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ORIGINAL ARTICLE

A large individual variation in both the infusion rate and the blood concentration of rocuronium necessary for obtain adequate surgical muscle relaxation during total intravenous anesthesia with propofol and remifentanil

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Abstract
Background Rocuronium (Rb) is ideal for continuous infusion but has a widely variable duration of action. We investigated the distribution of Rb infusion in a steady state of optimal muscle relaxation and the relationship between the measured and predicted blood Rb concentrations in laparoscopic surgery.
Methods Seventeen patients were anesthetized with propofol. Continuous Rb infusion was commenced at 7.5 μg/kg/min from 15 min after an initial Rb injection (0.6 mg/kg) and adjusted every 15 min to keep T_1 within 3–10 %. Blood concentration was measured at the first onset of steady state, predicted concentration was calculated pharmacokinetically, and 25 % recovery time was measured. The distribution of the predicted concentration and infusion rate was plotted by histogram, the median value and 95th percentile were calculated, and the relationship between measured and predicted concentrations was analyzed by regression analysis.
Results The rate during the stable state was 7.3 ± 2.1 μg/kg/min on average, 4 at minimum, 12 at maximum, and 12 at the 95th percentile. The predicted concentration was 1.7 ± 0.5 μg/ml on average, 0.8 at minimum, and 2.9 at maximum. The mean measured concentration was 1.4 ± 0.4 μg/ml. The predicted concentration was proportional to the measured concentration ($y = 0.91x$, $r = 0.475$; $p < 0.001$). A significant linear relationship was observed between the measured concentration and infusion rate ($y = 0.64 + 0.11x$, $r = 0.618$; $p < 0.05$).
Conclusion The measured blood concentration of Rb was comparable to the predicted value. Anesthesiologists can avoid overdose and attain a reliable muscle relaxant effect by maintaining a continuous dose by titration according to individual differences under muscle relaxant monitoring.

Keywords Rocuronium · Continuous infusion · Pharmacodynamics · Propofol · Laparoscopic surgery

Introduction

Rocuronium bromide (Rb), a nondepolarizing muscle relaxant, has a faster onset of action and lower metabolic rate than the traditional nondepolarizing muscle relaxants pancuronium bromide and vecuronium bromide. Rb is also unlikely to sustain prolonged muscle relaxation as a result of the accumulation of metabolites, as Rb metabolites are about 20 fold less metabolically active than Rb [1, 2]. These features make Rb an ideal drug for continuous infusion. However, studies on Rb have revealed large individual differences in the duration of action and the infusion rate necessary to obtain stable muscle relaxation [3]. If anesthesiologists are to use Rb as a muscle relaxant by continuous infusion, it will be useful to determine the optimal rate of continuous Rb infusion for sufficient muscle relaxation in the majority of patients, and also the time required for recovery after the Rb infusion is discontinued.

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Because the pharmacokinetics of Rb can be explained with the three-compartment model [1], the blood concentration of Rb can be predicted by pharmacokinetic simulation based on drug administration history. The blood concentration of Rb also explains the agent's muscle relaxant effect, as Rb has an extremely low metabolic rate and a metabolite without drug activity. To obtain stable muscle relaxation, it would be reasonable to simply maintain the Rb concentration at the level calculated to be sufficient for obtaining the desired effect in pharmacokinetic models.

The aims of this study were to measure the individual variation of the blood concentration of Rb, to calculate the rate of Rb infusion necessary for maintaining a surgical state of muscle relaxation by monitoring muscle relaxation, and to evaluate the accuracy of blood Rb concentrations calculated by pharmacokinetic simulation during laparoscopic surgery, a procedure in which surgeons often request sufficient muscle relaxation.

Methods and materials

This study was approved by our institutional ethical committee, and written informed consent was obtained from the patients before the surgery. Seventeen patients scheduled for laparoscopic surgery under general anesthesia with propofol (age, 20–65 years; ASA physical status 1 or 2) were enrolled in this study. Patients were excluded if any one of the following criteria applied: probably pregnant, abnormal serum electrolytes (Na^+, K^+, Cl^-), liver dysfunction (ALT and/or AST more than twice the normal range), renal dysfunction (serum creatinine greater than 2.0 mg/dl), emaciation [body mass index (BMI) less than 17], obesity (BMI more than 30), neuromuscular disorders, a history of hypersensitive reaction to Rb, systemic allergy, or hypothermia during anesthesia, or a history of treatment with drugs known to interact with Rb, such as aminoglycoside antibiotics, anticonvulsants, formulation lithium, or magnesium.

An epidural catheter was inserted before general anesthesia if the patient was also scheduled for epidural anesthesia during and/or after surgery. Remifentanil infusion was initiated at 0.5 μg/kg/min at least 5 min after the initial administration of oxygen by mask. Three minutes after initial remifentanil infusion, propofol was initiated at 4 μg/ml via a target-controlled infusion (TCI) pump.

After confirming loss of consciousness, the muscle contraction of the adductor pollicis in response to electrical stimulation of the ulnar nerve by a muscle relaxation monitor (TOF watch SX; MSD, Tokyo Japan) was continuously recorded and monitored (under manual ventilation) by a personal computer (Windows XP) running TOF Watch SX Monitor software (2.2. INT version). A hand adaptor was affixed to the palm of the hand and thumb to make an elastic preload and reproducible measurement. After stabilizing twitch height to the repetitive stimulation of 1 Hz twitch, the twitch was calibrated to 100 % and expressed as a percentage of control. The Rb dose for rapid intravenous injection was set at 0.6 mg/kg after the calibration was completed, based on the ideal body weight (IBW) derived from a body mass index (BMI) of 22. The tracheal tube was inserted after the maximum blocking effect (twitch height less than 10 %) was observed, subsequent controlled ventilation was initiated, and the stimulation mode was switched to train-of-four (TOF) on the TOF Watch SX monitor. The target concentration of propofol was titrated to maintain the bispectral index (BIS) in a range from 40 to 50. Analgesia was supported by the additional administration of local anesthetic from the epidural catheter or by changing the infusion rate of remifentanil in response to surgical stress. A forced-air warming device (Bair Hugger Model 750; Nihon Kohden, Tokyo, Japan) was attached to keep esophageal temperature above 36.0 °C and also to keep skin temperature of the hand with the acceleration sensor above 32.0 °C.

Continuous infusion of Rb was initiated at 7.5 μg/kg/min from 15 min after the first injection, and the infusion rate was changed every 15 min to keep the twitch height within the desired range of 3–10 %. The steady-state infusion rate for optimal muscle relaxation was determined whenever the infusion rate necessary to stay within the desired percent T_1 range remained unchanged for more than 15 min. At the first point of steady-state infusion, a 5-ml blood sample was obtained from an arterial catheter (placed for evaluation of invasive blood pressure) and stored for blood concentration measurement.

Table 1 Questionnaire to surgeons

Question 1. How did you feel about the muscle relaxation state of the patient during surgery?
A. Excellent: Easy to achieve surgical procedures without bucking or body movement
B. Good: No bucking or body movement to prevent surgical procedures
C. Fair: Additional muscle relaxation to some bucking or body movement
D. Bad: Interruption of surgical procedure by body movement of the patient
Question 2. Do you want to request the same management of muscle relaxation for the next case?
A. Yes, absolutely request the same management
B. Yes, maybe request the same management
C. Not really
D. Never, request other management

The Rb infusion was discontinued at the end of the laparoscopic surgery, and recovery from muscle relaxation was observed for as long as possible until the TOF ratio recovered above 0.9. If the propofol concentration dissipated to a waking level and the patient approached recovery of consciousness before the TOF ratio was recovered, sugammadex 2 mg/kg or a mixture of atropine sulfate 1 mg and neostigmine 2 mg was injected intravenously to antagonize the muscle relaxant. Once the muscle relaxation effect decreased and the TOF ratio increased above 0.9 (either through spontaneous recovery or administration of antagonist), nerve stimulation was discontinued and the patient was awakened. Before discharging the patient from the operating room, one of the surgeons filled out a questionnaire to evaluate the intraoperative management of muscle relaxation (Table 1).

The optimal Rb infusion rate for the steady-state muscle relaxant effect and the duration from the end of infusion to recovery of T_1 to 25 % were measured based on administration history and records from the TOF watch SX Monitor. In addition, the predicted blood concentration of Rb was calculated by pharmacokinetic simulation with TIVA Trainer software (ver.8, Euro SIVA) using the parameters reported by Wierda et al. [1].

The blood samples collected for measurement of Rb blood concentration were centrifuged for 15 min at 3,000 rpm to extract 2-ml samples of plasma and were immediately stored frozen at −20 °C after adding 1 ml 0.1 M dibasic sodium phosphate hydrate. The Rb concentrations were measured by liquid chromatography-tandem mass spectrometry.

For statistical analysis, a histogram representing the distribution of the predicted blood concentration and Rb infusion rate during stabilization was prepared and the median value (50th percentile) and 95th percentile were calculated to determine the ED_{50} and ED_{95}. The relationship between the measured and predicted blood concentrations of Rb was analyzed by regression analysis, and the median performance error (MPE) and median absolute performance error (MDAPE) were calculated to evaluate the discrepancy between measured and predicted values.

Values are shown as mean ± standard deviation. A p value <5 % is considered statistically significant.

Results

Seventeen patients were recruited for this study (Table 2). Only 13 of the patients were included in the analysis of the time to 25 % T_1 recovery, as the impact of the accelerometer during the surgery impeded appropriate evaluation in some of the cases. Rb blood concentration data on 15 patients were used, as a problem in sample processing corrupted the data of 2 cases.

Table 2 Patient characteristics

Characteristic	
Sex	
Female (*n*)	8
Male (*n*)	9
Age (years) mean ± SD (range)	56.1 ± 8.5 (36–65)
Weight (kg) mean ± SD (range)	61.6 ± 10.8 (46.6–85.5)
Height (cm) mean ± SD (range)	163.1 ± 7.3 (152–175)
BMI (kg/m^2) mean ± SD (range)	23.0 ± 2.9 (18.7–29.2)

BMI body mass index

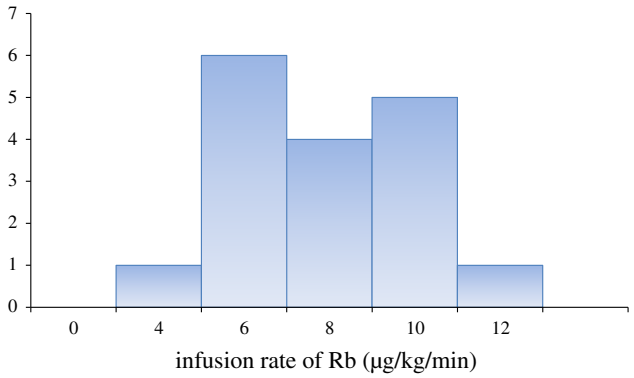

Fig. 1 Distribution of rate of Rb infusion during a stable state of optimal muscle relaxation. Infusion rate during the stable state of optimal muscle relaxation was 7.3 ± 2.1 (95 % CI: 6.27–8.33, $n = 17$) μg/kg/min on average, 4 μg/kg/min at minimum, 12 μg/kg/min at maximum, 7 μg/kg/min at median, and 12 μg/kg/min at 95th percentile

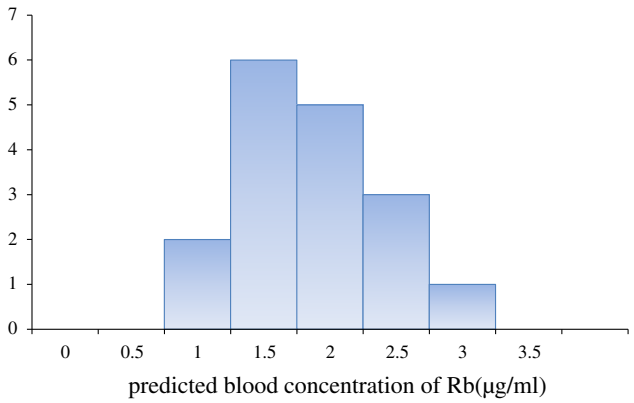

Fig. 2 Distribution of predicted blood concentration during a stable state of optimal muscle relaxation. Predicted blood concentration during the stable state of optimal muscle relaxation was 1.7 ± 0.5 (95 % CI: 0.67–1.95, $n = 17$) μg/ml on average, 0.8 μg/ml at minimum, 2.94 μg/ml at maximum, and 1.5 μg/ml at median

Figures 1 and 2 show distributions of the rate of Rb infusion and the predicted blood concentration during a stable state of optimal muscle relaxation. The infusion rate

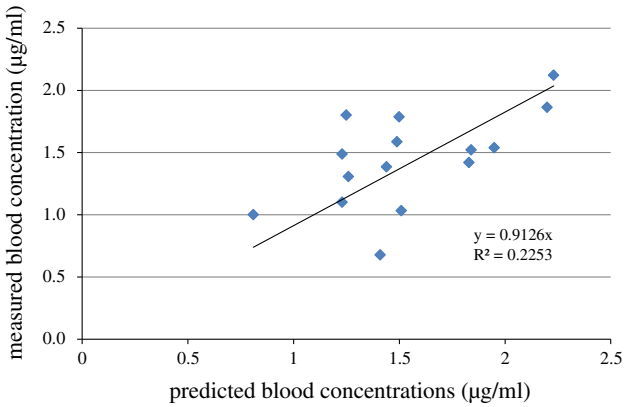

Fig. 3 Relationship between measured and predicted blood concentrations of Rb during stable state of optimal muscle relaxation. Mean measured blood concentration was 1.4 ± 0.4 (95 % CI: 0.30–1.61, $n = 15$) μg/ml. Predicted concentration was proportional to this measured concentration, with good correlation ($y = 0.91x$, $r = 0.475$, $p < 0.001$). Median performance error (MPE) and median absolute performance error (MDAPE) were −4.85 (%) and 19.15 (%), respectively

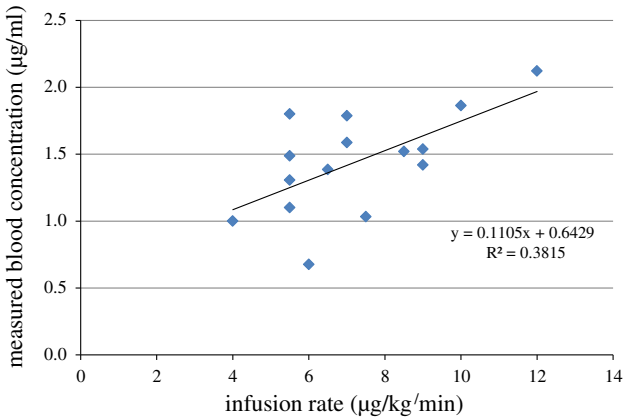

Fig. 4 Relationship between measured blood concentration and rate of Rb infusion during stable state of optimal muscle relaxation. A significant linear relationship was observed between the measured blood concentration and the infusion rate ($y = 0.64 + 0.11x$, $r = 0.618$, $p < 0.05$)

during the stable state of optimal muscle relaxation was 7.3 ± 2.1 μg/kg/min (95 % CI: 6.27–8.33, $n = 17$) on average, 4 μg/kg/min at minimum, 12 μg/kg/min at maximum, 7 μg/kg/min at median, and 12 μg/kg/min at the 95th percentile. The predicted blood concentration was 1.7 ± 0.5 μg/ml (95 % CI: 0.67–1.95, $n = 17$) on average, 0.8 μg/ml at minimum, 2.9 μg/ml at maximum, and 1.5 μg/ml at median.

Figure 3 shows the relationship between the measured and predicted blood concentrations of Rb during a stable state of optimal muscle relaxation. The mean measured blood concentration was 1.4 ± 0.4 μg/ml (95 % CI: 0.30–1.61, $n = 15$ μg/ml). The predicted concentration

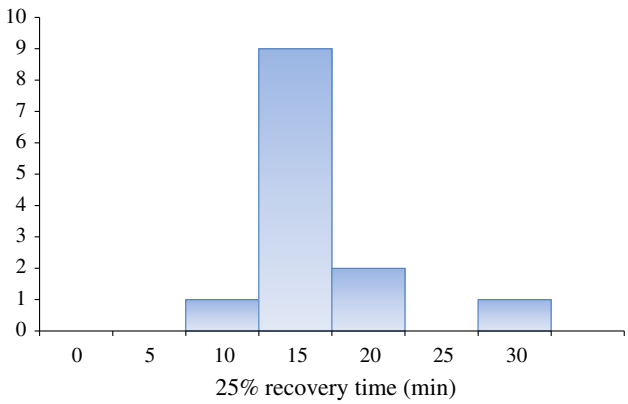

Fig. 5 Distribution of the time to 25 % T_1 recovery after end of Rb infusion. Time to 25 % recovery was 15.0 ± 4.7 min (95 % CI: 13.8–17.7 min), on average

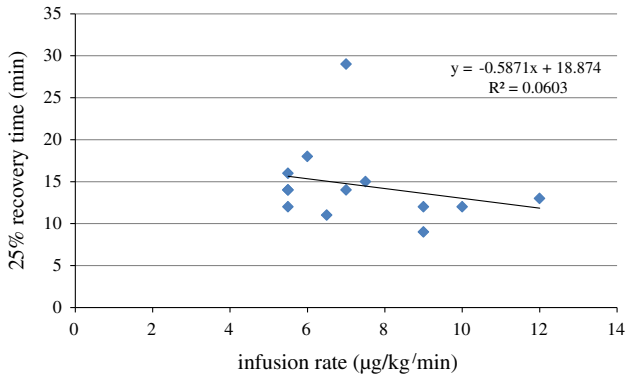

Fig. 6 Relationship of time to 25 % T_1 recovery with infusion rate after end of Rb infusion. Time to 25 % T_1 recovery was not significantly correlated with infusion rate

was proportional to this measured concentration, with good correlation ($y = 0.91x$, $r = 0.475$, $p < 0.001$). The median performance error (MPE) and median absolute performance error (MDAPE) were −4.85 (%) and 19.15 (%), respectively.

Figure 4 shows the relationship between measured blood concentration and rate of Rb infusion during a stable state of optimal muscle relaxation. A significant linear relationship was observed between the measured blood concentration and the infusion rate ($y = 0.64 + 0.11x$, $r = 0.618$, $p < 0.05$).

Figure 5 shows the distribution of the time to 25 % T_1 recovery after the end of Rb infusion: time to 25 % recovery was 15.0 ± 4.7 min (95 % CI: 13.8–17.7 min). Figures 6 and 7 show the relationship of the time to 25 % recovery with infusion rate and predicted blood concentration at the end of infusion, respectively. The time to 25 % T_1 recovery was not significantly correlated with the blood concentration or infusion rate.

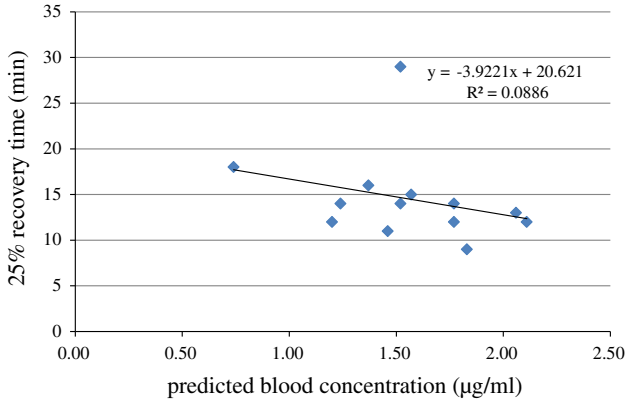

Fig. 7 Relationship of time to 25 % T_1 recovery after end of Rb infusion with predicted blood concentration

No adverse body movements, bucking, coughing, or other adverse events involving muscle relaxation were observed during the surgeries in this study. The postoperative questionnaire surveys showed that all the surgeons (100 %) were satisfied with, and actually preferred, optimal muscle relaxation by continuous Rb infusion with muscle relaxation monitoring.

Discussion

A clinical trial of Rb development in Japan determined that the average rate of Rb infusion was 7.5 μg/kg/min in a stable state of muscle relaxation during surgery under total intravenous anesthesia with propofol [4]. On this basis, the manufacturer recommended an initial Rb infusion rate of 7 μg/kg/min on the package insert [5]. The average infusion rate of 7.3 μg/kg/min obtained in our study was similar to that reported from the clinical trial; hence, we consider our patients similar to the patients of the trial study. The earlier study by Takagi et al. [4], however, yielded little information on individual differences or variations in the rates of continuous Rb infusion. This lack led to problems after the launch of Rb in Japan, because large individual differences prevent anesthesiologists from providing stable muscle relaxation with an averaged rate for continuous infusion of Rb. The present study confirmed that the infusion rate at surgically optimal muscle relaxation varied by as much as threefold in a range from 4 to 12 μg/kg/min. Individual differences in pharmacodynamics are also generally assumed to vary by threefold, so the same presumably holds true for Rb. Overall, however, a favorable approach for managing the individual differences in the continuous administration of Rb has been a challenge.

The present study confirmed that the predicted blood concentrations of Rb calculated by pharmacokinetic simulation with the parameters reported by Wierda et al. [1] were equal to the measured blood concentrations in our Japanese patients at the first onset of stable-state muscle relaxation. This finding suggests that the Rb concentration predicted by pharmacokinetic simulation can be substituted for a measured concentration in clinical practice. It also confirmed that maintenance of a stable Rb concentration can be achieved by adjusting the rate of Rb infusion, as the blood concentration of Rb was well correlated with the infusion rate in the stable state of muscle relaxation. This finding suggests that it would be reasonable to use the optimal Rb concentration predicted by pharmacokinetic simulation in an individual to maintain a stable state of muscle relaxation.

Muscle relaxants are administered to assure reliable immobilization. Anesthesiologists should note that sufficient muscle relaxation is only attainable in about 50 % of patients when the average value for Rb infusion is set. To manage a sufficient drug effect, the anesthesiologist should choose an effective concentration of 95 or 99 % (EC_{95} or EC_{99}) as the target drug concentration. Thus, pharmacodynamics information such as EC_{95} and EC_{99} is essential for obtaining stable and sufficient muscle relaxation with continuous infusion of Rb. Judging from distribution of the Rb infusion rate required to obtain the optimal muscle relaxation for surgery in the present study, we estimate that an initial rate of 12 μg/kg/min Rb for continuous infusion (a rate corresponding to EC_{95} in the present study) will lead to optimal muscle condition reliably in more than 95 % of patients. In addition, the EC_{95} in our study was almost equal to the values for the initial speed of Rb (from 10 to 12 μg/kg/min) on the package insert in the United States (Zemuron; Merck, Rahway, NJ, USA) [6].

The easiest method to ensure sufficient muscle relaxation is to increase the Rb infusion rate to ED_{95} or ED_{99}. These rates, however, deliver excessive doses for many patients, as uniformly high doses prolong the recovery from muscle relaxation. By adjusting the dose according to the individual differences determined through conventional muscle relaxant monitoring in lieu of a uniform dose such as ED_{95}, sufficient muscle relaxation can be maintained even at low Rb concentrations in blood. Some may request estimation of appropriate continuous Rb injection rates or blood concentrations according to individual variations using pharmacokinetics at the bedside, either in combination with or as an alternative to muscle relaxation monitoring. The questionnaire responses by the surgeons in the present study clearly evinced that the surgeons could perform the procedure with less difficulty when they used our proposed method for obtaining sufficient muscle relaxation.

Ito et al. reported that the recovery time of % T_1 from stable surgical muscle relaxation to 25 % was from 12 to

20 min, regardless of the duration of the infusion [7]. The patients in the present study recovered very quickly from stable surgical muscle relaxation after the continuous infusion was stopped, which suggests that the appropriate adjustment of Rb infusion using a muscle relaxation monitor eliminates the risk of residual muscle relaxant effects. The use of Rb continuous infusion in clinical anesthesia is also thought to improve safety because sugammadex, a specific antagonist to Rb that reverses muscle relaxation effect quickly and securely, is now available.

Although individual differences were large, the measured blood concentration of Rb was comparable to the predicted concentration during continuous Rb infusion at the rate necessary to obtain stable surgical muscle relaxation. An initial Rb infusion rate of 12 μg/kg/min (ED_{95}) was sufficient to maintain adequate muscle relaxation in almost all the patients, but not without posing a risk of overdose. To avoid overdose and obtain a reliable muscle relaxant effect during continuous Rb infusion, the dose should be maintained by titration according to individual differences under muscle relaxant monitoring.

Conflict of interest None.

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