What is adequate recovery of Neuromuscular Function?

Monitoring of Depth of Neuromuscular Blockade: Necessary in the Age of Sugammadex?

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Conflicts of Interest

Well Cornell Medical College

The topic was important because…
- Residual NMB is a risk whenever administering NMBAs
- Residual NMB is associated with adverse consequences
- Monitors and monitoring of depth of block are inadequate
- We are maintaining deep levels of NMB
What is adequate recovery of Neuromuscular Function?

Why discuss this at all?

Sugammadex

Medicine is Replete with Failed Therapies

- Antioxidants no Magic Bullet for Heart Disease in Women; Forbes.com
- Growth Hormone no “Magic Bullet” for Aging; Healthfinder.gov
- Chondroitin No Magic Bullet for Achy Joints, Study Says; ABC News
- The Ricochet of Magic Bullets; Summary of the Institute of Medicine Report

A Magic Bullet?

No...

Appropriate use of sugammadex will require an understanding of its pharmacodynamic properties.
What is adequate recovery of Neuromuscular Function?
What is adequate recovery of Neuromuscular Function?

Neostigmine and Atropine or Glycopyrrolate: Adverse Effects

- Arrhythmias
  - Bradycardia
  - Asystole
- Bronchospasm
- Nausea and vomiting
- Dry mouth
- Tension on intestinal anastomoses
- Failure of neuromuscular transmission

Spontaneous Recovery from Neuromuscular Block

Debaene, Anesthesiology 2003;98: 1042

Debaene, Anesthesiology 2003;98: 1042
What is adequate recovery of Neuromuscular Function?

**The Import of Monitoring**
- Definition of adequate recovery
- Site
- Stimuli
- Quantitative monitor

**Residual Neuromuscular Block is Associated with Adverse Consequences**
- Impaired TOFR of the suprahoid muscles
- Pharyngeal dysfunction
- Difficulty swallowing
- Increased postop pulmonary complications
- Impaired hypoxic ventilatory regulation
- Increased incidence of hypoxia
- Decreased ability to clench incisors
- Diplopia, difficulty sitting upright
- Prolonged PACU discharge times

**Signs of Residual Weakness vs. TOF Response**

<table>
<thead>
<tr>
<th>Clinical Test</th>
<th>Head-Lift</th>
<th>Leg-Lift</th>
<th>Retain Tongue Depressor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range of TOFR</td>
<td>0.48 – 0.75</td>
<td>0.50 – 0.65</td>
<td>0.68 – 0.95</td>
</tr>
<tr>
<td>Mean TOFR (mean ± SD)</td>
<td>0.54 ± 0.08</td>
<td>0.62 ± 0.09</td>
<td>0.86 ± 0.08</td>
</tr>
</tbody>
</table>

Kopman, Anesthesiology 86:1997, 755-7
What is adequate recovery of Neuromuscular Function?

Neuromuscular Block in Different Muscle Groups

Monitoring Sites

Monitoring at the Arm

Donati F, et al. Anesthesiology 1990; 70: 870
What is adequate recovery of Neuromuscular Function?

Monitoring at the Leg

The Common Peroneal Nerve

The Posterior Tibial Nerve

Available qualitative monitors of neuromuscular function.

Fade in the Train of Four Response

Twitch Response

Time
What is adequate recovery of Neuromuscular Function?

**Acceleromyography**

...to inform decisions regarding tracheal extubation.

**Incidence of Inadequate Recovery of Neuromuscular Function**

<table>
<thead>
<tr>
<th></th>
<th>Acceleromyography</th>
<th>Conventional TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium (mg)</td>
<td>68.9 ± 23.7</td>
<td>71.9 ± 27.6</td>
</tr>
<tr>
<td># Redoses</td>
<td>2 (0 - 8)</td>
<td>2 (0 - 8)</td>
</tr>
<tr>
<td>TOF Count at reversal</td>
<td>4 (1 - 4)</td>
<td>4 (1 - 4)</td>
</tr>
<tr>
<td>Time to extubation</td>
<td>8 (1 - 20)</td>
<td>6 (1 - 38)</td>
</tr>
<tr>
<td>TOFR &gt; .9</td>
<td>95.5%</td>
<td>70.0%*</td>
</tr>
<tr>
<td>0.7 ≤ TOFR ≤ 0.9</td>
<td>4.5%</td>
<td>16.7%</td>
</tr>
<tr>
<td>TOFR &lt; 0.7</td>
<td>0%</td>
<td>13.3%*</td>
</tr>
</tbody>
</table>

Murphy GS. Anesthesiology 2008; 109:389

**Objective measurement of neuromuscular function is required to increase patient safety.**

“The depth of block cannot be guessed, inferred, or “assessed” by subjective means, regardless of one’s vast clinical experience…”

Anesthesiology 2015;122:1183-5
What is adequate recovery of Neuromuscular Function?

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Necessary Information to Make Decisions Regarding Antagonism

- The pharmacokinetics and dynamics of the NMBA used
- Timing of last dose of relaxant
- Time to end of surgery
- The train-of-four ratio
- The site of monitoring
- The dose anticholinesterase at different depths of block

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Molecular Mechanisms of NMB Recovery

- ACh
- Ach Release
- AChE
- AChE Inhibitors
- nAChR
- NMBA
- Choline and Acetate
- AChE
- Inactive Metabolite
- Degradation

Adapted from: Zhang, Drugs Fut 2003;28:347-354

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Recovery 15 Minutes after Neostigmine

- Baurain, MJ. Br J Anaesth 1996;77:496

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What is adequate recovery of Neuromuscular Function?
What is adequate recovery of Neuromuscular Function?

Neostigmine Antagonism of Vecuronium

1 patient did not have a TOFR > 0.75 4 hours after vecuronium
8 patients who had a TOFR > 0.9 at administration of neostigmine developed a TOFR < 0.75 after neostigmine (40 µg/kg)
Neostigmine (20 µg/kg) 2 or 4 hours after vecuronium did not result in a decrease of the TOFR

Respiratory Function after either Neostigmine or Sugammadex

Recent Recommendations for Anticholinesterase Administration

<table>
<thead>
<tr>
<th>Traditional TOF Monitor</th>
<th>TOFC = 4</th>
<th>TOFC = 1-3</th>
<th>TOFC = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Fade</td>
<td>Fade</td>
<td>Neostigmine 50 µg/kg</td>
<td>Wait for further Recovery</td>
</tr>
<tr>
<td>Neostigmine 15-25 µg/kg</td>
<td>Neostigmine 40 µg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Kopman and Eikermann, Anaesthesia. 2009; 64:22-30
What is adequate recovery of Neuromuscular Function?

Molecular Mechanisms of NMB Reversal

ACh

Choline and Acetate

AChE Inhibitors

NMBA

Elimination

Inactive Metabolite

Degradation

Encapsulation

Host Molecule

Sugammadex: A γ-Cyclodextrin

Cyclodextrins

- A family of cyclic oligosaccharides
- Increase the aqueous solubility of compounds
- Used in deodorizing products
- Used for the separation and removal of compounds
  - Cholesterol
  - Toxins
- Increases the chemical stability of compounds
What is adequate recovery of Neuromuscular Function?

Sugammadex

Bom. Angew Chem 2002;41; 265.

Spontaneous Recovery from Rocuronium-Induced NMB

Gijzenbergh F. Anesthesiology 2005; 103:695-703

Sugammadex Reversal of Rocuronium-Induced NMB

Gijzenbergh F. Anesthesiology 2005; 103:695-703
What is adequate recovery of Neuromuscular Function?

- **Recovery of Strength after Rocuronium and Sugammadex or Succinylcholine**
  - Naguib, Anesth Analg 2007; 104:575

- **Speed of Recovery: Sugammadex vs. Neostigmine vs. Edrophenium**
  - Sugammadex
  - Edrophenium
  - Neostigmine

- **Recovery from Rocuronium-Induced Neuromuscular Block**
  - NMB with Rocuronium
  - Reappearance of T2
  - Reversal with Sugammadex or Neostigmine
  - Median Recovery Times: Sugammadex 1.4 min, Neostigmine 21.5 min

Cumulative Recovery Rate:
- Sugammadex, 2 mg/mL
- Neostigmine 0.05 mg/mL

Minutes to Recovery: 0, 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 115, 130
What is adequate recovery of Neuromuscular Function?

Recovery from Rocuronium-Induced Neuromuscular Block

- NMB with Vecuronium
- Appearance of T2
- Reversal with Sugammadex or Neostigmine

Minutes to Recovery

- Sugammadex, 2 mg/mL: Median Recovery Times
  - Sugammadex 2.1 min
  - Neostigmine 29.0 min

Cumulative Recovery Rate

Rocuronium and Sugammadex vs. Cisatracurium and Neostigmine

<table>
<thead>
<tr>
<th>Recovery Parameter</th>
<th>Rocuronium-Sugammadex</th>
<th>Cisatracurium-Neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOFR = 0.7</td>
<td>1.2 (0.7 – 2.9)</td>
<td>4.7 (2.4 – 10.9)</td>
</tr>
<tr>
<td>TOFR = 0.8</td>
<td>1.5 (0.7 – 3.4)</td>
<td>5.9 (3.2 – 15.6)</td>
</tr>
<tr>
<td>TOFR = 0.9</td>
<td>1.9 (0.7 – 6.4)</td>
<td>7.3 (4.2 – 28.2)</td>
</tr>
</tbody>
</table>


Sugammadex-facilitated Recovery of Neuromuscular Function

Vanaker BF. Anesth Analg 2007; 104:563
What is adequate recovery of Neuromuscular Function?

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**Speed of Recovery after Sugammadex**

<table>
<thead>
<tr>
<th>Administration of Sugammadex</th>
<th>Sugammadex Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 min after bolus (Gisenburg)</td>
<td>0.5 2.0 4.0 8.0</td>
</tr>
<tr>
<td>TOFC of 2 (Sorgenfrei)</td>
<td>71 15 2.9 1.1</td>
</tr>
<tr>
<td>TOFC of 2 (Shields)</td>
<td>4.3 1.3 1.1 N/A</td>
</tr>
<tr>
<td>TOFC of 2 (Suy)</td>
<td>6.5 1.5 1.2 N/A</td>
</tr>
<tr>
<td>PTC of 1-2 (Groudine)*</td>
<td>3.7 1.7 1.1 N/A</td>
</tr>
</tbody>
</table>

# Rocuronium 0.6 mg/kg
^ Rocuronium administered after bolus to maintain profound neuromuscular block

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**Sugammadex Reversal of Profound Rocuronium-Induced NMB**

<table>
<thead>
<tr>
<th>Sugammadex (mg/kg)</th>
<th>Placebo</th>
<th>2.0</th>
<th>4.0</th>
<th>6.0</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>122.1 ± 18.1</td>
<td>15.5 ± 5.4</td>
<td>15.8 ± 17.8</td>
<td>2.8 ± 0.6</td>
<td>1.9 ± 2.2</td>
</tr>
<tr>
<td>Min, Max</td>
<td>98.6, 139.4</td>
<td>50.5, 65.1</td>
<td>3.3, 46.6</td>
<td>2.2, 3.7</td>
<td>0.7, 6.9</td>
</tr>
</tbody>
</table>


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**Plasma Concentrations of Rocuronium After Sugammadex**

[Graph showing plasma concentrations and twitch height over time]

Epemolu et al. Anesthesiology 2003; 99:632
What is adequate recovery of Neuromuscular Function?

Renal Elimination of Rocuronium after Sugammadex

Sugammadex

Sugammadex 100 mg/mL
2 mL vial
5 mL vial

Sugammadex Dosing

- IV bolus over 10 seconds
- For Rocuronium and Vecuronium:
  - 1-2 P1/T: 4 mg/kg
  - T2: 2 mg/kg
- For Rocuronium only:
  - Within 3 min of administration: 1.2 mg/kg; 16 mg/kg
What is adequate recovery of Neuromuscular Function?

Sugammadex in Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>Intact RBF Spontaneous</th>
<th>No RBF Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Block</td>
<td>15.9 ± 2.7</td>
<td>1.5 ± 0.1^a</td>
</tr>
<tr>
<td>Min to 50% Recovery</td>
<td>27.4 ± 4.7</td>
<td>3.6 ± 0.1^a</td>
</tr>
<tr>
<td>Min to 90% Recovery</td>
<td>31.6 ± 5.4</td>
<td>4.6 ± 0.2^b</td>
</tr>
<tr>
<td>25-75% RI (min)</td>
<td>5.6 ± 1.1</td>
<td>1.1 ± 0.2^b</td>
</tr>
</tbody>
</table>

Bom, et al. Anesthesiology 2005; A1158

Sugammadex: Geriatric Patients

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Elderly</th>
<th>Old elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes to TOFR = 0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.2 – 7.4)</td>
<td>(0.9 – 8.8)</td>
<td>(0.9 – 9.9)</td>
</tr>
</tbody>
</table>

McDonagh et al. Anesthesiology 2007; A1583

Sugammadex: Cardiac Disease

Dahl et al. Anesthesiology 2007; A1581
What is adequate recovery of Neuromuscular Function?

**Sugammadex: Adverse Effects**
- Marked bradycardia
- Anaphylaxis and hypersensitivity
- Coagulopathy and bleeding (16 mg/kg)

**Inadequate Recovery with Sugammadex**

**Administration of Rocuronium or Vecuronium after Sugammadex**

<table>
<thead>
<tr>
<th>Minimum Waiting Time</th>
<th>NMBA and Dose to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 minutes</td>
<td>1.2 mg/kg Rocuronium</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.6 mg/kg Rocuronium or 0.1 mg/kg Vecuronium</td>
</tr>
</tbody>
</table>
What is adequate recovery of Neuromuscular Function?

Avoiding Residual Neuromuscular Block

- It's difficult to accomplish
- Requires at least four things
  - Proper monitoring of depth of block
  - Appropriately dosing neuromuscular blocking agents
  - Administering a correct dose of anticholinesterase
  - Waiting a little longer to extubate

Conclusions

- Sugammadex may change the paradigm for what is considered an acceptable level of recovery
- Proper dosing of sugammadex will require
  - Monitoring of neuromuscular block
  - Dosing adjustment based on level of block to be reversed