Sugammadex

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ABSTRACT

Sugammadex is the first selective antagonist to reverse neuromuscular blockade induced by rocuronium and vecuronium. The mechanism by which sugammadex works is superior to current neuromuscular block reversal strategies in terms of speed, efficacy and side effects. There is little contemporary guidance on the use of sugammadex in intensive care medicine. This review covers the key pharmacological features, clinical uses and cost-effectiveness in the context of intensive care practice.

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Sugammadex is the first selective relaxant binding agent used to rapidly reverse neuromuscular blockade induced by the aminosteroid neuromuscular blocking drugs (NMBDs) rocuronium, vecuronium and pancuronium.[1] First approved in the European Union in 2008, it is now registered in over 50 countries. Marketed as Bridion in Australia and New Zealand, it is increasingly used in anaesthesia practice and similarly has implications for intensive care.[2] This review describes the key pharmacological features, clinical uses and cost-effectiveness of sugammadex relevant to intensive care practice.

Structure and mechanism of action

Sugammadex is a modified cyclodextrin and the first of a new class of drugs effective for reversal of the aminosteroid NMBDs rocuronium, vecuronium and pancuronium. The name sugammadex relates to its structure: *su* refers to sugar and *gammadex* refers to its basic structural molecule, γ-cyclodextrin. γ-Cyclodextrin is a ring-shaped molecule consisting of eight sugars with a three-dimensional structure resembling a hollow, truncated cone. Its structure consists of a hydrophilic exterior and hydrophobic core. A hydrophobic interaction traps the aminosteroid NMBD in the core of the molecule to produce a water-soluble complex. Unmodified γ-cyclodextrin is not deep enough to accommodate the large structure of the aminosteroid agents, so it is modified by the addition of eight side-chains to extend the cavity, allowing the hydrophobic steroidal rings of the aminosteroid agents to be accommodated (Figure 1).[3] These side-chains contain a carboxyl group that forms an electrostatic bond with the positively charged aminosteroid quaternary groups. The end result is a highly stable "guest–host complex" with a very high association rate and a very low dissociation rate. The resultant rocuronium or vecuronium–sugammadex complex is pH- and temperature-independent and very stable.

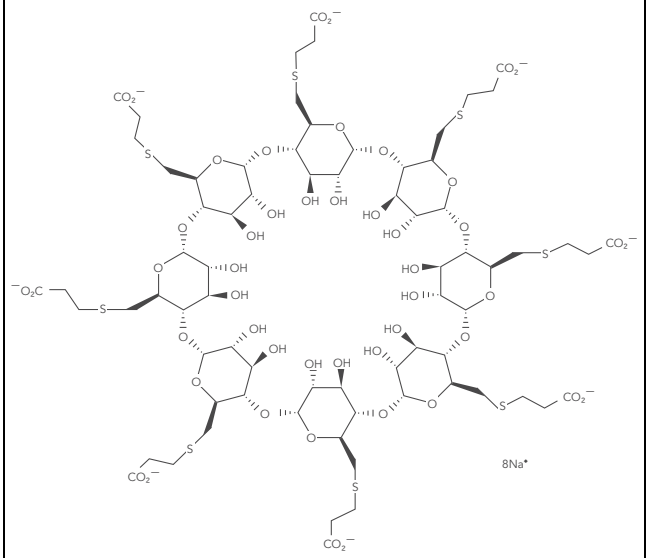
The reversal of the neuromuscular block by sugammadex consists of two phases. First sugammadex encapsulates rocuronium or vecuronium molecules in the plasma, resulting in the rapid reduction of free molecules. Then this reduction leads to a recruitment of all extravascular rocuronium or vecuronium molecules, including those from the neuromuscular junction, back into the bloodstream, where immediate encapsulation and inactivation occurs. The association–dissociation rate, at a concentration of 1 molar unit of sugammadex and rocuronium, is 25 000 000:1, which means that sugammadex encapsulates 25 million times as much rocuronium as it releases over a given period of time.[4] The affinity of sugammadex towards vecuronium is 2.5-fold less.

The sugammadex–NMBD complex is eliminated via the kidney, therefore the primarily hepatic elimination pathway of rocuronium and vecuronium is completely changed into a renal elimination pathway by binding to sugammadex.[5] It is important to note that reversal is independent of the degree of neuromuscular blockade. In practice, this allows even deep neuromuscular blockade to be predictably and reliably reversed.[1]

Dose and pharmacokinetics

Sugammadex is presented as 200 mg in 2 mL, or 500 mg in 5 mL, and is a clear, colourless solution. The drug is photosensitive and must be stored protected from ambient light. It does not require refrigeration, but should be stored at < 30°C. Its shelf-life is 3 years.[6] The recommended dose of sugammadex depends on the depth of neuromuscular block at the time of reversal (Table 1).[6] For all but rescue reversal, the use of a peripheral nerve stimulator is recommended to guide dose calculation. Recommended doses for reversal of equivalent depths of neuromuscular block of rocuronium and vecuronium are the same, with the exception of rescue reversal of vecuronium which has not been studied.[6] Clinical studies also indicate that while reversal of

Figure 1. Chemical structure of sugammadex, a modified cyclodextrin



vecuronium is effective, it is slower than reversal of rocuronium.[7-9] There are no published dose recommendations for reversal of pancuronium.

The pharmacokinetic profile of sugammadex is shown in Table 2. It does not undergo significant metabolism and about 90% is excreted in the urine within 48 hours.[5,10] Despite this, no dose adjustment is required in mild-to-moderate renal dysfunction.[6] Sugammadex is not recommended for patients with severe renal dysfunction or for use in dialysis patients.[6] However, trials in patients with severe renal dysfunction indicate that efficacy is maintained, and, although prolonged exposure to sugammadex occurs, this does not lead to adverse effects.[11] Recent evidence also indicates that sugammadex and the sugammadex–rocuronium complex are effectively removed by haemodialysis using a high-flux membrane.[12] Similarly, no adjustment is required in mild-to-moderate liver dysfunction; however, its pharmacokinetic profile has not been evaluated in the presence of severe liver dysfunction. Studies of pharmacokinetics in children and the elderly also indicate that a dose adjustment is not required.[13,14]

Drug interactions

There are no clinical reports of drug interactions for sugammadex with any drug used in intensive care. However, sugammadex may theoretically lead to *displacement interactions*, in which another drug (eg, flucloxacillin, fusidic acid) binds to sugammadex and displaces the bound muscle relaxant, resulting in a recurrence of block; or *capture interactions*, in which sugammadex binds another drug (eg, an oral contraceptive), reducing its efficacy.[15] Theoretically, it is possible that sugammadex can encapsulate cortisone, atropine and verapamil, but its affinity for these drugs is up to 700-fold less than its affinity for rocuronium and therefore unlikely to occur. Finally, a change in acid–base status, which affects cholinesterase inhibitor activity, does not influence the efficacy of sugammadex.[16]

NMBDs in the intensive care unit

NMBDs are advantageous in the intensive care unit to facilitate tracheal intubation, improve patient–ventilator synchrony, enhance gas exchange, and diminish the risk of ventilator-associated barotrauma. They are also used to reduce muscle oxygen consumption, and to manage patients with increased intracranial pressure. The ideal NMBD should produce rapid, titratable paralysis, have a rapid offset of action to allow for repeated neurological assessment, be immediately reversible (eg, in a "can't intubate, can't ventilate" situation), and have no adverse haemodynamic or physiological effects.

Suxamethonium is the only depolarising NMBD used to facilitate intubation or treat laryngospasm.[17,18] Although it has a rapid onset and a short duration of action, its use is limited because its actions cannot be reversed, and it has significant adverse effects including hypertension, bradycardia, masseter spasm, ventricular arrhythmia and increased

Table 1. Recommended dose of sugammadex for reversal of the aminosteroid neuromuscular blocking drugs

Neuromuscular blocking drug	Shallow block (TOF = 2)	Deep block (PTC = 1 to 2)	Immediate rescue reversal
Rocuronium	2 mg/kg	4 mg/kg	16 mg/kg
Vecuronium	2 mg/kg	4 mg/kg	Not known

TOF = train of four. PTC = post-tetanic count.

Table 2. Pharmacokinetic profile of sugammadex in adults

Pharmacokinetic parameter	Measure
Protein binding	< 1%
Volume of distribution at steady state	18 L
Elimination half-life	100 minutes
Plasma clearance	120 mL/minute
Metabolism	Negligible

intracranial pressure. Importantly, in the context of intensive care medicine, suxamethonium increases serum potassium concentration by 0.5–1.0 mEq/L due to an efflux of potassium from muscle cells, and must be used cautiously in patients with pre-existing hyperkalaemia. Suxamethonium is therefore contraindicated in patients with up-regulation of neuromuscular junction receptors, such as patients with major burn injury, demyelinating disease and spinal cord injury, where extrajunctional acetylcholine receptor expression increases in proportion to the magnitude of the injury. This can cause an exaggerated release of potassium, resulting in hyperkalaemia and cardiac arrest.[19]

Due to the limitations of suxamethonium, the non-depolarising NMBDs vecuronium and rocuronium are commonly prescribed in the ICU.[20] They are considered to have fewer adverse effects, but their longer duration of action often requires antagonism with a cholinesterase inhibitor such as neostigmine. There are important limitations associated with the cholinesterase inhibitors. First, they are ineffective in reversing profound neuromuscular blockade. Second, side effects are common and include bradycardia, hypotension, bronchoconstriction and nausea and vomiting. To alleviate these adverse effects, a muscarinic antagonist, commonly glycopyrrolate or atropine, is coadmistered. Adverse effects associated with the use of muscarinic antagonists include tachycardia, dry mouth and urinary retention.

Sugammadex and the difficult airway

It has been reported that at least one in four major airway events in hospital is likely to occur in the ICU or the emergency department.[21] The reported incidence of failed intubation in the emergency department is 3%–5%.[22,23] The incidence of difficult or failed intubation in the ICU is unknown,[22,23] but data from the anaesthesia literature suggests a lower incidence. In a series of 37 400 patients in a tertiary care hospital who underwent general anaesthesia with attempted direct laryngoscopy, the incidence of unexpected failure to intubate by direct laryngoscopy was reported at 0.43%.[24] A recent review of 50 000 operating room patients reported the incidence of impossible mask ventilation to be 0.15%. In this study, impossible mask ventilation was also associated with difficult intubation.[25] The reported incidence of major complications of airway management during anaesthesia (death, brain damage, emergency surgical airway and unanticipated intensive care unit admission) is reported as one in 22 000.[26]

The ability of sugammadex to rapidly reverse rocuronium has led to suggestions that it may be of use as a rescue strategy in the time-critical "can't intubate, can't ventilate" scenario.[15,27-29] In this situation, reversal of neuromuscular blockade facilitates onset of spontaneous ventilation and some recovery of upper airway tone which may be potentially lifesaving. However, sugammadex is not a panacea in this situation, and the need for caution when relying on sugammadex in this situation has recently been described.[30,31] A "can't intubate, can't ventilate" scenario may be created by multiple airway interventions in an anticipated or unanticipated difficult intubation, due to progressive swelling leading to airway deterioration.[26] Sugammadex use in this situation will reverse neuromuscular block, but will not necessarily restore a patent airway.

It has therefore been suggested that when failed intubation and failed ventilation is recognised early, the use of sugammadex is more likely to restore airway patency if it is administered before multiple airway interventions have occurred.[30] A further limitation of the use of sugammadex in the "can't intubate, can't ventilate" scenario may be the time taken from deciding to administer to actual administration of the drug. A simulated "can't intubate, can't ventilate" scenario found an average delay of 6.7 minutes to administration. This was due to the time taken to calculate, prepare and administer the correct dose, and was attributed to lack of awareness of the correct dose and the time spent drawing up the full 16 mg/kg dose.[32] Considering that the calculated dose of sugammadex for a 70 kg adult is 1120 mg, and the drug is presented commonly as a 200 mg in 2 mL solution vial, it is understandable that this would potentially be the source of considerable delay. Some authors encourage preparing sugammadex in a prelabelled syringe before induction if a "difficult airway' is suspected,[33,34] but this would have significant cost implications and we do not advocate this as routine practice.

The requirements for rocuronium or vecoronium within hours of sugammadex administration warrants consideration. The current recommendation is that rocuronium should not be administered within 24 hours of sugammadex.[6] However, animal studies indicate that following sugammadex, rocuronium can re-establish complete neuromuscular block after 30 minutes. Dose calculations indicate that a dose of rocuronium 1–1.5 mg/kg would be required after a dose of sugammadex 2 mg/kg, and a rocuronium dose of more than 2 mg/kg would be required after sugammadex 8 mg/kg. No dose calculation was performed for rocuronium after a sugammadex dose of 16 mg/kg.[35] Given the reduced efficacy of rocuronium in this situation, a simpler alternative may be to use suxamethonium or a benzylisoquinolinium non-depolarising muscle relaxant (ie, atracurium) in their usual doses, as the efficacy of these drugs is unaffected.[36]

Sugammadex as an alternative to suxamethonium

Suxamethonium is the traditional muscle relaxant of choice in rapid-sequence induction in the ICU. This is due to its rapid onset of action and predictable intubating conditions.[2]

Furthermore, given its "short" duration of action, it is used in patients with suspected "difficult airways" in the expectation that it will wear off quickly, with resumption of spontaneous ventilation, in the event that intubation is not possible. Recent evidence suggests, however, that this presumption is not reliable, and that unassisted ventilation may not occur sufficiently soon to avoid desaturation, even in patients who have been adequately preoxygenated.[37,38] This variability in duration of effect occurs due to differences in genotype for plasma cholinesterase.[38] Recent evidence has also indicated that suxamethonium use in rapid-sequence induction is associated with more rapid desaturation than rapid-sequence inductions using rocuronium.[39]

Rocuronium is now considered an acceptable alternative to suxamethonium for rapid-sequence induction. Its main limitation has been the prolonged duration of action resulting from the larger (ie, 1.2 mg/kg) doses that are required for comparable onset times. This has been of particular concern in the situation where a difficult intubation is anticipated. Sugammadex, with its ability to rapidly reverse neuromuscular blockade, abolishes this concern. This was highlighted by a multicentre North American clinical trial comparing rapid-sequence inductions with rocuronium (1.2 mg/kg) followed by sugammadex (16 mg/kg) 3 minutes later, and suxamethonium (1.5 mg/kg) with spontaneous offset.[40] The trial was performed with operating room patients deemed at risk for aspiration. Recovery of the first train-of-four twitch to 90% was almost twice as fast in the rocuronium–sugammadex group compared with the suxamethonium group (4.4 minutes v 6.2 minutes). These differences occurred despite a 3-minute delay in sugammadex administration. When recovery was timed from sugammadex administration, median recovery occurred in 2.2 minutes. A further study compared time to resumption of clinically adequate respiratory function after rocuronium–sugammadex compared with suxamethonium. Return of adequate respiratory function occurred more than 3 minutes faster in the rocuronium–sugammadex group.[41]

These studies indicate that the safety of rapid-sequence induction may be enhanced with use of rocuronium rather than suxamethonium, if sugammadex is available as rescue therapy. This is also particularly relevant in patients for whom suxamethonium is contraindicated and in patients who are at increased risk for difficult intubation. The availability of sugammadex does not, however, preclude the need for consideration of an awake technique of intubation in the setting of a known difficult airway.

Sugammadex for rocuronium anaphylaxis

Recent case reports have described the novel use of sugammadex in the management of rocuronium anaphylaxis, with time-related improvement in haemodynamic state after poor response to conventional treatment.[42-44] One possible theory is that as it effectively removes rocuronium from the circulation, it prevents ongoing antigen exposure and release of vasoactive mediators. The possibility of sugammadex removing allergenic drugs such as rocuronium has been critically reviewed.[45] It remains to be established whether or not rocuronium in an encapsulated form with sugammadex can react with rocuronium-reactive IgE antibodies. Clinical and laboratory data are not available on the possible sequestration by sugammadex of rocuronium from the antibody-combining sites of cell-bound IgE molecules. In-vitro findings and selective case reports on the specificity and strength of binding of aminosteroid NMBDs to sugammadex suggest that it may be a valuable new treatment for the rapid reversal of aminosteroid-induced anaphylaxis.[45] However, further research on the capacity of sugammadex to compete with IgE antibodies and to remove and encapsulate the drug from IgE–rocuronium complexes is needed before sugammadex can be recommended as a treatment for rocuronium-induced anaphylaxis. There is a theoretical concern that, in this setting, sugammadex may potentially bind other steroids concurrently administered and therefore reduce the efficacy of this conventional treatment for anaphylaxis. Thus, sugammadex at a dose of 16 mg/kg can be used as a potential adjunct to conventional management of anaphylaxis due to rocuronium, but clinicians should be aware that this is an "off-label" indication.[44]

Other roles for sugammadex in the ICU

Other indications for sugammadex in the ICU include reversal of induced neuromuscular blockade for short procedures; treatment of residual neuromuscular blockade in the immediate postoperative period,[2] when complete reversal of neuromuscular blockade is critical in avoiding postoperative mechanical ventilation (ie, in patients with myasthenia gravis);[46] and in patients in whom it is desirable to avoid the haemodynamic effects of the current anticholinesterase–anticholinergic drug combination.[2]

Adverse effects

Serious adverse effects occur in fewer than 1% of patients, and sugammadex is generally very well tolerated. The most common side effects include hypotension, slight cough and altered taste.[16] Hypersensitivity reactions have also been reported, such as flushing, rash and tachycardia.[47,48] More severe hypersensitivity reactions have also recently been described.[49] Despite these concerns, an assessment of the safety of sugammadex in healthy adult populations found it to be safe compared with neostigmine and placebo.[50]

Economic viability

The cost of sugammadex is currently high. In our centre, a 200 mg vial costs about $170. A recent economic viability study from the United Kingdom reviewed the use of sugammadex for both intraoperative "routine reversal" and rescue reversal in a failed intubation, and showed its use in these situations to be cost-effective. This was based on several assumptions that may impact on its generalisability and should be interpreted with caution.[28] Economic analyses showed that sugammadex appears more cost-effective when the value of any reduction in recovery time is greater, when the reduction in mortality compared with suxamethonium is greater, when the patient is younger, when there is a lower probability of a "cannot intubate, cannot ventilate" event, and for long procedures that do not require profound blockade throughout. A detailed economic assessment of sugammadex should be undertaken when more evidence is available, including evidence on resource use and the effects of sugammadex on health-related quality of life.

Conclusion

Sugammadex is the first of a new class of drug, the selective muscle-relaxant binding agents, and has important clinical implications for use in intensive care. It is effective for reversal of rocuronium and vecuronium and, importantly, has the capacity to rapidly and predictably reverse even deep neuromuscular blockade. This may have significant impact in reducing intensive care morbidity related to these NMBDs. Furthermore, sugammadex allows the replacement of suxamethonium in short procedures, with a safer combination of rocuronium for fast intubation and sugammadex for rapid reversal. Sugammadex should be readily available in all ICUs and integral to the modern intensivists' armamentarium.

Competing interests

None declared.

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