Ask The Experts: Clinical Case Discussions for Managing Reversal of Neuromuscular Blockade

A Live Webinar

Thursday, April 8, 2021
12:00 – 1:00 pm ET

Home Study Available

May 12, 2021 – May 12, 2022

FACULTY

Rachel C. Wolfe, Pharm.D., M.H.A., BCCCP, *Activity Chair*
Clinical Pharmacy Specialist
Perioperative and Surgical Critical Care
Barnes-Jewish Hospital
St. Louis, Missouri

Glenn S. Murphy, M.D.
Clinical Professor, Department of Anesthesiology
University of Chicago Pritzker School of Medicine
Director of Clinical Research
NorthShore University Health System
Evanston, Illinois

View faculty bios at ashpadvantage.com/nmbreversal

CE PROCESSING

Participants will process CE credit online at http://elearning.ashp.org/my-activities. CE credit will be reported directly to CPE Monitor. Per ACPE, CE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity.

ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

ACPE #: 0204-0000-21-400-L01-P
0204-0000-21-400-LH1-P

1.0 hour, application-based

The American Society of Health System Pharmacists is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The American Society of Health-System Pharmacists designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ASHP FINANCIAL RELATIONSHIP DISCLOSURE STATEMENT

Planners, presenters, reviewers, ASHP staff, and others with an opportunity to control CE content are required to disclose relevant financial relationships with ACCME-defined commercial interests. All actual conflicts of interest have been resolved prior to the continuing education activity taking place. ASHP will disclose financial relationship information prior to the beginning of the activity.

A relevant financial relationship is defined as a financial relationship between an individual (or spouse/partner) in control of content and a commercial interest, in any amount, in the past 12 months, and products and/or services of the commercial interest (with which they have the financial relationship) are related to the continuing education activity.

An ACCME-defined commercial interest is any entity producing, marketing re-selling, or distributing healthcare goods or services consumed by, or used on, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests—unless the provider of clinical service is owned, or controlled by, an ACCME-defined commercial interest.

Provided by ASHP
Supported by an educational grant from Merck

Ask the Experts: Clinical Case Discussions for Managing Reversal of Neuromuscular Blockade

Rachel C. Wolfe, Pharm.D., M.H.A., BCCCP
Perioperative Clinical Pharmacy Specialist, Barnes Jewish Hospital
St. Louis, Missouri

Glenn S. Murphy, M.D.
Anesthesiologist
Advocate Illinois Masonic Medical Center
Chicago, Illinois

Provided by ASHP
Supported by an educational grant from Merck

Relevant Financial Relationship Disclosure

The following persons in control of this activity's content have one or more relevant financial relationships.

Rachel Wolfe, Pharm.D.: Consultant and Speakers Bureau, Merck
Glenn Murphy, M.D.: Speakers Bureau and Advisory Board, Merck

All of the relevant financial relationships for the aforementioned individuals have been mitigated.

All others in control of the content of this activity do not have a relevant financial relationship (RFR) with an ineligible company.

As defined by the Standards of Integrity and Independence definition of ineligible company.

Learning Objectives

- Analyze reversal strategies for neuromuscular blockade in specific high-risk patient populations.
- Develop a neuromuscular blockade reversal strategy based on clinical and neuromuscular assessment of recovery.
- Select the most appropriate reversal agent and dose for the reversal of neuromuscular blockade in collaboration with other clinicians.

Midyear Webinar Highlights

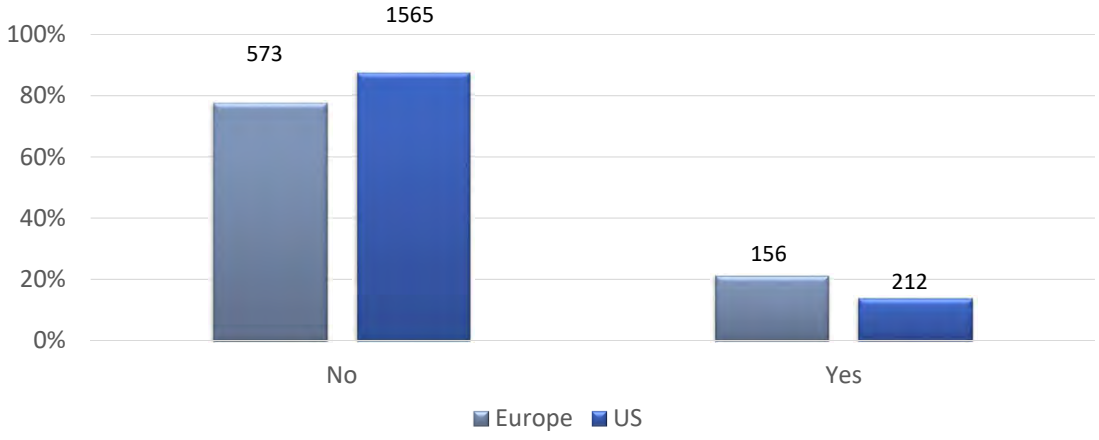
Rachel C. Wolfe, Pharm.D., M.H.A., BCCCP-*Activity Chair*
Clinical Pharmacy Specialist
Perioperative and Surgical Critical Care
Barnes-Jewish Hospital
St. Louis, Missouri

Safe Use of Non-Depolarizing Neuromuscular Blocking Agents (NMBAs)*

Selection	Dose	Monitoring	Reversal Strategy	Postop Outcomes
ROCURONIUM	0.6 – 1.2 MG/KG ROCURONIUM	TRADITIONAL AND MOST COMMON QUALITATIVE	ACETYLCHOLINESTERASE INHIBITOR NEOSTIGMINE	INCIDENCE OF RESIDUAL NEUROMUSCULAR BLOCKADE
VECURONIUM	0.08 – 0.1 MG/KG VECURONIUM			
CISATRACURIUM	0.15 – 0.2 MG/KG CISATRACURIUM	TECHNOLOGICALLY ADVANCED QUANTITATIVE	SELECTIVE RELAXANT BINDING AGENT SUGAMMADEX	PATIENTS AT RISK FOR POSTOPERATIVE PULMONARY COMPLICATION
NEOSTIGMINE	0.3 – 0.7 MG/KG NEOSTIGMINE			
SUGAMMADEX	2-16 MG/KG SUGAMMADEX			

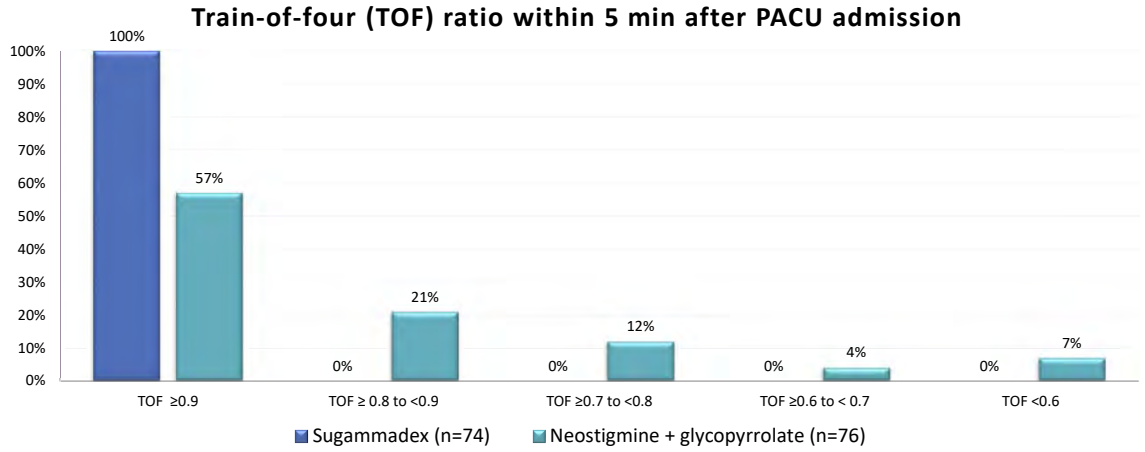
*Most common non-depolarizing NMBAs utilized in the US

Have you ever observed a patient exhibiting clinically significant residual neuromuscular blockade (rNMB) after the administration of an NMBA in the recovery room or postanesthesia care unit (PACU)?



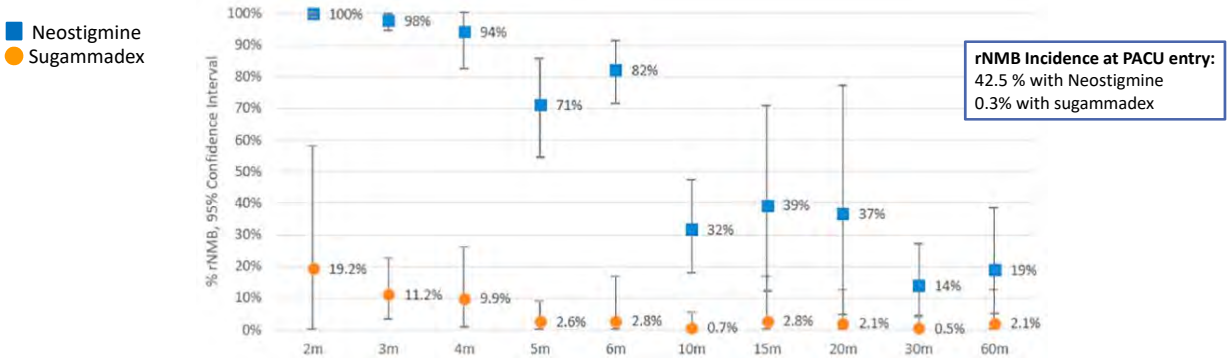
Naguib M et al. *Anesth Analg*. 2010; 111:110-9.

Neuromuscular Recovery Upon Arrival to PACU



Brueckmann B et al. *Br J Anaesth*. 2015; 115:743-51.

Proportion of Patients with rNMB at Timepoints After Reversal of Moderate Block

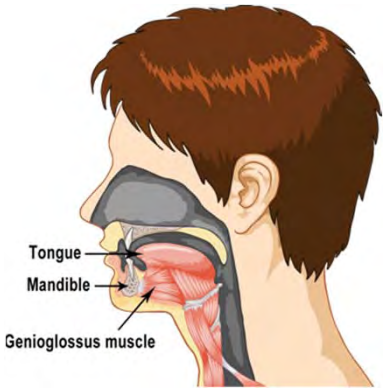


Neostigmine	#RCT	4	4	3	6	3	7	4	3	5	2
	# Patients	182	263	152	340	152	449	173	152	353	87
Sugammadex	# RCTs	3	3	2	4	2	3	2	2	3	2
	# Patients	112	212	93	241	93	241	93	93	241	93

Raval AD et.al. *J Clin Anesth.* 2020;64:109818.

Postoperative Respiratory Effects of NMBAs

- Impairment of the normal phasic activity of genioglossus muscle
  - Impacts pharyngeal airway patency
- Abnormal coordination of pharyngeal and upper esophageal muscles
  - Impacts aspiration risk
- Impairment of the peripheral chemoreflex loop at the carotid bodies
  - Impacts respiratory homeostasis



Miskovic A et al. *Br J Anaesth*. 2017; 118:317-34.
Broens S et al. *Anesthesiology*. 2019; 131:467-76.

Postoperative Pulmonary Complications (PPCs)

- Increased airway resistance
- Upper airway obstruction
- Hypoventilation
- Oxygen desaturation and hypoxia
- Impaired or misdirected swallowing
- Inability to cough
- Aspiration pneumonia
- Pneumonitis
- Pulmonary congestion
- Postoperative pneumonia
- Impaired hypoxic respiratory drive
- Reintubation

Cammu G. *Curr Anesthesiol Rep*. 2020; 27:1-6.

Factors Contributing to PPCs

Risk Factors for Postoperative Pulmonary Complications (PPCs)

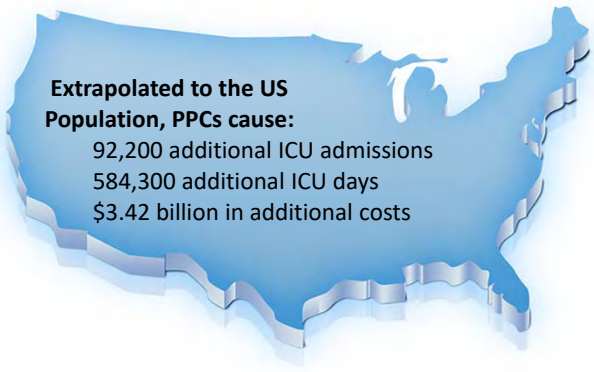
Emergent surgery	Severe respiratory disease (e.g., COPD)
NMBA utilization	Obstructive sleep apnea
Duration of procedure > 2 hours	Body mass index (BMI) > 40 kg/m^2
Intrathoracic or upper abdominal surgery	Chronic renal insufficiency
Preoperative SpO_2 ≤ 94%	Congestive heart failure
ASA class ≥3	History of recent respiratory infection
Age ≥ 60 yr	
Smoking status	
Poor functional health status	

Miskovic A et al. *Br J Anaesth*. 2017; 118:317-34.
Kirmeier E et al. *Lancet Respir Med*. 2019; 7:129-40.
Hristovska AM et al. *Cochrane Database Syst Rev*. 2017; 8:CD012763.

Annual Economic Burden of PPCs

2009 Patient Safety Summit convened to address the substantial clinical and economic costs of PPCs

- Each case of bronchospasm
  - 1 in 14 cases results in ICU admission
  - 1 additional hospital day
  - $1563 added cost per case
- Each case of respiratory failure
  - 1 in 2 cases results in ICU admission
  - 8 additional hospital days
  - $24,000 in added cost per case
- Other respiratory complications
  - 1 in 6 cases results in ICU admission
  - 3 additional hospital days
  - $5771 added cost per case



Shander A et al. *Crit Care Med.* 2011; 39:2163-72.
Thompson DA et al. *Ann Surg*. 2006; 243:547-52.

Management of Neuromuscular Blockade in the OR

Glenn S. Murphy, M.D.
Anesthesiologist
Advocate Illinois Masonic Medical Center
Chicago, Illinois

Case 1

A 2-hour laparoscopic abdominal colectomy was completed in a 78-year-old female. Use of a peripheral nerve stimulator at the adductor pollicis (hand) revealed 2 twitches to train-of-four (TOF) stimulation. Is it appropriate to use neostigmine to reverse neuromuscular blockade in a patient with 2 out of 4 twitches?

The RECITE-US Study

- Prospective observational study of the incidence of PRNB at 10 U.S. hospitals (academic and private practice)
- ASA class I-III patients undergoing abdominal surgery were assessed
- TOF ratios measured immediately before extubation

Results

- 255 patients enrolled
- Incidence of PRNB
  - 64.7% had TOF ratio < 0.9 at extubation
  - 31.0% had TOF ratio < 0.6 at extubation

PRNB-Post-operative residual neuromuscular blockade

Saager L et al. *J Clin Anesth*. 2019; 55:33-41

Tactile Assessment for the Reversibility of Rocuronium-Induced Neuromuscular Blockade with Neostigmine 0.07 mg/kg During Sevoflurane Anesthesia

Sevoflurane Anesthesia				
Groups	I (n=20)	II (n=20)	III (n=20)	IV (n=20)
Neostigmine Administration Trigger	TOF 1/4	TOF 2/4	TOF 3/4	TOF 4/4
Median time to achieve TOF ratio 0.9 (min)	28.6 (8.8-75.8)	22.6 (8.3-57.4)	15.6 (7.3-43.9)	9.7 (5.1-26.4)

Kim KS et al. *Anesth Analg*. 2004; 99:1080-5.

"We recommend reversal at 4 TOF responses with sevoflurane anesthesia for adequate neuromuscular recovery within 15 minutes"

Kim KS et al. *Anesth Analg*. 2004; 99:1080-5.

Efficacy of Tactile-guided Reversal with Neostigmine 0.07 mg/kg from Cisatracurium-induced Neuromuscular Blockade

Cisatracurium-induced Neuromuscular Blockade				
	I (n=16)	II (n=16)	III (n=16)	IV (n=16)
Neostigmine Administration Trigger	TOF 1/4	TOF 2/4	TOF 3/4	TOF 4/4
Median time to achieve TOF ratio 0.9 (min)	22.2 (13.9-44.0)	20.2 (6.5-70.5)	17.1 (8.3-46.2)	16.5 (6.5-143.3)

Kirkegaard H et al. *Anesthesiology.* 2002; 96:45-50.

"To achieve rapid (within 10 min) reversal to a TOF ratio of 0.7 in more than 87% of patients, three or four tactile responses should be present at the time of neostigmine administration. It was not possible within 30 min to achieve a TOF ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration"

Kirkegaard H et al. *Anesthesiology*. 2002; 96:45-50.

Neostigmine Administration After a Spontaneous Recovery to a Train-of-Four Ratio of 0.9 to 1.0

- 120 patients administered 1 X ED_{95} dose of rocuronium and given none thereafter (average dose 25 mg)
- Average duration of the cases was 163 minutes
- Results

  At the conclusion of surgery, 24 patients (21%) had not recovered TOF ratio of at least 0.9

Murphy GS et al. *Anesthesiology*. 2018; 128:27-37.

Case 2

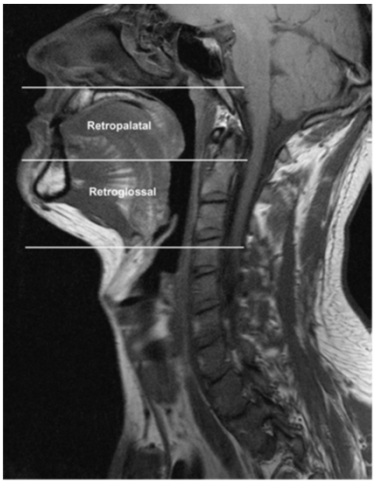
Bariatric surgery was just completed in a 280-kg patient with sleep apnea. Does the presence of morbid obesity in patients like this one have implications for choosing between neostigmine and sugammadex for reversal?

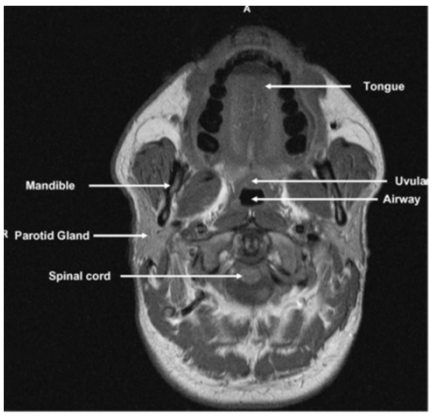
Morbid Obesity-Sleep Apnea: Respiratory Effects

- Pharyngeal muscle dysfunction -airway obstruction
- Higher incidence of reflux-increased risk for aspiration
- Limited ability to take a vital capacity breath-baseline atelectasis and hypoxemia
- Hypoxic ventilatory response impaired
- Increased risk of postoperative pulmonary complications

Thomas PS et al. *Thorax*. 1989; 44:382-6

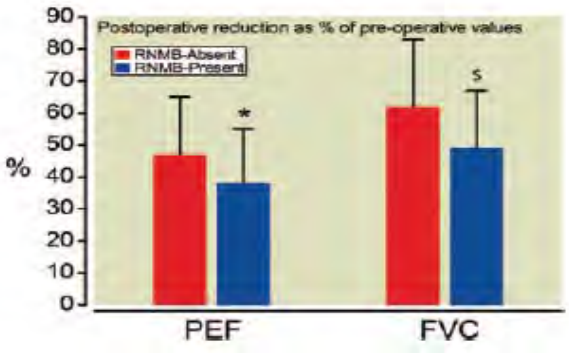
The Predisposition to Inspiratory Upper Airway Collapse during Partial Neuromuscular Blockade





Eikermann M et al. *Am J Respir Crit Care Med*. 2007; 175:9-15.

Residual Neuromuscular Blockade Affects Postoperative Pulmonary Function



Postoperative reductions in PEF and FVC values as the percentage of preoperative values in patients with (RNMB-present) and without (RNMB-absent) RNMB. The postoperative PEF and FVC reductions were greater in RNMB-present patients than RNMB-absent patients.

*P = 0.008, $ P = 0.001. PEF = peak expiratory flow; FVC = forced vital capacity; RNMB = residual neuromuscular blockade.

Kumar GP et al. *Anesthesiology.* 2012; 117:1234-44.

Residual Blockade-Hypoxic Ventilatory Control

- Increase in ventilation during hypoxia mediated primarily by chemoreceptors of the carotid bodies
- In vivo, administration of NMBAs decreases firing frequencies of isolated chemoreceptors in the carotid body (Wyon N et al. *Anesth Analg*. 1996; 82:1252-6)

Eriksson LI. *Anesth Analg*. 1999; 89:243-51.

Postoperative Respiratory Outcomes in Laparoscopic Bariatric Surgery: Comparison of a Prospective Group of Patients Whose Neuromuscular Blockade was Reversed with Sugammadex and a Historical One Reversed With Neostigmine

- Prospective group of 160 patients reversed with sugammadex
- Historical group of 160 patients reversed with neostigmine
- Primary endpoint: pathological changes in chest X-ray or need for postoperative ventilation

Results

- Chest X-ray changes:
  - 11 patients (6.9%) sugammadex group
  - 26 patients (16.3%) neostigmine group
    - OR 0.36, 95% CI: 0.18-0.8
- No significant difference in need for postoperative ventilation

Llaurado S et al. *Rev Esp Anestesiol Reanim*. 2014; 61:565-70.

Sugammadex Allows Fast-Track Bariatric Surgery

- 40 female morbidly obese patients undergoing bariatric surgery reversed from deep blockade with sugammadex or neostigmine
- Time to TOF ratio of $\geq$ 0.9 determined
- Sugammadex time to TOF $\geq$ 0.9: 3.1 ± 1.3 minutes
- Neostigmine time to TOF $\geq$ 0.9: 48.6 ± 18 minutes

Results

- Patients in the sugammadex group had higher SpO2, TOF ratio, ability to swallow, and ability to get into bed independently in the PACU (all $P<0.05$)
- Patients in the sugammadex group discharged earlier from the PACU

Carron M et al. *Obes Surg*. 2013; 23:1558-63.

Case 3

A surgical patient was given 0.6 mg/kg of rocuronium at the time of anesthetic induction. The surgery was completed 3 hours later. The patient was following commands, breathing well, squeezing the clinician's hand, and maintaining a 5-sec head lift. Is reversal of neuromuscular blockade needed in this patient?

Accelerometry of Adductor Pollicis Muscle Predicts Recovery of Respiratory Function from Neuromuscular Blockade

TOF Ratio	Inability to Sustain Head Lift >5 seconds
0.5 ± 0.16	1
0.83 ± 0.06	0
1.02 ± 0.01	0

Eikermann M et al. *Anesthesiology*. 2003; 98:1333-7.

Relationship between Normalized Adductor Pollicis Train-of-four Ratio and Manifestations of Residual Neuromuscular Block

Number of individuals with lost clinical muscle function at baseline and at three levels of NMB (n=12)				
Muscle function	**Baseline Ability**	**Block level 1 rTOF 0.85-0.95**	**Block level 2 rTOF 0.65-0.75**	**Block level 3 rTOF 0.45-0.55**
Tongue protrusion	0	0	0	0
Teeth clenching	0	2	4	8
Swallowing	0	0	0	4
5 second head raise	0	0	0	4
Speaking	0	0	0	0
Eye opening	0	0	0	0
Vision clarity	0	12	12	12
Handgrip strength, kg	37 ± 14 (14-70)	26 ± 7 (10-36)	16 ± 5 (8-23)	8 ± 4 (5-15)
Handgrip strength, % reduction	0	27 ± 15 (0-67)	51 ± 14 (27-82)	75 ± 10 (52-94)

Heier T et al. *Anesthesiology*. 2010; 113:825-33.

Diagnostic Attributes of the Clinical Tests: Sensitivity, Specificity, Positive, and Negative Predictive Values of an Individual Clinical Test for a Train-of-Four <90%				
	Sensitivity	**Specificity**	**Positive predictive value**	**Negative predictive value**
Inability to smile	0.29	0.80	0.47	0.64
Inability to swallow	0.21	0.85	0.47	0.63
Inability to speak	0.29	0.80	0.47	0.64
General weakness	0.35	0.78	0.51	0.66
Inability to lift head for 5 sec	0.19	0.88	0.51	0.64
Inability to lift leg for 5 sec	0.25	0.84	0.50	0.64
Inability to sustain hand grip for 5 sec	0.18	0.89	0.51	0.63
Inability to perform sustained tongue depressor test	0.22	0.88	0.52	0.64

Cammu G et al. *Anesth Analg.* 2006; 102:426-9.

No Reversal and Respiratory Complications

Design

- Propensity matched study at Vanderbilt University

Method

- 1320 surgical cases who received an NMBA and reversal with neostigmine compared with 1320 cases who did not receive reversal

Result

- The incidence of pneumonia in patients receiving an NMBA was 1.79 times that of propensity matched patients who did not receive an NMBA
- The incidence of pneumonia in patients receiving an NMBA without reversal was 2.26 times that of propensity matched cases who received reversal with neostigmine

Bulka C et al. *Anesthesiology*. 2016; 125:647-55.

Intermediate-Acting Nondepolarizing Neuromuscular Blocking Agents and Risk of Postoperative 30-Day Morbidity and Mortality, and Long-term Survival

- Retrospective study of 11,355 non-cardiac patients from 5 Veterans Affairs (VA) hospitals
- 8984 received NMBAs
- 7047 reversed with neostigmine
- Respiratory complications
  - Failure to wean
  - Re-intubation
  - Pneumonia

Comparison of Adverse Outcomes Rates Between Patients Receiving an NNMBD Not Followed by a Reversing Agent and an NNMBD Followed by a Reversing Agent

Analysis Method	OR/HR (95% CI)	*P* Value
Respiratory complications		
Unadjusted	4.20 (3.51-5.03)	**<.0001**
Multivariable adjusted	1.71 (1.24-2.37)	**<.0001**
Propensity Matched	1.75 (1.23-2.50)	**<.001**

Bronsert MR et al. *Anesth Analg.* 2017; 124:1476-83.

Neuromuscular blockade should ALWAYS be reversed unless the use of quantitative monitoring has demonstrated that spontaneous recovery to a TOF ratio of at least 0.9 has occurred

Case 4

An anesthetic was provided to a 78-year-old patient undergoing video-assisted thoracoscopic surgery. Is there clinical data available to use as the basis for deciding whether this patient should be given neostigmine or sugammadex as a reversal agent?

Neuromuscular and Clinical Recovery in Thoracic Surgical Patients Reversed With Neostigmine or Sugammadex

- 200 patients undergoing thoracoscopic surgery were enrolled in this prospective observational study (before/after)
- Neuromuscular blockade was reversed with either neostigmine or sugammadex
- Optimal neuromuscular management practices were followed (no quantitative monitoring)
- Clinical recovery was followed until discharge

Results

- Less optimal operative conditions in the neostigmine group
- Incidence of PRNB: 80% neostigmine vs. 6% sugammadex at extubation
  61% neostigmine vs. 1% sugammadex at PACU admission
- More unpleasant symptoms of muscle weakness in the neostigmine group (median number 4 [1-8] vs. 1 [0-2] in the sugammadex group)

Murphy GS et al. *Anesth Analg*. 2020 (epub ahead of print)

Prospective study of residual neuromuscular blockade and postoperative respiratory complications in patients reversed with neostigmine *versus* sugammadex

- Prospective observational study of 558 patients
- Cisatracurium-no reversal / cisatracurium-neostigmine
  Rocuronium-no reversal / rocuronium-sugammadex (2-4 mg/kg)
- TOF ratios assessed in PACU with an acceleromyography monitor
- Patients examined for major respiratory complications (pneumonia or atelectasis) on chest X-ray until the time of discharge from the hospital

Martinez-Ubieto J et al. *Minerva Anesthesiologica*. 2016; 82:735-42.

Major Respiratory Complications According to NMBA and Reversal Agent Used

Major Complications	Cisatracurium + Neostigmine	Cisatracurium + No Reversal	Rocuronium + No Reversal	Rocuronium + Sugammadex
No	84 (91.3%)	128 (92.8%)	215 (90.3%)	86 (98.9%)
Yes	8 (8.7%)	10 (7.2%)	23 (9.7%)	1 (1.1%)

Martinez-Ubieto J et al. *Minerva Anesthesiologica*. 2016; 82:735-42.

Retrospective Analysis of 30-day Unplanned Readmission Rates after Major Abdominal Surgery with Reversal by Sugammadex or Neostigmine

- Single-center, retrospective, observational study of the effect of neostigmine and sugammadex on 30-day unplanned readmission rates, hospital length of stay (LOS), and hospital costs
- Data for 1479 patients (sugammadex 355, neostigmine 1124) undergoing major abdominal surgery between 2010 and 2017 analyzed
- Propensity score matching and generalized mixed-effects modeling was performed

Results

- In the sugammadex group (compared with the neostigmine group)
  - -Incidence of 30-day unplanned readmission was 34% lower
  - -Hospital LOS was 20% shorter
  - -Hospital charges were 24% lower

    (all $P < 0.05$)

Oh TK et et al. *Br J Anaesth*. 2019; 122:370-8.

Sugammadex *versus* Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER)

- Multicenter (12 hospitals) observational matched cohort study
- Adult patients undergoing elective inpatient non-cardiac surgical procedures (2014-2018) with general anesthesia receiving an NMBA and reversal were included
- The composite primary outcome was major PPC, defined as pneumonia, respiratory failure, or other pulmonary complications

Results

- 22,856 patients receiving sugammadex were matched with 22,856 patients given neostigmine
- In multivariable analysis, sugammadex use was associated with a 30% reduced risk of pulmonary complications, 47% reduced risk of pneumonia, and 55% reduced risk of respiratory failure, compared with neostigmine.

Kheterpal S et al. *Anesthesiology*. 2020; 132:1371-81.

Randomized Controlled Trial of Sugammadex or Neostigmine for Reversal of Neuromuscular Blockade: Incidence of Pulmonary Complications in Older Adults Undergoing Prolonged Surgery

- Open-label, assessor-blinded, randomized controlled trial of 200 patients age ≥ 70 yr undergoing surgery ≥ 3 hr
- At surgical closure, patients were randomized to receive sugammadex 2 mg/kg or neostigmine 0.07 mg/kg for rocuronium reversal. The primary endpoint was incidence of postoperative pulmonary complications

Results

- There was no significant difference between sugammadex and neostigmine in the primary endpoint of PPC (33% vs. 40%, respectively; odds ratio [OR] 0.74)
- In an exploratory analysis, there were fewer 30-day hospital readmissions in the sugammadex group compared with the neostigmine group (5% vs. 15%; OR 0.30, 95% CI 0.08, 0.91; P=0.03)

Togioka MM et al. *Brit J Anaesth*. 2020; 124:553-561.

Utilization Patterns of Perioperative Neuromuscular Blockade Reversal in the United States: A Retrospective Observational Study From the Multicenter Perioperative Outcomes Group

- Retrospective observational study from Multicenter Perioperative Outcomes Group
- Designed to identify patient, procedure, and provider characteristics associated with choice of reversal agent
- Data collected from 24 institutions between 2014-2018
- Examined ASA class I-IV adult patients undergoing non-cardiac surgery

Results

- Data analyzed for 934,798 patients
- Sugammadex used in 40% of cases
- Sugammadex use was associated with TOF count of 0-2 vs. 3-4 before reversal, amount of NMBA used, advanced age, male sex, **thoracic surgery**, congestive heart failure, and ASA class III and IV

Dubovoy TZ et al. *Anesth Analg*. 2020; 131:1510-19.

Special Populations: Renal Failure and Morbid Obesity

Rachel C. Wolfe, PharmD, MHA, BCCCP
Perioperative Clinical Pharmacy Specialist
Barnes-Jewish Hospital
St. Louis, Missouri

Case 5

A 47-year-old male received a total of 70 mg of rocuronium throughout his 4-hour kidney transplant surgery (SCr pre-transplant: 5.8 mg/dL). At the end of the case, the TOF was 2 out of 4. Can sugammadex be given as a reversal agent?

Sugammadex in Severe Renal Failure

- Concerns and Considerations
  - Prolonged clearance times → increased exposure
    - T½ of 2 hours increases to 4, 6, and 19 hours with mild, moderate, and severe renal impairment, respectively
    - 5-17-fold higher overall exposure in patients with severe renal function
  - Stability of the rocuronium-sugammadex complex and potential for recurarization
    - Estimated that for every 25 million complexes formed, only one dissociates
  - Adverse effects
    - Hypersensitivity, residual NMB, recurarization, re-intubation, hypoxemia, postoperative pneumonia
    - Cardiac effects: bradycardia, hypotension, arrhythmias, cardiac arrest
    - Renal function effects

Bridion (sugammadex) Package Insert. Merck & Co., Inc. January 2021.

Sugammadex in ESRD

Design	• Two-center retrospective observational study
Aim	• Review the short-term safety and effectiveness of sugammadex in surgical patients with end-stage renal disease (ESRD)
Population	• Adult surgical patients on preoperative renal replacement therapy • 158 patients (48 renal transplantation, 110 other procedures)
Outcomes	• Incidence of postoperative tracheal reintubation within 48 hours
Results	• No evidence of NMB recurrence in any case • No reintubation due to residual NMB • No documentation of anaphylaxis • 24 (18%) initially reversed with neostigmine 0.7 mg/kg (max 5 mg) required subsequent reversal with sugammadex due to residual neuromuscular blockade

Adams DR et al. *Anaesthesia.* 2020; 75(3):348-52.

Sugammadex in Renal Transplantation

Design
- Single-center, retrospective study

Aim
- Safety and efficacy of sugammadex in the immediate perioperative period and over 6-month follow-up

Population
- 99 consecutive patients who underwent living renal transplantation
- Patient characteristics
  - Median SCr (mg/dL): 5.6 (4.5-7.5)
  - Median BUN (mg/dL): 30 (24.5-34.5)
  - eGFR (mL/min/1.73 m^2): 8 (6-11)
  - Median rocuronium dose (mg): 160 mg (130-185)
  - Median sugammadex dose (mg): 200 mg (200-200)

Results
- No complications related to recurarization noted in first 48-72 hours
  - Airway obstruction, hypoxemia, tracheal reintubation, muscular weakness
- No adverse events observed postop or for the 6-month follow-up period

Ono Y et al. *JA Clin Rep.* 2018; 4(1):56.

Sugammadex Effects on Transplanted Kidney Function

Design
- Retrospective case-control study evaluating effects of sugammadex on graft function

Population
- 66 patients who underwent renal transplantation
- Relevant labs collected at 6-, 12-, 24-, 48-, and 72-hours post-transplant

Rocuronium + Sugammadex (R+S) n=30	Cisatracurium + Neostigmine (C+N) n=36
• Median SCr (mg/dL): 7.95 (5.65-11.25)	• Median SCr (mg/dL): 7.1 (5.4-9.10)
• Median BUN (mg/dL): 26.5 (14-72)	• Median BUN (mg/dL): 60 (42-79)
• Ischemic time (hr): 10 (8-14)	• Ischemic time (hr): 9 (7-14)
• Postop dialysis: 7 patients	• Postop dialysis: 10 patients

Results
- No differences in baseline characteristics
- Recovery of kidney function post-transplantation
  - SCr and BUN at 6, 12, 24 hours were significantly lower in R+S group than in C+N group
- Use of R+S did not affect relevant kidney recovery outcomes in the first week after transplantation

Vargas M et al. *Transplant Proc.* 2020; 10:1-7.

Sugammadex in ESRD

- Not FDA-approved for CrCl < 30 mL/min
- Well designed clinical trials are lacking
- No indication of NMB recurrence due to dissociation of the rocuronium-sugammadex complex
- No signals of increased incidence of ADRs due to prolonged exposure
- No apparent adverse effects on kidney function

Case 6

- A 195-kg (BMI 56.7 kg/m^2, IBW 80 kg, CBW 126 kg) male is undergoing a laparoscopic sleeve gastrectomy. At the end of the case, the TOF is 3/4. If sugammadex is used for reversal, which body weight should be used to calculate the dose?

BMI: body mass index; IBW: ideal body weight; CBW: corrected body weight

Factors Influencing Dosing in Obesity

Increase in adipose tissue mass	Increase in cardiac output
Increase in lean body mass	Changes in regional blood flow
Increase in organ mass	Changes in plasma protein binding
Increase in blood volume	Increase in drug clearance

Morbid Obesity

- Bariatric surgery patients are at high risk of upper airway collapse
- Neuromuscular blockade should be fully reversed before tracheal extubation

Neostigmine in Obesity

- Typical dose: 30, 40, 50 mcg/kg based on total body weight and depth of blockade
  - Competitive mechanism of action
  - Maximum dose of 5 mg
  - Ceiling effect
- Limited data in the obese population
  - Recovery to TOF 0.9 is prolonged in female overweight and obese patients
    - Suzuki et. al.
      - Normal weight group [6.9 (2.0, 3.0–10.7) min]*
      - Overweight groups [14.6 (7.7, 3.3–28.5) min]*
      - Obese [25.9 (6.7, 13.5–41.0) min]*
    - Joshi et. al.
      - Normal weight group (9.18 ± 2.99 min)¥
      - Overweight (12.18 ± 4.29 min)¥
      - Obese patients (13.78 ± 4.30 min)¥

Morbid obesity not included

- Commonly associated with residual NMB in normal weight patients

*[Mean (SD, range)]
¥(mean ± SD)

Suzuki T et.al. *Br J Anaesth.* 2006;97(2):160-163.
Joshi SB et. al. *Indian J Anaesth.* 2015;59(3):165-170.

Sugammadex in Morbid Obesity

- Concerns and considerations
  - Dose-related adverse effects if dosed based on total body weight
    - Hypersensitivity, bradycardia, hypotension, arrhythmias, cardiac arrest
  - Residual NMB incidence if lower than recommended doses are used
    - Increased risk for residual NMB in a patient population at high risk of pulmonary complications
  - Recurarization if lower than recommended doses are used
  - Time needed to achieve complete reversal (TOF ≥ 0.9)
  - Cost of reversal with doses based on total body weight

Sugammadex PK in Morbid Obesity

Design	• Randomized, multicenter, international, double-blinded pharmacokinetic trial
Groups	• Moderate-NMB: Sugammadex 2 mg/kg dosed on total body weight (TBW) (n=38) • Moderate-NMB: Sugammadex 2 mg/kg dosed on IBW (n=38) • Moderate-NMB: Neostigmine 5 mg + Glycopyrrolate 1 mg (n=38) • Deep-NMB: Sugammadex 4 mg/kg dosed on TBW (n=38) • Deep-NMB: Sugammadex 4 mg/kg dosed on IBW (n=36)
Population	• Age >18 yr; ASA class III; BMI ≥ 40 kg/m^2 • Planned surgery requiring NMB with rocuronium or vecuronium
Outcomes	• Area under the concentration-time curve from zero to infinity (AUC_{0-inf}) • AUC from zero to the last quantifiable concentration (AUC_{0-last}) • Maximum plasma concentration (C_{max}), Total clearance (CL) • Volume of distribution during the terminal elimination phase (V_d) • Apparent first-order terminal elimination half-life ($T_{½}$) • PK linearity

Mostoller K et.al. *Clin Transl Sci.* 2021;14:737-44.

Sugammadex PK in Morbid Obesity

- Results
  - Pharmacokinetic linearity and exposure (AUC and C_{max}) increased in a dose-dependent manner in patients with morbid obesity
  - CL, Vd, T½ remained stationary
  - Supports TBW dosing of sugammadex
  - Due to dose linearity, reasonable to extrapolate to other doses
- Important consideration
  - Molar ratios of sugammadex to NMBA and the resultant concentration gradient
    - Pulls the NMBA away from the neuromuscular junction and back into the plasma for encapsulation

Mostoller K et.al. *Clin Transl Sci.* 2021;14:737-44.

Sugammadex Dosing in Morbidly Obese: TBW vs. IBW

Design
- Randomized, multicenter, international, double-blinded efficacy trial

Groups
- Moderate-NMB: Sugammadex 2 mg/kg dosed on TBW (n=38)
- Moderate-NMB: Sugammadex 2 mg/kg dosed on IBW (n=38)
- Moderate-NMB: Neostigmine 5 mg + Glycopyrrolate 1 mg (n=38)
- Deep-NMB: Sugammadex 4 mg/kg dosed on TBW (n=38)
- Deep-NMB: Sugammadex 4 mg/kg dosed on IBW (n=36)

Population
- Age >18 yr; ASA class III; BMI ≥ 40 kg/m^2
- Planned surgery requiring NMB with rocuronium or vecuronium

Outcomes
- Time to TOF ratio ≥ 0.9 for TBW vs. IBW, pooled across depths of blockade and NMBA (primary)
- Pooled proportion of patients with prolonged recovery, defined as ≥ 10 min to TOF ratio ≥ 0.9

Horrow JC et al. *BMC Anesthesiol.* 2021; 21(1):62.

Baseline Demographics and Results

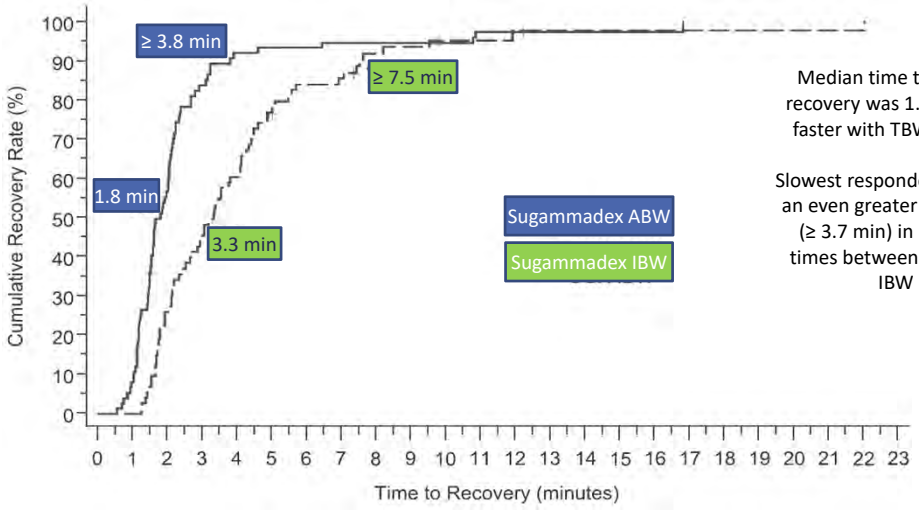
	Sugammadex 2 mg/kg TBW	Sugammadex 2 mg/kg IBW	Sugammadex 4 mg/kg TBW	Sugammadex 4 mg/kg IBW	Neostigmine + Glycopyrrolate
Age (yr)	48 ± 14	48 ± 15	47 ± 11	49 ± 1	48 ± 14
BMI (kg/m^2)	45.8 ± 4.5	47.2 ± 5.7	45.4 ± 5	46.5 ± 5.7	47.3 ± 4.7
TBW (kg)	127 ± 21	135 ± 17	131 ± 20	131 ± 21	135 ± 20
IBW (kg)	63 ± 7	65 ± 7	66 ± 7	63 ± 6	65 ± 8
Time to rTOF ≥ 0.9	1.7 min (95% CI 1.5 to 2.1)	3.4 min (95% CI 2.2 to 4.4)	Not reported	Not reported	34.5 min (95% CI 27.0 to 67.4)

BMI: body mass index; TBW: total body weight; IBW: ideal body weight; CBW: corrected body weight; rTOF: train of four ratio

Horrow JC et al. *BMC Anesthesiol.* 2021; 21(1):62.

Cumulative Percentage with TOF ratio ≥ 0.9

Pooled across depth of blockade

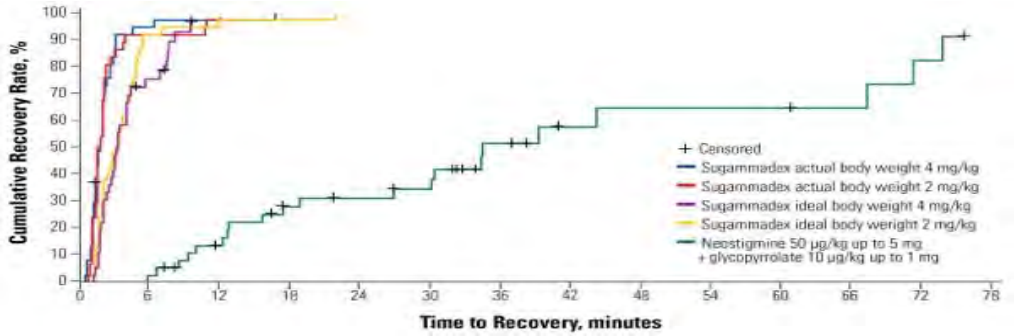


Median time to clinical recovery was 1.5 minutes faster with TBW vs. IBW

Slowest responders showed an even greater difference (≥ 3.7 min) in recovery times between TBW and IBW

Horrow JC et al. *BMC Anesthesiol.* 2021; 21(1):62.

Recovery Based on Actual Body Weight



Using actual body weight with sugammadex speeds reversal in morbidly obese patients. May 14 2020. https://www.anesthesiologynews.com/Multimedia/Article/05-20/Using-Actual-Body-Weight-With-Sugammadex-Speeds-Reversal-in-Morbidly-Obese-Patients/58393

Safety

- Dosing on IBW resulted in no safety advantage
- Delayed recovery times observed could increase incidence of residual NMB after extubation
- Recurarization (TOF <0.9 after TOF ≥ 0.9)
  - 24/186 with TOF recorded > 15 min after reaching TOF 0.9
    - 2/24 experienced recurarization
      - 1 in neostigmine group, 1 in sugammadex 2 mg/kg IBW group
      - No events in sugammadex 4 mg/kg IBW or ABW groups

Horrow JC et al. *BMC Anesthesiol.* 2021; 21(1):62.

Corrected Body Weight

Design	• Randomized, single-center, parallel-group, safety assessor-blinded, non-inferiority study
Groups	• Sugammadex 4 mg/kg dosed on TBW when post-tetanic count (PTC) 1 or 2 (n=47) • Sugammadex 4 mg/kg dosed on CBW when PTC 1 or 2 (n=49) • CBW= (TBW-IBW) 0.4 + IBW • Spontaneous recovery (n=22)
Population	• Age 18-60 yr; ASA class I-III; BMI ≥ 40 kg/m^2 • Laparoscopic bariatric surgery: general anesthesia with deep NMB (TOF 0, PTC ≤ 2)
Outcomes	• Time to TOF ratio 0.9 (primary) • Time to TOF ratio 0.8 (secondary) • Time to TOF ratio 0.7 (secondary)

Li D et al. *J Int Med Res.* 2021; 49(1):1-12.

Results

	CBW	TBW	Control
Age (yr)	31.4 ± 7.3	31 ± 6.8	29.7 ± 6.8
BMI (kg/m^2)	44.8 (41.9-49.1)	44.8 (41.9-49.1)	46.5 (42.9-49.2)
TBW (kg)	132 (121.5-146.5)	128 (118-144)	132.5 (122.8-142)
IBW (kg)	65 (60-77.5)	63 (58-72)	63.5 (59.3-73.3)
Rocuronium dose (mg)	156 (138-180)	163 (134-183)	155.5 (142.3-173.5)
Sugammadex dose (mg)	377 (336.4-406.8)	512 (472-576)*	0
Time to TOF ≥ 0.9	2.24 ± 0.65 min (95% CI, 2.06-2.43)	2.05 ± 0.72 min (95% CI, 1.84-2.26)	

*P< 0.001
BMI: body mass index; TBW: total body weight; IBW: ideal body weight; CBW: corrected body weight; TOF: train of four

Li D et. al. *J Int Med Res.* 2021; 49(1):1-12.

CBW is non-inferior to TBW dosing

- Prespecified non-inferiority margin between CBW and TBW: 0.5 minutes
- Mean differences in the recovery time from sugammadex administration
  - TOF ratios of 0.9 → 0.20 minutes (95% CI, 0.08 to 0.47 minutes)
  - TOF ratios of 0.8 → 0.22 minutes (95% CI, 0.03 to 0.47 minutes)
  - TOF ratios of 0.7 → 0.19 minutes (95% CI, 0.04 to 0.42 minutes)
- Non-inferiority confirmed
  - All three upper limits of the 95% CIs were lower than the prespecified 0.5-minute non-inferiority margin

Li D et. al. *J Int Med Res.* 2021; 49(1):1-12.

Sugammadex in Morbid Obesity

- FDA-approved dosing on TBW
- Clinical trials evaluate a variation of IBW, TBW, CBW in both deep and moderate blockade
- Slower reversal rate and recurarization noted with IBW dosing
- TBW dosing does not result in an increase in adverse effects
- Potential that CBW will be the best of both worlds – but is it enough difference to impact cost?

Consider these practice changes

1. Increase awareness among postanesthesia care unit (PACU) personnel about signs and symptoms of residual NMB.
2. Work with interprofessional team to develop standard handover process in PACU.
3. Review access to reversal agents for moderate/deep block and rapid sequence intubation.
4. Ensure appropriate use of sugammadex 16 mg/kg dose.
5. Initiate a drug-use review as a step in developing guidelines for use of neuromuscular blockade (NMB) reversal agents.
6. Actively assess for risk factors associated with residual NMB in all patients who will be receiving a neuromuscular blocking agent (NMBA).

Take a moment to reflect on changes you would make based on what you learned today.