Journal of Anesthesia & Clinical Research

Zaouter et al., J Anesth Clin Res 2017, 8:7
DOI: 10.4172/2155-6148.1000740

Review Article Open Access

A Short Update on Sugammadex with a Special Focus on Economic Assessment of its Use in North America

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Received date: Jun 06, 2017; **Accepted date:** Jul 01, 2017; **Published date:** Jul 04, 2017

Abstract

Sugammadex offers significant advantages over the current anticholinesterase reversal drugs. Sugammadex used has been approved for the United Stated and for Canada since December 2015 and February 2016, respectively. The present article aims to provide a straightforward and concise review of the most recent literature describing its clinical advantages in routine use. A thorough and cost-effective evaluation has been conducted specifically for North America to determine if its price justifies its inclusion into regular patients' care. The search examined the relevant literature from January 2013 to October 2016. The present narrative review describes how sugammadex could play a crucial role in the modern conduct of anesthesia. The particular emphasis on sugammadex cost-effective analysis performed in this article suggests that this new reversal agent should be considered for a wider use in North America.

Keywords: Gamma-cyclodextrins; Reversal agent; Delayed emergence from anesthesia; Drug-related side effects and adverse reactions, Anaphylaxis, Cost-benefit analysis

Introduction

Worldwide, neuromuscular blockade (NMB) is reversed mostly with neostigmine, an anticholinesterase drug. However, this association of medications encompasses several threatening side effects, such as arrhythmias [1] and bronchospasms, when neostigmine outlasts the vagolytic action of the anticholinergic agents [2]. Also, neostigmine has noteworthy flaws such as a slow onset of action, as well as the impossibility to reverse deep NMB. In addition, high doses of neostigmine could trigger muscle weakness and consequently respiratory complication [3,4]. Sugammadex is a modified cyclic oligosaccharide that embraces all the characteristics of an ideal NMB reversal agent. It is a ring-shaped molecule with hydrophilic properties on its outside allowing it to be water-soluble. The inner side is hydrophobic which attracts amino-steroidal neuromuscular blocking agents (NMBA) [5]. Rapid plasmatic amino steroidal muscle relaxant encapsulation creates a concentration gradient that extracts NMBA molecules from the neuromuscular junction to shift back to the plasma. These features result in a significantly faster and safer reversal compared to standard anticholinesterase drugs [6]. Microcalorimetry tests have demonstrated that bonds with rocuronium are preserved for a longer period with a lower dissociation rate than vecuronium [7]. Consequently, rocuronium is the most common NMBA administered when sugammadex is used as a reversal agent. From its approval, sugammadex has been used in almost 60 countries, and over 15 million doses have been administered [8]. Since December 2015 and February 2016, sugammadex is available in the United-States and Canada, respectively. Thus, the present paper reviews the clinical use of sugammadex providing readers a short but comprehensive overview. A search of the PubMed database was conducted in November 2016, examining the literature during the past four years (from January 2013 to October 2016). The cut-off time for this review was chosen to assess and compile the most recent knowledge on the use, advantages, safety and economic viability of sugammadex. Then, the article focused with particular attention on the economic viability in North America simulating its use and the related cost-effectiveness in concrete clinical scenarios to determine whether its cost justifies its inclusion into routine care.

Objectives of the present review:

After reading this review, the reader should be able to:

1. Prescribe the appropriate dose of sugammadex according to the depth of NMB and according to the characteristics of particular population groups.

2. Have a thorough understanding of sugammadex intraoperative and postoperative advantages.

3. Have a thorough understanding of sugammadex's safety profile.

4. Have a critical judgment on the benefit to integrate sugammadex into clinical practice not only for patients' safety purposes but also for economic advantages.

Which is The Right Dose of Sugammadex According to The Depth of The Nmb and How Long Does it Take to Fully Reverse Nmb in Comparison to Neostigmine?

Superficial/shallow neuromuscular block (reappearance of the fourth twitch)

Sugammadex has been shown to be efficient in reversing superficial block defined as a reappearance of 4 twitches after a train-of-four (TOF) with a ratio between the first response and the last one <0.4 [9].

In this clinical situation, 2 $mgkg^{-1}$ sugammadex are sufficient to obtain a TOF ratio ≥ 0.9 in less than 2 min.

Moderate neuromuscular blockade (TOF count 1 to 3)

Sugammadex is also effective in reversing quickly moderate NMB defined as a TOF count of 2 [10]. In 98 patients recruited in a multicenter randomized trial with moderate levels of NMB, Blobner et al. [11] found that the mean length of time necessary to obtain a TOF ratio of 0.9 with 2.0 $mgkg^{-1}$ sugammadex was 1.5 min, whereas 18.6 min were required with 50 μgkg^{-1} of neostigmine. Blobner and collaborators have also shown that predictability of response was greater with sugammadex than neostigmine, with 98% of sugammadex patients versus only 11% of neostigmine patients recovering to a TOF ratio of 0.9 within 5 min [11]. Interestingly, the efficacy to reverse moderate NMB does not differ whether anesthesia is maintained with halogenated agents or with propofol [12]. Sugammadex has also been shown to reverse efficiently rocuronium moderate NMB in both Caucasian and Chinese subjects [13].

Therefore, we recommend 2 $mgkg^{-1}$ sugammadex to reverse moderately deep NMB (1 to 3 twitches present) in order to obtain a TOF ratio ≥ 0.9 within 2 min.

Deep neuromuscular blockade (Post-Tetanic Count=1-2)

One of the most compelling factors of sugammadex is its ability to reverse - reliably and quickly - deep NMB defined as 0 twitches after a TOF stimulation or 1 to 2 twitches after a tetanic stimulation, Post-Tetanic Count=1-2 (PTC=1-2) [9,10]. Recently, Rahe-Meyer et al. [14] enrolled patients from 10 different institutions in Germany. At the end of the surgery, 140 patients with a PTC=1-2 received randomly 4.0 $mgkg^{-1}$ sugammadex or placebo. Spontaneous recovery from deep rocuronium-induced NMB is on average 40 times slower than sugammadex. Four $mgkg^{-1}$ sugammadex reversed deep NMB rapidly and consistently (2 min, interquartile 1.6-2.8 min). When neostigmine is used to reverse deep NMB, a mean of 50.4 min is necessary to reach a TOF ratio of 0.9 [9]. Doses of sugammadex below 1 mg.kg-1 have been shown to be initially effective to reverse rocuronium-induced deep NMB, but lead to the gradual reappearance of the NMB in both adults [15] and children [16]. In contrast, sugammadex doses ranging from 1 to 2 mg.kg-1 have shown to reverse rocuronium-induced deep NMB with significant time variability (TOF ratio ≥ 0.9 is obtained from 1.8 to 15.2 min) [17]. At present, we recommend 4 $mgkg^{-1}$ sugammadex to reverse deep NMB in order to obtain a TOF ratio ≥ 0.9 within 2 min.

Profound neuromuscular blockade (can't intubate, can't ventilate scenario)

Sugammadex is also effective for urgent reversal in emergency situations such as 'can't intubate, can't ventilate' even when a high-dose of rocuronium is administered. Chambers et al. [18] performed a systematic review and found three randomized clinical trials that compared 16 mg.kg-1 sugammadex with placebo or succinylcholine. In these trials, sugammadex was administered 3 or 5 min after 1 or 1.2 $mgkg^{-1}$ rocuronium, respectively. Chambers et al. [18] concluded that after a profound NMB, recovery of neuromuscular transmission after sugammadex was markedly faster than after placebo or than spontaneous recovery from succinylcholine. Lee et al. [19] are the only ones to compare the time to recover to a TOF ratio ≥ 0.9 between the administration of 1 $mgkg^{-1}$ succinylcholine and 16 $mgkg^{-1}$ sugammadex administered 3 min after an intubating dose of 1.2 $mgkg^{-1}$ rocuronium. Time to recovery was significantly faster for the association rocuronium-sugammadex compared with succinylcholine with 4.4 ± 0.7 *vs.* 7.1 ± 1.6 min, respectively. In the rocuronium-sugammadex group, 87% of the patients reached a TOF ratio of 0.9 in less than 3 min, which was shorter than in the succinylcholine group by 4 to 5 min. Although sugammadex has been shown to be rapid and efficient to reverse rocuronium-induced profound NMB, it has been reported that it could require up to 17 min to fully reverse a profound block [20]. The reason is probably related to the wide range of individual responses and receptor affinity to a single dose of rocuronium [21]. Nevertheless, it seems that there is an agreement that rapid sequence induction (RSI) performed with the rocuronium-sugammadex association could bring some advantages [22,23]. The combination is compelling especially because it does not induce fasciculations, which increase oxygen consumption during apnea [24]. It also allows regaining spontaneous ventilation on average 3 min earlier compared to succinylcholine [25]. Table 1 summarizes the dosage of sugammadex according to the neuromuscular blockade depth and the relative time necessary to fully reverse it.

Sugammadex	Immediate rescue reversal PTC=0	Deep NBM TOF=0 PTC=1-2	Moderate NMB TOF count=1-3	Superficial NMB TOF ratio
Dose	16 $mgkg^{-1}$ [40]	4 $mgkg^{-1}$ [10]	2- 4 $mgkg^{-1}$ [10,16]	2 $mgkg^{-1}$ [16]
Time to reach a TOF ratio ≥ 0.9	4.4 min [40]	3.3-1.5 min [10]	2.3-1.5 min [10,16]	1,5 min [16]
Abbreviation: NMB: Neuromuscular Blockade; ENT: Ear Nose and Throat				

Table 1: The dosage of sugammadex according to the neuromuscular blockade depth and the relative time necessary to fully reverse it.

Considerations for Specific Population Groups

Pediatric

According to a recent review, 2 $mgkg^{-1}$ of sugammadex seems to be a safe dosage to reverse moderate NMB for this population [26]. A difference is that the onset time seems faster but the recovery time is similar to the adult population [27]. Sugammadex is not recommended in infants below 2 years of age [10].

Pregnant and breastfeeding women

Only one recent multicenter randomized controlled trial enrolling 240 patients undergoing a C-section has been published showing the non-inferiority of 1 $mgkg^{-1}$ rocuronium for rapid-sequence induction compared with 1 $mgkg^{-1}$ succinylcholine. In the rocuronium group, sugammadex was given to reverse NMB. No difference in the Apgar score between the two groups was noticed. Less resistance during laryngoscopy and a lower incidence of postoperative myalgia were found in the group receiving rocuronium and sugammadex [28]. Since there is only little oral absorption, sugammadex can be administrated safely in breastfeeding women [10]. The rocuronium-sugammadex combination has been claimed to be an advantage in parturients with neurologic disease [29]. Sugammadex is now part of the UK Obstetric Anaesthetist Association's newest algorithm for management after failed tracheal intubation as rocuronium can be fully reversed by sugammadex within 3 min instead of 9 min to reach spontaneous recovery using succinylcholine [30].

Obese patients

It is generally recommended to administer sugammadex according to the body weight [31]. In contrast, Loupec et al. [32] advocate that in morbidly obese patients, 4 $mgkg^{-1}$ sugammadex using ideal body weight provides satisfactory reversal of deep rocuronium-induced NMB. To support this statement, they conducted a randomized controlled trial in 50 morbidly obese patients. They found that reversal of deep NMB occurred within 10 min in 93% (255 ± 62 sec) and in 77% (429 ± 102 sec) of the patients when they received 4 $mgkg^{-1}$ or 2 $mgkg^{-1}$ of sugammadex based on the ideal body weight, respectively. Objections have been raised because dosage according to the body weight could reverse NMB more rapidly, [33] but Loupec et al. claimed that longer recovery time was not clinically significant [32]. Other authors advocate that for morbidly obese patients, the total sugammadex dose could be safely reduced to the ideal body weight (IBW) + 40% [34].

Elderly patients

The time required to reach a TOF ratio of 0.9 is longer in patients older than 69 years [27]. However, this difference is not clinically significant and does not justify different dose recommendations [10].

Advantages of Sugammadex Use During Daily Practice

Advantages of sugammadex when a deep NMB is performed

Maintenance of deep NMB appears to offer better postoperative pain relief and optimal surgical conditions during laparoscopic surgeries [35,36], orthopedic fracture repositioning, dislocation reduction, laparotomy, and mucosectomy [37]. However, anesthesiologists are still worried to use deep levels of NMB until the end of the surgery because of the impossibility to reverse reliably and satisfactorily such a deep NMB [38]. Deep NMB maintained by rocuronium until the end of the surgery, and reversed with sugammadex seems to be a combination that increases the quality of certain operational conditions, especially in obese patients. Table 2 summarizes the intraoperative advantages of deep NMB.

Intraoperative advantages	Type of surgery / Patients	References
Best surgical conditions performing deep neuromuscular blockade	Laparoscopic surgery, bariatric surgery	Madsen [35,36]
Deep NMB until the end of the surgery	orthopedic fracture repositioning, dislocation reduction, laparotomy, and mucosectomy	Dubois et al. [37]
Faster reversal than neostigmine	Patients with diminished respiratory reserve (i.e. patients with obstructive lung disease, sleep apnoea and neuromuscular disease)	Schaller et al. [10]
Abbreviation: NMB, Neuromuscular Blockade; ENT, Ear Nose and Throat		

Table 2: Intraoperative advantages using sugammadex as reversal agent.

Advantages of sugammadex during the postoperative period

Although anesthesiologists believe that postoperative residual paralysis induced by non-depolarizing NMBA occurs in less than 1% of the cases [39], residual curarization is a very frequent complication that could involve up to 83% of the patients in the postoperative period even with the introduction of shorter-acting muscle relaxants [40]. Residual blockade can trigger adverse postoperative pulmonary events, pharyngeal dysfunction, the need for urgent tracheal reintubation and prolonged stay in post-anesthesia care unit (PACU) [41]. Reversal with sugammadex appears to be associated with significantly less postoperative pulmonary complications, especially in the elderly population [42]. Also, sugammadex seems to be associated with a shorter length of stay in PACU, because of a faster diaphragmatic recovery, less pain [43] and fewer episodes of PONV. Table 3 summarizes the postoperative advantages using sugammadex as a reversal agent.

Postoperative advantages	Evidence	References
Less perioperative respiratory adverse events	Reduced pulmonary complications in elderly ASA 3/4 patients	Ledowski et al. [42]
Less PONV		Ledowski et al. [42]
Less pain		Castro et al. [43]
Abbreviation: PONV, Postoperive Nausea and Vomiting; ASA, American Society of Anesthesiologist physical status.		

Table 3: Postoperative advantages using sugammadex as reversal agent.

Advantages of Sugammadex in Patients with Comorbidities

Patients with muscular or neuromuscular disease

Patients with muscular and neuromuscular diseases could be challenging for the anesthesiologists who need to perform an endotracheal intubation to offer the best surgical conditions. The challenge is caused by the extreme sensitivity of this population to NMBAs, which could lead to an overlong period of mechanical ventilation that could trigger respiratory and cardiovascular

complications and also result in death [44]. Therefore, the combination rocuronium-sugammadex seems to be a safe and reliable option for patients with myasthenia gravis, multiple sclerosis, dermatomyositis, Sjogren's syndrome, Becker muscular dystrophy, Duchene muscular dystrophy, myotonic dystrophy, spinal muscular atrophy, Strumpell-Lorrain disease, and amyotrophic lateral sclerosis [10,42,45-50]. The rocuronium-sugammadex combination has been studied mainly in patients with myasthenia gravis. De Boer et al. [51] have published the largest case series (n=21) of patients with myasthenia gravis presenting an Osserman class II (n=13) or class III (n=8) receiving steroidal muscle relaxants followed by sugammadex. At the end of surgery, 2 or 4 mg kg^{-1} sugammadex were administered to reverse moderate or deep NMB, respectively. Time to recover to a TOF ratio ≥ 0.9, was 80 sec. (range 30 to 268) and 165 sec. (range 105 to 240) for moderate and deep NMB, respectively. In their case series, no patient had residual postoperative muscle paralysis and all were discharged from the PACU to the surgical ward without problem. Their results were similar to 20 other case reports describing patients with myasthenia gravis receiving the appropriate amount of sugammadex to reverse muscle paralysis found upon completion of the surgery. Only one case report described that RSI using high-dose of rocuronium followed by an adequate dose of sugammadex in a myasthenic patient is possible and should be a strategy to bear in mind for this type of population in the emergency setting [52]. In contrast, Kiss et al. [53] were the first to describe the inefficacy of a high dose of sugammadex (12 $mgkg^{-1}$) to reverse promptly and efficiently NMB in a myasthenic patient with an Osserman score of III with a pre-endotracheal intubation TOF ratio of 0.97 receiving 30 mg of rocuronium. Unfortunately, the authors did not present the reason for the delay in recovery and no postoperative complications were presented.

Patients with liver dysfunction

Sugammadex seems to be safe and well tolerated in patients with liver dysfunction undergoing hepatic surgery as demonstrated by Fujita et al. [54]. They administered a bolus of rocuronium followed by a continuous infusion in 31 patients. In their observational study, no patients showed evidence of residual paralysis postoperatively and no adverse event related to the use of sugammadex was reported. One case report also described its safe use in a patient with acute porphyria [55]. The reason why it is safe to use it in this population is probably related to the sugammadex-rocuronium compound excretion occurring mainly *via* urine, thus not interacting with the liver function [7].

Patients with renal failure

The kidney excretes sugammadex rapidly and unchanged. Thus, its clearance could be delayed in patients with severe kidney failure. A prospective study has shown that 4 $mgkg^{-1}$ sugammadex could be used to reverse rocuronium-induced deep NMB in patients with severe renal failure (creatinine clearance <30 $mlmin^{-1}$) without residual postoperative NMB [56]. Nevertheless, clinicians should bear in mind that a substantial variability in the times to reach a TOF ratio of 0.9 in these patients with chronic renal failure might be observed [56]. Such variability could be explained by the kidney donor status [57]. When the transplanted kidney comes from a recently deceased donor the renal function does not recover instantly [57]. However, considering the limited number of trials and patients with severe renal impairment exposed to prolonged sugammadex-rocuronium complex, caution should be maintained in this population. A recent case report describing a patient with severe renal impairment who received 1.2 $mgkg^{-1}$ rocuronium at the induction and deep NMB during surgery presented an episode of recurarization 3 h after injection of 6 $mgkg^{-1}$ sugammadex and attainment of a TOF ratio of 0.9 before extubation [58]. Bellod et al. described a similar case of delayed recurarization in a patient with known chronic renal failure 2 h after arrival in the PACU, despite that the appropriate dose of sugammadex was injected at the end of surgery [59]. Bellod and colleagues managed this event successfully by administrating a second dose of sugammadex in the PACU. Postoperative neuromuscular monitoring to detect potentially delayed recurarization should be implemented in patients with renal failure throughout a prolonged postoperative period. The sugammadex-rocuronium compound has been shown to be dialyzable with a reduction of 70 % of its plasma concentration after the first session and reduced by 50% after the following sessions [22,60]. Of particular interest for patients with severe renal failure requiring a RSI, is the significantly lower increase in potassium concentration when the combination rocuronium-sugammadex is injected compared to succinylcholine [61].

Advantages of sugammadex in case of rocuronium-induced anaphylactic shock

Anaphylaxis is a rare but life-threatening complication. Its incidence in anesthesia is estimated to range from 1 in 10000 to 1 in 20000 cases [62]. In anesthesia, the drugs inducing more frequently an anaphylactic reaction are the NMBA with the following incidence: succinylcholine (61%), atracurium (19.5%), cisatracurium (6%), vecuronium (4.5%), rocuronium (4%), pancuronium (3%), and mivacurium (2%) [63]. The incidence of anaphylaxis induced by sugammadex is significantly lower than those related to NMBA injection [64]. *Via* its peculiar action, sugammadex has been suggested as a novel treatment therapy to inhibit mast cells and basophils activation triggering anaphylaxis. This hypothesis was confirmed by evidence from several case reports describing hemodynamic and respiratory restoration few minutes after sugammadex administration [62]. However, a recent case report described the inefficacy of low doses of sugammadex to reverse rocuronium-induced anaphylaxis [65]. Lately, Raft et al. [66] reported that even high doses of sugammadex (14 $mgkg^{-1}$) could be ineffective to reverse a rocuronium-induced anaphylaxis. Platt et al. [67] support the inefficacy of sugammadex to reverse rocuronium-induced anaphylaxis publishing the first case-control study on this topic describing 13 patients with a presumed rocuronium-induced anaphylaxis who received a sugammadex injection. They concluded that sugammadex does not interfere with the correction of the immune disorder caused by rocuronium but could improve the hemodynamic parameters by increasing the muscle tone thus increasing cardiac preload [67]. Platt's trial encompasses a substantial methodological flaw because there was no case to use as control [68]. Thus, further studies on that matter should be conducted to draw final conclusions looking specifically at the timing of sugammadex administration, which has been suggested to be a crucial element to gain clinical benefit [69]. In a case of an anaphylaxis reaction, conventional treatment using epinephrine and fluid loading must be the first line treatment and sugammadex as a second line might be envisioned.

Essential Knowledge to Use Sugammadex Safely

Metabolism

Sugammadex and the rocuronium/sugammadex complex are water-soluble and are quickly excreted *via* urine [5]. The elimination half-life of sugammadex is on average 2 h in adult anesthetized patients with normal renal function. Because of its unique architecture, it has a low penetration of the blood–brain barrier and a low placenta transfer [7].

Interactions

Sugammadex possesses a positively charged quaternary nitrogen chain, which allows a strong and unique affinity for rocuronium. In contrast, both endogenous and exogenous steroidal molecules have a negligible affinity to sugammadex, because they do not have a three-dimensional profile that permits strong bonds with this quaternary nitrogen chain. Consequently, affinity for cortisone, hydrocortisone, and aldosterone is 120-fold weaker than the one for rocuronium. Furthermore, affinity for atropine, verapamil, and ketamine is 400 to 700-fold lower than for rocuronium [7]. Zwiers et al. [70] analyzed the probability of the most common drugs used along with sugammadex to displace it. Among all the molecules studied, toremifene, fusidic acid, and flucloxacillin are the only molecules noticed to displace rocuronium from sugammadex. Theoretically, these molecules could generate a delay in reaching a TOF ratio of ≥ 0.9. Nonetheless, a RCT including 24 patients did not encounter residual postoperative muscle relaxation with concomitant prescription of diclofenac or flucloxacillin [71]. Gulec et al. [72] have recently conducted a randomized trial in 60 children undergoing adenotonsillectomy receiving saline or dexamethasone 0,5 $mgkg^{-1}$ after induction. At the end of surgery, anesthesia was terminated, and when 2 twitches of the TOF reappeared, all patients were given 2 $mgkg^{-1}$ sugammadex. There was no significant difference between groups neither in the time to recover a TOF ratio of 0.9 nor in the time to meet the extubation criteria [72]. Dexamethasone seems to decrease the effectiveness of sugammadex to reverse rocuronium-induced NMB in a dose-dependent fashion [42]. Hence, high-dose of dexamethasone used concomitantly with sugammadex should be done with caution until further research can provide more evidence. Antibiotics are known to potentiate NMB and consequently limiting the effect of the traditional anticholinesterase reversal agent. Hudson et al. [73] have conducted a study to determine whether antibiotics could reduce sugammadex's ability to reverse steroidal muscle relaxant agents. Analyzing data from 197 patients from 19 different sites, they found that antibiotics known to interfere with acetylcholine release (kanamycin, gentamicin, vancomycin, clindamycin and bacitracin) did not disturb the capacity of sugammadex (4 $mgkg^{-1}$) to reverse NMB induced by rocuronium. Magnesium is also a factor known to inhibit neuromuscular transmission [74]. However, it seems that pre-treatment with magnesium does not alter the efficacy of the recommended dose of sugammadex after moderate and deep blockade with rocuronium [75-78]. A recent case report described the successful reversal of rocuronium using sugammadex in a patient with pre-eclampsia who received magnesium intraoperatively [79]. Finally, sugammadex may interact with hormonal contraceptive drugs *via* unwanted binding, potentially reducing their clinical efficacy. Thus, female patients should be informed of the reduced efficacy of hormonal contraceptives if they receive a dose of sugammadex [80]. Finally, to avoid precipitation, sugammadex should not be injected concomitantly with drugs that affect serotonin type 3 receptors (such as ondansetron), ranitidine and verapamil [60].

Adverse Effects

Hypersensitivity and Anaphylaxis

Anaphylaxis is a life-threating complication. In more than 58% of the time, the causal agent is a NMBA [81]. However, allergic anaphylaxis to sugammadex is a rare event [64]. Nonetheless, hypersensitivity is the main reason why the American Food and Drug Association raised concern and delayed approval of sugammadex [82]. In 2014, Tsur et al. [64] screened all previously reported cases on sugammadex anaphylactic reactions. They found a total of 15 probable cases of anaphylaxis to sugammadex. Anaphylaxis occurred within 5 min of sugammadex administration. None of these 15 patients who developed an allergic reaction to sugammadex died [64]. The reason why patients can develop hypersensitivity to sugammadex without previous exposure is still unknown. Tsur and colleagues hypothesized a sensitization of cyclodextrins found in foods and cosmetics [64]. To obtain the FDA approval, the company selling sugammadex sponsored a hypersensitivity trial in awake volunteers in 2014 [82]. Three hundred seventy-five individuals received an intravenous bolus of saline, 4 mg.kg-1 sugammadex or 16 $mgkg^{-1}$ sugammadex. One subject met the criteria for anaphylaxis after an injection of 16 $mgkg^{-1}$ sugammadex. In 2014, the same company published post-marketing data concerning 11.5 million sugammadex exposures. From these exposures, they retrieved 273 reports of anaphylaxis with 237 of 241 patients improving with conventional. By the end of 2015, after additional site inspections and sensitivity investigations, the FDA approved sugammadex [82]. In summary, the rate of anaphylactic reaction is low, and an episode can be managed with standard therapy most of the time [69,83].

Longer clotting time and increased bleeding

In a randomized, placebo-controlled, three-period cross-over trial, De Kam et al. [84] described a dose-related transient prolongation of the prothrombin time and the partial thromboplastin time in 8 healthy subjects. The same authors conducted a randomized, double-blind, placebo-controlled, four-period cross-over study and found that when healthy subjects received either unfractionated heparin or low-molecular-weight heparin, both moderate (4 $mgkg^{-1}$) and high (16 $mgkg_{-1}$) doses of sugammadex did not clinically affect partial thromboplastin time nor anti-Xa activity [85]. In a prospective investigation, Raft et al. [86] looked at the effects of sugammadex administration on routine coagulation tests and bleeding. Their findings do not support that 2 or 4 $mgkg^{-1}$ sugammadex is associated with a longer clotting time. Another double-blinded randomized study enrolling patients undergoing orthopedic surgery confirms that sugammadex does not increase the bleeding risk [87].

QTc prolongation

Transient prolongation of the QT interval (>500 ms) following the administration of sugammadex has been described in patients anesthetized with sevoflurane or propofol [88,89]. However, several large studies proved that sugammadex does not seem to trigger significant QT/QTc prolongation [90], even with extremely high doses of sugammadex (32 $mgkg^{-1}$) [91]. Sugammadex does not seem to produce effects on cholinesterase, nicotinic or muscarinic receptors,

consequently minimizing the risk of cardiovascular side effects. To the contrary, the association neostigmine-atropine is known to have significant cardiovascular effects and is clearly associated with significant QTc prolongation [90].

Respiratory adverse events

Negative pressure pulmonary edema is a rare complication that occurs after general anesthesia, especially after extubation in the elderly population. Suzuki et al. experienced a case of negative pressure pulmonary edema after tracheal extubation following reversal of rocuronium using sugammadex. They have attributed residual muscular blockade on the upper airway muscle associated with large inspiratory forces created by the faster respiratory muscles recovery after sugammadex injection [92]. Basaranoglu et al. [93] described an episode of respiratory distress caused by a rapid increase in chest wall rigidity after sugammadex decurarization. They attributed this event to opioid-induced chest rigidity. McGuire and Dalton reported an unexpected finding in 9 consecutive patients. They observed laryngospasms occurring two minutes after the administration of sugammadex. The laryngospasm was spontaneously reversible, and no casualties were reported [94]. Nevertheless, the clinical relevance of these findings should be elucidated with further trials.

Is Sugammadex Cost-effective?

Economic impact of sugammadex

Although no large-scale randomized study has been conducted to determine sugammadex's economic impact, recent literature gathers more and more clues that sugammadex might actually be cost effective. According to Chamber's [18] and Paton's [95] economic analysis, sugammadex cost-effectiveness relies on two concepts. The first concept is that faster recovery time can be achieved using sugammadex compared to neostigmine. The second concept is that time saving could be converted into valuable activities. Rapid NMB reversal can lower the operating room (OR) occupancy with the consequential potential to increase the OR workflow especially for short cases [96,97]. Also, by eliminating postoperative residual curarization and related pulmonary complications, sugammadex might reduce the costs related to the time necessary to discharge the patients from the PACU, which would result in a more rapid turnover between surgeries [42,98-101].

Economic evaluation in real clinical scenario

Our hypothesis to sustain the favorable cost-effectiveness of sugammadex relies on the conversion of the time saved *via* a rapid NMB reversal with less postoperative complication into extra-surgical time to perform more surgical interventions. Thus, we performed an economic assessment analyzing:

1. The 'value of each minute of OR time saved'
2. The 'value of each minute of PACU time saved'
3. The 'value of each minute of length of hospital stay saved'

We based our analysis on the most recent operating time cost evaluation in Canada and United States. In Canada, the cost has been estimated, on a per-minute basis, to range from 10 to 40 $Can [102]. In the United States, it has been previously estimated to be of 2000 $US per hour (30 $US per minute) [103]. In our economic evaluation, we calculated - conservatively - the expense considering that each OR minute costs 10 $Can (or 30 $US). The price of sugammadex was calculated on the assumption that a patient has a weight of 75 kg. The cheapest combination of vials was used, and any unused drug in a vial was considered wasted. A vial with the smallest dose of sugammadex contains 200 mg and corresponds to approximately 100 $Can and 100 $US. Reversing rocuronium-induced NMB with sugammadex, we could hypothesize that the cost per case corresponds to:

y=z - k - x

y=cost of a case using sugammadex

z=sugammadex cost per case

k=time saved per case

x=operation staff value per minute

'Value of each minute of OR time saved' – evaluation

A) In patients with superficial blockade (reappearance of the fourth twitch): Sugammadex could reduce the mean time to reach a TOF ratio of 0.9 by 17 min [9]. Patients with shallow NMB need 2 mg.kg-1 sugammadex to reverse rocuronium-induced blockade, which, on average, corresponds to 150 mg. The dose is obtained using 1 vial.

y=100 $Can-17 min x 10 $Can, y'=100 $US-17 min x 30 $US

y=100 $Can-170 $Can, y'=100 $US-510 $US,

y=-70 $Can, y'=-410 $US

In this case the OR time saved will lower the cost related to surgery by 70 $Can and 410 $US in Canada and in the United States, respectively.

B) In patients with moderate NMB (TOF count=1-3): Randomized controlled trials comparing rocuronium and sugammadex with rocuronium and neostigmine suggested that sugammadex reduces the mean time to reach a TOF ratio of 0.9 by 18.6 min [11]. Patients with moderate NMB should be given 2-4 mg.kg-1 sugammadex to reverse rocuronium-induced blockade, which, on average, corresponds to 225 mg. The last dose is obtained with 2 vials (200 $Can and 200 $US).

y=200 $Can-18.6 min x 10 $Can, y'=200 $US-18.6 min x 30 $US

y=200 $Can-186 $Can, y'=200 $US-558 $US

y=14 $Can, y'=-358 $US

In this case the OR time saved will not lower the cost related to the surgery but increase it by 14 $Can. On the contrary, in the United States, it might save up to 358 $US.

C) In patients with deep NMB (PTC=1-2): Patients with deep NMB require 4 mg.kg-1 sugammadex to reverse rocuronium-induced blockade, which corresponds to 300 mg. The dose is obtained with 2 vials. Sugammadex reduces the mean time to obtain a TOF ratio ≥ 0.9 by 47.5 min in this clinical condition (50.4 min reversing with neostigmine–2.9 min reversing with sugammadex) [9].

y=200 $Can- 47.5 min x 10 $Can, y'=200 $Can-47.5 min x 30 $US

y=200 $Can-475 $Can, y'=200 $US-1425 $US

y=-275 $Can, y'=1225 $US

In this case, the OR time saved will lower the cost related to the surgery by 275 $Can and by 1225 $US in Canada and in the United States, respectively.

D) Clinical case scenarios: 1) *Case scenario 1*: An adenotonsillectomy takes on average 40 min when performed under moderate NMB and reversed with sugammadex [106]. We could assume that if NMB is reversed with neostigmine the total length of the procedure will take an additional 17 min (to completely reverse the blockade to a 0.9 TOF ratio) [9]. Considering an 8 h OR schedule (480 min) and assuming 20 min of turnover between two adenotonsillectomies, 8 cases could be performed using sugammadex (480 min/(40 min for surgery+20 min for turnover)=8). In contrast, only 6.2 cases could be performed using neostigmine (Total OR working hour/adenotonsillectomy conducted using neostigmine=480/(40+17+20)=6.2). Thereby, sugammadex could be considered cost-effective in short surgeries with moderate NMB (i.e. adenotonsillectomy) because it provides extra-surgical time to perform almost two more cases per day. In the United States, it could be assumed that sugammadex could also lower the daily OR cost by 716 $US (358×2).

2) *Case scenario 2*: A bariatric laparoscopic procedure in obese patients with a BMI ≥ 40 $kg.m^{-2}$ takes on average 90 min when performed under moderate NMB and reversed with sugammadex [97]. Supposing 30 min of turnover between two procedures in an 8 h OR schedule (480 min), 4 cases could be performed (total OR working hour/ bariatric laparoscopic procedure under moderate NMB reversed using sugammadex+min for turnover=480/90+30=4). Only 3.3 cases could be carried out per day reversing the NMB with neostigmine.

Time to perform a bariatric laparoscopic procedure under moderate NMB reversed with neostigmine was calculated as such: [bariatric laparoscopic procedure performed under moderate NMB+min for turnover=(115+30)=145 min. Total OR working hour/ bariatric laparoscopic reversed using neostigmine + min for turnover =480/(115+30)=480/145=3.3].

Again, even for this clinical case scenario, sugammadex could be considered cost-effective because it offers extra-surgical time to perform at least one more case per day, lowering the operational cost by 358 $US.

3) *Case scenario 3*: A laparoscopic hysterectomy takes on average 70 min when performed under deep NMB and reversed with sugammadex [104]. In an 8 h OR schedule (480 min) and assuming 30 min of turnover between two laparoscopic hysterectomies, 4.8 cases could be performed using sugammadex (total OR working hour/ laparoscopic hysterectomy performed under deep NMB reversed using sugammadex + min for turnover=480/70+30=4.8). In contrast, only 3.25 cases could be carried out using neostigmine. Time to perform a laparoscopic hysterectomy using neostigmine was calculated as such: (laparoscopic hysterectomy performed under deep NMB and reversed with sugammadex–time to reverse the blockade with sugammadex) +time to reverse with neostigmine a deep NMB+min for turnover=(70–2.9)+50.4=117.5 min. Total or working h/laparoscopic hysterectomy performed using neostigmine+min for turnover=480/(117.5+30)=480/147.5=3.25. Hence, sugammadex can be considered cost-effective for laparoscopic procedures performed under deep NMB (i.e. laparoscopic hysterectomy) because it could lower both the surgical cost (by 275 $Can or 1225 $US for each case) and provide extra-surgical time to perform 1.55 (4.8-3.25) more cases per day. Table 4 summarizes the evaluation of the value of each minute of OR time saved using suagammadex.

Clinical Case scenarios	Number of additional cases performed per day	Budget balance per OR day in Canada ($Can)	Budget balance per OR day in United States ($US)
Short surgery with moderate NMB	2	-28	716
Long surgery with moderate NMB	1	-14	358
Short surgery with deep NMB	2	550	2450

Abbreviation: NMB: Neuromuscular Blockade; $Can: Canadian dollars; $US: United States dollars.

Table 4: Outline of the value of each min of OR time saved using suagammadex.

Evaluation of both the 'value of each minute of PACU' and the 'value of each minute of hospital length of stay time saved'

Such estimation was difficult to perform because data in the literature is insufficient to determine the impact of the type of reversal agent on postoperative pulmonary complications (i.e. incidence of atelectasis, pneumonia, pulmonary edema) with the related increased cost (i.e. antibiotic therapy and the extended length of hospital stay). In addition, quantitative neuromuscular monitoring is underused in North America [105]. Thus, the association between postoperative neuromuscular recovery and the presence of residual NMB leading to postoperative complication is difficult to verify and inferences are hard to establish. However, two assumptions could be formulated. First, it could be expected that sugammadex brings potential favorable economic repercussion within the elderly population that is prone to develop postoperative pulmonary complications [99]. The latter consideration is of paramount importance bearing in mind that the elderly population will drastically increase in the near future [106]. Second, it could be assumed that administrating sugammadex routinely would force anesthesiologists to monitor the muscle relaxation depth. Hence, it could be claimed that using sugammadex, the incidence of postoperative residual curarization may lower along with the related pulmonary complications that increase patients' hospital length of stay [97].

Our economic evaluation for North America shows that sugammadex appears to be cost-effective. It seems that it allows performing a higher number of different surgical interventions accomplished under both moderate and deep NMB. It also appears that sugammadex lowers the daily OR cost for surgeries requiring deep NMB in both Canada and United States. In the United States, sugammadex could also lower the OR cost for surgeries requiring moderate NMB. Several european cost-effectiveness investigations are in-line with our estimation [95-97]. A recent Canadian investigation also confirmed our analysis using a discrete event simulation model specifically developed to explore the effect of sugammadex versus neostigmine on the OR efficiency and postoperative patients' outcome. The authors that have conducted this research advocate that using sugammadex to reverse moderate NMB is likely to lower the incidence of residual NMB. When it is administrated to reverse deep NMB, sugammadex is likely to increase the OR efficiency and lower the rate of postoperative residual curarization. Our analysis has several

limitations; it does not take into consideration the rate of both surgery cancellation and emergency intervention. Also, the calculation of the OR time cost was based on an investigation conducted in a teaching hospital. The length of the procedure encompassing teaching time could be longer in comparison with a non-teaching hospital. Therefore, the estimation may be underestimated for a non-teaching hospital. Another limit is that reports regarding the cost-effectiveness of sugammadex on both the 'value of each minute of PACU' and 'length of hospital stay' saved are scarce and may depend on institutional habits due to the large differences in staff practice and logistics from one center to another. Finally, there is a lack of prospective large sample size conducted in North America on this topic.

Conclusions

Although more expensive than the traditional reversal agents, sugammadex shows exceptional and unique features. It is more predictable and allows much faster recovery than neostigmine for both superficial and moderate NMB. In addition, sugammadex can reverse deep NMB while neostigmine is not efficient. The sugammadex-related incidence of adverse events is very low; it can be used safely to reverse rocuronium in patients with neuromuscular disease, liver dysfunction or renal failure. However, it seems essential to routinely use quantitative neuromuscular monitoring to determine the correct dose of sugammadex. Finally, our cost-effective economic evaluation revealed that sugammadex could decrease the operating room cost allowing, concomitantly, to perform a higher number of surgical interventions within the same daily operation schedule time. Nevertheless, prospective cost-effective studies should be conducted in North America to ascertain our evaluation.

Acknowledgement

No conflict of interest to declare.

The present review has been conducted without funding.

References

1. Srivastava A, Hunter JM (2009) Reversal of neuromuscular block. Br J Anaesth 103: 115-129.
2. Woods BD, Sladen RN (2009) Perioperative considerations for the patient with asthma and bronchospasm. Br J Anaesth 103: i57-i65.
3. Meyer MJ, Bateman BT, Kurth T, Eikermann M (2013) Neostigmine reversal doesn't improve postoperative respiratory safety. BMJ 346: f1460.
4. Sasaki N, Meyer MJ, Malviya SA, Stanislaus AB, MacDonald T, et al. (2014) Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. Anesthesiology121: 959-968.
5. Gijsenbergh F, Ramael S, Houwing N, van Iersel T (2005) First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. Anesthesiology 103: 695-703.
6. Park JY (2015) Benefits and risks of sugammadex. Korean J Anesthesiol 68: 1-2.
7. Hemmerling TM, Zaouter C, Geldner G, Nauheimer D (2010) Sugammadex--a short review and clinical recommendations for the cardiac anesthesiologist. Ann Card Anaesth 13: 206-216.
8. Jahr JS, Miller JE, Hiruma J, Emaus K, You M, et al. (2015) Sugammadex: A Scientific Review Including Safety and Efficacy, Update on Regulatory Issues, and Clinical Use in Europe. Am J Ther 22: 288-297.
9. Fuchs-Buder T, Meistelman C, Raft J (2013) Sugammadex: clinical development and practical use. Korean J Anesthesiol; 65: 495-500.
10. Schaller SJ, Fink H (2013) Sugammadex as a reversal agent for neuromuscular block: an evidence-based review. Core Evid 8: 57-67.
11. Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, et al. (2010) Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. Eur J Anaesthesiol; 27: 874-881.
12. Vanacker BF, Vermeyen KM, Struys MMRF, Rietbergen H, Vandermeersch E, et al. (2007) Reversal of rocuronium-induced neuromuscular block with the novel drug sugammadex is equally effective under maintenance anesthesia with propofol or sevoflurane. Anesth Analg 104: 563-568.
13. Wu X, Oerding H, Liu J, Vanacker B, Yao S, et al. (2014) Rocuronium blockade reversal with sugammadex vs. neostigmine: randomized study in Chinese and Caucasian subjects. BMC Anesthesiol 14: 53.
14. Rahe-Meyer N, Berger C, Wittmann M, Solomon C, Abels E, et al. (2015) Recovery from prolonged deep rocuronium-induced neuromuscular blockade: A randomized comparison of sugammadex reversal with spontaneous recovery. Anaesthesist 64: 506-512.
15. Eleveld DJ, Kuizenga K, Proost JH, Wierda JMKH (2007) A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex. Anesth Analg 104: 582-584.
16. Iwasaki H, Takahoko K, Otomo S, Sasakawa T, Kunisawa T, et al. (2014) A temporary decrease in twitch response following reversal of rocuronium-induced neuromuscular block with a small dose of sugammadex in a pediatric patient. J Anesth 28: 288-290.
17. Groudine SB, Soto R, Lien C, Drover D, Roberts K (2007) A randomized, dose-finding, phase II study of the selective relaxant binding drug, Sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. Anesth Analg 104: 555-562.
18. Chambers D, Paulden M, Paton F, Heirs M, Duffy S, et al. (2010) Sugammadex for reversal of neuromuscular block after rapid sequence intubation: a systematic review and economic assessment. Br J Anaesth 105: 568-575.
19. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, et al. (2009) Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. Anesthesiology 110:1020-1025.
20. Van Gestel L, Cammu G (2013) Is the effect of sugammadex always rapid in onset? Acta Anaesthesiol Belg 64: 41-47.
21. Esteves S (2015) Can residual paralysis be avoided?: A critical appraisal of the use of sugammadex. Eur J Anaesthesiol 32: 663-665.
22. Schepens T, Cammu G (2014) Neuromuscular blockade: what was, is and will be. Acta Anaesthesiol Belg 65: 151-159.
23. Della Rocca G, Di Marco P, Beretta L, De Gaudio AR, Ori C, et al. (2013) Do we need to use sugammadex at the end of a general anesthesia to reverse the action of neuromuscular bloking agents? Position Paper on Sugammadex use. Minerva Anestesiol 79: 661-666.
24. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, et al. (2015) Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth 115: 827-848.
25. Ezri T, Boaz M, Sherman A, Armaly M, Berlovitz Y (2016) Sugammadex: An Update. J Crit Care Med 2: 16-21.
26. Black AE, Flynn PER, Smith HL, Thomas ML, Wilkinson KA, et al. (2015) Development of a guideline for the management of the unanticipated difficult airway in pediatric practice. Paediatr Anaesth 25: 346-362.
27. Yamamoto S, Yamamoto Y, Kitajima O, Maeda T, Suzuki T (2015) Reversal of neuromuscular block with sugammadex: a comparison of the corrugator supercilii and adductor pollicis muscles in a randomized dose-response study. Acta Anaesthesiol Scand 59: 892-901.
28. Stourac P, Adamus M, Seidlova D, Pavlik T, Janku P, et al. (2016) Low-Dose or High-Dose Rocuronium Reversed with Neostigmine or Sugammadex for Cesarean Delivery Anesthesia: A Randomized Controlled Noninferiority Trial of Time to Tracheal Intubation and Extubation. Anesth Analg 122: 1536-1545.

29. Stourac P, Krikava I, Seidlova J, Strazevska E, Huser M, et al. (2013) Sugammadex in a parturient with myotonic dystrophy. Br J Anaesth 110: 657-678.
30. Mushambi MC, Kinsella SM, Popat M, Swales H, Ramaswamy KK, et al. (2015) Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. Anaesthesia 70: 1286-1306.
31. Carron M, Veronese S, Foletto M, Ori C (2013) Sugammadex allows fast-track bariatric surgery. Obes Surg 23: 1558-1563.
32. Loupec T, Frasca D, Debaene B (2016) Dose of sugammadex in morbidly obese patients - a reply. Anaesthesia 71: 731-732.
33. Carron M, Zarantonello F, Ori C (2016) Dose of sugammadex in morbidly obese patients. Anaesthesia 71: 730-731.
34. Schmartz D, Guerci P, Fuchs-Buder T (2013) Sugammadex dosing in bariatric patients. Anesthesiology 118: 754.
35. Madsen MV, Staehr-Rye AK, Claudius C, Gätke MR (2016) Is deep neuromuscular blockade beneficial in laparoscopic surgery? Yes, probably. Acta Anaesthesiol Scand 60: 710-716.
36. Madsen MV, Gätke MR, Springborg HH, Rosenberg J, Lund J, et al. (2015) Optimising abdominal space with deep neuromuscular blockade in gynaecologic laparoscopy--a randomised, blinded crossover study. Acta Anaesthesiol Scand 59: 441-447.
37. Dubois PE, Mulier JP (2013) A review of the interest of sugammadex for deep neuromuscular blockade management in Belgium. Acta Anaesthesiol Belg 64: 49-60.
38. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A (2014) Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. Br J Anaesth 112: 498-505.
39. Donati F (2013) Residual paralysis: a real problem or did we invent a new disease? Can J Anaesth J Can Anesth 60: 714-729.
40. Ledowski T, Hillyard S, O'Dea B, Archer R, Vilas-Boas F, et al. (2013) Introduction of sugammadex as standard reversal agent: Impact on the incidence of residual neuromuscular blockade and postoperative patient outcome. Indian J Anaesth 57: 46-51.
41. http://www.apsf.org/newsletters/html.
42. Ledowski T (2015) Sugammadex: what do we know and what do we still need to know? A review of the recent (2013 to 2014) literature. Anaesth Intensive Care 43: 14-22.
43. Castro DS, Leão P, Borges S, Gomes L, Pacheco M, et al. (2014) Sugammadex reduces postoperative pain after laparoscopic bariatric surgery: a randomized trial. Surg Laparosc Endosc Percutan Tech 24: 420-423.
44. Racca F, Mongini T, Wolfler A, Vianello A, Cutrera R, et al. (2013) Recommendations for anesthesia and perioperative management of patients with neuromuscular disorders. Minerva Anestesiol 79: 419-433.
45. Wefki Abdelgawwad Shousha AA, Sanfilippo M, Sabba A, Pinchera P (2014) Sugammadex and reversal of neuromuscular block in adult patient with duchenne muscular dystrophy. Case Rep Anesthesiol 2014: 680568.
46. Kendigelen P, Tutuncu AC, Ashyralyyeva G, Hamamcioglu EA, Kaya G (2015) Sugammadex usage in a patient with dermatomyositis. J Clin Anesth 27: 438-439.
47. Franco-Hernández JA, Muñoz Rodríguez L, Ortiz de Landázuri PJ, García Hernández A (2013) Use of sugammadex in Strumpell-Lorrain disease: a report of two cases. Braz J Anesthesiol Elsevier 63: 113-115.
48. Carron M, Iepparielloo G, Ori C (2013) Sugammadex in a patient with Sjogren's syndrome and polymyositis. Br J Anaesth 111: 1034-1035.
49. Stewart PA, Phillips S, De Boer HD (2013) Sugammadex reversal of rocuronium-induced neuromuscular blockade in two types of neuromuscular disorders: Myotonic dystrophy and spinal muscular atrophy. Rev Esp Anestesiol Reanim 60: 226–229.
50. Kelsaka E, Karakaya D, Zengin EC (2013) Use of sugammadex in a patient with amyotrophic lateral sclerosis. Med Princ Pract 22: 304-306.
51. de Boer HD, Shields MO, Booij LH (2014) Reversal of neuromuscular blockade with sugammadex in patients with myasthenia gravis: a case series of 21 patients and review of the literature. Eur J Anaesthesiol 31: 715-721.
52. Casarotti P, Mendola C, Cammarota G, Della Corte F (2014) High-dose rocuronium for rapid-sequence induction and reversal with sugammadex in two myasthenic patients. Acta Anaesthesiol Scand 58:1154-1158.
53. Kiss G, Lacour A, d'Hollander A (2013) Fade of train-of-four ratio despite administration of more than 12 mg kg (-1) sugammadex in a myasthenia gravis patient receiving rocuronium. Br J Anaesth 110: 854-855.
54. Fujita A, Ishibe N, Yoshihara T, Ohashi J, Makino H, et al. (2014) Rapid reversal of neuromuscular blockade by sugammadex after continuous infusion of rocuronium in patients with liver dysfunction undergoing hepatic surgery. Acta Anaesthesiol Taiwanica Off J Taiwan Soc Anesthesiol 52: 54-58.
55. Buijs EJ, Scholten JG, Ros JJ (2014) Successful administration of sugammadex in a patient with acute porphyria: A case report. Eur J Anaesthesiol 31: 439-441.
56. Panhuizen IF, Gold SJA, Buerkle C, Snoeck MMJ, Harper NJN, et al. (2015) Efficacy, safety and pharmacokinetics of sugammadex 4 mg kg-1 for reversal of deep neuromuscular blockade in patients with severe renal impairment. Br J Anaesth 114: 777-784.
57. de Souza CM, Tardelli MA, Tedesco H, Garcia NN, Caparros MP, et al. (2015) Efficacy and safety of sugammadex in the reversal of deep neuromuscular blockade induced by rocuronium in patients with end-stage renal disease: A comparative prospective clinical trial. Eur J Anaesthesiol 32: 681-686.
58. Lobaz S, Sammut M, Damodaran A (2013) Sugammadex rescue following prolonged rocuronium neuromuscular blockade with "recurarisation" in a patient with severe renal failure. BMJ Case Rep; 2013: bcr2012007603.
59. Bellod A Jr, March X, Hernandez C, Villalonga A (2014) Delayed recurarisation after sugammadex reversal. Eur J Anaesthesiol 31: 710-712.
60. Sokol-Kobielska E (2013) Sugammadex - indications and clinical use. Anaesthesiol Intensive Ther 45: 106-410.
61. Sabo D, Jahr J, Pavlin J, Philip B, Shimode N, et al. (2014) The increases in potassium concentrations are greater with succinylcholine than with rocuronium-sugammadex in outpatient surgery: a randomized, multicentre trial. Can J Anaesth J Can Anesth 61: 423-432.
62. Plaud B (2014) A new option for the treatment of anaphylaxis linked to steroidal neuromuscular blockers: How much value should we grant to case reports? Can J Anaesth J Can Anesth 61: 511-518.
63. Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM (2012) Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007). Minerva Anestesiol 78: 868-878.
64. Tsur A, Kalansky A (2014) Hypersensitivity associated with sugammadex administration: a systematic review. Anaesthesia 69: 1251–1257.
65. Hakozaki T, Murakawa M (2016) Rocuronium-induced anaphylaxis not improved by low dose sugammadex: a case report. Anaesth Intensive Care 44: 522.
66. Raft J, Belhadj-Tahar N, Meistelman C (2014) Slow recovery after sugammadex bolus after rocuronium-induced anaphylaxis. Br J Anaesth 112: 1115-1116.
67. Platt PR, Clarke RC, Johnson GH, Sadleir PHM (2015) Efficacy of sugammadex in rocuronium-induced or antibiotic-induced anaphylaxis. A case-control study. Anaesthesia 70: 1264-1267.
68. Whitehead A (2016) Sugammadex in anaphylaxis. A case-control study? Anaesthesia 71: 236-237.
69. Takazawa T, Mitsuhata H, Mertes PM (2016) Sugammadex and rocuronium-induced anaphylaxis. J Anesth 30: 290-297.
70. Zwiers A, van den Heuvel M, Smeets J, Rutherford S (2011) Assessment of the potential for displacement interactions with sugammadex: a pharmacokinetic-pharmacodynamic modelling approach. Clin Drug Investig 31: 101-111.
71. Kam P-J de, Heuvel MW van den, Grobara P, Zwiers A, Jadoul JL, et al. (2012) Flucloxacillin and diclofenac do not cause recurrence of neuromuscular blockade after reversal with sugammadex. Clin Drug Investig 32: 203-212.

72. Gulec E, Biricik E, Turktan M, Hatipoglu Z, Unlugenc H (2016) The Effect of Intravenous Dexamethasone on Sugammadex Reversal Time in Children Undergoing Adenotonsillectomy. Anesth Analg 122: 1147-1152.
73. Hudson ME, Rietbergen H, Chelly JE (2014) Sugammadex is effective in reversing rocuronium in the presence of antibiotics. BMC Anesthesiol 14: 69.
74. Eikermann M, Houle TT (2016) Antagonism of neuromuscular block: all things are poison; only the dose makes a thing not a poison. BJA Br J Anaesth 116: 157-159.
75. Unterbuchner C, Ziegleder R, Graf B, Metterlein T (2015) Magnesium-induced recurarisation after reversal of rocuronium-induced neuromuscular block with sugammadex. Acta Anaesthesiol Scand 59:536–40.
76. Rhee WJ, Lee SY, Lee JH, Choi SR, Lee S-C, et al. (2015) The effect of high concentration of magnesium with ropivacaine, gentamicin, rocuronium, and their combination on neuromuscular blockade. Korean J Anesthesiol 68: 50–61.
77. Czarnetzki C, Tassonyi E, Lysakowski C, Elia N, Tramer MR (2014) Efficacy of sugammadex for the reversal of moderate and deep rocuronium-induced neuromuscular block in patients pretreated with intravenous magnesium: a randomized controlled trial. Anesthesiology 121: 59–67.
78. Germano Filho PA, Cavalcanti IL, Barrucand L, Verçosa N (2015) Effect of magnesium sulphate on sugammadex reversal time for neuromuscular blockade: a randomised controlled study. Anaesthesia 70: 956-961.
79. Song S, Yoo BH, Kim K-M, Lee S (2014) Reversal of rocuronium induced neuromuscular blockade using sugammadex in a patient with eclampsia treated by magnesium intraoperatively. Korean J Anesthesiol 67: S102-s103.
80. Dalton J, Van Hasselt G (2016) Sugammadex - time of onset: nine months. Anaesthesia 71:115–6.
81. Conte B, Zoric L, Bonada G, Debaene B, Ripart J (2014) Reversal of a rocuronium-induced grade IV anaphylaxis via early injection of a large dose of sugammadex. Can J Anaesth J Can Anesth 61: 558-562.
82. http://www.apsf.org/newsletters/html/2016/February/06_Sugammadex.htm
83. Tokuwaka J, Takahashi S, Tanaka M (2013) Anaphylaxis after sugammadex administration. Can J Anaesth J Can Anesth 60: 733-734.
84. De Kam P-J, Grobara P, Prohn M, Hoppener F, Kluft C et al. (2014) Effects of sugammadex on activated partial thromboplastin time and prothrombin time in healthy subjects. Int J Clin Pharmacol Ther 52: 227-236.
85. De Kam P-J, Kruithof AC, van Lierop M-J, Moerland M, Dennie J, et al. (2014) Lack of a clinically relevant effect of sugammadex on anti-Xa activity or activated partial thromboplastin time following pretreatment with either unfractionated or low-molecular-weight heparin in healthy subjects. Int J Clin Pharmacol Ther 52: 631-641.
86. Raft J, Guerci P, Harter V, Fuchs-Buder T, Meistelman C (2015) Biological evaluation of the effect of sugammadex on hemostasis and bleeding. Korean J Anesthesiol 68: 17–21.
87. Rahe-Meyer N, Fennema H, Schulman S, Klimscha W, Przemeck M, et al. (2014) Effect of reversal of neuromuscular blockade with sugammadex versus usual care on bleeding risk in a randomized study of surgical patients. Anesthesiology 121:969–77.
88. Kim Y-H. (2016) Sugammadex: watch out for new side effects. Korean J Anesthesiol 69: 427-428.
89. de Kam P-J, Grobara P, Dennie J, Cammu G, Ramael S, et al. (2013) Effect of sugammadex on QT/QTc interval prolongation when combined with QTc-prolonging sevoflurane or propofol anaesthesia. Clin Drug Investig 33: 545-551.
90. Staikou C, Stamelos M, Stavroulakis E (2014) Impact of anaesthetic drugs and adjuvants on ECG markers of torsadogenicity. Br J Anaesth 112: 217–30.
91. de Kam P-J, van Kuijk J, Prohn M, Thomsen T, Peeters P (2010) Effects of sugammadex doses up to 32 mg/kg alone or in combination with rocuronium or vecuronium on QTc prolongation: a thorough QTc study. Clin Drug Investig 30: 599-611.
92. Suzuki M, Inagi T, Kikutani T, Mishima T, Bito H (2014) Negative pressure pulmonary edema after reversing rocuronium-induced neuromuscular blockade by sugammadex. Case Rep Anesthesiol 2014: 135032.
93. Basaranoglu G, Bakan M, Umutoglu T (2013) Does sugammadex increase the susceptibility of opioid induced chest wall rigidity? Minerva Anestesiol 79: 1099.
94. McGuire B, Dalton AJ (2016) Sugammadex, airway obstruction, and drifting across the ethical divide: a personal account. Anaesthesia 71: 487-492.
95. Paton F, Paulden M, Chambers D, Heirs M, Duffy S, et al. (2010) Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. Br J Anaesth 105: 558-567.
96. Carron M, Baratto F, Zarantonello F, Ori C (2016) Sugammadex for reversal of neuromuscular blockade: a retrospective analysis of clinical outcomes and cost-effectiveness in a single center. Clin Outcomes Res CEOR 8: 43-52.
97. De Robertis E, Zito Marinosci G, Romano GM, Piazza O, Iannuzzi M, et al. (2016) The use of sugammadex for bariatric surgery: analysis of recovery time from neuromuscular blockade and possible economic impact. Clin Outcomes Res CEOR 8: 317-322.
98. Fuchs-Buder T, Meistelman C, Schreiber JU (2012) Is sugammadex economically viable for routine use. Curr Opin Anaesthesiol 25: 217-220.
99. Ledowski T, Falke L, Johnston F, Gillies E, Greenaway M, et al. (2014) Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: sugammadex, neostigmine or no reversal. Eur J Anaesthesiol 31: 423-429.
100. Ledowski T, Ong JS, Flett T (2015) Neuromuscular monitoring, muscle relaxant use, and reversal at a tertiary teaching hospital 2.5 years after introduction of sugammadex: changes in opinions and clinical practice. Anesthesiol Res Pract 2015: 367937.
101. Dogan E, Akdemir MS, Guzel A, Yildirim MB, Baysal Yildirim Z, et al. (2014) A Miracle That Accelerates Operating Room Functionality: Sugammadex. BioMed Res Int 2014: e945310.
102. Welk B, Winick-Ng J, McClure A, Vinden C, Dave S, et al. (2016) The impact of teaching on the duration of common urological operations. Can Urol Assoc J 10: 172.
103. Harrington DT, Roye GD, Ryder BA, Miner TJ, Richardson P, et al. (2007) A time-cost analysis of teaching a laparoscopic entero-enterostomy. J Surg Educ 64: 342-345.
104. Dubois PE, Putz L, Jamart J, Marotta M-L, Gourdin M, et al. (2014) Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy: a randomised controlled trial. Eur J Anaesthesiol 31: 430-436.
105. Kotake Y, Ochiai R, Suzuki T, Ogawa S, Takagi S, et al. (2013) Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. Anesth Analg 117: 345-551.
106. Giacalone M, Zaouter C, Mion S, Hemmerling TM (2016) Impact of age on anaesthesiologists' competence: A narrative review. Eur J Anaesthesiol 33: 787-793.