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Review

The potential risks of sugammadex

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Sugammadex provides fast and safe recovery from neuromuscular blockade without causing major adverse effects, and its clinical use is increasing. However, there are some reports on the potential risks of sugammadex, such as severe bradycardia, interactions with steroids, coagulopathy, and neuronal damage. Although these potential risks are not clearly proven, they are considered to be dose-dependent and occur more frequently with the free-form of sugammadex. Until further pieces of evidence are accumulated, it is prudent to be aware of these potential risks and avoid an overdose of sugammadex.

Keywords: Adverse effects; Blood coagulation disorders; Bradycardia; Drug interactions; Neurotoxicity syndromes; Sugammadex.

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INTRODUCTION

Almost ten years have passed since sugammadex was launched in Europe in 2008. It has successfully entered the market, despite being relatively expensive, and many studies have proven its efficacy and safety [1–5]. According to the results of recent meta-analyses, sugammadex showed faster recovery after neuromuscular blockade in adults as compared to neostigmine [1–3]. It also reduced the incidence of residual neuromuscular blockade and postoperative endotracheal intubation as well as reduced the frequency of overall adverse effects as compared to neostigmine [1–3]. In children, sugammadex has also been shown to provide faster recovery after neuromuscular blockade as compared to neostigmine, and the overall adverse effects are not different from that of neostigmine [4,5].

Sugammadex provides fast and safe recovery from neuromuscular blockade without major adverse effects, and its clinical use is increasing [6]. Most of the studies have emphasized the efficacy and safety of sugammadex, but some have also reported its potential risks. These potential risks have been reported but not explicitly proven yet. This article aims to review the relevant literature on the potential risks associated with sugammadex, such as severe bradycardia, interaction with steroids, coagulopathy, and neuronal damages.

STRUCTURAL CHARACTERISTICS OF SUGAMMADEX

Sugammadex has a γ-cyclodextrin structure comprising a hydrophilic outer surface and a lipophilic inner hollow space [7]. Due to this unique structure, rocuronium binds to the inner space of sugammadex, thereby undergoing inactivation and is subsequently excreted out of the body (Fig. 1). However, the inner space of sugammadex can also bind to drugs other than rocuronium. Theoretically, two types of drug interactions can occur with sugammadex, namely, displacement interactions and capturing interactions [8]. Displacement interactions mean other drugs can bind to sugammadex by displacing rocuronium resulting in a slow recovery after neuromuscular blockade. Capturing interactions mean sugammadex can bind to drugs other than rocuronium, thereby reducing the plasma concentration and effects of those bound drugs [8].

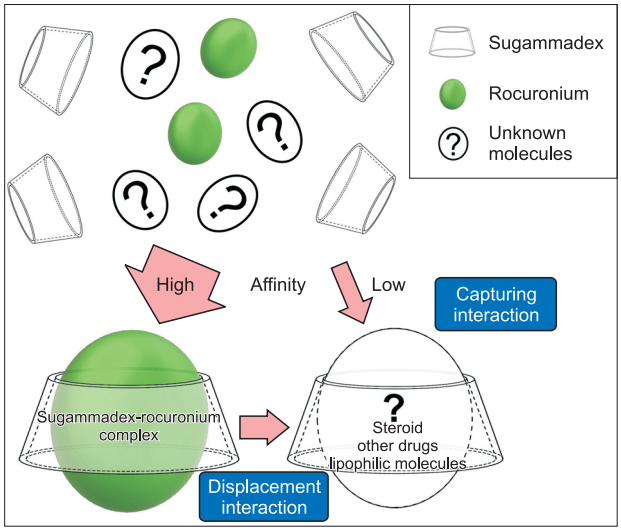

Fig. 1. Displacement and capturing interactions of sugammadex.

However, the affinity of sugammadex to rocuronium is higher than that of other drugs, and in the presence of rocuronium, sugammadex forms a complex with rocuronium only [9]. In clinical settings, drug interactions between sugammadex and other drugs seldom occur and, therefore, leads to no cause for concern. However, if the amount of sugammadex is excessive, or if the levels of the free-form of the drug increases, anesthesiologists should consider drug interactions with other drugs or molecules as well.

POTENTIAL RISKS

Severe bradycardia

Few years after sugammadex was launched, cardiovascular collapse along with severe bradycardia after administration of sugammadex was reported [10,11]. Most of those cases were considered to be hypersensitivity reactions, but only a few were confirmed since the estimation of serum tryptase or skin tests were rarely performed. Many of the suspected hypersensitivity cases might not be actual hypersensitivity ones, and moreover, the incidence of bradycardia after sugammadex administration was reported to be 1–2%, which is higher than the reported incidence of anaphylaxis (only 0.04%) [12–14]. In addition, cardiovascular adverse effects, such as prolongation of corrected QT interval, hypotension, and cardiac arrest were also reported in preclinical and clinical trials with sugammadex [15–18].

As the use of sugammadex increased, the frequency of serious cardiovascular events after administration of sugammadex was reported in a higher frequency. Recently, several cases of severe bradycardia without hypersensitivity reactions were also reported [15,19]. Although the mechanisms are not clear yet, this response is considered to be dose-dependent and occur more frequently in the presence of underlying heart diseases [13]. Therefore, until more reports and studies are accumulated, it is advisable to use only the optimal dose of sugammadex and prepare for the occurrence of severe bradycardia.

Interaction with steroids

Sugammadex reverses neuromuscular blockade by encapsulating the steroidal neuromuscular blockers. There was a concern for corticosteroid inhibition during reversal of neuromuscular blockade by sugammadex because of the structural similarity of steroidal neuromuscular blockers and steroids [20]. In 2014, Rezonja et al. [20] reported that dexamethasone treatment inhibited sugammadex-induced reversal of rocuronium in in vitro culture of innervated primary human muscle cells. In their study, dexamethasone inhibited recovery by sugammadex from rocuronium-induced neuromuscular blockade in a dose-dependent manner. Although being in vitro study, the results are significant as this was the first study to show a possibility that steroids might interfere with the effects of sugammadex. However, successive in vivo studies showed different results. Buonanno et al. [21] estimated the time to recovery (from sugammadex administration to train-of-four [TOF] ratio > 0.9) in control, dexamethasone after induction, and dexamethasone before reversal groups. The differences in time to recover among the three groups were not significantly different. In other studies, steroid administration did not prolong sugammadex reversal [22–24]. Although there was no prolongation of rocuronium reversal by sugammadex, there was a report that the blood concentration of dexamethasone was decreased after administration of sugammadex [23]. In addition, Gunduz et al. [25] estimated the blood concentration of steroid hormones before and after sugammadex or neostigmine administration. They reported no significant change in the serum cortisol and progesterone concentration, but temporary increase in serum aldosterone and testosterone concentration after administration

of sugammadex. Overall, these studies have shown that the change in the concentration of steroids varied after sugammadex administration, thus it is difficult to conclude definitively how sugammadex interacts with steroids. Fortunately, there are no reports implying that steroids can cause prolongation of rocuronium reversal by sugammadex.

Coagulopathy

Several studies have reported that sugammadex changes the coagulation parameters. Dirkmann et al. [26] added sugammadex to blood samples collected from healthy volunteers and performed coagulation tests. The results showed increased prothrombin time (PT, 9.1%), activated partial thromboplastin time (aPTT, 13.1%), and clotting time (CT; INTEM, 22.4%; EXTEM, 33.1%); and decreased factor VIII (7%), IX (7.8%), XI (6.9%), and XIII (4.3%) after adding sugammadex. Another in vitro study using thromboelastography showed an increase in reaction time, coagulation time, and time to maximum rate of thrombus formation; and decrease in the angle, maximum amplitude, and maximum rate of thrombus formation after adding sugammadex in a dose-dependent manner [27]. In vivo administration of sugammadex also showed an increase in CT three minutes after administration of sugammadex, but the extent of increase was small (about 10 s), and after 30 min it returned to the baseline level [28]. The other studies also showed a clinically insignificant increase in PT and PTT after in vivo administration of sugammadex [29,30]. Dirkmann et al. [26] described the significant changes in the coagulation parameters in in vitro studies as 'in vitro artifacts'. Phospholipids are essential to initiate coagulation cascade, and therefore, they are included in the coagulation test reagents. The authors explained that the free-form of sugammadex encapsulated these phospholipids within the lipophilic inner space and inhibited the coagulation process. Therefore, the anticoagulant effects of sugammadex might not be prominent in vivo.

In addition, the bleeding tendency after administration of sugammadex is controversial. There are contradictory reports stating that sugammadex increases postoperative bleeding [29] as well as it does not [30]. Overall these studies have shown that sugammadex alters the coagulation parameters in clinical settings, but the extent of the change is small. However, it might be safe to consider coagulopathy until further research findings are available.

Neuronal damage

Palanca et al. [31] reported that sugammadex caused neuronal apoptosis in in vitro culture of cortical neurons obtained from the cerebral cortex of rats. The in vitro study of Aldasoro et al. [32] showed that sugammadex complex with rocuronium or vecuronium causes minimal neuronal apoptosis, but the free-form of the drug causes significant neuronal apoptosis. They warned against sugammadex-induced brain damage if the blood-brain barrier is damaged since sugammadex cannot across an intact blood-brain barrier. They also proposed that a minimum dose of sugammadex should be administered to prevent significant neurotoxicity resulting from the free-form of the drug.

However, another study has shown neuroprotective effects of sugammadex in the cerebral ischemic reperfusion injury model of rats [33]. So far, sugammadex showed neurotoxicity in in vitro models but also showed neuroprotective effects in in vivo ischemic reperfusion injury models. Since there are few studies on the neuronal effects of sugammadex, it is considered too premature to discuss the neuronal effects here.

APPROPRIATE DOSE OF SUGAMMADEX

The potential risks presented above are dose-dependent and more frequent with the free-form of sugammadex. Therefore, it is better to avoid using more than the optimal dose of the drug. The manufacturer of sugammadex, Merck & Co., Inc. (USA) recommend tailored dosing of sugammadex based on the depth of neuromuscular block required (Table 1). However, despite the use of neuromuscular block-

Table 1. Recommended Dose of Sugammadex

Level of neuromuscular block	Dose of sugammadex
Light block: Reappearance of fourth twitch (T4) in response to TOF stimulation	1 mg/kg*
Moderate block: Reappearance of second twitch (T2) in response to TOF stimulation	2 mg/kg†
Deep block: 1–2 PTCs and no twitch responses to TOF stimulation	4 mg/kg†

TOF: train-of-four, PTC: post-tetanic counts. *Dose obtained from the reference [35], †doses obtained from package insert recommendations.

ers, many anesthesiologists do not perform neuromuscular monitoring [6]. Many anesthesiologists use routine dose empirically without estimating the depth of neuromuscular blockade at the time of administration of the reversal agent [6,34]. Empirical dosing is likely to result in excessive or insufficient doses of sugammadex, both of which are harmful. Another problem is that, during most of the anesthetic procedures, the depth of neuromuscular blockade is shallow at the time of administration of the reversal agent [34]. This seems to reflect the tendency of the anesthesiologists in using only minimal neuromuscular blockers to reduce the associated risks. The manufacturer of sugammadex, however, recommends administration of the same dose of sugammadex for a moderate block as required for a shallow block, although this could lead to overdosing. A study of the dose of sugammadex at the reappearance of four twitches (T4) to TOF stimulation showed that it is possible to achieve fast and safe neuromuscular reversal with 1 mg/kg of the drug [35].

In addition, many studies suggest that the dose of sugammadex should be reduced in obese patients with dose calculations based on the ideal body weight [36–38]. Although there are warnings and concerns about reducing the dose of sugammadex in obese patients [39,40], the level of evidence of these claims are still low. Many anesthesiologists have concerns in reducing the dose of neuromuscular reversal agents, and these might be a big obstacle to reduce the dose of sugammadex. Therefore, neuromuscular monitoring is essential when using sugammadex to address these concerns because of the associated risks of sugammadex and other neuromuscular blockers.

CONCLUSION

The potential risks with sugammadex presented here have several implications. First, these adverse reactions are dose-dependent and are more frequent with the free-form of the drug. Therefore, the anesthesiologists should pay more attention to prevent overdose of sugammadex. Second, they are reported more prominently in vitro than in in vivo. This might be because the capturing interaction of sugammadex was exaggerated due to the limited in vitro environmental characteristics. There is no doubt that sugammadex is a safe and effective drug. However, anesthesiologists need to be cautious about the potential risks until further evidence is accumulated.

SUPPLEMENTARY MATERIALS

Supplementary data containing Korean version of this article is available at https://doi.org/10.17085/apm.2019.14.2.117.

CONFLICTS OF INTEREST

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

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