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Review

Advantages and pitfalls of clinical application of sugammadex

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Sugammadex, a modified γ-cyclodextrin, is one of the drugs focused on in the anesthetic field because it provides rapid and complete reversal from neuromuscular blockade (NMB) by encapsulating rocuronium. Its introduction has revolutionized anesthesia practice because it is a safe, predictable, and reliable neuromuscular antagonist. Hence, its use has increased worldwide. Further, it has been in the spotlight for recovering from deep NMB in laparoscopic surgery and improving the surgical condition. Recently, studies have been conducted on the postoperative outcome after deep NMB and use of sugammadex in various clinical conditions. However, with increase in sugammadex use, reports regarding its complications are increasing. Appropriate dosing of sugammadex with quantitative neuromuscular monitoring is emphasized because under-dosing or over-dosing of sugammadex might be associated with unexperienced complications. Sugammadex is now leaping into an ideal reversal agent, changing the anesthesia practice.

Keywords: Complications; Neuromuscular blockade; Review; Rocuronium; Sugammadex.

INTRODUCTION

Sugammadex, a modified γ-cyclodextrin, is a novel reversal agent with a selective binding capacity to steroidal neuromuscular blocking drugs (NMBDs) such as rocuronium. It has been in the spotlight as a novel reversal agent since discovery because of the quality of recovery from neuromuscular blockade (NMB), which is rapid, reliable, and less side effects [1,2]. In addition, it aids in optimizing the surgical condition during laparoscopic surgery [3]. It has been nearly 10 years since sugammadex was introduced clinically. Hence, the known benefits and new areas of interest in its clinical use are presented in this review.

CLINICALLY SPOTLIGHTED ADVANTAGES OF SUGAMMADEX

Role of sugammadex in difficult airway management

Researchers developed the idea of using sugammadex in the "cannot intubate, cannot ventilate" state because it rapidly reverses NMB [4–6]. As the prescription guideline represent that sugammadex can reverse successfully 3 min after rocuronium administration for the intubation when it is used as 16 mg/kg, it could be one of the rescue management in the emergency situation of airway management after use of rocuronium. However, many researchers have suggested that sugammadex cannot be a part of the difficult airway algorithm and should not be used as the "silver bullet" for difficult airway management, instead alternative strategies such as surgical air-

way should be considered [7–10].

Effect of sugammadex on QTc

Conventional reversal with neostigmine and atropine is associated with significant corrected QT (QTc) prolongation. On the contrary, sugammadex has nearly no effect on QTc [11]; however, it has some effect on QT prolongation [12]. In the case of Brugada syndrome, neostigmine or pyridostigmine can increase parasympathetic drive and lead to bradycardia [13]. Hence, sugammadex seems to be an ideal NMB reversal agent in Brugada syndrome.

Specific disease and sugammadex

Sugammadex provides rapid and reliable reversal from NMB and therefore, it has been successfully introduced for patients with neuromuscular disease or those with potential for postoperative respiratory dysfunctions such as Duchenne muscular dystrophy [14], amyotrophic lateral sclerosis [15], and myasthenia gravis [16–18]. In addition, its introduction for short-term muscle relaxation during electroconvulsive therapy (ECT) decreased the time to restoration of spontaneous ventilation and side effects of ECT [19,20]. Hence, use of sugammadex as a safe NMB reversal agent is expanding among patients with significant comorbidities.

USE OF SUGAMMADEX IN A SPECIAL CLINICAL SITUATION

Optimal dose of sugammadex for an obese patient

It is well known that the appropriate dose of sugammadex is consistent with the NMB status, which is determined by neuromuscular monitoring. Under-dosing may lead to residual NMB (RNMB), thus requiring an additional dose for complete reversal. However, the optimal dose of sugammadex for obese patients is under debate. Van Lancker et al. [21] compared the extubation time among morbidly obese patients administered with different doses (set by real body weight, ideal body weight [IBW], IBW + 20%, and IBW + 40%) of sugammadex and concluded that a dose of 2 mg/kg of IBW + 40% resulted in safe recovery from NMB. In addition, Llauradó et al. [22] reported that sugammadex dose calculated by IBW is insufficient for reversing both deep and moderate NMBs in morbidly obese patients. Badaoui et al. [23] reported that the dose of sugammadex for the reversal of deep NMB in the obese patient was 130–150% of weight based dosage (4 mg/ calculated IBW). However, other researchers have questioned the methodology and results [24]. Sanfilippo et al. [25] reported that sugammadex doses calculated based on only IBW are sufficient for rapid and safe NMB reversal, with no RNMB. A recent study demonstrated that sugammadex dosed at 1.5 mg/kg of IBW successfully reversed moderate NMB in obese patients [26]. In addition, Duarte et al. [27] concluded that IBW can be used to calculate the sugammadex dose to reverse moderate NMB in morbidly obese patients. However, despite these controversies, sugammadex should be administered based on the NMB status with quantitative neuromuscular monitoring before as well as after sugammadex administration [28].

Drug interaction with sugammadex

A concern that magnesium sulfate can affect rocuronium-induced NMB reversal with sugammadex existed because magnesium potentiates NMB [29]. However, a randomized study demonstrated that magnesium did not alter the efficacy of sugammadex [30]. In addition, effective and complete reversal of rocuronium-induced NMB with sugammadex (2 mg/kg) was observed in a pregnant woman treated with magnesium (60 mg/kg) intraoperatively [31]. Further, it was reported that pretreatment with magnesium did not significantly affect sugammadex reversal time for moderate NMB [32]. In addition, magnesium did not affect the reversal effects of sugammadex in animal studies [33,34]. However, administration of magnesium after rocuronium-induced NMB reversal with sugammadex may lead to recurarization, requiring continuous neuromuscular monitoring [35].

Sugammadex was developed from cyclodextrins, which were used to dissolve steroids, and therefore, there were concerns regarding interaction between sugammadex and steroids. Recently, a study reported concerns regarding the potential risk of contraception failure with estrogen or progestogen containing oral contraceptives after sugammadex use [36]. According to in vitro studies, sugammadex may bind to progestogen and therefore, progestogen exposure would decrease after sugammadex use. Administration of a bolus of sugammadex is considered equivalent to a missing dose of oral contraceptives. It is recommended that an

additional, non-hormonal contraceptive or alternative birth control method should be used for 7 days after sugammadex is administered to a patient taking an oral contraceptive. However, clinical data related to pregnancy is lacking. In animal studies, sugammadex did not affect pregnancy or progesterone levels in pregnant rats in the first trimester [37]. In addition, no changes in the clinical course of pregnancy and no stillbirth or miscarriage were noted. A randomized clinical study demonstrated that sugammadex is not associated with adverse effects on steroid hormones such as progesterone and cortisol, except for a temporary increase in aldosterone and testosterone levels [38]. However, whether to include this matter in the consent form is still under debate.

Can we use sugammadex in the patient with renal failure?

According to the prescriber's information, because the sugammadex–rocuronium complex is eliminated mainly by renal excretion, severe renal failure is a contraindication. In a patient with creatinine clearance less than 30 mL/min, urinary excretion of the sugammadex–rocuronium complex was found to be reduced [39] and potential dissociation of the complex was noted. However, the recovery time (train-of-four [TOF] ratio: 0.9) after using sugammadex (2 mg/kg) was not significantly different between patients with renal impairment and normal patients (0.9–2 min vs. 1.65 min) as well as no RNMB was noted [40]. According to a pharmacokinetic study, there are large differences in the pharmacokinetics of rocuronium and sugammadex between patients with severe renal failure and healthy controls [39]. Lobaz et al. [41] reported that failure of NMB reversal was successfully managed using sugammadex in an elderly patient with severe renal failure. Furthermore, in another patient with severe renal failure, sugammadex was successfully used as a rescue following prolonged NMB with recurarization [41]. In an animal study, sugammadex rapidly and effectively reversed rocuronium-induced NMB in cats with both renal pedicles ligated [42]. A study reported that although sugammadex could rapidly reverse NMB without recurarization in patients with renal failure, the urinary excretion of rocuronium and sugammadex was reduced and total plasma clearance was considerably lower in patients with renal failure compared with controls [39]. Moreover, no clinical data on long-term disposition of the sugammadex–rocuronium complex, which is retained in the body of a patient with renal failure, are available. Thus, although the sugammadex-rocuronium complex is dialysable through high-flux dialysis [43], the use of sugammadex in patients with severe renal failure should be carefully considered, with appropriate postoperative neuromuscular monitoring [44,45]. Recently, in an elderly patient with end-stage renal failure, erratic infiltration of subcutaneous rocuronium was successfully managed with sugammadex and the duration of action was sufficient to neutralize the ongoing absorption of subcutaneous rocuronium [46].

Failure of reversal, recurarization, and resensitization?

Sugammadex is considered as a novel and promising drug for reversal of rocuronium-induced NMB. However, some studies have reported delayed recovery with sugammadex, wherein time intervals after administration of sugammadex (4 mg/kg) were reported to be 24.6 and 22.3 min until recovery of TOF ratio to 0.9 [47,48]. These unexpected long recovery times were often associated with inadequate neuromuscular monitoring and under-dosing of sugammadex. In addition, they were associated with the old age of patients, slow hemodynamic circulation, pulmonary disease, obesity, and renal failure in some cases [49]. However, cases of failure of sugammadex to reverse rocuronium-induced NMB have begun to be reported. Ortiz-Gómez et al. [50] reported a case of failure to reverse NMB with a large dose of sugammadex (9.74 mg/kg). Further, they suggested that this might be an "extreme outlier" with a marked rightward shift of the dose-response curve and there would be cases in which rapid reversal cannot be achieved with sugammadex. Interestingly, Carollo and White [51] reported a case of recurarization after administration of an adequate dose of sugammadex in an 8-month-old baby. Sugammadex was dosed at 4 mg/kg for NMB reversal with a TOF count of 2 and reversal was achieved rapidly; however, respiratory failure and a decline in the TOF response (TOF count: 2) were observed during the recovery in the intensive care unit. Recently, a report indicated that rescue administration of sugammadex (200 mg) after administration of neostigmine (50–70 mg/kg) for NMB reversal can result in a paradoxical reduction in the TOF ratio. This is because complete removal of rocuronium from the neuromuscular junction by sugammadex may lead to a desensitized block, similar to a phase-2 block, due to excessive intrasynaptic acetylcho-

line made available after high-dose neostigmine administration [52].

Can we use sugammadex in rocuronium-induced anaphylaxis?

In contrast to the anaphylaxis due to sugammadex, Jones and Turkstra [53] suggested the possibility of using sugammadex in the case of rocuronium-induced anaphylaxis. They suggested that the property of sugammadex to encapsulate rocuronium can be a rationale for effectively removing free rocuronium molecules from the circulation and slowing down or halting the immunological process. This suggestion was clinically applied by McDonnell et al. [54]. They administered sugammadex (500 mg) to a patient with cardiovascular collapse due to an anaphylactic reaction to rocuronium during anesthesia induction and found that sugammadex improved the hemodynamic state. Moreover, another case of rocuronium-induced anaphylaxis with clinical improvement triggered by sugammadex was reported [55]. However, it was believed that sugammadex would not mitigate rocuronium-induced anaphylaxis because according to an in vitro study, encapsulation of rocuronium by sugammadex does not stop basophil activation by the rocuronium [56]. The antigenic portion of the rocuronium molecule containing the ammonium group protrudes from the cyclodextrin host, thereby exposing the ammonium group to the complementary immunoglobulin E (IgE) antibodies [56,57]. However, despite these debates, successful management of rocuronium-induced anaphylactic reactions with sugammadex has been continuously reported [58], even in the case of refractory to conventional treatment [59]. According to the cutaneous model of anaphylaxis in rocuronium-sensitized patients, sugammadex was effective in attenuating the type-1 hypersensitivity reaction triggered by rocuronium [60]. In an animal study, the degranulation of mast cells in the rat liver, which were increased in numbers by rocuronium, was mitigated by sugammadex [61]. An intradermal injection of sugammadex and rocuronium, mixed in an equal molecular ratio, prevented rocuronium-induced IgE-mediated anaphylactic skin reaction [62]. These studies suggested that sugammadex may be beneficial for treating rocuronium-induced anaphylaxis. However, not all patients with rocuronium-induced anaphylaxis recovered rapidly with sugammadex. In addition, Raft et al. [63] reported that even large doses (14 mg/kg) of sugammadex did not induce recovery from anaphylaxis. Hakozaki and Murakawa [64] reported that a low dose of sugammadex could not improve rocuronium-induced anaphylaxis. The overall risk-benefit ratio seems to favor sugammadex administration in the rocuronium associated hypersensitivity with potentially life-threatening consequences [65]. However, one should be aware of the potential side effects of sugammadex, sugammadex-induced anaphylaxis.

SIDE EFFECTS AND PRECAUTIONS OF SUGAMMADEX USE

Hypersensitivity and anaphylaxis

Although hypersensitivity to sugammadex is a rare event, the consequences can be serious, such as cardiovascular collapse. Anaphylactic reaction associated with sugammadex was also reported in Korea [66], and now it is considered as an emerging trigger of perioperative anaphylaxis [67]. A systematic review on hypersensitivity associated with sugammadex suggests the possibility of hypersensitivity reaction and caution required during the critical 5-min period immediately following the administration because most of the cases have occurred within 5 min [68]. Moreover, a prompt treatment is required because it is not only easier to manage but also presents a better prognosis than a delayed treatment. However, because the biphasic anaphylactic attack can develop as a severe second attack, closed monitoring is required [69]. Hypersensitivity to sugammadex can be confirmed by an intradermal skin test with a 1:100 dilution or a 1:1,000 dilution of sugammadex [70–72]. The suggested investigative procedure is as follows: tryptase test of preoperative serum (at least one or two samples after the onset of symptoms), skin test, and immunoassay for sugammadex-reactive IgE antibodies [73]. However, studies have revealed that hypersensitivity is not always mediated with sugammadex-specific IgG or IgE [74,75]. Recently, it has been reported that sugammadex-associated anaphylaxis is not induced by sugammadex molecule alone but by the rocuronium and sugammadex complex and sugammadex molecule [76,77]. Thus, anesthesiologists should take more precautions.

Acute coronary syndrome

One of the noteworthy side effects of sugammadex is

coronary vasospasm. Ko et al. [78] reported a case of coronary spasm in a patient with variant angina, which might have been triggered by sugammadex. However, a recent animal study suggested that sugammadex has no direct effect on the vascular tone [79]. Some researchers have thought that the effect of sugammadex on the coronary artery is due to hypersensitivity reactions such as Kounis syndrome [80,81]. Recently, a case of sugammadex-induced Kounis type III syndrome (hypersensitivity-induced acute coronary stent thrombosis) was reported [81]. Hence, anesthesiologists should consider acute coronary syndrome and should take precautions when using sugammadex for emergence from anesthesia.

Pulmonary complications after sugammadex use

Sometimes, the potency of sugammadex for rapid and reliable NMB reversal results in unwanted events such as pulmonary complications. Sugammadex has been reported to cause upper-airway obstructions such as laryngospasm or bronchospasm [82,83]. Suzuki et al. [84] reported a case of negative pressure pulmonary edema after sugammadex administration which might have been caused by increased upper airway collapsibility due to diaphragm-generated large inspiratory forces, decreasing pharyngeal patency. Eskander et al. [85] reported two cases of bronchospasm after coadministration of desflurane and sugammadex and suspected that desflurane-induced respiratory irritation may increase the risk of sugammadex-induced bronchospasm.

Other potential risks of sugammadex

Other potential risks of sugammadex, such as severe bradycardia, interactions with steroids, coagulopathy, and neuronal damage, are well described in a previous review [86]. The review suggested that administration of supratherapeutic doses of sugammadex results in these complications and presence of excessive sugammadex molecules in free-form might be associated with these risks.

RECENT CLINICAL INTERESTS REGARDING SUGAMMADEX

Is deep NMB really beneficial?

Recently, benefits of using sugammadex have been questioned [87]. Most of the publications have presented limited advantages of sugammadex such as improved surgical conditions. However, the long-term effects of deep NMB for the surgical outcome or reduction in complication rates have not been well established. Moreover, a recent study reported no added benefit of deep NMB over moderate relaxation in bariatric surgery [88]. Another study reported marginal improvement in surgical conditions with deep NMB in low-pressure laparoscopic cholecystectomy [89]. Further, deep NMB with lower intra-abdominal pressure were reported to provide few cardiopulmonary benefits during laparoscopic colorectal surgery [90]. Moreover, deep NMB did not improve the surgical view during laparoscopic ventral hernia repair and showed benefits only during suturing of the hernial defect [91]. However, studies on post-surgical outcomes are recent. Oh et al. [92] reported that deep NMB not only improved the surgical condition but also reduced postoperative pain in lumbar spinal surgery. Mulier and Dillemans [93] revealed that continuous deep NMB is an independent factor associated with fewer complications after bariatric surgery. Kim et al. [94] reported that compared with neostigmine, sugammadex may increase the quality of physiological recovery in early postoperative periods after ophthalmic surgery. Boon et al. [95] reported that compared with use of low-dose NMBD, use of high-dose NMBD for anesthesia induction during retroperitoneal laparoscopic surgery and reversal with sugammadex showed a lower incidence of unplanned 30-day readmissions. Oh et al. [96] revealed that unplanned 30-day readmission after major abdominal surgery decreased with sugammadex use. Chae et al. [97] indicated that reversal with sugammadex decreased the incidence of delayed discharge.

Intraoperative neuromonitoring and sugammadex

These days, many surgical procedures require intraoperative neuromonitoring using a neural integrity monitor. In the case of ear, nose, and throat surgery, facial or recurrent laryngeal nerve monitoring is required for NMB reversal and sugammadex can be an option for the rapid and effective reversal from rocuronium-induced deep NMB [98–100].

Economic issue and under-dosing techniques of sugammadex

Although sugammadex is useful for the reversal of rocuronium-induced deep NMB and seems more reliable than

neostigmine, it cannot replace neostigmine because it is expensive [101]. Interestingly, researchers are studying the use of under-dose of sugammadex as a cost-effective strategy [102]. However, although no report on the sugammadex under-dosing method for rocuronium-induced NMB reversal is available, some clinical trials have been reported. In addition, no study or evidence on the safety and cost-effectiveness of the sugammadex under-dosing method has been reported. Moreover, based on dose-finding studies, under-dosing of sugammadex is associated with RNMB. A recent study revealed that elderly patients are at greater risk for RNMB when low-dose sugammadex is administered [103]. Hence, sugammadex should be dosed based on the quantitative analysis of neuromuscular monitoring [104].

Sugammadex defiantly decreased the postoperative pulmonary complications

Recent multicenter trials revealed that sugammadex defiantly decreased postoperative pulmonary complications in 45,712 adult patients undergoing noncardiac surgery [105]. The incidence of postoperative pulmonary complications such as pneumonia, respiratory failure, and pneumothorax was lower in the sugammadex group than that in the neostigmine group (3.5% vs. 4.8%; odds ratio, 0.70; 95% confidence interval, 0.63–0.77). Hence, lower incidence of RNMB with sugammadex use can be translated into lower incidence of postoperative pulmonary complications [106].

CONCLUSION

Use of sugammadex has increased worldwide since its introduction because it reverses NMB safely and reliably. Initially, it was in the spotlight because it reversed deep NMB in surgeries such as laparoscopic surgery. However, most of the studies were focused only on the surgical condition and a few studies were focused on sugammadex-associated surgical outcome or complication. Recently, studies are being conducted on postoperative outcomes after deep NMB and on the use of sugammadex in various conditions. Reports regarding sugammadex-associated complications are increasing with increase in its use and therefore, anesthesiologists should be vigilant of new complications. An anesthesiologist should be aware of interactions between sugammadex and other drugs and should consider conditions or disease of the patient. Primarily, an appropriate dose of sugammadex should be determined based on quantitative neuromuscular monitoring. Under-dosing or over-dosing of sugammadex should be avoided as it may lead to RNMB or other complications.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: Ki Tae Jung. Data acquisition: Hyung Young Lee, Ki Tae Jung. Supervision: Ki Tae Jung. Writing—original draft: Hyung Young Lee, Ki Tae Jung. Writing—review & editing: Ki Tae Jung.

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