2016 Winter Anesthesia Conference

New Drugs in Anesthesia

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St. Louis College of Pharmacy
Director, The Center for Clinical Pharmacology
## Disclosures:

<table>
<thead>
<tr>
<th>Company</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEN Healthcare</td>
<td>Consultant</td>
</tr>
<tr>
<td>Astra-Zeneca</td>
<td>Grand Rounds lecture</td>
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<tr>
<td>Medicines Co</td>
<td>Attended a consultants meeting</td>
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</table>
New Drugs in Anesthesia

1. Historical perspective
2. New propofol formulations (fospropofol)
3. Sugammadex
4. New opioid delivery systems
5. Remimazolam
6. Sedasys
7. Other new drugs & drugs in development
New drug development in anesthesia

1980s: midazolam, propofol, sufentanil, alfentanil, isoflurane, atracurium, vecuronium

1990s: sevoflurane, desflurane, remifentanil, ondansetron, granisetron, dolasetron, tropisetron, cisatracurium, doxacurium, mivacurium, rapacuronium, rofecoxib, dexmedetomidine, levobupivacaine, ropivacaine

2000s: rocuronium, parecoxib/valdecoxib

2008: fosaprepitant, fospropofol, methylnaltrexone, alvimopan

mivacurium, atracurium, l-bupivacaine, rapacuronium, rofecoxib, parecoxib/valdecoxib
General issues in new drug development

**BUSINESS MODEL**
- Market size
- Development costs
- Sales
- Margins
- Return on investment

**Unmet need**
- Clinical
- Financial

**Strategies**

**Costs: Overall trend in R&D efficiency (inflation-adjusted)**

General strategies for new drug development:

1. Synthesis of novel active compounds
   “new chemical entities”, IND, NDA
2. Single enantiomers of marketed drugs
3. Prodrugs of marketed drugs (avoid solubility problems)
4. Reformulation of marketed drugs
5. New routes of administration for marketed drugs
6. Generic versions of marketed drugs

Kilpatrick: Curr Opin Anaesthesiol 2006;19:385-9
Propofol

• 2,6-diisopropylphenol in lipid emulsion
  (Intralipid: soybean oil, egg yolk lecithin, glycerol)
• Standard for anesthetic induction, procedural & ICU sedation
• Market continues to expand (sedation)
• Top 1 to 3 drug in ICU pharmacy costs

What’s the problem?
• bacterial contamination (EDTA, sulfite)
• emulsion stability
• hyperlipidemia
• pain on injection (20-60%)
• “propofol infusion syndrome”
• Everybody wants to use it (gastroenterologists, pediatricians, emergency dept, etc)

(target of new formulations)
Propofol

The big “problem”: propofol label
"For general anesthesia or sedation, propofol should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.”

“Solution(s)”: 
1. Petition FDA to change label 
2. Develop a new formulation (specifically for sedation)

“Any new medication or sedation device/monitoring system that can be demonstrated to further promote sedation safety may make prior concerns seem less relevant” (www.gastro.org)
Propofol: Alternative Formulations

Propofol phosphonomethyl ester prodrug
fospropofol (ProQuest PG-1002, Guilford GPI-15715, MGI GPI-15715, Aquavan®, Eisai Lusedra®)
Developed for procedural sedation

Anesthesiology 2005;103:860-76
• 8 min conversion half-life to propofol
• Slow onset (6.5 ± 4.5 min to sedation at 6.5 mg/kg)
• Difficult to titrate
Approved (2008) for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures

Side Effects:
1. Respiratory depression: (1-3% of pts)
2. Hypoxemia: (4% at standard dosing, 27% at higher doses)
   Occurred in pts able to respond purposefully; retention of purposeful responsiveness did not prevent hypoxemia
3. Hypotension: (4% at standard dosing, 6% at higher doses)
4. LOC: (4-16% incidence, duration 2-20 min)
Fospropofol disodium injection

5. **Paresthesias**
   - Most frequent adverse reactions in clinical trials (50-75%)
   - Includes burning, tingling, stinging, and/or pruritus
   - Usually manifested in the perineal region
     10. male genital paresthesia
     9. genital burning sensation
     8. vaginal burning sensation
     7. burning genital pain
     6. burning perineal pain
     5. burning anal discomfort
     4. stinging buttock pain
     3. stinging groin pain
     2. miscellaneous burning (chest, ear, nose)
     1. *non-specific sensory disturbance in pubic area*
Fospropofol

- Delayed onset of clinical effect
- Difficult to titrate
- High incidence of side effects
- Administer only by persons trained in administration of general anesthesia, not involved in the diagnostic or therapeutic procedure
- Controlled substance (CIV, US)

Unlikely to revolutionize the practice of anesthesia
Computer-assisted personalized sedation (CAPS) for minimal-moderate sedation

Developed for automated propofol sedation with patient monitoring (ECG, HR, BP, RR, SaO$_2$, exhaled CO$_2$, response to auditory command)

May stop or decrease but not increase rate of propofol infusion

More complex than open-loop system (Diprifusor®); not a true closed-loop system which titrates drug to effect

US approval May 2013:
Indicated for IV administration of 1% propofol for initiation and maintenance of minimal-to-moderate sedation in ASA I and II pts ≥18yr undergoing colonoscopy and esophagogastroduodenoscopy
Must only be used in hospitals and/or healthcare facilities where an anesthesia professional is immediately available for assistance or consultation as needed. Definition of ‘immediate availability of an anesthesia professional’ will be determined by each individual facility.

Team member monitoring the patient and managing sedation should not be involved in the conduct of the procedure.

SEDASYS® System should be used by a physician-led team trained in administering moderate sedation and trained in the management of under and over sedation. At a minimum, the member of the physician-led team who is administering sedation must have training in the management of the cardiorespiratory effects of propofol when administered using computer-assisted personalized sedation systems.

Prospective users of the SEDASYS® System should complete an approved device training program before using the System.
Neuromuscular monitoring

stimulate

monitor twitch

single twitch height (% control)

Ulnar nerve
\[ \downarrow \]
adductor pollicis {thumb}

Facial nerve
\[ \downarrow \]
corrugator supercilii (orbicularis oculi) {eyebrow}

Train of four

<table>
<thead>
<tr>
<th>4</th>
<th>4</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>4</th>
<th>4</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.7</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.4</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

TOF count

TOF ratio \((T_4/T_1)\)

Goal:

TOF ratio > 0.9

Shallow block: TOF count 4 with decrement (fade)

Moderate block: TOF count 1–3

Deep block: TOF count 0; post-tetanic count (PTC) ≥ 1 (profound or intense block)

Extreme block: TOF count 0, PTC 0

Kopman: Anesth Analg 2015;120:51-8
Neuromuscular monitoring

Respiratory function, airway integrity & clinical tests as a function of TOF ratio

- Swallow, airway, teeth clench lost at TOFR < 0.9
- Head lift, tongue, hand grip lost at TOFR 0.4-0.7
- VT & FRC preserved, even at low TOFR

Recommended target to avoid residual NMB: TOF ratio > 0.9

Note: Considerable interpatient variability; curves are approximations only!

Donati: Can J Anaesth 2013;60:714-29
Neuromuscular monitoring

Qualitative (visible, tactile, “mechanomyography”):

- OK for counting twitch (TOFC)
- Cannot reliably detect TOFR decrement if TOFR > 0.4
- Cannot reliably detect fade from 50Hz tetanus
- Can reliably detect fade from 100Hz tetanus at TOFR 0.8-0.9, thus this is best (but painful, and cannot retest for 5-10 min)

Quantitative:

- Electromyography
- Kinemyography
- Acceleromyography

Donati: Can J Anaesth 2013;60:714-29
Neuromuscular monitoring

NMB technologies & quantitative TOFR thresholds to assess paralysis

<table>
<thead>
<tr>
<th>Year</th>
<th>TOFR≥0.7 MMG</th>
<th>TOFR≥0.8 MMG</th>
<th>TOFR≥0.9 MMG</th>
<th>TOFR≥1.0 AMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1942</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970</td>
<td></td>
<td></td>
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<td>1990</td>
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<tr>
<td>2000</td>
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<tr>
<td>2004</td>
<td></td>
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</tbody>
</table>

**Clinical tests corresponding to various TOFR thresholds**

- **TOFR<0.7**
  - MIP>25 cm H2O
  - vital capacity>15ml/kg
  - tidal volume
  - sustained eye opening
  - handgrip
  - tongue protrusion

- **0.7<TOFR<0.9**
  - MIP>50 cm H2O
  - head-lift test
  - leg-lift test
  - tongue depressor test
  - handgrip

- **TOFR>0.9**
  - no clinical test available to date

**Qualitative detection of decrement or fade and measured TOFR**

- **TOF≈0.4**
  - DBS≈0.6
  - Tetanus 50Hz, 5 sec ≈ 0.4

- **Tetanus 100Hz, 5 sec ≈ 0.85**
  - no qualitative instrumental test available to date

**Acceleromyography and TOFR ≥ 1.0 are the recommended standard**
Clinical Problems:

1. Residual paralysis remains common (4-84%); risks=airway obstruction, aspiration, hypoxemia, vent. failure

2. Most practitioners unaware of residual paralysis
   • 80% they’ve never seen clinically significant PACU paralysis
   • 60% estimate the incidence is <1%

3. Most practitioners do not know what constitutes adequate recovery from neuromuscular blockade

4. Most practitioners do not routinely use quantitative NMB monitoring to ensure adequate recovery (TOFR >0.9)

4. Adequate reversal often not documented
Antagonism ("reversal") of neuromuscular blockade

- Neostigmine (40-70 µg/kg) and edrophonium (70-100 µg/kg) are the AChE inhibitors.
- Edrophonium has much faster onset & time to peak effect vs neostigmine.
- Edrophonium & neostigmine have similar elimination rates and duration of effect.
- Edrophonium & neostigmine equi-effective at reversing moderate blockade.
- Edrophonium less effective than neostigmine in reversing deep blockade by atracurium.
- Elimination: neostigmine 50% renal; edrophonium 75% renal (renal insufficiency prolongs both NMB and AChE inhibitors).

Common misperceptions:
- Neostigmine has a longer duration than edrophonium.
- Neostigmine is more effective than edrophonium.
But, practically, neostigmine is more commonly used.

Naguib, in Evers, Maze, Kharasch: Anesthetic Pharmacology
Problems with current AChE inhibitors:

1. Long time to peak effect (neostigmine)
2. Unable to reverse “profound” neuromuscular block
3. Incomplete reversal
4. Nonselective inhibition of all AChE
   - (↑ ACh in nicotinic (NMJ) & muscarinic (autonomic) synapse
   - causes side effects: bradycardia, hypotension, etc
   - requires muscarinic antagonist (atropine, glycopyrrolate)
   - causes side effects: tachycardia, dry mouth, confusion/CNS
Sugammadex

Selective Relaxant Binding Agent

- All 4 neuromuscular blocker (NMB) hydrophobic rings fit in ring core
- roc- > vec- >> pancuronium
- Rapidly binds plasma NMB, reduces free concentration
- Concentration gradient draws drug from NMJ by passive diffusion
- Total plasma NMB concentration (free & bound) increases
- Encapsulated complex is freely filtered at glomerulus
<table>
<thead>
<tr>
<th>Use</th>
<th>NMB description</th>
<th>NMB measurement</th>
<th>sugammadex dose</th>
<th>time for return to TOFR&gt;0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>conventional reversal</td>
<td>shallow-moderate block</td>
<td>TOF count 2-4</td>
<td>2 mg/kg</td>
<td>3-5 min</td>
</tr>
<tr>
<td>conventional reversal</td>
<td>profound block</td>
<td>TOFC 0, TOFR 0, post-tetanic count (PTC) ≥ 1</td>
<td>4 mg/kg</td>
<td>3-5 min</td>
</tr>
<tr>
<td>“recue” (failed rapid sequence intubation with 4 x ED95 rocuronium)</td>
<td>extreme block</td>
<td>TOF count 0, PTC 0</td>
<td>16 mg/kg</td>
<td>3-5 min</td>
</tr>
</tbody>
</table>

Sugammadex (100 mg/ml); 2 ml & 5 ml single-dose vials for bolus injection

Duvaldestin: Expert Opin Pharmacother 2010;11:2759-71
# Sugammadex vs anticholinesterases: conventional reversal

## Clinical effect

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine</th>
<th>Edrophonium</th>
<th>Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOF ratio at 2 min (%)</strong></td>
<td>16 ± 7*</td>
<td>30 ± 14*</td>
<td>73 ± 16</td>
</tr>
<tr>
<td><strong>Time to TOF ratio (min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>10 ± 6*</td>
<td>3 ± 3*</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>0.8</td>
<td>16 ± 8*</td>
<td>4 ± 2*</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td>0.9</td>
<td>17 ± 10*</td>
<td>6 ± 1*</td>
<td>1.8 ± 1.0</td>
</tr>
<tr>
<td><strong># pts achieving TOF ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td>9</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>0.8</td>
<td>5</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>0.9</td>
<td>5</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td><strong># pts achieving TOF ratio 0.9</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 min</td>
<td>0 (0%)*</td>
<td>0 (0%)*</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>≤ 5 min</td>
<td>1 (5%)*</td>
<td>0 (0%)*</td>
<td>20 (100%)</td>
</tr>
</tbody>
</table>

* *p*<0.05 vs sugammadex
# Sugammadex vs anticholinesterases: conventional reversal

## Side effects

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine</th>
<th>Edrophonium</th>
<th>Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum change in HR (%)</td>
<td>+16*</td>
<td>+2</td>
<td>+3</td>
</tr>
<tr>
<td>Maximum change in MAP (%)</td>
<td>+7</td>
<td>+8</td>
<td>+4</td>
</tr>
<tr>
<td>PACU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth (#)</td>
<td>17*</td>
<td>19*</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* p<0.05 vs sugammadex

**Sugammadex:**
Faster reversal after normal levels of blockade, fewer side effects

Sacan: Anesth Analg 2007;104:569-74
Sugammadex vs neostigmine: conventional reversal

Time from sugammadex or neostigmine (at reappearance of TOFC=2 after NMB) to achieve TOF T4/T1 ratio=0.9

**Rocuronium**
- Sugammadex (2 mg/kg)
- Neostigmine (0.05 mg/kg)
- Median (Q1,Q3) recovery time:
  - Sugammadex: 1.4 min (1.2,1.7)
  - Neostigmine: 22 min (10,42)

**Vecuronium**
- Sugammadex (2 mg/kg)
- Neostigmine (0.05 mg/kg)
- Median (Q1,Q3) recovery time:
  - Sugammadex: 2.1 min (1.8,3.4)
  - Neostigmine: 29 min (12,76)

Sugammadex vs neostigmine: faster reversal, less interpatient variability. Sugammadex equally effective (3 min): rocuronium and vecuronium.

Sugammadex prescribing information
## Sugammadex vs neostigmine: conventional reversal

Systematic review of sugammadex (2-4 mg/kg) vs neostigmine for reversal of moderate & deep neuromuscular blockade
- 17 randomised controlled trials with 1553 participants

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex vs neostigmine relative risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall signs of residual postop paralysis</td>
<td>0.46 [0.29, 0.71]</td>
<td>0.0004</td>
</tr>
<tr>
<td>Minor signs of residual postop paralysis</td>
<td>0.51 [0.32, 0.80]</td>
<td>0.0034</td>
</tr>
<tr>
<td>Risk of reintubation</td>
<td>0.13 [0.02, 1.06]</td>
<td>0.057</td>
</tr>
<tr>
<td>Drug-related adverse events</td>
<td>0.72 [0.54, 0.95]</td>
<td>0.021</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.94 [0.79, 1.13]</td>
<td>0.54</td>
</tr>
<tr>
<td>Emesis</td>
<td>0.87 [0.65, 1.17]</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Rocuronium to TOFC=0, 1-2 posttetanic count (profound blockade)

Reversal: sugammadex (4 mg/kg)
neostigmine (70 µg/kg) + glycopyrrolate

Sugammadex vs neostigmine: faster reversal, less interpatient variability
sugammadex equally effective (3 min): rocuronium and vecuronium

Median (range) recovery time
sugammadex 2.7 min (1.2, 16.1)
neostigmine 49 min (13, 146)

Lemmens: BMC Anesthesiol 2010;10:15
Recovery after rocuronium/sugammadex vs succinylcholine

- Time to 90% recovery of:
  - Twitch height
  - TOF ratio

Median (range) recovery time:
- SUX (1 mg/kg) 11 min (5-16)
- Sugammadex (16 mg/kg) 3 min after rocuronium (1.2 mg/kg) 6 min (4-14)

Anesth Analg 2007;104:575-81
Duvaldestin: Expert Opin Pharmacother 2010;11:2759-71
Sugammadex: Pharmacology, warnings and precautions

- PK: elimination $t^{1/2}$ 2 hr; 99% renal excretion, 90% excreted in 24 hr
- Reverse only rocuronium and vecuronium
- Do not reverse pancuronium, (cis)atracurium, succinylcholine
- Administer over 10 sec (compatible with saline, Ringer’s lactate)
- Hypersensitivity in 0.3% of healthy volunteers and in pts; anaphylaxis has occurred in patients (without prior exposure)
- Marked bradycardia, some causing cardiac arrest, has occurred within min
- Renal impairment: $t^{1/2}$ 4, 6, 19 hr in mild, moderate, severe renal impairment; not recommended in pts with severe renal impairment, including dialysis
- Drug interactions: none except hormonal contraceptives
- Hormonal contraceptives: Pts using any hormonal contraceptive (oral, implant) must use an additional, non-hormonal method of contraception for 7 days
- Pediatrics: Safety and effectiveness not established in pts ≤ 17 yr
- If re-administration of a NMB drug is required after reversal with sugammadex, use a nonsteroidal drug (i.e. benzylisoquinolininium: atracurium, cisatracurium)
Sugammadex

Potential advantages vs current AChE inhibitors:
1. Rapid onset
2. Rapid peak effect (after 5 min, 100% of pts have TOFR>0.9 vs 0% with neostigmine)
3. Can reverse “routine”, “profound” and “extreme” NMB
4. Fast recovery from RSI dose rocuronium + sugammadex (6 min) vs 11 min with SUX
5. No inhibition of AChE
   • no autonomic side effects: bradycardia, hypotension, etc
   • no muscarinic antagonist (atropine, glycopyrrolate)
   • no muscarinic side effects: tachycardia, dry mouth, confusion/CNS
Potential disadvantages vs current AChE inhibitors:

1. Specificity (only steroid NMBs: roc-, vec- pan-curonium)
2. “Dose inflation” of NMB drugs
3. Overuse of profound blockade (potential for recall due to lack of movement)
4. Unwarranted (dangerous) abandonment of monitoring
5. Interaction with hormonal contraceptives:
   - Decreases progestogen exposure (34% of AUC)
   - **Oral** contraceptives: Equivalent to one missed daily dose
   - **Non-oral** hormonal contraceptives: patient must use an additional contraceptive for the next 7 days
6. FDA concern: anaphylactic/anaphylactoid drug reactions
7. Cost? Cost-effectiveness?
## Sugammadex - Cost comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost / dose (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine reversal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neostigmine + glycopyrrolate</td>
<td>0.05 mg/kg, 0.1 mg/kg</td>
<td>2-3</td>
</tr>
<tr>
<td>Edrophonium + atropine</td>
<td>0.05-0.07 mg/kg, 0.6-1.2 mg</td>
<td>27-34</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>2 to 4 mg/kg</td>
<td>60-119</td>
</tr>
<tr>
<td><strong>Immediate reversal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>1 mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>Rocuronium plus sugammadex*</td>
<td>1.2 mg/kg, 16 mg/kg</td>
<td>364</td>
</tr>
</tbody>
</table>

*Both rocuronium (£6 per dose) and sugammadex (£358 per dose) are given

Costs from eVadis on November 2012, based on a 70kg adult
July, 2008: European Commission (EC) approval
- routine reversal of rocuronium, vecuronium in adults
- immediate reversal of rocuronium in adults
- routine reversal of rocuronium in children (2-17 yr)

March, 2008: FDA Anesthetics & Life Support Drugs Advisory Committee votes to approve sugammadex

August, 2008: FDA issues sugammadex “not approvable” letter due to safety concerns (hypersensitivity) [1st rejection]

2009-2011: Merck conducts study to assess potential for hypersensitivity on initial and repeat exposure to sugammadex

2012: Merck refiles sugammadex NDA with FDA
July, 2013: FDA cancels discussion of sugammadex at July Anesthetic and Analgesic Drug Products Advisory Committee

September, 2013: FDA announces sugammadex NDA not approved in present form due to "operational aspects of a hypersensitivity study" [2nd rejection]

November, 2014: Merck refiles sugammadex NDA with FDA

March, 2015: FDA cancels March, 2015 review at Anesthetic & Analgesic Drug Products Advisory Committee [3rd rejection]

FDA plans to conduct additional site inspections related to the hypersensitivity study before any Advisory Committee meeting.

2015: FDA accepts resubmission of sugammadex NDA. FDA approves sugammadex December 15, 2015

January, 2016: Expected US availability of sugammadex

I need more relaxation.

Give more muscle relaxant!

But the patient has only 1 barely detectable twitch

I shouldn’t give more, and ablate twitch but.......
More muscle relaxation does not necessarily mean better surgeons
François Donati, PhD, MD, and Sorin J. Brull, MD, FCARCSI (Hon.)

What is the effect of deep versus shallow neuromuscular blockade on surgeons’ assessment of operating conditions?

- Surgeons judged relaxation suboptimal in ¾ of cases, even with deep blockade
- Depth of NMB makes a difference in ~¼ of pts, without identifying which pts most likely to benefit or how deep the block needs to be in those pts
- NMB alone cannot make surgical conditions optimal in all, even in most, cases
- Multiple costs of deep NMB until end of surgery
  - If wait until TOFC=4 then give AChE → time wasted in OR
  - Large dose of sugammadex (4 mg/kg at a PTC of 1–2; $200)
  - Or, prolonged PACU stay

More evidence of the real benefit of keeping patients deeply paralyzed until the end of surgery needs to be provided before this practice can be recommended, regardless of whether sugammadex is available
Peripherally acting mu opioid receptor antagonists (PAMORA)

- Selectively block endogenous/exogenous opioid effects mediated by peripheral mu receptors
- Block deleterious effects of gut mu opioid agonists but preserve analgesia
- Do not penetrate the blood-brain barrier
- Do not reverse CNS opioid analgesia
- Do not cause withdrawal in opioid-tolerant patients
- New drug class, approved April/May 2008

Moss: Mayo Clin Proc 2008;83:1116-30
### Peripherally acting mu opioid receptor antagonists (PAMORA)

<table>
<thead>
<tr>
<th></th>
<th>methylNaltrexone 2008</th>
<th>naloxegol 2014</th>
<th>alvimopan 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved indication</strong></td>
<td>opioid-induced constipation in adults with chronic non-cancer pain</td>
<td>opioid-induced constipation in adults with chronic non-cancer pain</td>
<td>accelerate restoration of bowel function pts with postop ileus after bowel resection and primary anastomosis</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>subQ</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>every other day</td>
<td>daily</td>
<td>twice daily, start preop, 1 week maximum</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>mechanical bowel obstruction</td>
<td>mechanical bowel obstruction, CYP3A4 strong inhibitors</td>
<td>opiate use &gt;1 week restricted to hospital use</td>
</tr>
</tbody>
</table>

Moss: Mayo Clin Proc 2008;83:1116-30  
Intravenous non-opioid analgesics

**Intravenous Ibuprofen** (Caldolor®)  
Approved June 2009

**Indications:**
1) mild to moderate pain (infuse over 30 min)
2) management of moderate-severe pain as an adjunct to opioids
3) treatment for fever in adults

**Intravenous Acetaminophen** (Ofirmev®)  
Approved November, 2010

**Indications:**
1) mild to moderate pain (infuse over 15 min)
2) management of moderate-severe pain as an adjunct to opioids
3) treatment of fever

**Intravenous Diclofenac** (Dyloject®)  
Approved December, 2014

Reformulation of IV diclofenac, in cyclodextrin

**Indications:**
1) mild to moderate pain in adults (bolus over 15 sec)
2) moderate-severe pain alone or in combination with opioids in adults
Practice Guidelines for Acute Pain Management in the Perioperative Setting

An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management

Whenever possible, anesthesiologists should use multimodal pain management therapy.

Preop patient preparation includes premedication as part of a multimodal analgesic pain management program.

Unless contraindicated, all patients should receive an around-the-clock regimen of NSAIDs, COXIBs, and/or acetaminophen.

**NSAIDs and COXIBs**

Preop: oral COX-2, oral acetaminophen (APAP)
Intraop: IV NSAID (ketorolac, diclofenac, ibuprofen), IV APAP
Postop: oral NSAID, oral COX-2, IV NSAID, IV APAP
Intravenous diclofenac

Reformulation of IV diclofenac, in cyclodextrin
Permits IV bolus (old formulation was 1-2 hr infusion)

Indications:
1) mild to moderate pain in adults
2) moderate-severe pain alone or in combination with opioids in adults

Dosage:
• 37.5 mg by IV bolus injection over 15 sec
• May repeat every 6 hours, not to exceed 150 mg/day

Warnings & Contraindications (usual for NASIDs):
• Cardiovascular
• Gastrointestinal
• Renal insufficiency
COX-1 vs COX-2 selectivity of several NSAIDs

- Rofecoxib >50-fold COX-2 selective
- celecoxib 5- to 50-fold COX-2 selective
- etodolac, meloxicam, diclofenac, piroxicam, sodium salicylate <5-fold COX-2 selective
- ibuprofen, naproxen, aspirin, indomethacin, ketoprofen, flubiprofen, ketorolac

Log IC$_{50}$ ratio (WHMA COX-2/COX-1)

Gan: Curr Med Res Opin 2010;26:1715-31
Warner: PNAS 1999;96:7563-8
Diclofenac inhibits platelet aggregation to a greater extent than COX-2-selective inhibitors.

Mean ± SE time-weighted average inhibition vs baseline over 8 hr post dose on day 6.
Oral vs IV acetaminophen: Does it matter?

Single-dose periop IV acetaminophen for postop pain: Systematic review
- 37% of pts had ≥50% pain relief over 4h vs 16% with placebo (NNT=4.0)
- 30% less opioid used over 4 h; 16% less over 6 h, vs placebo
- Did not reduce opioid-induced adverse events

IV vs oral acetaminophen:
- Earlier onset of pain relief (8 vs 37 min)
- Earlier peak pain relief (15 vs 60 min)
- Equal pain relief at 45 min
- Less pain relief after 2 hr
- IV (1, 1.5, 2g) dose-dependently impairs platelet aggregation & thromboxane B2 release. Not seen with 1g oral

Issues & questions:
- Cost (1g*): $35.40 IV, $0.04 PO
- Cost-effectiveness?

Oscier: Anaesthesia 2009;64:65-72
McNicol: Br J Anaesth 2012;106:764-75
Moller: Br J Anaesth 2005;94:642-8
Munsterhjelm: Anesthesiology 2005;103:712-7
### Injectable nonopioid analgesics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Effectiveness</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>ketorolac</td>
<td>15-30 mg IV q6h (max 120mg/d x 5d)</td>
<td>≥30% pain reduction; opioid-sparing</td>
<td>$1.60</td>
</tr>
<tr>
<td>diclofenac</td>
<td>37.5mg IV q6h (max 150mg/d)</td>
<td>≥30% pain reduction; opioid-sparing</td>
<td>$15.80</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>400-800 mg IV q6h (max 3200 mg/d)</td>
<td></td>
<td>$7.40</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>1g IV q6h (max 4g/d)</td>
<td>less pain reduction; less opioid-sparing</td>
<td>$35.40</td>
</tr>
</tbody>
</table>

IV diclofenac: acts more rapidly than ketorolac (onset 10 vs 30 min) but is otherwise similar in efficacy to IV ketorolac, which costs much less.

*Med Lett Drugs Ther. 2015;57:171-2*
Abuse-deterrent opioid formulations

Formulation mechanisms to deter opioid abuse

- Controlled release of drug
- Co-formulation with opioid antagonist (naloxone)
- Tablet that resist crushing or grinding
- Gelling agents that confound injection by hypodermic needle
- Reduced amount of intact drug produced by vaporization
- Increased difficulty extracting pure opioid after dissolution
- Increased crushed particle size that resists nasal mucosal absorption
- Substances that burn/irritate nasal mucosa if crushed and snorted

Med Lett Drugs Ther. 2015;57:119-21
Abuse-deterrent opioid formulations

Abuse-deterrent opioids

- **OxyContin®**: ER oxycodone more difficult to crush; forms viscous gel when dissolved, difficult to inject
- **Targiniq ER®**: ER oxycodone/naloxone; if crushed and used IV or intranasally, naloxone antagonizes oxycodone
- **Oxado®**: IR oxycodone with inactive ingredient; causes nasal burning
- **Embeda®**: ER morphine pellets with sequestered core of naloxone. If swallowed, naloxone core passes through gut intact; if crushed, chewed or dissolved, naloxone released and antagonizes morphine
- **Hysingla®**: ER hydrocodone; forms viscous gel when dissolved, difficult to inject
- **Zohydro ER®**: ER hydrocodone; forms viscous gel when dissolved, difficult to inject

Med Lett Drugs Ther. 2015;57:119-21
Buprenorphine patch, extended release (Butrans®)

Indication: management of severe chronic pain requiring daily, around-the-clock, long-term opioid treatment where alternative treatment options are inadequate

7-day patch (5, 7.5, 10, 15, and 20 µg/hr)

Problem:
- High-affinity binding & partial agonism prevents binding and clinical effects of opioid agonists
- Opioid agonist blockade similar to that by therapeutic doses of naltrexone

Approach:
- Stop buprenorphine 5d before surgery; start full agonist opioids to prevent withdrawal
- Use non-opioid agonists perioperatively (NSAIDs, ketamine, dexmedetomidine)
Novel delivery mechanisms for pain medications

- Fentanyl effervescent buccal transmucosal tablet (Fentora®)
- Fentanyl sublingual tablet (Abstral®)
- Fentanyl buccal soluble film (Onsolis®)
- Fentanyl pectin nasal spray (Lazanda®)
- Buccal buprenorphine (Belbuca®)
- Fentanyl, inhaled liposome-encapsulated (AeroLEF®, dc’d 2010)
- Fentanyl, heated inhaled
- Sufentanil sublingual tablet
- Intranasal ketorolac (Sprix®)
- Intranasal morphine (Rylomine®) (US Phase III, Europe Phase II, Archimedes Pharma)
- Intranasal ketamine (Ereska®; US, Europe, Phase II; DC’d 2015)
Fentanyl iontophoretic transdermal system (Ionsys®)

- Low-intensity electrical field moves fentanyl through the skin into the bloodstream (iontophoresis)
- Pre-programmed (up to six 40 µg doses/hr)
- Equi-effective as IV PCA morphine for acute postop pain
- Needle-free, no pumps/poles

Fentanyl iontophoretic transdermal system (ITS) vs morphine IV PCA for postoperative pain management

- 1941 pts: Orthopedic, thoracic, pelvic, breast, abdominal, pelvic, total hip replacement surgery

- Fraction of pts in fentanyl ITS and morphine IV PCA groups reporting global pain assessments of “good” or “excellent” in the first 24 hr were equivalent (80% vs 81%)

- Overall discontinuation rates not significantly different between groups (17% vs 12%)

- No differences in side effects

- Nurses and anesthesiologists estimated fentanyl ITS to require 44% less staff time than IV-PCA
New Drugs in Anesthesia 20XX?

Somewhere, over the rainbow

New delivery mechanisms

New molecules
Sufentanil sublingual NanoTab®

Zalviso® (sufentanil 15 µg SL microtablet system) for PCA of moderate-to-severe acute pain in hospitalized adults (abdom. surgery, TKA, THA). FDA IND filed Sept 2013; EC approval Sept 2015

ARX-02: sufentanil SL NanoTab® for breakthrough cancer pain (Φ2 complete)

ARX-03: MD- or nurse-administered SL sufentanil/triazolam for mild procedural sedation, anxiety reduction, pain relief (Φ2 complete)

ARX-04: mod-to-severe acute pain, battlefield $ civilian trauma or injury (Φ2 complete)
CNS 7056; Remimazolam ("remi-midazolam")

remifentanil

remimazolam; human brain
Ki 29 nM vs 12,300 nM

Development: GlaxoSmithKline → CeNeS → PAION → → →
Ono (Japan), Yichang Humanwell (China), Hana Pharm (S Korea) R-Pharm (Russia)

Kilpatrick: Curr Opin Anaesthesiol 2006; 19:385-9
Kilpatrick: Anesthesiology 2007; 107:60-6
A placebo- and midazolam-controlled, phase I, single ascending-dose study evaluating the safety, pharmacokinetics, pharmacodynamics of remimazolam:

Part I. Safety, efficacy, and basic pharmacokinetics

Part II: Population pharmacokinetic & pharmacodynamic modeling & simulation

• Remimazolam (0.075 - 0.20 mg/kg) induced peak sedation levels similar to or higher than midazolam (0.075 mg/kg)

• Median recovery times after approximately equieffective doses of remimazolam (0.10 and 0.15 mg/kg) and midazolam (0.075 mg/kg) were 10 and 40 min, respectively
Remimazolam

Population PK-PD modeling and simulation

BIS score after a 1-min, 9 mg IV infusion of remimazolam

Context-sensitive half-times for remimazolam (0.075 mg/kg/h) and midazolam (50 mg/h)

Anesth Analg 2012;115:284-96
Remimazolam

Phase IIa, randomized comparison of single-dose remimazolam and midazolam in upper GI endoscopy

- Single-dose remimazolam (0.1–0.2 mg/kg) induced rapid sedation with quick recovery
- Safety profile similar to that of midazolam (0.075 mg/kg)
- Warrants further development (0.15 mg/kg)
Innovative short-acting general anesthetic/sedative being developed by PAION initially for use in minor medical interventions (procedural sedation)

Rapid offset due to metabolism by tissue esterases widely distributed throughout the body

Remimazolam currently in clinical development:
- US: Procedural sedation (e.g. colonoscopy, Phase IIb complete; PAION-US launched 10/2014; US Phase III colonoscopy launch April, 2015; bronchoscopy next)
- Europe & Japan: General anaesthesia (Japan Phase III complete 11/2013; Europe Phase III ongoing)
- ICU sedation (Phase II start 9/2012, terminate 8/2013, “unclear PK result in long-term administration”; will restart in EU)

Neurosteroids: 
Back to the future? 
Again??

- Neuroactive steroid anaesthetics: alfaxalone, alfadolone, pregnanolone, minaxolone, eltanolone
- Safest anesthetics: therapeutic index (LD/ED) 20-30 for neurosteroids, 8-10 for midazolam/ketamine, 4-6 for barbiturates/propofol
- Withdrawn from market for safety; problems with formulation
- Now being reformulated, redeveloped

- Alfaxalone + alfadolone in Cremophor (Althesin®) → hypersensitivity → withdrawn 1984
- Alfaxalone reformulated in hydroxypropyl β-cyclodextran → approved for veterinary use, 2012
- Alfaxalone reformulated in sulfobutyl ether β-cyclodextrin (Phaxan®) → Phase I trial completed April, 2014

Goodchild: Anesth Analg 2015;120:1025-31
New etomidate analogues

- Methoxycarbonyl-etomidate (MOC-etomidate)
- Cyclopropyl MOC-etomidate (CPPM, ABP-700)
- Carboetomidate
- MOC-carboetomidate

Labile ester
New etomidate analogues

Cyclopropyl MOC-etomidate (CPPM, ABP-700)

- Compared with etomidate: Half as potent, more rapidly metabolized, shorter duration of sedative-hypnotic effect, less adrenal suppression
- Hypnotic and EEG recovery occurs in only 4 min
- Recovery times independent of infusion duration
- Adrenocortical recovery faster than etomidate (half-time: 215 vs 1,623 min)
- Adrenocortical responsiveness 90 min after infusion not different from propofol
- Currently in Phase I clinical trials

Campagna: Anesthesiology 2014;121:1203-16
Raines: Int Anesthesiol Clin. 2015;53:63-75
Sodium channels and pain

- Nav1.7: α-subunit of voltage-gated Na channel expressed at high levels in peripheral sensory neurons, most notably nociceptive small-diameter dorsal root ganglia neurons

- Loss of function mutations in SCN9A cause non-functional Nav1.7 protein; causes Congenital Insensitivity to Pain (inability to perceive any form of pain; all other aspects of ANS & PNS are unchanged)

### Na\(_v\) channel modulators that have reached clinical development for the treatment of pain

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Pharmacology</th>
<th>Phase</th>
<th>Therapeutic indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD3161</td>
<td>AstraZeneca</td>
<td>Nav1.7</td>
<td>I</td>
<td>Neuropathic/Inflammatory pain (IV, intradermal)</td>
</tr>
<tr>
<td>CNV1014802</td>
<td>Convergence</td>
<td>Nav1.7</td>
<td>II</td>
<td>Neuropathic pain, trigeminal neuralgia (oral)</td>
</tr>
<tr>
<td>DSP-2230</td>
<td>Dainippon Sumitomo</td>
<td>Nav1.7/1.8</td>
<td>I</td>
<td>Neuropathic pain (oral)</td>
</tr>
<tr>
<td>NKTR-171</td>
<td>Nektar</td>
<td>Broad Nav(_v)</td>
<td>I</td>
<td>Neuropathic pain (oral)</td>
</tr>
<tr>
<td>PF-04531083</td>
<td>Pfizer</td>
<td>Nav1.8</td>
<td>I</td>
<td>Neuropathic/Inflammatory pain (oral)</td>
</tr>
<tr>
<td>PF-05089771</td>
<td>Pfizer</td>
<td>Nav1.7</td>
<td>II</td>
<td>Neuropathic/Inflammatory pain erythromelalgia (oral)</td>
</tr>
<tr>
<td>TTX</td>
<td>WEX</td>
<td>TTX-S Nav(_v)</td>
<td>III</td>
<td>Neuropathic/Inflammatory cancer pain (IV)</td>
</tr>
<tr>
<td>XEN402</td>
<td>Xenon/Teva</td>
<td>Nav1.7</td>
<td>II</td>
<td>Neuropathic/Inflammatory pain erythromelalgia (topical)</td>
</tr>
<tr>
<td>XEN403</td>
<td>Xenon</td>
<td>Nav1.7</td>
<td>I</td>
<td>Neuropathic/Inflammatory pain erythromelalgia (oral)</td>
</tr>
</tbody>
</table>

Global market for anesthesia drugs ~$4.1B; annual growth rate 4.8% through 2014 (Healthcare Finance News, March 2010)

Number of new molecular entities will be low. Particularly unless/until new targets are identified

Number of reformulations will increase
- New combinations, new controlled-release matrix, new routes of administration, abuse deterring agents
- IR/ER hydrocodone combo, morphine/oxycodone IR/CR combo, OTbuprenorphine, fentanyl patch, effervescent fentanyl tablets, iontophoretic fentanyl, nebulized fentanyl, buprenorphine implant, etc
- Pain management products will focus on tamper resistance & abuse deterrence

Increasing number of drugs developed for perioperative use as secondary indication, after primary development for other indications (antiemetics, COX-2 inhibitors, etc)