Postanesthesia Care

Residual Neuromuscular Blockade in Critical Care

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Neuromuscular blockade is a pharmacological adjunct for anesthesia and for surgical interventions. Neuromuscular blockers can facilitate ease of instrumentation and reduce complications associated with intubation. An undesirable sequela of these agents is residual neuromuscular blockade. Residual neuromuscular blockade is linked to aspiration, diminished response to hypoxia, and obstruction of the upper airway that may occur soon after extubation. If an operation is particularly complex or requires a long anesthesia time, residual neuromuscular blockade can contribute to longer stays in the intensive care unit and more hours of mechanical ventilation. Given the risks of this medication class, it is essential to have an understanding of the mechanism of action of, assessment of, and factors affecting blockade and to be able to identify factors that affect pharmacokinetics. (Critical Care Nurse. 2012;32[3]:e1-e10)

Surgery, anesthesia, and other interventions in critical care are facilitated by the use of nondepolarizing neuromuscular blocking agents (NMBAs).1 NMBAs are used in critical care units, emergency departments, and operating rooms to provide muscular relaxation during surgery, decreased resistance during closed reduction, decreased overall oxygen demand, and decreased intracranial pressure.1,2 Use of NMBAs is often credited as an essential component of balanced anesthesia and is important in reducing laryngeal trauma during intubation.2,3 However, these medications are also associated with the risk for residual neuromuscular blockade (RNMB) after surgery (also termed postoperative residual curarization or PORC).4 RNMB rates are linked to incomplete metabolism and excretion of the drugs at the end of surgery; the reported rate is 11% to 88%.4,5 The wide range is due to the differences in methods and control of confounding variables, such as medication duration and length and type of surgery. RNMB is more prevalent in patients with renal impairment than in patients with normal kidney function.2,3 To manage and assess patients who received NMBAs during surgery or other procedures requires nurses to understand the current evidence on potential complications associated with these agents.

NMBAs blunt or abolish the neuromuscular protective reflexes of coughing, gagging, and blinking. In the immediate period after anesthesia, this loss of muscular strength can lead to aspiration, impaired ventilatory response to hypoxia, and obstruction of the upper part of the airway.2 Long duration of anesthesia and problems with metabolism and excretion of the medications can also result in prolonged duration of mechanical ventilation and longer stays in the critical care unit.2,8 RNMB is an important clinical concern after anesthesia because of the vulnerability of the patients to adverse postoperative events. The priority in caring for patients with RNMB is recognition, monitoring, and intervention to ensure optimal outcomes. In this article, we describe the mechanisms of action of NMBAs,
provide background knowledge on NMBAs and their reversal agents, discuss assessment and monitoring of blockade, identify patient and environmental factors that affect the pharmacokinetics of the blockers, and illustrate the clinical application of this information.

The Neuromuscular Junction

The neuromuscular junction is the site of action of NMBAs (Figure 1). A stimulated skeletal nerve releases acetylcholine from the terminal end into the synaptic space. Acetylcholine then binds temporarily (a few milliseconds) to thousands of nicotinic receptors and excites the muscle fiber. Nicotinic receptors open sodium channels that then produce muscle contraction. Termination of this effect is a result of the basal lamina, a fine connective tissue that fills the synaptic space. This space contains acetylcholinesterase, an enzyme that breaks down the acetylcholine in the milliseconds after release, producing muscle relaxation.

Mechanisms of Action of NMBAs

Nondepolarizing NMBAs compete with acetylcholine to bind to the postsynaptic nicotinic receptors (Figure 2). Approximately 70% of receptors must be bound by NMBAs to prevent muscle contraction. NMBAs have specificity for the nicotinic receptors at the neuromuscular junction. Nevertheless, additional sites of nicotinic receptors include the autonomic ganglia and carotid body chemoreceptors. A possible clinical problem is blockade within the muscarinic receptors in the lungs and heart, which may produce bronchospasm and cardiac dysrhythmias, respectively. Each N MBA has a different pharmacokinetic profile (Table 1).

Mechanisms of Action of Reversal Agents

Neostigmine, edrophonium, and pyridostigmine are acetylcholinesterase inhibitors used to reverse the action of NMBAs. These 3 reversal
agents inactivate acetylcholinesterase and allow an increase in the concentration of acetylcholine and competitive binding to the nicotinic receptors (Figure 3). This action reestablishes neuromuscular transmission by acetylcholine and increases muscle strength.2,11,12

If the concentration of acetylcholine at the junction is not high enough when the acetylcholinesterase inhibitors are administered, reversal does not occur. If neuromuscular blockade is profound, patients may become refractory to the effects of acetylcholinesterase inhibitors despite an increased dose because the concentration of acetylcholine is insufficient. Therefore, use of these inhibitors has limitations when reversal of NMBAs is desired.2,13 Acetylcholinesterase inhibitors have relative contraindications in patients with a history of cardiac dysrhythmias or asthma,2,3,10 because the muscarinic effects of acetylcholinesterase inhibitors can be associated with atrioventricular block or bronchospasm.

Neostigmine is commonly used to reverse nondepolarizing neuromuscular blockade and is often administered at the end of surgery to facilitate extubation and speed the return of neuroprotective reflexes. Neostigmine has a narrow margin of safety, and doses must be carefully calculated.12,13 As a whole, the acetylcholinesterase inhibitors are more effective in the reversal of light or moderate blockade than in the reversal of deep blockade; however, neostigmine is more effective than pyridostigmine or edrophonium in the reversal of deep blockade.14,15 Neostigmine produces muscarinic effects throughout the body, including the cardiovascular system and exocrine glands. Clinically, the effects are manifested as bradycardia, bronchospasm, and excessive salivation. In order to minimize these parasympathetic effects, doses must be carefully calculated.
effects, anticholinergic medications, including atropine and glycopyrrolate, must be administered along with the neostigmine.14 Having a patient return to surgery for a complication such as bleeding can be a concern for the anesthesia team if a reversal agent has been administered. Reestablishment of blockade will be less predictable in onset and duration for the half-life time of the particular agent used.2,14,15

Pyridostigmine, an analogue of neostigmine,10 is thought to be associated with a lower incidence of muscarinic side effects than neostigmine is.3,3 As with neostigmine, anticholinergic medications are administered concurrently to block muscarinic stimulation. Both neostigmine and pyridostigmine form covalent bonds at the anionic and esteratic sites on the acetylcholinesterase molecule, whereas edrophonium binds via competitive inhibition. These differences in binding contribute to the faster onset of action of edrophonium. Edrophonium is clinically effective with vecuronium and atracurium. This medication is frequently used as a diagnostic tool for myasthenia gravis.1,10,12,13

Possible Reversal Agent

Sugammadex is a novel reversal medication used in Europe; currently it is not approved by the Food and Drug Administration for use in the United States. Sugammadex is a selective reversal agent that terminates the neuromuscular blockade via direct encapsulation when it binds with high affinity to the aminosteroid NMBA's rocuronium and vecuronium. The possible benefits and risks of this medication on patients' outcomes have yet to be delineated.3,14,15

Financial Impact of Reversal

Reversal of neuromuscular blockade is associated with a shorter time in the operating room. Use of muscle relaxation aids in anatomical manipulation and reduces resistance to instrumentation.20,21 However, reversal allows prompt extubation and the end of the surgery. In a retrospective study of 9670 US surgical cases in which NMBA's were administered, Zhang et al19 assessed the impact of pharmacological reversal upon time in the operating room. The types of surgery included thoracic, cardiac, vascular, abdominal, peripheral, urological, and neurological. Except for cardiac surgery, time in the operating room was decreased 12 to 46 minutes when neostigmine, pyridostigmine, or edrophonium was administered.

Clinical Monitoring of Neuromuscular Blockade

Three assessment techniques are used to check the degree of blockade: physical assessment with clinical observation, acceleromyography, and use of a peripheral nerve stimulator for train-of-four (TOF) responses.2,22-24

One of the most important clinical observations when an NMBA is administered is the order in which muscles are affected by the medication.2,9 The first muscles affected are those of the eyes, face, and neck that produce rapid movements. The next groups affected are those of the extremities, abdomen, and chest. The large muscles of the diaphragm are affected last. As the NMBA is cleared from the body, the muscles recover in the reverse order. The muscular competency of the upper part of the airway is the last to return.2,15

A common method of monitoring the return of muscular strength is asking a patient to raise his or her head and hold it up for 5 seconds. If more than 30% of receptors are blocked, the patient will not be able to hold the head suspended above the pillow for 5 seconds. This method requires a patient who is cooperative and has no neurological impairment.20,22

With acceleromyography, an instrument with a piezoelectric transducer is used to measure the acceleration of a muscle. When a muscle moves, it generates an electric signal, which is displayed as a numerical value called a TOF ratio.22 Acceleromyography is more often used for detection of residual paralysis in research and during surgery than in postoperative clinical practice; its efficacy after surgery has not been established.23 Because patients in the recovery phase of anesthesia have increased motor movement, the occurrence of artifact increases and the reliability of the instrument is diminished. Another concern is the lack of consensus about the TOF ratio needed to exclude clinically important RNMB.23,25

TOF is an assessment that involves stimulation of peripheral nerves. A series of 4 light shocks are applied to a peripheral nerve, and visual observation of the muscular response to each shock is used to measure the degree of neuromuscular blockade. The most commonly used sites for stimulation are the facial and ulnar nerves. A total of 4 shocks of 2 Hz each are administered, and a ratio between the strength of the fourth shock relative to the first shock (T1/T4) is estimated. Decreasing amplitude of muscle twitches,
referred to as fade, is directly relative to the amount of NMBA present. If more than 75% of nicotinic receptors are blocked, a noticeable fade will be apparent; a complete loss of twitches indicates that 100% of the receptors are blocked. TOF assessment can be more difficult in patients who have peripheral edema or electrolyte imbalances than in other patients. TOF results are used to determine the dosage of reversal agents, and TOF assessment is the most common method used to monitor neuromuscular blockade perioperatively. 

Figure 4 Train-of-4 suppression. Reprinted from Nagelhout and Plaus, with permission. © Elsevier (2010).

Factors That Affect the Pharmacokinetics of NMBAs

Multiple factors affect a patient’s response to NMBAs and acetylcholinesterase inhibitors, including fluid and electrolyte imbalances, hypothermia, drug-drug interactions, previous neurological diseases, and genetic variables. 

Fluid and Electrolyte Imbalances

Sodium, potassium, magnesium, and calcium are vital to normal neuromuscular function. Diminished extracellular levels of sodium can promote an increased duration of neuromuscular blockade. Potassium deficiencies also can intensify the response to NMBAs, thereby extending the recovery time from the medications. High levels of magnesium produce a slowing of action potentials in neurons. Clinically, the slowing is manifested as decreased reflex response. High serum levels of magnesium can lead to neuromuscular blockade without administration of NMBAs. Calcium deficiency prolongs the action of NMBAs by inhibiting neuromuscular transmission.

Hypothermia

Unintentional hypothermia continues to occur despite the best efforts of members of the anesthesia, surgery, and perianesthesia teams. A cascade of detrimental physiological effects accompanies hypothermia in patients who were anesthetized. Additionally, the
temperature of blood that is perfusing muscles must be normothermic to restore respiratory mechanics.28,29 Hypothermia can profoundly influence pharmacokinetics of a number of medications, including NMBAs. Hypothermia causes delayed elimination of NMBAs and acetylcholinesterase inhibitors and impairs respiratory muscular efforts, the stability of hemodynamic parameters, and oxygenation.24,26-28 Hypothermia in patients arriving at a postanesthesia area is a handoff cue that medications will be slowly metabolized during phase I recovery.10,30 Table 2 is an example of a handoff report for a patient with RNMB.

In patients not given NMBAs, hypothermia affects muscles by lengthening the time to contraction, an effect that may be due to a decrease in myofilament sensitivity to calcium.25 The twitch response is decreased 2% to 10% per degree Celsius reduction in the muscle temperature. In patients given NMBAs, pharmacokinetic changes occur because of the effects of hypothermia on drug disposition. These effects may be attributed to alterations in the cytochrome P450 enzyme system.31-34 Vecuronium is an NMBA of intermediate duration that undergoes hepatic metabolism by cytochrome P450 enzymes.35 Hepatic elimination also involves the P-glycoprotein system, which is a carrier-mediated active transport system that can be affected by temperature.28,30-32 Hypothermia also plays a role in pharmacokinetic changes that occur with other NMBAs. Rocuronium is structurally similar to vecuronium, with a slightly faster onset of action and lower potency. Rocuronium is also taken up via the liver but is excreted mostly unchanged into the bile.31 Similar to vecuronium, rocuronium is associated with a temperature-dependent decrease in plasma clearance, leading to increased duration of action and time to spontaneous recovery.

A third neuromuscular blocker, atracurium, is eliminated by Hofmann degradation (cleavage of the chemical structure) and plasma esterase hydrolysis of the ester moiety.22 Despite this unique

<table>
<thead>
<tr>
<th>SBAR element</th>
<th>Residual neuromuscular blockade</th>
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<tbody>
<tr>
<td><strong>S</strong> (Situation)</td>
<td>Case types: neurosurgery, transplant, trauma, plastic surgery with extensive repair</td>
</tr>
<tr>
<td><strong>B</strong> (Background)</td>
<td>Hypothermia, Multiple transfusions, History of neuromuscular diseases, History of renal or hepatic insufficiency, Unstable hemodynamic status, Muscle wasting, Poor nutrition, Electrolyte imbalances, Administration of high doses of neuromuscular agents, Drug-drug interactions, Acidosis</td>
</tr>
<tr>
<td><strong>A</strong> (Assessment)</td>
<td>High venous oxygen saturation, Low tidal volumes, Lack of respiratory drive, Difficulty with maintaining airway, 1-2 twitch response with train of 4 after reversal, Diminished level of consciousness</td>
</tr>
<tr>
<td><strong>R</strong> (Response)</td>
<td>Support ventilation, Support airway positioning, Maintain oxygenation, Warm, Monitor arterial blood gases, Track vital signs, Identify drug-drug interactions, Monitor electrolytes, Monitor electrocardiogram, Administer reversal agents as indicated</td>
</tr>
</tbody>
</table>
method of elimination, hypothermia also increases the duration of action of atracurium and the time to recovery.28,29,31

The effects of hypothermia on neostigmine have also been studied.29,31,34 Heier et al29 analyzed plasma samples of neostigmine to assess possible pharmacokinetic alterations. During hypothermia, the volume of distribution of neostigmine decreased and the time of onset of maximum effect increased slightly. However, hypothermia had no effects on clearance, duration of action, or maximum effect of the drug. Thus, any delayed reversal of NMBAs in patients with hypothermia must be attributed to the effect of the hypothermia on the NMBA and not the neostigmine.21,22,24,33,34

**Drug-Drug Interactions**

Many medications can interact with NMBAs.10,11,12,13,31 Interactions can magnify or diminish the efficacy of an NMBA within the neuromuscular junction. Compounds that may potentiate blockade include inhaled anesthetics, antibiotics (especially aminoglycosides), magnesium, and calcium channel blockers. Inhalational anesthetics create a synergistic effect with nondepolarizing NMBA to prolong the blockade, and aminoglycosides block presynaptic release of acetylcholine. Magnesium antagonizes calcium-dependent release of acetylcholine, and calcium channel blockers most likely enhance blockade either by blocking release of acetylcholine or by acting on the postsynaptic membrane.34,35

Medications that antagonize blockade include corticosteroids, theophylline, and anticonvulsants, including phenytoin and carbamazepine. Patients who have been taking phenytoin and carbamazepine long-term usually require increased doses of NMBAs. Of interest, acute administration of phenytoin actually potentiates the blockade. Carbamazepine increases the metabolism of NMBAs. Corticosteroids have antagonizing effects on the blockade.9,10,36,37 In addition, in some circumstances, corticosteroids may actually have an additive effect, which may potentiate prolonged weakness and myopathy. Careful evaluation of medications before surgery can identify patients who may need decreased doses of NMBAs.11,24,16,30 Table 3

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**Table 3** Medications that interact with nondepolarizing neuromuscular blockers

<table>
<thead>
<tr>
<th>Medications</th>
<th>Names of medication</th>
<th>Possible mechanisms of drug-drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased neuromuscular blocking effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthetics systemic/inhaled/local</td>
<td>Ketamine, lidocaine, bupivacaine</td>
<td>Synergistic/additive effect</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Tobramycin, gentamicin, amikacin, polymixin B, colistin, tetracycline, clindamycin</td>
<td>Inhibition of acetylcholine release at neuromuscular junction</td>
</tr>
<tr>
<td>Antiarrhythmic agents</td>
<td>Procainamide, quinidine, high-dose magnesium</td>
<td>Inhibition of acetylcholine release</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Hydrochlorothiazide, low-dose furosemide</td>
<td>Additive effects</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Nicardipine</td>
<td>Additive effects, Decreased clearance of neuromuscular blockers, Additive pharmacodynamic effects</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td>Unknown mechanism</td>
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<tr>
<td><strong>Decreased neuromuscular blocking effects</strong></td>
<td></td>
<td></td>
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<tr>
<td>Corticosteroids</td>
<td>Hydrocortisone, prednisone, dexamethasone</td>
<td>Unknown mechanism, Prolonged weakness and myopathy</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Theophylline, aminophylline</td>
<td>Antagonistic effect</td>
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<tr>
<td>Hydantoins</td>
<td>Phenytoin, fosphenytoin</td>
<td>Unknown mechanisms</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Increased metabolism of neuromuscular blockers (hepatically metabolized agents)</td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
<td>Antagonistic at doses of 1-4 mg/kg</td>
</tr>
</tbody>
</table>

*Based on data from Westfall and Westfall,11 Nagelhout and Plaus,24 Donati and Vevan,36 Kindler et al,37 Jaramillo et al,38 and Ramachandran and O’Brien.39*
gives examples of drugs that interact with NMBAs.

**Neurological and Muscular Diseases**

Any disease that affects acetylcholine, nerve conduction, or motor function must be considered when administering, monitoring, and reversing neuromuscular blockade. All disciplines involved in a surgical case need documentation of thorough preoperative assessment so that clinical judgments can be made on the basis of subsequent assessments. Table 4 gives examples of neuromuscular diseases that influence NMBAs.

**Genetics**

The pharmacokinetics of neuromuscular blockade are genetically based. Pharmacogenomics is the branch of pharmacology in which the genetic variations of receptors and enzymes needed for the metabolism of drugs are studied. Hepatic metabolism by cytochrome P450 enzymes is affected by a patient’s sex and genetics and influences the administration of NMBAs. This enzyme system consists of more than 50 genes that play a major role in drug metabolism. The rare genetic disorder plasma cholinesterase deficiency can profoundly influence the duration of action and metabolism of succinylcholine. Idiosyncratic reactions to many drug classes are attributed to genetic influence.

**Summary**

NMBAs are high-risk medications that require clinicians to be knowledgeable about the complexity of responses of individual patients. Adverse events such as RNMB may be more prevalent than previously documented. Any transfer of a patient who has received an NMA should include handoff information about the NMB administered and the results of monitoring to provide essential data for the basis of ongoing assessments. Critical care nurses must be aware of the importance of monitoring patients given NMBAs, the agents used to reverse blockade, and the risks and adverse outcomes associated with the blocking agents.

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**Table 4** Examples of neuromuscular diseases that influence neuromuscular blocking agents

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>Cerebrovascular accident</td>
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<tr>
<td>Parkinson disease</td>
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<tr>
<td>Multiple sclerosis</td>
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<td>Amyotrophic lateral sclerosis</td>
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<tr>
<td>Myasthenia gravis</td>
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<td>Muscular dystrophies</td>
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* Based on data from Drain and Burton and Alexander.

In this patient, the RNMB was attributed to the postoperative hypothermia. Even after her blood pressure stabilized, acute renal failure developed and continuous renal replacement therapy was started. The physicians, nurses, and pharmacists worked together to titrate the necessary medications. Slowly, the medication effects were reversed, and the patient began to follow commands. After 36 hours, reversal was complete and weaning from mechanical ventilation could begin. The variables identified that affected the rate of reversal were hypothermia, electrolyte shifts, infusion of multiple blood products, and variable levels of perfusion to the vital organs. The pharmacokinetics of cisatracurium in this patient was atypical, requiring attentive assessment by all of the providers involved in her care.
Financial Disclosures
None reported.

References
CNE Test  Test ID C1233: Residual Neuromuscular Blockade in Critical Care

Learning objectives: 1. Identify the mechanism of action of 3 common neuromuscular blocking agents. 2. Describe advantages and disadvantages of using neuromuscular blockade during surgical procedures. 3. Discuss the assessment and monitoring of a patient after neuromuscular blockade.

1. Which of the following side effects can be the result of residual neuromuscular blockade?
   a. Decreased risk of aspiration  
   b. Increased response to hypoxia  
   c. Increased mechanical ventilation hours  
   d. Decreased length of stay in the intensive care unit

2. Which of the following is a rationale for use of neuromuscular blocking agents (NMBAs) during surgery?
   a. Decreases muscular relaxation to facilitate intubation  
   b. Increases overall oxygen demand  
   c. Increases intracranial pressures  
   d. Decreases risk of laryngeal trauma during intubation

3. What can increase the likelihood that a patient may develop residual neuromuscular blockade?
   a. Renal impairment  
   b. Short surgical procedures  
   c. Fasting before surgery  
   d. Oral rather than intravenous administration

4. Which of the following statements is true regarding the neuromuscular junction?
   a. A stimulated skeletal nerve muscle releases nicotinic acid from the terminal end to the synaptic space.  
   b. Acetylcholine binds permanently to nicotinic receptors.  
   c. Nicotinic receptors open the sodium channels that then produce muscular contraction.  
   d. Acetylcholinesterase is the enzyme that causes muscle contraction.

5. Which of the following are potential clinical problems produced by blockade of the muscarine receptors in the heart and lungs during neuromuscular blockade?
   a. Bronchospasm and blood pressure changes  
   b. Bronchospasm and cardiac dysrhythmias  
   c. Increased secretions and cardiac dysrhythmias  
   d. Increased secretions and blood pressure changes

6. Which of the following patient conditions would cause the nurse to question the administration of acetylcholinesterase inhibitors to reverse NMBAs?
   a. Acute renal failure and asthma  
   b. Asthma and myasthenia gravis  
   c. Cardiac dysrhythmias and acute renal failure  
   d. Cardiac dysrhythmias and asthma

7. Which of the following is a disadvantage of using NMBA reversal in surgical patients?
   a. Allows prompt extubation at the end of the case  
   b. Shortens time in the operating room  
   c. Causes less predictable onset of effect if patient must have neuromuscular blockade reestablished  
   d. Leads to decreased secretions and tachycardia

8. The patient is unable to hold his head up off the pillow for 5 seconds after surgery. The nurse suspects this is due to what percentage of neuromuscular receptor blockage?
   a. 1%  
   b. 4%  
   c. 20%  
   d. 35%

9. Successful reversal of neuromuscular blockade would be demonstrated by which of the following train-of-4 reactions?
   a. 0 of 4 twitches displayed  
   b. 1 of 4 twitches displayed  
   c. 2 of 4 twitches displayed  
   d. A noticeable fade is present

10. Which of the following is a long-acting NMBA?
    a. Pancuronium  
    b. Atracurium  
    c. Cisatracurium  
    d. Rocuronium

11. Which of the following can increase the duration of neuromuscular blockade?
    a. Increased sodium levels  
    b. Increased potassium levels  
    c. Decreased magnesium levels  
    d. Decreased calcium levels

Program evaluation

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<th>Objective</th>
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<td>Objective 3</td>
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