

SUGAMMADEX



"Magic Circle", oil on canvas, John William Waterhouse.

On the 8th night, Shahrazad continued....

“Dam you, you dog. It was you who did this to me and wounded my heart’s darling. You have caused me pain and robbed him of his youth, so that for three years he has been neither dead nor alive”.

To which I replied: “Dirty whore, filthiest of the fornicators....”

I drew my sword and aimed a deadly blow at her...She burst out laughing and said, “Off you dog! What is past cannot return and the dead cannot rise again, but God has given the man who did this to me into my power. Because of him there has been an unquenchable fire in my heart and a flame that cannot be hidden”.

Then, as she stood there, she spoke some unintelligible words and added: “Through my magic, become half stone and half man”.

“It was then that I became as you see me now, unable to stand or to sit, neither dead nor alive...every day she tortures me by giving me a hundred lashes with her whip until the blood flows down over my shoulders. Then she dresses me in a hair shirt of the kind I am wearing on my upper half, over which she places this splendid gown”.

The king turned to the youth and said: “Although you have freed me from one worry, you have added another to my cares. Where is this woman.....”

“She comes out once each day at sunrise, and the first thing she does is to strip me and give me a hundred lashes. I weep and call out but I cannot move to defend myself....”

“By God young man”, said the King, “I shall do you a service for which I shall be remembered and which will be recorded until the end of time”.

....The King in a weak voice said: “You dammed woman, do you deserve that anyone should talk to you or speak with you?”

“Why is that?” she asked.

“Because all day long you torture your husband, although he cries for help, and from dusk to dawn he stops me from sleeping as he calls out his entreaties....”

“With your permission”, she replied, “I shall release him”.

“Do that”, said the King, “and allow me to rest”.

“I hear and obey”, she replied...

...she took a bowl filled it with water and spoke some words over it. As the water boiled and bubbled like a pot boiling on the fire, she sprinkled her husband with it and said: “I conjure you by the words that I have recited, if you are in this state because of my magic, revert from this shape to what you were before”.

A shudder ran through the young man and he rose to his feet, overjoyed at his release, calling out, "I bear witness that there is no god but God and that Muhammad is the Apostle of God, may God bless him and give him peace".

His wife shouted at him, saying "Go and don't come back, or else I shall kill you!"

*Night 8 in
"The Arabian Nights",
(or "Tales of the Thousand and One Nights")
c. Ninth - Tenth Century A.D*

The great king, travelling through an enchanted land, encounters the horrific sight of a young man half turned to stone - neither alive nor dead. The young man tells him that his wife is actually an enchantress. Following his discovery of her infidelity, after which he wounds her lover rendering him "neither dead nor alive", by way of fearful revenge she cast this dreadful spell upon him. The King unable to bear this situation disguises himself as the sorceress's wounded lover and then commands her to reverse the spell she has put on her tormented husband. She reluctantly obeys and makes a counter-spell that reverses her husband's lithic paralysis.

On occasions we have need to paralyze our patients with a powerful spell in the form of the potion rocuronium. In this way we render them trapped as if within stone - not dead, yet though not seemingly alive either. In order to reverse our spell we have at our disposal a new and powerful counter potion. This comes to us in the form of sugammadex.

SUGAMMADEX

Introduction

Sugammadex is the first of a new class of drug known as a **selective relaxant binding agent (SRBA)**.

It *selectively* binds the **aminosteroid** non-depolarizing muscle relaxants:

- **Rocuronium** (Rocuronium bromide is a quaternary aminosteroid analogue of vecuronium bromide).
- Vecuronium
- Pancuronium

In this way it is a more ideal reversal agent for these relaxants compared to the traditional reversal with neostigmine and atropine.

A potential practical drawback however, can be sourcing the drug, dose calculation and preparation leading to substantial delays in administration in a “can’t intubate, can’t ventilate” scenario.

It rapidly reverses neuromuscular block induced by rocuronium, vecuronium and pancuronium regardless of the depth of the block.

Sugammadex reverses neuromuscular blockade more rapidly than neostigmine.

Sugammadex does not have an equal affinity with all aminosteroids. **Rocuronium** is the best studied agent.

Chemistry

Sugammadex is a modified gamma cyclodextrin which is a **selective relaxant binding agent (SRBA)**.

Preparation

Vials:

- Containing 100 mg/mL in 2 mL or 5 mL; (i.e. 200 mg in 2 mL or 500 mg in 5 mL).

Mechanism of Action

Sugammadex forms a complex with the neuromuscular blocking agents rocuronium, vecuronium and pancuronium and so reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. The gamma-

cyclodextrin component has a hydrophilic exterior and hydrophobic core that traps the aminosteroid ring of the aminosteroid neuromuscular blocking agents.

This results in the reversal of neuromuscular blockade induced by **rocuronium** or **vecuronium**.

The main advantage of sugammadex is reversal of neuromuscular blockade without relying on inhibition of acetylcholinesterase. It directly combines with the aminosteroid neuromuscular blocking agents and **has no effect on the cholinergic nervous system**.

Therefore it does not cause the autonomic instability produced by anticholinesterases such as neostigmine, and antimuscarinic agents such as atropine do not need to be co-administered.

In addition, neostigmine cannot be used to reverse profound blockade.

Sugammadex administration is therefore associated with much greater cardiovascular and autonomic stability than the traditional reversal agents.

It is also quick acting compared to neostigmine. It can reverse the effects of **rocuronium** in about **2 minutes**.

It is a better reversal option for rocuronium than neostigmine and atropine in cases where intubation has failed and a quick reversal is desired.

Pharmacodynamics

Sugammadex rapidly reverses neuromuscular block induced by rocuronium, vecuronium and pancuronium regardless of the depth of the block.

Sugammadex reverses neuromuscular blockade more rapidly than neostigmine.

Sugammadex does not have an equal affinity with all aminosteroids.

Rocuronium is the best studied agent. With optimal dosing sugammadex can reverse the effects of rocuronium within **2 minutes**.

Pharmacokinetics

Administration:

- Sugammadex is administered IV

Distribution:

- The steady-state volume of distribution of sugammadex is approximately 11 to 14 liters.

- Neither sugammadex nor the complex of sugammadex and rocuronium bind to plasma proteins or erythrocytes.
- Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose.
- It is unknown if sugammadex crosses the human placenta
- It is unknown if sugammadex is excreted into breast milk, but this is thought likely.

Metabolism:

- Sugammadex is excreted by the kidney unchanged in the urine.
- Aminosteroid - Sugammadex complexes** are also excreted renally.
- The elimination half-life of sugammadex in adults with normal renal function is 2.0 hours
 - Renal failure will prolong the half life of sugammadex.

Indications

The specific reversal of the aminosteroid neuromuscular blocking agents :

1. **Rocuronium**
2. Vecuronium (less well studied)

Pancuronium should also be reversible in theory, but this has not been definitely established in clinical practice.

Contraindications/ Precautions

1. Hypersensitivity to the active substance or to any of the additives
2. Even if recovery from neuromuscular blockade is complete, other drugs used in the anaesthetic period can depress respiratory function and, therefore, ventilatory support may still be required.
3. Sugammadex should not be used to reverse blockade induced by muscle relaxants other than rocuronium or vecuronium.

Pregnancy:

Sugammadex is classified as a B2 drug with respect to pregnancy.

Category B2 drugs are those drugs which which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Sugammadex has been shown to provide an effective and well tolerated reversal of neuromuscular blockade induced by **rocuronium** use during caesarean sections.

Sugammadex is considered safe to use during pregnancy.

Breast feeding:

Considered safe.

Published reports describing the use of sugammadex during breastfeeding have not been located.

Sugammadex is rapidly metabolised and eliminated from the maternal circulation, which may limit the amount of sugammadex excreted into breast milk.

Infants exposed to sugammadex via breast milk are unlikely to experience harmful effects.

Breastfeeding may be resumed once the mother is alert and comfortable to do so

Adverse Effects

1. Allergic reactions, (rare).
2. Sugammadex may affect haemostasis by interfering with the coagulation cascade. Patients with pre-existing coagulation abnormalities should therefore be monitored for activated partial thromboplastin time, prothrombin time and INR after receiving sugammadex.
3. Prolongation of the QTc interval has been noted in some patients receiving sugammadex, however torsades des pointes has not occurred. QTc prolongation may be a concern in situations where sugammadex is given with other drugs that affect the QT interval.

Dosing

Sugammadex does not have an equal affinity with all aminosteroids

Rocuronium is the best studied agent.

For rocuronium reversal:

For routine reversal of **rocuronium**:

- **Adult, child >2 years: IV bolus, 4 mg/kg**

There are no clinical data to recommend sugammadex for immediate reversal of vecuronium-induced blockade.

For immediate reversal of **rocuronium** blockade:

- **Adults: 16 mg/kg IV bolus.** Reversal is achieved within about **2 minutes**.

For vecuronium reversal:

Onset of action seems to be slower for vecuronium than for rocuronium

Optimal dosing is not known.

Pancuronium:

Reversal of pancuronium (a bis-quaternary) seems to require larger doses of sugammadex than are needed to antagonize rocuronium.

Optimal dosing is not known.

References:

1. Australian Medicines Handbook, January 2017.
2. Sugammadex in Aust Presc, Vol 32 No. 33, June 2009.
3. Sugammadex in RWH Pregnancy & Breast feeding Guidelines, 15 February 2017

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