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ORIGINAL ARTICLE

Comparative potentiating effects of remimazolam, propofol and sevoflurane on rocuronium-induced neuromuscular block: a randomized controlled trial

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Abstract

Background Remimazolam is a new type of ultra-short-acting benzodiazepine. The aim of this study was to investigate the effects of remimazolam, propofol and sevoflurane anesthesia on rocuronium-induced neuromuscular block.

Methods Ninety-nine consenting patients were randomly assigned to a remimazolam group (R-group), sevoflurane group (S-group), or propofol group (P-group). Train-of-four (TOF) responses evoked on the abductor digiti minimi muscle to ulnar nerve stimulation following bolus administration of 0.9-mg/kg rocuronium were monitored with electromyography-based neuromuscular monitor. The primary outcomes were times from administration of rocuronium to first reappearance of post-tetanic count (PTC). Free plasma concentrations of rocuronium were concurrently measured at these events.

Results Ninety patients were analyzed. No significant differences were seen in time to first PTC among the three groups. Mean (± standard deviation) and median (inter-quartile range) times for the reappearance of TOF counts 1 and 2 were significantly prolonged in S-group [50.7 ± 13.9 min, $P = 0.043$ and 61.6 (54.3–78.0) min, $P = 0.020$, respectively], when compared with P-group [42.6 ± 10.3 min and 52.9 (45.4–58.8) min, respectively]. However, no significant differences were seen between S-group and R-group. Median (inter-quartile range) free plasma concentration of rocuronium measured at first PTC was significantly lower in R-group [1255 (1126–1717) ng/mL] than in P-group [1717 (1592–1961) ng/mL, $P = 0.031$].

Conclusions These results suggest that the potentiating effects of remimazolam on rocuronium-induced neuromuscular block are weaker than those of sevoflurane and similar to those of propofol.

Keywords Remimazolam · Rocuronium · Neuromuscular block · Benzodiazepine · Neuromuscular monitoring

Introduction

Remimazolam is a new type of ultra-short-acting benzodiazepine anesthetic drug [1] that acts on γ-aminobutyric acid type A ($GABA_A$) receptors. With a structure similar to that of midazolam, remimazolam is a high-affinity, selective ligand for the benzodiazepine binding site on the $GABA_A$ receptor but shows no clear selectivity for other sites [2]. Diazepam, another benzodiazepine, has a muscle-relaxing effect by binding to benzodiazepine 1 and benzodiazepine 2 binding sites and increasing the affinity of γ-aminobutyric acid for $GABA_A$ receptors [3]. The function of binding to benzodiazepine 2 binding sites is specifically important for skeletal muscle relaxation [4]. However, no reports appear to have investigated the potentiating effects of remimazolam on neuromuscular block produced by rocuronium. In addition, remimazolam has the protein-binding rate of 92% and binds to predominantly serum albumin [1], which may affect the protein binding of rocuronium and lead to greater amounts of free, non-protein bound rocuronium available.

It is well known that sevoflurane prolongs the duration of action of non-depolarizing neuromuscular blocking agents [5]. The times to reappearance and recovery of the first response in the train-of-four (TOF) stimulation after a single dose of rocuronium is thus prolonged during sevoflurane anesthesia compared with propofol anesthesia [5–7].

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Remimazolam has been increasingly used for general anesthesia in recent years, but there are few reports of interactions with neuromuscular blocking agents. Knowledge of the risk of prolonged neuromuscular blockade during general anesthesia is important for clinical safe management. Here, we hypothesized that remimazolam would augment rocuronium-induced neuromuscular block. The purpose of this study was to assess the influence of remimazolam on rocuronium by comparison with the influences of sevoflurane and propofol on rocuronium-induced neuromuscular block. In addition to neuromuscular monitoring with an AF-201P™ electromyography (EMG)-based neuromuscular monitor (Nihon Kohden, Tokyo, Japan), we also used the total and free plasma concentration and the protein-binding property of rocuronium as an evaluation method.

Methods

Study design

This study was approved by Nihon University Itabashi Hospital Certified Clinical Research Review Board (Itabashi-ku, Tokyo, Japan) on March 1st, 2023 (RK-230214-2, Chairperson Prof Hisamitsu Ishihara) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrolled at the University Hospital Medical Information Network (registration number UMIN000050637, principal investigator: Sato Hanae, Date of registration: March 20th, 2023). The study followed the CONSORT statement. We followed the pharmacodynamic studies of neuromuscular blocking agents III [8].

Study population

Patients aged 20–65 years old undergoing elective surgery under general anesthesia were enrolled in the study. We excluded patients with American Society of Anesthesiologists physical status class > III, a history of allergic reactions to neuromuscular blocking agents, hepatic or renal disorders, neuromuscular diseases, or benzodiazepine regular users. In addition, patients receiving medications known to affect neuromuscular function were excluded.

Randomization

The study was an open-label, single-center, randomized controlled trial. Patients were randomized in a 1:1:1 ratio to a remimazolam group (R-group), propofol group (P-group) and sevoflurane group (S-group). Group assignments were made using opaque envelopes before study commencement by a member of the clinical research department not involved in recruitment, coordination, or data collection.

Perioperative management

After arrival in the operating room, standard monitors (electrocardiogram, non-invasive blood pressure, pulse oximetry and bispectral index monitors) were applied to all patients. Intravenous access was established on the forearm or in the dorsal venous network of the hand. After preoxygenation, R-group ($n = 33$) underwent induction of anesthesia with fentanyl at 1–2 μg/kg and continuous infusions of remifentanil at 0.1–0.5 μg/kg/min and remimazolam at 12 mg/kg/h. Thereafter, the infusion rate of remimazolam was decreased to 1–2 mg/kg/h, targeting a bispectral index of 40–60. In P-group ($n = 33$), anesthesia was induced with fentanyl at 1–2 μg/kg, continuous infusion of remifentanil at 0.1–0.5 μg/kg/min, and target-controlled infusion of propofol at 3–4 μg/mL by target controlled infusion pump (TE-371; Terumo, Tokyo, Japan), targeting a bispectral index of 40–60. In S-group ($n = 33$), anesthesia was induced with fentanyl at 1–2 μg/kg, continuous infusion of remifentanil at 0.1–0.5 μg/kg/min, and intravenous propofol at 2 mg/kg, followed by controlled ventilation with 1.5–2.0% sevoflurane in oxygen, targeting a bispectral index of 40–60. An upper body forced-air warming device (3 M™ Bair Hugger™; 3 M Japan, Tokyo, Japan) was used throughout surgery to ensure that core and peripheral temperatures were kept above 35 ℃ and 32 ℃, respectively. End-tidal carbon dioxide was maintained at 35–40 mmHg.

Neuromuscular management

The AF-201P™ was applied on the arm opposite intravenous access after induction of anesthesia and prior to rocuronium administration. After cleaning the skin where the sensor was to be attached using alcohol wipes, single-use surface electrodes (NM-345Y™; Nihon Kohden) for the AF-201P™ were placed over the ulnar nerve and abductor digiti minimi muscle, in accordance with the instructions from the manufacturer. After application and calibration of the device, TOF measurements were repeated every 15 s.

Stable baseline TOF responses were confirmed for a few minutes, then rocuronium was administered at 0.9 mg/kg in a running infusion. Post-tetanic count (PTC) stimulations were performed every 3 min until first appearance of the PTC response (first PTC). To prevent facilitation of TOF recovery [9], PTC stimulation was stopped after first PTC responses were observed. Spontaneous recovery of rocuronium-induced neuromuscular block was taken as observation of TOF counts of 1 and 2. When three consecutive TOF counts of 2 were observed, sugammadex was administered at 2 mg/kg to achieve reversal to a TOF ratio of 0.9.

Plasma concentration of rocuronium assay

We collected 2 mL of venous blood at the time of first PTC and at TOF counts of 1 and 2. The blood samples were centrifuged and the plasma maintained at – 80 ℃ until assay. The total plasma concentration of rocuronium was measured by high-performance liquid chromatography (HPLC) and free plasma concentration of rocuronium by HPLC after ultracentrifugation. ACQUITY UltraPerformance LC™ and Xevo TQ-S micro tandem quadrupole mass spectrometer (Waters TA Instruments, New Castle, DE, USA) was used for HPLC. For free plasma concentration of rocuronium using ultracentrifugation, a himac CS100GXL ultracentrifuge with a RP-100AT2 rotor (HITACHI Ltd, Tokyo, Japan) was used at 436,000×*g* for 3.25 h at 10 ℃ to collect the middle layer of the plasma. The assay device showed a linear relationship between the drug concentration and peak height in a range of 10–5000 ng/ml. The correlation coefficients were greater than 0.999. The intra-day relative error of 25, 2500, and 5000 ng/ml rocuronium were 3.9% (co-efficient of variation, 6.3%), − 4.9% (co-efficient of variation, 2.2%), and 1.7% (co-efficient of variation, 1.2%), respectively. The inter-day relative error of 25, 2500, and 5000 ng/ml rocuronium were 6.4% (co-efficient of variation, 4.1%), − 1.4% (co-efficient of variation, 2.7%), and 5.2% (co-efficient of variation, 2.7%), respectively. The protein-binding property of rocuronium were determined as the free plasma concentration of rocuronium ratio to the total plasma concentration of rocuronium.

Study outcomes

The primary outcomes of this study were the times from administration of rocuronium to first reappearance of PTC. Secondary outcomes were the times from administration of rocuronium to TOF counts 1 and 2, time from administration of sugammadex 2 mg/kg to a TOF ratio of 0.9, and the total and free plasma concentrations and protein-binding property of rocuronium at first PTC and TOF counts of 1 and 2.

Sample size and statistical analysis

To estimate sample size, we used previous data on the first appearance of PTC (27.3 [8.9] min) as the mean [standard deviation] time for the first appearance of PTC following administration of rocuronium at 0.9 mg/kg [10]. We considered a 30% difference in first reappearance time (a difference of approximately three cycles of PTC stimulation) observed between the R-group, P-group and S-group as clinically significant. To provide adequate power (80%) with an alpha error of 5%, we calculated that 75 patients would need to be included in this study. We thus set a sample size of 99 patients in anticipation of some loss to dropout.

Statistical analysis

We used the Kolmogorov–Smirnov test and F test to determine whether data showed normal distributions. The Tukey multiple comparison test after one-way analysis of variance was used for parametric data and the Steel–Dwass multiple comparison test after the Kruskal–Wallis test was used for non-parametric data to analyze differences in outcomes between the three groups. All statistical analyses were performed using EZR (Easy R) version 1.64 (Jichi Medical University Saitama Medical Centre, Saitama, Japan) [11]. Values of $P < 0.05$ were considered indicative of statistical significance.

Results

Descriptive data

A total of 99 patients were enrolled in this study between March 2023 and November 2023. Nine patients were excluded because of dislodgement of the sensor ($n = 3$), unstable nerve stimulation due to postural changes ($n = 5$) and withdrawal of consent to participate ($n = 1$). As a result, 90 patients were included in the final analyses (Fig. 1). No significant differences in patient characteristics were evident among the three groups (Table 1).

Primary results

Primary outcomes of the study are shown in Table 2. No significant difference was seen in time to first PTC from rocuronium administration among the three groups. (P-group 26.1 min, S-group 31.6 min, R-group 35.1 min) ($P = 0.513$; S-group vs R-group, $P = 0.584$; S-group vs P-group, $P = 0.088$; R-group vs P-group).

Secondary results

Secondary outcomes of the study are also shown in Table 2. Recovery times from rocuronium administration to TOF counts of 1 and 2 were significantly longer in S-group than in P-group, but no significant differences were noted between S-group and R-group or between P-group and R-group. However, the total and free plasma concentration of rocuronium measured at first PTC was significantly lower in R-group than in P-group, with no significant differences between S-group and R-group or between P-group and S-group. In addition, total and free plasma concentrations of rocuronium measured at TOF counts of 1 and 2 were significantly lower in S-group than in P-group, while no significant differences were found between S-group and R-group or between P-group and R-group. No significant differences between any groups were

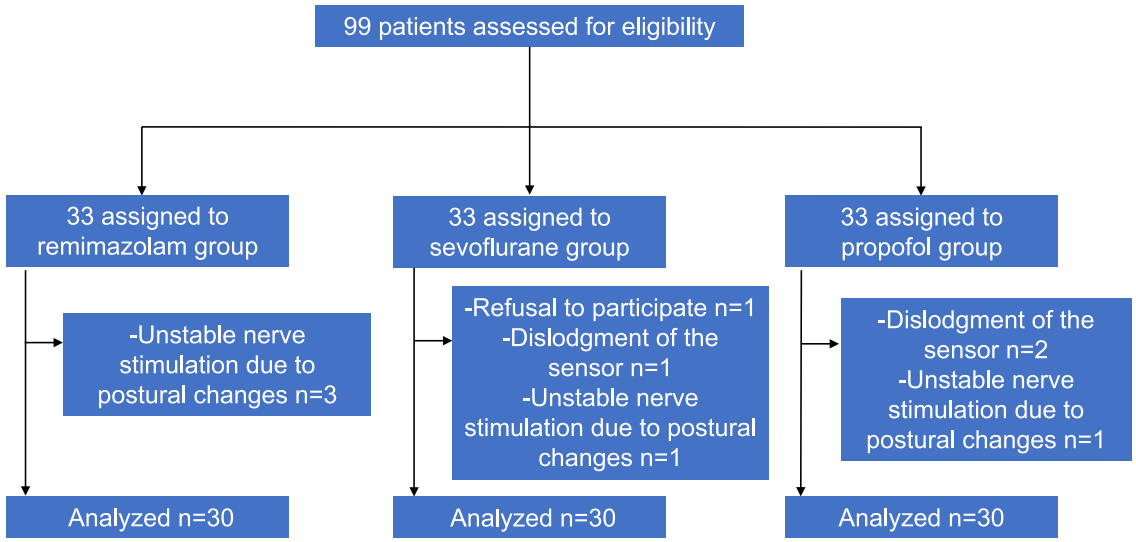

Fig. 1 Flowchart of the study

Table 1 Subject characteristics

	All subjects ($n=90$)	Propofol ($n=30$)	Remimazolam ($n=30$)	Sevoflurane ($n=30$)
Patient characteristics				
Female, *n* (%)	42 (47)	12 (40)	16 (53)	14 (47)
Age (yr)	44 ± 13	40 ± 13	47 ± 12	43 ± 12
Weight (kg)	68 ± 15	68 ± 14	69 ± 15	69 ± 17
BMI (kg/m^2)	24 ± 4.3	23 ± 3.6	25 ± 4.6	25 ± 4.6
ASA (I/II/III)	33 / 57 / 0	10 / 20 / 0	11 / 19 / 0	12 / 18 / 0
Type of surgery				
Orthopedic, *n* (%)	45 (50.0)	12 (40.0)	15 (50.0)	18 (60.0)
Otorhinolaryngology, *n* (%)	19 (21.1)	11 (36.7)	3 (10.0)	4 (13.3)
Oral surgery, *n* (%)	9 (10.0)	5 (16.7)	2 (6.7)	3 (10.0)
Urology, *n* (%)	6 (6.7)	0 (0)	5 (16.7)	1 (3.3)
Other, *n* (%)	11 (12.2)	2 (6.7)	5 (16.7)	4 (13.3)
Preoperative blood sampling data				
TP (g/dL)	7.3 ± 0.4	7.3 ± 0.4	7.2 ± 0.4	7.3 ± 0.4
Alb (g/dL)	4.5 [4.3–4.8]	4.7 [4.5–4.8]	4.4 [4.2–4.8]	4.4 [4.3–4.7]

Data expressed as number (%), mean ± SD, or median [interquartile range]

Alb albumin, *TP* total protein

seen in the protein-binding property of rocuronium measured at first PTC and TOF counts of 1 or 2. Recovery times from administration of sugammadex to a TOF ratio of 0.9 did not differ among the three groups, and in all patients TOF ratio > 0.9 could be observed.

Discussion

To the best of our knowledge, this represents the first randomized control trial to investigate the potentiating effects

Table 2 Primary and secondary outcomes of this study

	Propofol	Remimazolam	Sevoflurane
Supramaximal current (mA)	33.0 [27.0–44.3]	30.0 [24.0–42.0]	30.0 [24.8–39.0]
Baseline compound muscle action potential (mV)	13.3 ± 3.2	13.9 ± 3.9	13.8 ± 3.2
Onset time (s)	106 [91–122]	92 [73–118]	99 [68–126]
Time to first PTC (min)	26.1 [23.2–27.9]	35.1 [25.8–43.5]	31.6 [20.8–38.4]
Time to TOF count of 1 (min)	42.6 ± 10.3	47.7 ± 13.3	50.7 ± 13.9 *
Time to TOF counts of 2 (min)	52.9 [45.4–58.8]	54.4 [46.8–66.5]	61.6 [54.3–78.0] **
Time to reach TOF ratio ≥ 0.9 after the reversal with sugammadex (s)	103 [86–120]	106 [91–135]	92 [80–120]
Total plasma concentration of rocuronium			
First PTC (ng/mL)	2436 [2270–2824]	1819 (1687–2315) #	1883 (1664–3138)
TOF count of 1 (ng/mL)	1443 [1244–1662]	1413 [1025–1608]	1269 [1014–1383] ##
TOF counts of 2 (ng/mL)	1116 ± 257	968 ± 264	877 ± 187 ###
Free plasma concentration of rocuronium			
First PTC (ng/mL)	1717 [1592–1961]	1255 [1126–1717] +	1320 [1073–2102]
TOF count of 1 (ng/mL)	1020 [896–1146]	986 [722–1097]	844 [665–930] ++
TOF counts of 2 (ng/mL)	744 [695–820]	645 [519–821]	618 [557–663] +++
Protein binding property of rocuronium			
First PTC (%)	31.3 ± 4.6	29.9 ± 3.5	30.2 ± 5.7
TOF count of 1 (%)	30.3 ± 4.5	31.7 ± 4.2	32.1 ± 5.5
TOF counts of 2 (%)	30.3 ± 4.2	31.4 ± 3.0	31.3 ± 4.6

Results are expressed as mean ± SD, or median [inter-quartile range]. We used the Tukey multiple comparison test after one-way analysis of variance for parametric data and the Steel–Dwass multiple comparison test after the Kruskal–Wallis test for non-parametric data

TOF train-of-four, *PTC* post-tetanic count, *CI* confidence interval

*$P = 0.043$, 95% CI [0.21–15.97] *vs* propofol

**$P = 0.020$ *vs* propofol

#$P = 0.011$ *vs* propofol

##$P = 0.004$ *vs* propofol

###$P = 0.001$ 95% CI [− 391.10 to − 87.13] *vs* propofol

+$P = 0.031$ *vs* propofol

++$P < 0.001$ *vs* propofol

+++$P < 0.001$ *vs* propofol

of remimazolam on rocuronium-induced neuromuscular block and to compare the effects of remimazolam with those of propofol and sevoflurane. The results of this study demonstrated that the effects of remimazolam on the duration of action of rocuronium to reach first PTC and TOF counts of 1 and 2 did not differ from the effects of propofol and sevoflurane. While there were significant differences in times to recover to TOF counts of 1 and 2 between sevoflurane and propofol anesthesia, but not, remimazolam and propofol anesthesia. It would be therefore reasonable to understand that the potentiating effects of remimazolam on rocuronium-induced neuromuscular block is weaker than sevoflurane and similar to propofol. However, the fact that total and free plasma concentrations of rocuronium at the time to detect first PTC was significantly lower in R-group than P-group may partly show a somewhat stronger neuromuscular effect of remimazolam. It is therefore likely that the significant difference in plasma concentration of rocuronium during remimazolam anesthesia had no clinical impact probably because of below the threshold levels and redistribution effects at the neuromuscular junction. In this regard, further investigation is needed.

We have previously reported that the potentiating effects of midazolam, a typical benzodiazepine derivative, on vecuronium-induced neuromuscular block were significantly weaker than those of sevoflurane and similar to those of propofol in clinical settings [5]. On the other hand, midazolam has been shown to significantly prolong the durations of action of vecuronium and atracurium, compared with diazepam [12]. An animal study also showed that midazolam had dose-dependent enhancing effects on neuromuscular block induced by vecuronium and tubocurarine [13]. In addition, supratherapeutic concentrations of midazolam could potentiate the action of rocuronium by increasing

adenosine concentrations, [14] resulting in depression of quantal acetylcholine release from motor nerve terminals [15, 16]. Since remimazolam is given by continuous infusion with higher clinical doses than midazolam, remimazolam may much more strongly inhibit prejunctional neuromuscular transmission. This idea is supported by the present results, which show that remimazolam minimized total and free plasma concentration of rocuronium at first PTC.

As seen in previous studies, our study also demonstrated that sevoflurane had a marked inhibitory effect and prolonged recovery times from rocuronium administration to TOF counts of 1 and 2 [5, 6, 17]. The fact that total and free plasma concentrations of rocuronium measured at TOF counts of 1 and 2 were significantly lower with sevoflurane than with propofol shows a pharmacodynamic effect of sevoflurane on rocuronium-induced neuromuscular block. However, no significant differences were seen in the time to observation of first PTC or the total and free plasma concentration of rocuronium at the time of first PTC appearance. The plasma concentration of sevoflurane presumably does not immediately reach equilibrium with the neuromuscular junction because inhalation of sevoflurane for at least 30 min is needed to achieve stable potentiating effects on neuromuscular block [18].

Rocuronium is an amino steroid compound and approximately 40% binds to plasma proteins [19]. The free rocuronium that remains unbound to proteins can exert neuromuscular blocking effects. On the other hand, the protein-binding rates of propofol and remimazolam have been reported as 97–99% [20] and approximately 92% [1], respectively. Drugs having such high degrees of protein binding may displace coadministered drugs from their binding sites to plasma proteins. This would lead to greater amounts of free, non-protein bound rocuronium available for distribution to the neuromuscular junction. As such drug interactions could result in augmentation of the rocuronium-induced neuromuscular blockade, we measured and compared the protein-binding rates of rocuronium in each group. However, the protein-binding rates of rocuronium did not differ among the three groups. Gray and colleagues hypothesized that phenytoin with an 80% protein-binding rate may augment vecuronium-induced neuromuscular block by increasing the concentration of free active drug after displacing vecuronium from protein-binding sites [21]. Conversely, Spacek and colleagues argued that acute administration of phenytoin augments rocuronium-induced neuromuscular block without influencing the extent of rocuronium protein binding [22]. This discrepancy of the results may arise from differences in the protein-binding properties of vecuronium (90% [21]) and rocuronium (42% [19]). The effect of displacing rocuronium from albumin may thus be less, when compared to vecuronium. In addition, it is unlikely that remimazolam would affect the dissociation of rocuronium from the protein, given that the number of molecules of the drug is considerably smaller than that of albumin.

Our study showed several limitations that should be kept in mind when interpreting the results. First, the effects of remimazolam on prolonging recovery times from rocuronium administration to first PTC and TOF counts of 1 and 2 were unremarkable. If the present examinations had been performed in elderly patients who were more susceptible to the effects of neuromuscular block induced by rocuronium, [7] the effects of remimazolam may have been significantly increased. Further investigation is warranted to determine the potentiating effects of remimazolam on rocuronium-induced neuromuscular block with age. Second, we did not compare the recovery times to the shallow and minimal neuromuscular block that may be easy to detect influence of anesthetics. In this study, we preferred to evaluate the facilitated recovery with sugammadex. Further investigation is needed to determine the effects of remimazolam on the TOF ratios during rocuronium-induced shallow and minimal neuromuscular block. Third, the involved mechanism of neuromuscular effects of remimazolam is unclear and may act at outside the neuromuscular junction. Despite adequate reversibility of sugammadex was observed in the present study, we should pay attention to postoperative patient's behavior and motor function after using remimazolam. Fourth, this study had an open-label design, which may have led to measurement bias, but all neuromuscular assessments were objectively monitored by EMG based neuromuscular monitor, minimizing the influence of subjective assessments.

In conclusion, the results of this study showed that the potentiating effects of remimazolam on rocuronium-induced neuromuscular block are weaker than those of sevoflurane and similar to those of propofol in clinical settings. It is therefore suggested that changes in duration of the action of rocuronium with different anesthetics should be objectively evaluated to adequately manage neuromuscular block.

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Author contributions Experiment design: TI, HS, ST, and TS. Data collection: TI, HS, MY, OK, MY, MM, AD and ST. Data analysis: TI, ST, and TS. Discussion of data: TI, ST, and TS. Writing of paper: TI and TS. Review of paper: ST and TS. Study supervision: TS. All authors read and approved the final manuscript.

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Data availability All data relevant to the study are included in the article.

Declarations

Conflict of interest Takagi S has received speaker fees from Nihon-Kohden, Inc, Japan. Itaya T has received speaker fees from Mundip-

harma Inc, Japan. Sato H, Kitajima O, Doshu-Kajiura A, Matsui M, Yumoto M, Yamamoto M and Suzuki T have no competing interests.

References

1. Kim KM. Remimazolam: pharmacological characteristics and clinical applications in anesthesiology. Anesth Pain Med (Seoul). 2022;17:1–11.
2. Hu Q, Liu X, Wen C, Li D, Lei X. Remimazolam: an updated review of a new sedative and anaesthetic. Drug Des Devel Ther. 2022;16:3957–74.
3. Peck J, Urits I, Crane J, McNally A, Noor N, Patel M, Berger AA, Cornett EM, Kassem H, Kaye AD, Viswanath O. Oral muscle relaxants for the treatment of chronic pain associated with cerebral palsy. Psychopharmacol Bull. 2020;50:142–62.
4. Sanger DJ, Benavides J, Perrault G, Morel E, Cohen C, Joly D, Zivkovic B. Recent developments in the behavioral pharmacology of benzodiazepine (omega) receptors: evidence for the functional significance of receptor subtypes. Neurosci Biobehav Rev. 1994;18:355–72.
5. Suzuki T, Munakata K, Watanabe N, Katsumata N, Saeki S, Ogawa S. Augmentation of vecuronium-induced neuromuscular block during sevoflurane anaesthesia: comparison with balanced anaesthesia using propofol or midazolam. Br J Anaesth. 1999;83:485–7.
6. Lowry DW, Mirakhur RK, McCarthy GJ, Carroll MT, McCourt KC. Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia. Anesth Analg. 1998;87:936–40.
7. Takagi S, Kitajima O, Yamamoto M, Matsui M, Suzuki T. Potentiation by sevoflurane of rocuronium-induced neuromuscular block is greater in older than younger adult patients: a randomised controlled trial. Br J Anaesth. 2020;125:351–3.
8. Fuchs-Buder T, Brull SJ, Fagerlund MJ, Renew JR, Cammu G, Murphy GS, Warlé M, Vested M, Fülesdi B, Nemes R, Columb MO, Damian D, Davis PJ, Iwasaki H, Eriksson LI. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents III: The 2023 Geneva revision. Acta Anaesthesiol Scand. 2023;67:994–1017.
9. Brull SJ, Silverman DG. Tetanus-induced changes in apparent recovery after bolus doses of atracurium or vecuronium. Anesthesiology. 1992;77:642–5.
10. Sato H, Iwasaki H, Doshu-Kajiura A, Katagiri S, Takagi S, Luthe SK, Suzuki T. Comparison of two electromyography-based neuromuscular monitors, AF-201P and TetraGraph, in rocuronium-induced neuromuscular block: a prospective comparative study. Anaesth Crit Care Pain Med. 2022;41: 101145.
11. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
12. Driessen JJ, Crul JF, Vree TB, Egmond J, Booij LH. Benzodiazepines and neuromuscular blocking drugs in patients. Acta Anaesthesiol Scand. 1986;30:642–6.
13. Driessen JJ, Vree TB, Egmond JV, Booij LH, Crul JF. Interaction of midazolam with two non-depolarizing neuromuscular blocking drugs in the rat in vivo sciatic nerve-tibialis anterior muscle preparation. Br J Anaesth. 1985;57:1089–94.
14. Narimatsu E, Niiya T, Kawamata M, Namiki A. Adenosine and adenosine uptake inhibitors potentiate the neuromuscular blocking action of rocuronium mediated by adenosine A(1) receptors in isolated rat diaphragms. Anaesthesiol Scand. 2008;52:1415–22.
15. Todd KJ, Robitaille R. Purinergic modulation of synaptic signalling at the neuromuscular junction. Pflugers Arch. 2006;452:608–14.
16. Correia-de-Sá P, Sebastião AM, Ribeiro JA. Inhibitory and excitatory effects of adenosine receptor agonists on evoked transmitter release from phrenic nerve ending of the rat. Br J Pharmacol. 1991;103:1614–20.
17. Sakata H, Ishikawa Y, Ishihara G, Oyama N, Itami T, Umar MA, Sano T, Yamashita K. Effect of sevoflurane anesthesia on neuromuscular blockade produced by rocuronium infusion in dogs. J Vet Med Sci. 2019;81:425–33.
18. Suzuki T, Iwasaki K, Fukano N, Hariya S, Saeki S, Ogawa S. Duration of exposure to sevoflurane affects dose-response relationship of vecuronium. Br J Anaesth. 2000;85:732–4.
19. Ezzine S, Yamaguchi N, Varin F. Determination of interstitial rocuronium concentrations in the muscle tissue of anesthetized dogs by microdialysis. J Pharmacol Toxicol Methods. 2004;49:121–9.
20. Ishii-Maruhama M, Higuchi H, Nakanou M, Honda-Wakasugi Y, Yabuki-Kawase A, Maeda S, Honda-Wakasugi Y, Yabuki-Kawase A, Maeda S, Miyawaki T. In vitro changes in the proportion of protein-unbound-free propofol induced by valproate. J Anesth. 2018;32:688–93.
21. Gray HS, Slater RM, Pollard BJ. The effect of acutely administered phenytoin on vecuronium-induced neuromuscular blockade. Anaesthesia. 1989;44:379–81.
22. Spacek A, Nickl S, Neiger FX, Nigrovic V, Ullrich OW, Weindmayr-Goettel M, Schwall B, Taeger K, Kress HG. Augmentation of the rocuronium-induced neuromuscular block by the acutely administered phenytoin. Anesthesiology. 1999;90:1551–5.