

Sugammadex

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Introduction

There are a large number of publications which describe the use of cyclodextrins (CDs) in numerous fields, including biomedicine, cosmetics, food industry, wastewater remediation and catalysis.¹ These drugs contain a number of glucose monomers in a ring, creating a cone shape: α (alpha), β (beta), and γ (gamma) cyclodextrins with 6, 7 and 8 glucose subunits respectively. With a hydrophobic interior and hydrophilic exterior, they can form complexes with hydrophobic compounds often conferring solubility and stability to other drugs. The inclusion compounds of cyclodextrins with hydrophobic molecules are able to penetrate body tissues; these can be used to release biologically active compounds under specific conditions.²

Sugammadex is a unique, selective relaxant binding agent (SRBA) which reverses aminosteroid-induced neuromuscular blockade. It is an alternative to anticholinesterases in anaesthesia and allows use and reversal of rocuronium as a substitute for suxamethonium for rapid sequence induction (RSI).^{3,4}

Mechanism of action

Sugar gamma cyclodextrins (sugammadex) is a gamma-cyclodextrin that has been modified by the addition of eight negatively charged carboxyl thioether groups to its sixth carbon position resulting in a hydrophilic exterior and a lipophilic centre (Figure 1).² This addition does several things. It enlarges the inner cavity, allowing it to better accommodate and encapsulate large molecular aminosteroids such as rocuronium, vecuronium and to a lesser degree pancuronium (Table I). The negatively charged groups also form electrostatic bond interactions with the positively charged quaternary nitrogen of the aminosteroid molecule. This results in a 1:1 noncovalent complex between

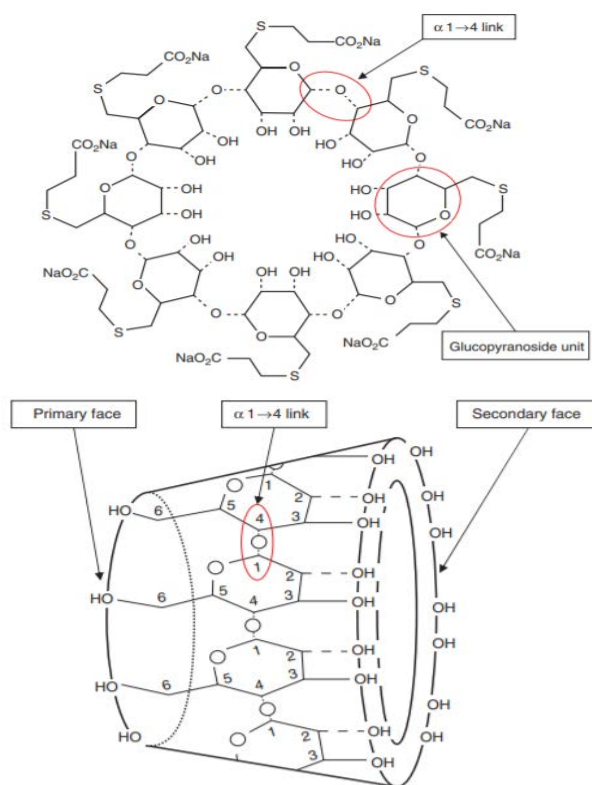


Figure 1: Structure of sugammadex showing eight glucopyranoside units linked via α 1 \rightarrow 4 linkages to maintain a doughnut-like shape. The negatively charged OH groups at the rims create the primary and secondary faces. These are responsible for the water solubility of the molecule. In contrast, the interior is lined by carbon atoms, which with the α 1 \rightarrow 4 linkages create the lipophilic core.²

sugammadex and rocuronium.⁵ This inclusion complex is maintained by a combination of intermolecular (van der Waals) forces, hydrogen bonds, and hydrophobic interactions, and is therefore very stable.^{2,5}

Sugammadex works via two mechanisms: firstly, on entering the plasma it encapsulates the circulating aminosteroid rendering it inactive, secondly, it promotes dissociation of the aminosteroid from the neuromuscular junction (NMJ) by creating a concentration gradient from the NMJ to the plasma where it is also encapsulated. Sugammadex also diffuses out of the plasma into the extracellular fluid compartment, encapsulating any unbound aminosteroid it encounters. This

Table I: Percentage binding of neuromuscular blocking agents by sugammadex⁴

Neuromuscular blocking agent	Amount bound by sugammadex
Rocuronium	95%
Vecuronium	90%
Pancuronium	61%
Atracurium	4.5%
Mivacurium	0%

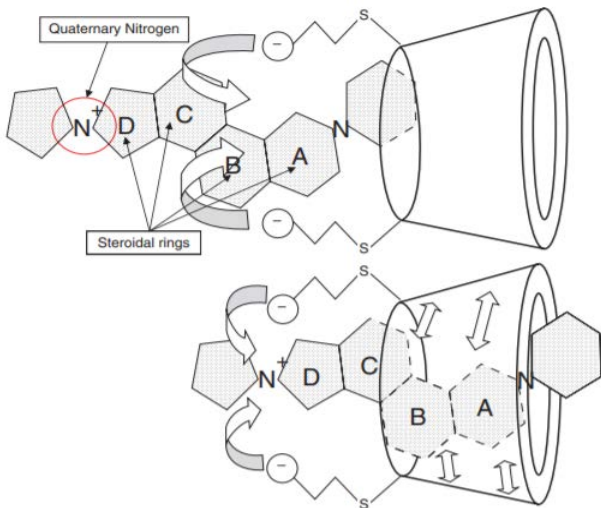


Figure 2: The encapsulation process: sugammadex carboxyl groups interact with the steroidal rings A, B, C and D of the aminosteroid NMBA molecule drawing it into the cavity of the cyclodextrin where additional non-covalent attractions (\leftrightarrow) hold the molecule securely in place.² (Video illustrating encapsulation: <https://youtu.be/BJhuA8Dlp50>)

encapsulation allows for neuromuscular blockade to be rapidly terminated. Unlike anticholinesterase drugs, sugammadex has no effect on acetylcholinesterase (AChE). This obviates the need for anticholinergic drugs, thus avoiding their side effects.^{2,6}

Pharmacokinetics

The pharmacokinetics of sugammadex shows a dose-dependent linear relationship over the dose range of 0.1–32 mg/kg.^{3,5} One safety study has suggested that this linear relationship extends up to 96 mg/kg.⁷ In the healthy adult

population sugammadex has an estimated volume of distribution of 11–14 litres, an elimination half-life of 1.8 hours and clearance of 88 ml/min. It is not metabolised and is excreted almost exclusively unchanged by the kidneys with more than 90% being renally excreted within 24 hours.³ Excretion via faeces or expired air was < 0.02% of the dose.⁸

The administration of sugammadex alters the pharmacokinetics of rocuronium with the rocuronium-sugammadex complex behaving in a similar manner to sugammadex, with elimination of rocuronium being shifted from the biliary system to predominantly renal excretion.^{3,5}

Dosing

Sugammadex is available as a clear 100 mg/ml intravenous solution with each millilitre containing 9.7 mg sodium; it comes in a 1, 2 or 5 ml composition; has a shelf life of three years; is photosensitive, and should thus be stored protected from ambient light at < 30 °C. It must be administered via a rapid bolus intravenous injection. The dose of sugammadex required to ensure complete reversal is dependent on the depth of block, the timing and dose of rocuronium. As such, three dosing regimens are recommended depending on the degree of blockade (Table II).⁴ Adequate reversal of the neuromuscular blocking agent (NMBA) is determined by a TOF > 0.9, where the height of the fourth twitch is 90% of the height of the first twitch.

It is important to note that there is a great variability in recovery times after administration of sugammadex at all depths block, and therefore neuromuscular monitoring is recommended until complete reversal is clinically achieved. Reduced doses

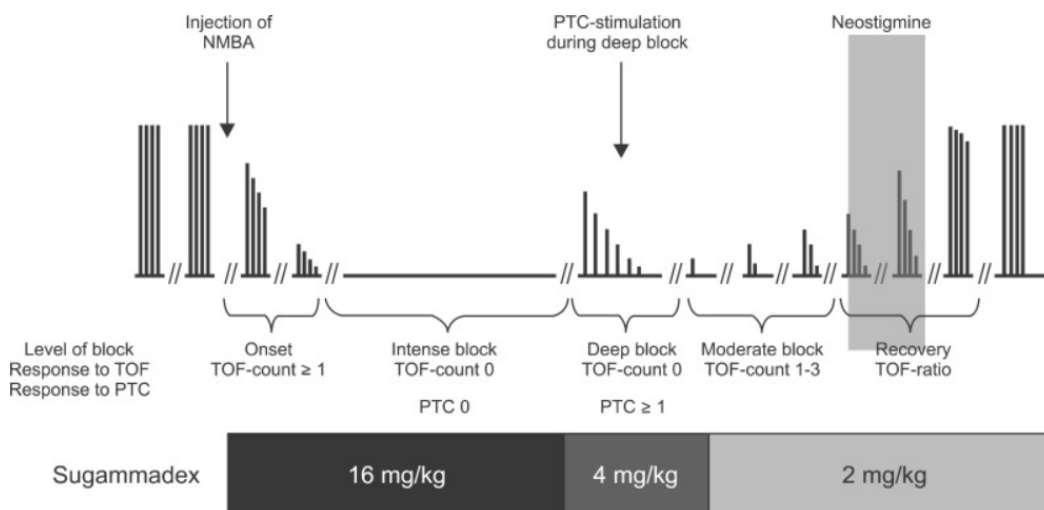


Figure 3: Recommended doses of sugammadex depending on the degree of neuromuscular blockade. NMBA – neuromuscular blocking agent, PTC – post tetanic count, TOF – train-of-four⁹

Table II: Table showing dose of sugammadex required to reverse different levels of rocuronium neuromuscular blockade³

Type of block	Dose of sugammadex	Time to TOF > 0.9
Routine = TOF count 2 or more	2 mg/kg	2 minutes (17 minutes for neostigmine) ⁹
Moderate = PTC 1–2	4 mg/kg	3 minutes (not possible with neostigmine)
Profound = 3–5 minutes post NMBA (no response to TOF or PTC)	16 mg/kg	1.5 minutes (faster than spontaneous recovery from succinylcholine)

Table III: Re-administration of rocuronium or vecuronium after routine reversal (up to 4 mg/kg sugammadex)¹⁰

Minimum waiting time	NMBA and dose to be administered
5 minutes	Rocuronium 1.2 mg/kg (results in slower onset 2–5 minutes and shorter duration of blockade 17–46 minutes) ⁴
4 hours	Rocuronium 0.6 mg/kg or vecuronium 0.1 mg/kg
24 hours	Normal NMBA dose (particularly in patients with mild/moderate renal impairment after routine reversal with sugammadex and/or after immediate reversal with 16 mg/kg sugammadex)

of sugammadex (< 2 mg/kg) are associated with prolonged recovery times and incomplete reversal and are therefore not recommended.

Should the patient require repeat neuromuscular blockade after having received a dose of sugammadex, the recommendation is to use an alternative group of NMBA, e.g. succinylcholine or a benzylisoquinolinium. It is also possible to re-paralyse the patient with rocuronium, but the dose required depends on the sugammadex given and the time since administration (Table III).^{3,8}

Side effects and precautions

Hypersensitivity

Hypersensitivity although rare, is far the most concerning side effect of sugammadex, with a literature review highlighting that this can be rapid and severe in nature (anaphylaxis) with most cases presenting within five minutes of sugammadex exposure. The mechanism of this reaction is not clear but may involve previous food and pharmaceutical CD exposure. It is estimated that the incidence of these reactions is at < 1%, this is likely to increase with higher drug dose (16 mg/kg)⁵, frequent and repeated use of sugammadex.^{3,11} Interestingly sugammadex has been shown to be successful in some cases of rocuronium induced anaphylaxis.⁶

Coagulation

Earlier studies suggested an increase in activated partial thromboplastin time (aPTT) possibly by the transient inhibition of factor Xa. A transient increase in activated aPTT and prothrombin time (PT) at 10 minutes that normalises by one hour in doses of 4 mg/kg has not been associated with adverse clinical consequences. Further studies are needed to review the effect of higher doses of sugammadex.¹²

Arrhythmias

Prolongation of QTc interval has been described but with the same rate as in the placebo group; this can also be observed with several anaesthetic agents, therefore its significance is highly questionable, particularly in the 2–4 mg/kg dose and even up to the 32 mg/kg dose.^{6,9} A wide variety of other arrhythmias are described, with the most notable being bradycardia. However, compared to neostigmine, the overall incidence is lower in both the adult and paediatric population for sugammadex.⁶

Neurotoxic

Animal studies suggested that sugammadex may be neurotoxic, but it also highlighted that the penetration of sugammadex across the blood–brain barrier is minimal, reducing this potential risk in humans.³

Common side effects

Dysgeusia, headache, fatigue, nausea, vomiting, dizziness, urticaria and abdominal pains.³

Drug interactions

Co-administration of sugammadex is not recommended with ondansetron, verapamil and ranitidine due to physical incompatibility. The effect of sugammadex is not altered by administration of magnesium and appears to be equally effective with both intravenous and volatile anaesthesia.³ The main drug interactions that take place with sugammadex are displacement and capture reactions. Displacement reactions occur when a drug displaces rocuronium from its sugammadex-rocuronium complex causing theoretical risk of re-occurisation. Drugs with this capability are toremifene, fusidic acid, flucloxacillin and diclofenac. Such reactions have not been correlated into clinical practice.³ Capturing reactions reduce the efficacy of other drugs when sugammadex encapsulates them. The most significant is with oral contraceptives, progesterone levels are reduced more than oestrogen, making hormonal contraception less effective.⁴ Subsequently affected women need to be counselled appropriately and use extra contraception precautions for seven days following administration of sugammadex.³ Cortisone and remifentanyl are also bound with minimal clinical effects.⁴

Implications for practice

Sugammadex vs neostigmine

A great concern with NMBA is residual neuromuscular blockade with consequent muscle weakness and potential critical respiratory events. Reversal with anticholinesterases is also associated with several pitfalls due to the muscarinic effects and relatively slow onset of action. Studies have shown that sugammadex is predictable with a reproducible response compared to neostigmine, and is superior in producing complete reversal of neuromuscular blockade from both routine and moderate levels, occurring up to 17 times faster with sugammadex.¹³ A systematic review found no difference in the occurrence of nausea and vomiting or any major life-

threatening postoperative event when comparing sugammadex and neostigmine use.¹⁴

The diaphragm and abdominal muscles are the most resistant muscles of the body to NMBA. Oftentimes the surgeon could complain about the intensity of the block because the diaphragm had already started to recover whereas the peripheral muscles such as the adductor pollicis were fully paralysed with no response at the TOF.⁵ Sugammadex allows the anaesthetist to further paralyse the patient up to the end of the surgical procedure, e.g. laparoscopic surgery.

Some anaesthetists are reluctant to use sugammadex because the cost is significantly higher when compared with neostigmine, however the direct cost must be balanced against the potential risks and complications of incomplete neuromuscular recovery (Table IV).

Table IV: Estimated cost for each ampoule in a public hospital

Drug	Estimated cost
Suxamethonium	R11.73
Glycopyrrolate	R18.76
Neostigmine	R5.52–R6.75
Sugammadex	R758.36

Rocuronium-sugammadex vs suxamethonium

When appropriately dosed (16 mg/kg), sugammadex reverses profound rocuronium-induced neuromuscular blockade within 1.3–9 minutes¹³ without the suxamethonium's adverse events such as hyperkalaemia, myalgia, increased intracranial, or intraocular pressure, and the most fatal one – malignant hyperthermia. In addition, sugammadex can also be considered in the 'can't intubate, can't ventilate' (CICV) situation after the administration of rocuronium. It must however be noted that return of neuromuscular function does not necessarily equate to the return of spontaneous ventilation. Sugammadex could also be considered at any stage of surgery to reverse deep neuromuscular block when intraoperative neuro-monitoring is necessary or to facilitate electroconvulsive therapy when compared with suxamethonium.

Special considerations

Specific populations

Even though the recovery time in the **elderly** population (> 75 years) tends to be slower, the same dose is recommended as for younger adults. This is most likely due to a reduced cardiac output in the elderly.⁸ There was originally insufficient information on the use of sugammadex in children < 7 years, and subsequently it was not endorsed for use in neonates and infants.⁸ Recent data from phase 2 trials and a meta-analysis has shown that sugammadex is equally effective and safe in the **paediatric** population.⁶ The use of sugammadex during **pregnancy** has not been studied, and is therefore not recommended despite minimal placental transfer. It may have a role in RSI in obstetrics.

In **obese** patients the dose of sugammadex should be based on actual body weight. There have been suggestions to dose it at ideal body weight plus 40%, but this has been associated with slower recovery times and may lead to an increased risk of inadequate reversal.³

Neurological disease

Sugammadex has been shown to be a safe and effective alternative to neostigmine in patients with myasthenia gravis. There are in fact several studies of its safe use in other neurological conditions including myotonic dystrophy, amyotrophic lateral sclerosis, Duchene's muscular dystrophy and Huntington's disease.¹⁵

Cardiorespiratory disease

Sugammadex has been safely used in patients with pulmonary diseases such as bronchiectasis and cystic fibrosis. Bronchospasm has been documented following administration in a small number of cases. Sugammadex has been used effectively in patients with cardiac failure and post cardiac transplant with prolonged recovery time in comparison to the normal population.³

Renal disease

Sugammadex provides rapid reversal of deep rocuronium induced neuromuscular blockade in renal and control patients, with it being noted that its action was significantly slower at achieving a TOF > 0.9 in renally impaired patients compared to the normal population at 3.1 versus 1.9 minutes respectively. Clearance of the complex was significantly reduced and remained detectable in many subjects with severe renal impairment (creatinine clearance ≤ 30 ml/min) up to seven days post administration. Subsequently its use in this population is not recommended.¹⁶

Liver disease

For mild to moderate hepatic impairment no dose adjustment is required as the drug is renally excreted. Caution should be exercised in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy.⁸

Conclusion

The advent of sugammadex has created a reliable reversal for profound neuromuscular blockade with aminosteroid NMBA. It is advantageous in that it avoids the side effects often associated with anticholinesterase and suxamethonium. Its present limitations seem to be confined to its cost and its inability to reverse non-aminosteroidal agents. The **calabadiions** (1 and 2), a cucurbituril derivative, reverse aminosteroidal as well as the benzylisoquinoline neuromuscular agents, ketamine, etomidate and local anaesthetic agents.⁴ This may be an alternative in the near future.

Conflict of interest

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