The Use and Abuse of Muscle Relaxants

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Disclosure

• Several of the slides in this presentation are the property of Merck
• I am on a Merck advisory board
• Several of the slides have also been used in PCTH 201.
Learning Expectations

- You will understand the use of muscle relaxants better
- You will respect the power and danger associated with use of muscle relaxants
- You will learn of some serious problems with misuse of muscle relaxants
- You will review a Canadian study of post-operative residual paralysis
- You will learn of a not-yet-licensed reversal agent.
The Crazy Neurologist

- “isolated limb” technique
- “Let’s study the CO2 level at which it is impossible to hold your breath”
- “I’ll go first because I’m tough” (plus none of the “volunteers” willing to proceed until the neurologist’s attempt was done)
- Tourniquet left arm – inflated to 300 mm Hg– IV and arterial lines placed
The Crazy Neurologist

• O2 by mask
• Curare injected into IV
• We watched....
  ▫ And watched...
    • And watched...
• No movement – he must be really tough!
• Senior resident very uneasy – masks and bags neurologist
The Crazy Neurologist

- Tourniquet had deflated due to leak
- Neurologist paralysed and unable to let us know
- He survived but had a psychotic breakdown - hospitalised
- When he returned to work some months later, all “volunteers” refused to participate in study
Implications

• Imagine what it would feel like to be fully conscious but unable to communicate in any way or move muscles!!
• Extraordinarily frightening – the negative associated with “misuse” of muscle relaxants
Uses for Muscle Relaxants

- Intubation – paralysis of upper airway muscles so that endotracheal tube can be placed
- Surgical relaxation – paralysis of abdominal, and thoracic muscles during surgery so that surgery is possible in these areas of powerful muscles
- Control of ventilation in the ICU when patients are unable to tolerate ventilation
Principle of Use

- Muscle relaxants **KILL** in the absence of controlled ventilation
- Muscle relaxants must NEVER be used alone
- All persons receiving muscle relaxants MUST receive drugs capable of providing deep sedation or anesthesia
The Million Lawsuits

- U.S. has more lawyers than the rest of the world combined
- In 1980’s a new type of anesthesia for cardiac surgery was described: extreme high dose narcotics – excellent control of pulse and blood pressure – widely adopted in N.A.
- After 5 years, over 1 million lawsuits in U.S. for RECALL during surgery – Why??
The Million Lawsuits

• Anesthetic technique:
  ▫ Small dose of benzodiazepine
  ▫ Huge dose of narcotic (3 mg/kg morphine or 100 – 150 ug/kg fentanyl or 10-15 ug/kg sufentanil) as bolus
  ▫ Muscle relaxant – usually pancuronium
  ▫ Very smooth anesthesia
  ▫ Narcotic effect lasted for 24 – 36 hours
The Million Lawsuits

• What are the components of an anesthetic?:
  ▫ 1. Anesthesia – unconsciousness – can vary from quite light sleep to very deep unconsciousness
  ▫ 2. Analgesia – control of pain associated with surgery or mechanical ventilation
  ▫ 3. Amnesia – complete loss of awareness of the surgical event

What was missing in the high narcotic anesthetic?
The Million Lawsuits

• AMNESIA
  ▫ Narcotics do not provide amnesia although they can create very deep “sleep-like state”
  ▫ Muscle relaxants – absolutely no amnesia – only action is to paralyse muscles – no CNS effects
  ▫ In Canada, during the same period, using similar anesthetic techniques, there were NO lawsuits for recall during cardiac surgery
  ▫ Why??
The Million Lawsuits

- Canadians are more conservative than Americans (clinically, not politically)
- Canadian anesthetists turned on very low doses of vapour anesthetics (halothane or isoflurane) during cardiac surgery as an addition to the high narcotic doses
- Anesthetic vapours are profoundly effective as amnesticics, even in very low doses
My personal screw-ups

• Emergency physician – extremely high strung – asked me to be her anesthetist for a “nose job” being done under local anesthesia
• The plan was to add small amounts of sedation if she could not tolerate surgery
• She became quite agitated as local was being injected and I injected a small dose of midazolam
• As I injected, I noted that the label on the syringe said “succinylcholine”
My own screw-ups

• The dose of succinylcholine was small but the patient was also small
• I told the surgeon to stop, went to the patient’s head, told her what had happened and provided ventilation by bag and mask
• She recovered quickly but even though I was in direct verbal communication with her and reassured her that she would be well, she was terrified by the experience
• Did little to raise my profile with my emergency physician colleagues
Another screw-up (my own)

- Patient was lovely woman having minor abdominal surgery
- I induced anesthesia with propofol and added rocuronium for relaxation and intubation and started ventilation
- THE PHONE RANG!!
Another screw-up (my own)

- I was V/P Medicine for Providence Health Care at the time and the phone call was from a very aggressive reporter for the Vancouver Sun who wanted to know why I had not fired a surgeon who, he claimed, was incompetent
- Angry discussion
- I noticed that I had forgotten to turn on the anesthetic vapour and slammed down phone – turned on vapour – about 10 minutes without vapour – propofol probably gave amnesia for around 5 minutes
Another screw-up (my own)

- When surgery was over, I notified PACU nurse that the patient might have recall and asked her to get in touch with me immediately if patient mentioned recall
- Patient had recall! – I explained exactly what had happened – that the problem was not something wrong with her, and that it would probably never recur
Another screw-up (my own)

- Recorded on patient’s chart exactly what had happened
- Notified CMPA (Canadian physician insurer) and was told to withhold information from patient and write nothing on the chart
- Patient forgave me – she just wanted to know what had happened and appreciated that I did not lie to her
What have I learned from all of this?

1. muscle relaxants are dangerous and should only be used with care and respect
2. recall during anesthesia, while paralysed, is a terrifying experience for a patient and they need re-assurance that it wasn’t caused by some medical problem of their own
3. patients deserve to be told everything – Canadians are not interested in lawsuits, they are interested in explanations and regret
How they work?

• Depolarizers:
  ▫ Succinylcholine
  ▫ “irreversible” combination with receptors at neuromuscular endplate to cause depolarization and contraction of the myofibril followed by blockage of acetylcholine
  ▫ Dependent upon “serum”, or “plasma” cholinesterase for normal metabolism – cannot be reversed by additional drugs
  ▫ Relatively short acting except in conditions of genetic lack of serum cholinesterase
How do they work?

- **Non-depolarizers:**
  - Curare-like: curare, atracurium, cis-atracurium, mivacurium
  - Steroid-based: pancuronium, vecuronium, rocuronium (most popular), rapicuronium (withdrawn due to cardiac deaths in children in U.S.)
  - “reversible” – competitive block with acetylcholine – no depolarization – reversed with acetylcholinesterase inhibitors which raise concentration of acetylcholine that competes with the muscle relaxant to reverse the block
How well do Canadian anesthetists reverse muscle relaxants?

- The majority of anesthesiologists reverse non-depolarizing muscle relaxants (usually rocuronium) with neostigmine (acetylcholinesterase inhibitor) and glycopyrrolate (anti-muscarinic) – neostigmine is a “stupid” drug which reverses all the effects of acetylcholine (nicotinic and muscarinic) on the body.
- This leads to muscarinic side-effects such as bronchospasm, excessive salivation, excessive bronchial secretions and bradycardia.
- These side-effects are prevented by adding the anti-muscarinic drug to the reversal cocktail.
Mechanisms of action

**Edrophonium:**
Electrostatic attraction/hydrogen bonding

**Neostigmine/Pyridostigmine/Physostigmine:**
Covalent bonding
How well do Canadian anesthetists reverse muscle relaxants?

• BUT:
  ▫ Are patients fully reversed?
  ▫ Are the correct doses of reversal used?
  ▫ Are the reversals given at the correct time?
  ▫ Are there any risks with less than ideal reversal?
How well do Canadian anesthetists reverse muscle relaxants?

- Risks of less than ideal reversal:
  - Good evidence (Murphy in a number of papers) that patients have reduced airway reflexes and esophageal contractility when not fully reversed
  - Good evidence (Murphy and others) that there is an increased risk of aspiration, pneumonia, hypoxemia and delayed discharge when patients arrive in the recovery room with residual paralysis
RECITE Trial

- RECITE – Residual Curarization and its Incidence at Tracheal Extubation
- Study of “usual” practice at 8 Canadian sites from Halifax to Vancouver
- Measured degree of relaxation during surgery, at time of extubation and at time of admission to recovery room
- Anesthesiologist, surgeon, and principal investigator blinded to data collection
- Anesthesiologists provided anesthesia without any interference from the study protocol
RECITE Trial

- All patients having open abdominal or laparoscopic abdominal surgery
- Only requirement to anesthesiologists: must use a non-depolarizing muscle relaxant (this is usual practice across the country)
- Muscle relaxation – neuromuscular function was assessed using acceleromyography (TOF-Watch® SX) at tracheal extubation and arrival in PACU
RECITE Study Sites
Study consortium and interim analysis

- 17% TOF < 0.6
- 11% TOF 0.6-0.69
- 11% TOF 0.7-0.79
- 46% TOF > 0.89
- 15% TOF 0.8 - 0.89
Overall Incidence of rNMB at extubation – 54% - overall incidence of rNMB in the PACU – 46%
Incidence of rNMB at tracheal extubation - 54% - no difference between sub-groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidence rNMB – no. of patients (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male (n=38) vs. female (n=112)</td>
<td>19 (50) vs. 62 (55.4)</td>
<td>0.58*</td>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;50 (n=90) vs. ≥50 (n=60)</td>
<td>47 (52.2) vs. 34 (56.7)</td>
<td>0.62*</td>
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<tr>
<td>BMI</td>
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<tr>
<td>&lt; 30 (n=92) vs. ≥30 (n=58)</td>
<td>50 (54.3) vs. 31 (53.4)</td>
<td>1.00*</td>
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<tr>
<td>ASA class</td>
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<tr>
<td>I (n=37) vs. II (n=85) vs. III (n=28)</td>
<td>23 (62.2) vs. 45 (52.9) vs. 13 (46.4)</td>
<td>0.43**</td>
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<tr>
<td>Type of surgery</td>
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<tr>
<td>Open abdominal (n=68) vs. laparoscopic (n=81)</td>
<td>36 (52.9) vs. 44 (54.3)</td>
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<td>Reversal agent usage</td>
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<tr>
<td>No (n=37) vs. yes (n=113)</td>
<td>17 (45.9) vs. 64 (56.6)</td>
<td>0.34*</td>
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<tr>
<td>PNS usage</td>
<td></td>
<td></td>
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<tr>
<td>No (n=49) vs. yes (n=101)</td>
<td>24 (49.0) vs. 57 (56.4)</td>
<td>0.48*</td>
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</table>
Incidence of rNMB at arrival in PACU - 46% - no differences between sub-groups

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<td><strong>Sex</strong></td>
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<td>14 (50) vs. 47 (44.3)</td>
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<td><strong>Age</strong></td>
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<tr>
<td>&lt;50 (n=90) vs. ≥50 (n=60)</td>
<td>33 (40.2) vs. 28 (53.8)</td>
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<td><strong>BMI</strong></td>
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<td>&lt; 30 (n=92) vs. ≥30 (n=58)</td>
<td>34 (40.5) vs. 27 (54)</td>
<td>0.15*</td>
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<td><strong>ASA class</strong></td>
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<td>I (n=37) vs. II (n=85) vs. III (n=28)</td>
<td>17 (51.5) vs. 35 (44.3) vs. 9 (40.9)</td>
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<td>Open abdominal (n=68) vs. laparoscopic (n=81)</td>
<td>32 (51.6) vs. 29 (40.8)</td>
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<td><strong>Reversal agent usage</strong></td>
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<td>No (n=37) vs. yes (n=113)</td>
<td>10 (32.3) vs. 51 (49.5)</td>
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<td><strong>PNS usage</strong></td>
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<td>No (n=45) vs. yes (n=89)</td>
<td>17 (37.8) vs. 44 (49.4)</td>
<td>0.27*</td>
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Impact of reversal agents (neostigmine) used in 75.3% of cases

<table>
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<tr>
<th></th>
<th>Total</th>
<th>No reversal</th>
<th>Reversal</th>
<th>p value*</th>
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<td>37</td>
<td>113</td>
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<tr>
<td>rNMB</td>
<td>81</td>
<td>17 (45.9%)</td>
<td>64 (56.6%)</td>
<td>0.34</td>
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<tr>
<td>No rNMB</td>
<td>69</td>
<td>20 (54.1%)</td>
<td>49 (43.4%)</td>
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<tr>
<td>PACU</td>
<td>134</td>
<td>31</td>
<td>103</td>
<td>0.1</td>
</tr>
<tr>
<td>rNMB</td>
<td>61</td>
<td>10 (32.3%)</td>
<td>51 (49.5%)</td>
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<tr>
<td>No rNMB</td>
<td>73</td>
<td>21 (67.7%)</td>
<td>52 (50.5%)</td>
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Conclusions

- There were no significant difference between Canadian sites (NO! your site is not better than all the rest)
- The total dose of rocuronium used was associated with residual paralysis – higher doses = more residual paralysis
- The use of subjective NMB monitoring lowered the incidence of residual paralysis slightly but not significantly
Reversal agent: Suggamadex
A modified γ-cyclodextrin
Mechanism of action

rocuronium + sugammadex = a perfect fit
Suggamadex

- Combines with rocuronium irreversibly
- Extremely rapid action (around 1 minute) compared with neostigmine
- No effects upon muscarinic receptors
- Very clean side-effect profile
- Will reverse even very large doses of rocuronium in 75 seconds or less
- Not available in Canada
Key points

- Neuromuscular blocking agents relax skeletal muscle but produce no unconsciousness, amnesia, or analgesia.

- Depolarizing neuromuscular blockers are nicotinic acetyl-choline receptor (nAChR) agonists whereas nondepolarizing blockers are competitive nAChR agonists.

- Succinylcholine has significant side effects, including life-threatening hyperkalemia and cardiac arrest.

- The more potent a nondepolarizing neuromuscular blocker the slower its speed of onset.

- The action of nondepolarizing neuromuscular blockers can be reversed by acetylcholinesterase inhibitors and sugammadex.
Questions?

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