduce the hydrolysis of succinylcholine by inhibiting pseudocholinesterase. Organophosphate pesticides, for example, cause an irreversible inhibition of acetylcholinesterase and can prolong the action of succinylcholine by 20–30 min. Echothiophate eye drops, used in the past for glaucoma, can markedly prolong succinylcholine by this mechanism.

B. Nondepolarizing Relaxants

In general, small doses of nondepolarizing relaxants antagonize a depolarizing phase I block. Because the drugs occupy some ACh receptors, depolarization by succinylcholine is partially prevented.

If enough depolarizing agent is administered to develop a phase II block, a nondepolarizer will potentiate paralysis.

Dosage

Because of the rapid onset, short duration, and low cost of succinylcholine, many clinicians believe that it is still a good choice for routine intubation in adults. The usual adult dose of succinylcholine for intubation is 1–1.5 mg/kg intravenously. Doses as small as 0.5 mg/kg will often provide acceptable intubating conditions if a defasciculating dose of a nondepolarizing agent is not used. Repeated small boluses (10 mg) or a succinylcholine drip (1 g in 500 or 1000 mL, titrated to effect) can be used during surgical procedures that require brief but intense paralysis (eg, otolaryngological endoscopies). Neuromuscular function should be frequently monitored with a nerve stimulator to prevent overdosing and to watch for phase II block. The availability of intermediate-acting nondepolarizing muscle relaxants has reduced the popularity of succinylcholine infusions. In the past, these infusions were a mainstay of ambulatory practice in the United States.

Because succinylcholine is not lipid soluble, it has a small volume of distribution. Per kilogram, infants and neonates have a larger extracellular space than adults. Therefore, dosage requirements for

pediatric patients are often greater than for adults. If succinylcholine is administered *intramuscularly* to children, a dose as high as 4–5 mg/kg does not always produce complete paralysis.

Succinylcholine should be stored under refrigeration (2–8°C), and should generally be used within 14 days after removal from refrigeration and exposure to room temperature.

Side Effects & Clinical Considerations

Succinylcholine is a relatively safe drug—assuming that its many potential complications are understood and avoided. Because of the risk of hyperkalemia, rhabdomyolysis, and cardiac arrest in children with undiagnosed myopathies, succinylcholine is considered relatively contraindicated in the routine management of children and adolescent patients. Most clinicians have also abandoned the *routine* use of succinylcholine for adults. Succinylcholine is still useful for rapid sequence induction and for short periods of intense paralysis because none of the presently available nondepolarizing muscle relaxants can match its very rapid onset and short duration.

A. Cardiovascular

Because of the resemblance of muscle relaxants to ACh, it is not surprising that they affect cholinergic receptors in addition to those at the neuromuscular junction. The entire parasympathetic nervous system and parts of the sympathetic nervous system (sympathetic ganglions, adrenal medulla, and sweat glands) depend on ACh as a neurotransmitter.

Succinylcholine not only stimulates nicotinic cholinergic receptors at the neuromuscular junction, it stimulates all ACh receptors. The cardiovascular actions of succinylcholine are therefore very complex. Stimulation of nicotinic receptors in parasympathetic and sympathetic ganglia, and muscarinic receptors in the sinoatrial node of the heart, can increase or decrease blood pressure and heart rate. Low doses of succinylcholine can produce negative chronotropic and inotropic effects, but higher doses usually increase heart rate and contractility and elevate circulating catecholamine levels. In most patients, the hemodynamic consequences are inconsequential in comparison to the effects of the induction agent and laryngoscopy.

Children are particularly susceptible to profound bradycardia following administration of succinylcholine. Bradycardia will sometimes occur in adults when a second bolus of succinylcholine is administered approximately 3–8 min after the first dose. The dogma (based on no real evidence) is that the succinylcholine metabolite, succinylmonocholine, sensitizes muscarinic cholinergic receptors in the sinoatrial node to the second dose of succinylcholine, resulting in bradycardia. Intravenous atropine (0.02 mg/kg in children, 0.4 mg in adults) is normally given prophylactically to children prior to the first and subsequent doses, and *usually* before a second dose of succinylcholine is given to adults. Other arrhythmias, such as nodal bradycardia and ventricular ectopy, have been reported.

B. Fasciculations

The onset of paralysis by succinylcholine is usually signaled by visible motor unit contractions called fasciculations. These can be prevented by pretreatment with a small dose of nondepolarizing relaxant. Because this pretreatment usually antagonizes a depolarizing block, a larger dose of succinylcholine is required (1.5 mg/kg). Fasciculations are typically not observed in young children and elderly patients.

C. Hyperkalemia

Normal muscle releases enough potassium during succinylcholine-induced depolarization to increase serum potassium by 0.5 mEq/L. Although this is usually insignificant in patients with normal baseline potassium levels, it can be life-threatening in patients with preexisting hyperkalemia. The increase in potassium in patients with burn injury, massive trauma, neurological disorders, and several other conditions (Table 11–5) can be large and catastrophic. Hyperkalemic cardiac arrest can prove to be quite refractory to routine cardiopulmonary resuscitation, requiring calcium, insulin, glucose, bicarbonate, and even cardiopulmonary bypass to support the circulation while reducing serum potassium levels.

TABLE 11–5 Conditions causing susceptibility to succinylcholine-induced hyperkalemia.

Burn injury
Massive trauma
Severe intraabdominal infection
Spinal cord injury
Encephalitis
Stroke
Guillain-Barré syndrome
Severe Parkinson's disease
Tetanus
Prolonged total body immobilization
Ruptured cerebral aneurysm
Polyneuropathy
Closed head injury
Hemorrhagic shock with metabolic acidosis
Myopathies (eg, Duchenne's dystrophy)

Following denervation injuries (spinal cord injuries, larger burns), the immature isoform of the ACh receptor may be expressed inside and outside the neuromuscular junction (up-regulation). These extrajunctional receptors allow succinylcholine to effect widespread depolarization and extensive potassium release. Life-threatening potassium release is *not* reliably prevented by pretreatment with a nondepolarizer. The risk of hyperkalemia usually seems to peak in 7–10 days following the injury, but the exact time of onset and the duration of the risk period vary. The risk of hyperkalemia from succinylcholine is minimal in the first 2 days after spinal cord or burn injury.

D. Muscle Pains

Patients who have received succinylcholine have an increased incidence of postoperative myalgia. The efficacy of nondepolarizing pretreatment is controversial. Administration of rocuronium (0.06–0.1 mg/kg) prior to succinylcholine has been reported to be effective in preventing fasciculations and reducing postoperative myalgias. The relationship between fasciculations and postoperative myalgias is also inconsistent. The myalgias are theorized to be due to the initial unsynchronized contraction of muscle groups; myoglobinemia and increases in serum creatine kinase can be detected following administration of succinylcholine. Perioperative use of nonsteroidal antiinflammatory drugs may reduce the incidence and severity of myalgias.

E. Intragastric Pressure Elevation

Abdominal wall muscle fasciculations increase intragastric pressure, which is offset by an increase in lower esophageal sphincter tone. Therefore, despite being much discussed, there is no evidence that the risk of gastric reflux or pulmonary aspiration is increased by succinylcholine.

F. Intraocular Pressure Elevation

Extraocular muscle differs from other striated muscle in that it has multiple motor end-plates on each cell. Prolonged membrane depolarization and contraction of extraocular muscles following administration of succinylcholine transiently raise intraocular pressure and theoretically could compromise an injured eye. However, there is no evidence that succinylcholine leads to worsened outcome in patients with "open" eye injuries. The elevation in intraocular pressure is not always prevented by pretreatment with a nondepolarizing agent.

G. Masseter Muscle Rigidity

Succinylcholine transiently increases muscle tone in the masseter muscles. Some difficulty may initially be encountered in opening the mouth because of incomplete relaxation of the jaw. A marked increase in tone preventing laryngoscopy is abnormal and can be a premonitory sign of malignant hyperthermia.

H. Malignant Hyperthermia

Succinylcholine is a potent triggering agent in patients susceptible to malignant hyperthermia, a hypermetabolic disorder of skeletal muscle (see Chapter 52). Although some of the signs and symptoms of neuroleptic malignant syndrome (NMS) resemble those of malignant hyperthermia, the pathogenesis is completely different and there is no need to avoid use of succinylcholine in patients with NMS.

I. Generalized Contractions

Patients afflicted with myotonia may develop myoclonus after administration of succinylcholine.

J. Prolonged Paralysis

As discussed above, patients with reduced levels of normal pseudocholinesterase may have a longer than normal duration of action, whereas patients with atypical pseudocholinesterase will experience markedly prolonged paralysis.

K. Intracranial Pressure

Succinylcholine may lead to an activation of the electroencephalogram and slight increases in cerebral blood flow and intracranial pressure in some patients. Muscle fasciculations stimulate muscle stretch receptors, which subsequently increase cerebral activity. The increase in intracranial pressure can be attenuated by maintaining good airway control and instituting hyperventilation. It can also be prevented by pretreating with a nondepolarizing muscle relaxant and administering intravenous lidocaine (1.5–2.0 mg/kg) 2–3 min prior to intubation. The effects of intubation on intracranial pressure far outweigh any increase caused by succinylcholine, and succinylcholine is NOT contraindicated for rapid sequence induction of patients with intracranial mass lesions or other causes of increased intracranial pressure.

L. Histamine Release

Slight histamine release may be observed following succinylcholine in some patients.

Nondepolarizing Muscle Relaxants

Unique Pharmacological Characteristics

In contrast to depolarizing muscle relaxants, there is a wide selection of nondepolarizing muscle relaxants (Tables 11–6 and 11–7). Based on their chemical structure, they can be classified as benzylisoquinolinium, steroidal, or other compounds. It is often said that choice of a particular drug depends on its unique characteristics, which are often related to its structure; however, for most patients, the differences among the intermediate-acting neuromuscular blockers are inconsequential. In general, steroidal compounds can be vagolytic, but this property is most notable with pancuronium and clinically unimportant with vecuronium or rocuronium. Benzylisoquinolines tend to release histamine. Because of structural similarities, an allergic history to one muscle relaxant strongly suggests the possibility of allergic reactions to other muscle relaxants, particularly those in the same chemical class.

A. Suitability for Intubation

None of the currently available nondepolarizing muscle relaxants equals succinylcholine's rapid onset of action or short duration. However, the

TABLE 11–6 A summary of the pharmacology of nondepolarizing muscle relaxants.

Relaxant	Chemical Structure[1]	Metabolism	Primary Excretion	Onset[2]	Duration[3]	Histamine Release[4]	Vagal Blockade[5]
Atracurium	B	+++	Insignificant	++	++	+	0
Cisatracurium	B	+++	Insignificant	++	++	0	0
Pancuronium	S	+	Renal	++	+++	0	++
Vecuronium	S	+	Biliary	++	++	0	0
Rocuronium	S	Insignificant	Biliary	+++	++	0	+
Gantacurium	C	+++	Insignificant	+++	+	+	0

[1]B, benzylisoquinolone; S, steroidal; C, chlorofumarate.
[2]Onset: +, slow; ++, moderately rapid; +++, rapid.
[3]Duration: +, short; ++, intermediate; +++, long.
[4]Histamine release: 0, no effect; +, slight effect; ++, moderate effect; +++, marked effect.
[5]Vagal blockade: 0, no effect; +, slight effect; ++, moderate effect.

TABLE 11–7 Clinical characteristics of nondepolarizing muscle relaxants.

Drug	ED_{95} for Adductor Pollicis During Nitrous Oxide/Oxygen/Intravenous Anesthesia (mg/kg)	Intubation Dose (mg/kg)	Onset of Action for Intubating Dose (min)	Duration of Intubating Dose (min)	Maintenance Dosing by Boluses (mg/kg)	Maintenance Dosing by Infusion (μg/kg/min)
Succinylcholine	0.5	1.0	0.5	5–10	0.15	2–15 mg/min
Gantacurium[1]	0.19	0.2	1–2	4–10	N/A	—
Rocuronium	0.3	0.8	1.5	35–75	0.15	9–12
Mivacurium[2]	0.08	0.2	2.5–3.0	15–20	0.05	4–15
Atracurium	0.2	0.5	2.5–3.0	30–45	0.1	5–12
Cisatracurium	0.05	0.2	2.0–3.0	40–75	0.02	1–2
Vecuronium	0.05	0.12	2.0–3.0	45–90	0.01	1–2
Pancuronium	0.07	0.12	2.0–3.0	60–120	0.01	—
Pipecuronium[2]	0.05	0.1	2.0–3.0	80–120	0.01	—
Doxacurium[2]	0.025	0.07	4.0–5.0	90–150	0.05	—

[1]Not commercially available in the United States.
[2]No longer available in the United States.

onset of nondepolarizing relaxants can be quickened by using either a larger dose or a priming dose. The ED_{95} of any drug is the effective dose of a drug in 95% of individuals. For neuromuscular blockers, one often specifies the dose that produces 95% twitch depression in 50% of individuals. One to two times the ED_{95} or twice the dose that produces 95% twitch depression is usually used for intubation. Although a larger intubating dose speeds onset, it exacerbates side effects and prolongs the duration of blockade. For example, a dose of 0.15 mg/kg of pancuronium may produce intubating conditions in 90 sec, but at the cost of more pronounced tachycardia—and a block that may be irreversible (by neostigmine) for more than 60 min. The consequence of a long duration of action is the ensuing difficulty in completely reversing the blockade and a subsequent increased incidence of postoperative pulmonary complications. As a general rule, the more potent the nondepolarizing muscle relaxant, the slower its speed of onset; the "explanatory dogma" is that greater potency necessitates a smaller dose, with fewer total drug molecules, which in turn, decreases the rate of drug binding opportunities at the neuromuscular junction.

The introduction of short- and intermediate-acting agents has resulted in the greater use of priming doses. Theoretically, giving 10% to 15% of the usual intubating dose 5 min before induction will occupy enough receptors so that paralysis will quickly follow when the balance of relaxant is administered. Use of a priming dose can produce conditions suitable for intubation as soon as 60 sec following administration of rocuronium or 90 sec following administration of other intermediate-acting nondepolarizers. A priming dose does not *usually* lead to clinically significant paralysis, which requires that 75% to 80% of the receptors be blocked (a neuromuscular margin of safety). In some patients, however, the priming dose produces distressing dyspnea, diplopia, or dysphagia; in such instances, the patient should be reassured, and induction of anesthesia should proceed without delay. Priming can additionally cause measureable deterioration in respiratory function (eg, decreased forced vital capacity) and may lead to oxygen desaturation in patients with marginal pulmonary reserve. These negative side effects are more common in older, sicker patients.

Muscle groups vary in their sensitivity to muscle relaxants. For example, the laryngeal

muscles—whose relaxation is important during intubation—recover from blockade more quickly than the adductor pollicis, which is commonly monitored by the peripheral nerve stimulator.

B. Suitability for Preventing Fasciculations

To prevent fasciculations and myalgias, 10% to 15% of a nondepolarizer intubating dose can be administered 5 min before succinylcholine. When administered only shortly before succinylcholine, myalgias, but not fasciculations, will be inhibited. Although most nondepolarizers have been successfully used for this purpose, tubocurarine and rocuronium have been most popular (precurarization); tubocurarine is no longer available in the United States.

C. Maintenance Relaxation

Following intubation, muscle paralysis may need to be maintained to facilitate surgery, (eg, abdominal operations), to permit a reduced depth of anesthesia, or to control ventilation. There is great variability among patients in response to muscle relaxants. Monitoring neuromuscular function with a nerve stimulator helps to prevent over- and underdosing and to reduce the likelihood of serious residual muscle paralysis in the recovery room. Maintenance doses, whether by intermittent boluses or continuous infusion (Table 11–7), should be guided by the nerve stimulator *and* clinical signs (eg, spontaneous respiratory efforts or movement). In some instances, clinical signs may precede twitch recovery because of differing sensitivities to muscle relaxants between muscle groups or technical problems with the nerve stimulator. Some return of neuromuscular transmission should be evident prior to administering each maintenance dose, if the patient needs to resume spontaneous ventilation at the end of the anesthetic. When an infusion is used for maintenance, the rate should be adjusted at or just above the rate that allows some return of neuromuscular transmission so that drug effects can be monitored.

D. Potentiation by Inhalational Anesthetics

Volatile agents decrease nondepolarizer dosage requirements by at least 15%. The actual degree of this postsynaptic augmentation depends on both the inhalational anesthetic (desflurane > sevoflurane > isoflurane and enflurane > halothane > N_2O/O_2/narcotic) and the muscle relaxant employed (pancuronium > vecuronium and atracurium).

E. Potentiation by Other Nondepolarizers

Some combinations of nondepolarizers produce a greater than additive (synergistic) neuromuscular blockade. The lack of synergism (ie, the drugs are only additive) by closely related compounds (eg, vecuronium and pancuronium) lends credence to the theory that synergism results from slightly differing mechanisms of action.

F. Autonomic Side Effects

In clinical doses, the nondepolarizers differ in their relative effects on nicotinic and muscarinic cholinergic receptors. Some older agents (tubocurarine and, to a lesser extent, metocurine) blocked autonomic ganglia, reducing the ability of the sympathetic nervous system to increase heart contractility and rate in response to hypotension and other intraoperative stresses. In contrast, pancuronium (and gallamine) block vagal muscarinic receptors in the sinoatrial node, resulting in tachycardia. All newer nondepolarizing relaxants, including atracurium, cisatracurium, vecuronium, and rocuronium, are devoid of significant autonomic effects in their recommended dosage ranges.

G. Histamine Release

Histamine release from mast cells can result in bronchospasm, skin flushing, and hypotension from peripheral vasodilation. Both atracurium and mivacurium are capable of triggering histamine release, particularly at higher doses. Slow injection rates and H_1 and H_2 antihistamine pretreatment ameliorate these side effects.

H. Hepatic Clearance

Only pancuronium and vecuronium are metabolized to any significant degree by the liver. Active metabolites likely contribute to their clinical effect. Vecuronium and rocuronium depend heavily on biliary excretion. Clinically, liver failure prolongs pancuronium and rocuronium blockade, with less effect on vecuronium, and no effect on pipecuronium. Atracurium, cisatracurium, and

mivacurium, although extensively metabolized, depend on extrahepatic mechanisms. Severe liver disease does not significantly affect clearance of atracurium or cisatracurium, but the associated decrease in pseudocholinesterase levels may slow the metabolism of mivacurium.

I. Renal Excretion

9 Doxacurium, pancuronium, vecuronium, and pipecuronium are partially excreted by the kidneys, and their action is prolonged in patients with renal failure. The elimination of atracurium, cisatracurium, mivacurium, and rocuronium is independent of kidney function.

General Pharmacological Characteristics

Some variables affect all nondepolarizing muscle relaxants.

A. Temperature

Hypothermia prolongs blockade by decreasing metabolism (eg, mivacurium, atracurium, and cisatracurium) and delaying excretion (eg, pancuronium and vecuronium).

B. Acid–Base Balance

Respiratory acidosis potentiates the blockade of most nondepolarizing relaxants and antagonizes its reversal. This could prevent complete neuromuscular recovery in a hypoventilating postoperative patient. Conflicting findings regarding the neuromuscular effects of other acid–base changes may be due to coexisting alterations in extracellular pH, intracellular pH, electrolyte concentrations, or structural differences between drugs (eg, monoquaternary versus bisquaternary; steroidal versus isoquinolinium).

C. Electrolyte Abnormalities

Hypokalemia and hypocalcemia augment a nondepolarizing block. The responses of patients with hypercalcemia are unpredictable. Hypermagnesemia, as may be seen in preeclamptic patients being managed with magnesium sulfate (or after intravenous magnesium administered in the operating room), potentiates a nondepolarizing blockade by competing with calcium at the motor end-plate.

TABLE 11–8 Additional considerations in special populations.

Pediatric	Succinylcholine – should not be used routinely Nondepolarizing agents – faster onset Vecuronium – long-acting in neonates
Elderly	Decreased clearance – prolonged duration, except with cisatracurium
Obese	Dosage 20% more than lean body weight; onset unchanged Prolonged duration, except with cisatracurium
Hepatic disease	Increased volume of distribution Pancuronium and vecuronium – prolonged elimination due to hepatic metabolism and biliary excretion Cisatracurium – unchanged Pseudocholinesterase decreased; prolonged action may be seen with succinylcholine in severe disease
Renal failure	Vecuronium – prolonged Rocuronium – relatively unchanged Cisatracurium – safest alternative
Critically ill	Myopathy, polyneuropathy, nicotinic acetylcholine receptor up-regulation

D. Age

Neonates have an increased sensitivity to nondepolarizing relaxants because of their immature neuromuscular junctions (Table 11-8). This sensitivity does not necessarily decrease dosage requirements, as the neonate's greater extracellular space provides a larger volume of distribution.

E. Drug Interactions

As noted earlier, many drugs augment nondepolarizing blockade (see Table 11–4). They have multiple sites of interaction: prejunctional structures, postjunctional cholinergic receptors, and muscle membranes.

F. Concurrent Disease

The presence of neurological or muscular disease can have profound effects on an individual's response 10 to muscle relaxants (Table 11–9). Cirrhotic liver disease and chronic renal failure often result in an increased volume of distribution and a lower plasma concentration for a given dose of

TABLE 11–9 Diseases with altered responses to muscle relaxants.

Disease	Response to Depolarizers	Response to Nondepolarizers
Amyotrophic lateral sclerosis	Contracture	Hypersensitivity
Autoimmune disorders Systemic lupus erythematosus Polymyositis Dermatomyositis	Hypersensitivity	Hypersensitivity
Burn injury	Hyperkalemia	Resistance
Cerebral palsy	Slight hypersensitivity	Resistance
Familial periodic paralysis (hyperkalemic)	Myotonia and hyperkalemia	Hypersensitivity?
Guillain–Barré syndrome	Hyperkalemia	Hypersensitivity
Hemiplegia	Hyperkalemia	Resistance on affected side
Muscular denervation (peripheral nerve injury)	Hyperkalemia and contracture	Normal response or resistance
Muscular dystrophy (Duchenne type)	Hyperkalemia and malignant hyperthermia	Hypersensitivity
Myasthenia gravis	Resistance	Hypersensitivity
Myasthenic syndrome	Hypersensitivity	Hypersensitivity
Myotonia Dystrophica Congenital Paramyotonia	Generalized muscular contractions	Normal or hypersensitivity
Severe chronic infection Tetanus Botulism	Hyperkalemia	Resistance

water-soluble drugs, such as muscle relaxants. On the other hand, drugs dependent on hepatic or renal excretion may demonstrate prolonged clearance (Table 11-8). Thus, depending on the drug chosen, a greater initial (loading) dose—but smaller maintenance doses—might be required in these diseases.

G. Muscle Groups

The onset and intensity of blockade vary among muscle groups. This may be due to differences in blood flow, distance from the central circulation, or different fiber types. Furthermore, the relative sensitivity of a muscle group may depend on the choice of muscle relaxant. In general, the diaphragm, jaw, larynx, and facial muscles (orbicularis oculi) respond to and recover from muscle relaxation sooner than the thumb. Although they are a fortuitous safety feature, persistent diaphragmatic contractions can be disconcerting in the face of complete adductor pollicis paralysis. Glottic musculature is also quite resistant to blockade, as is often confirmed during laryngoscopy. The ED_{95} for laryngeal muscles is nearly two times that for the adductor pollicis muscle. Good intubating conditions are usually associated with visual loss of the orbicularis oculi twitch response.

Considering the multitude of factors influencing the duration and magnitude of muscle relaxation, it becomes clear that an individual's response to neuromuscular blocking agents should be monitored. Dosage recommendations, including those in this chapter, should be considered guidelines that require modification for individual patients. Wide variability in sensitivity to nondepolarizing muscle relaxants is often encountered in clinical practice.

ATRACURIUM

Physical Structure

Like all muscle relaxants, atracurium has a quaternary group; however, a benzylisoquinoline structure is responsible for its unique method of degradation. The drug is a mixture of 10 stereoisomers.

Metabolism & Excretion

Atracurium is so extensively metabolized that its pharmacokinetics are independent of renal and hepatic function, and less than 10% is excreted unchanged by renal and biliary routes. Two separate processes are responsible for metabolism.

A. Ester Hydrolysis

This action is catalyzed by nonspecific esterases, not by acetylcholinesterase or pseudocholinesterase.

B. Hofmann Elimination

A spontaneous nonenzymatic chemical breakdown occurs at physiological pH and temperature.

Dosage

A dose of 0.5 mg/kg is administered intravenously for intubation. After succinylcholine, intraoperative relaxation is achieved with 0.25 mg/kg initially, then in incremental doses of 0.1 mg/kg every 10–20 min. An infusion of 5–10 mcg/kg/min can effectively replace intermittent boluses.

Although dosage requirements do not significantly vary with age, atracurium may be shorter acting in children and infants than in adults.

Atracurium is available as a solution of 10 mg/mL. It must be stored at 2–8°C, as it loses 5% to 10% of its potency for each month it is exposed to room temperature. At room temperature, it should be used within 14 days to preserve potency.

Side Effects & Clinical Considerations

Atracurium triggers dose-dependent histamine release that becomes significant at doses above 0.5 mg/kg.

A. Hypotension and Tachycardia

Cardiovascular side effects are unusual unless doses in excess of 0.5 mg/kg are administered. Atracurium may also cause a transient drop in systemic vascular resistance and an increase in cardiac index independent of any histamine release. A slow rate of injection minimizes these effects.

B. Bronchospasm

Atracurium should be avoided in asthmatic patients. Severe bronchospasm is occasionally seen in patients without a history of asthma.

C. Laudanosine Toxicity

Laudanosine, a tertiary amine, is a breakdown product of atracurium's Hofmann elimination and has been associated with central nervous system excitation, resulting in elevation of the minimum alveolar concentration and even precipitation of seizures. Concerns about laudanosine are probably irrelevant unless a patient has received an extremely large total dose or has hepatic failure. Laudanosine is metabolized by the liver and excreted in urine and bile.

D. Temperature and pH Sensitivity

Because of its unique metabolism, atracurium's duration of action can be markedly prolonged by hypothermia and to a lesser extent by acidosis.

E. Chemical Incompatibility

Atracurium will precipitate as a free acid if it is introduced into an intravenous line containing an alkaline solution such as thiopental.

F. Allergic Reactions

Rare anaphylactoid reactions to atracurium have been described. Proposed mechanisms include direct immunogenicity and acrylate-mediated immune activation. IgE-mediated antibody reactions directed against substituted ammonium compounds, including muscle relaxants, have been described. Reactions to acrylate, a metabolite of atracurium and a structural component of some dialysis membranes, have also been reported in patients undergoing hemodialysis.

CISATRACURIUM

Physical Structure

Cisatracurium is a stereoisomer of atracurium that is four times more potent. Atracurium contains approximately 15% cisatracurium.

Metabolism & Excretion

11 Like atracurium, cisatracurium undergoes degradation in plasma at physiological pH and temperature by organ-independent Hofmann elimination. The resulting metabolites (a monoquaternary acrylate and laudanosine) have no neuromuscular blocking effects. Because of cisatracurium's greater potency, the amount of laudanosine produced for the same extent and duration of neuromuscular blockade is much less than with atracurium. Nonspecific esterases are not involved in the metabolism of cisatracurium. Metabolism and elimination are independent of renal or liver failure. Minor variations in pharmacokinetic patterns due to age result in no clinically important changes in duration of action.

Dosage

Cisatracurium produces good intubating conditions following a dose of 0.1–0.15 mg/kg within 2 min and results in muscle blockade of intermediate duration. The typical maintenance infusion rate ranges from 1.0–2.0 mcg/kg/min. Thus, it is more potent than atracurium.

Cisatracurium should be stored under refrigeration (2–8°C) and should be used within 21 days after removal from refrigeration and exposure to room temperature.

Side Effects & Clinical Considerations

Unlike atracurium, cisatracurium does not produce a consistent, dose-dependent increase in plasma histamine levels following administration. Cisatracurium does not alter heart rate or blood pressure, nor does it produce autonomic effects, even at doses as high as eight times ED_{95}.

Cisatracurium shares with atracurium the production of laudanosine, pH and temperature sensitivity, and chemical incompatibility.

PANCURONIUM

Physical Structure

Pancuronium consists of a steroid ring on which two modified ACh molecules are positioned (a bisquaternary relaxant). The steroid ring serves as a "spacer" between the two quaternary amines. Pancuronium resembles ACh enough to bind (but not activate) the nicotinic ACh receptor.

Metabolism & Excretion

Pancuronium is metabolized (deacetylated) by the liver to a limited degree. Its metabolic products have some neuromuscular blocking activity. Excretion is primarily renal (40%), although some of the drug is cleared by the bile (10%). Not surprisingly, elimination of pancuronium is slowed and neuromuscular blockade is prolonged by renal failure. Patients with cirrhosis may require a larger initial dose due to an increased volume of distribution but have reduced maintenance requirements because of a decreased rate of plasma clearance.

Dosage

A dose of 0.08–0.12 mg/kg of pancuronium provides adequate relaxation for intubation in 2–3 min. Intraoperative relaxation is achieved by administering 0.04 mg/kg initially followed every 20–40 min by 0.01 mg/kg.

Children may require moderately larger doses of pancuronium. Pancuronium is available as a solution of 1 or 2 mg/mL and is stored at 2–8°C but may be stable for up to 6 months at normal room temperature.

Side Effects & Clinical Considerations

A. Hypertension and Tachycardia

12 These cardiovascular effects are caused by the combination of vagal blockade and sympathetic stimulation. The latter is due to a combination of ganglionic stimulation, catecholamine release from adrenergic nerve endings, and decreased catecholamine reuptake. Large bolus doses of pancuronium should be given with caution to patients in whom an increased heart rate would be particularly detrimental (eg, coronary artery disease, hypertrophic cardiomyopathy, aortic stenosis).

B. Arrhythmias

Increased atrioventricular conduction and catecholamine release increase the likelihood of ventricular arrhythmias in predisposed individuals. The combination of pancuronium, tricyclic antidepressants,

and halothane has been reported to be particularly arrhythmogenic.

C. Allergic Reactions

Patients who are hypersensitive to bromides may exhibit allergic reactions to pancuronium (pancuronium bromide).

VECURONIUM

Physical Structure

Vecuronium is pancuronium minus a quaternary methyl group (a monoquaternary relaxant). This minor structural change beneficially alters side effects without affecting potency.

Metabolism & Excretion

Vecuronium is metabolized to a small extent by the liver. It depends primarily on biliary excretion and secondarily (25%) on renal excretion. Although it is a satisfactory drug for patients with renal failure, its duration of action is somewhat prolonged. Vecuronium's brief duration of action is explained by its shorter elimination half-life and more rapid clearance compared with pancuronium. Long-term administration of vecuronium to patients in intensive care units has resulted in prolonged neuromuscular blockade (up to several days), possibly from accumulation of its active 3-hydroxy metabolite, changing drug clearance, and in some patients, leading to the development of a polyneuropathy. Risk factors seem to include female gender, renal failure, long-term or high-dose corticosteroid therapy, and sepsis. Thus, these patients must be closely monitored, and the dose of vecuronium carefully titrated. Long-term relaxant administration and the subsequent prolonged lack of ACh binding at the postsynaptic nicotinic ACh receptors may mimic a chronic denervation state and cause lasting receptor dysfunction and paralysis. Tolerance to nondepolarizing muscle relaxants can also develop after long-term use. Fortunately, the use of unnecessary paralysis has greatly declined in critical care units.

Dosage

Vecuronium is equipotent with pancuronium, and the intubating dose is 0.08–0.12 mg/kg. A dose of 0.04 mg/kg initially followed by increments of 0.01 mg/kg every 15–20 min provides intraoperative relaxation. Alternatively, an infusion of 1–2 mcg/kg/min produces good maintenance of relaxation.

Age does not affect initial dose requirements, although subsequent doses are required less frequently in neonates and infants. Women seem to be approximately 30% more sensitive than men to vecuronium, as evidenced by a greater degree of blockade and longer duration of action (this has also been seen with pancuronium and rocuronium). The cause for this sensitivity may be related to gender-related differences in fat and muscle mass, protein binding, volume of distribution, or metabolic activity. The duration of action of vecuronium may be further prolonged in postpartum patients due to alterations in hepatic blood flow or liver uptake.

Side Effects & Clinical Considerations

A. Cardiovascular

Even at doses of 0.28 mg/kg, vecuronium is devoid of significant cardiovascular effects. Potentiation of opioid-induced bradycardia may be observed in some patients.

B. Liver Failure

Although it is dependent on biliary excretion, the duration of action of vecuronium is usually not significantly prolonged in patients with cirrhosis unless doses greater than 0.15 mg/kg are given. Vecuronium requirements are reduced during the anhepatic phase of liver transplantation.

ROCURONIUM

Physical Structure

This monoquaternary steroid analogue of vecuronium was designed to provide a rapid onset of action.

Metabolism & Excretion

Rocuronium undergoes no metabolism and is eliminated primarily by the liver and slightly by the kidneys. Its duration of action is not significantly affected by renal disease, but it is modestly

prolonged by severe hepatic failure and pregnancy. Because rocuronium does not have active metabolites, it may be a better choice than vecuronium in the rare patient requiring prolonged infusions in the intensive care unit setting. Elderly patients may experience a prolonged duration of action due to decreased liver mass.

Dosage

Rocuronium is less potent than most other steroidal muscle relaxants (potency seems to be inversely related to speed of onset). It requires 0.45–0.9 mg/kg intravenously for intubation and 0.15 mg/kg boluses for maintenance. A lower dose of 0.4 mg/kg may allow reversal as soon as 25 min after intubation. Intramuscular rocuronium (1 mg/kg for infants; 2 mg/kg for children) provides adequate vocal cord and diaphragmatic paralysis for intubation, but not until after 3–6 min (deltoid injection has a faster onset than quadriceps), and can be reversed after about 1 hr. The infusion requirements for rocuronium range from 5–12 mcg/kg/min. Rocuronium can produce a prolonged duration of action in elderly patients. Initial dosage requirements are modestly increased in patients with advanced liver disease, presumably due to a larger volume of distribution.

Side Effects & Clinical Considerations

14 Rocuronium (at a dose of 0.9–1.2 mg/kg) has an onset of action that *approaches* succinylcholine (60–90 s), making it a suitable alternative for rapid-sequence inductions, but at the cost of a much longer duration of action. This intermediate duration of action is comparable to vecuronium or atracurium.

Rocuronium (0.1 mg/kg) has been shown to be a rapid (90 s) and effective agent (decreased fasciculations and postoperative myalgias) for precurarization prior to administration of succinylcholine. It has slight vagolytic tendencies.

OTHER RELAXANTS

Muscle relaxants, primarily of historical interest, are either no longer manufactured or not clinically used. They include tubocurarine, metocurine, gallamine, alcuronium, rapacuronium, and decamethonium. Tubocurarine, the first muscle relaxant used clinically, often produced hypotension and tachycardia through histamine release; its ability to block autonomic ganglia was of secondary importance. Histamine release could also produce or exacerbate bronchospasm. Tubocurarine is not metabolized significantly, and its elimination is primarily renal and secondarily biliary. Metocurine, a closely related agent, shares many of the side effects of tubocurarine. It is primarily dependent on renal function for elimination. Patients allergic to iodine (eg, shellfish allergies) could exhibit hypersensitivity to metocurine preparations, as they contain iodide. Gallamine has the most potent vagolytic properties of any relaxant, and it is entirely dependent on renal function for elimination. Alcuronium, a long-acting nondepolarizer with mild vagolytic properties, is also primarily dependent on renal function for elimination. Rapacuronium has a rapid onset of action, minimal cardiovascular side effects, and a short duration of action. It was withdrawn by the manufacturer following multiple reports of serious bronchospasm, including a few unexplained fatalities. Histamine release may have been a factor. Decamethonium was an older depolarizing agent.

More recently, doxacurium, pipecuronium, and mivacurium are no longer commercially available in the United States. Mivacurium is a benzylisoquinolinium derivative, which is metabolized by pseudocholinesterase; therefore, its duration of action may be prolonged in pathophysiological states that result in low pseudocholinesterase levels. The usual intubating dose is 0.2 mg/kg, with the steady state infusion rate being 4-10 mcg/kg/min. Mivacurium releases histamine to about the same degree as atracurium; the resulting cardiovascular effects can be minimized by slow injection. Doxacurium is a potent long-acting benzylisoquinolinium compound that is primarily eliminated by renal excretion. Adequate intubating conditions are achieved in 5 min with 0.05 mg/kg. It is essentially devoid of cardiovascular and histamine-releasing side effects. Pipecuronium, on the other hand, is a bisquarternary steroidal compound similar to pancuronium, without the

vagolytic effects. Onset and duration of action are also similar to pancuronium; elimination is primarily through renal (70%) and biliary (20%) excretion. The usual intubating dose ranges from 0.06-0.1 mg/kg; its pharmacologic profile is relatively unchanged in elderly patients.

NEWER MUSCLE RELAXANTS

Gantacurium belongs to a new class of nondepolarizing neuromuscular blockers called chlorofumarates. It is provided as a lyophilized powder, because it is not stable as an aqueous solution; therefore, it requires reconstitution prior to administration. In preclinical trials, gantacurium demonstrated an ultrashort duration of action, similar to that of succinylcholine. Its pharmacokinetic profile is explained by the fact that it undergoes nonenzymatic degradation by two chemical mechanisms: rapid formation of inactive cysteine adduction product and ester hydrolysis. At a dose of 0.2 mg/kg (ED_{95}), the onset of action has been estimated to be 1-2 min, with a duration of blockade similar to that of succinylcholine. Its clinical duration of action ranged from 5-10 min; recovery can be accelerated by edrophonium, as well as by the administration of exogenous cysteine. Cardiovascular effects suggestive of histamine release were observed following the use of three times the ED_{95} dosage.

AV002 (CW002) is another investigational nondepolarizing agent. It is a benzylisoquinolinium fumarate ester-based compound with an intermediate duration of action that undergoes metabolism and elimination similar to that of gantacurium.

CASE DISCUSSION

Delayed Recovery from General Anesthesia

A 72-year-old man has undergone general anesthesia for transurethral resection of the prostate. Twenty minutes after conclusion of the procedure, he is still intubated and shows no evidence of spontaneous respiration or consciousness.

What is your general approach to this diagnostic dilemma?

Clues to the solution of complex clinical problems are usually found in a pertinent review of the medical and surgical history, the history of drug ingestions, the physical examination, and laboratory results. In this case, the perioperative anesthetic management should also be considered.

What medical illnesses predispose a patient to delayed awakening or prolonged paralysis?

Chronic hypertension alters cerebral blood flow autoregulation and decreases the brain's tolerance to episodes of hypotension. Liver disease reduces hepatic drug metabolism and biliary excretion, resulting in prolonged drug action. Reduced serum albumin concentrations increase free drug (active drug) availability. Hepatic encephalopathy can alter consciousness. Kidney disease decreases the renal excretion of many drugs. Uremia can also affect consciousness. Diabetic patients are prone to hypoglycemia and hyperosmotic, hyperglycemic, and nonketotic coma. A prior stroke or symptomatic carotid bruit increases the risk of intraoperative cerebral vascular accident. Right-to-left heart shunts, particularly in children with congenital heart disease, allow air emboli to pass directly from the venous circulation to the systemic (possibly cerebral) arterial circulation. A paradoxic air embolism can result in permanent brain damage. Severe hypothyroidism is associated with impaired drug metabolism and, rarely, myxedema coma.

Does an uneventful history of general anesthesia narrow the differential?

Hereditary atypical pseudocholinesterase is ruled out by uneventful prior general anesthesia, assuming succinylcholine was administered. Decreased levels of normal enzyme would not result in postoperative apnea unless the surgery was of very short duration. Malignant hyperthermia does not typically present as delayed awakening, although prolonged somnolence is not

unusual. Uneventful prior anesthetics do not, however, rule out malignant hyperthermia. Persons unusually sensitive to anesthetic agents (eg, geriatric patients) may have a history of delayed emergence.

How do drugs that a patient takes at home affect awakening from general anesthesia?

Drugs that decrease minimum alveolar concentration, such as methyldopa, predispose patients to anesthetic overdose. Acute ethanol intoxication decreases barbiturate metabolism and acts independently as a sedative. Drugs that decrease liver blood flow, such as cimetidine, will limit hepatic drug metabolism. Antiparkinsonian drugs and tricyclic antidepressants have anticholinergic side effects that augment the sedation produced by scopolamine. Long-acting sedatives, such as the benzodiazepines, can delay awakening.

Does anesthetic technique alter awakening?

Preoperative medications can affect awakening. In particular, anticholinergics (with the exception of glycopyrrolate, which does not cross the blood–brain barrier), opioids, and sedatives can interfere with postoperative recovery. Patients with low cardiac output may have delayed absorption of intramuscular injections.

Intraoperative hyperventilation is a common cause of postoperative apnea. Because volatile agents raise the apneic threshold, the $Paco_2$ level at which spontaneous ventilation ceases, moderate postoperative hypoventilation may be required to stimulate the respiratory centers. Severe intraoperative hypotension or hypertension may lead to cerebral hypoxia and edema.

Hypothermia decreases minimum alveolar concentration, antagonizes muscle relaxation reversal, and limits drug metabolism. Arterial hypoxia or severe hypercapnia ($Paco_2$ > 70 mm Hg) can alter consciousness.

Certain surgical procedures, such as carotid endarterectomy, cardiopulmonary bypass, and intracranial procedures, are associated with an increased incidence of postoperative neurological deficits. Subdural hematomas can occur in severely coagulopathic patients. Transurethral resection of the prostate is associated with hyponatremia from the dilutional effects of absorbed irrigating solution.

What clues does a physical examination provide?

Pupil size is not always a reliable indicator of central nervous system integrity. Fixed and dilated pupils in the absence of anticholinergic medication or ganglionic blockade (eg, the formerly used hypotensive agent, trimethaphan), however, may be an ominous sign. Response to physical stimulation, such as a forceful jaw thrust, may differentiate somnolence from paralysis. Peripheral nerve stimulation also differentiates paralysis from coma.

What specific laboratory findings would you order?

Arterial blood gases and serum electrolytes, particularly sodium, may be helpful. Computed tomographic scanning may be necessary if unresponsiveness is prolonged. Increased concentrations of inhalational agent provided by respiratory gas analysis, as well as processed electroencephalogram (EEG) measurements, may assist in determining if the patient is still under the effects of anesthesia. Slow EEG signals can be indicative of both anesthesia and cerebral pathology. Processed EEG awareness monitors can also be employed with the realization that low numbers on the bispectral index can be caused both by anesthetic suppression of the EEG and ischemic brain injury.

What therapeutic interventions should be considered?

Supportive mechanical ventilation should be continued in the unresponsive patient. Naloxone, flumazenil, and physostigmine may be indicated, depending on the probable cause of the delayed emergence, if drug effects are suspected and reversal is considered both safe and desirable.

SUGGESTED READING

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