Sugammadex
beyond the rose-colored glasses

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Disclosure

Sugammadex: Beyond the rose-colored glasses
Abhishek Karnwal, MD

I have no relevant financial relationships with the manufacturer(s) or any commercial product(s) and/or provider of commercial products or services discussed in this CME activity.

I do not intend to discuss unapproved/ investigative use of commercial product(s)/device(s) in my presentation.
See everything through rose-colored glasses and be happy with the subtle things in your life

Objectives

- What is Sugammadex
- Why do I need it
- Development and FDA approval
- Indications
- Side effects
- Cost
- Take Home points
Su-gamma-dex

- Novel pharmacologic agent (FDA 2015)
- Reversal agent for skeletal muscle relaxants
- Unique mechanism of action - Encapsulation
- 1st noncompetitive antagonist
Why do I need Sugammadex?

Neuromuscular blocking agents (NMBA)
Neuromuscular blocking agents (NMBA)

An integral component of anesthesia
- intubation
- Immobility
- relaxation of the skeletal muscles for specific surgical procedures.

Types of NMBAs

**Non-Depolarizing NMBA**
- Aminosteroids
  - Pancuroium
  - Pipecuronium
  - Vecuronium
  - Rocuronium

**Depolarizing NMBA**
- Succinylcholine

**Benzyisoquinolininiums**
- D-Tubocurarine (1st)
- Atracurium
- Cisatracurium
- Doxacurium
- Mivacurium
Succinycholine

- resemble acetylcholine
- Fast onset (45-60 sec)
- Short half-life-duration 6-10 min
- Useful for RSIs
- diffuse from NMJ rapidly

Sch -Contraindications

- h/o malignant hyperthermia
- **Risk of severe hyperkalemia**
- **Ach receptor upregulation**
  - inherited myopathies
  - Crush / burns after 48-72h
  - severe infections with exotoxin production
  - prolonged total body immobilization
Sch- Complications

- Trismus (0.001-0.1%)
- Fasciculation
- Bradycardia
- Increased IOP/ ICP

Nondepolarizing NMBAs

Aminosteroidal compounds
- Pancuronium
- Pipecuronium
- Vecuronium
- Rocuronium

Benzylisoquinolinium compounds:
- D-Tubocurarine - 1st - not in use
- Atracurium
- Cisatracurium
- Doxacurium
- Mivacurium
Neuromuscular monitoring

- indirect determination of neuromuscular transmission
- Recommended whenever a NMB is used (Eriksson 2003)

Train-of-four (TOF) twitch response
- Electric current applied to ulnar N. in bursts of 4.
- Response in adductor pollicis measured
- Ratio of amplitude of 4th:1st twitch = TOF ratio

- If TOF ratio 0.4 - 0.9 → muscle contraction seen or sensed equally.
- Visual or palpated twitches - unreliable
Reversal of NMBAs

- Cholinesterase inhibitors (neostigmine, edrophonium)
- Allow spontaneous ventilation and tracheal extubation
- TOF 4/4, sustained tetanus
- Also need Anticholinergics - Glycopyrrolate / Atropine
- Most clinicians rely on subjective tests to assess neuromuscular function prior to extubation
Residual neuromuscular blockade

- Significant problem (20-60%)
- Affects postoperative ventilation
- Critical postop respiratory events:
  - Hypoxemia, atelectasis, pneumonia, PACU LOS
- 28% of pediatric patients

RESIDUAL BLOCK?

- Association with increased rates of postoperative pulmonary complications, mortality, and coma

**Residual neuromuscular block is a risk factor for postoperative pulmonary complications**

A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium


Departments of Anaesthesia and Intensive Care, Copenhagen University Hospital, Rigshospitalet and Glostrup Hospital, Denmark

**Is Associated with Impaired Clinical Recovery**

Glenn S. Murphy, MD, Joseph W. Szokol, MD, Michael J. Avram, PhD, Steven B. Greenberg, MD, Torin Shear, MD, Jeffery S. Vender, MD, Jayla Gray, BA, and Elizabeth Landry, BA
Problems?

- Succinylcholine - rapid onset and offset but many AEs & CIs
- What would the alternative be for R.S.I?
- Rocuronium - rapid onset but in a ‘cannot intubate cannot ventilate’ situation return to spontaneous breathing is slow
- Reversal of deep NM blockade is not possible

More Problems?

- Residual blockade vs inadequate blockade
- Lack NM monitoring despite recommendation
- unrecognized residual blockade
  (Grayling 2007, Eriksson 2003)
- Reversal with neostigmine/edrophonium + parasympatholytic → cumbersome/ CVS effects and PONV.
The answer - Sugammadex?

- A γ cyclodextrin molecule
- 8 glucose molecules forming a ring
- Designed to encapsulate aminosteroids, esp. rocuronium
- rocuronium > vecuronium >> pancuronium
- Binds irreversibly in a 1:1 ratio forming an H2O soluble complex
Neuromuscular transmission and blockage at the neuromuscular junction.


History

- Cyclodextrins known to inactivate Steroidal compounds.
- Rocuronium has a steroid nucleus
- 1990s - Dr. Anton Bom speculated that rocuronium can bond with cyclodextrins.
- Initial studies - Rocuronium formed weak complex with Cyclodextrins.
- Modifications - Cavity size and charge
- Tight complex between the quaternary nitrogen of rocuronium + negatively charged side-chains.
History

- 1999: 1st batch of **Org 25969** (aka sugammadex) produced.
- 3 mins after 0.6 mg/kg of rocuronium
- 8 mg/kg of Org 25969 completely reversed neuromuscular blockade.

- 2005-2018: sugammadex in 15 million patients
- Approved in 57 countries


Speed of onset

- It is ....fast

![Image of turtle and sugammadex]
FDA approval

- 2007: FDA application for approval submitted.
- 2008: 1st regulatory approval (European Union)
- 2008: FDA Advisory Committee unanimously recommend approval.
- However, FDA denied approval
- Concerns over hypersensitivity and anaphylactic reactions
- Prolonged aPTT and PT noted in an in-vitro study.
- Effects on cardiac arrhythmias and QT prolongation unclear
- Further studies requested.

FDA approval

- 2009-2014 Multiple studies
- Mild transient increase in PT and aPTT, but resolved within an hour.
- Rahe-Meyer et al: randomized 1184 patients, hip or knee replacement
  sugammadex n = 596, usual care n = 588).
- Bleeding events: Transfusion, 24-h drain volume, drop in Hb, DVT
  17 (2.9%) sugammadex and 24 (4.1%) usual care patients.
- No anaphylaxis.
- No increase in bleeding or transfusion in sugammadex group

FDA approval

Re: Arrhythmia

• analysis of phase 2 and 3 clinical studies + postmarketing data.

• QTc was not prolonged with sugammadex.

• More Arrhythmia with Neostigmine + Glyco combination

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Arrhythmias

Neostigmine vs Sugammadex

<table>
<thead>
<tr>
<th>Arrhythmia-Related Investigations, Signs and Symptoms</th>
<th>Neostigmine (+glycopyrrolate) N=881</th>
<th>Sugammadex N=1078</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>69 (7.8)</td>
<td>25 (2.9)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>42 (4.8)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Decreased HR</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Increased HR</td>
<td>4 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>4 (0.5)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Syncope</td>
<td>3 (0.3)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>20 (2.3)</td>
<td>16 (1.8)</td>
</tr>
</tbody>
</table>

Data reported as n (%)  
Pooled Phase 1-3 Dataset (8 randomized clinical trials)
Post marketing Incidence of Bradycardia

- In 11.5 million sugammadex exposures, 73 reports of bradycardia related events have been reported (<0.01%)
  - 32 cases of bradycardia within minutes of sugammadex administration in stable patients (+ cardiac arrest in 6 pts)
    - 7 cases recovered without intervention
    - 16 cases responsive to atropine alone
    - 8 cases of combination therapy with vasopressors, atropine, and CPR
    - 1 case solely reports CPR
  - 41 remaining classes had a heterogeneous presentation
    - 7 cases associated with anaphylaxis
    - 6 cases report cardiac arrest

Torsadogenicity

- Reversal of neuromuscular block with anticholinesterase-anticholinergic combinations has been associated with significant QTc prolongation

- Not reported with sugammadex (even at high doses)
Allergic reactions

- 375 awake subjects were given 3 groups (4 mg/kg, 16 mg/kg, or saline)
- 1/375 anaphylactic reactions.
- treated with steroids and diphenhydramine,
- mechanism was unclear (no tryptase or sugammadex specific IgG/IgE).

- Reactions included:
  - Cutaneous reactions: urticaria, pruritus, erythema
  - Sneezing, rhinorrhea
  - Nausea, vomiting
- One case of anaphylaxis following first 16 mg/kg dose
  - No epinephrine used, resolved with steroids and antihistamines

Post marketing data

- Surgical patients (42 trials, n=3519)
  - Phase 1-3 studies (≤ 0.1%)

- 11.5 million patients have received sugammadex as of March 2015
  - 273 reports of anaphylaxis; 4 deaths
  - Post-marketing incidence (0.024%)

- Some perspective for rates of anaphylaxis
  - Rocuronium – 1 in 2,500 (0.04%)
  - Anectine – 1 in 2,080 (0.05%)

NLM identifier: NCT0216035.
**Allergy to light exposed Sugammadex?**

- Anaphylactic shock after sugammadex x 2 cases
- No history of prior sugammadex administration.
- Serum tryptase concentrations elevated
- Basophil activation test positive for sugammadex in only 1 patient
- BAT positive for light-exposed sugammadex solution in both patients
- Possible allergic reaction to a denatured compound of sugammadex by light exposure.

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**Anaphylactic Reactions to Native and Light-Exposed Sugammadex Suggested by Basophil Activation Test: A Report of 2 Cases**

Takamori Yamao, MD, PhD, Tetsuzi Suzuki, MD, PhD, Yuki Murose, MD, Hitomasa Nagata, MD, and Shizuki Kurogi, MD, PhD

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**2012:** 2nd FDA application

**2013:** FDA reported protocol violations

**2015:** FDA approval on December 16, 2015
Initial clinical trials

- 110 adult patients, randomized to receive rocuronium or succinylcholine for Intubation
Limited Pediatric data

- Awaiting FDA approval in children
- Few early studies have shown utility and safety in kids
- A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants. Principal Investigator: A. Karnwal
- A Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to <2 Years, MK-8616 PN169. Principal Investigator: A. Karnwal

Case reports in neuro-myopathic conditions

- De Boer et al: duchenne muscular dystrophy
  - Myasthenia gravis
  - Heart transplantation
- Takeda et al: 12 yr old myotonic dystrophy
  - VATS, Thymectomy
- Pickard et al: 14 m old myasthenia gravis
  - for percutaneous Gastrostomy, Orchiopexy
Case report

- 10 month-old, 5.9 kg infant
- Anesthesia induced with propofol + fentanyl
- Easy bag-valve-mask ventilation → vecuronium 0.1 mg/kg
- DL x3 failed
- Difficulty maintaining bag-valve-mask ventilation
- Stomach to insufflated, SpO2 to 75%.
- Procedure abandoned
- Sugammadex (8 mg/kg) was administered.
- 25 sec- Spontaneous ventilation.
- 90 sec- SpO2 returned to 99-100%.

Pediatric studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Details</th>
<th>Time (mins) to TOF &gt;0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghoneim et al</td>
<td>40</td>
<td>Sugammadex 4mg/kg or Neo 40 mcg/kg</td>
<td>Sugammadex 1.4 ± 1.2 Neo 25 ± 6 min</td>
</tr>
<tr>
<td>Ozgun et al</td>
<td>60</td>
<td>Reversal Sugammadex 4/kg or Neo 60 mcg/kg</td>
<td>Sugammadex 2.2 ± 1 Neo 19 ± 3 min</td>
</tr>
<tr>
<td>Kara et al</td>
<td>80</td>
<td>Reversal Sugammadex 2/kg or Neo 30 mcg/kg</td>
<td>Sugammadex 2.4 Neo 45 min</td>
</tr>
</tbody>
</table>

All 3 studies Faster extubation, recovery, No AEs
Neonatal data

- Limited
- 3 case reports and one open-label trial (abstract)
- Sugammadex in 3 neonates following abdominal surgery
- Neuromuscular blockade with rocuronium rapidly reversed with sugammadex (2-4 mg/kg)
- No adverse effects were noted.

Neonatal data

- 23 neonates
- Ages: 8 x 1 day, 15 x 1-7 days old.
- Mean weight 2.8 kg
- At the end of surgery, profound neuromuscular block in all patients.
- Reversal with sugammadex 4 mg/kg
- TOF to 0.9 in a median time of 1.3 min
  - (range: 0.6–3.0 min)
- No Residual neuromuscular blockade
- No Adverse events
- No changes in vital signs after the administration of sugammadex.
Sugammadex in the management of rocuronium-induced anaphylaxis

- 33 F, severe anaphylactic shock after rocuronium.
- Ineffective traditional management x 19 mins
- 500 mg sugammadex was administered
- Immediate hemodynamic improvement
- Exact mechanism unknown.


Metabolism

- Determined with single center, open labeled, non-randomized study
  - $^{14}$C-labeled sugammadex
  - Volunteers given 4 mg/kg bolus dose
  - n = 6 (healthy males)
- Clearance
  - Approx 70% excreted in 6 hours
  - Approx 90% in 24 hours
  - <0.02% detected in feces or exhaled air
- Metabolism
  - 95% of radioactivity detected in urine attributable to sugammadex
  - Suggests very limited metabolism
- In short: cleared rapidly, almost exclusively by kidneys, and minimal to no metabolism

Dosing

• Administered as a single bolus injection.

• Rocuronium and vecuronium
  – 4 mg/kg \(\rightarrow\) deep blockade
  – 2 mg/kg \(\rightarrow\) moderate blockade

• Rocuronium only
  – 16 mg/kg
    • is only recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium.

• Use actual body weight in obesity

<table>
<thead>
<tr>
<th>Sugammadex dose (actual body weight)</th>
<th>Indication</th>
<th>Average time to TOF ratio of 0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 mg/kg</td>
<td>Immediate reversal for rocuronium doses of 1.2 mg/kg</td>
<td>1.5 min</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>Reversal of deep neuromuscular blockade</td>
<td>3 min</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>Reversal of moderate neuromuscular blockade</td>
<td>2 min</td>
</tr>
</tbody>
</table>


• Recent studies comparing low doses of Sugammadex
• 0.5mg- 1mg-2 mg/kg were also efficacious

• Under-dosing of sugammadex lead to recurrence of neuromuscular block after initial successful transient reversal
Redosing steroidal NMBA after Sugammadex

- Expect delayed onset and shorter duration of action
- Re-administration of vec/roc after 16 mg/kg of sugammadex → recommend 24 hr wait time
- If wait time cant be observed consider nonsteroidal NMBA

Table 1: Re-administration of Rocuronium or Vecuronium after Reversal (up to 4 mg/kg BRIDION)

<table>
<thead>
<tr>
<th>Minimum Waiting Time</th>
<th>NMBA and Dose to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 minutes</td>
<td>1.2 mg/kg rocuronium</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium</td>
</tr>
</tbody>
</table>

Bridion package insert
What about the cost

50 kg patient

Sugammadex 4 mg/kg
200 mg vial
93.00

Neostigmine 3.5 mg = $12.00
+ Glycopyrrolate 0.7 mg = $11.00
$23.00

Savings
$60.00

Source: CHLA pharmacy

What about the cost

• Anesthetic drugs tend to be inexpensive.
• Other costs of surgery, are much higher.
• Average outpatient Hernia repair costs $5000-7000 based on insurance and other factors.
• Effective, immediate and complete reversal of neuromuscular blockade vs a tiny increase in overall healthcare cost.
• Cost of treating complications of residual paralysis.
What about the cost

• Although S is more costly than other anesthetic drugs, when looking at its cost impact overall on the health care of the surgical patient its amount is not significant.

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**What about the cost**

<table>
<thead>
<tr>
<th></th>
<th>Neostigmine group</th>
<th>Sugammadex group</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 surgery</td>
<td>1.14 ± 0.22</td>
<td>1.09 ± 0.22</td>
<td>.278</td>
</tr>
<tr>
<td>T2 reversal</td>
<td>0.09 ± 0.15</td>
<td>0.02 ± 0.01</td>
<td>.001</td>
</tr>
<tr>
<td>T3 OR discharge</td>
<td>0.13 ± 0.11</td>
<td>0.09 ± 0.04</td>
<td>.005</td>
</tr>
<tr>
<td>T4 OR time</td>
<td>2.01 ± 0.28</td>
<td>1.51 ± 0.24</td>
<td>.103</td>
</tr>
<tr>
<td>Initial recovery score</td>
<td>12.29 ± 1.25</td>
<td>12.04 ± 1.47</td>
<td>.410</td>
</tr>
<tr>
<td>Best recovery score</td>
<td>12.72 ± 0.45</td>
<td>13.81 ± 0.37</td>
<td>.351</td>
</tr>
<tr>
<td>Time PACU discharge</td>
<td>0.53 ± 0.40</td>
<td>0.47 ± 0.31</td>
<td>.543</td>
</tr>
<tr>
<td>Total time OR + PACU</td>
<td>3.02 ± 0.41</td>
<td>2.49 ± 0.38</td>
<td>.064</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>3.34 ± 0.74</td>
<td>3.38 ± 1.41</td>
<td>.457</td>
</tr>
</tbody>
</table>

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Operating room discharge after deep neuromuscular block reversed with sugammadex compared with shallow block reversed with neostigmine: a randomized controlled trial.

Purvis L1, Ollier D2, Iannitelli M3, Harada M4, Denosco G5, Dukes P2.
What about the cost

- Simulation model based on OR turnovers x 1 month
- TOF 0.9 was verified prior to tracheal extubation
- Use of sugammadex (rather than neostigmine) saved 33.5 hrs of staff overtime
- saved an average of 62 min per OR day


A discrete event simulation model of clinical and operating room efficiency outcomes of sugammadex versus neostigmine for neuromuscular block reversal in Canada
Ralph P. Insigna, Cédric Joyal, Alexandra Goyette, and André Galarneau

What about the cost

Sugammadex can be cost-effective if time saved = clinical productivity (extra cases)

No evidence to support this currently
Drug Interactions

- **Tamoxifen (SERM)**
  - Selective estrogen receptor modulator (SERM)
    -FDA approved for breast cancer treatment
  - High binding affinity for sugammadex
  - Usually high plasma concentrations
    - May displace vecuronium or rocuronium from Bridion
    - Potential for delay in recovery of TOF ratio to 0.9

- **Oral contraceptives**
  - Sugammadex may bind to progesterone
  - Considered equivalent to missing one dose of oral contraceptive
    - Official recommendation → 7 days of alternate form of birth control after administration of sugammadex
  - 15.6% of patients receiving GA at MMC were female of child bearing age (13-50)

Use in Specific Populations

- **Renal Function**
  - Not recommended in patients with severe renal impairment
    - Crcl < 30 ml/min
    - High flux dialysis is effective at removing sugammadex/rocuronium complex*

Key learning points

• Sugammadex is a novel pharmacologic agent

• Different mechanism - encapsulation

• Eliminates residual neuromuscular blockade

• Can reverse deep blockade

• Useful in myopathic conditions

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Key learning points

• Adverse effects with sugammadex are usually minor

  (nausea, vomiting, pain, hypotension, headache)

• Severe adverse effects rare: bradycardia and anaphylactoid reactions.
Key learning points

- Cost of using sugammadex must be balanced in each individual patient with indications and side effects
- Well-designed, sufficiently powered and controlled studies are still needed before recommending the routine use of deep NMB and the subsequent routine administration of sugammadex.

Questions?

SO MOMMY, IF COLUMBUS DIDN'T COME HERE, NOBODY WOULD HAVE FOUND US?