Muscle Relaxants in ICU

A Renaissance?

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Changing Utilisation Patterns

- Frequent use → 91% British ICU’s (1981)¹
- No prolonged use → German ICU’s (2002)²
- 13% ventilated patients → Multinational (2004)³
- 26% SIRS/ventilated → Switzerland (2005-2006)⁴

¹Merriman HM. Intensive Care Med 1981; 7: 217-224
DIRTY LITTLE SECRET

SORRY ABOUT YOUR CATS

Say it with balloons!!
Muscle Relaxants in ICU: Coming Out of the Closet?
The Pharmacology of Airway Management in Critical Care

Christian Consilvio, MD¹, Ware G. Kuschner, MD², and Geoffrey K. Lighthall, MD, PhD¹

Indications

Fumarates: Unique nondepolarizing neuromuscular blocking agents that are antagonized by cysteine

Hannah Church
Sue Sinclair
Tessa Oelofse

Suxamethonium in the intensive care unit: “Fool me once, shame on you; fool me twice, shame on me”

Sugammadex:
Cyclodextrins,
Development of Selective Binding Agents, Pharmacology, Clinical Development, and Future Directions

Clinical implications of new neuromuscular concepts at agents: So long, neostigmine! So long, sux!☆

Arezou Sadighi Akha, MD, MSa, Joseph Rosa III, MDb,
Jonathan S. Jahr, MDb,* Alvin Lić, Kianusch Kial, MD, MSb

Chingmah Lee MDa, Ronald L. Katz MD
Facilitate Mechanical Ventilation
Facilitate Mechanical Ventilation: Effects of neuromuscular blockade

- **Ventilatory parameters:**
  - Compliance: ↑ or ↔
  - Airway pressures: ↓ or ↔
  - Residual volume: ↑ or ↓ or ↔
  - Atelectasis: ↑ or ↓ or ↔

- **Oxygenation:**
  - Inconsistent effect short-term

- **Clinical Outcomes:**
  - Greater illness severity → greater use of NMB
  - Greater illness severity → poorer outcomes
  - NMB associated with poor outcomes
Facilitate Mechanical Ventilation: Conventional guidelines¹,²,³

- Patient-ventilator dysynchrony
- Inadequate ventilation
- Non-conventional / Uncomfortable ventilatory strategies
  - Inverse-ratio ventilation
  - Prone positioning
  - High PEEP
  - High frequency ventilation
  - Permissive hypercapnoea

Where all other means tried without success

¹Clinica practice guidelines for sustained neuromuscular blockade. Am J Health System Pharm 2002; 59:179-95
²Playfor et al. Paediatr Anaesth 2007; 17(9):881-7
³Murphy et al. Crit Care Clin; 17(4): 925-42
Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

Laurent Papazian, M.D., Ph.D., Jean-Marie Forel, M.D., Arnaud Gacouin, M.D., Christine Penot-Ragon, Pharm.D., Gilles Perrin, M.D., Anderson Loundou, Ph.D., Samir Jaber, M.D., Ph.D., Jean-Michel Arnal, M.D., Didier Perez, M.D., Jean-Marie Seghboyan, M.D., Jean-Michel Constantin, M.D., Ph.D., Pierre Courant, M.D., Jean-Yves Lefrant, M.D., Ph.D., Claude Guérin, M.D., Ph.D., Gwenaël Prat, M.D., Sophie Morange, M.D., and Antoine Roch, M.D., Ph.D.,
for the ACURASYS Study Investigators*
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- Multicentre, double-blind, prospective, randomised
- 340 patients
- ARDS
  - Early: < 48 hrs
  - Severe: $\text{PaO}_2/\text{FiO}_2 < 150$
- Cisatracurium vs placebo
- Cisatracurium
  - 48 hours
  - Constant, high dose infusion (37.5mg/hr) → ensure paralysis
  - No neuromuscular monitoring
Primary outcome: ↓ 90-day mortality

- Cisatracurium 31.6% vs placebo 40.7% (p=0.08)
- Correcting baseline imbalances (PaO$_2$/FiO$_2$):
  Hazard ratio = 0.68
  (95% CI 0.48-0.98; p=0.04)
- PaO$_2$/FiO$_2$ < 120:
  Mortality 30.8% vs 44.6% (p=0.04)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cisatracurium (N=177)</th>
<th>Placebo (N=162)</th>
<th>Relative Risk with Cisatracurium (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (% [95% CI])</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>At 28 days</td>
<td>42 (23.7 [18.1–30.5])</td>
<td>54 (33.3 [26.5–40.9])</td>
<td>0.71 (0.51–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>In the ICU</td>
<td>52 (29.4 [23.2–36.5])</td>
<td>63 (38.9 [31.7–46.6])</td>
<td>0.76 (0.56–1.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>In the hospital</td>
<td>57 (32.2 [25.8–39.4])</td>
<td>67 (41.4 [34.1–49.1])</td>
<td>0.78 (0.59–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>No. of ventilator-free days†</strong></td>
<td></td>
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</tr>
<tr>
<td>From day 1 to day 28</td>
<td>10.6±9.7</td>
<td>8.5±9.4</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>From day 1 to day 90</td>
<td>53.1±35.8</td>
<td>44.6±37.5</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td><strong>No. of days without organ failure, from day 1 to day 28</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No cardiovascular failure</td>
<td>18.3±9.4</td>
<td>16.6±10.4</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>No coagulation abnormalities</td>
<td>22.6±8.9</td>
<td>20.5±9.9</td>
<td></td>
<td>0.05</td>
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<tr>
<td>No hepatic failure</td>
<td>21.3±9.6</td>
<td>19.1±10.6</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>No renal failure</td>
<td>20.5±10.1</td>
<td>18.1±11.6</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>None of the four</td>
<td>15.8±9.9</td>
<td>12.2±11.1</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td><strong>No. of days outside the ICU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From day 1 to day 28</td>
<td>6.9±8.2</td>
<td>5.7±7.8</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>From day 1 to day 90</td>
<td>47.7±33.5</td>
<td>39.5±35.6</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)</td>
<td>22.3 (15.8–30.5)</td>
<td>18.8 (12.2–27.8)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td><strong>Barotrauma — no. (% [95% CI])‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>9 (5.1 [2.7–9.4])</td>
<td>19 (11.7 [7.6–17.6])</td>
<td>0.43 (0.20–0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumothorax — no. (% [95% CI])‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>7 (4.0 [2.0–8.0])</td>
<td>19 (11.7 [7.6–17.6])</td>
<td>0.34 (0.15–0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MRC score — median (IQR)‡</strong></td>
<td></td>
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</tr>
<tr>
<td>At day 28</td>
<td>55 (46–60)</td>
<td>55 (39–60)</td>
<td>1.07 (0.80–1.45)</td>
<td>0.49</td>
</tr>
<tr>
<td>At ICU discharge</td>
<td>55 (43–60)</td>
<td>55 (44–60)</td>
<td>0.92 (0.71–1.19)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Patients without ICU-acquired paresis‡</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>By day 28 — no./total no. (% [95% CI])</td>
<td>68/96 (70.8 [61.1–79.0])</td>
<td>52/77 (67.5 [56.5–77.0])</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>By ICU discharge — no./total no. (% [95% CI])</td>
<td>72/112 (64.3 [55.1–72.6])</td>
<td>61/89 (68.5 [58.3–77.3])</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>

*Denotes statistical significance at the 0.05 level.
Appendix 7 Table: Respiratory variables during the first seven study days

PaO₂:FiO₂ was higher and PaCO₂ lower in the NMBA group on day 7.

<table>
<thead>
<tr>
<th></th>
<th>H24 NMBA</th>
<th>H24 placebo</th>
<th>H72 NMBA</th>
<th>H72 placebo</th>
<th>Day 7 NMBA</th>
<th>Day 7 placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tidal volume</strong></td>
<td>6.3±0.8</td>
<td>6.3±0.8</td>
<td>6.6±1.5</td>
<td>6.5±1.4</td>
<td>7.0±1.8</td>
<td>6.9±1.7</td>
</tr>
<tr>
<td>(ml/kg of predicted body weight)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>171</td>
<td>159</td>
<td>165</td>
<td>151</td>
<td>115</td>
<td>108</td>
</tr>
<tr>
<td><strong>Plateau pressure</strong></td>
<td>24±5</td>
<td>23±5</td>
<td>23±5</td>
<td>23±5</td>
<td>23±6</td>
<td>23±5</td>
</tr>
<tr>
<td>(cm of water)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>172</td>
<td>157</td>
<td>164</td>
<td>143</td>
<td>116</td>
<td>110</td>
</tr>
<tr>
<td><strong>Total PEEP (cm of water)</strong></td>
<td>10.4±2.8</td>
<td>10.6±3.0</td>
<td>9.2±3.0</td>
<td>9.7±3.3</td>
<td>8.8±3.2</td>
<td>9.2±3.4</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>172</td>
<td>159</td>
<td>166</td>
<td>151</td>
<td>118</td>
<td>115</td>
</tr>
<tr>
<td><strong>Respiratory system compliance</strong></td>
<td>34±14</td>
<td>36±14</td>
<td>36±21</td>
<td>36±14</td>
<td>39±26</td>
<td>39±25</td>
</tr>
<tr>
<td>(mL/cm of water)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>171</td>
<td>157</td>
<td>162</td>
<td>142</td>
<td>113</td>
<td>103</td>
</tr>
<tr>
<td><strong>PaO₂:FiO₂</strong></td>
<td>164±72</td>
<td>168±72</td>
<td>166±70</td>
<td>157±68</td>
<td>177±72†</td>
<td>160±62</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>172</td>
<td>159</td>
<td>167</td>
<td>152</td>
<td>118</td>
<td>117</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.35±10</td>
<td>7.35±0.08</td>
<td>7.39±0.8</td>
<td>7.38±0.09</td>
<td>7.43±0.08</td>
<td>7.42±0.10</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>172</td>
<td>159</td>
<td>169</td>
<td>153</td>
<td>142</td>
<td>134</td>
</tr>
<tr>
<td><strong>PaO₂ (mm Hg)</strong></td>
<td>93±38</td>
<td>96±44</td>
<td>87±32</td>
<td>85±30</td>
<td>87±27</td>
<td>85±26</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>172</td>
<td>159</td>
<td>169</td>
<td>153</td>
<td>142</td>
<td>134</td>
</tr>
<tr>
<td><strong>PaCO₂ (mm Hg)</strong></td>
<td>45±11</td>
<td>44±9</td>
<td>44±10</td>
<td>44±9</td>
<td>41±11†</td>
<td>43±12</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
<td>172</td>
<td>159</td>
<td>169</td>
<td>153</td>
<td>142</td>
<td>134</td>
</tr>
</tbody>
</table>
36 patients with early ARDS

Randomised to cisatracurium for 48 hours or placebo

Cisatracurium @ 48hrs:

- Pulmonary: IL-1β ↓
- Serum: IL-6 ↓
  - IL-6
  - IL-8

Improved lung protective ventilation:

- Prevent even brief dysynchrony
- Prevent dysynchrony-induced alveolar collapse/overdistention
- Control/homogenisation - PEEP/Tidal volume
Pulmonary inflammatory markers

Serum inflammatory markers
Table 2. Changes in ventilatory parameters during the study period

<table>
<thead>
<tr>
<th>Group</th>
<th>Inclusion</th>
<th>24 Hrs</th>
<th>48 Hrs</th>
<th>72 Hrs</th>
<th>96 Hrs</th>
<th>120 Hrs</th>
<th>p Value RM ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PaO₂, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NMBA</td>
<td>51.1 ± 9.9</td>
<td>45.7 ± 9.2</td>
<td>46.9 ± 10.0</td>
<td>45.6 ± 9.0</td>
<td>43.5 ± 7.6</td>
<td>41.5 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Control</td>
<td>47.2 ± 9.8</td>
<td>44.7 ± 7.1</td>
<td>43.2 ± 6.5</td>
<td>43.7 ± 7.3</td>
<td>41.4 ± 5.2</td>
<td>41.7 ± 6.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Arterial pH</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>NMBA</td>
<td>7.32 ± 0.14</td>
<td>7.35 ± 0.0</td>
<td>7.35 ± 0.07</td>
<td>7.35 ± 0.08</td>
<td>7.40 ± 0.07</td>
<td>7.43 ± 0.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control</td>
<td>7.35 ± 0.11</td>
<td>7.35 ± 0.1</td>
<td>7.38 ± 0.08</td>
<td>7.36 ± 0.07</td>
<td>7.38 ± 0.07</td>
<td>7.37 ± 0.09</td>
<td>&lt;.001</td>
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<tr>
<td><strong>FiO₂</strong></td>
<td></td>
<td></td>
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<tr>
<td>NMBA</td>
<td>0.80 ± 0.15</td>
<td>0.66 ± 0.1</td>
<td>0.57 ± 0.15</td>
<td>0.55 ± 0.15</td>
<td>0.49 ± 0.15</td>
<td>0.47 ± 0.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control</td>
<td>0.71 ± 0.19</td>
<td>0.63 ± 0.1</td>
<td>0.61 ± 0.14</td>
<td>0.59 ± 0.14</td>
<td>0.55 ± 0.14</td>
<td>0.57 ± 0.16</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Total PEEP, cm H₂O</strong></td>
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<td></td>
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<tr>
<td>NMBA</td>
<td>13.2 ± 2.7</td>
<td>12.5 ± 2.4</td>
<td>11.4 ± 2.5</td>
<td>10.8 ± 2.7</td>
<td>9.6 ± 2.8</td>
<td>9.0 ± 2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control</td>
<td>11.0 ± 2.7</td>
<td>11.2 ± 2.5</td>
<td>11.0 ± 2.4</td>
<td>10.6 ± 2.4</td>
<td>10.3 ± 2.4</td>
<td>9.9 ± 2.9</td>
<td>&lt;.001</td>
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<tr>
<td><strong>PIP, cm H₂O</strong></td>
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<tr>
<td>NMBA</td>
<td>35.8 ± 3.6</td>
<td>34.0 ± 5.2</td>
<td>32.2 ± 5.4</td>
<td>32.5 ± 5.8</td>
<td>28.9 ± 5.2</td>
<td>29.2 ± 3.6</td>
<td>&lt;.001</td>
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<tr>
<td>Control</td>
<td>34.9 ± 5.0</td>
<td>33.9 ± 4.8</td>
<td>33.5 ± 4.2</td>
<td>33.7 ± 4.3</td>
<td>33.5 ± 4.8</td>
<td>32.3 ± 5.3</td>
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<td><strong>Pplat, cm H₂O</strong></td>
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<tr>
<td>NMBA</td>
<td>27.5 ± 4.4</td>
<td>26.1 ± 4</td>
<td>25.2 ± 4.9</td>
<td>24.4 ± 4.7</td>
<td>23.1 ± 4.6</td>
<td>23.4 ± 4</td>
<td>NS</td>
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<tr>
<td>Control</td>
<td>24.8 ± 5.7</td>
<td>25.3 ± 4.9</td>
<td>25.0 ± 4.9</td>
<td>25.7 ± 5.3</td>
<td>25.8 ± 5.2</td>
<td>24.5 ± 5.4</td>
<td>.008</td>
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<tr>
<td><strong>MV, L/min</strong></td>
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<tr>
<td>NMBA</td>
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<td>11.2 ± 1.8</td>
<td>11.1 ± 2.0</td>
<td>11.1 ± 1.8</td>
<td>10.8 ± 1.8</td>
<td>10.6 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Control</td>
<td>10.2 ± 2.3</td>
<td>10.3 ± 2.3</td>
<td>10.6 ± 2.6</td>
<td>10.9 ± 2.4</td>
<td>11.2 ± 2.4</td>
<td>11.1 ± 2.4</td>
<td>NS</td>
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<tr>
<td><strong>Vt, mL/kg IBW</strong></td>
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</tr>
<tr>
<td>NMBA</td>
<td>6.5 ± 0.7</td>
<td>6.6 ± 0.8</td>
<td>6.6 ± 0.8</td>
<td>6.6 ± 0.8</td>
<td>7.2 ± 1.5</td>
<td>7.0 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Control</td>
<td>7.0 ± 0.7</td>
<td>7.1 ± 0.8</td>
<td>7.1 ± 0.7</td>
<td>7.1 ± 0.9</td>
<td>7.3 ± 1.0</td>
<td>7.2 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Not significant.
• 36 patients with early ARDS
• Randomised to cisatracurium for 48 hours or placebo
• Cistracurium @ 48hrs:
  ↓*Pulmonary:* IL-1β  ↓*Serum:* IL-6
  IL-6  IL-8  IL-8
• Improved lung protective ventilation:
  Prevent even brief dysynchrony
  Prevent dysynchrony-induced alveolar collapse/overdistention
  ↑Control/homogenisation - PEEP/Tidal volume
Therapeutic Hypothermia

• Current practice¹ - routine use: Prevent shivering: 81% of units
  Treat shivering: 12% of units

• Adverse effects of shivering:
  Increased O₂ consumption
  Delayed cooling
  Discomfort
  Impaired ventilation and general patient care

• Specific concerns:
  Altered pharmacokinetics/pharmacodynamics
  Mask seizures (status epilepticus = 44%¹)
  Impaired neurological assessment

Management of $\uparrow$ICP

Claimed benefits:

- $\downarrow$Airway pressure $\rightarrow$ $\uparrow$Intrathoracic pressure $\rightarrow$ $\uparrow$Cerebral venous drainage
- $\downarrow$Muscle activity $\rightarrow$ $\downarrow$O$_2$ consumption $\rightarrow$ Improved cerebral O$_2$
- $\downarrow$Posturing
- $\downarrow$Ventilator dysynchrony

Prevent acute $\uparrow$ in ICP
Management of ↑ICP

Evidence:

• Vecuronium prevents ↑’s in ICP during suctioning¹

• Reduction in VO₂ minimal (8.7%)²

• Clinical outcomes³: Slight ↓ mortality

↑ Severely disabled/vegetative survivors

↔ Good/moderate functioning survivors

¹Werba et al. Anaesthetist 1986; 40:328-331
Abdominal Compartment Syndrome

World Society of Abdominal Compartment Syndrome Guidelines 2007
# Abdominal Compartment Syndrome

## Evidence

- **Case reports**

- **De Laet et al**¹:

  10 critically ill patients with intraabdominal hypertension
  Bolus cisatracurium
  Reduction in IAP: 18mmHg → 14mmHg (4mmHg)
  No effect on haemodynamics/ urine output
  No effect on ventilatory parameters reported

---

Post-procedural Immobility

- **Precious airway:**
  - Difficult intubation
  - Airway injury/abnormality

- **Vulnerable surgical site:**
  - Plastic/reconstructive
  - Vascular anastamosis
  - Airway surgery e.g. tracheal resection
Abnormal Muscular Activity

- Tetanus
- Neuroleptic malignant syndrome
- Drug overdose/withdrawal
- Status epilepticus
Cisatracurium in “weakening doses” assists in weaning from sedation and withdrawal following extended use of inhaled isoflurane

Mehrengise K. Cooper, FRCPCH; Scot T. Bateman, MD

Pediatr Crit Care Med 2007 Vol. 8, No. 1

- 4-year old asthmatic-severe exacerbation
- Prolonged mechanical ventilation
- Prolonged isoflurane therapy
- Choreoathetoid movements on stopping isoflurane- withdrawal
- Cisatracurium infusion @ weakening doses allowed weaning from:
  - Isoflurane
  - Mechanical ventilation
<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged weakness</td>
<td>Pressure sores</td>
</tr>
<tr>
<td>VAP</td>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Inadequate - sedation</td>
<td>Nerve injuries</td>
</tr>
<tr>
<td>- analgesia</td>
<td>Keratitis/corneal abrasions</td>
</tr>
<tr>
<td>Psychological - PTSD</td>
<td>Myositis ossificans</td>
</tr>
<tr>
<td>- Depression</td>
<td>Inadequate ventilation - circuit disconnection</td>
</tr>
<tr>
<td>Enteral intolerance</td>
<td>- loss of airway</td>
</tr>
<tr>
<td>Tachyphylaxis</td>
<td>Impaired assessment - neurological</td>
</tr>
<tr>
<td></td>
<td>- acute abdomen</td>
</tr>
<tr>
<td></td>
<td>- angina</td>
</tr>
</tbody>
</table>
Inadequate Sedation/Analgesia

Paralysis + recall +/- pain →
- Loss of control
- Fear of dying
- Feeling cared for

Patients’ Recollections of Therapeutic Paralysis in the Intensive Care Unit
Nancy Ballard, Lois Robley, Darcy Barrett, Danielle Fraser and Inocencia Mendoza
© 2006 American Association of Critical-Care Nurses
Published online http://www.ajcconline.org
Posttraumatic Stress Disorder/Depression

- Neuromuscular blockade:
  - ↑ PTSD
  - ↔ Depression

- ↑ Duration of sedation:
  - ↑ PTSD
  - ↑ Depression

Enteral Intolerance

No effect:

- Gastric emptying
- GI absorption
- Enteral tolerance

**Table: Gastric emptying in mechanically ventilated critically ill patients: effect of neuromuscular blocking agent**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>NMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/l)</td>
<td>6.5±3.8</td>
<td>7.7±3.2</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>102±75</td>
<td>98±67</td>
</tr>
<tr>
<td>AUC$_{0-60}$ (mg min$^{-1}$ l$^{-1}$)</td>
<td>82±42</td>
<td>88±46</td>
</tr>
<tr>
<td>AUC$_{0-120}$ (mg min$^{-1}$ l$^{-1}$)</td>
<td>360±262</td>
<td>355±256</td>
</tr>
<tr>
<td>Residual volume 1 h (ml)</td>
<td>110±65</td>
<td>125±85</td>
</tr>
<tr>
<td>Residual volume 2 h (ml)</td>
<td>95±76</td>
<td>105±90</td>
</tr>
</tbody>
</table>

**No difference between groups**

Nosocomial Pneumonia / VAP

- NMB → ↓clearance of secretions → atelectasis → pneumonia
- ↑ VAP¹
- Reflection baseline illness severity²
- Baseline variables controlled for:
  - No ↑ VAP³

# Prolonged Weakness

<table>
<thead>
<tr>
<th>Prolonged recovery:</th>
<th>Accumulation - relaxant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- metabolites</td>
</tr>
<tr>
<td>Drug interactions</td>
<td></td>
</tr>
<tr>
<td>Electrolyte</td>
<td></td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
</tr>
<tr>
<td>derangements</td>
<td></td>
</tr>
<tr>
<td><strong>Myopathy:</strong></td>
<td></td>
</tr>
<tr>
<td>Critical illness myopathy</td>
<td></td>
</tr>
<tr>
<td>Critical illness polyneuropathy</td>
<td></td>
</tr>
<tr>
<td>Critical illness myopathy/neuropathy</td>
<td></td>
</tr>
<tr>
<td>Critical illness neuromuscular abnormalities</td>
<td></td>
</tr>
<tr>
<td>Acute quadriplegic myopathy syndrome</td>
<td></td>
</tr>
<tr>
<td>ICU acquired weakness</td>
<td></td>
</tr>
</tbody>
</table>
Prolonged Recovery

Steroidal NMB
- Pancuronium
- Vecuronium
- Rocuronium

Organ-dependent metabolism:
- Renal
- Hepatic

Active metabolites¹
End-organ dysfunction → accumulation²,³
↑ Risk prolonged blockade¹,³
↓ Cost/dose/duration with TOF monitoring³

²Wang et al.  J Med Hypotheses 2011; 76(1):100-1
³Sessler CN.  Chest 2004; 126(4):1018-1022
Prolonged Recovery

**Benzylisoquinolininiums**
- Atracurium
- Cisatracurium

Organ-independent metabolism;
- Hoffman degradation
- Ester hydrolysis (plasma)

Inactive metabolites¹
Atracurium
- neurotoxic metabolite → Laudanosine¹
- histamine release

Predictable duration blockade²,³,⁴
Reduced risk prolonged blockade²
Reduced risk ICUAW²
No need for TOF monitoring²,⁴

²Sessler CN.  Chest 2004; 126(4):1018-1022
**Drug interactions**

- **Succinylcholine** is potentiated by:
  - Inhibitors of plasma cholinesterase e.g. neostigmine, organophosphorous compounds e.g. ecothiopate, ester local anaesthetic agents, metoclopramide, hexafluorenium, alkylating agents e.g. cyclophosphamide, trimetaphan, esmolol, etomidate
  - Decrease in effective plasma cholinesterase, e.g. homozygous atypical plasma cholinesterase, pregnancy, liver disease

- **Non-depolarizing NMBDs** are potentiated by:
  - Calcium channel blockers, e.g. verapamil, diltiazem
  - Antibiotics, e.g. aminoglycosides (neomycin, gentamicin, vancomycin, kanamycin), erythromycin, tetracycline, lincomycin, clindamycin, metronidazole
  - Local anaesthetic agents, quinidine
  - Immunosuppressant drugs, e.g. cyclosporine, azathioprine
  - H₂ receptor antagonists
  - Trimetaphan
  - Lithium carbonate

**Additional causes of prolonged NM blockade**

¹Tripatthi et al.  CEACCP 2006; 6(3): 119-223
Critical illness myopathy

Critical illness myopathy/neuropathy

Acute necrotising myopathy

ICU Control

Acute quadriplegic myopathy syndrome

ICU acquired weakness (ICUAW)

Critical illness neuromuscular abnormalities (CINMA)

CIM Patient
(Neuro)myopathy

• Acute severe asthma
  + mechanical ventilation
  + high-dose steroids
  + NMB

  Acute myopathy¹,²

• Other populations
  - Sepsis + MODS³
  - Mechanical ventilation + SIRS⁴

  Association
  - Inconsistent
  - Methodological flaws

¹Douglass J.  Am Rev Respir Dis 1992; 146:517-519
²Leatherman et al.  Am J Respir Crit Care Med 1996; 153: 1686-1690
Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study

Steffen Weber-Carstens*†1,2, Maria Deja†1,2, Susanne Koch1,2, Joachim Spranger3, Florian Bubser1,2, Klaus D Wernecke4, Claudia D Spies1,2, Simone Spuler5 and Didier Keh1,2
Neuromuscular dysfunction acquired in critical illness: a systematic review

No association with NMB:
11 of 12 studies
A diagram illustrating the factors contributing to ICU-acquired weakness (ICUAW) and muscle wasting. Key factors include:

- Severe sepsis, systemic inflammation
- Multiple organ failure
- Bedrest, sedation, disuse, trauma
- Insulin resistance
- Hyperglycemia
- Corticosteroids
- Neuromuscular blockers
- IL-1, IL-6, IFN-γ, TNF-α, Complement C3a, C5a, IL-10, TGF-β

The diagram outlines pathways involving:

- Predominant type II muscle fibre atrophy
- Selective myosin loss
- Non-excitable muscle membrane

Protein degradation and synthesis are also indicated, leading to muscle atrophy, less fibre type specific.
Conclusion

- Redefined role in respiratory failure - acute, severe ARDS
- Therapeutic hypothermia → expansion
- Miscellaneous indications → cyclical flux will continue
- Adverse effects overstated
- Use of neurological monitoring to ↑ nerve stimulation
- Nerve stimulation → unnecessary (with cisatracurium)
- Cisatracurium = drug of choice