Promoting Safety in the Perioperative Setting: Best Practices in Neuromuscular Blockade and Reversal

Proceedings of a Midday Symposium and Live Webinar at the 51st ASHP Midyear Clinical Meeting and Exhibition

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www.cemidday.com

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Promoting Safety in the Perioperative Setting:  
Best Practices in Neuromuscular Blockade and Reversal

Agenda

11:30 a.m. – 11:40 a.m.  
Welcome and Introductions  
Deborah Wagner, Pharm.D., FASHP

11:40 a.m. – 12:15 p.m.  
Overview of Current Anesthesia Practice  
Michael R. England, M.D.

12:15 p.m. – 12:40 p.m.  
Postoperative Complications  
Deborah Wagner, Pharm.D., FASHP

12:40 p.m. – 12:50 p.m.  
Value-based Considerations for Monitoring and Therapy  
Deborah Wagner, Pharm.D., FASHP  
Michael R. England, M.D.

12:50 p.m. – 1:00 p.m.  
Faculty Discussion and Audience Questions  
All Faculty

Faculty

Deborah Wagner, Pharm.D., FASHP, Activity Chair  
Clinical Pharmacist U-M Health System  
Clinical Associate Professor of Pharmacy  
College of Pharmacy  
Clinical Associate Professor of Anesthesiology  
Medical School  
University of Michigan  
Ann Arbor, Michigan

Michael R. England, M.D.  
Assistant Professor of Anesthesiology  
Tufts Medical School  
Senior Cardiac Anesthesiologist  
Tufts Medical Center  
Boston, Massachusetts
Disclosure Statement

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Activity Overview

Over the last 25 years, anesthesia has become significantly safer resulting in a dramatic decrease in anesthesia-related mortality rates. Recent literature has focused particularly on the incidence of postoperative residual blockade after administration of neuromuscular blockers with an incidence of over 50% upon arrival in the postanesthesia care unit. This issue, as well as side effects related to current agents, makes it imperative that regardless of whether anesthetic drugs are administered in the hospital setting or in an ambulatory surgery center, physicians and pharmacists should be aware of the agents and their risks. This symposium will focus on current agents and their limitations, and the monitoring and reversal of neuromuscular blockade in the postsurgical setting, including evidence-based recommendations for common complications.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Review commonly administered neuromuscular blocking agents, their purpose, and potential side effects.
- Apply current monitoring strategies for reversal of neuromuscular blockade using patient scenarios.
- Recommend strategies to minimize safety risks associated with residual paralysis.
- Discuss risk factors for postoperative nausea and vomiting and provide evidence-based input on appropriate prevention and treatment.

Additional Educational Opportunities about Anesthesia Coming in 2017

- Ask the Experts webinar – Faculty will explore issues raised by participant questions in today’s symposium (1 hour CPE). Available on-demand May 22, 2017

For more information and to sign up to receive e-mail updates about this topic, visit

www.cemidday.com
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Faculty

Deborah Wagner, Pharm.D., FASHP, Activity Chair
Clinical Pharmacist U-M Health System
Clinical Associate Professor of Pharmacy
College of Pharmacy
Clinical Associate Professor of Anesthesiology
Medical School
University of Michigan
Ann Arbor, Michigan

Deborah Wagner, Pharm.D., is Clinical Pharmacist at U-M Health System in Ann Arbor, Michigan. She is also Clinical Professor for the University of Michigan College of Pharmacy and Clinical Professor in the Department of Anesthesiology in the School of Medicine at the University of Michigan.

After receiving her Doctor of Pharmacy degree from the University of Michigan College of Pharmacy, Dr. Wagner was involved with home-care delivery, nursing home services, cardiology and critical care, operating room pharmacy services, and outpatient pharmacy management.

At the University of Michigan, Dr. Wagner is currently responsible for Operating Room pharmacy practice in the areas of pediatric and obstetric anesthesia and coordination of clinical services provided by three satellite operating room pharmacies. She is also the current pediatric safety coordinator for the health care system and chair of the Pediatric Medication Safety Committee.

Dr. Wagner precepts Pharm.D. students and pharmacy residents, and teaches for the College of Pharmacy, School of Medicine, and Graduate Nurse Practitioner program. She actively participates in the development of clinical research studies within the Department of Anesthesiology. Dr. Wagner provides pain management consultation for the pediatric acute pain service and is a member of the hospitals pain and sedation steering committee. She has developed standardized pain management strategies for intravenous acetaminophen, elastomeric pain pumps, low dose lidocaine and ketamine infusion.

Dr. Wagner is a current member of the Anesthesiology Medication Safety and Quality Assurance committees within the Department of Anesthesiology and is responsible for review of risk management reports for children and women at the University of Michigan Health System. She was the 2015 recipient of the ISMP medication safety “CHEERS” award and was a finalist for the 2011 Award for Excellence in Medication Safety at the University of Michigan Hospitals and Health System for advancements in pain management therapy and safe practice.
Michael R. England, M.D., is Assistant Professor of Anesthesiology at Tufts Medical School in Boston Massachusetts. He is also Senior Cardiac Anesthesiologist at Tufts Medical Center. In addition to teaching medical residents, Dr. England is an active member of the medical school, serving on the teaching faculty and serving for 30 years on the admissions committee.

Dr. England earned his Bachelor of Art degree from Cornell College and his Doctor of Medicine degree from Case Western Reserve School of Medicine. He received his initial training in anesthesia at Massachusetts General Hospital (MGH), completed his fellowship in cardiac anesthesiology at New England Medical Center (NEMC), and completed his Intensive Care Unit (ICU) fellowship at MGH.

Dr. England has served the director of cardiac anesthesia during most of his tenure at NEMC (Tufts Medical Center), a busy advanced heart failure center for the region which has performed a record number of heart transplants.

Dr. England is a member of the American Society of Anesthesiologists, the Society of Critical Care Anesthesiologists, and in 2013 served as President of the Massachusetts Society of Anesthesiologists. He has authored numerous peer-reviewed papers and book chapters as well as presented nationally and internationally in cardiology and anesthesia.
CE IN THE MIDDAY

Promoting Safety in the Perioperative Setting: Best Practices in Neuromuscular Blockade and Reversal

Deborah Wagner, Pharm.D., FASHP, Activity Chair
U-M Health System, University of Michigan
Ann Arbor, Michigan

Michael R. England, M.D.
Tufts Medical School, Tufts Medical Center
Boston, Massachusetts

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Learning Objectives

• Review commonly administered neuromuscular blocking (NMB) agents, their purpose, and potential side effects.
• Apply current monitoring strategies for reversal of neuromuscular blockade using patient scenarios.
• Recommend strategies to minimize safety risks associated with residual paralysis.
• Discuss risk factors for postoperative nausea and vomiting (PONV) and provide evidence-based input on appropriate prevention and treatment.
Michael R. England, M.D.

Overview of Current Anesthesia Practice
– Involving the use of paralytic agents
– Focus on moderate vs. deep blockade
– Current monitoring tools and practice patterns
– Including the need for Rapid Sequence Induction (RSI)

Then describe the ways, whys, and hows it may be all improved

Are you involved in operating room (OR) medications?

A. Yes
B. No

In current clinical practice, how often is the train-of-four (TOF) monitor used routinely?

A. 5%
B. 10%
C. 50%
D. 100%
When is a patient considered “fully reversed” after use of a NMB agent?

A. When they can squeeze your hand
B. When you can feel four twitches on the TOF monitor
C. When the TOF ratio is >0.9%

What percentage of patients are inadequately reversed upon entry to the post-anesthesia care unit (PACU) after getting NMB agents?

A. 0%
B. 5%
C. 30-40%
D. >50%

Succinylcholine (SDC) is the “safest” agent for a rapid sequence induction (RSI) for a “full stomach”?
Rather than 1.2 mg/kg rocuronium

A. Yes
B. No
What is “anesthesia”?

Triad of Anaesthesia

- Triad of anaesthesia
- Amnesia
- Analgesia
- Muscle relaxation

From The New Yorker 1/14/08
What do we use to produce “anesthesia”?

- Amnesia
  - Sedatives/Hypnotics
    - Midazolam, propofol, inhalational agents
- Analgesia
  - Narcotics or “non-narcotics”
- Neuromuscular blocking (NMB) agents
  - Depolarizing – Succinylcholine (SDC)
    - Two acetylcholine (ACH) molecules
  - Non-depolarizing agents – large steroid moieties
    - Rocuronium, vecuronium
  - Non-depolarizing agents – benzylisoquinolines
    - Atracurium/cisatracurium, mivacurium (eliminated by Hoffman elimination)

Muscle Relaxants
A major part of our anesthesia quiver

- Either depolarizing or non-depolarizing

Rocuronium
a Quaternary Aminosteroid

- Vecuronium analog
- Fast onset – intermediate acting to compete with ACH
- ED90 of 0.3 mg/kg
- ED90 is the dose required to produce 90% depression of the twitch response
Monitoring the Neuromuscular Junction (NMJ)

Train-of Four (TOF)

Only used by 10% of caregivers!

NMJ Receptor Blockade

Neuromuscular Monitoring

- Qualitative
  - Peripheral nerve stimulator (PNS)
  - Train-of-four (TOF) count
  - Reappearance of T2
  - TOF fade
  - Post-tetanic count (PTC)

- Quantitative
  - TOF-Watch®
  - TOF ratio
  - TOF ratio 0:1.0
  - Residual block: TOF ratio <0.9
  - T1 (first twitch) ratio

NMJ=neuromuscular blocking agent
How do we “reverse” the effects of neuromuscular blocking agents?

• If we are using a depolarizing agent
  – Depends on enzymatic elimination (starting at 9 minutes)
  • Or tincture of time if there is an enzyme deficiency
• If we are using a non-depolarizing agent
  – We have to wait until there is evidence of two twitches if we are using a TOF monitor (or an accelerometer)
    • Tactile quantification is lost at TOF >0.4%
    • Accelerometers will display the ratio of twitch heights
• Then we must administer an acetylcholinesterase inhibitor and an agent to minimize the side effects of these agents
  – Thereby raising the level of ACh to compete with the NMB
• What is the optimal dose of inhibitor (neostigmine) 50 μg/kg?
Neostigmine

Brought to you by only one maker!
Now we “gotch ya”
cost?
Should this continue to be the standard of care?

• Are we really adequately monitoring the pharmacodynamics of our NMB agents?
  – Using the TOF correctly?
  – Are we keeping the patients too paralyzed in fear of appearing to let them move (signs of life)
    • Is this really a sign of a bad anesthetic?
  – What happens if surgery is stopped suddenly?
    • Can we adequately/predictably reverse our paralysis?
  – What if we can’t intubate/ventilate after RSI?

Enter Sugammadex

- Rigid ring shaped sugars
- Outside is hydrophilic water soluble
- The hole in the middle of the ring is hydrophobic that permits lipophilic moieties to enter

Sugammadex

• It was developed to selectively bind rocuronium (fast, short acting, non-depolarizing steroid NMB agent)
  – It binds to vecuronium with much lower affinity
• It has no affinity for other NMB agents
  – SDC, mivacurium, atracurium, or cisatracurium
• First human studies in 2005
• Has been given to 6000 patients in trials
Sugammadex

- European Union approval in 2008
- FDA new drug application (NDA) in 2007
  - Concerns centered around safety
    - Re-exposure (hypersensitivity, anaphylaxis)
    - Bleeding
    - Cardiac arrhythmias, prolonged QT interval
- In 2013, bleeding and cardiac issues resolved
- In 2014, reports demonstrated 1 patient met the anaphylaxis criteria after 16 mg/kg
  - Mechanism unclear – no tryptase or IgE, IgG
- FDA approval December 2015


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Sugammadex for Reversal of Neuromuscular Blockade

- Can reverse neuromuscular blockade
  - Moderate block 2 mg/kg (one or two twitches)
    - Mean time to recovery 1.5 minutes — TOF 0.9
    - 19 minutes for neostigmine
  - Deep blockade – 4 mg/kg (PTC of 1-2) in 3 minutes
    - Neostigmine is not able to do this
- Can reverse rocuronium dose 1.2 mg/kg
  - 16 mg/kg faster than spontaneous recovery from SDC


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Recovery Times

**Sugammadex vs. Neostigmine**

Graph showing recovery times for sugammadex and neostigmine.

Patient Case

- 25 year-old male scheduled for laparoscopic appendectomy
- Past Medical History (PMH) not an issue
- Body Mass Index (BMI) 45 kg/m²
- Mallampatti 3 (uvula not well visualized)

Case Raises Issues

- The patient needs their airway secured as quickly as possible to minimize aspiration risk
- What is the best agent to accomplish this?
  - For many succinylcholine, but there are issues
    - Myalgia, hyperkalemia
  - Now rocuronium 1.2 mg/kg provides intubating conditions as fast as succinylcholine
- What to do if we can’t intubate/ventilate?
  - Now which is better?

Time for a Decision
Which drug would you suggest?

How many people would reach for?
A. Succinylcholine
B. Rocuronium (1.2 mg/kg)
### Time to Recovery for First Twitch 10% of Baseline

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Number of patients</th>
<th>Mean time in minutes (SD)</th>
<th>Median time in minutes (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium 1.2 mg/kg and sugammadex 16 mg/kg</td>
<td>55</td>
<td>4.4 (0.7)</td>
<td>4.2 (3.5-7.7)</td>
</tr>
<tr>
<td>Succinylcholine 1 mg/kg</td>
<td>55</td>
<td>7.1 (1.6)</td>
<td>7.1 (3.8-10.5)</td>
</tr>
</tbody>
</table>


### Advantages of Sugammadex vs. Neostigmine/Glycopyrrolate

- It will permit flexible administration of NMB agent
  - Maintaining deep blockade until end of surgery
    - Reverse quickly (with one PTC) 4 mg/kg
    - Reliably (not possible with neostigmine)
  - Risk of postoperative residual neuromuscular blockade (RNMB) in PACU using sugammadex
    - Has been shown to be reduced
      - From 43% to 0%


### Adverse Reactions to Sugammadex

<table>
<thead>
<tr>
<th>Body system</th>
<th>2 mg/kg (n=495)</th>
<th>4 mg/kg (n=1921)</th>
<th>16 mg/kg (n=98)</th>
<th>Placebo (n=544)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision site pain</td>
<td>8%</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Procedural complication</td>
<td>1%</td>
<td>1%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>Airway issues</td>
<td>1%</td>
<td>1%</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Anesthesia complications</td>
<td>1%</td>
<td>1%</td>
<td>9%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>RNMB (PACU)</td>
<td>0%</td>
<td>&lt;1%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>


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### Adverse Reactions to Sugammadex

<table>
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<th>4 mg/kg</th>
<th>16 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>26%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>12%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1%</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2%</td>
<td>&lt;2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Pain</td>
<td>48%</td>
<td>52%</td>
<td>36%</td>
<td>38%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### Concerns with Sugammadex

- **Is incompatible with**
  - Verapamil
  - Ondansetron
  - Ranitidine
- **Most common (dose-related) hypersensitivity reactions**
  - Nausea
  - Pruritus
  - Urticaria

### Pharmacokinetics of Sugammadex

- **No metabolism**
- **Renal clearance = glomerular filtration rate (GFR)(88 mL/min)**
- **Plasma half-life = 2 hours (>90% gone in 24 hr)**
- **Linear pharmacokinetics (PK)(dose range 0.1-96 mg/kg)**
- **Low potential for drug-drug interactions**
- **Similar PK for surgical/non-surgical patients**
- **No dose adjustment for age, gender, weight**
- **Not recommended for patients in renal failure**
Re-dosing of Sugammadex

Normal GFR

<table>
<thead>
<tr>
<th>Minimal Waiting time</th>
<th>NMB agent to be administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Five minutes</td>
<td>1.2 mg/kg rocuronium</td>
</tr>
<tr>
<td>Four hours</td>
<td>0.6 mg/kg rocuronium</td>
</tr>
<tr>
<td></td>
<td>0.1 mg/kg vecuronium</td>
</tr>
</tbody>
</table>

- When 1.2 mg/kg of rocuronium is given within 30 minutes sugammadex
- Onset of NMB may be delayed up to 4 minutes and duration shortened by 15 minutes
- If 16 mg/kg used, wait 24 hours!


Progesterone Levels after Sugammadex

- In vitro binding studies indicate that sugammadex may bind to progesterone
- It may be equivalent to missing a dose of birth control pills (BCP)
- It is suggested that if a BCP is taken on the day sugammadex is given, a back-up method of birth control be used for up to 7 days
- In the case of non-oral hormonal contraceptives, use additional methods to prevent pregnancy for 7 days!


To Prevent Unwanted Pregnancy

You have been given a drug called sugammadex.
Sugammadex is an anesthesia drug that helps restore muscle strength after surgery. Sugammadex can interfere with progestin-based birth control. This includes many birth control pills, injectable hormonal birth control such as Depo-Provera injection and hormonal intra-uterine systems, implants, or a vaginal ring. This effect is similar to missing one oral contraceptive pill. To prevent unintended pregnancy, you should use a backup method of birth control for one week (7 days).

Tufts Medical Center Patient Information.
Answers to Questions

- In current practice only 10% of caregivers use the TOF
- A patient is fully “reversed” when TOF ratio is >0.9%
- 30-40% patients entering the PACU have evidence of residual blockade
- Probably 1.2 mg/kg is “SAFER” because it is possible to reverse using 16 mg/kg sugammadex
  - No reversal possible using SDC 1 mg/kg – must wait 9 minutes for one twitch to appear!

In Conclusion

- Sugammadex
  - May not be more expensive than the combination of
    - Neostigmine/glycopyrrolate
  - Does not share the side effect profile of neostigmine/glycopyrrolate
    - Can reliably reverse a moderate and deep blockade with less side effects and residual paralysis
  - This will alter NMB agent administration!
- Use carefully in situations where GFR is low
  - Dose for re-intubation and timing/type of NMB agent
- May affect progesterone levels
- In general – is more appropriate medical therapy!

Postoperative Complications

Deborah Wagner, Pharm.D., FASHP
Why Side Effects Matter

- Nausea and vomiting occurs 20-30% and is the second most common complaint postoperatively.
- High-risk groups as high as 80%.
- Guess what’s the first complaint...
- Although postoperative nausea and vomiting (PONV) implies the procedure itself is responsible, the biggest contributors are:
  - Anesthetic agents (baseline risks) and Patient Risk Factors.
- Incidence of post discharge nausea and vomiting.

The Gastrointestinal Tract

- Enterochromaffin (EC) cells
- Widely distributed throughout gastrointestinal (GI) tract within the epithelium.
- Synthesizes 90% of serotonin (5-HT) in the presence of tryptophan hydroxylase (TPH-1) from chemical and mechanical stimuli.
- Activates afferent vagal nerve endings in gut wall and stimulates the dorsal brainstem via the nucleus tractus solitarius.
- 5-HT3 antagonists (serotonin receptor).

Chemoreceptor Trigger Zone (CTZ)

- Located in the bottom of the fourth ventricle in the area postrema.
- Lacks blood-brain barrier.
- Permeable endothelium detects emetogenic substances.
- Sends triggers to vomiting center with stimulation of dopaminergic (D2) and serotonergic (5-HT3) receptors.
Why Receptor Activity is Important

Willingness to Pay

How much are patients willing to pay to avoid PONV?

Factors

- Income
- Previous PONV
- PONV in PACU
- Importance of avoiding PONV

Parents of patients

- 150 parents surveyed
- Vomiting ranked as highest undesirable effect
- Parents willing to pay $28.89 for prevention

PONV Risk Score in Adults

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>1</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>1</td>
</tr>
<tr>
<td>History of PONV</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative Opioids</td>
<td>1</td>
</tr>
</tbody>
</table>

Sum = 0 ... 4


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Risk Factors for Post Discharge Nausea and Vomiting (PDNV)

<table>
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<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Gender</td>
<td>1</td>
</tr>
<tr>
<td>History of PONV</td>
<td>1</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
<td>1</td>
</tr>
<tr>
<td>Use of Opioids in PACU</td>
<td>1</td>
</tr>
<tr>
<td>Nausea in PACU</td>
<td>1</td>
</tr>
<tr>
<td>Sum</td>
<td>0-5</td>
</tr>
<tr>
<td>Risk increases to 20, 30, 50, 60, and 80% for each additional risk factor</td>
<td></td>
</tr>
</tbody>
</table>


Neuromuscular Blocking Agent Antagonists

  - Level of evidence 2A
- PONV is twice as common after use of glycopyrrolate
- Muscarinic effects on the GI tract
- Clinical Trials prior to 1998
  - Relevant dose-related emetogenic effect
- Clinical Trials post 1998
  - No difference or higher incidence with higher doses


Postoperative Outcomes with Residual Neuromuscular Blockade

- Retrospective analysis of 1444 patients receiving a non-depolarizing NMB
  - 722 sugammadex, 212 neostigmine, 510 no reversal
- Endpoints of unwanted events in the PACU
- Doses
  - Sugammadex 2.7 mg/kg (1.1-7.4)
  - Neostigmine 2.4 mg (0.8-3.8 mg)
- NMB – 97.5% rocuronium
- Incidence of PONV 21.5% (neostigmine) vs. 13.6% (sugammadex), p<0.05

### University of Michigan PONV Adult Algorithms

#### Table 1: Prophylaxis for PONV in the ADULT Patient

<table>
<thead>
<tr>
<th>Risk Factors (1 point each):</th>
<th>Risk Score</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>1 Low Risk</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 Non-smoker</td>
<td></td>
</tr>
<tr>
<td>Status of PONV in Family</td>
<td>3 High Risk</td>
<td></td>
</tr>
<tr>
<td>Use of preoperative narcotics</td>
<td>4 Higher Risk</td>
<td></td>
</tr>
</tbody>
</table>

**DRUGS**
- Ondansetron
- Prochlorperazine
- Metoclopramide
- Dexamethasone
- Promethazine
- Dimenhydrinate
- Scopolamine

### Table 2: Rescue of Prophylaxis Failure & Post-discharge Care for the ADULT Patient

- Rescue treatment: consider oral administration, nothing used pending

**Considerations:**
- **Ondansetron:** Combined with haloperidol, does not increase the risk of QTC prolongation.
- **Granisetron:** in patients who fail ondansetron due to possible alternate metabolism
- **Consider alternative modalities** in patients at high risk of PONV or when concerned about side effects or allergy with standard medications.
  - Seaband P6 acu-stimulation: applied at induction
  - Ginger gum: provide education for patient to chew 500-1000 mg in a semi-recumbent position due to the risk of aspiration
- **For Pregnant or Lactating Women:** Drugs of choice are dipherhydratrine and Ondansetron – scopolamine use is not recommended during pregnancy.
Postoperative Nausea & Vomiting (PONV)

Case Presentation
• 65-year-old female with BMI 28 kg/m², HTN, COPD (smoker), OSA, history of PONV
• Robotic laparoscopic appendectomy
• Induced with fentanyl 150 mcg, propofol 200 mg, and rocuronium 70 mg IV
• Given 2 mg hydromorphone, 12.5 mg diphenhydramine, and 4 mg dexamethasone
• Plan for postoperative opioids on discharge

HTN=hypertension, COPD=chronic obstructive pulmonary disease, OSA=obstructive sleep apnea

What were the patient’s risk factors for PONV with reversal?

A. Female gender
B. History of PONV
C. Smoking history
D. Postop opioids
E. Young age

Which of the following pharmacological prophylaxis measures should not have been considered?

A. Ondansetron
B. Haloperidol
C. Aprepitant
D. Propofol
Other Issues to Consider

Current Reversal Agents
(edrophonium, neostigmine, pyridostigmine)

- Inhibit acetylcholine breakdown to increase concentration of acetylcholine at neuromuscular junction
- Exert potent parasympathomimetic activity (↓ heart rate, ↑ peristalsis, ↑ secretions, bronchospasm)
- Onset of action: edrophonium 1-2 min; neostigmine 7-11 min; pyridostigmine 15-20 min
- Rapidity of reversal: edrophonium > neostigmine > pyridostigmine.
- Use of glycopyrrolate and atropine to block muscarinic effect/cardiovascular effects

Risks Associated with Reversal Omission

- Number Needed to Harm = 30
- Increased risk of pulmonary aspiration
- Reduction of hypoxic ventilator response
- Patient discomfort
- Drug interactions at the neuromuscular junction
NMB Agent Association with Postoperative Pneumonia

<table>
<thead>
<tr>
<th>NMB Analysis</th>
<th>Received an NMB (n = 1,485)</th>
<th>Did Not Receive an NMB (n = 1,485)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed postoperative pneumonia</td>
<td>26 surgical cases</td>
<td>27 surgical cases</td>
</tr>
<tr>
<td>Prevalence risk rate</td>
<td>9.62</td>
<td>5.22</td>
</tr>
<tr>
<td>Incidence per 10,000 person-days at risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMB Hospital Analysis</td>
<td>No Reversal (n = 1,023)</td>
<td>Reversal with NMB (n = 1,192)</td>
</tr>
<tr>
<td>Developed postoperative pneumonia</td>
<td>149 surgical cases</td>
<td>79 surgical cases</td>
</tr>
<tr>
<td>Prevalence risk rate</td>
<td>25.30</td>
<td>17.19</td>
</tr>
<tr>
<td>Incidence per 10,000 person-days at risk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| NMB = nondepleting neuromuscular blocking agent.


Effect of ASA Physical Status Score and Age on Pulmonary Outcomes

ASA=American Society of Anesthesiologists

Accidental Awareness Distribution by Phases of Care

Results of the 5th National Audit Project (NAPS)


The RECITE Study: The Incidence of Residual Neuromuscular Blockade


Recovery Status of Patients on Floor Arrival

Postoperative Residual Neuromuscular Blockade

Case Presentation
- 69 year-old male, ASA physical status score 3, height 70 inches, BMI >35 kg/m², allergies to diphenhydramine and tramadol
- General anesthesia (GA) planned for exploratory laparotomy with hernia repair and possible bowel resection
- Induction with 100 mg of succinylcholine, 1 mg midazolam, and 200 mcg fentanyl at 9:15 a.m.
- Inhaled anesthetic, isoflurane, discontinued at 11:45 a.m.
- Intraoperatively received 12 mg morphine, ondansetron 4 mg, esmolol for blood pressure control, and 20 mg vecuronium

Postoperative Residual Neuromuscular Blockade continued
- Twitch monitoring
  - 11 a.m. 1/4
  - 11:15 a.m. 1/4
  - 11:30 a.m. 4/4
  - 11:45 a.m. 1/4
  - 12 p.m. 1/4
- Reversal agents administered
  - 12:14 p.m. 5 mg neostigmine and 0.8 mg glycopyrrolate
- Reversal complete at 12:51 p.m. (4/4 twitches) but significant respiratory support required with possible pulmonary edema
- Discharge from PACU at 16:15 p.m.

Despite full reversal with current methods for neuromuscular blockade reversal and a train of four >0.9 postoperative residual block may still occur.
A. True
B. False
Risk factors in the patient included which of the following?

A. ASA status
B. BMI
C. Use of neuromuscular blockers
D. Use of inhaled anesthetics

Value-based Considerations for Monitoring and Therapy
Deborah Wagner, Pharm.D., FASHP

Roadblocks, Barriers, and Cost...
Finding the Way
Building a logical course
Sugammadex Cliffs Notes

• What does the evidence tell us about reduction in postoperative complications?
• What patient populations will benefit?
• What is your current method of monitoring for neuromuscular blockade?
• What percentage of your patients are routinely reversed with neostigmine?
• What is your primary intermediate-acting neuromuscular blocker?
• What are the implications of cost effectiveness data for strategies to reduce postoperative complications?

Cost of Adverse Postop Respiratory Events

• $62,704 per adverse respiratory event
  — Cost data derived from the hospital's internal cost-accounting database (TSI)

• $60,933 per respiratory complication
  — Cost data from University of Pennsylvania

Cost of Adverse Postop Respiratory Events

• Charges $97,200 (no reintubation) vs. $223,600 (reintubation); costs $24,700 (no reintubation) vs. $62,300 (reintubation)
  — Compares charges to costs specifically for reintubations; focus on ICU, but include a fair chunk of postop reintubations
• ICU day 1 mechanical ventilation $10,794; no mechanical ventilation $6,667
Can sugammadex reduce the incidence of respiratory complications?

- 27.9% of 558 patients presented with postoperative residual curarization (PORC). The incidence was:
  - cisatracurium 34%
  - cisatracurium-neostigmine 28.6%
  - rocuronium 34%
  - rocuronium-sugammadex 1.15%

- The global incidence of minor critical respiratory events (CREs) was 14.5%. The incidence was:
  - cisatracurium 27.5%
  - cisatracurium-neostigmine 17.4%
  - rocuronium 10.5%
  - rocuronium-sugammadex 2.3%

- The global incidence of major CREs was 7.5%, and was significantly higher in patients with TOFr <0.9 upon admission to the PACU.
Cost Effectiveness: Productivity Loss with Sugammadex vs. Neostigmine for Reversal of Rocuronium-Induced NMB

Questions to Consider...

• Can you identify groups of patients at higher risk for residual blockade so as to restrict sugammadex usage?
  – No, no statistically significant differences observed in the incidence of residual NMB according to gender, age, body mass index, ASA physical status, type of surgery, or comorbidities (all p > 0.13)

• If restricted to patients who have residual neuromuscular blockade following reversal of neostigmine, how many would receive sugammadex?
  – Close to half (56.5%) at PACU arrival
  – Would result in an additional expenditure of $414,000/yr + $684,000 for neostigmine
  – Additionally would require quantitative monitoring purchase

One Year Trend in Neostigmine Use at University of Michigan Health System (UMHS) 3/1/15 - 2/29/16

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Cases Using Neostigmine</th>
<th>Total Number of Cases</th>
<th>Rate of Cases w/ Neostigmine usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC</td>
<td>2310</td>
<td>7398</td>
<td>31.2%</td>
</tr>
<tr>
<td>EAA</td>
<td>1691</td>
<td>6871</td>
<td>24.6%</td>
</tr>
<tr>
<td>KEC</td>
<td>351</td>
<td>6049</td>
<td>5.8%</td>
</tr>
<tr>
<td>LD</td>
<td>44</td>
<td>2065</td>
<td>2.1%</td>
</tr>
<tr>
<td>LSC</td>
<td>112</td>
<td>3706</td>
<td>3.0%</td>
</tr>
<tr>
<td>MOTT</td>
<td>3977</td>
<td>17880</td>
<td>22.2%</td>
</tr>
<tr>
<td>UH</td>
<td>13289</td>
<td>30197</td>
<td>44.0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>21,774</strong></td>
<td><strong>74,166</strong></td>
<td><strong>29.4%</strong></td>
</tr>
</tbody>
</table>

Actual Reintubations = 149 (0.2%) → 66 unplanned ICU Admissions
Estimated PACU Mechanical Ventilation = 1,028 (1.4%)
CVC=cardiovascular center, EAA=East Ann Arbor, KEC=Kellogg eye center, LD=labor and delivery, LSC=Livonia center for specialty care, MOTT=Mott children’s hospital, UH=University hospital

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Trend in Neostigmine Use and TOF Documentation at UMHS from 2004-2014

<table>
<thead>
<tr>
<th>Patient/Case Characteristics</th>
<th>Did Not Receive Neostigmine</th>
<th>Received Neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N=135,633</td>
<td>N=18,510 [13.6%]</td>
<td>N=117,123 [86.4%]</td>
</tr>
<tr>
<td>Last Recorded TOF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/4</td>
<td>347 (1.9)</td>
<td>3,557 (2.1)</td>
</tr>
<tr>
<td>1/4</td>
<td>478 (3.6)</td>
<td>6,987 (6.0)</td>
</tr>
<tr>
<td>2/4</td>
<td>518 (2.8)</td>
<td>7,751 (6.6)</td>
</tr>
<tr>
<td>3/4</td>
<td>425 (2.3)</td>
<td>7,170 (6.1)</td>
</tr>
<tr>
<td>4/4</td>
<td>4,187 (22.6)</td>
<td>82,457 (70.4)</td>
</tr>
<tr>
<td>Undocumented</td>
<td>12,563 (87.9)</td>
<td>9,201 (7.9)</td>
</tr>
</tbody>
</table>

Sugammadex Economic Evaluation UMHS

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex 2 mL (100 mg/mL) Single-dose vial</th>
<th>Neostigmine* 10 mL (1 mg/mL) Single-dose use</th>
<th>Glycopyrrolate 1 mL (0.2 mg/mL) Single-dose vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per vial</td>
<td>$90</td>
<td>$64</td>
<td>$8</td>
</tr>
<tr>
<td>Cost per dose (based on weight 70 kg)</td>
<td>$164</td>
<td>$64</td>
<td>$24</td>
</tr>
</tbody>
</table>

Cost based on UMHS purchase price
*Average dose 3.1 mg according to billing data 1Q2016

Sugammadex Economic Evaluation at UMHS

Annual number of cases: 18,000
80% of cases; n=14,400
20% of cases; n=3600

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex Single-dose vial</th>
<th>Neostigmine 10 mL Single-dose use</th>
<th>Glycopyrrolate Single-dose vial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$1,296,000 (2mg/kg)</td>
<td>$1,152,000</td>
<td>$432,000</td>
</tr>
<tr>
<td></td>
<td>+ $590,400 (4 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$1,886,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$302,400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Formulary Considerations

• High-risk patients (e.g., morbid obesity, significant respiratory disease or reduced respiratory reserve, sleep apnea, significant coronary disease, history of arrhythmias, major abdominal/chest surgery or history of PONV)
  – TOF = 4 at a dose of 2 mg/kg
• Patients with TOF count ≤3 to eliminate residual paralysis with dose adjustments based on TOF counts
  – 2 mg/kg for TOF count of 2 or 3 for moderate block
  – 4 mg/kg for TOF count of 1 or 0 with a post-tetanic count (PTC) ≥1 for deep neuromuscular block

Formulary Considerations at UMHS (cont.)

• Anesthesia or Emergency Department attending physicians for the emergent reversal of RSI profound neuromuscular blockade with rocuronium (1.2 mg/kg) approximately 3 minutes after administration when unable to intubate or ventilate patient
  – Dose 16 mg/kg
• Drug interactions with oral contraceptives managed by automated page to provider prior to surgery for patients identified in preop assessment as being on oral contraceptives. Documentation in the medical record that patient was informed to use alternative contraceptive methods for at least 7 days.
Creating an Medication Order in Computerized Pharmacy Order Entry (CPOE)

Take Home Thoughts

• Use shorter-acting neuromuscular blocking agents
• Routine reversal of neuromuscular blockade
• Use of neuromuscular monitoring either quantitative or qualitative
• Early reversal of neuromuscular blockade
• Minimize reversal side effects
• Utilize new therapies

Which of these changes in your practice are you likely to make after today’s presentation?

• Educate staff on common issues with associated with anesthesia.
• Investigate incidence of residual paralysis, related patient events and neuromuscular monitoring plans used at their institution.
• Educate staff on current and future strategies for neuromuscular blockade reversal.
• Incorporate evidence-based guidelines for postoperative nausea and vomiting in their institution’s order set.
• Evaluate cost effectiveness of implementation of new strategies for neuromuscular blockade reversal.
# University of Michigan PONV Adult Algorithms

## Table 1: Prophylaxis for PONV in the ADULT Patient

**Risk Factors (1 point each):**
- Female
- Non-smoker
- History of PONV or Motion Sickness
- Use of postoperative opioids (oral or IV)

Discuss PONV prophylaxis with surgical team before administration.

<table>
<thead>
<tr>
<th>RISK SCORE</th>
<th>DRUGS</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None or Dexamethasone</td>
<td>Low Risk</td>
</tr>
<tr>
<td>1</td>
<td>Diphenhydramine</td>
<td>Moderate Risk</td>
</tr>
<tr>
<td>2</td>
<td>Haloperidol (&lt;70yrs)</td>
<td>High Risk</td>
</tr>
<tr>
<td>3</td>
<td>Haloperidol (&lt;70yrs)</td>
<td>Highest Risk</td>
</tr>
<tr>
<td>4</td>
<td>Haloperidol (&lt;70yrs)</td>
<td>History of Post-Discharge Nausea/Vomiting</td>
</tr>
</tbody>
</table>

Consider Total IV Anesthesia (TIVA) or Total IV TIVA.

Aprepitant (if failed PONV prophylaxis), Scopolamine TDP, or Aprepitant.
Table 2: Rescue of Prophylaxis Failure & Post-discharge Care for the ADULT Patient

Drugs given in OR

Review intraoperative antiemetic drug administration, including dose and timing

PACU Rescue of Prophylaxis Failure

Ondansetron and/or Diphenhydramine

DO NOT REDOSE Ondansetron or Haloperidol within 6 hrs:
Dexamethasone within 24 hrs

Continued PONV

Prochlorperazine

FAILED PACU PONV Rescue

Promethazine or Haloperidol
(DO NOT REDOSE Haloperidol within 6 hrs)

Scopolamine TDP

Granisetron

Successful PACU PONV Rescue

If any one is present:
- Hx of post-discharge nausea and vomiting (PDNV)
- Hx of failed multi-drug prophylaxis (any PONV in someone who received 3 or more drugs/modalities of prophylaxis excluding baseline prevention strategies)
- Current PONV requiring 2 or more drugs for treatment or associated with >60 minutes prolongation of PACU stay

PDNV Prophylaxis Plan

Ondansetron ODT 8mg 10 tabs DC RX

Consider:
- Scopolamine TDP
- Seaband™
- Ginger gum 256 QID
- Must provide discharge instructions re: purchase from retail pharmacy
Assessment Test

This assessment test has been provided as a study aid only. Follow the prompts at the end of the presentation to claim credit. Credit must be claimed within 60 days of completing the activity.

1. In current clinical practice, how often is the train-of-four (TOF) monitor used routinely?
   a. 5%
   b. 10%
   c. 50%
   d. 100%

2. When is a patient considered “fully reversed” after the use of a neuromuscular blocking agent?
   a. When they can squeeze your hand.
   b. When you can feel four twitches on the TOF monitor.
   c. When the TOF ratio is >0.9.

3. What percent of patients are inadequately reversed upon entry to the post-anesthesia care unit (PACU) after getting neuromuscular blocking agents?
   a. 0%
   b. 5%
   c. 30-40%
   d. >50%

4. Is succinylcholine the “safest” agent for a rapid sequence induction (RSI) for a full stomach (rather than 1.2 mg/kg rocuronium)?
   a. Yes.
   b. No.

5. Case Presentation: A 65-year-old female with a body mass index (BMI) of 28 kg/m2, hypertension, COPD (history of smoking), obstructive sleep apnea, and a history of PONV is admitted for robotic laparoscopic appendectomy. She is induced with fentanyl 150 mcg, propofol 200 mg, and rocuronium 70 mg IV. Additionally she receives 2 mg hydromorphone, 12.5 mg diphenhydramine, and 4 mg dexamethasone and her team plans for postoperative opioids on discharge. All of the following were the patient’s risk factors for PONV with reversal EXCEPT?
   a. Female gender.
   b. History of PONV.
   c. Smoking history.
   d. Postop opioids.
6. Which of the following pharmacological prophylaxis measures should not have been considered for PONV?
   a. Ondansetron.
   b. Haloperidol.
   c. Aprepitant.

7. Despite full reversal with current methods for NMB and a TOF greater than 0.9 postoperative residual block may still occur.
   a. True.
   b. False.