CLINICAL PHARMACOLOGY OF NEUROMUSCULAR BLOCKING AGENTS

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HISTORY OF NEUROMUSCULAR BLOCKING AGENTS AND CLINICAL DEVELOPMENT
HISTORY

1494 - Tales of travelers killed by poison darts

1551 - Ourari” or “cururu” meaning “bird killer”

1812 - Curarized cat kept alive by artificial respiration

1912 - Curare used to prevent fractures during ECT

1941 - Initial use by Griffith, Culler, and Rovenstine

1951 - Succinylcholine chloride first used in Stockholm
INTRODUCTION OF NEW DRUGS

1494 - 1942  Curare
1947 - 1951  Succinylcholine chloride, Gallamine, Metocurine, Decamethonium
1960’s      Alcuronium
1970’s      Pancuronium bromide, Fazadinium
1980’s      Vecuronium bromide, Atracurium besylate
1990        Pipecuronium bromide
1991        Doxacurium chloride
1992        Mivacurium chloride
1994        Rocuronium bromide
1999        Rapacuronium bromide
STRUCTURAL CLASSES OF NONDEPOLARIZING RELAXANTS

- Steroids: Rocuronium bromide, Vecuronium bromide, Pancuronium bromide, Pipecuronium bromide
- Naturally occurring benzylisoquinolines: curare, metocurine
- Benzylisoquinoliniums: Atracurium besylate, Mivacurium chloride, Doxacurium chloride
THE IDEAL RELAXANT

• Nondepolarizing
• Rapid onset
• Dose-dependent duration
• No side-effects
• Elimination independent of organ function
• No active or toxic metabolites
ONSET OF PARALYSIS IS AFFECTED BY:

• Dose (relative to ED$_{95}$)
• Potency (number of molecules)
• $K_{eo}$ (chemistry/blood flow)
• Clearance
• Age
Neuromuscular Blocking Agents and Patient Evaluation

Assessing Postoperative Neuromuscular Function
Assessing Postoperative Neuromuscular Function

CLINICAL ASSESSMENT

✦ Sustained 5-second head lift
✦ Ability to appose incisors (clench teeth)
✦ Negative inspiratory force > – 40 cm H₂O
✦ Ability to open eyes wide for 5 seconds
✦ Hand-grip strength
✦ Sustained arm/leg lift
✦ Quality of speaking voice
✦ Tongue protrusion
Assessing Postoperative Neuromuscular Function

Train-of-Four (TOF) Fade Ratio

**Normal Response**

\[ \frac{T_4}{T_1} = 100\% \]

**Partial Curarization**

\[ \frac{T_4}{T_1} = 50\% \]
Assessing Postoperative Neuromuscular Function

THE ORIGIN OF THE GOLD STANDARD

<table>
<thead>
<tr>
<th>TOF Ratio</th>
<th>Vital Capacity</th>
<th>Inspiratory Force</th>
<th>Peak Exp. Flow Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control =100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>60%</td>
<td>91</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>70%*</td>
<td>97</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>80%</td>
<td>100</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>90%</td>
<td>100</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>100%</td>
<td>100</td>
<td>97</td>
<td>99</td>
</tr>
</tbody>
</table>

* Historically regarded as the Gold Standard

NEW DATA SUGGEST THAT A TOF OF 0.90 MAY BE NEEDED TO ENSURE NORMAL FUNCTION

Kopman: A TOF > 0.90 compatible with normal clinical tests (Anesthesiology. 1997;86:765)

Eriksson: Pharyngeal function normal at TOF 0.90 (Anesthesiology. 1997;87:1035)
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
Assessing Postoperative Neuromuscular Function

TOF FADE RATIO: CONCLUSION

- Recovery is inadequate if fade is detected\(^1,2\)
- Clinical trials are needed to demonstrate measurement techniques for TOF ratios of 0.90\(^2\)

\(^1\) Eriksson, LI, et al. *Anesthesiology*. 1997;87:1035
Neuromuscular Blockers: Chemical Structure & Key Characteristics

**Aminosteroids**

- **Vagolytic**
  - Partially block cardiac muscarinic receptors involved in heart rate slowing, resulting in increased heart rate:
    - rapacuronium > pancuronium > rocuronium > vecuronium
- Generally do not promote histamine release
  - Exception: rapacuronium
- Organ-dependent elimination
  - Kidneys and liver
Neuromuscular Blockers: Chemical Structure & Key Characteristics

**Benzylisoquinolines**

- Absence of vagolytic effect
  - these drugs do not block cardiac-vagal (muscarinic) receptors
- Histamine release
  - dTc > atracurium > mivacurium > cisatracurium
  - can cause rare bronchospasm, decreased blood pressure, increase of heart rate
- Generally organ-independent elimination
  - esp: atracurium, cisatracurium, mivacurium
- Noncumulative

## Classification of Neuromuscular Blockers by Duration of Action (Minutes)

<table>
<thead>
<tr>
<th>Ultra-Short</th>
<th>Short</th>
<th>Intermediate</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical duration (injection to T25)</strong></td>
<td>6 - 8</td>
<td>12 - 20</td>
<td>30 - 45</td>
</tr>
<tr>
<td><strong>Recovery time (injection to T95)</strong></td>
<td>&lt;15</td>
<td>25 - 30</td>
<td>50 - 70</td>
</tr>
<tr>
<td><strong>Recovery index (T25 to T75)</strong></td>
<td>2 - 3</td>
<td>6</td>
<td>10 - 15</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>succinylcholine ¹</td>
<td>mivacurium ²</td>
<td>cisatracurium ³</td>
</tr>
</tbody>
</table>

Assumes bolus dose = 2x ED₉⁵

¹Anectine® (succinylcholine chloride) Package Insert  
²Mivacron® (mivacurium chloride) Package Insert  
³Nimbex® (cisatracurium besylate) Package Insert  
⁴Nuromax® (doxacurium chloride) Package Insert
DURATION OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS

- Ultra-Short: Succinylcholine chloride
- Short: Mivacurium chloride
- Intermediate: Rocuronium bromide, Vecuronium bromide, Atracurium besylate
- Long: Pancuronium bromide, curare, metocurine, Pipecuronium bromide, Doxacurium chloride
CARDIOVASCULAR PROFILE OF NEUROMUSCULAR BLOCKING AGENTS

Hemodynamics, histamine release, and other aspects
### HISTAMINE RELEASING POTENTIAL

<table>
<thead>
<tr>
<th>Significant</th>
<th>Insignificant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubocurarine</td>
<td>+ + +</td>
</tr>
<tr>
<td>Metocurine</td>
<td>++</td>
</tr>
<tr>
<td>Atracurium besylate</td>
<td>+</td>
</tr>
<tr>
<td>Mivacurium chloride</td>
<td>+</td>
</tr>
<tr>
<td>Succinylcholine chloride</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Rocuronium bromide ±</td>
</tr>
<tr>
<td></td>
<td>Vecuronium bromide ±</td>
</tr>
<tr>
<td></td>
<td>Pancuronium bromide ±</td>
</tr>
<tr>
<td></td>
<td>Pipecuronium bromide ±</td>
</tr>
<tr>
<td></td>
<td>Doxacurium chloride ±</td>
</tr>
</tbody>
</table>
Muscle Relaxants

Pancuronium

• Vagolytic: increases heart rate, may require beta blockade
• Easy to use
• Intermediate duration of action
• Slower onset
• Not reversed at end of case
Muscle Relaxants

Vecuronium

- No effects on HR, BP
- Requires reconstitution
- Reliable and controllable duration of action
- Slower onset
- Stable hemodynamics/no histamine release
Muscle Relaxants

Rocuronium

• No effects on HR, BP
• Easy to use, liquid, no refrigeration
• Reliable and controllable duration of action
• Fast onset
• Stable hemodynamics/no histamine release
Effects of Rocuronium on Heart Rate

Effects of Rocuronium on Mean Arterial Pressure

Effects of Rocuronium on Histamine Release

Muscle Relaxants

Rapacuronium

- Minimal effects on HR, BP
- Controllable duration of action
- Fast onset
- Stable hemodynamics/minimal histamine release
- Potential for bronchospasm led to its removal in 2001
COSTS OF NEUROMUSCULAR BLOCKING AGENTS AND SELECTION CRITERIA
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
Rationale for Selection of NMBAs:

- 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