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Effects of different Sugammadex doses on the Train of Four Ratio Recovery Progression during Rocuronium-induced Neuromuscular Blockade in the Rat Phrenic nerve - hemidiaphragm

Running title: Sugammadex doses & TOFR recovery pattern
Abstract

Background: In this study, we used an ex-vivo model to investigate the recovery pattern of both the train-of-four (TOF) ratio and first twitch tension of TOF (T1), and determined their relationship during recovery from rocuronium-induced neuromuscular blockade at various concentrations of sugammadex.

Methods: Tissue specimens of the phrenic nerve-diaphragm were obtained in 60 adult Sprague-Dawley rats. Each specimen was immersed in an organ bath filled with Krebs buffer solution and stimulated with the TOF pattern using indirect supramaximal stimulation at 20-second intervals. After a 30-minute stabilization period, rocuronium loading and booster doses were serially administered at 10-minute intervals in each sample until > 95% depression of T1 was confirmed. Specimens were randomly allocated to either the control group (washout) or to one of the five sugammadex concentration groups (SGX0.75, SGX1, SGX2, SGX4, and SGX8, respectively). Recovery from neuromuscular blockade was monitored using T1 and TOF ratio simultaneously until the recovery of T1 to >95% and that of TOF ratio to >0.9.

Results: Statistically significant intergroup differences were observed between the recovery patterns of T1 and the TOF ratio (TOFR, p<0.050), except between SGX2 and SGX4. TOFR/T1 values were maintained at nearly 1 in the control, SGX0.75, and SGX1 groups; however, those were exponentially decayed in the SGX2, SGX4, and SGX8.

Conclusions: Recovery of the TOF ratio may be influenced by the sugammadex dose, and TOF ratio of 1.0 may be achieved before full T1 recovery if administration of sugammadex exceeds that of rocuronium.

Keywords: Neuromuscular blockade; Neuromuscular blocking agent; Neuromuscular physiology; Rocuronium; Sugammadex.
Introduction

Sugammadex is a prime antagonist of aminosteroidal neuromuscular blocking agents (NMBAs), especially rocuronium; Before the introduction of sugammadex, however, the indirect mechanism of antagonism of the rocuronium-induced neuromuscular block has a ceiling effect, and is limited by the depth of the neuromuscular block at the time of reversal [1].

In the clinical setting, recovery of neuromuscular blockade is monitored through responses of the innervated muscle under indirect neuronal stimulation, particularly that of the ulnar nerve at the wrist level and the adductor pollicis muscle [2]. Patients with partial neuromuscular block usually show TOF and the TOF ratio of < 0.7. TOF ratio of >0.9 by mechanomyography or electromyography-type monitor and that of > 1.0 by acceleromyography-type monitor are considered as complete recovery [2]. However this definition was mostly established when the recovery of neuromuscular blockade was done by anticholinesterases. During blockade with nondepolarizing neuromuscular blocking agents (NMBA), TOF fade occurs as a result of the presynaptic cholinergic autoreceptors’ activity, which is influenced by concentrations of NMBA and ACh at the neuromuscular junction [3].

Anticholinesterase administration was the main method for antagonism of neuromuscular blockade based on the action mechanism of increase in the acetylcholine (ACh) level at the neuromuscular junctions, and thereby competitive binding with rocuronium at the postsynaptic nicotinic acetylcholine receptors (nAChR) [4,5]. In contrast, sugammadex-induced antagonism is irrelevant from the modulation of ACh release or cholinergic activity [6]. Sugammadex directly encapsulates and inactivates rocuronium in a 1:1 ratio at the molecular level [7,8]. As such, we assumed that TOF ratio recovery pattern by sugammadex might be different from those of anticholinesterase-induced recovery from neuromuscular blockade because the sugammadex has no effect on ACh release or metabolism at the neuromuscular junction [6]. During sugammadex-induced neuromuscular recovery, TOF ratio recovers to nearly 1.0 immediately after injecting sugammadex. However, patient
complaints of muscle weakness have sometimes been reported even when extubation is performed after securing the TOF ratio of >0.9. Indeed, it has been reported on several occasions that the TOF ratio recovery was preceded twitch recovery in clinical settings during sugammadex-induced neuromuscular recovery [9-11].

As such, we hypothesized that at different doses of sugammadex for reversal of neuromuscular blockade, rocuronium has different elimination rates from neuromuscular junction, and the different affinities of rocuronium to the pre- and post-synaptic AChR may affect recovery of both T1 and the TOF ratio, which may be hindered during anticholinesterase-induced recovery from neuromuscular blockade. The primary objective of this study was to assess recovery progressions of the T1 and TOF ratio after administration of different doses of sugammadex, and to compare the results obtained with those at spontaneous recovery; the secondary objective was to examine the inter-group differences of the recovery of the TOF ratio at the same T1 twitch tension during recovery from rocuronium-induced neuromuscular blockade.
Materials and Methods

Basic study design and sample preparation

The study protocol was approved by the Ethics Committee of the Laboratory of Animal Research, Asan Institute of Life Science (Seoul, Republic of Korea) on July 1, 2017 (Protocol No.2017-13-114). All animals were bred at constant ambient temperature of 22 °C under regular diurnal cycle, and food and water were supplied ad libitum. The phrenic nerve-hemidiaphragm tissues were immersed in Krebs buffer solution (120 mM NaCl, 2.5 mM CaCl2, 4.7 mM KCl, 1.2 mM MgSO4, 1.2 mM KH2PO4, 25 mM NaHCO3, and 11mM α-D-glucose) and maintained at 35°C with continuous bubbling of a mixture of 95% O2 and 5% CO2 to ensure tissue viability throughout the study period. The sizes and weights of the tissues were measured and compared between groups (Table 1). In all experiment, sugammadex and rocuronium (Bridion® and Esmeron®, respectively; MSD Korea, Seoul, Republic of Korea), and afaxalone (Alfaxan®; Careside Co. Ltd, Gyeonggi-do, Republic of Korea). was used.

Protocol for the main experiment

Sixty male Sprague-Dawley rats of average weight of 354.8 ± 36.9 g (range 298.5 – 438.9 g) were used in the study. The rats were anesthetized with intraperitoneal injection of 10 ml/kg of afaxalone. The thoracic cages were immediately isolated and the phrenic nerve-hemidiaphragm tissues were obtained. The tissues were fixed to a frame with electrodes and subsequently immersed in a 100-ml organ bath containing 75 ml of oxygenated Krebs buffer solution. For each specimen, the tendinous portion of the diaphragm was hooked to a Grass FT03 Force Transducer (Grass Technologies; West Warwick, RI, USA), and a resting tension of 40 mN was applied. The phrenic nerve was fixed to a platinum bipolar electrode and stimulated using a Grass S88 Stimulator (Grass Technologies; West Warwick, RI, USA). With regard to TOF simulation, supramaximal stimulation was delivered using a square wave pulse of 0.2 msec at 20-second intervals at 2 Hz for total 2 seconds’ duration. All
waveforms were displayed and stored using the PowerLab 4/26 data acquisition system (AD Instruments; Sydney, Australia) and LabChart 7 software (AD Instruments; Colorado Springs, CO, USA).

The phrenic nerve-hemidiaphragm tissues were randomly allocated to either a control group (washout) or one of the five groups of different sugammadex doses (0.75, 1, 2, 4, or 8 times equimolar doses of rocuronium to produce >95% T1 depressions; SGX0.75, SGX1 SGX2, SGX4, and SGX8, respectively); a random number was generated by using Microsoft Office Excel 2013 program. We sorted the six groups into two categories: high-dose group, sugammadex at ≥ 2 times the equimolar dose of rocuronium; low-dose group, sugammadex at the level of or less than the equimolar dose of rocuronium. Twitch tensions and TOF ratio were serially monitored during a 30 min-stabilization time. After the stabilization period, a 400-µg loading dose of rocuronium was added to the organ bath. Subsequently, 200-µg booster doses of rocuronium were added when the five consecutive T1 depressions were ≤ 3% of the previous T1 twitch tension, or 10 minutes after the previous dose. Booster dosing was stopped when T1 depression of ≥ 95% was achieved. The loading dose was set to the amount that produce no change of the T1 twitch tension but changes of the TOF ratio within 3% of that before the loading dose. Booster doses were set to the level of the first booster that produced a change of the T1 twitch tension, and the total number of boost administration was ≤ 10.

The study protocol is summarized in Fig 1.

The concentration of rocuronium required to obtain a reduction of T1 of > 95% was noted in the control and the five sugammadex groups. For the comparisons, first, rocuronium dose-responses were plotted and regression curves were obtained, and group-wise comparison of the values was performed. TOF ratios were obtained while monitoring the T1 depression, and the regression curves were compared among the groups. Second, intergroup progressions of the TOF ratios by % recovery of the T1 at the different sugammadex doses were compared among the groups.
Statistical analysis

The sample size was calculated based on the previous experiment and pilot study, which suggested that 10 samples per group were sufficient at $\alpha = 0.05$, power = 0.80, and a dropout rate of 10%. Results are expressed as mean $\pm$ standard deviation (SD). All doses are expressed as $\mu$M. Statistical analysis was carried out using SPSS Ver. 13.0 software (SPSS Inc., Chicago, IL, USA). Recovery data were plotted by fitting the nonlinear regression curves to the group data. The equation model was selected when the $R^2 > 0.8$ by using curve estimation at the SPSS Ver 13.0 To describe recovery of the T1 and TOF ratio, the following equation was used: $y = \Omega x + b$; where $y$ represents TOF ratio progression, $x$ represents T1 recovery, and $\Omega$ represents the slope of the regression curve ($R^2 = 0.87$).

For simultaneous group-wise comparison of the progression of recovery of the T1 and TOF ratio by time, the variable (TOFR/T1 product; which contained data of TOF ratio over T1 at specific time-point) was calculated using the following equations: $y = \lambda x$, or $y = \lambda^*1/x$, where $y$ and $x$ represent the TOFR/T1 product and time, respectively, while $\lambda$ represents the slope of the regression curve ($R^2 = 0.91, 0.83$ in the different groups). Different $\Omega$ and $\lambda$ values mean the speed of T1 recovery to $>95\%$, TOF ratio to $>0.9$, or speed of increment of decay of TOFR/T1 product. The mean group values of $\Omega$ and $\lambda$ were compared using the Mann Whitney U test. Statistical significance was accepted for a p-value of $<0.05$. 
**Results**

The specimen sizes and weights were similar in the six groups (Table 1). In the control, SGX0.75, and SGX1 groups, reappearance of the T1 before that of the TOF ratio (Fig. 2A, B, and C) and in sequence, those of the T2, T3, and T4 were observed. However, in the SGX2, SGX4, and SGX8 groups, simultaneous reappearance of the T1 and T4 was observed and the TOF ratio of $\geq 0.7$ was obtained from the start of recovery (Fig. 2D, E, and F). Intergroup comparison was conducted for the progression of the TOF ratio by T1 recovery. Based on the results in Fig. 2, the slopes ($\Omega$) of the control, SGX0.75, and SGX1 groups (Fig. 3A) were steeper than those of SGX2, SGX4, and SGX8. (Fig 3B) The combined T1 recovery and TOF ratio was expressed as a single variable (TOFR/T1 product), and the values of these variables were plotted versus time (Fig. 4). In the control, SGX0.75, and SGX1, regression curve was fitted using the following equation: $y = \lambda x$; where $y$ represents the TOFR/T1, $x$ represents the recovery time with 5% T1 recovery as the zero point, and $\lambda$ represents the slope (Fig. 4A). In these groups, no statistically significant differences of $\lambda$ were observed. In the SGX2, SGX4, and SGX8 groups, the regression curve was fitted using the following equation: $y = \lambda*1/x$, where the variables represent the same parameters as those for the equation, $y = \lambda x$. (Fig. 4B)
Discussion

This ex-vivo experiment demonstrates that the patterns of recovery of the TOF ratio of the SGX2, SGX4 and SGX8 groups were significantly different from those of the control, SGX0.75, or SGX1 groups.

During onset and recovery of neuromuscular blockade, the action of neuromuscular blocking agents (NMBAs) is determined by competitive binding of ACh and NMBAs to the postsynaptic nAChRs at the neuromuscular junctions [12]. The conventional strategy of reversal of the neuromuscular blockade involved the used of pharmacological tools to increase ACh levels, and thereby increased binding of the agent at the postsynaptic nAChR by inhibiting acetylcholinesterase in the region of the postsynaptic nAChRs. In contrast, sugammadex binds the ‘guest’ molecules in 1:1 ratio and chelate those; thus, sugammadex has no effects on the release and levels of ACh at the neuromuscular junctions during its action to reverse the neuromuscular blockade [6]. Several receptors are mediate the release and modulation of the ACh at neuromuscular junctions. In general, ACh release on the variable neuronal signal frequency is modulated through fine tuning of several receptors at the presynaptic membrane by the amounts of released molecules; ACh and adenosine [13]. TOF ratio is the most common and valuable mode during the neuromuscular monitoring, which is performed by four time of 2Hz stimulation [2]. At this low frequency stimulation of $\leq 5$ Hz, presynaptic muscarinic M$_1$AChRs and adenosine A$_1$ receptors are predominant and modulate release of adequate amount of ACh [13,14]. The ACh molecules transmit the neuronal signal to the post synaptic junction via the postsynaptic nAChR, and affect the presynaptic neuronal nAChRs, which have a positive feedback on the ACh release. During nondepolarizing N MBA-induced neuromuscular blockade, TOF fade and TOF ratio are considered as phenomena related to the presynaptic neuronal nAChRs [3,15,16]. A recent study reported that these phenomena are related to the postsynaptic receptor type [16]; those authors conducted an in-vivo experiment, the TOF fade occurred only under blockade of the
postjunctonal nAChRs with α-bungarotoxin (α-BTX) or α-conotoxin, but not under that of the presynaptic nAChR with specific blockers alone. Moreover, co-administration of α-BTX or α-conotoxin during presynaptic nAChR blockade resulted in a prominent TOF fade. Other studies reported that the presynaptic nAChR was a regulatory factor of the amount of ACh per neural stimulus [16,17]. Faria et al. [16] reported that blockade with dihydro-β-erythrodine (DhβE) was effective to decrease the level of prejunctional ACh release, which was consistent with the findings from another study using a cell culture model [17]. Decrease of ACh release cause the onset of a neuromuscular blockade, and the onset was slow under blockade of the postjunctonal nAChRs only, but accelerated under that of prejunctional AChRs with DhβE [18]. Therefore, the postsynaptic and presynaptic actions of NMBA on the nAChRs affect the efficacy of neuromuscular blockade [19]. Considering these results, the relationship between pre- and postsynaptic receptor function is an important determinant of TOF fade and TOF ratio. Conventional strategy for reversal of neuromuscular block with anticholinesterase administration does not have capability to eliminate the NMBA at the neuromuscular junction, leading to prolonged neuromuscular blocking activities after the initial administration of the anticholinesterase. TOF fade and TOF ratio are prominent for the duration of NMBA action at the postsynaptic nAChRs. Sugammadex does not have the ability to inactivate the neuromuscular blockade at the neuromuscular junction [6,8], but causes immediate reduction of the NMBA concentration outside the neuromuscular junction. This causes rapid transfer of NMBAs, due to the concentration gradient across the neuromuscular junction [6]; thus, reduction of NMBA concentration and their activities at the neuromuscular junction attenuates the TOF fade and increases the TOF ratio, which explains the results of our ex-vivo experiment. We sorted the six groups into two categories to enable clear description and easy understanding for the readers: high-dose group, sugammadex at ≥ 2 times the equimolar dose of rocuronium; low-dose group, sugammadex at the level of or less than the equimolar dose of rocuronium. In the high-dose groups, rapid drop of
rocuronium concentration in the Krebs buffer solution allowed rapid exit of rocuronium molecules from the neuromuscular junction, and thereby, achieved attenuation and disappearance of TOF fade even in the early recovery period; whereas in the low-dose group, rocuronium molecules remained at the neuromuscular junction under sugammadex, and TOF fade and TOF ratio were maintained until adequate decrease of rocuronium, due to the concentration gradient across the neuromuscular junction. Therefore, we obtained similar results in the low dose groups to those of spontaneous recovery. In the Fig. 3A, as TOF ratio recovered in parallel with T1 recovery and showed prominent TOF fade in low dose group, y axis values (TOF ratio) often start from low and converge to 1. On the contrary, TOF fade was attenuated and TOF ratio showed high even in the early recovery of T1 in high dose group. As such, the slope of the regression curve, Ω, of low dose groups were steeper than those of high dose groups. In the Fig. 4, we demonstrated the simultaneous progression of % T1 recovery and TOF ratio by time. We generated one value (TOFR/T1 product) by using T1 recovery and TOF ratio, which were converted by % value. In the low dose group, as the T1 recovery preceded TOF ratio, TOFR/T1 was ≤ 1. As such, it was well represented by the equation of y = λx. In contrast, those in the high dose group were ≥ 1 and showed decay pattern, because TOF fade was attenuated and TOF ratio showed higher than T1 recovery.

Our study has several limitations. First, we conducted an ex-vivo experiment and disregarded the pharmacokinetic component of rocuronium action, since the phrenic nerve-hemidiaphragm tissue specimens were examined in the organ bath filled with Krebs buffer solution. The overall recovery time to >95% T1 was > 30 minutes in the low dose of group, and was shortened to < 15 minutes in the high dose of sugammadex group. In the clinical settings, however, the recovery time is ≤ 5 minutes [20,21] considering the dose of SGX used. Reports have indicated that administration of sugammadex 2 mg/kg for moderate neuromuscular block and 4 mg/kg for deep neuromuscular block achieved recovery time of ≤ 3 and 5 minutes to the TOF ratio of > 0.9, respectively [21-23]. The
discrepancy in results of the recovery pattern between the in-vivo and ex-vivo approaches suggested that the result should be interpreted differently considering that the NMBA-induced neuromuscular blockade is fully and rapidly recovered in a clinical settings, which might hindered our results and made it disappeared without noticed. As such, although the postoperative residual block is still an annoying problem, even in the new era of SGX-induced recovery from a neuromuscular block [24,25], we should cautiously judge the clinical implications of the findings of the current ex-vivo study.

Second, this study focused on the nicotinic AChR subtype at the presynaptic and postsynaptic junction. Sugammadex has no action at the neuromuscular junction, and rocuronium has no action on the other receptors at the neuromuscular junction; this study only focused on the nAChRs, which are the primary action site of ACh and NMBAs during neuromuscular block. However, as we described above, several receptors modulate ACh release in different environments [13,14], and we tried to maintain a consistent environment and neural stimulation throughout the study period. We used TOF stimulation of four times of 2-Hz supramaximal stimulation, which is the same mode used for the clinical neuromuscular monitoring. The method of obtaining the phrenic nerve-hemidiaphragm tissue specimen had the disadvantage of temporary hypoxia and damage to the tissue specimen during preparation that involves cutting-out of the thorax from the rat. To minimize these drawbacks, we made attempts to oxygenate the rat, and remove the thorax immediately after the aorta was cut, and performed trimming of the specimen in a petri dish containing Krebs buffer solution aerated with a mixture of 95% O₂ and 5% CO₂.

In conclusion, the high dose of sugammadex rapidly reversed the neuromuscular block induced by rocuronium. However, the recovery pattern of the TOF ratio differ according to the dose of sugammadex, especially, at the condition that the amount of sugammadex is high enough comparing with that of rocuronium used. In that condition, high values of TOF ratio may be achieved even without full recovery of the T1 twitch tension. The TOF ratio alone might insufficient to indicate full
recovery of the neuromuscular blockade without full recovery of the T1 twitch. Therefore, clinicians should use an appropriate dose of sugammadex and full recovery of both the TOF ratio and T1 twitch.
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Table 1. Characteristics of the rats and tissue specimens

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SGX</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.75 (n=10)</td>
<td>1 (n=10)</td>
</tr>
<tr>
<td>BW (g)</td>
<td>296.43 ± 13.65</td>
<td>303.72 ± 16.89</td>
</tr>
<tr>
<td>wWt (mg)</td>
<td>±11.91</td>
<td>±17.89</td>
</tr>
<tr>
<td>Size (cm²)</td>
<td>1.98 ±0.09</td>
<td>1.84 ±0.09</td>
</tr>
</tbody>
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Data are expressed as the mean ± SD. BW: body weight of the rat. wWt: wet weight of the hemidiaphragm. Size: size (width x length) of the hemidiaphragm. There were no statistically significant differences between the groups (p >0.05).
Enrolled 60 Sprague-Dawley rats;  
Breded at 22°C under diurnal cycle  
Food & water ad libitum

Rat anesthetized  
Phrenic nerve-diaphragm tissue harvested

Allocated to one of different groups;  
washout, SGX0.75, 1, 2, 4, 8 groups

Stabilization in the oxygenated Krebs solution  
for 30 min.

Stimulation mode;  
TOF with 20 sec interval

ROC dose-response;  
Loading dose; 400 µg  
Booster dose; 200 µg

Administration interval;  
10 min pr  
consecutive T1 depression <3%  
Booster dose;  
repeated administration until T1 >  
95% depression

SGX administration;  
Allocated doses of SGX 0, 0.75, 1, 2, 4, 8 times of equimolar doses of ROC used

Fig. 1. Study protocol. SGX: sugammadex; ROC: rocuronium.
Fig. 2. Recovery progression of the T1 and TOF ratio in each group: A) Control (washout); B) SGX0.75; C) SGX1; D) SGX2; E) SGX4; F) SGX8. Recovery of the TOF ratio (red triangle symbol, red line) in accordance with the T1 recovery (blue circle, blue line) was detected after T1 spontaneous recovery or low dose sugammadex (A, B, and C). At the high-dose sugammadex (D, E, and F), however, the TOF fade was attenuated or undetected at the first TOF ratio. SGX: sugammadex; TOF: train-of-four stimulation; T1: first twitch tension of the TOF; TOFR: TOF ratio.
Fig. 3. T1 vs TOF ratio progression in all groups. The nonlinear regression equation was estimated and selected at $R^2$ of > 0.7; the differences of slope were compared. There were no statistical differences between the control, SGX0.75, and SGX1. In the SGX2, SGX4, and SGX8 groups, the slopes were lower as compared to those in the other group. Omega: slope constant for each regression curve; SGX: sugammadex; TOF: train-of-four; T1: first twitch tension of the TOF; TOFR: TOF ratio.
Fig. 4. Relationship between the T1 and TOF ratio was converted to a variable (TOFR/T1 product) and expressed as a function of time. A) TOFR/T1 products of control (filled circle symbol, solid line), SGX0.75 (diamond symbol, dash line), and SGX1 (triangle symbol, dash-dot line) groups. B) TOFR/T1 products of SGX2 (open circle symbol, solid line), SGX4 (triangle symbol, dash line), and SGX8 (square symbol, dash-dot line) groups. The regression equations of SGX0.75 and SGX1 were...
in accordance with those of the control group (linear pattern; \( y = \lambda * x + b \)); whereas, that in the SGX2, SGX4 and SGX8 groups, the most suitable equation was expressed by exponential decay (\( y = \lambda * \frac{1}{x} + 1 \)), with significant difference as compared to those of the control, SGX0.75, and SGX1 groups.

Lambda: slope constant for each regression curve; SGX: sugammadex; TOF: train-of-four; T1: the first twitch tension of TOF; TOFR: TOF ratio.