Method for Prediction of Efficacy of Sugammadex Administered to Recover from Rocuronium-Induced Neuromuscular Blockade in Gynecological Laparoscopic Surgery Cases

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Sugammadex (SDX), a neuromuscular blocking-reversal agent, quickly reverses neuromuscular blockade induced by rocuronium (RCR). SDX dosage is set according to the state of neuromuscular blockade determined with a neuromuscular monitoring device. However, in clinical situations, such a devise is not frequently used. Here, we report construction of a method for theoretically setting SDX dose by which the optimum reverse time (RT) can be obtained for individual patients even when the device is not available. The subjects were 42 adult female patients who underwent laparoscopic surgery from 1 August 2015 to 31 March 2016, during which RCR and SDX were administered. We formulated an equation for theoretically calculating the RCR residual ratio (RR) in blood after SDX administration. Furthermore, we examined the relationship between RR and RT. Based on the results obtained, we developed a method for predicting RT using RR. The number of subjects with a prediction error of RT within ±1 min was 36 (87.8%) of 41 in multiple regression analysis. We could predict RT following SDX administration by using the RT prediction expression with RR obtained for subjects administered RCR during the surgery. Furthermore, our results suggest that the SDX dose able to achieve optimum RT may be set prior to surgery on the basis of the present methodology.

Key words sugammadex; rocuronium; gynecological laparoscopic surgery; reverse time prediction

It has been reported that the period of hospitalization could be reduced, and patient QOL and surgical results improved by use of laparoscopic surgery as compared to a laparotomy in the field of gynecology. With laparoscopic surgery, use of a neuromuscular blocking agent is required for expanding the surgical field and preventing sudden body motion. Rocuronium (RCR), a widely used neuromuscular blocking agent, is known to have a reduced bradycardia effect when used for gynecological laparoscopic surgery and less bioaccumulation because an active metabolite is absent, and a significantly shorter time of onset of action is available and reduced time for completing tracheal intubation can be achieved. Meanwhile, at the completion of the surgery, sugammadex (SDX) is often used as a neuromuscular blocking-reversal agent for shortening the time of recovery from muscle relaxation and preventing a residual relaxation effect. SDX, a derivative of γ-cycloextrin, has also been reported to reverse neuromuscular blockade more quickly and safety than conventional cholinesterase inhibitors by forming an inclusion compound with RCR in blood to reduce the concentration of the neuromuscular blocking agent in the neuromuscular junction. The dose of SDX is set according to the state of neuromuscular blockade producing muscle relaxation, which can be determined with a neuromuscular monitoring device. In cases when a monitoring device was not available, residual neuromuscular blockade has been reported to occur in 8.0–9.4% of patients administered SDX, with complete reverse unattainable. Thus, the recent recommendations stated that the reversal of neuromuscular blockade should be monitored using the monitoring device. However, in clinical situations, such a monitor is not frequently used for the assessment of neuromuscular blockade. Therefore, until the monitoring devise is available in every institution, it is necessary to develop a methodology for setting SDX dose that attains optimum reverse time (RT) with presently available data.

For the present study, we enrolled patients who underwent gynecological laparoscopic surgery and attempted to construct a method for theoretically setting SDX dose by which the optimum RT can be obtained for individual patients even when the monitoring device is not available.

MATERIALS AND METHODS

The study was performed after receiving approval from the ethics committees of Saiseikai Yokohamashi Tobu Hospital and Tokyo University of Pharmacy and Life Sciences. We also received permission to use opt-out in which potential participants are given the opportunity to decline further contact about the study instead of written informed consent because this study was retrospective study.

We formulated an expression for theoretical calculation of the residual ratio (RR) of RCR in blood after SDX administration. We also retrospectively examined the relationship between RR and RT by setting the train-of-four (TOF) ratio...
for recovery at 0.9 after SDX administration as an index of efficacy. Based on our results, we constructed a novel method for predicting RT by use of RR.

We enrolled 42 adult female patients who underwent laparoscopic surgery in the Department of Obstetrics and Gynecology, Saiseikai Yokohamashi Tobu Hospital from August 1, 2015 to March 31, 2016. During surgery, each was administered RCR as a neuromuscular blocking agent and then SDX at completion of the operation to reverse the effect when a shallow neuromuscular block (time of T2 reappearance) remained. Furthermore, an outlier test was performed using the RT of all subjects obtained to excluding RT outlier data from analysis.

We used the RR of RCR as an index to express RCR levels in blood before and after SDX administration. RR was defined as the ratio of the level of protein unbound RCR ([C], μM) multiplied by the unbound fraction (fu: 0.698). For [C], the value was calculated with an ORSYS blood level simulator (DOE mL, Ltd., Hokkaido, Japan) using the values of the pharmacokinetic parameter reported by Zsenohradzsky et al. in which the elements of hepatic function are not taken into account.

\[\text{RR} = \left(\frac{[C]}{[C]\times fu}\times 100\right)\]

Where, as shown in Eq. 2, \([C]\times fu\) is the RCR concentration ([C], μM) multiplied by the unbound fraction (fu: 0.698). For [C], the value was calculated with an ORSYS blood level simulator (DOE mL, Ltd., Hokkaido, Japan) using the values of the pharmacokinetic parameter reported by Zsenohradzsky et al. in which the elements of hepatic function are not taken into account.

\[\text{[C]} = \frac{[S]}{[S]\times [C]\times fu}\] (2)

Meanwhile, \([C]\times fu\) was calculated using equations that took into consideration the coupling ability between SDX and RCR, as shown below.

Initially, Eq. 3 for the SDX-RCR coupling constant is shown. Where, \([S]\) is the concentration of free SDX (μM) and \([SC]\) the concentration of the SDX-RCR complex (μM).

\[K = \frac{[SC]}{[S]\times [C]}\] (3)

The total concentration of SDX ([S]tot, μM) is expressed with Eq. 4, thus \([SC]\) can be expressed with Eq. 5.

\[[S]_{\text{tot}} = [S] + [SC]\] (4)

\[\text{[SC]} = \frac{K\times [C]}{1 + K\times [C]}\] (5)

[C] can be expressed with Eq. 6 and \([C]\) is the concentration (μM) of RCR after SDX administration.

\[\text{[C]} = \frac{[SC]}{[C] + \frac{1}{fu\times [C]}\times [C]\times fu\times [C] + [C]}\] (6)

Then, Eq. 7, the quadratic equation of \([C]\), is obtained using Eqs. 5 and 6.

\[\frac{K}{fu}\times [C]\times fu\times [C] - \left(K\times [C] - K\times [S]_{\text{tot}}\times \frac{1}{fu}\times [C]\times fu\times [C] - [C] = 0\right)\] (7)

For \([S]_{\text{tot}}\), the value obtained by Eq. 9 is used.

\[\text{[S]}_{\text{tot}} = \frac{D_s\times 1000}{Vd\times MW}\] (9)

\[Vd = 4.29 + 0.03\times (Wt - 81.8)\] (10)

For an index of efficacy, the reverse time for recovery of the TOF ratio to 0.9 after SDX administration was used. The TOF ratio is the ratio of response (T4/T1) to the first stimulus (T1) and that to the fourth stimulus (T4) for 4 continuing stimuli, repeated every 0.5 s. TOF ratio is reduced as the neuromuscular blocking agent is more effective. For measurement of the ratio, a TOF Watch SX of Nihon Kohden Corporation, Tokyo, Japan was used. The RT and RR values calculated by use of Eqs. 1–10 were analyzed for each subject with simple linear regression to obtain the RT prediction expression.

In multiple regression analysis, for selection of explanatory variables when RT was used as a dependent variable, a total of 16 examination items, namely, age, kind of disease, anesthesia, height (Ht, m), weight (Wt, kg), standard body weight (StWt, kg), body mass index (BMI), albumin (ALB) (g/dL), blood urea nitrogen (BUN) (mg/dL), serum creatinine (Scr, mg/dL), alkaline phosphatase (ALP) (U/L), γ-glutamyl transpeptidase (γ-GTP) (U/L), total bilirubin (T-Bil, mg/dL), [C] (μM), SDX dose per weight (D/Wt, mg/kg), and RR, were utilized. StWt was calculated by using Ht with Eq. 11. For [C], the value obtained by the ORSYS device was used.

\[\text{StWt} = Ht^2 \times 22\] (11)

Then, the correlation between RT and each item was determined for selecting explanatory variables under the following three conditions: RR included, items other than RR that showed a significant correlation with RT, and items with a biological or medical relationship with RT. Multiple regression analysis was performed using the explanatory variables selected as noted above for obtaining an RT prediction expression.

For evaluating our RT prediction expression obtained by use of simple and multiple regression analyses, the following items were used: error obtained by subtracting predicted RT value from actual value, mean prediction error (ME), mean absolute prediction error (MAE), and root mean squared error (RMSE) calculated with Eqs. 12–14. The predicted value was regarded as unfavorable when the error was greater than ±1 min. ME, MAE, and RMSE expressed prediction bias, prediction accuracy, and dispersion of prediction expression, respectively. Values closer to 0 were considered to indicate a
more suitable prediction expression.

\[
\text{ME} = \frac{1}{N} \sum_{i=1}^{N} (at - pt_i) \\
\text{MAE} = \frac{1}{N} \sum_{i=1}^{N} |at - pt_i| \\
\text{RMSE} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (at - pt_i)^2}
\]

Where, \( N \) is the number of samples (41), \( at \) (min) is the actual time of RT, and \( pt \) (min) the predicted RT.

For testing for outliers, the Smirnov–Grubbs test was used. For simple linear regression analysis and for testing the correlation coefficient in the examination of the correlation between RT and each investigation item used as continuous variables, Pearson’s product-moment correlation coefficient was used. For testing the correlation coefficient in the examination of RT and each investigation item used as ordinal variables, Spearman’s rank-correlation coefficient was used. For calculating the power of multiple regression analysis, we used G*Power (version 3.1.9.2). For calculating the power of multiple regression analysis, we used EZR which is a graphical user interface for R (version 2.13.0). For calculating the power of multiple regression analysis, we used G*Power (version 3.1.9.2). For testing the correlation coefficient in the examination of the correlation between RT and each investigation item, with 3 selection criteria considered, \( StWt, Scr, T-Bil, \) and RR were selected as explanatory variables for multiple regression analysis. Those results suggested a positive relationship between RR and RT for each patient, though the correlation was not significant (\( r=0.165, p=0.303 \)).

RESULTS

For RT, the value for 1 of the 42 subjects was an outlier in Smirnov–Grubbs test findings (RT=5.75, \( p=0.0153 \)) and excluded from analysis. Table 1 shows characteristics of the present subjects. None was diagnosed with renal or hepatic impairment.

Table 2 shows RT values obtained with the TOF Watch SX® as well as calculated RR values. No relationship between RR and RT was observed.

The relationship between RR and RT in each subject, as shown in Table 2, was examined using simple regression analysis. RT prediction using RR was obtained with Eq. 15. Those results suggested a positive relationship between RR and RT for each patient, though the correlation was not significant (\( r=0.165, p=0.303 \)).

For selecting explanatory variables with RT as a dependent variable in multiple regression analysis, the correlation between RT and each item shown in Table 1 was examined. Those results are shown in Table 3. Among the examined items, with 3 selection criteria considered, \( StWt, Scr, T-Bil, \) and RR were selected as explanatory variables for multiple regression analysis. Those results showed that the \( p \) value for the explanatory variables as a whole revealed significance (\( F \) test, \( p=0.000205 \)) and the variance inflation factors of the explanatory variables were 1.04 –1.09 so that they were not affected by multicollinearity. Equation 16 was thus obtained for RT prediction.

\[
RT = 0.0610 \cdot StWt + 3.60 \cdot Scr + 1.39 \cdot T-Bil + 0.646 \cdot RR - 4.68
\] (16)

For the RT prediction expressions shown in Eqs. 15 and 16, the relationships between the measured and predicted RT values are shown in graph form (Fig. 1). Furthermore, Error, ME, MAE, and RMSE values were calculated (Fig. 2, Table 4). As a result, with Eq. 16, a nearly 1:1 relationship (1:0.91) was

### Table 1. Characteristics of Subjects Administered Rocuronium and Sugammadex

| Age; years | 42.2 (10) |
| Disease type | 
| ovarian disease | 21 (51%) |
| adenomyosis uteri | 2 (5%) |
| uterine myoma | 18 (44%) |
| Anesthesia type | 
| desflurane | 33 (80%) |
| sevoflurane | 8 (20%) |
| Height; cm | 158 (5) |
| Weight; kg | 55.1 (9.6) |
| Standard body weight; kg | 55.0 (3.8) |
| BMI | 22.0 (3.4) |
| ALB; g/dL | 4.50 (0.27) |
| BUN; mg/dL | 12.0 (3.0) |
| Scr; mg/dL | 0.608 (0.088) |
| ALP; U/L | 195 (51) |
| γ-GTP; U/L | 25.5 (29) |
| Total bilirubin; mg/dL | 0.589 (0.27) |
| [C]; µM | 1.99 (0.71) |
| Sugammadex dose per weight; mg/kg | 2.23 (0.83) |
| RR; % | 0.712 (0.17) |
| RT; min | 2.14 (0.97) |

Values are mean (S.D.) or number (proportion). BMI body mass index, ALB albumin, BUN blood urea nitrogen, Scr serum creatinine, ALP alkaline phosphatase, γ-GTP γ-glutamyl transpeptidase, [C] the level of rocuronium concentration just before sugammadex administration, RR residual ratio, RT reverse time.
observed between measured and predicted RT. The results for 34 (82.9%) of the 41 subjects had an error within ±1 min with Eq. 15 and 36 (87.8%) of 41 with Eq. 16, which showed a greater percentage for Eq. 16. Further, ME, MAE, and RMSE were closer to 0 with Eq. 16 as compared to Eq. 15. On the basis of these findings, we concluded that Eq. 16 is more suitable for predicting RT.

DISCUSSION

RCR is widely used as a neuromuscular blocking agent during surgery in the gynecology field, while SDX is often administered as a muscle relaxation reversal agent at the completion of surgery. In the present study, we focused on the relationship between the level of RCR in blood before and after SDX administration and RT. Based on those findings, we con-
structed a method for theoretically setting SDX dose by which the optimum RT can be obtained for individual patients even when a neuromuscular monitoring device is not available.

When the Fig. 3 scheme is clinically used, we thought that there is no time to measure the $[C_r]$ for calculating $D_v$. Thus, we considered using the ORSYS blood level simulator which can calculate the $[C_r]$ immediately and be placed in operating room. However, in a future study, it is necessary to measure the RCR concentration actually for improving the probability of this prediction method.

In the present study, the RR value for RCR was used as an index of quantitative changes in its level in blood before and after SDX administration. As shown in Eq. 1, RR is the ratio of $[C_r]$ to $[C]$. We used blood residual ratio instead of the residual RCR concentration in blood as an index, because we considered that RT could be evaluated by using that ratio before and after SDX administration, with the effect of individual differences in RCR concentration needed for onset of effect reduced.

For establishing a method for RT prediction using RR, analyses were made using data obtained from each subject. Initially, RR and RT obtained from the subjects were analyzed using simple regression to obtain Eq. 15, by which a positive relationship between them was suggested, though significance was not found ($r=0.165, p=0.303$). Those results suggested that RT cannot be accurately predicted for individual patients using RR alone (Fig. 1A). Next, we selected explanatory variables from data obtained at the time of SDX administration, which were used to examine the relationship between the explanatory variables and RT of each subject with multiple regression analysis. As a result, the $p$ value for the explanatory variables as a whole became significant ($F$ test, $p=0.000205$), from which Eq. 16 was obtained as an RT prediction expression.

The reasons for selecting $StWt$, $Scr$ and $T-Bil$ as explanatory variables other than RR are as follows. First, all had a significant correlation with RT (Table 3). Creatinine correlates with muscle mass, as it is the final metabolite of muscle. With greater muscle mass, the time to reduce RCR concentration in the neuromuscular junction is increased, thus $Scr$ was considered to be a good explanatory variable of RT. $StWt$ indicates physical effects, excluding that of body fat. As physical effects have increased influence, RCR concentration reduction requires a longer time period, thus it was thought to be proper to use $StWt$ as an explanatory variable for RT. However, since $Ht$, which has a correlation with $StWt$, showed a smaller correlation coefficient than $StWt$ (Table 3), $StWt$ was selected as an explanatory variable for RT. Furthermore, $T-Bil$ is related to hepatic and biliary disorders. RCR is excreted mainly to bile in an unchanged form and RCR excretion is prolonged when $T-Bil$ level is elevated, thus $T-Bil$ was considered to be appropriate for use as an explanatory variable of RT.

In multiple regression analysis, for the purpose of examining the validity of using 4 variables including RR, the power was calculated by use of a one-tailed test with an effect size of 0.35 and a error of 0.05. The power was determined to be 0.82, indicating that the 4 explanatory variables would not cause problems for the analysis.

The RT prediction expressions obtained in simple (Eq. 15) and multiple (Eq. 16) regression analyses were then compared. Our results showed a nearly 1 : 1 relationship ($r=0.91$) with Eq. 15, between the measured and predicted values for RT (Fig. 1). In addition, 34 (82.9%) of the 41 subjects showed an error value within ±1 min with Eq. 15, while 36 (87.8%) showed that with Eq. 16, the latter being greater (Fig. 2). ME, MAE, and RMSE with Eq. 16 were closer to 0 as compared to Eq. 15 (Table 4). Thus, Eq. 16 demonstrated a smaller error value and higher precision for prediction than Eq. 15, suggesting it to be more appropriate for RT prediction. In this manner, we constructed a method for predicting RT on the basis of RR with high precision.

One of the subjects had a longer RT value that was considered to be an outlier (RT=5.75, $p=0.0153$). Nevertheless, even when using Eq. 16 for prediction, 4 (9.8%) of the 41 subjects were considered to have a greater residual muscle relaxing effect than predicted with an Error greater than 1 min. In the subject with the largest Error value, measured RT was 2.16 min greater than the predicted value (Fig. 2B).

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**Fig. 3. Schema of Method Used for Determining Sugammadex (SDX) Dose by Obtaining Target Reverse Time (RT) for Individual Patients**

RT reverse time, $Scr$ serum creatinine, $StWt$ standard body weight, $T-Bil$ total bilirubin, $Wt$ weight, RR residual ratio, $Vd$ volume of distribution, RCR rocuronium, $[C]$ the level of rocuronium concentration just before sugammadex administration, SDX sugammadex, $[C_r]$ the level of protein unbound rocuronium after sugammadex administration, $[S_u]$ total concentration of sugammadex, $D_s$ sugammadex dose.
causes for prolonged RT induced by SDX are reported to be renal dysfunction,\textsuperscript{33} dialysis,\textsuperscript{34,35} advanced age,\textsuperscript{36} decline in cardiac output,\textsuperscript{37} and edematous disorder.\textsuperscript{38} However, none of those factors were applicable in these subjects including the outlier. Thus, this individual difference in efficacy could not be explained by previous reports. Accordingly, we considered that factors other than those investigated may contribute to individual differences and additional studies are considered necessary.

RT after SDX administration was able to be determined by a prediction expression obtained with using RR. However, since the prediction expression was prepared using data from actual subjects, a similar patient group should be employed when considered clinical application. In a future study, we intend to examine individual differences in SDX efficacy in greater detail, for instance, in different various types of anesthesia and surgery in male patients.

As for clinical application of the present prediction expression, we will analyze whether an SDX dose based on the target value of RT can be obtained for individual patients even under a condition in which a neuromuscular monitoring device is unavailable. Specifically, we set target RT before surgery, and calculate a value of RT can be obtained for individual patients even under a condition in which a neuromuscular monitoring device is not available, which should greatly contribute to improvement in QOL for affected patients.

**Conflict of Interest** The authors declare no conflict of interest.

**REFERENCES**


