anaesthesia itself did not cause any significant decreases in BIS values at 15 min after spinal anaesthesia.

The relationship between spinal thoracic levels of sensory block and BIS values after propofol administration is illustrated in Figure 3A–D. The correlation coefficients between spinal thoracic levels at 15 min after spinal anaesthesia and BIS values were 0.800, 0.848, 0.804, and 0.801, respectively, between 1 and 5, 6 and 10, 11 and 15, and 16 and 20 min after the estimated effect-site concentration of propofol attained a constant level of 3.0 μg ml^{-1} ($P<0.001$ for each value).

Discussion

The present study demonstrates that BIS significantly correlates with the spread of spinal sensory block under conditions of identical predicted effect-site concentration of propofol. We conducted this study under deep sedation because the BIS value may be affected by arousal, movement, cough, or noise under light or no sedation.[7 8] Our results suggest that depth of sedation with propofol is influenced by the height of the spinal sensory block at 15 min after spinal anaesthesia.

The proposed mechanisms of the sedative effects induced by spinal anaesthesia include systemic general anaesthetic effects of absorbed local anaesthetics, rostral spread of the local anaesthetics through cerebrospinal fluid with direct actions on the brain, and decreased facilitatory sensory input to the reticular activating system due to loss of proprioceptive inputs from skin, muscles, or joints.[1 13 14] However, no previous studies have demonstrated that the sedative effect is due to the spread of spinal anaesthesia or to the dose of intrathecally administered local anaesthetics. The present study revealed that the local anaesthetics delivered to the brain after systemic absorption into the circulation is not the only cause of the decrease in BIS values because the dose of bupivacaine was identical in all patients in this study. The depth of sedation induced by spinal anaesthesia depends on the extent of spinal sensory block.

There are several studies examining the effects of the different levels of spinal anaesthesia on BIS values in patients with light to no sedation.[2 5 6] Our results are consistent with these studies,[2 5 6] suggesting that a higher spinal anaesthesia deepens the level of depth of sedation, mirrored by the BIS, compared with a lower spinal anaesthesia. However, in these previous studies, the differential spread of spinal anaesthesia was produced by different doses or baricity of the local anaesthetic. Our study demonstrated that the sedative effect of spinal block produced by equal dose of the same anaesthetic was dependent on the level

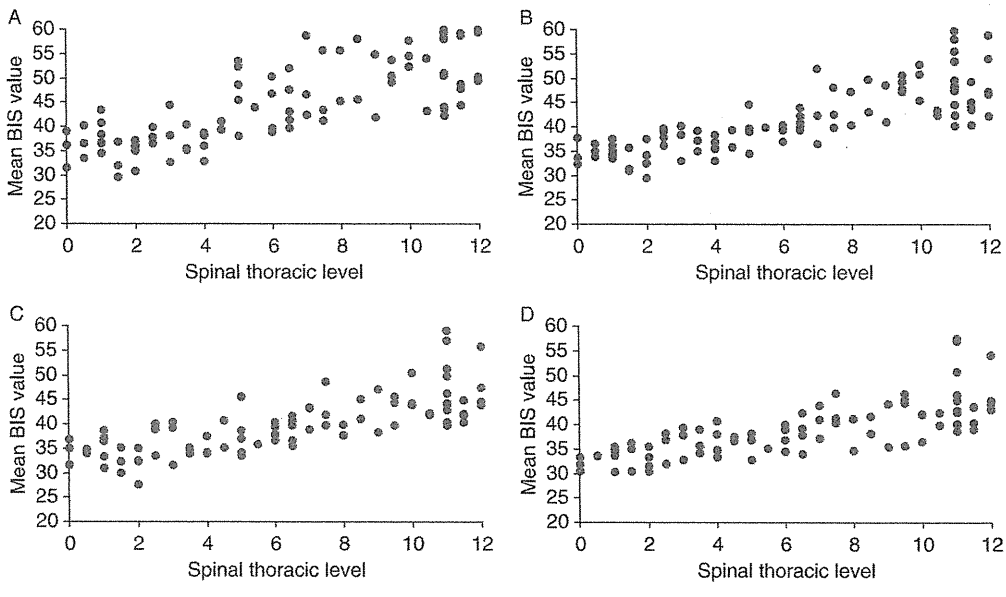

Fig 3 Scattergram showing the relationship between spinal thoracic level of spinal sensory blockade at 15 min after spinal anaesthesia and BIS values during the periods between 1 and 5 min (A), 6 and 10 min (B), 11 and 15 min (C), and 16 and 20 min (D) after the effect-site concentration attained a constant level of 3.0 μg ml^{-1}. The points represent the mean values calculated from data for the 5 min interval for individual patients. The vertical axis represents BIS values. The horizontal axis represents the spinal thoracic level in which 0.0, 1.0, and 2.0 correspond to C8, Th1, and Th2, respectively. The spinal levels are the mean values of the right and left spinal thoracic levels; therefore, the spinal levels are represented as 0.0, 0.5, 1.0, 1.5, 2.0, and so on. The correlation coefficients between spinal levels and BIS values were 0.800, 0.848, 0.804, and 0.801, respectively, at 1–5, 6–10, 11–15, and 16–20 min after the effect-site concentration of propofol reached and remained at 3.0 μg ml^{-1}. The regression coefficients on each linear regression line were 1.7074, 1.3977, 1.1284, and 1.0270, respectively, at 1–5, 6–10, 11–15, and 16–20 min.

of spinal sensory block at 15 min after spinal anaesthesia when the estimated effect-site concentration of propofol remained at 3.0 $\mu g\ ml^{-1}$. In contrast to our findings, Toprak and colleagues[15] reported that the requirements of sedatives were decreased by spinal anaesthesia, although this decrease did not significantly correlate with the level of the spinal sensory block. In Toprak and colleagues' study, spinal anaesthesia was administered with 10 and 17.5 mg of hyperbaric bupivacaine and the obtained mean anaesthetic levels were close to each other, at Th7 and Th9, in the two groups compared.[15] The proximity of the spinal levels could explain the difference between their results and ours. From their study, it appears that it is the dose of spinally administered local anaesthetics that affects the sedative effect induced by spinal anaesthesia. Conversely, the present study revealed that the sedative effect, mirrored by BIS values, is dependent on the height of spinal sensory block at 15 min after spinal anaesthesia, when the dose and baricity of the local anaesthetic for spinal anaesthesia remain unchanged.

The spinal thoracic level did not significantly correlate with BIS values before sedation at 15 min after spinal anaesthesia in our study. It has been reported that spinal anaesthesia alone leads to a significant decrease in BIS values in patients and healthy volunteers.[2–4] In Pollock and colleagues'[4] study, the volunteers were placed in a darkened room with soft music to measure BIS values before and after spinal anaesthesia. In contrast, our patients were undergoing surgery in a well-lit operating theatre, were free to communicate with medical staff, and were spoken to by the anaesthetist to assess the height of spinal block every minute, which would have repeatedly stimulated the patients. It is possible that those stimuli may have counteracted the sedative effects of spinal anaesthesia before the induction of general anaesthesia in our study. Furthermore, it was reported that the sedative effect induced by spinal anaesthesia starts to appear at 15 or 20 min after spinal anaesthesia.[3 5] Thus, evaluation of the effect of spinal anaesthesia on the depth of sedation at 15 min after spinal anaesthesia might have been too early. These two factors might explain why there was no correlation between BIS values and the level of spinal anaesthesia at 15 min after spinal anaesthesia.

There are a few limitations to the present study. First, the attending anaesthetist was not blinded to the study; however, the level of spinal anaesthesia was determined before data collection and analysis. The bias of the attending anaesthetist could not have affected the BIS values because the data collection was automatically made from the monitor recording system. Secondly, 15 min may not be long enough for the local anaesthetic to cease its maximal rostral spread after spinal anaesthesia. Hence, the spinal level at 15 min post-spinal administration is not likely to be the same as that during the later periods after propofol administration. In our study, correlation was evaluated between the spinal level at 15 min after spinal administration and BIS values during the fixed time periods after patients were sedated with propofol. However, according to our study protocol, the time period from administration of spinal anaesthesia to setting up the concentration of TCI was approximately equal in all the patients. The consumption of propofol from the induction of anaesthesia to the periods evaluated was also approximately equal among patients, when adjusted for body weight. Therefore, the calculated BIS value during each period can be evaluated for comparison with the spinal sensory level at 15 min after spinal administration.

The present study demonstrated that BIS values significantly correlate with the level of spinal block assessed at 15 min after spinal anaesthesia under deep sedation with propofol in young and middle-aged patients. The depth of sedation induced by spinal anaesthesia is influenced by the spread of spinal sensory block.

Conflict of interest

None declared.

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BJA

Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients

T. Suzuki*, O. Kitajima, K. Ueda, Y. Kondo, J. Kato and S. Ogawa

Department of Anaesthesiology, Nihon University School of Medicine, 30-1, Oyaguchi Kamimachi, Itabashi-Ku, Tokyo 173-8610, Japan

* Corresponding author. E-mail: suzukit@cd5.so-net.ne.jp

Editor's key points

- The efficacy of sugammadex in older patients has not been defined.
- Reversal of profound rocuronium block (PTC 2) was compared in older and younger patients.
- Full recovery was achieved with sugammadex in all patients but was slower in the older ones.
- Age-related cardiovascular changes are a possible explanation.

Background. This study compared the reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients.

Methods. Fifteen younger (20–50 yr) and 15 older (≥70 yr) patients were sequentially enrolled in this study. After induction of anaesthesia and laryngeal mask insertion, contraction of the adductor pollicis muscle in response to ulnar nerve stimulation was quantified using acceleromyography during 1.0–1.5% end-tidal sevoflurane and remifentanil anaesthesia. All patients initially received rocuronium 1 mg kg^{-1}, followed by 0.02 mg kg^{-1} when a post-tetanic count (PTC) of 1 or 2 was observed. After completion of surgery, at reappearance of 1–2 PTC, the time required for a single bolus dose of 4 mg kg^{-1} sugammadex to produce recovery to a train-of-four (TOF) ratio of 0.9 was recorded.

Results. There were no differences in the total dose of rocuronium administered between the younger [mean (SD): 93.4 (17.5) mg] and the older [97.5 (32.2) mg] groups. In all patients, adequate recovery of the TOF ratio to 0.9 was achieved after administration of sugammadex, although it was significantly slower in the older [3.6 (0.7) min, $P<0.0001$] than in the younger group [1.3 (0.3) min]. There were no clinical events attributable to recurarization.

Conclusions. Sugammadex can adequately restore neuromuscular function in older patients, although a longer time is required to recover from profound rocuronium-induced neuromuscular block than in younger patients.

Keywords: age factors; monitoring, neuromuscular function; neuromuscular block, antagonism; neuromuscular block, rocuronium; sugammadex

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Traditionally, anticholinesterases have been used to antagonize residual non-depolarizing neuromuscular block. However, they have limited efficacy in adequately reversing profound neuromuscular block induced by neuromuscular blocking agents with an intermediate duration of action.[1–5] For example, the time from administration of rocuronium 0.45 mg kg^{-1} to recovery of the train-of-four (TOF) ratio to 0.9 could not be significantly shortened by the maximum dose of neostigmine 0.07 mg kg^{-1} given 5 min after rocuronium (mean value: 42.1 min) in adult patients when compared with the time for spontaneous recovery (54.3 min).[1] It is therefore recommended that antagonism with neostigmine should be delayed until at least the second twitch of the TOF response is detectable to completely restore neuromuscular function.[6] Even in these circumstances, it takes up to 10 min to achieve the full effect of anticholinesterases.[7] In comparison, sugammadex, a modified gamma cyclodextrin, is a selective relaxant binding agent specifically designed to encapsulate rocuronium,[8] which can, therefore, promptly restore neuromuscular function regardless of any levels of neuromuscular block as the dose is increased.[9–11] If the marked reductions in recovery time are replicated in routine clinical practice, sugammadex contributes to save time and has the potential to be cost-effective compared with neostigmine.[12] Chemically encapsulating the rocuronium molecule with sugammadex results in a rapid decrease in plasma concentration of free rocuronium and induces rocuronium molecules to extensively diffuse from the neuromuscular junction into plasma along the concentration gradient of free rocuronium.[13] Therefore, in older patients with a low cardiac output[14] and regional blood flow,[15] a slower increase in the plasma concentration of sugammadex and a slower facilitated recovery by sugammadex would be expected, when compared with younger adults. However, the age-related change in the efficacy of sugammadex has not been completely investigated. The only study[16] carried out in elderly patients showed a slower recovery from the time of reappearance of the second twitch in the TOF to a TOF ratio of 0.9 following sugammadex 2 mg kg^{-1} with increasing patient age. The average time of 3.6 min required

to attain a TOF ratio of 0.9 in patients aged ≥75 yr is significantly longer when compared with the 2.3 min in younger adults aged 18–64 yr. The efficacy of sugammadex in the reversal of deep neuromuscular block in the elderly has not been examined. Therefore, the aim of this study was to compare the reversibility of profound rocuronium-induced neuromuscular block, quantified by a mode of the post-tetanic counts (PTCs), with sugammadex between younger and older patients.

Methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 30 adult female patients consented to participate in this study. Patients were ASA physical status I–III, aged between 20 and 50 yr (younger) or ≥70 yr (older), and undergoing elective gynaecological surgery under general anaesthesia. None of the patients had neuromuscular, hepatic, or renal disorders, or were taking any drug known to interact with neuromuscular blocking agents. Patients whose BMI was ≥25 or <18.5 were excluded from the study. Premedication consisted of ranitidine 150 mg administered orally before going to bed on the day before surgery and on the morning of surgery. On arrival at the operating theatre, all patients were monitored with ECG, non-invasive arterial pressure, and pulse oximetry. Ringer's solution (8–10 ml kg^{-1} h^{-1}) was given i.v. in the right forearm. Patients were sequentially enrolled into the study groups on the basis of their age; each group comprised 15 patients. The neuromuscular block was monitored at the adductor pollicis muscle. General anaesthesia was induced with fentanyl 2–4 μg kg^{-1} and propofol 2.5 mg kg^{-1} i.v. while patients received 100% oxygen through an anaesthesia facemask. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anaesthesia was maintained with sevoflurane 1.0–1.5% end-tidal and remifentanil 0.2–0.3 μg kg^{-1} min^{-1}. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R™ (Nihon Kohden, Tokyo, Japan). The rectal temperature of the patients was monitored using a Mon-a-Therm™ (Mallinckrodt, Anesthesia Products Inc., St Louis, MO, USA) and was maintained at >36°C using a warming mattress blanket (Thermacare™ and Medi-Therm II™, Gaymer Industries, Inc., NY, USA) and warmed i.v. fluids. Skin temperature over the adductor pollicis muscle was recorded every 15 s throughout the experiment using a surface probe in the acceleromyograph and maintained at >32°C. After a stable depth of anaesthesia was obtained, the ulnar nerve at the wrist was stimulated supramaximally with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph (TOF-Watch SX™, Organon Ltd, Dublin, Ireland). All data were collected on a computer and monitored throughout the study. After the control TOF, stimuli were administered for a minimum of 10 min to stabilize the TOF responses.[17] Then, all patients received rocuronium 1 mg kg^{-1} i.v. The ulnar nerve was repeatedly stimulated in a TOF mode at 2 Hz every 15 s. A PTC mode was initially applied 5 min after obtaining complete neuromuscular block and repeated every 6 min.[18] Whenever 1 or 2 PTCs were observed, rocuronium 0.02 mg kg^{-1} was given until the end of the surgical procedure. All patients received sugammadex 4 mg kg^{-1} when a PTC of 1–2 was present after the last dose of rocuronium, and the time required for facilitated recovery to a TOF ratio of 0.9 was recorded. The TOF ratio of 0.9 normalized by the baseline TOF ratio was monitored.[17 19] Sevoflurane and remifentanil were continued during recovery from neuromuscular block. Patients were monitored for postoperative respiratory events, such as respiratory distress and decrease in Sp_{O_2}, caused by recurarization, for 24 h after operation.

The sample size was calculated based on previous data on the averaged recovery time from profound rocuronium-induced neuromuscular block to a TOF ratio of 0.9, facilitated by sugammadex 4 mg kg^{-1} in younger adult patients [1.7 (0.7) min].[20] We considered a 50% increase (2.55 min) in the recovery time to be clinically relevant. To obtain statistically significant results with α=0.05 and a power of 0.80 required 12 patients in each group. To compensate for any dropouts, we enrolled 15 patients in each group. Data are presented as mean (SD) and (range). Statistical analysis was performed using the StatView™ software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student's *t*-test was used for comparing data between the two groups. A *P*-value of <0.05 was considered statistically significant.

Results

Data from all the 30 patients could be included in the analyses. The mean age in the younger patients was 38.4 (3.5) yr and 75.9 (6.1) for the older group (Table 1). The duration of anaesthesia was significantly longer in older [177.5 (45.7) min, *P*=0.0015] than in the younger patients [118.5 (32.8) min]. However, the total dose of rocuronium given did not differ between the older [97.5 (32.2) mg] and the younger groups [93.4 (17.5) mg]. In all the patients, sugammadex was given at a PTC of 1–2. The time for facilitated recovery to a TOF ratio of 0.9 was significantly longer in the older [3.6 (0.7) (2.4–4.5) s, *P*<0.0001] than in the younger adults group [1.3 (0.3) (0.8–2.0) s]. There were no clinical events attributable to recurarization with rocuronium after operation.

Table 1 Patient characteristics. Data are presented as mean (SD) (range).

Monitoring muscle	Younger adult	Elderly
Age (yr)	38.4 (3.5) (32–46)	75.9 (6.1) (70–91)
Weight (kg)	57.2 (4.0)	55.9 (8.6)
Height (cm)	164.0 (7.5)	156.0 (10.0)

Discussion

This study shows that the speed of facilitated recovery from profound rocuronium-induced neuromuscular block with sugammadex 4 mg kg^{-1} is age-related. The total recovery time to a TOF ratio of 0.9 in older patients is approximately three-fold longer than that in younger adults (3.6 *vs* 1.3 min). Although sugammadex is extremely useful to restore neuromuscular function even from profound rocuronium-induced neuromuscular block irrespective of age when compared with neostigmine, caution is recommended when using sugammadex, even with neuromuscular monitoring, especially in older patients.

Our results show that, even in older patients, reversal with sugammadex does not have to be delayed until the second twitch of the TOF response or spontaneous respiration is detectable, as is required with neostigmine. This indicates that a profound depth of neuromuscular block can be maintained during anaesthesia right up to the end of the surgery. For some thoracic and abdominal surgery, PTC stimulation is used to maintain a sufficient depth of neuromuscular block. A PTC level of at least 5 is required to achieve total diaphragmatic paralysis in response to tracheal suction.[21] So far, PTC stimulation has been clinically used to estimate the approximate interval to reappearance of the first twitch in response to TOF stimulation during intense neuromuscular block.[22] However, the rapid reversal effects of sugammadex are changing the use of PTC for maintaining deep neuromuscular block during clinical anaesthesia. The present study could contribute to this by demonstrating the safety and effectiveness of reversing a deep rocuronium-induced neuromuscular block with sugammadex.

Our study does not elucidate why complete recovery from an intense rocuronium-induced neuromuscular block after administration of sugammadex is slower in older patients. However, the onset of action of sugammadex injected is likely to be dependent on cardiac output and muscle blood flow. Especially in females, cardiac output decreases modestly with an age-related decline in heart rate.[14] Limb blood flow decreases progressively with advancing age, even in healthy men.[15] This lower blood flow may be explained by age-related reduced vascular conductance, the loss of muscle volume, and decline in oxygen consumption. Age-associated arteriosclerosis also contributes to further decrease in peripheral perfusion. A lower regional blood flow would result in a slower increase in the plasma concentration of sugammadex and a slower decrease in the plasma concentration of free rocuronium. Hence, free rocuronium molecules cannot rapidly diffuse from the neuromuscular junction into the plasma. Therefore, it seems reasonable that an age-related reduction in cardiac output and muscle blood flow is a primary cause of the slower recovery of neuromuscular function after sugammadex.

Volatile anaesthetics cause marked peripheral vasodilation. If simultaneously, arterial pressure can be maintained and cardiac output can be increased, a greater blood flow to the peripheral tissues will be expected during inhalation anaesthesia. This was verified in younger patients. When receiving 0.8–1.2% isoflurane in combination with 66% nitrous oxide, muscle blood flow in the forearm progressively increased in patients 18–34 yr of age. In contrast, forearm blood flow in patients 60–79 yr of age significantly decreased when compared with baseline values during isoflurane anaesthesia.[23] Although sevoflurane, as was used in our study, has quite similar cardiovascular actions to isoflurane, sevoflurane-induced reduction of left ventricular function, such as end-diastolic volume, ejection fraction, and cardiac output, is much greater in magnitude when compared with isoflurane.[24] It can therefore be estimated that the peripheral blood flow might have typically decreased in the older patients in our study. These changes in blood flow to peripheral tissues produced by sevoflurane may have contributed to the age-related variation in the recovery with sugammadex from rocuronium-induced neuromuscular block.

We did not strictly fix the end-tidal concentration of sevoflurane to an age-adjusted minimum alveolar concentration (MAC) value and used a concentration of 1–1.5% according to routine clinical practice. This means that elderly patients may have received a greater MAC. Sevoflurane significantly enhances the effect of neuromuscular blocking agent[25] and therefore, the efficacy of sugammadex may theoretically be diminished during sevoflurane anaesthesia. However, sugammadex has been shown to be equally effective for reversal of rocuronium-induced neuromuscular block during sevoflurane or propofol anaesthesia.[26–28] It is therefore conceivable that sevoflurane does not pharmacodynamically inhibit chemical binding between rocuronium and sugammadex. In contrast, it remains possible that the difference in sevoflurane concentration between the two groups may affect the reduction in cardiac output and regional blood flow as mentioned above and consequently change actions of sugammadex in older patients. In addition, the longer duration of sevoflurane anaesthesia in the older patients may have contributed.

In conclusion, sugammadex can restore neuromuscular function in older patients. However, a longer time is required for recovery from profound rocuronium-induced neuromuscular block than in younger patients. Further studies are warranted to examine the effective dose of sugammadex required in older patients for more rapid reversal of neuromuscular block.

Conflict of interest

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ORIGINAL ARTICLE

A randomized trial to identify optimal precurarizing dose of rocuronium to avoid precurarization-induced neuromuscular block

Naoko Fukano · Takahiro Suzuki · Kiyoko Ishikawa · Hitoshi Mizutani · Shigeru Saeki · Setsuro Ogawa

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Abstract
Purpose The aim of this study was to examine the safe precurarizing dose of rocuronium required to avoid neuromuscular block after precurarization.
Methods Twenty-four female patients were randomly allocated into two groups of 12 patients each. General anesthesia was induced and maintained with remifentanil and propofol, and a laryngeal mask was inserted without the aid of a neuromuscular blocking agent. Patients were randomized to receive either 0.03 or 0.06 mg/kg rocuronium as a precurarizing dose. Neuromuscular block was monitored using acceleromyographic train-of-four (TOF) of the adductor pollicis muscle. Three minutes after the precurarization, all patients received suxamethonium 1.5 mg/kg and were graded on severity of fasciculations.
Results The average TOF ratio was kept above 0.9 even 3 min after precurarization with 0.03 mg/kg rocuronium. In contrast, in patients who received 0.06 mg/kg rocuronium, the ratios significantly decreased to 0.72 (0.14) [mean (SD), $P < 0.004$] and 0.68 (0.18) ($P < 0.006$) 2 min and 3 min after the precurarization, respectively. No visible muscle movement was observed following suxamethonium injection, except that one patient who received 0.03 mg/kg rocuronium showed very fine muscle movements of the fingertips.
Conclusion Rocuronium at 0.06 mg/kg is an overdose for precurarization. The results of the present study demonstrate that a safe and effective precurarizing dose of rocuronium is 0.03 mg/kg.

Keywords Precurarization · Rocuronium · Suxamethonium · Neuromuscular block

N. Fukano · T. Suzuki (✉) · K. Ishikawa · H. Mizutani · S. Saeki · S. Ogawa
Department of Anesthesiology, Surugadai Nihon University Hospital, 1-8-13, Kanda-Surugadai, Chiyoda-Ku, Tokyo 101-8309, Japan
e-mail: suzukit@cd5.so-net.ne.jp

Introduction

Many anesthetics can reduce lower and upper esophageal sphincter tone and tend to promote gastroesophageal regurgitation into the pharynx [1]. Therefore, rapid sequence intubation is frequently used to decrease the risk of pulmonary aspiration of gastric contents in a patient with a full stomach. Suxamethonium enables us to considerably shorten the interval from the patient's loss of consciousness following hypnotics to tracheal intubation and is considered to be appropriate for rapid sequence intubation [2, 3]. For such occasions, precurarization with a small dose of a nondepolarizing neuromuscular blocking agent has been widely used to prevent muscle fasciculation induced by suxamethonium and rise in intraabdominal pressure [3–6]. However, the technique may cause difficulty in breathing [7, 8], gastroesophageal regurgitation, and pulmonary aspiration associated with overdosage of precurarization [9]. The theoretical calculation using published pharmacodynamic and pharmacokinetic data showed that a dose of rocuronium equivalent to 10% of the ED_{95} (ED_{95} = 0.3 mg/kg) would rarely produce a measurable neuromuscular effect and should be therefore recommended as an appropriate dose for precurarization [10]. However, in previous studies [5, 11–13], 20–30% of the ED_{95} of rocuronium was generally used for precurarization, and effectiveness for defasciculation was examined. Although it is anticipated that a larger dose of rocuronium can greatly

suppress suxamethonium-induced fasciculation, the risk of a significant neuromuscular block in several minutes after the precurarization dosing may become greater. Unfortunately, the neuromuscular effect of precurarization has never been certified with any objective neuromuscular monitoring in clinical settings. Therefore, the main purpose of this study was to identify the optimal dose of rocuronium to avoid both neuromuscular block associated with precurarization and fasciculation induced by suxamethonium.

Materials and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 24 adult female patients consented to participate in this study. Patients were ASA physical status I or II, 20–60 years of age, undergoing elective surgery. None of the patients had a difficult airway, previous history of hypertension, neuromuscular, hepatic, and renal disorders, or was taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index (BMI) was ≥25 or <18.5 were also excluded from the study. Premedication consisted of orally administered ranitidine 150 mg the night before and on the morning of surgery and i.m. midazolam 0.03–0.04 mg/kg. On arrival at the operating room, all patients were monitored with ECG, noninvasive blood pressure measurement, and pulse oximetry. An i.v. infusion of acetated Ringer's solution, 8–10 ml/kg/h, was started via the intravenous route. Anesthesia was induced with a continuous infusion of remifentanil at 0.5 μg/kg/min and a bolus of propofol 2 mg/kg. After confirming the bispectral index value of 60 or less (BIS monitor A-2000; Aspect Medical Systems, Norwood, MA, USA), a laryngeal mask was inserted without the aid of a neuromuscular blocking agent. Anesthesia was maintained with remifentanil 0.2 μg/kg/min and propofol 4–6 mg/kg/h. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a Multigas Unit AG-920R (Nihon Kohden, Tokyo, Japan). Patient rectal temperature was monitored using a Mon-a-Therm (Mallinckrodt; Anesthesia Products, St. Louis, MO, USA) and was maintained at >36°C using a warming mattress and blanket (Thermacare and Medi-Therm II; Gaymer Industries, NY, USA) and warmed i.v. fluids. Skin temperature over the thenar muscle was recorded every 15 s throughout the experiment using a surface probe equipped in an acceleromyographic device and maintained at >32°C. After a stable depth of anesthesia was obtained, the unilateral ulnar nerve was stimulated at the wrist with supramaximal and square-wave stimuli of 0.2-ms duration, which was delivered in a train-of-four (TOF) mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph (TOF-Watch SX; Organon, Dublin, Ireland). After the control TOF stimuli were administered for a minimum of 10 min to stabilize the responses [14], the T_1 value was readjusted to 100% and the patients received a precurarizing dose of rocuronium at either 0.03 or 0.06 mg/kg via computer-generated randomization. During a waiting time of 3 min, the time course of the TOF ratios was recorded. The TOF ratios were normalized by the baseline values [14]. Three minutes after the precurarizing dose, all patients received suxamethonium 1.5 mg/kg i.v. and were graded on severity of fasciculation using a four-point scale (0, no visible muscle movement; 1, very fine muscle movement of the face or the fingertips; 2, small fasciculations on the trunk and/or extremities; 3, strong fasciculations on the trunk and/or extremities) [12] by a staff anesthesiologist who was blinded to the grouping. Onset from the time of administration of suxamethonium to maximum depression of T_1 was monitored.

The results of the previous study showed that the fourth twitch height was significantly larger than the T_1 height when the TOF responses were measured by acceleromyography and before an injection of neuromuscular blocking agent. Calculation of sample size was based on the averaged baseline TOF ratio was 1.11 (0.09) [mean (SD)] [14], and a significant neuromuscular block induced by precurarization was defined as less than 90% [15] of the baseline TOF ratio ($1.11 \times 0.9 = 0.99$). For the results to have statistical significance with $\alpha = 0.05$ and $\beta = 0.80$, one needed to recruit 10 patients in each group. To allow for dropouts, we enrolled 12 patients in each group. Data are presented as mean (SD). Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). Analysis of variance was used for multiple comparisons. If a significant P value of <0.05 was obtained in multiple comparisons, further group comparisons were made using the Bonferroni post hoc test. Unpaired Student's t test was used for two-group comparisons. A P value <0.05 was considered statistically significant.

Results

Data from all 24 patients could be included in the analyses. Patient characteristics did not differ between the two groups (Table 1). In 0.03 mg/kg group, an averaged TOF ratio was maintained above 0.9 even 3 min after precurarization (Table 2), and a significant depression in the TOF ratio was shown only in 3 patients, at 2 and 3 min after precurarization, but the ratio was maintained at more than 0.7 (Fig. 1a). In the 0.06 mg/kg group, a significant neuromuscular block was observed in all patients (Fig. 1b),

and averaged TOF ratios significantly decreased to 0.72 (0.13) ($P < 0.004$) and 0.66 (0.16) ($P < 0.006$), at 2 and 3 min, respectively, after precurarization (Table 2). No visible muscle movement (scale 0) was observed following suxamethonium injection, except in 1 patient who had received 0.03 mg/kg rocuronium and showed very fine muscle movements of the fingertips (scale 1). There was a statistically significant difference in the onset times of suxamethonium-induced neuromuscular block between the 0.03 mg/kg group [79.5 (12.3) s, $P = 0.032$] and the 0.06 mg/kg group [93.9 (14.5) s].

Discussion

The present study could identify that a safe precurarizing dose of rocuronium for surgical patients was 0.03 mg/kg. The dose of about 0.06 mg/kg rocuronium that had been commonly studied for precurarization [5, 11, 12] induced a potentially risky neuromuscular block within 3 min while awaiting induction of anesthesia and was therefore regarded as overdosing. Furthermore, to effectively prevent suxamethonium-induced muscle fasciculation, rocuronium 0.03 mg/kg was proven to be a sufficient dose.

Suxamethonium has the superior feature of rapid onset of action and enables shortening the interval from the patient's loss of consciousness following hypnotics to tracheal intubation. Particularly in an emergent patient with a full stomach, the incidence of pulmonary aspiration during induction of general anesthesia will be three to four times higher than that for patients undergoing proposed elective surgery [16]. Therefore, establishing a fast and profound neuromuscular block is required for rapid sequence intubation. Although priming [17] and timing principles [18] using rapid-onset rocuronium have been reported to be effective for rapid sequence intubation, suxamethonium seems to be clinically preferred rather than rocuronium as a neuromuscular blocking agent for patients with specific risks of pulmonary aspiration. In fact, a survey of variation of rapid sequence induction techniques in Wales reported that suxamethonium was currently used for 97% of cesarean sections, 94% of bowel obstructions, and 85% of appendectomies; in contrast, rocuronium was used only in 2–12% of patients [2]. A retrospective case-review analysis of 250 patients undergoing appendectomy in a 1-year period also revealed that suxamethonium use was 80%, with 96% of these patients receiving rocuronium precurarization [3]. To prevent several side effects associated with suxamethonium-induced muscular fasciculation, including an increase in intragastric pressure, precurarization seems to be important. The barrier pressure, which is the difference between intragastric pressure (mean value, 10 cmH_2O) and lower esophageal sphincter pressure (36 cmH_2O) normally prevents reflux of gastric contents into the esophagus [19]. However, in patients with a full stomach, basal intragastric pressure may rise, and many induction anesthetics reduce the lower esophageal sphincter tone [1]. In addition, it should not be surprising that intragastric pressure rises as high as 40 cmH_2O as a result of suxamethonium-induced fasciculation [20]. Under specific conditions in which the lower sphincter is not closing tightly enough, precurarization may be necessary to prevent fasciculation because the increases in intragastric pressure are directly related to the intensity of fasciculation [20]. As just described, such a combination of precurarization with rocuronium and suxamethonium is still predominantly used for rapid sequence induction and therefore should be safely and effectively applied. The present study is considered meaningful to be able to optimize the precurarizing dose of rocuronium in clinical anesthesia. Based on the results of this study, rocuronium 0.03 mg/kg is sufficient to prevent fasciculation on the trunk and may avoid increasing intraabdominal pressure.

Table 1 Patient characteristics

	0.03 mg/kg group	0.06 mg/kg group
Age (years)	40.2 (12.0)	37.6 (11.5)
Weight (kg)	54.3 (5.4)	56.2 (8.0)
Height (cm)	158.5 (4.9)	161.2 (8.0)

Data are presented as mean (SD); no significant differences were seen between the groups

Table 2 Change in the train-of-four (TOF) ratios after precurarization

	1 min	2 min	3 min
0.03 mg/kg group	1.01 (0.01)	0.94 (0.09)	0.91 (0.12)
	(range, 0.98–1.03)	(range, 0.79–1.05)	(range, 0.70–1.06)
0.06 mg/kg group	0.98 (0.04)	0.72 (0.13)*	0.66 (0.16)*
	(range, 0.89–1.04)	(range, 0.54–0.97)	(range, 0.37–0.88)

Data are presented as percent (%) of control and mean (SD) (range)

* $P < 0.05$ when compared with the baseline value

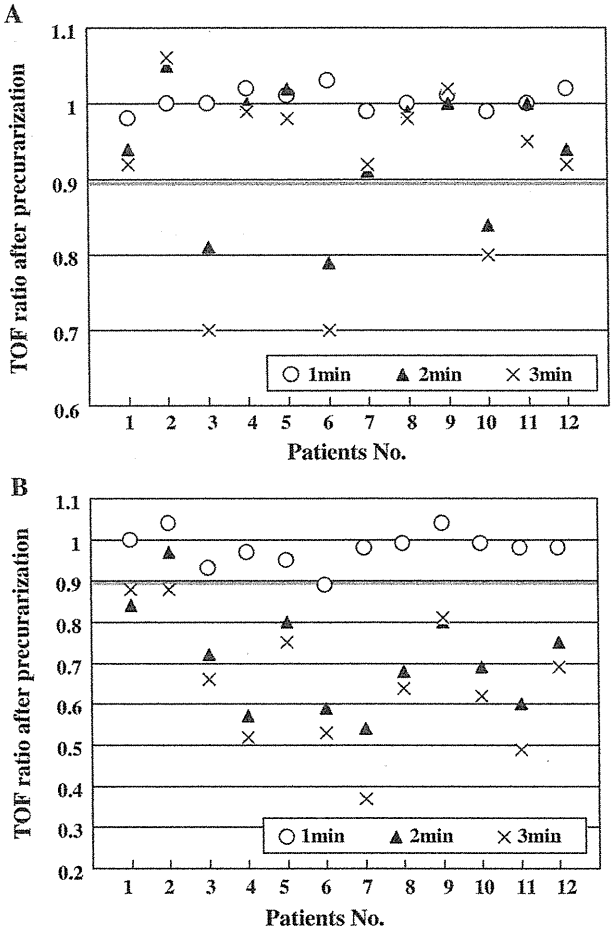

Fig. 1 Detailed train-of-four (*TOF*) ratios after precurarization in each patient in 0.03 mg/kg group (**a**) and 0.06 mg/kg group (**b**). Data were normalized by each baseline train-of-four ratio recorded before precurarization. *Circles*, *triangles*, and *multisymbols* on the graph show the train-of-four ratios observed 1, 2, and 3 min after precurarization, respectively

It was reported that rocuronium was the best drug to prevent muscle fasciculation following suxamethonium injection [5]. In the study, a pretreatment of 0.06 mg/kg rocuronium and an interval of 4 min to suxamethonium injection could completely prevent fasciculation in 85% of patients. Suxamethonium-induced fasciculation certainly would be effectively inhibited if the pretreatment dose of rocuronium was greater than a nonparalyzing dose. However, the intensity of neuromuscular block induced by the precurarizing dose of rocuronium was not clarified even though neuromuscular function was monitored throughout the study [5]. Three minutes after the precurarizing dose of 0.06 mg/kg rocuronium, we could show that an averaged TOF ratio was significantly depressed from 1.0 to 0.68. A TOF ratio below 0.9 observed at the adductor pollicis muscle exposes awake patients to the potentially unpleasant experience of difficulty in swallowing. At that time, the upper esophageal sphincter muscle resting tone markedly decreases [15]. Although precurarization should be applied to patients with a full stomach, it seems very possible that the risk of pulmonary aspiration of gastric contents may be even higher when rocuronium is overdosed [9]. It is therefore suggested, from our results, that the appropriate dose of rocuronium for safe and effective precurarization is 0.03 mg/kg.

Precurarization with a nondepolarizing neuromuscular blocking agent can prevent fasciculation; however, this simultaneously reduces the neuromuscular blocking potency of suxamethonium and also delays the onset of depolarizing neuromuscular block [21]. In the present study, a faster onset of suxamethonium-induced neuromuscular block was obtained in patients pretreated with 0.03 mg/kg rocuronium. It should be considered that too large a precurarization dose may conversely make suxamethonium less effective and delay the timing of tracheal intubation.

We set the administration interval between the precurarizing dose of rocuronium and suxamethonium to 3 min in accordance with conventional practice. Timing of administration is important, because the benefits of precurarization may be weakened if suxamethonium is given too soon or, equally, if it is given too late. Based on the characteristics of rapid onset and intermediate duration of action of rocuronium, a longer waiting time for suxamethonium accelerates rocuronium to dissociate from the neuromuscular junction. Further studies are warranted to clarify a relationship between the precurarizing dose of rocuronium and the waiting time to suxamethonium administration.

In this study, the neuromuscular effects of precurarizing doses of rocuronium were observed during maintenance of anesthesia. Twitch responses evoked by the repetitive TOF mode gradually increase during baseline stimulation and reach a plateau at around 10 min [14]. In the middle of the staircase phenomenon, neuromuscular block induced by a small dose of rocuronium might not be correctly evaluated; therefore, the present study required stabilizing the responses before precurarization. In the protocol of this study, not only the effects of precurarization but also other influencing factors on the degree of neuromuscular block must be considered. The duration of anesthesia with opioid and propofol before an administration of neuromuscular blocking agent increases the intensity of neuromuscular block [22]. In addition, the longer duration of baseline nerve stimulation can further decrease the onset of action of rocuronium [23]. It is likely that the peripheral vasodilation caused by anesthetics and muscle blood flow increased by muscle contractions to nerve stimulation may be involved in the augmentation of neuromuscular block. It is possible that an optimal precurarizing dose of

rocuronium may be larger in awake patients who are not peripherally stimulated by a nerve stimulator.

The patients enrolled in this study were all Japanese women. Asian people are more sensitive to rocuronium-induced block than Caucasian people [24]. Racial differences may therefore impact on the optimal dose of rocuronium for precurarization. In addition, women are more sensitive to rocuronium and require about 30% less rocuronium than men to achieve the same degree of neuromuscular block [25]. However, it was reported that a precurarizing dose of rocuronium affected men and women equally [26].

In conclusion, precurarization with 0.03 mg/kg rocuronium induces no significant depression of the TOF ratios in most patients during a waiting time of 3 min and can certainly prevent suxamethonium-induced fasciculation. We consider that 0.06 mg/kg rocuronium causes a marked neuromuscular block that potentially triggers pulmonary aspiration of gastric contents.

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Conflict of interest No relationships between authors and any company or organization with a vested interest in the outcome of the study.

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ORIGINAL ARTICLE

Onset of rocuronium-induced neuromuscular block evaluated subjectively and accerelomyographically at the masseter muscle

Osamu Kitajima · Takahiro Suzuki · Naoko Fukano · Shigeru Saeki · Setsuro Ogawa · Yoshikazu Noda

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Abstract
Purpose The main aim of this study was to compare the onset times of rocuronium evaluated subjectively and by acceleromyography at the masseter muscle (MM).
Methods Forty female patients were sequentially enrolled in this study. In the first 20 patients, neuromuscular block was evaluated subjectively. After induction of anesthesia with fentanyl and propofol, both the left masseter and ulnar nerves were stimulated in 2-Hz train-of-four (TOF) mode using peripheral nerve stimulators. Contractions of the MM were felt with an anesthesiologist's left hand holding an anesthesia facemask; those of the adductor pollicis (APM) were visually observed. All the patients received a bolus of rocuronium, 0.6 mg/kg. Onset times after rocuronium were defined as the duration until the contractions became impalpable at the MM or invisible at the APM. At the time contraction of the MM had not been felt, intubating conditions were assessed. In the next 20 patients, contractions of the MM and the APM were concurrently quantified using acceleromyography after induction of anesthesia and laryngeal mask insertion. Following 0.6 mg/kg rocuronium, onset of the action was recorded.
Results Onset of the action of rocuronium at the MM evaluated subjectively [mean (SD), 70.3 (17.7) s] was similar to that monitored acceleromyographically [73.3 (27.6) s, $P > 0.05$], and significantly shorter than that at the APM acceleromyographically [111.0 (34.8) s, $P = 0.016$]. Intubating conditions of 20 patients were graded either excellent or good.
Conclusion Subjective evaluation of contractions of the MM by an anesthesiologist's hand may be reliable to determine faster timing for safe tracheal intubation.

Keywords Masseter muscle · Rocuronium · Neuromuscular block · Tracheal intubation

Introduction

The time course of neuromuscular block is generally evaluated at the adductor pollicis muscle (APM). However, the onset of neuromuscular block is much slower at the APM than at the larynx [1], diaphragm [2], and masseter muscle (MM) [3–5]. It is therefore suggested that neuromuscular block at the APM cannot ensure faster timing of tracheal intubation during rapid sequence induction. Intubating conditions should be evaluated by relaxation of the respiratory muscles, specifically by ease of laryngoscopy, vocal cord position, and patient's reaction to intubation [6]. However, direct measurements of neuromuscular block in the larynx and diaphragm are not easy in clinical anesthesia. We previously reported that disappearance of contractions of the MM could be felt subjectively and easily with an anesthesiologist's hand following an injection of vecuronium and could ensure safe and faster timing of tracheal intubation [5]. However, because the MM contractions were only sensed by an anesthesiologist's hand, it was undeniable that the results of the previous study might include some evaluator bias. A further objective study was warranted to establish reliability of the previous results. The main purpose of this study was to compare onset times

O. Kitajima · T. Suzuki (✉) · N. Fukano · S. Saeki · S. Ogawa
Department of Anesthesiology, Surugadai Nihon University Hospital, 1-8-13 Kanda-Surugadai, Chiyoda-Ku, Tokyo 101-8309, Japan
e-mail: suzukit@cd5.so-net.ne.jp

Y. Noda
Department of Anesthesia, Social Insurance Sagamino Hospital, 1-2-30 Futinobe, Sagamihara, Kanagawa 229-0006, Japan

Table 1 Evaluation of intubating conditions [7]

Variable assessed	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate/moving	Closed
Diaphragmatic movement or cough after tracheal intubation	None	Slight	Vigorous/sustained

Excellent all qualities are excellent, *good* all qualities are either excellent or good, *poor* the presence of a single quality listed under poor

of rocuronium at the MM evaluated by tactile means and acceleromyography and to determine whether subjective monitoring was useful to determine onset of rocuronium-induced neuromuscular block and allow faster tracheal intubation.

Materials and methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 40 adult female patients consented to participate in this study. Patients were ASA physical status I or II, 23–47 years of age, undergoing elective gynecological surgery. None of the patients had neuromuscular, hepatic, or renal disorders or were taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index (BMI) was $\geq$25 or <18.5 were also excluded from the study. Premedication consisted of orally administered ranitidine 150 mg before going to bed on the day before surgery and in the morning of the day of surgery. On arrival at the operating room, all patients were monitored with ECG, noninvasive blood pressure, and pulse oximetry. The first 20 patients were assigned to evaluate the onset of rocuronium-induced neuromuscular block at the MM and APM subjectively using peripheral nerve stimulators. Surface-stimulating electrodes were attached percutaneously on the left ulnar nerve at the wrist and the left masseter nerve at the space formed by the zygomatic arch superiorly the mandibular notch inferiorly, and two peripheral nerve stimulators (Innervator NS-252; Fisher & Paykel Electronics, Auckland, New Zealand) were used to separately stimulate the ulnar and masseter nerves [5]. General anesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg while patients received 100% oxygen through an anesthesia facemask. After loss of consciousness, the nerves were concurrently stimulated with square-wave stimuli of 0.2-ms duration, delivered in a train-of-four (TOF) mode at 2 Hz every 12 s. For the ulnar nerve, output current of 50 mA was applied; however, 30 mA was used to stimulate the masseter nerve to avoid stimulation of other facial muscles and direct stimulation of the MM [6]. Contractions of the MM were palpated with an anesthesiologist's left palm lifting the patient's jaw and holding an anesthesia facemask [5], and contractions of the APM was visually observed by another evaluator. Then, the patients received an i.v. bolus dose of rocuronium, 0.6 mg/kg. The onset time at the MM was defined as the duration until the contracting response of the MM was become impalpable, and that at the APM was defined as the duration until adduction of the thumb could not be visually observed. Immediately after the onset at the MM was confirmed, the patient's trachea was intubated with a 7.0-mm-ID endotracheal tube (Portex Tracheal Tube; Smiths Medical International, Kent, UK) and the intubating conditions (Table 1) [7] were assessed.

The next 20 patients were allocated to monitor rocuronium-induced neuromuscular block acceleromyographically. Anesthesia was induced with fentanyl 2 μg/kg and propofol 2 mg/kg, and laryngeal mask insertion was accomplished without aid of neuromuscular blocking agents. Anesthesia was maintained by a continuous infusion of propofol 4–5 mg/kg/h and intermittent administrations of fentanyl as required. After a stable depth of anesthesia was obtained, the left ulnar and masseter nerves were stimulated with square-wave stimuli of 0.2-ms duration, which was delivered in a TOF mode at 2 Hz every 15 s. The left ulnar nerve was stimulated at the supramaximal current (range, 40–50 mA); the unilateral facial nerve was stimulated at a current of 30 mA. Contraction of the ipsilateral MM (Fig. 1) or APM was measured using an acceleromyograph (TOF-Watch SX; Organon, Dublin, Ireland). A transducer was attached percutaneously on the masseter adherent to the mandible and the volar aspect of the thumb at the interpharyngeal joint. After the control TOF stimuli were administered for a minimum of 10 min to stabilize the TOF responses [8], all the patients received rocuronium 0.6 mg/kg i.v., and onset of the action was recorded. Onset time was defined from the administration of rocuronium to maximum depression of the first twitch (T_1) of the TOF. Times from administration of rocuronium to spontaneous recovery of T_1 to 10% of the control value were observed.

The sample size was calculated based on the preliminary data on an averaged onset time of rocuronium 0.6 mg/kg observed at the MM (75 $\pm$ 12 s). We considered a 20% difference (>15 s) in the onset times measured by tactile and acceleromyographical means at the MM to be clinically different. To obtain statistically significant results with $\alpha = 0.05$ and a power of 0.9, it was necessary that

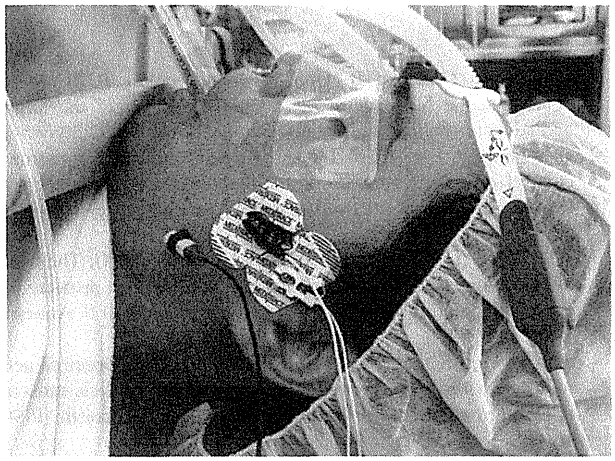

Fig. 1 Placement of surface electrodes stimulating the masseter nerve and an acceleration transducer measuring the contraction of the masseter muscle

15 patients should be included in this study. Allowing for dropouts from the study, we finally enrolled 20 patients. Data are presented as mean (SD). Statistical analysis was performed using StatView software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student *t* test was used for two group comparisons. A P value <0.05 was considered statistically significant.

Results

Data from all 40 patients could be included in the analyses. No differences were found in patient characteristics between the groups (Table 2). There was no difference between the onset times of rocuronium observed subjectively and acceleromyographically at both MM and APM (Table 3). Onset of the action of rocuronium obtained at the MM was significantly faster than those at the APM (Table 3). When evaluating the rocuronium-induced neuromuscular block subjectively, the intubating condition was graded excellent in 12 patients and good in 8 patients; none of the patients had poor intubating condition. In the group AMG, the time from an administration of rocuronium to spontaneously recover to 10% of control of T_1 was significantly shorter in the MM [25.4 (8.2) min, $P = 0.045$] than the APM [34.6 (10.8)].

Table 2 Patient characteristics

Characteristic	Subjective evaluation	Acceleromyography
Age (years)	39.2 (7.1)	41.1 (8.4)
Weight (kg)	51.0 (7.3)	53.4 (6.0)
Height (cm)	156.0 (4.7)	156.9 (5.4)

Data are presented as mean (SD); no significant differences were seen between the groups

Table 3 Onset of the action of rocuronium 0.6 mg/kg

Location	Subjective evaluation	Acceleromyography
Masseter	70.3 (17.7)*	73.3 (27.6)#
Adductor pollicis	143.3 (29.5)	111.0 (34.8)

Data are presented as mean (SD); no significant differences were seen between the groups

* $P < 0.0001$ when compared between the muscles

$P = 0.016$ when compared between the muscles

Discussion

This study demonstrated that the onset time of rocuronium-induced neuromuscular block evaluated subjectively did not differ from that monitored acceleromyographically at the MM. Intubating conditions when contractions of the MM had not been felt by an evaluator's hand were all graded as clinically acceptable conditions. Based on the results of this study, it is likely that subjective evaluation of contractions of the MM during the masseter nerve stimulation is a reliable method to know the onset of rocuronium-induced neuromuscular block and enable faster and safe tracheal intubation. Particularly in a patient with a full stomach, monitoring of the MM contraction during rapid sequence induction may be useful to hasten the timing of tracheal intubation and decrease the risk of pulmonary aspiration.

Previous studies [3, 4] revealed that the onset of rocuronium-induced neuromuscular block occurred significantly faster at the MM than at the APM. Unfortunately, the acceleromyographic monitoring was performed in such studies during a steady state of general anesthesia after laryngeal mask insertion [3] or tracheal intubation [4]. It was true that the results of the previous studies could provide some meaningful information about pharmacodynamic differences of rocuronium between the MM and APM. However, the studies were not really sufficient to apply the acceleromyography at the MM in the clinical setting. The important characteristic of rapid onset of paralysis at the MM should be utilized during induction of general anesthesia to assess the optimal timing for tracheal intubation; however, it is hard to monitor the MM objectively because an acceleration transducer cannot correctly assess the jaw movement during mask-to-face ventilation. Consequently, to perform MM monitoring in the clinical setting, we palpated contractions of the MM evoked by a simple peripheral nerve stimulator during mask ventilation, and subjectively assessed the onset of paralysis based on the disappearance of contractions [5]. Concern was greatest

for some bias of the evaluator in the previous study, but it is deniable because the onset times of rocuronium evaluated subjectively and acceleromyographically were similar. This procedure was proven to be of clinical use for determining the earliest suitable time at which laryngoscopy and tracheal intubation could be performed.

Our study has a limitation that must be acknowledged. Ideally, the TOF stimuli should be delivered in the same stimulation frequency when the onset times of neuromuscular block would be compared because a faster stimulation frequency greatly increases blood flow to the monitored muscle and should produce a shorter equilibration of rocuronium [9]. Therefore, the onset of the action of rocuronium observed subjectively might cause minor delays if the nerves were stimulated every 15 s.

Paralysis of the MM was significantly faster than that of the APM. The faster onset of the action of rocuronium at the MM may be caused by the large volume of blood flow to the centrally located muscles [3] and the faster transfer rate of neuromuscular blocking drugs between the plasma and the neuromuscular junction [10]. The shorter duration of action of rocuronium measured at the MM may also result from greater perfusion and more rapid washout of rocuronium, when compared to the APM [11].

In the present study, we did not assign the patients randomly, and at first evaluated the onset time of rocuronium subjectively. If the acceleromyographical study were to be done first, it is likely that the results might be prejudicial for an evaluator and influence the onset time subjectively evaluated from diminishing contractions of the MM.

In conclusion, tactile assessment of muscle paralysis of the MM after administration of rocuronium enables faster tracheal intubation and may improve patient safety.

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Conflict of interest There are no relationships between authors and any company or organization with a vested interest in the outcome of the study.

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The effects of age on maintenance of intense neuromuscular block with rocuronium

T. FURUYA, T. SUZUKI, A. KASHIWAI, J. KONISHI, M. AONO, N. HIROSE, J. KATO and S. OGAWA
Department of Anaesthesiology, Nihon University School of Medicine, Tokyo, Japan

Background: Increasing age is associated with a longer duration of action of neuromuscular block. The aim of this study was to determine the influence of ageing on the recovery of the post-tetanic count (PTC) from rocuronium-induced neuromuscular block.

Methods: Twenty-two younger (20–60 years) and 22 older (> 70 years) patients were enrolled in this study. After induction of anaesthesia with fentanyl and propofol, all patients initially received 1 mg/kg rocuronium and neuromuscular block were evaluated by contractions of the adductor pollicis muscle to ulnar nerve train-of-four stimulation using an acceleromyograph. Subsequently, intense rocuronium-induced block was determined every 6 min using the PTC during 1.0–1.5% sevoflurane and remifentanil anaesthesia. When the first response to the PTC stimulus was detected, 0.2 mg/kg rocuronium was additionally administered, and again, spontaneous recovery of neuromuscular function was monitored until the first response to the PTC reappeared.

Results: Median values (range) of the times from the administration of 1 mg/kg and 0.2 mg/kg rocuronium until recovery of the first detectable PTC were significantly longer in the older [51.0 (27–100) min, $P < 0.0001$ and 30.0 (12–66) min, $P = 0.0036$, respectively] than the younger patients [31.5 (21–45) min and 18.0 (12–36) min, respectively].

Conclusion: The times from rocuronium injection to reappearance of the first response to PTC stimulation are approximately twofold longer and more variable in older than younger patients. Hence, the dosing interval of rocuronium should be adjusted using neuromuscular monitoring when maintaining intense neuromuscular block, especially in older patients.

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AGEING is accompanied by decreases in hepatorenal blood flow and function. Because steroidal non-depolarizing neuromuscular blocking agents are eliminated through some combination of these means, alteration in pharmacokinetics and duration of action are to be expected. Actually, rates of plasma clearance for rocuronium decrease with increasing age and are inversely proportional to the duration of neuromuscular blockade produced by rocuronium.[1] It is therefore recommended that subsequent doses should be administered only after reappearance of some train-of-four (TOF) responses in the elderly surgical patients. However, even in older patients, maintenance of intense neuromuscular block is required to prevent unintentional coughs, hiccups, muscle stiffness and body movement that seriously disturb the surgical procedure, especially in patients undergoing thoracoabdominal surgery or microscopically controlled endoscopic surgery. To achieve this, a post-tetanic count (PTC) of zero at the adductor pollicis muscle[2] accurately indicate intense neuromuscular block. The time from administration of rocuronium to the first response of the adductor pollicis to PTC stimulation was expected to be longer with advancing age, although there is so far no report in the literature to support our assumption. Therefore, the present study was designed to determine the effects of age on the duration of rocuronium-induced intense neuromuscular block between older and younger adult patients.

Methods

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 44 patients consented to participate in this study. Patients were American Society of Anesthesiologists

Financial support: *Departmental funding.*

physical status I–II, aged between 20–60 years or 70 years of age or older, and undergoing elective surgery under general anaesthesia. None of the patients had neuromuscular, hepatic or renal disorders, nor were they taking any drug known to interact with neuromuscular blocking agents. Patients whose body mass index was ≥ 25 or < 18.5 kg/m^2 were excluded from the study. Premedication consisted of 150 mg ranitidine administered orally before going to bed on the night before surgery and on the morning of surgery. On arrival at the operating room, all patients were monitored with electrocardiogram and non-invasive blood pressure and pulse oximetry. Acetated Ringer's solution (8–10 ml/kg/h) was intravenously infused in the left forearm of the patients via a cannula. General anaesthesia was induced with 2 μg/kg fentanyl and 1–2 mg/kg propofol intravenously (i.v.) while patients received 100% oxygen through an anaesthesia face mask. Patients' tracheae were intubated after rocuronium-induced complete neuromuscular block, and anaesthesia was maintained with 1.0–1.5% end-tidal sevoflurane and a continuous infusion of 0.1–0.3 μg/kg/min remifentanil and fentanyl as required. Ventilation was adjusted to maintain end-tidal carbon dioxide between 4.3 and 5.1 kPa using a BP-608EV (Omron Colin Inc., Tokyo, Japan). The rectal temperature of the patients was maintained at > 36°C using a warming mattress blanket (Bair Hugger model 750, Arizant Healthcare Inc., Eden Prairie, MN, USA). Using a surface probe equipped in the acceleromyographic device, skin temperature over the adductor pollicis muscle was recorded every 15 s throughout the experiment and maintained at > 32°C.

Rocuronium regimen and neuromuscular monitoring

After induction of anaesthesia, neuromuscular monitoring was started using an acceleromyograph (TOF-Watch SX, Organon Ltd, Dublin, Ireland). Stabilization and calibration of the monitoring were performed according to good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents.[3] The acceleration transducer was placed in the Hand Adaptor (Organon Ltd) to increase the precision of acceleromyography,[4] and the fingers were fixed to the arm board. To enhance stabilization, a 50 Hz tetanic stimulus was applied over 5 s on the ulnar nerve at the wrist. Thereafter, the nerve was stimulated with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s, and contraction of the ipsilateral adductor pollicis was measured using an acceleromyograph. When the response to TOF was stabilized, calibration and supramaximal stimulation was ensured by the built-in calibration function (CAL2) of the acceleromyograph. After obtaining stable baseline in at least 2 min, all patients received 1 mg/kg rocuronium i.v. A PTC mode was initially applied 5 min after obtaining complete neuromuscular block and repeated every 6 min.[5] When the first response to PTC stimulation was detected, 0.2 mg/kg rocuronium was administered. The times from initial and second administration of rocuronium to the first detectable response to PTC stimulation were recorded. The times were compared between elderly and younger adult patients.

Statistics

The sample size was calculated based on previous data on the average interval between administration of 1 mg/kg rocuronium and the first response to PTC in younger adult patients (35.2 ± 9.5 min).[6] We considered a 25% increase in the time interval as being clinically relevant. To obtain statistically significant results with $\alpha = 0.05$ and a power of 0.80, it was necessary that 20 patients be included in each group. To compensate for any dropouts, we enrolled 22 patients in each group. Data are presented as median value (range) or mean (standard deviation). Statistical analysis was performed using the StatView software for Windows (SAS Institute, Cary, NC, USA). The Mann–Whitney test or unpaired Student's *t*-test was used for comparing data between the two groups. A *P*-value of < 0.05 was considered statistically significant.

Results

Data from two patients in the younger group were excluded from analysis because of repeated system errors of the PTC mode. Except for age, patient characteristics did not differ between the two groups (Table 1). Median values (range) of the times from

Table 1

The characteristics of the patients.

	Younger patients	Older patients
Age (year)	39.6 (11.7) (19–58)	76.2 (6.4) (70–91)*
Gender (M : F)	14 : 6	16 : 6
Height (cm)	165.4 (12.5)	159.8 (9.5)
Weight (kg)	63.8 (12.0)	57.8 (7.4)

*$P < 0.05$ vs. younger patients. Data are presented as mean (standard deviation) (range).

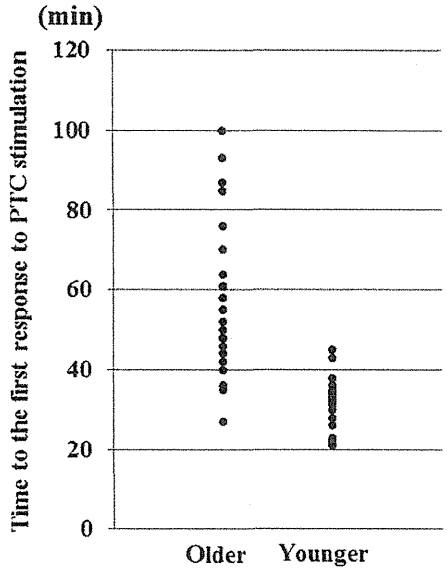

Fig. 1. The times from the administration of 1 mg/kg rocuronium to the first detectable response to the post-tetanic count (PTC) stimulation in older and younger patients.

the administration of 1 mg/kg and 0.2 mg/kg of rocuronium to the first response to PTC stimulation were significantly longer in the older [51.0 (27–100) min, $P < 0.0001$ and 30.0 (12–66) min, $P = 0.0036$, respectively] than younger patients [31.5 (21–45) min and 18.0 (12–36) min, respectively]. More than twofold greater variability of the times from the administration of 1 mg/kg rocuronium to the first detectable PTC was shown in older patients when compared with younger patients (Fig. 1).

Discussion

This study shows that a median value of the time interval between rocuronium injection and reappearance of the first response to PTC stimulation is significantly age-related and approximately twofold longer in older patients than younger adults. In addition, a more intriguing result we showed is a wider variability of duration of the action of rocuronium-induced intense neuromuscular block until detection of the first PTC. Even in healthy elderly patients, the pharmacokinetic changes impact on duration of the action of rocuronium are unpredictable, and therefore, the dosing interval of rocuronium should be adjusted according to the patient's inter-individual variation, and neuromuscular monitoring should be used to maintain an intense neuromuscular block.

The results of previous studies have indicated that recovery from rocuronium-induced neuromuscular block to reappearance of TOF responses, i.e. duration to moderate neuromuscular block, is prolonged in older patients when compared with younger adults because the elimination of rocuronium from the patient's body decreases in relation to age-dependent decreases in hepatic and renal blood flow.[1] In addition, the dose of rocuronium, calculated on the basis of actual body weight, may actually be overdosing for the elderly because of the decreased muscle mass and increased fat mass and a lower volume of distribution of rocuronium in older patients, which may result in a higher plasma concentration of rocuronium even when the same dose of rocuronium was administered.[1] However, a difference in the duration of rocuronium-induced intense neuromuscular block between older and younger adults has not been reported. Baykara and colleagues reported that the first response to PTC stimulation appeared earlier in children than adults following rocuronium injection,[7] while the time from administration of 1 mg/kg rocuronium until detection of the first PTC did not differ between elderly and younger adult patients (38.5 vs. 35.2 min).[6] The interval between onset of rocuronium action and the first detectable response to PTC stimulation monitored in elderly patients of this study was much longer (57.4 min) than that of Baykara study. It is reasonable to assume that age-associated decline in the clearance of rocuronium is related to a decline in physiological function, which explains the significantly slower recovery of the PTC from rocuronium-induced neuromuscular block in elderly patients. The study by Baykara and colleagues was done during intravenous anaesthesia using propofol and opioid,[6] while our present results were obtained during sevoflurane anaesthesia. It is therefore likely that sevoflurane may contribute to the longer duration of action of rocuronium in elderly patients of this study. Sevoflurane pharmacodynamically potentiates neuromuscular blockade,[8] and especially in older patients, decreases peripheral blood flow[9] and may reduce the elimination of rocuronium from the neuromuscular junction.

The result of the present study regarding wide variability of duration of the action of rocuronium shown in elderly patients can be supported by the previous result[10] reported by Arain and colleagues. The study demonstrated that there was a greater variability of each time range of the duration of neuromuscular blockade by 0.6 mg/kg rocuronium

(33–119 min) and 0.1 mg/kg vecuronium (35–137) for the recovery of T1 in the TOF responses to 25% of control in elderly patients. In contrast to the steroidal neuromuscular blocking agents primarily eliminated in the bile, the action of atracurium and cisatracurium eliminated by Hofmann elimination is independent of ageing and predictable even in elderly patients.[10–12] It is anticipated that the duration of intense neuromuscular block produced by atracurium and cisatracurium unresponsive to the PTC stimulation should also be unaffected by advanced age, however, further studies will be needed to verify the prediction.

PTC stimulation has previously been investigated and clinically used to estimate the approximate interval to reappearance of the first twitch in response to TOF stimulation during deep neuromuscular blockade.[5] However, the PTC mode is also useful for maintaining intense or deep neuromuscular block to prevent unintentional patient's movement during clinical anaesthesia. A previous study demonstrated that a PTC level of zero observed at the adductor pollicis muscle was necessary to achieve total diaphragmatic paralysis.[2] Therefore, to ensure an intense neuromuscular block and to prevent unexpected bucking or coughing during physical and autonomic surgical stress, the PTC stimulation mode is very informative.

In conclusion, the duration of rocuronium-induced intense neuromuscular block is markedly prolonged in older patients. It is, therefore, recommended to monitor neuromuscular function and adjust the dosing interval of rocuronium accordingly, particularly in elderly patients.

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Address:
Takahiro Suzuki
Department of Anaesthesiology
Nihon University School of Medicine
30-1 Oyaguchi Kamimachi
Itabashi-Ku, Tokyo 173-8610
Japan
e-mail: suzukit@cd5.so-net.ne.jp