Sugammadex (Bridion)

Quite possibly the most interesting drug
NOT approved by the FDA... Yet.

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Disclosure Statement:

I do not have any financial interests or other relationships with the manufacturers of any products or providers of services that I will be discussing today.

Sugammadex has not been approved by the FDA.
Objectives

- Briefly review “Balanced Anesthesia” and the role of neuromuscular blocking agents (NMBAs)
- Discuss need for improved reversal of NMBAs
- Describe Sugammadex (Bridion) pharmacology, toxicology, efficacy, and safety.
- Discuss the beneficial impacts of sugammadex on anesthesia and patient safety
- Discuss experience in Europe
- Provide update on FDA approval status in the U.S.
- Quiz!

Balanced Anesthesia

Combination of intravenous drugs and inhalation agents used to provide hypnosis, amnesia, analgesia, muscle relaxation, and reduced reflexes with minimal disturbance of physiologic function.
Balanced Anesthesia & Importance of Appropriate Neuromuscular Blockade

**Indications for NMBAs**
- Facilitate Intubation
- Optimize Mechanical Ventilation
- Prevent movement and muscle spasms
- Prevent elevated intracranial pressure
- Prevent tetanus and neuromuscular seizures
- Reduce muscular O2 demand during hypoxemia and tremors

Balanced Anesthesia

Example:
- Propofol for induction
- Midazolam for amnesia/anxiolysis
- Lidocaine for pain/intubation
- Fentanyl for analgesia
- Succinylcholine and Rocuronium for neuromuscular blockade
Common Anesthetic Agents

**Induction and Anesthesia**
Thiopental (Pentothal)
Ketamine (Ketalar)
Methohexital (Brevital)
Propofol (Diprivan)
Midazolam (Versed)
Diazepam (Valium)
Etomidate (Amidate)

**Opioid Analgesics**
Fentanyl
Morphine
Hydromorphone
Sufentanil
Alfentanil
Remifentanil
Meperidine

Neuromuscular Blocking Agents

**Depolarizing NMBAs:** Bind to cholinergic receptors on the motor endplate, causing initial depolarization on the endplate membrane followed by blockade of neuromuscular transmission.

**Nondepolarizing NMBAs:** Competitively inhibit the acetylcholine (Ach) receptor on the motor endplate.
Depolarizing NMBAs

**Succinylcholine** – The only Depolarizing NMA in the U.S.
- **Uses:** Intubation (RSI) and laryngospasm
- **Onset:** Rapid (less than 1 minute)
- **Duration:** 7-8 minutes
- **Reversal:** None
- **Adverse Effects:** Hypertension, tachycardia, bradycardia, ventricular arrhythmias, hyperkalemia, increased intracranial pressure, and malignant hyperthermia.
- **Approximately 1 in 3200 patients are homozygous for a defective pseudocholinesterase and may remain paralyzed for three to eight hours after a single dose**

Non-Depolarizing NMBAs

There are many **Non-Depolarizing NMBAs**, each with a different time of onset and duration of effect.

In general, the Non-Depolarizing NMBAs have an onset of action of 1-5 minutes and a half-life ranging from 5 to 300 minutes

Most common in U.S. | Duration:
--- | ---
- Rocuronium (Zemeron, Esmeron) | 15-85 minutes
- Vecuronium (Norcuron) | 25-40 minutes
- Pancuronium (Pavulon) | 60-90 minutes
Reversal of NMBAs

**Acetylcholinesterase inhibitors** which increase [Ach] in the NMJ (nicotinic receptors).
- Neostigmine (Prostigmin)
- Edrophonium (Tensilon)

It is important to also co-administer a **muscarnic antagonist** in order to prevent significant side effects.
- Atropine
- Glycopyrrolate (Robinul)

Reversal of NMBAs

**AChE inhibitors** in the reversal of neuromuscular block can cause:
- Bradycardia
- Hypersalivation
- Bronchospasm
- Increased bronchial secretions
- Urinary frequency
- Nausea and vomiting

**Coadministration of antimuscarinic agents aids in preventing cholinergic effects... but may result in:**
- Tachycardia
- Dryness of mouth and nose
- Mydriasis
- Urinary retention
Other Limitations of NMBA Reversal by Acetylcholinesterase Inhibitors:

- Relatively slow in reversal of neuromuscular blockade
- Wide variation in response time between patients
- Limited efficacy for reversal of deep NM blockade
- Efficacy influenced by maintenance anesthetics
- Well-known side effect profile
- Require concomitant administration of anticholinergics
- Rebound NMB is possible and does occur (dangerous!)

So… What is Sugammadex?
Cyclodextrins

Cyclodextrins are cyclic oligosaccharides and are defined by the number of glucopyranoside units they contain.
- 6 units - α
- 7 units – β
- 8 units - γ

Cyclodextrins have the following properties:
- Lipophilic cavity and hydrophilic exterior
- These characteristics enable CDs to form water-soluble inclusion complexes

Cyclodextrins are used in many products in the U.S. and around the world

**Pharmaceutical applications:**
- Prostaglandin E1 (Caverject®)
- Ziprasidone maleate (Geodon®)
- Diclofenac ophthalmic (Voltaren®)
- Itraconazole (Sporanox®)

**Dietary applications:**
- Carrier and stabilizer of flavors and colors
- Fat-soluble vitamins and polyunsaturated fatty acids
- Frozen dairy desserts
- Estimated daily intake of γ-CD from dietary means = 4.1 g/person/day.

**Other Applications:** Febreze! (beta-cyclodextrin)
Foods that often contain γ-CD

Processed beverages, soups, dressings, gravy, sauces, puddings, gelatin, fruit fillings, instant coffee, instant tea, coffee non dairy creamers, compressed sweets, chewing gum, breakfast cereals, savory snacks, crackers, spices, seasonings.

It is also used as a carrier for vitamins and polyunsaturated fatty acids in dry food mixes and in dietary supplements, as a flavor modifier in soy milk, and as a stabilizer in bread spreads, frozen dairy desserts, baked goods, bread, fruit-based fillings, fat-based fillings, processed cheese, and dairy desserts.

Sugammadex (Bridion)

- γ-Cyclodextran
- 8 sugar molecule
- Central lipophilic cavity
- Highly water soluble
- Not metabolized
- Renally eliminated
New drug class “Selective Relaxant Binding Agent” (SRBA)

Indication: Reversal of neuromuscular blockade induced by rocuronium or vecuronium.

Highly selective affinity for rocuronium and vecuronium.

Effectively and quickly reverses blockade at any level.

Does not bind succinylcholine or cisatracurium.

**Sugammadex (Bridion)**

**Dosing and Administration**

**Adults**
- Sugammadex can be used to reverse different levels of rocuronium or vecuronium-induced neuromuscular blockade:

  **Routine reversal**
  - A dose of 4.0 mg/kg sugammadex is recommended if recovery has reached 1 – 2 post-tetanic counts (PTC) following rocuronium- or vecuronium-induced blockade. Median time to recovery of the T₄/T₁ ratio to 0.9 is around 3 minutes.
  - A dose of 2.0 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to the reappearance of T₂ following rocuronium- or vecuronium-induced blockade. Median time to recovery of the T₄/T₁ ratio to 0.9 is around 2 minutes.

  **Immediate reversal**
  - If there is a clinical need for immediate reversal following administration of rocuronium, a dose of 16.0 mg/kg sugammadex is recommended. Administration of 16.0 mg/kg sugammadex 3 minutes following a bolus dose of 1.2 mg/kg rocuronium bromide provides a median time to recovery of the T₄/T₁ ratio to 0.9 of approximately 1.5 minutes.
Sugammadex (Bridion)

**Efficacy studies:**
Pivotal Trials 19.4.301 and 19.4.302

**Objectives:**

**Trial 19.4.301**
- Reversal of shallow rocuronium or vecuronium-induced neuromuscular blockade with sugammadex versus neostigmine

**Trial 19.4.302**
- Reversal of profound rocuronium and vecuronium-induced blockade with sugammadex compared with neostigmine

### Recovery of TOF Ratio to 0.9*

**Trial 19.4.301**

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Agent</th>
<th>Sugammadex 2.0 mg/kg</th>
<th>Neostigmine 50 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rocuronium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>1.4*</td>
<td>17.6</td>
</tr>
<tr>
<td>Range</td>
<td>0.9-5.4</td>
<td>3.7-106.9</td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>2.1*</td>
<td>18.9</td>
</tr>
<tr>
<td>Range</td>
<td>1.2-64.2</td>
<td>2.9-76.2</td>
</tr>
</tbody>
</table>
Recovery after Sugammadex 2.0 mg/kg or Neostigmine 50 mcg/kg at Reappearance of T_2

Recovery of TOF Ratio to 0.9*

*Trial 19.4.302

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Agent</th>
<th>Sugammadex 4.0 mg/kg</th>
<th>Neostigmine 70 mcg/kg</th>
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</thead>
<tbody>
<tr>
<td>Rocuronium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>2.7*</td>
<td>49.0</td>
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<tr>
<td>Range</td>
<td>1.2-16.1</td>
<td>13.3-145.7</td>
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<tr>
<td>Vecuronium</td>
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<td></td>
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<tr>
<td>n</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>3.3*</td>
<td>49.9</td>
</tr>
<tr>
<td>Range</td>
<td>1.4-68.4</td>
<td>46.0-312.7</td>
</tr>
</tbody>
</table>
Conclusions – Trials 19.4.301 and 19.4.302

- Faster recovery compared with neostigmine after rocuronium- and vecuronium-induced block
- No cases of residual paralysis or reoccurrence of blockade during the period of neuromuscular monitoring or at recovery
- Rapid reversal of both shallow and profound rocuronium- and vecuronium-induced NMB
Sugammadex (Bridion)

Additional Efficacy Study:
Trial 19.4.303
Rocuronium/Sugammadex vs. Succinylcholine

Objective:
- Reversal of profound rocuronium-induced neuromuscular block with sugammadex compared to spontaneous recovery from succinylcholine

Patient Allocation and Study Design

- Randomized (n=115)
  - Rocuronium 1.2 mg/kg
    - n=57
    - Sugammadex 16 mg/kg at 3 min
  - Succinylcholine 1.0 mg/kg
    - n=58
    - Spontaneous recovery

- Time to recovery to T1 10%
- Time recovery to T1 90%
Conclusions – Trial 19.4.303

- Reversal of profound rocuronium-induced (1.2 mg/kg) neuromuscular block with sugammadex was significantly faster than spontaneous recovery from succinylcholine.
- Sugammadex offers the possibility of immediate reversal of rocuronium-induced block in the event of failed intubation.
Special Population Studies:

- No differences observed in cardiac or pulmonary patients
- No dosage adjustments necessary for a single dose in patients with renal impairment however AUC is increased significantly.
- Not recommended for use in patients with severe renal impairment, including those requiring dialysis
- Consistent efficacy results over all trials
- Well tolerated, clear safety profile

Drug and Laboratory Interactions

In vitro binding selectivity studies were performed to determine if sugammadex binds other drugs:

- Drugs used in anesthesia
- Drugs / hormones with steroidal nucleus
- Drugs acting on steroidal receptors
- Commonly prescribed medications
- > 300 compounds tested
- Minor binding was found with several hormones and antibiotics...
Drug and Laboratory Interactions

- Progesterone contraceptives: 34% reduction in AUC leading to temporary decrease in efficacy
- Toremifene (Fareston) (Selective Estrogen Receptor Modulator) may reduce efficacy of sugammadex if given on the same day
- Fusidic acid (antibiotic) may reduce or delay the efficacy of sugammadex if administered pre-operatively
- Doses of 4 mg/kg and 16 mg/kg of sugammadex resulted in prolongations of aPTT by 17 and 22% respectively and of PT(INR) by 11 and 22% respectively. These changes were of short duration (≤ 30 minutes)

Experience with Sugammadex in Europe

- Approved in Europe in 2008, thousands of doses given.
- Has been used extensively in Finland, England, France, Italy etc.
- No unexpected adverse reactions
- Utilization has been restricted due to high cost:
  - Procedures where coughing during extubation is a major risk factor (aneurysm repair, craniotomies, lumbar, and spine surgery)
  - Procedures where there is a high risk for intubation failure (obese, neck/chest trauma, tumors)
  - Assessment of neurological function in traumatic brain injury by Neurologist, when patient is intubated in the field.
Status of Sugammadex in U.S.

March 2008 – 11 Member FDA Advisory panel reviewed 30 Phase I, II and III trials including a total of 2390 patients and voted unanimously to approve.

July 2008 – European Union approves Sugammadex

August 2008 – FDA rejects drug citing an ADR rate of 5.1% of all patients exposed to any dose of sugammadex plus an NBA. Reactions included anesthetic complications, dysgeusia, bleeding complications, and hypersensitivity reactions.

Status of Sugammadex in U.S.

Higher incidence of adverse drug reactions occurred in patients receiving doses greater than 32 mg/kg. (Recommended dose is 2-4 mg/kg).

Hypersensitivity reactions led to comprehensive skin testing studies which demonstrated that sugammadex is not an allergen.

The FDA also had concerns about animal toxicology studies that demonstrated binding of sugammadex in bone and tooth and questioned how this could affect patients. Dosing in animal studies was much higher than comparable human doses. More studies underway.
Status of Sugammadex in U.S.

Dozens of new safety and efficacy studies, all demonstrating that sugammadex is effective and well tolerated.

It is expected that the FDA will re-evaluate sugammadex this upcoming year...

Why the delays? Among other factors, ownership of the molecule changed hands 3 times in the last 5 years (Organon, Schering-Plough, then finally Merck).

Status of Sugammadex in U.S.

Rejected by the FDA again this past September...

- The agency is very concerned about how recent ADR sensitivity studies were conducted, citing problems with environmental controls.
- Problems with “paper trail” from Organon > Schering > Merck.
- Continued use in 50 countries throughout Europe and Asia with no unexpected issues!
- Cost for product in US not yet disclosed.
- Suggestions that we will see FDA approval by the second quarter of 2014.
Questions or Comments?

Thank you!