CHAPTER 12

Cholinesterase Inhibitors & Other Pharmacologic Antagonists to Neuromuscular Blocking Agents

KEY CONCEPTS

1. The primary clinical use of cholinesterase inhibitors, also called anticholinesterases, is to reverse nondepolarizing muscle blockade.
2. Acetylcholine is the neurotransmitter for the entire parasympathetic nervous system (parasympathetic ganglions and effector cells), parts of the sympathetic nervous system (sympathetic ganglions, adrenal medulla, and sweat glands), some neurons in the central nervous system, and somatic nerves innervating skeletal muscle.
3. Neuromuscular transmission is blocked when nondepolarizing muscle relaxants compete with acetylcholine to bind to nicotinic cholinergic receptors. The cholinesterase inhibitors indirectly increase the amount of acetylcholine available to compete with the nondepolarizing agent, thereby reestablishing neuromuscular transmission.
4. In excessive doses, acetylcholinesterase inhibitors can paradoxically potentiate a nondepolarizing neuromuscular blockade. In addition, these drugs prolong the depolarization blockade of succinylcholine.
5. Any prolongation of action of a nondepolarizing muscle relaxant from renal or hepatic insufficiency will probably be accompanied by a corresponding increase in the duration of action of a cholinesterase inhibitor.
6. The time required to fully reverse a nondepolarizing block depends on several factors, including the choice and dose of cholinesterase inhibitor administered, the muscle relaxant being antagonized, and the extent of the blockade before reversal.
7. A reversal agent should be routinely given to patients who have received nondepolarizing muscle relaxants unless full reversal can be demonstrated or the postoperative plan includes continued intubation and ventilation.
8. In monitoring a patient's recovery from neuromuscular blockade, the suggested end points are sustained tetanus for 5 sec in response to a 100-Hz stimulus in anesthetized patients or sustained head lift in awake patients. If neither of these end points is achieved, the patient should remain intubated and ventilation should be continued.
9. Sugammadex exerts its effects by forming tight complexes in a 1:1 ratio with steroidal neuromuscular blocking agents.
10. Cysteine causes inactivation of gantacurium via metabolic degradation and adduct formation.

Incomplete reversal of neuromuscular blocking agents and residual post-procedure paralysis are associated with morbidity; therefore, careful evaluation of neuromuscular blockade and appropriate pharmacologic antagonism are strongly recommended whenever muscle relaxants are administered. The primary clinical use of cholinesterase inhibitors, also called anticholinesterases, is to reverse nondepolarizing muscle blockade. Some of these agents are also used to diagnose and treat myasthenia gravis. More recently, newer agents, such as cyclodextrins and cysteine, with superior ability to reverse neuromuscular blockade from specific agents, are being investigated with promising results. This chapter reviews cholinergic pharmacology and mechanisms of acetylcholinesterase inhibition and presents the clinical pharmacology of commonly used cholinesterase inhibitors (neostigmine, edrophonium, pyridostigmine, and physostigmine). It concludes with a brief description and mechanisms of action of some unique reversal agents.

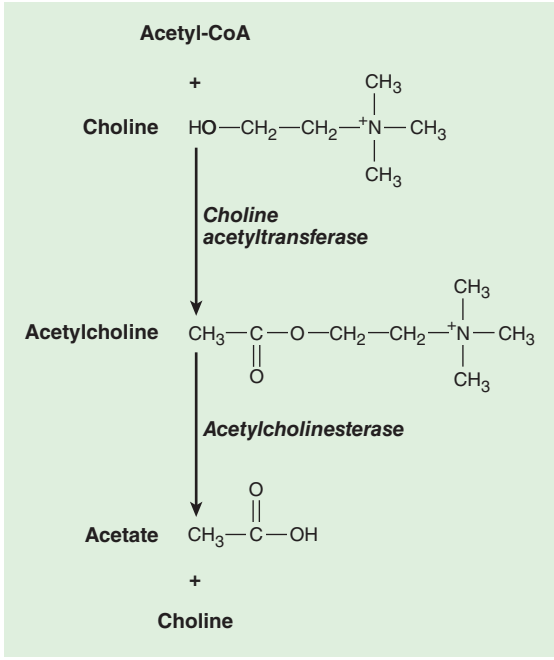

FIGURE 12–1 The synthesis and hydrolysis of acetylcholine.

Cholinergic Pharmacology

The term cholinergic refers to the effects of the neurotransmitter acetyl*choline*, as opposed to the adrenergic effects of nor*adrenaline* (norepinephrine). Acetylcholine is synthesized in the nerve terminal by the enzyme cholineacetyltransferase, which catalyzes the reaction between acetylcoenzyme A and choline (Figure 12–1). After its release, acetylcholine is rapidly hydrolyzed by acetylcholinesterase (true cholinesterase) into acetate and choline.

Acetylcholine is the neurotransmitter for the entire parasympathetic nervous system (parasympathetic ganglions and effector cells), parts of the sympathetic nervous system (sympathetic ganglions, adrenal medulla, and sweat glands), some neurons in the central nervous system, and somatic nerves innervating skeletal muscle (Figure 12–2).

Cholinergic receptors have been subdivided into two major groups based on their reaction to the alkaloids muscarine and nicotine (Figure 12–3). Nicotine stimulates the autonomic ganglia and skeletal muscle receptors (nicotinic receptors), whereas muscarine activates end-organ effector cells in bronchial smooth muscle, salivary glands, and the sinoatrial node (muscarinic receptors). The central nervous system has both nicotinic and muscarinic receptors. Nicotinic receptors are blocked by muscle relaxants (also called neuromuscular blockers), and muscarinic receptors are blocked by anticholinergic drugs, such as atropine. Although nicotinic and muscarinic receptors differ in their response to some agonists (eg, nicotine, muscarine) and some antagonists (eg, vecuronium vs atropine), they both respond to acetylcholine (Table 12–1). Clinically available cholinergic agonists resist hydrolysis by cholinesterase. Methacholine and bethanechol are primarily muscarinic agonists, whereas carbachol has both muscarinic and nicotinic agonist activities. Methacholine by inhalation has been used as a provocative test in asthma, bethanechol is used for bladder atony, and carbachol may be used topically for wide-angle glaucoma.

When reversing neuromuscular blockade, the primary goal is to maximize nicotinic transmission with a minimum of muscarinic side effects.

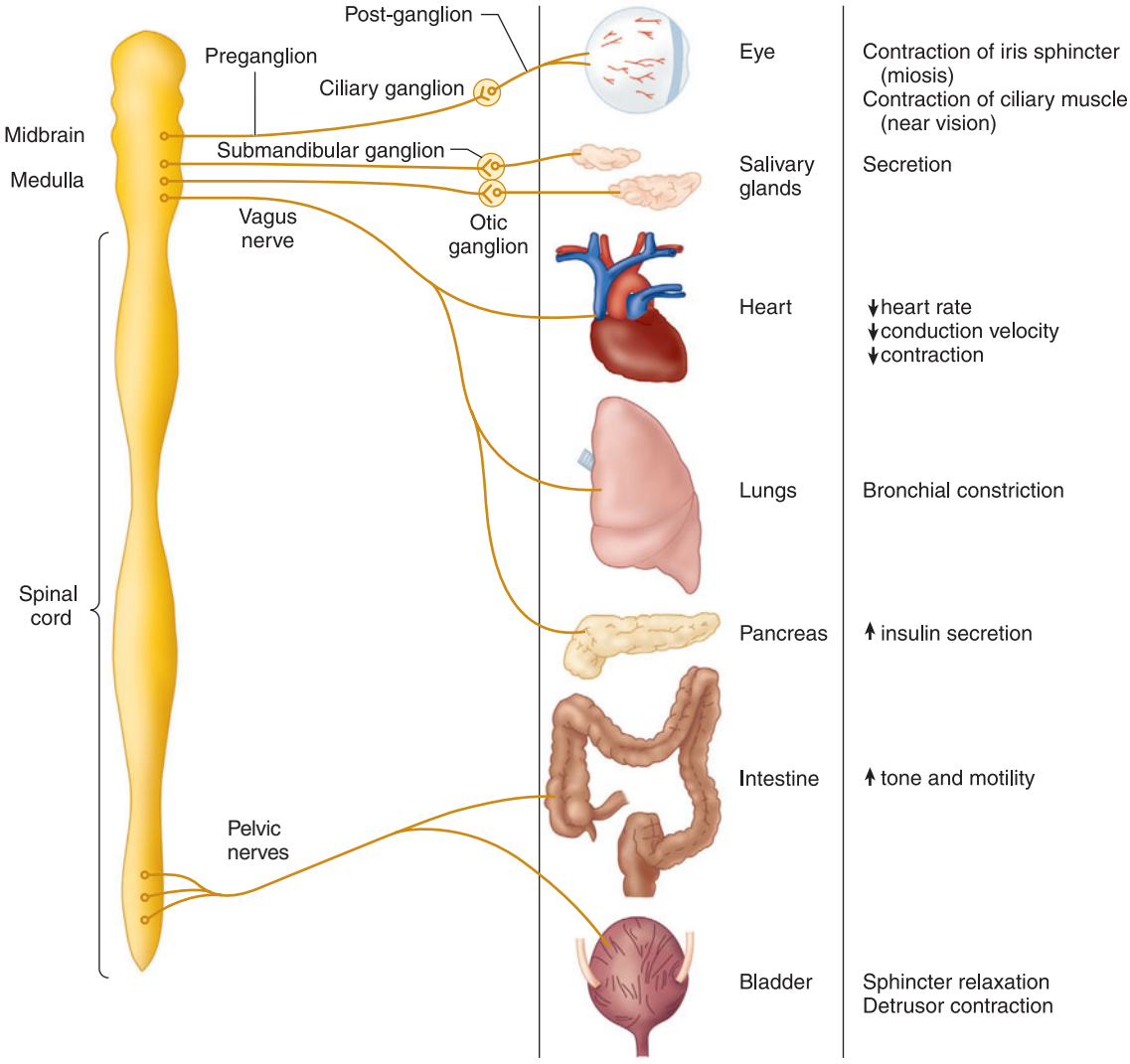

FIGURE 12–2 The parasympathetic nervous system uses acetylcholine as a preganglionic and postganglionic neurotransmitter.

MECHANISM OF ACTION

3 Normal neuromuscular transmission critically depends on acetylcholine binding to nicotinic cholinergic receptors on the motor endplate. Nondepolarizing muscle relaxants act by competing with acetylcholine for these binding sites, thereby blocking neuromuscular transmission. Reversal of blockade depends on gradual diffusion, redistribution, metabolism, and excretion from the body of the nondepolarizing relaxant (*spontaneous reversal*), often assisted by the administration of specific reversal agents (*pharmacological reversal*). Cholinesterase inhibitors *indirectly* increase the amount of acetylcholine available to compete with the nondepolarizing agent, thereby reestablishing normal neuromuscular transmission.

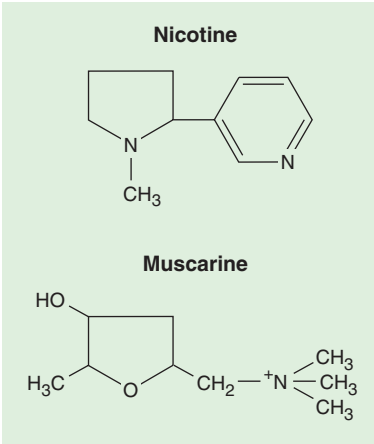

FIGURE 12–3 The molecular structures of nicotine and muscarine. Compare these alkaloids with acetylcholine (Figure 12–1).

Cholinesterase inhibitors inactivate acetylcholinesterase by reversibly binding to the enzyme. The stability of the bond influences the duration of action. The electrostatic attraction and hydrogen bonding of edrophonium are short-lived; the covalent bonds of neostigmine and pyridostigmine are longer lasting.

TABLE 12–1 Characteristics of cholinergic receptors.

	Nicotinic	Muscarinic
Location	Autonomic ganglia Sympathetic ganglia Parasympathetic ganglia Skeletal muscle	Glands Lacrimal Salivary Gastric Smooth muscle Bronchial Gastrointestinal Bladder Blood vessels Heart Sinoatrial node Atrioventricular node
Agonists	Acetylcholine Nicotine	Acetylcholine Muscarine
Antagonists	Nondepolarizing relaxants	Antimuscarinics Atropine Scopolamine Glycopyrrolate

Organophosphates, a special class of cholinesterase inhibitors, form very stable, irreversible bonds to the enzyme. They are used in ophthalmology and more commonly as pesticides. The clinical duration of the cholinesterase inhibitors used in anesthesia, however, is probably most influenced by the rate of drug disappearance from the plasma. Differences in duration of action can be overcome by dosage adjustments. Thus, the normally short duration of action of edrophonium can be partially overcome by increasing the dosage. Cholinesterase inhibitors are also used in the diagnosis and treatment of myasthenia gravis.

Mechanisms of action other than acetylcholinesterase inactivation may contribute to the restoration of neuromuscular function. Edrophonium seems to have prejunctional effects that enhance the release of acetylcholine. Neostigmine has a direct (but weak) agonist effect on nicotinic receptors. Acetylcholine mobilization and release by the nerve may also be enhanced (a presynaptic mechanism).

4 In excessive doses, acetylcholinesterase inhibitors paradoxically potentiate a nondepolarizing neuromuscular blockade. Standard dogma states that neostigmine in high doses may cause receptor channel blockade; however, clinical evidence of this is lacking. In addition, these drugs prolong the depolarization blockade of succinylcholine. Two mechanisms may explain this latter effect: an increase in acetylcholine (which increases motor end-plate depolarization) and inhibition of pseudocholinesterase activity. Neostigmine and to some extent pyridostigmine display some limited pseudocholinesterase-inhibiting activity, but their effect on acetylcholinesterase is much greater. Edrophonium has little or no effect on pseudocholinesterase. In large doses, neostigmine can cause a weak depolarizing neuromuscular blockade.

CLINICAL PHARMACOLOGY

General Pharmacological Characteristics

The increase in acetylcholine caused by cholinesterase inhibitors affects more than the nicotinic receptors of skeletal muscle (Table 12–2). Cholinesterase

TABLE 12–2 Muscarinic side effects of cholinesterase inhibitors.

Organ System	Muscarinic Side Effects
Cardiovascular	Decreased heart rate, bradyarrhythmias
Pulmonary	Bronchospasm, bronchial secretions
Cerebral	Diffuse excitation[1]
Gastrointestinal	Intestinal spasm, increased salivation
Genitourinary	Increased bladder tone
Ophthalmological	Pupillary constriction

[1]Applies only to physostigmine.

inhibitors can act at cholinergic receptors of several other organ systems, including the cardiovascular and gastrointestinal systems.

Cardiovascular receptors—The predominant muscarinic effect on the heart is bradycardia that can progress to sinus arrest.

Pulmonary receptors—Muscarinic stimulation can result in bronchospasm (smooth muscle contraction) and increased respiratory tract secretions.

Cerebral receptors—Physostigmine is a cholinesterase inhibitor that crosses the blood–brain barrier and can cause diffuse activation of the electroencephalogram by stimulating muscarinic and nicotinic receptors within the central nervous system. Inactivation of nicotinic acetylcholine receptors in the central nervous system may play a role in the action of general anesthetics. Unlike physostigmine, cholinesterase inhibitors used to reverse neuromuscular blockers do not cross the blood–brain barrier.

Gastrointestinal receptors—Muscarinic stimulation increases peristaltic activity (esophageal, gastric, and intestinal) and glandular secretions (eg, salivary). Postoperative nausea, vomiting, and fecal incontinence have been attributed to the use of cholinesterase inhibitors.

Unwanted muscarinic side effects are minimized by prior or concomitant administration of anticholinergic medications, such as atropine sulfate or glycopyrrolate. The duration of action is similar among the cholinesterase inhibitors. Clearance is due to both hepatic metabolism (25% to 50%) and renal excretion (50% to 75%). Thus, any prolongation of action of a nondepolarizing muscle relaxant from renal or hepatic insufficiency will probably be accompanied by a corresponding increase in the duration of action of a cholinesterase inhibitor.

5

As a rule, no amount of cholinesterase inhibitor can immediately reverse a block that is so intense that there is no response to tetanic peripheral nerve stimulation. Moreover, the absence of any palpable single twitches following 5 sec of tetanic stimulation at 50 Hz implies a very intensive blockade that cannot be reversed. Excessive doses of cholinesterase inhibitors may actually prolong recovery. Some evidence of spontaneous recovery (ie, the first twitch of the train-of-four [TOF]) should be present before reversal is attempted. The posttetanic count (the number of palpable twitches after tetanus) generally correlates with the time of return of the first twitch of the TOF and therefore the ability to reverse intense paralysis. For intermediate-acting agents, such as atracurium and vecuronium, a palpable posttetanic twitch appears about 10 min before spontaneous recovery of the first twitch of the TOF. In contrast, for longer-acting agents, such as pancuronium, the first twitch of the TOF appears about 40 min after a palpable posttetanic twitch.

6

The time required to fully reverse a nondepolarizing block depends on several factors, including the choice and dose of cholinesterase inhibitor administered, the muscle relaxant being antagonized, and the extent of the blockade before reversal. For example, reversal with edrophonium is usually faster than with neostigmine; large doses of neostigmine lead to faster reversal than small doses; intermediate-acting relaxants reverse sooner than long-acting relaxants; and a shallow block is easier to reverse than a deep block (ie, twitch height >10%). Intermediate-acting muscle relaxants

therefore require a lower dose of reversal agent (for the same degree of blockade) than long-acting agents, and concurrent excretion or metabolism provides a proportionally faster reversal of the short- and intermediate-acting agents. These advantages can be lost in conditions associated with severe end-organ disease (eg, the use of vecuronium in a patient with liver failure) or enzyme deficiencies (eg, mivacurium in a patient with homozygous atypical pseudocholinesterase). Depending on the dose of muscle relaxant that has been given, spontaneous recovery to a level adequate for pharmacological reversal may take more than 1 hr with long-acting muscle relaxants because of their insignificant metabolism and slow excretion. Factors associated with faster reversal are also associated with a lower incidence of residual paralysis in the recovery room and a lower risk of postoperative respiratory complications.

7 A reversal agent should be routinely given to patients who have received nondepolarizing muscle relaxants unless full reversal can be demonstrated or the postoperative plan includes continued intubation and ventilation. In the latter situation, adequate sedation must also be provided.

A peripheral nerve stimulator should also be used to monitor the progress and confirm the adequacy of reversal. In general, the higher the frequency of stimulation, the greater the sensitivity of the test (100-Hz tetany > 50-Hz tetany or TOF > single-twitch height). Clinical signs of adequate reversal also vary in sensitivity (sustained head lift > inspiratory force > vital capacity > tidal volume).

8 Therefore, the suggested end points of recovery are sustained tetanus for 5 sec in response to a 100-Hz stimulus in anesthetized patients or sustained head or leg lift in awake patients. Newer quantitative methods for assessing recovery from neuromuscular blockade, such as acceleromyography, may further reduce the incidence of residual postoperative neuromuscular paralysis.

Specific Cholinesterase Inhibitors

NEOSTIGMINE

Physical Structure

Neostigmine consists of a carbamate moiety and a quaternary ammonium group (Figure 12–4). The former provides covalent bonding to acetylcholinesterase. The latter renders the molecule lipid insoluble, so that it cannot pass through the blood–brain barrier.

Dosage & Packaging

The maximum recommended dose of neostigmine is 0.08 mg/kg (up to 5 mg in adults), but smaller

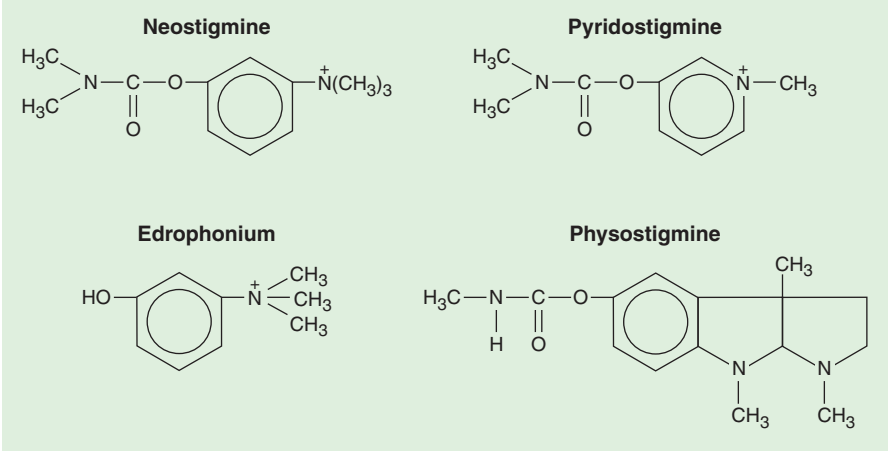

FIGURE 12–4 The molecular structures of neostigmine, pyridostigmine, edrophonium, and physostigmine.

TABLE 12–3 The choice and dose of cholinesterase inhibitor determine the choice and dose of anticholinergic.

Cholinesterase Inhibitor	Usual Dose of Cholinesterase Inhibitor	Recommended Anticholinergic	Usual Dose of Anticholinergic per mg of Cholinesterase Inhibitor
Neostigmine	0.04–0.08 mg/kg	Glycopyrrolate	0.2 mg
Pyridostigmine	0.1–0..25 mg/kg	Glycopyrrolate	0.05 mg
Edrophonium	0.5–1 mg/kg	Atropine	0.014 mg
Physostigmine[1]	0.01–0.03 mg/kg	Usually not necessary	NA

[1]Not used to reverse muscle relaxants.

amounts often suffice and larger doses have also been given safely (Table 12–3). Neostigmine is most commonly packaged as 10 mL of a 1 mg/mL solution, although 0.5 mg/mL and 0.25 mg/mL concentrations are also available.

Clinical Considerations

The effects of neostigmine (0.04 mg/kg) are usually apparent in 5min, peak at 10 min, and last more than 1 hr. If reversal is not complete in 10 min after 0.08 mg/kg, the time for full recovery of neuromuscular function will depend on the nondepolarizing agent used and the intensity of blockade. In practice, many clinicians use a dose of 0.04 mg/kg (or 2.5 mg) if the preexisting blockade is mild to moderate and a dose of 0.08 mg/kg (or 5 mg) if intense paralysis is being reversed. The duration of action is prolonged in geriatric patients. Muscarinic side effects are minimized by prior or concomitant administration of an anticholinergic agent. The onset of action of glycopyrrolate (0.2 mg glycopyrrolate per 1 mg of neostigmine) is similar to that of neostigmine and is associated with less tachycardia than is experienced with atropine (0.4 mg of atropine per 1 mg of neostigmine). It has been reported that neostigmine crosses the placenta, resulting in fetal bradycardia. Thus, *theoretically*, atropine may be a better choice of an anticholinergic agent than glycopyrrolate in pregnant patients receiving neostigmine, but there is no evidence that this makes any difference in patient outcomes. Neostigmine is also used to treat myasthenia gravis, urinary bladder atony, and paralytic ileus.

PYRIDOSTIGMINE

Physical Structure

Pyridostigmine is structurally similar to neostigmine except that the quaternary ammonium is incorporated into the phenol ring. Pyridostigmine shares neostigmine's covalent binding to acetylcholinesterase and its lipid insolubility.

Dosage & Packaging

Pyridostigmine is 20% as potent as neostigmine and may be administered in doses up to 0.25 mg/kg (a total of 20 mg in adults). It is available as a solution of 5 mg/mL.

Clinical Considerations

The onset of action of pyridostigmine is slower (10–15 min) than that of neostigmine, and its duration is slightly longer (>2 h). Glycopyrrolate (0.05 mg per 1 mg of pyridostigmine) or atropine (0.1 mg per 1 mg of pyridostigmine) must also be administered to prevent bradycardia. Glycopyrrolate is preferred because its slower onset of action better matches that of pyridostigmine, again resulting in less tachycardia.

EDROPHONIUM

Physical Structure

Because it lacks a carbamate group, edrophonium must rely on noncovalent bonding to the acetylcholinesterase enzyme. The quaternary ammonium group limits lipid solubility.

Dosage & Packaging

Edrophonium is less than 10% as potent as neostigmine. The recommended dosage is 0.5–1 mg/kg. Edrophonium is available as a solution containing 10 mg/mL; it is available with atropine as a combination drug (Enlon-Plus; 10 mg edrophonium and 0.14 mg atropine per mL).

Clinical Considerations

Edrophonium has the most rapid onset of action (1–2 min) and the shortest duration of effect of any of the cholinesterase inhibitors. Reduced doses should not be used, because longer-acting muscle relaxants may outlast the effects of edrophonium. Higher doses prolong the duration of action to more than 1 hr. Edrophonium may not be as effective as neostigmine at reversing intense neuromuscular blockade. In equipotent doses, muscarinic effects of edrophonium are less pronounced than those of neostigmine or pyridostigmine, requiring only half the amount of anticholinergic agent. Edrophonium's rapid onset is well matched to that of atropine (0.014 mg of atropine per 1 mg of edrophonium). Although glycopyrrolate (0.007 mg per 1 mg of edrophonium) can also be used, it should be given several minutes prior to edrophonium to avoid the possibility of bradycardia.

PHYSOSTIGMINE

Physical Structure

Physostigmine, a tertiary amine, has a carbamate group but no quaternary ammonium. Therefore, it is lipid soluble and is the only clinically available cholinesterase inhibitor that freely passes the blood–brain barrier.

Dosage & Packaging

The dose of physostigmine is 0.01–0.03 mg/kg. It is packaged as a solution containing 1 mg/mL.

Clinical Considerations

The lipid solubility and central nervous system penetration of physostigmine limit its usefulness as a reversal agent for nondepolarizing blockade, but make it effective in the treatment of central anticholinergic toxicity caused by overdoses of atropine or scopolamine. In addition, it reverses some of the central nervous system depression and delirium associated with use of benzodiazepines and volatile anesthetics. Physostigmine (0.04 mg/kg) has been shown to be effective in preventing postoperative shivering. It reportedly partially antagonizes morphine-induced respiratory depression, presumably because morphine reduces acetylcholine release in the brain. These effects are transient, and repeated doses may be required. Bradycardia is infrequent in the recommended dosage range, but atropine should be immediately available. Because glycopyrrolate does not cross the blood–brain barrier, it will not reverse the central nervous system effects of physostigmine. Other possible muscarinic side effects include excessive salivation, vomiting, and convulsions. In contrast to other cholinesterase inhibitors, physostigmine is almost completely metabolized by plasma esterases, so renal excretion is not important.

OTHER CONSIDERATIONS

Recovery from neuromuscular blockade is influenced by the depth of block at the time of antagonism, clearance and half-life of the relaxant used, and other factors that affect neuromuscular blockade (Table 12–4), such as drugs and electrolyte

TABLE 12–4 Factors potentiating neuromuscular blockade.

Drugs
Volatile anesthetics
Antibiotics: Aminoglycosides, polymyxin B, neomycin, tetracycline, clindamycin
Dantrolene
Verapamil
Furosemide
Lidocaine
Electrolytes and acid–base disorders
Hypermagnesemia
Hypocalcemia
Hypokalemia
Respiratory acidosis
Temperature
Hypothermia

disturbances. In addition, some specific agents with the potential of reversing the neuromuscular blocking effects of nondepolarizing muscle relaxants merit brief discussion.

NON-CLASSIC REVERSAL AGENTS

Besides cholinesterase inhibitors, two unique drugs (sugammadex and L-cysteine) are currently under investigation in the United States; these agents act as selective antagonists of nondepolarizing neuromuscular blockade. Sugammadex is able to reverse aminosteroid-induced neuromuscular blockade, whereas cysteine has been shown to reverse the neuromuscular blocking effects of gantacurium and other fumarates.

SUGAMMADEX

Sugammadex is a novel selective relaxant-binding agent that is currently available for clinical use in Europe. It is a modified gamma-cyclodextrin (*su* refers to sugar, and *gammadex* refers to the structural molecule gamma-cyclodextrin).

Physical Structure

Its three-dimensional structure resembles a hollow truncated cone or doughnut with a hydrophobic cavity and a hydrophilic exterior. Hydrophobic 9 interactions trap the drug (eg, rocuronium) in the cyclodextrin cavity (doughnut hole), resulting in tight formation of a water-soluble guest–host complex in a 1:1 ratio. This terminates the neuromuscular blocking action and restrains the drug in extracellular fluid where it cannot interact with nicotinic acetylcholine receptors. Sugammadex is essentially eliminated unchanged via the kidneys.

Clinical Considerations

Sugammadex has been administered in doses of 4–8 mg/kg. With an injection of 8 mg/kg, given 3 min after administration of 0.6 mg/kg of rocuronium, recovery of TOF ratio to 0.9 was observed within 2 min. It produces rapid and effective reversal of both shallow and profound rocuronium-induced neuromuscular blockade in a consistent manner. Because of some concerns about hypersensitivity and allergic reactions, sugammadex has not yet been approved by the US Food and Drug Administration.

L-CYSTEINE

L-cysteine is an endogenous amino acid that is often added to total parenteral nutrition regimens 10 to enhance calcium and phosphate solubility. The ultrashort-acting neuromuscular blocker, gantacurium, and other fumarates rapidly combine with L-cysteine *in vitro* to form less active degradation products (adducts). Exogenous administration of L-cysteine (10–50 mg/kg intravenously) given to anesthetized monkeys 1 min after these neuromuscular blocking agents abolished the block within 2–3 min; this antagonism was found to be superior to that produced by anticholinesterases. This unique method of antagonism by adduct formation and inactivation is still in the investigative stage, especially in terms of its safety and efficacy in humans.

CASE DISCUSSION

Respiratory Failure in the Recovery Room

A 66-year-old woman weighing 85 kg is brought to the recovery room following cholecystectomy. The anesthetic technique included the use of isoflurane and vecuronium for muscle relaxation. At the conclusion of the procedure, the anesthesiologist administered 6 mg of morphine sulfate for postoperative pain control and 3 mg of neostigmine with 0.6 mg of glycopyrrolate to reverse any residual neuromuscular blockade. The dose of cholinesterase inhibitor was empirically based on clinical judgment. Although the patient was apparently breathing normally on arrival in the recovery room, her tidal volume progressively diminished. Arterial blood gas measurements revealed a $Paco_2$ of 62 mm Hg, a Pao_2 of 110 mm Hg, and a pH of 7.26 on a fraction of inspired oxygen (Fio_2) of 40%.

Which drugs administered to this patient could explain her hypoventilation?

Isoflurane, morphine sulfate, and vecuronium all interfere with a patient's ability to maintain a normal ventilatory response to an elevated $Paco_2$.

Why would the patient's breathing worsen in the recovery room?

Possibilities include the delayed onset of action of morphine sulfate, a lack of sensory stimulation in the recovery area, fatigue of respiratory muscles, and splinting as a result of upper abdominal pain.

Could the patient still have residual neuromuscular blockade?

If the dose of neostigmine was not determined by the response to a peripheral nerve stimulator, or if the recovery of muscle function was inadequately tested after the reversal drugs were given, persistent neuromuscular blockade is possible. Assume, for example, that the patient had minimal or no response to initial tetanic stimulation at 100 Hz. Even the maximal dose of neostigmine (5 mg) might not yet have adequately reversed the paralysis. Because of enormous patient variability, the response to peripheral nerve stimulation must always be monitored when intermediate- or long-acting muscle relaxants are administered. Even if partial reversal is achieved, paralysis may worsen if the patient hypoventilates. **Other factors (in addition to respiratory acidosis) that impair the reversal of nondepolarizing muscle relaxants include intense neuromuscular paralysis, electrolyte disturbances (hypermagnesemia, hypokalemia, and hypocalcemia), hypothermia (temperature <32°C), drug interactions (see Table 11–4), metabolic alkalosis (from accompanying hypokalemia and hypocalcemia), and coexisting diseases (see Table 11–8).**

How could the extent of reversal be tested?

Tetanic stimulation is a sensitive but uncomfortable test of neuromuscular transmission in an awake patient. Because of its shorter duration, double-burst stimulation is tolerated better than tetany by conscious patients. Many other tests of neuromuscular transmission, such as vital capacity and tidal volume, are insensitive as they may still seem normal when 70% to 80% of receptors are blocked. In fact, 70% of receptors may remain blocked despite an apparently normal response to TOF stimulation. The ability to sustain a head lift for 5 sec, however, indicates that fewer than 33% of receptors are occupied by muscle relaxant.

What treatment would you suggest?

Ventilation should be assisted to reduce the respiratory acidosis. Even if diaphragmatic function seems to be adequate, residual blockade can lead to airway obstruction and poor airway protection. More neostigmine (with an anticholinergic) could be administered up to a maximum recommended dose of 5 mg. If this does not adequately reverse paralysis, mechanical ventilation and airway protection should be instituted and continued until neuromuscular function is fully restored.

SUGGESTED READING

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