Contemporary Use of Paralytics in the Critically Ill

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Pharmacy Grand Rounds
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Objectives

• Review the pharmacology of neuromuscular blocking agents
• Discuss applications of neuromuscular blockade in the critically ill adult
• Identify complications of paralytics and considerations for their use
How comfortable are you with recommending paralytics?

- Very comfortable
- Somewhat comfortable
- Uncomfortable
- Get them as far away from me as possible
History of Paralysis

• “The decision to treat a patient in the intensive care unit with neuromuscular blocking agents is a difficult one that is guided more commonly by individual practitioner preference than by standards based on evidence-based medicine.”

  Society of Critical Care Medicine, 2002
Neuromuscular Junction

- Acetylcholine
- Depolarizing
- Non-depolarizing

- Na⁺
- Ca²⁺

Greenberg et al. *Crit Care med* 2013;41:1332-44.
Depolarizing Neuromuscular Blocker

Acetylcholine
Depolarizing
Non-depolarizing
Non-depolarizing Neuromuscular Blocker

Acetylcholine
Depolarizing
Non-depolarizing

Na⁺ Na⁺ Na⁺ Na⁺ Na⁺ Na⁺ Na⁺ Na⁺ Na⁺

Ca²⁺ Ca²⁺ Ca²⁺ Ca²⁺ Ca²⁺ Ca²⁺ Ca²⁺ Ca²⁺

<table>
<thead>
<tr>
<th>MOA</th>
<th>Succinylcholine</th>
<th>Vecuronium</th>
<th>Rocuronium</th>
<th>Atracurium</th>
<th>Cisatracurium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Depolarizing</td>
<td>Aminosteroidal</td>
<td>Non-depolarizing</td>
<td>Benzylisoquinolinium</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus*</td>
<td>1</td>
<td>0.08 - 0.1</td>
<td>0.6 - 1</td>
<td>0.4 - 0.5</td>
<td>0.1 - 0.2</td>
</tr>
<tr>
<td>Infusion†</td>
<td>--</td>
<td>0.8 - 1.7</td>
<td>8 - 12</td>
<td>5 - 20</td>
<td>1 - 3</td>
</tr>
<tr>
<td>Onset (s)</td>
<td>60</td>
<td>180</td>
<td>75</td>
<td>110</td>
<td>150</td>
</tr>
<tr>
<td>Duration (m)</td>
<td>10</td>
<td>33</td>
<td>33</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>Elimination</td>
<td>Plasma cholinesterase</td>
<td>Hepatic, renal excretion</td>
<td>Hepatic, renal excretion</td>
<td>Hofmann elimination</td>
<td>Hofmann elimination</td>
</tr>
<tr>
<td>Other Effects</td>
<td>Initial fasciculations Hyperkalemia, Hyperthermia</td>
<td>Vagolytic (high doses)</td>
<td>Vagolytic (high doses)</td>
<td>Histamine release</td>
<td>--</td>
</tr>
</tbody>
</table>

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*mg/kg
†mcg/kg/min

Intensive Care Unit Applications

• **Respiratory**
  • Acute respiratory distress syndrome
  • Status asthmaticus

• **Compartmental syndromes**
  • Increase intracranial pressure
  • Intraabdominal hypertension

• **Procedural uses**
  • Therapeutic hypothermia

• **Miscellaneous uses**
Acute Respiratory Distress Syndrome

**Berlin criteria**
- Within 1 week of insult
- Bilateral pulmonary infiltrates
- Non-cardiac related edema
- \( \text{PaO}_2/\text{FiO}_2 \leq 300 \) with PEEP \( \geq 5 \text{ mmHg} \)

- ↑Tidal volumes
- Active exhalation
- Ventilator asynchrony

- Atelectrauma
- Biotrauma
- Volutrauma

Lung Injury


PEEP = positive end expiratory pressure
Paralysis in ARDS

Paralysis

↑ arterial oxygenation

↓ spontaneous respiration

↓ work of breathing

↓ pulmonary blood flow

ACURASYS

- **Design**
  - Multicenter, randomized, placebo-controlled, double blind
  - N = 340

- **Intervention**
  - Protective ventilation strategy **PLUS**
    - Cisatracurium 15 mg bolus then 37.5 mg/hr infusion x 48 hrs
    - Placebo

- **Population**
  - Mechanical ventilation for moderate-severe ARDS
    - PaO\textsubscript{2}/FiO\textsubscript{2} < 150

PEEP = positive end expiratory pressure

ACURASYS

- 90-day mortality HR 0.68 (p = 0.04)
- ↓Barotrauma, ↑ventilator- and organ failure-free days
- No differences in ICU-acquired muscle weakness

Paralysis
Placebo

Limitations

• Under powered
• No difference in crude mortality
• Lack of true blinding
• Depth of paralysis not measured
• Lack of long-term paresis follow up
• Optimal dosing strategy unknown
ROSE

- Assess the efficacy and safety of early neuromuscular blockade in patients with moderate to severe acute respiratory distress syndrome

<table>
<thead>
<tr>
<th>Hypoxemia inclusion criterion</th>
<th>ACURASYS</th>
<th>ROSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF &lt; 150 on PEEP ≥ 5 mmHg</td>
<td>PF &lt; 150 on PEEP ≥ 8 mmHg, or SF</td>
<td></td>
</tr>
<tr>
<td>PEEP</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Blinding</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sedation (control)</td>
<td>Deep</td>
<td>Light</td>
</tr>
<tr>
<td>Sample size</td>
<td>340</td>
<td>1,408</td>
</tr>
<tr>
<td>Long-term outcomes</td>
<td>None</td>
<td>3, 6, 12-mo phone interviews</td>
</tr>
</tbody>
</table>

PEEP = positive end expiratory pressure
PF = PaO₂/FiO₂
SF = SaO₂/FiO₂

Agent Selection in ARDS

- Studies limited to cisatracurium
  - Less laudanosine
  - Less histamine release, hypotension
  - High cost

- Retrospective cohort (N = 76)
  - NBMA within 72 h for moderate-severe ARDS
  - No differences in clinical outcomes
  - Atracurium significantly lower cost
    - Per patient: $166 vs. $2,256

Moore et al. Respir Care 2017; Epub ahead of print.
Status Asthmaticus

Positive pressure mechanical ventilation

Hyperventilation ↑Airway pressure

Barotrauma +/- Hemodynamic collapse

Paralysis

Improved minute ventilation

Relax overworked muscles

Tight control of RR, lung volumes

↑ventilator synchrony

deBacker et al. CHEST 2017;151:697-706.
Adnet et al. 2001

- Retrospective cohort (n = 101)
  - Status asthmaticus requiring mechanical ventilation
  - NMBA + sedation vs. sedation alone

- Outcomes
  - ↑ ICU stay and MV time with NMBAs

Paralysis vs. No paralysis:
- Multi-organ failure: p = 0.007
- VAP: p < 0.0001
- Myopathy: p = 0.010
- Mortality: p = 0.844

NMBA = neuromuscular blocking agent
MV = mechanical ventilation
VAP = ventilator-associated pneumonia

Status Asthmaticus

Griffin et al. 1992
- Case series (n = 3) + literature review (n = 15)
- Steroidal NMBAs resulted in severe myopathy

Leatherman et al. 1996
- Retrospective cohort (n = 107)
- Muscle weakness associated with ↑ duration of paralysis and steroid use
- No differences with non-steroidal NMBAs

Behbehani et al. 1999
- Retrospective cohort (n = 86)
- ↑2.1-fold odds myopathy every day of paralysis
- Dosage and type of NMBA no effect on myopathy

NMBA = neuromuscular blocking agent

Traumatic Brain Injury

• Cerebral vasodilation
• Cerebral edema
• Traumatic masses

Suctioning
Tests/procedures
Iatrogenic stimuli

Cough
Agitation
Posturing

↑Intracranial Pressure

Paralysis in ↑ ICP

- Prolong mechanical ventilation
- Mask post-traumatic seizures
- Prohibit neurologic exam
- ↓shivering
- ↓cough reflex
- ↓energy expenditure
- ↓positive end-expiratory pressure
- ↑ventilation

Hsiang et al. 1994

- Retrospective database review (n = 514)
  - Severe head injury (GCS ≤ 8)
  - Paralysis ≥ 12 hours vs. no paralysis

- Outcomes
  - ↑ ICU stay with NMBAs
Increased Intracranial Pressure

**Prielipp et al. 1997**
- Prospective, open-label study (n = 8)
- Traumatic head injury patients
- Bolus doxacurium (0.05 mg/kg) followed by continuous infusion (0.015 mg/kg)
- No changes in blood pressure or ICP
- Did not report adverse events or myopathies

**Schramm et al. 1998**
- Randomized controlled trial (n = 14)
- Neurosurgical patients
- Bolus atracurium (0.75 mg/kg) or cisatracurium (0.15 mg/kg)
- Atracurium ↓ICP, CPP, CBF, and MAP
- Cisatracurium no changes in ICP, CPP, or CBF

CPP = cerebral perfusion pressure
CBF = cerebral blood flow
MAP = mean arterial pressure

Abdominal Compartment Syndrome

Third spaced fluids
Tense abdominal closures
Pain

↓ abdominal wall compliance

↑ Intra-abdominal Pressure

IAP = Intra-abdominal pressure
IAH = Intraabdominal hypertension
ACS = Abdominal compartment syndrome

Paralysis in ↑ IAP

- Avoid surgery
- Allow time for intervention
- ↓ abdominal muscle tone
- ↑ abdominal wall compliance

De Waele et al. 2003

- 81 y/o male, GI bleed, surgical management
  - 12 units packed reds, 4L+ crystalloid
  - IAP 26 mmHg, ↓ urine output

- Cisatracurium 10 mg bolus
- Cisatracurium 5 mcg/kg/min infusion
Prospective cohort study (n = 10)
- Cisatracurium 0.15 mg/kg IV bolus in sustained IAP ≥ 12 mmHg, organ dysfunction
- ↓IAP with NMBA at 15, 30 minutes, with subsequent recovery, no differences in MAP, APP, CVP, HR

Prospective observational study (n = 478)
- Surgical/medical management algorithm of IAH/ACS including NMBAs (unspecified)
- ↑survival 50% to 72% (p = 0.015)
Therapeutic Hypothermia

- ↓ body temperature
- ↓ shivering
- ↓ peripheral O₂ consumption
- ↓ time to goal temperature
- ↑ Paralysis
- ↑ heat, metabolic rate
- ↑ ICP
- ↓ brain tissue O₂

Jurado et al. 2011

• Retrospective chart review (n = 123)
  • NMBA 2 hours after cooling or onset of shivering
  • Vecuronium 0.8 mcg/kg/min vs. 0.05 mg/kg q2h

• Continuous infusion
  • Quicker recovery from blockade
  • Quicker time to extubation

• Intermittent boluses
  • Quicker to goal TOF
  • Less total NMBA exposure

TOF = train of four
ROSC = return of spontaneous circulation
OR = odds ratio
Post-Arrest Therapeutic Hypothermia

**Salciccioli et al. 2013**
- Prospective observational study (n = 111)
- NMBA (unspecified) within 24 hours of ROSC
- Cooled to 35-56 °C
- ↑ survival with NMBA (OR 7.23, CI 1.6-33.4)

**Lascarrou et al. 2014**
- Retrospective cohort study (n = 144)
- Cisatracurium 10 mg bolus then 10 mg/hr continuous infusion
- Cooled to 32 °C
- NMBAs ↓ ICU mortality, ↑ pneumonia

TOF = train of four
ROSC = return of spontaneous circulation
OR = odds ratio

Miscellaneous Uses

• Intubation
• Tetanus
• Neuroleptic malignant syndrome
• Serotonin syndrome
• Organophosphate poisoning
• Opioid-induced chest wall rigidity

Coruh et al. CHEST 2013;143:1145-6.
Are Paralytics Worth It?

- Optimization of mechanical ventilation
  - ↓ barotrauma
  - Transient ↓ IAP
  - ↓ shivering

- Acquired neuromuscular disorders
- Mask neurologic status
- Prolonged ICU stay
- Potential for under-sedation
- High risk medication
- Cost

Concomitant Supportive Therapies

- Artificial respiration
- Analgesia
- Sedation
- VTE prophylaxis
- Corneal lubrication
- Secretion suctioning
- Re-positioning, bunny boots
- Head of bed elevation

Monitoring

Train-of-Four

- Ulnar, facial, or posterior tibial nerve
- Muscle twitch

- Is this necessary?
  - Titration to TOF
  - Titration to effect
Reversal

- **Acetylcholinesterase inhibitors**
  - ↑Acetylcholine at neuromuscular junction
  - ↓Residual neuromuscular blockade
  - Concomitant antimuscarinics
  - DO NOT give if near full neuromuscular recovery

- **Sugammadex**
  - Tight complex with steroidal NMBA
  - Reversal of rocuronium blockade in ~3 minutes
  - Not studied in the ICU population

Which agent has the quickest onset and duration of action?

- Vecuronium
- Succinylcholine
- Atracurium
- Rocuronium
- Cisatracurium
All patients receiving paralytics should routinely be administered pharmacological therapy for reversal of neuromuscular blockade.

- True
- False
Conclusion

• Neuromuscular blocking agents can provide depolarizing or non-depolarizing paralysis
• There are a wide variety potential applications for neuromuscular blockade in the intensive care unit
• Intensive care unit providers should be vigilant with regards to providing appropriate supportive care while patients are paralyzed
Acute Respiratory Distress Syndrome

- Meta-analysis of 48h cisatracurium infusion
  - 3 studies, n = 431

Mortality
  - 28-day
  - ICU
  - Hospital
Barotrauma
ICU-acquired weakness

Risk ratio

Favors Paralysis
Favors Control

Alhazzani et al. Critical Care 2013;17:R43.
Intubation

- **Cochrane review 2017**
  - 34 RCTs, n = 3565
  - NMBAs ↑ ease of tracheal intubation
  - NMBAs ↓ upper airway discomfort and injury

- **Cochrane review 2015**
  - 50 RCTS, n = 4151
  - Improved intubation conditions with succinylcholine compared to rocuronium


RCT = randomized controlled trial
Monitoring

Bispectral Index

BIS 44
EMG
EEG

I/O