Reliable Recovery and Organ-Independent Elimination

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Neuromuscular Agents:
Costs of Care

• Cost of care ≠ acquisition cost
• The real, substantial savings accrue from use of intermediate- and short-acting drugs because:
  • Inexpensive, long-acting drugs are associated with prolonged postoperative recovery
  1
  • Fast recovery means shorter risk periods of residual blockade. This translates into fewer postoperative complications, as shown in the Berg study
  2
  • Postoperative complications are very expensive
  Avoiding these is where the real cost savings accrue

Current Concepts in Neuromuscular Blockade

Program Overview

• Key Points
  • Appropriate selection of NMBs enhances recovery
  • Use of predictable-recovery relaxants may reduce complications
  • Use of predictable-recovery, intermediate- and short-acting NMBs may achieve cost savings
Assessing Postoperative Neuromuscular Function

ASSESSING TOF FADE RATIO

• Patients are often returned to the PACU with residual paralysis\(^1\)
• The TOF ratio of 0.70 may be inadequate for discharge of an ambulatory patient\(^1\)
• TOF ratios \(\geq 0.40\) are difficult to assess clinically\(^2\)

\(^1\)Viby-Mogensen J, et al. Anesthesiology. 1979;50:539
\(^2\)Kopman AF, et al. Anesthesiology. 1994;81:1394
Assessing Postoperative Neuromuscular Function

CLINICAL ASSESSMENT

- Sustained 5-second head lift
- Ability to appose incisors (clench teeth)
- Negative inspiratory force > – 40 cm H$_2$O
- Ability to open eyes wide for 5 seconds
- Hand-grip strength
- Sustained arm/leg lift
- Quality of speaking voice
- Tongue protrusion

Kopman AF, et al. Anesthesiology, 1997:86;765
Rationale for Selection of NMBs:

- Cardiovascular stability
- Nondepolarizing vs depolarizing
- Organ-independent elimination
- Clinically significant active or toxic metabolites
- Predictability of duration
- Cumulative effects
- Reversibility
- Time to onset
- Stability of solution
- Cost
Cisatracurium: Precision You Can Count On

- Hemodynamic stability
  - Causes no clinically significant dose-related elevations in mean plasma histamine concentrations at doses up to 8 x ED$_{95}$
  - Maintains heart rate and mean arterial pressure even in CABG and CV compromised patients
  - Causes no dose-related effects on mean arterial blood pressure or heart rate at doses up to 8 x ED$_{95}$
Cisatracurium: Precision You Can Count On

• Predictable duration/recovery
  • Provides predictable duration and recovery, regardless of renal or hepatic function
  • Maintenance dose of 0.03 mg/kg lasts approximately 20 minutes
• Noncumulative properties
  • Less risk of prolonged recovery time with maintenance dosing
  • Rate of spontaneous recovery following infusion is independent of infusion duration and similar to recovery rate with initial doses
  • Reversal given at 10% recovery can be achieved in less than 10 minutes
Cisatracurium: Spontaneous Twitch Recovery

Spontaneous Recovery After Infusion

- 38 infused patients studied (ASA I or II)
  - 11-minute to 249-minute cisatracurium infusions (mean = 109.2 minutes)
  - Mean 5%-95% recovery interval: 33.2 ± 1.8 min
  - Mean 25%-75% recovery interval: 15.0 ± 0.6 min
  - Recovery intervals independent of infusion duration

Spontaneous Recovery After Infusion

Determinants of Speed of Reversal

- Depth of Block
- Dose of Antagonist
- The Antagonist Itself
- Presence of Anesthetic Gases
- Spontaneous Recovery Rate or the $T_{1/2}$ of the Relaxant
Cisatracurium or Rocuronium Recovery

- Controlled study of 40 healthy patients undergoing elective surgery
  - 0.15 mg/kg cisatracurium (3 x ED$_{95}$)
  - 0.2 mg/kg cisatracurium (4 x ED$_{95}$)
  - 0.9 mg/kg rocuronium (3 x ED$_{95}$)
  - 1.2 mg/kg rocuronium (4 x ED$_{95}$)

Cisatracurium or Rocuronium Recovery

<table>
<thead>
<tr>
<th></th>
<th>Mean Time to 25% Recovery</th>
<th>Standard Deviation of Mean Recovery Times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 x ED&lt;sub&gt;95&lt;/sub&gt;</td>
<td>4 x ED&lt;sub&gt;95&lt;/sub&gt;</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>64</td>
<td>80</td>
</tr>
</tbody>
</table>

Cisatracurium: Precision You Can Count On

- Study to compare variability in offset between 2 NMBs with different elimination pathways
  - 277 patients studied
    - Initial bolus dose of 0.15 mg/kg and maintenance doses of 0.03 mg/kg cisatracurium
    - Initial bolus dose 0.1 mg/kg and maintenance doses of 0.02 mg/kg vecuronium
  - Variability in duration of recovery examined in adult (18-64) and elderly (≥65 years) patients

Cisatracurium: Precision You Can Count On

## Pharmacodynamic Dose Response*
During Opioid/Nitrous Oxide/Oxygen Anesthesia

<table>
<thead>
<tr>
<th>Initial dose of Cisatracurium (mg/kg)</th>
<th>Time to 90% Block (min)</th>
<th>Time to Maximum Block (min)</th>
<th>5% Recovery (min)</th>
<th>25% Recovery† (min)</th>
<th>95% Recovery (min)</th>
<th>T₄:T₁ Ratio‡ &gt;70% (min)</th>
<th>25% – 75% Recovery Index (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 (2xED₉₅) (n=98)</td>
<td>3.3 (1.0 – 8.7)</td>
<td>5.0 (1.2 – 17.2)</td>
<td>33 (15 – 51)</td>
<td>42 (22 – 62)</td>
<td>64 (25 – 93)</td>
<td>64 (32 – 91)</td>
<td>13 (5 – 30)</td>
</tr>
<tr>
<td>0.15 (3xED₉₅) (n=39)</td>
<td>2.6 (1.0 – 4.4)</td>
<td>3.5 (1.6 – 6.8)</td>
<td>46 (28 – 65)</td>
<td>55 (44 – 74)</td>
<td>76 (60 – 103)</td>
<td>75 (63 – 98)</td>
<td>13 (11 – 16)</td>
</tr>
<tr>
<td>0.2 (4xED₉₅) (n=30)</td>
<td>2.4 (1.5 – 4.5)</td>
<td>2.9 (1.9 – 5.2)</td>
<td>59 (31 – 103)</td>
<td>65 (43 – 103)</td>
<td>81 (53 – 114)</td>
<td>85 (55 – 114)</td>
<td>12 (2 – 30)</td>
</tr>
</tbody>
</table>

### Adults

* Values shown are medians of means from individual studies. Values in parentheses are ranges of individual patient values.
† Clinically effective duration of block.
‡ Train-of-four ratio.
§ n = the number of patients with time to maximum block data.
‖ Propofol anesthesia.
Typical Clinical Applications for Cisatracurium

- Cases $\geq$ 60 minutes
- Cardiac surgery
- Cases where predictable recovery is important
Cisatracurium is:

• **Safe**
  - Organ-independent elimination
  - Can be used in a wide variety of patients, in both OR & ICU (including those with renal or hepatic impairment)
  - Low-risk side effect profile

• **Stable**
  - Minimal effect on MAP or HR
  - No dose-related histamine release events at 8x ED$_{95}$

• **Smart**
  - Predictable duration and recovery
  - Noncumulative – less risk of prolonged recovery
  - Cost-conscious solution

**Summary: Cisatracurium Is a Versatile Option**
Clinical Profile of Mivacurium

- Short duration / rapid recovery
  - Short elimination half-life (approx. 2 min)
  - Spontaneous recovery rate of 20 minutes to $T_{25\%}$ @ 0.20 mg/kg dose
  - Spontaneous recovery rate of 23 minutes to $T_{25\%}$ @ 0.25 mg/kg dose

- Established cardiovascular profile
  - No clinically significant effect on MAP or HR
Dosing for Continuous Infusion

Background Anesthesia: Opioid/N₂O/0₂

- Upon evidence of spontaneous recovery from initial bolus dose:
  - Initial infusion rate: 9-10 µg/kg/min
  - Average infusion rate: 5-7 µg/kg/min
- Infusion rate should be adjusted according to the response to peripheral nerve stimulation.
- An infusion rate of 5-7 µg/kg/min (range 1-15) may be expected to maintain neuromuscular blockade within 89% and 99% for extended periods in adults
- Children require higher infusion rates (avg. 14 µg/kg/min, range 5 to 31 µg/kg/min)
Mivacurium: Mean Spontaneous Recovery Curves of Single Twitch

- Recovery index is always independent of dose and duration of administration

Mivacurium: Mean Spontaneous Recovery Curves of Single Twitch

• Due to metabolism, recovery from mivacurium, even after repeated doses, is predictably the same.

• Once recovery time from first dose is established, it is virtually the same for all subsequent equipotent doses.

Savarese et al., Anesthesiology. 1988;68:723
Mivacurium: Histamine Release

- Single injection of 0.20 mg/kg over 30 seconds: minimal BP changes

- Divided doses 0.25 mg/kg: injections over 30 seconds cause little or no histamine release, minimal BP changes

Savarese JJ, et al. Anesthesiology. 1989;70:386
Atypical Cholinesterase and Mivacurium

• Metabolized by plasma cholinesterase
  • Do not use in patients suspected to be homozygous for the atypical plasma cholinesterase gene
• Heterozygotes for atypical plasma cholinesterase gene: 1/25 (3% – 4%) of population. Duration of block approx. 10 minutes longer after 0.15 mg/kg initial dose.
• Atypical homozygotes (1/2,500 of population)
  • May be paralyzed 3 – 4 hrs at a dose of 0.20 mg/kg mivacurium vs 16-20 minutes in normals
Clinical Applications for Mivacurium

- Ambulatory surgery cases where achievement of rapid recovery is essential
- Surgeries of \( \leq 30 \text{ min} \)
- Surgeries of indeterminate length
- Cases where rapid spontaneous recovery is desired
Summary: Mivacurium

Mivacurium

• An ideal choice for patients undergoing short- or indeterminate-length procedures

• Short duration / rapid recovery
  • Short elimination half-life
  • Recovery rate of 20 minutes to $T_{25\%}$ from 0.2 mg/kg dose

• Established safety profile
  • No clinically significant effects on MAP or HR with proper dose administration
  • Noncumulative

• Convenient
  • Room temperature storage
  • No reconstitution
Clinical, economic, and legal issues all center around one consideration: SAFETY

It is higher quality clinical practice, cheaper in the long run, and less risky to use drugs which enable fast recovery. Even for cases of 3-4 hours or more, relaxation should be provided by continuous infusion of intermediate or short-acting drugs.
Current Concepts in Neuromuscular Blockade

**SUMMARY:**

- Judgments about drug choice that ensure better patient care must be vigorously defended.
- Avoidance of expensive complications may be enhanced when intermediate- or short-acting relaxants are used.
The Goal…

- A nondepolarizing neuromuscular blocking agent to replace succinylcholine
  - Fast onset of neuromuscular block
  - Rapid spontaneous recovery of neuromuscular function
  - Absence of side effects associated with the use of depolarizing neuromuscular blockers
The Most Recent Development...
The Most Recent Development…

Gantacurium

430A, 0.19 mg/kg

1 minute

5%

TOF = 0.86 in 9 min
### Onset of Neuromuscular Block following Administration of Bolus Doses of Gantacurium

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Time to Max T1 Suppression (sec)</th>
<th>T1 Suppression at 60 Sec (%)</th>
<th>Maximum T1 Depression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.188</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>0.250</td>
<td>122.5 (82.4-145)</td>
<td>69.9 (43.0-97.8)</td>
<td>97.0 (95-100)</td>
</tr>
<tr>
<td>0.375</td>
<td>92.8 (70-111)</td>
<td>86.6 (81-97)</td>
<td>100 (100-100)</td>
</tr>
<tr>
<td>0.625</td>
<td>74.1 (40-123)</td>
<td>91.0 (60-100)</td>
<td>100 (100-100)</td>
</tr>
<tr>
<td>0.875</td>
<td>71.0 (45-89.2)</td>
<td>93.8 (87.7-96.2)</td>
<td>97.4 (95-100)</td>
</tr>
<tr>
<td></td>
<td>53.6 (37-70)</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
</tr>
</tbody>
</table>
GW280430A vs. Succinylcholine at the Adductor Pollicis

<table>
<thead>
<tr>
<th></th>
<th>Min to Max Block</th>
<th>T1 = 25% (min)</th>
<th>T1 = 95% (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GW280430A (0.36 mg/kg)</td>
<td>1.7 ± 0.2</td>
<td>7.0 ± 0.5</td>
<td>9.8 ± 1.3</td>
</tr>
<tr>
<td>GW280430A (0.54 mg/kg)</td>
<td>1.5 ± 0.3</td>
<td>9.3 ± 2.1</td>
<td>15.2 ± 3.7</td>
</tr>
<tr>
<td>Succinylcholine (1 mg/kg)</td>
<td>1.5 ± 0.2</td>
<td>9.2 ± 1.6</td>
<td>12.1 ± 2.0</td>
</tr>
</tbody>
</table>
### GW280430A vs. Succinylcholine at the Laryngeal Adductors

<table>
<thead>
<tr>
<th></th>
<th>Min to Max Block</th>
<th>T1 = 25% (min)</th>
<th>T1 = 95% (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GW280430A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.36 mg/kg)</td>
<td>1.1 ± 0.3</td>
<td>7.2 ± 1.1</td>
<td>12.2 ± 2.1</td>
</tr>
<tr>
<td><strong>GW280430A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.54 mg/kg)</td>
<td>0.9 ± 0.2</td>
<td>9.3 ± 2.1</td>
<td>16.1 ± 4.1</td>
</tr>
<tr>
<td><strong>Succinylcholine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 mg/kg)</td>
<td>0.8 ± 0.3</td>
<td>7.3 ± 1.9</td>
<td>11.1 ± 1.9</td>
</tr>
</tbody>
</table>
Spontaneous Recovery following the Administration of Gantacurium

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Clinical Duration of Action (min)</th>
<th>Total Duration of Action (min)</th>
<th>T1 5% - T4:T1 ≥ 0.9 RI (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.188</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>0.250</td>
<td>5.5 (3.5-7.1)</td>
<td>9.9 (8.2-11.6)</td>
<td>5.8 (4.5-7.1)</td>
</tr>
<tr>
<td>0.375</td>
<td>6.9 (4.8-9.2)</td>
<td>12.5 (8.2-16.7)</td>
<td>7.2 (4.1-10.1)</td>
</tr>
<tr>
<td>0.625</td>
<td>7.5 (5.6-10.2)</td>
<td>12.6 (9.4-16.5)</td>
<td>6.6 (5.1-11.1)</td>
</tr>
<tr>
<td>0.875</td>
<td>9.4 (8.2-10.7)</td>
<td>14.2 (12.3-16.6)</td>
<td>8.1 (5.9-11.4)</td>
</tr>
<tr>
<td></td>
<td>9.9 (8.7-11.5)</td>
<td>14.5 (12.7-16.4)</td>
<td>6.3 (5.4-6.7)</td>
</tr>
</tbody>
</table>
Spontaneous and Edrophonium-Induced Recovery from Gantacurium-Induced Neuromuscular Block

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
<th>Spontaneous Recovery</th>
<th>Mean (range)</th>
<th>Edrophonium-Induced Recovery</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-75% RI (Min)</td>
<td>0.25</td>
<td>3.2 (2.9-3.5)</td>
<td></td>
<td>1.46 (1.8-1.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.375</td>
<td>2.6 (1.7-4.7)</td>
<td></td>
<td>0.87 (0.41-1.4)</td>
<td></td>
</tr>
<tr>
<td>T1 25%-T4:T1 &gt; 0.9 RI (Min)</td>
<td>0.25</td>
<td>5.3 (4.8-6.1)</td>
<td></td>
<td>3.7 (2.9-4.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.375</td>
<td>5.1 (3.3-9.0)</td>
<td></td>
<td>2.4 (1.7-2.7)</td>
<td></td>
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</table>
Maximal MAP and HR Changes within 5 min of Gantacurium Administration
Hemodynamic Effects of Gantacurium and Mivacurium
Maximum Effect: 100% NMB
Peak Effect: 55 sec
5% Recovery: 4.5 min
TOF = 0.9: 10.5 min
Gantacurium...

- An $\alpha$-chlorofumarate
- A nondepolarizing neuromuscular blocking agent
  - Has a rapid onset of effect
  - Has an ultra-short duration of action
  - Is readily antagonized by edrophonium
Gantacurium

May improve safety of using nondepolarizing neuromuscular blocking agents as part of a balanced anesthetic