Clinical Research

Effect-site concentration of remimazolam at loss and recovery of responsiveness during general anesthesia: a simulation study

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Background: The objective of this study was to investigate the effect-site concentration (Ce) of remimazolam at loss of response (LOR) and recovery of response (ROR) in patients underwent general anesthesia using simulation. In addition, the relationships between patient's factors and simulated Ce at LOR and ROR were examined.

Methods: The medical records of 81 patients who underwent elective surgery under general anesthesia using remimazolam with simulation of Ce between August 4, 2021 and October 12, 2021, were retrospectively reviewed. Remimazolam was administered as an induction dose of 6 or 12 mg/kg/h until the patient became unresponsive, followed by 0.3–2 mg/kg/h to maintain BIS values below 60. Simultaneously, simulations of manual infusion mode were performed using Asan Pump software and the Ce of remimazolam was simulated using the Schüttler model. Whenever infusion rate of remimazolam was manually changed, the simulated Ce was confirmed almost simultaneously. LOR and ROR, defined as unresponsive and eye-opening to verbal commands, respectively, were recorded in the Asan Pump program.

Results: The median (1Q, 3Q) simulated Ce at LOR and ROR were 0.7 (0.5, 0.9) and 0.3 (0.2, 0.4) µg/ml, respectively. LOR was achieved in 1.9 min after remimazolam infusion with cumulative doses of 0.3 mg/kg. There was a significant relationship between age and simulated Ce at ROR (Ce at ROR = −0.0043 × age + 0.57, r = 0.30, P = 0.014).

Conclusions: For optimal dosage adjustment, simulating Ce while administering remimazolam with a weight-based dose during anesthesia is helpful. Elderly patients may recover from anesthesia at lower Ce of remimazolam.

Keywords: Anesthesia; Computer simuation; Concentration; Hypnotic; Remimazolam.

INTRODUCTION

Remimazolam, a novel ultra-short-acting benzodiazepine invented out of 'soft drug' development, has recently (January 2021) been approved as a general anesthetic by the Ministry of Food and Drug Safety (MFDS) in South Korea. It has advantages over currently used hypnotic agents including rapid onset/offset, predictable duration of action, organ-in-

dependent metabolism, availability of a reversal drug, and maintenance of stable hemodynamics, and is increasingly being used as a hypnotic component of total intravenous anesthesia (TIVA) [1–5]. Pharmacokinetics and pharmacodynamics of remimazolam were characterized by relatively high clearance, small steady-state volume of distribution, short elimination half-life, short context-sensitive half-life, linear kinetics, and dose-related depth and duration of sedation [6–8]. Due to these pharmacologic properties, remimazolam concentration accurately represents its hypnotic effect; thus, knowing accurate remimazolam concentrations is beneficial in anesthesia practice. As most drugs act at sites remote from the bloodstream, hysteresis, a phenomenon denoting time lag between the measured plasma drug concentration and the observed drug effect may occur [9]. Therefore, the pharmacologic effect can be determined based on either the plasma concentration (Cp) or effect-site concentration (Ce); however, Ce rather than the Cp reflects the clinical effects of intravenous anesthetics better [10,11].

Target-concentration controlled infusion (TCI) systems, which allow drugs to be administered to achieve and maintain a desired target concentration [12], would be useful in administering remimazolam during anesthesia for optimal dosing adjustment. Currently, no commercial TCI device for remimazolam is available; thus, it has no choice but to be administered as a variable rate continuous infusion at the infusion rate approved by the MFDS (i.e., 6 or 12 mg/kg/h for induction, followed by 1 mg/kg/h [2 mg/kg/h of maximal infusion rate] for maintenance).

The Schüttler model, a three-compartment model that can be applied for administering remimazolam via effect-site target-controlled infusion method including body weight as a covariate, significantly affecting the volume of distribution in the central compartment [8]. As a result, the Ce of remimazolam varies from one person to another depending on body weight, even if administered with the same body weight-based dose. Consequently, considering optimal dosage titration, it would be helpful to simulate the Ce while administering remimazolam with the conventional weight-based dosing strategy during the induction and maintenance of anesthesia.

The objective of this retrospective study, therefore, was to investigate the simulated Ce of remimazolam at the loss of responsiveness (LOR) to a verbal command during anesthesia induction and at the recovery of responsiveness (ROR) during emergence using the data obtained in the process of clinical practice of patients who underwent general anesthe-

sia with remimazolam. In addition, the relationship between the simulated Ce of remimazolam at LOR and ROR and the patient's factors, such as age and sex, were evaluated.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board (no. 2021-1747). The medical records of patients who underwent elective surgery under general anesthesia with remimazolam at our institution between August 4 and October 12, 2021, were retrospectively reviewed. Inclusion criteria included patients administered with remimazolam as a hypnotic component of TIVA throughout induction and maintenance of anesthesia and patients who administered remimazolam while conducting concentration simulations and having the complete result files of simulation.

General anesthesia was identically conducted according to our institution's standard anesthesia protocol for general surgery in all patients. The patients in this study fasted from midnight on the day of surgery and received no premedication. Upon arrival in the operating room, standard monitoring processes, including an electrocardiograph, pulse oximeter, noninvasive blood pressure monitor, train-of-four, end-tidal carbon dioxide partial pressure, and the bispectral index (BIS™, Covidien, USA) were applied in all cases. All data were recorded continuously until the end of anesthesia. After pre-oxygenation with 100% oxygen via facial mask, the anesthetic dosing strategies were employed in all patients as follows. Remimazolam (Byfavo™ Inj, Hana Pharm Co., Ltd, Korea) was administered as an initial induction dose of 6 or 12 mg/kg/h at the discretion of the attending anesthesiologist using a syringe pump (Perfusor®, Space, B. Braun Melsungen AG, Germany). After starting remimazolam infusion, LOR, defined as the patient becoming unresponsive to loud verbal commands (open your eyes), was assessed frequently to determine the induction of anesthesia. After confirming LOR, the infusion rate of remimazolam was adjusted to 1 or 2 mg/kg/h and remifentanil was administered via target Ce controlled infusion using the Minto model [13]. Endotracheal intubation was facilitated by administration of rocuronium at 0.6 mg/kg. Patients were then ventilated with a mixture of air and oxygen (fraction of inspired oxygen, 0.5); mechanical ventilation was adjusted to maintain an end-tidal carbon dioxide partial pressure of 35–45 mmHg. Consequently, the remimazolam infusion rate was adjusted within 0.3–2.0 mg/kg/h to maintain BIS values at less than 60

during the maintenance of anesthesia. Target Ce values of remifentanil were titrated within a range of 3–20 ng/ml to maintain stable hemodynamics (blood pressure and heart rate within 20% above or below baseline values).

In our institutional anesthesia practice for general surgery, whenever remimazolam is administered during general anesthesia in general surgery patients, simulations of the manual infusion mode of remimazolam is simultaneously performed using the Asan Pump software (version 2.1.3, Bionet, Korea; http://www.fit4nm.org/download/, last accessed: August 27, 2012) to evaluate Ce of remimazolam. Accordingly, in all patients of the present study, simulations of the manual infusion mode of remimazolam were simultaneously performed using the Asan Pump software. Concurrently, remimazolam Ce was automatically simulated using pharmacokinetic parameters and blood-brain equilibration rate constant (k_{e0}) proposed by Schüttler et al. [8]. The pharmacokinetic parameters and k_{e0} used for simulating Ce of remimazolam are presented in Table 1. Whenever the infusion rate of remimazolam of the syringe pump was manually changed, similar changes in values were made in the Asan Pump program simultaneously, and then the simulated Ce was confirmed. The Asan Pump infusion profiles including the infusion rate of remimazolam for all patients were automatically recorded in a .csv file format. In addition, during the simulation, the user can record clinical events (e.g., endotracheal intubation, loss of consciousness, extubation) in the pop-up window of the Asan pump program. Thus, in our routine anesthesia practice using remimazolam with concentration simulations, the anesthesiologists recorded LOR

Table 1. Pharmacokinetic Parameters and Blood-brain Equilibration Rate Constant (k_{e0}) Used to Simulate Effect-site Concentration of Remimazolam

Parameter	Values
V_1 (L)	0.0627 × body weight
V_2 (L)	14.5
V_3 (L)	15.5
CL (L/min)	1.14
Q_2 (L/min)	1.04
Q_3 (L/min)	0.19
k_{e0} (1/min)	0.27

V_1: central volume of distribution, V_2: rapid peripheral volume of distribution, V_3: slow peripheral volume of distribution, CL: clearance, Q_2: inter-compartmental clearance of rapid peripheral compartment, Q_3: inter-compartmental clearance of slow peripheral compartment. Pharmacokinetic parameters and k_{e0} from the Schüttler model [13]. The k_{e0} was estimated against Modified Observer's Assessment of Alertness/Sedation Scale.

in event recording window of the Asan pump program; the time points when the patients reached LOR were automatically recorded in simulation result files of the Asan pump program.

On the closure of the surgical wound, opioids (e.g., fentanyl 50 μg or oxycodone 4 mg) and ramosetron 0.3 mg were administered for postoperative pain, nausea and vomiting control. At the end of the procedure, remimazolam and remifentanil were discontinued. The neuromuscular blockade was antagonized using sugammadex or a combination of neostigmine and glycopyrrolate according to the attending anesthesiologist's discretion. During emergence, recovery of anesthesia was assessed by ROR, defined as a patient's ability to open their eyes in response to verbal commands. The anesthesiologists recorded ROR in the event recording window of the Asan pump program; the time points when the patients reached ROR were also automatically recorded in simulation result files. When patients met the extubation criteria (BIS values ≥ 80 and train-of-four ratio > 0.9 for more than 1 min), they were extubated and transferred to a post-anesthesia care unit (PACU). Flumazenil, a specific antagonist of benzodiazepines, was administered based on the discretion of the attending anesthesiologists when the patients became drowsy again in the operating room or PACU after recovering consciousness.

Data collection

We reviewed the medical records of eligible patients, including electronic medical records and simulation result files of the Asan pump. The following data were collected from electronic medical records and simulation result files of Asan Pump program: patient demographic data, infusion rate of remimazolam during anesthesia induction, duration of remimazolam infusion, total dose of remimazolam, and mean infusion rate of remimazolam. In addition, the time from the start of remimazolam infusion to LOR confirmation, the cumulative dose to induce LOR, and the simulated Ce of remimazolam at LOR and ROR were collected from the simulation result files of the Asan Pump program.

Statistical analyses

Statistical analyses were conducted with SigmaStat version 3.5 for Windows (Systat Software, Inc., USA). Data were expressed as mean ± SD for normally distributed continuous variables, medians (1Q, 3Q) for non-normally distribut-

ed continuous variables, and numbers for categorical variables. The relationships between the age and simulated Ce at LOR and ROR were analyzed with linear regression. The differences in simulated Ce at LOR and ROR according to patient's sex were analyzed using the Mann–Whitney Rank Sum Test, respectively. The time to LOR and wight-based dose of remimazolam to induce LOR according to the infusion rate of remimazolam were compared using the Mann–Whitney Rank Sum Test. P values of less than 0.05 were considered statistically significant for all analyses.

Investigation of the pharmacodynamic relationship between the simulated Ce of remimazolam and ROR using logistic regression

After the association between the simulated Ce at LOR or ROR and the patient's factor were analyzed, we performed a population pharmacodynamic modeling only for the remimazolam Ce (at LOR or ROR), showing a significant relationship with the patient's factor.

The observed ROR was recorded as 0 and 1 for unresponsiveness state and responsiveness states, respectively. The pharmacodynamic relationship between the probability of ROR and remimazolam Ce was analyzed using a sigmoid Emax model:

$$\text{Probability of recovery of responsiveness} = 1 - \frac{Ce^{\gamma}}{Ce_{50}^{\gamma} + Ce^{\gamma}}$$

where Ce is the Ce of remimazolam, Ce_{50} is the value of Ce concentration associated with a 50% probability of ROR, and γ is the steepness of the concentration vs. response relationship. The likelihood, L, of the observed response, R, was described by the equation:

$$\text{Likelihood} = R \times \text{Prob} + (1 - R) \times (1 - \text{Prob})$$

where Prob is the probability of ROR. Model parameters were estimated using the option "LIKELIHOOD LAPLACE METHOD = conditional" in the NONMEM (Nonlinear Mixed Effects Modeling) software (version VII level 5, ICON Development Solutions, Ireland). The inter-individual random variability (IIV) of Ce_{50} was modeled using a log-normal distribution, whereas IIV of γ was fixed to zero. A forward inclusion approach was used in consecutive NONMEM runs to determine whether the patient's factor is a significant covariate for Ce_{50}. The statistical significance of the patient's factor inclusion as a covariate was tested using –2

log likelihood of the model with NONMEM. An α level of 0.05, which corresponds to a 3.84 reduction in objective function value (OFV), was considered to represent a significant improvement of the model (Chi-square distribution, degree of freedom = 1, P < 0.05) [14]. Non-parametric bootstrap analysis served to validate the models internally (fit-4NM 3.3.3, Eun-Kyung Lee and Gyu-Jeong Noh, Korea; https://cran.r project.org/src/contrib/Archive/fit4NM/, last accessed: October 29, 2012) [15]. The original data set was randomly sampled to generate 2000 bootstrap replicates; 95% confidence intervals (CIs) of nonparametric bootstrap replicates were determined and compared with the final values of the model parameters.
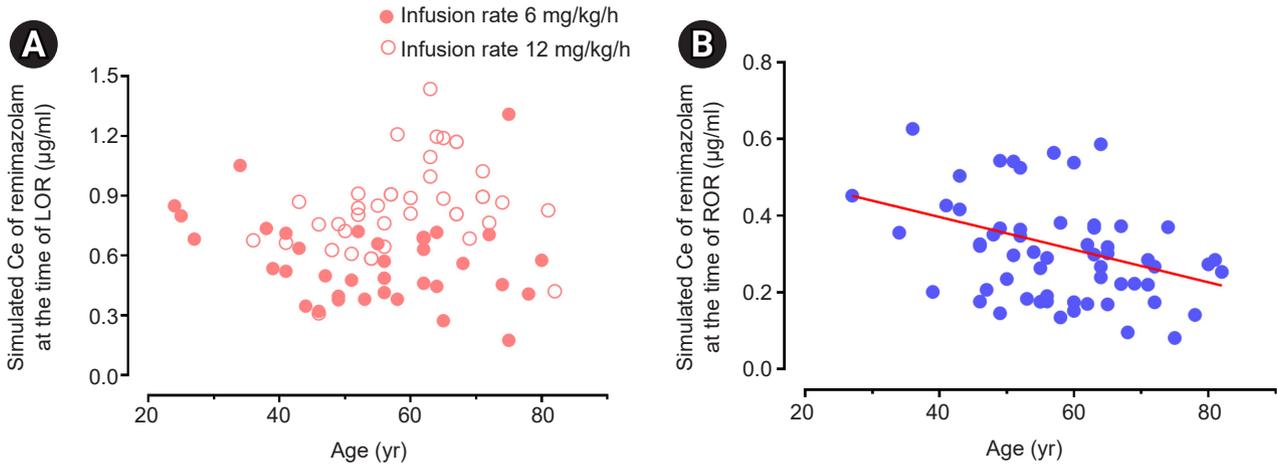
RESULTS

A total of the 81 eligible patients (40 patients in the remimazolam induction dose 6 mg/kg/h group and 41 patients in the remimazolam induction dose 12 mg/kg/h group) were included in data analysis. The demographic and clinical characteristics of the patients are shown in Table 2. During induction, the median (1Q, 3Q) simulated Ce of remimazolam at LOR was 0.7 (0.5, 0.9) μg/ml. All patients lost response to verbal command in a median of 1.9 min after the start of remimazolam infusion with the cumulative dose of 0.3 mg/kg. In the subgroup analysis (between induction dose 6 mg/kg/h and 12 mg/kg/h groups), there were significant differences in the simulated Ce of remimazolam at LOR, the time to reach LOR, and the cumulative dose of remimazolam to induce LOR. The median (1Q, 3Q) simulated Ce of remimazolam at LOR was higher in 12 mg/kg/h group than 6 mg/kg/h group (0.8 [0.7, 0.9] vs. 0.5 [0.4, 0.7] μg/ml, P < 0.001) (Fig. 1). The patients who received remimazolam 12 mg/kg/h reached LOR faster compared with those who received remimazolam 6 mg/kg/h (1.9 [1.7, 1.9] vs. 2.2 [1.9, 2.5] min, P < 0.001). The median (1Q, 3Q) cumulative dose of remimazolam required to induce LOR was larger in 12 mg/kg/h group than 6 mg/kg/h group (0.36 [0.33, 0.40] vs. 0.22 [0.18, 0.25] mg/kg, P < 0.001). There was no significant relationship between age and simulated Ce at LOR (P = 0.199 for 6 mg/kg/h group and P = 0.0674 for 12 mg/kg/h group, respectively) (Fig. 2). The simulated Ce of remimazolam at LOR was not significantly different according to the patient's sex (P = 0.299 for 6 mg/kg/h group and P = 0.342 for 12 mg/kg/h group).

During the emergence, when the median (1Q, 3Q) simulated Ce of remimazolam was 0.3 (0.2, 0.4), patients recov-
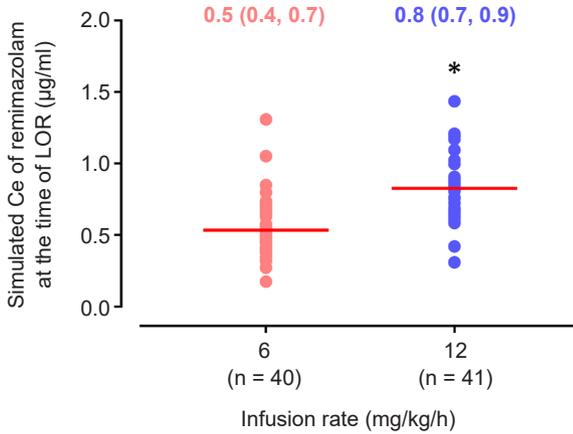
Fig. 1. Simulated effect-site concentration (Ce) at the time of loss of responsiveness (LOR). Data are expressed as median (1Q, 3Q). Red horizontal lines indicate median values. *P < 0.001 vs. infusion rate 6 (Mann-Whitney Rank Sum Test).

ered response to verbal command (Fig. 3). Age was significantly correlated with the simulated Ce at ROR with a negative slope (Ce at ROR = −0.0043 × age + 0.57, r = 0.30, P = 0.014) (Fig. 2). The simulated Ce of remimazolam at ROR was not significantly different according to the patient's sex (P = 0.818).

When the relation between the simulated Ce of remimazolam at LOR or ROR and the patient's factor was assessed, the simulated Ce at ROR correlated only with the patient's age. Therefore, we only evaluated the pharmacodynamic relationship between the remimazolam Ce at ROR and the probability of ROR using a population pharmacodynamic modeling incorporating age as a covariate. After exploring the base model, we included age as a covariate in $Ce_{50,ROR}$ (effect-stie concentration of remimazolam, associated with 50% probability for recovery of responsiveness) to investi-

Fig. 2. The relationship between age and simulated effect-site concentration (Ce) at the time of loss of responsiveness (LOR, A) and at the time of recovery of responsiveness (ROR, B). Red solid line represents linear regression of the Ce at ROR vs. Age (Ce at ROR = −0.0043 × age + 0.57, r = 0.30, P = 0.014).

Table 2. Demographics and Characteristics of Patients

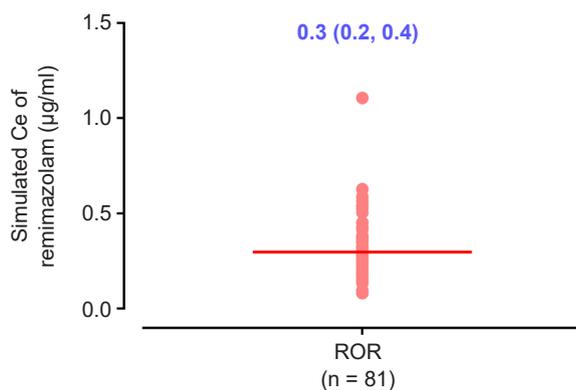| Clinical variables	Total (n = 81)	Infusion rate of remimazolam during anesthesia induction	
		6 mg/kg/h (n = 40)	12 mg/kg/h (n = 41)
Age (yr)	56.6 ± 12.7	53.7 ± 14.3	59.4 ± 10.5
Weight (kg)	58.5 (51.2, 66.5)	56.7 (51.1, 66.6)	60.6 (51.2, 66.7)
Height (cm)	159.1 (153.5, 186.0)	159.1 (153.5, 186.0)	159.1 (153.5, 186.0)
Sex, M/F	30/51	10/30	20/21
ASA class, I/II	40/41	23/17	17/24
Total duration of remimazolam infusion (min)	106.5 ± 54.5	121.3 ± 79.1	117.0 ± 59.1
Total dose of remimazolam (mg)	140.1 (80.4, 185.2)	92.6 (61.0, 181.1)	155.2 (121.6, 200.4)
Mean infusion rate of remimazolam during anesthesia maintenance (mg/kg/h)	0.7 (0.5, 0.9)	0.6 (0.5, 0.9)	0.8 (0.7, 1.0)

Data are expressed as mean ± SD, median (1Q, 3Q), or count as appropriate. ASA: American Society of Anesthesiologists. Mean infusion rate during anesthesia maintenance was calculated as follows:

$$\text{Mean infusion rate during anesthesia maintenace} = \frac{\text{Dose administered during anesthesia maintenance (mg)}}{\text{Body weight (kg)} \times \text{maintenance infusion duration (h)}}$$

gate whether age has a significant effect on Ce value at ROR. This pharmacodynamic modeling including age significantly improved the performance of the basic model based on the likelihood ratio test, with a decrease in the OFV (total 6.8, P < 0.01). Table 3 summarizes the estimated pharmacokinetic parameters of the basic and final model and the non-parametric bootstrap results. The medians of the pharmacokinetic parameters estimated by the bootstrap data set were generally similar to the final pharmacokinetic parameter estimate with the 95% CIs being narrow overall, indicating that the final parameters were adequately estimated. The pharmacodynamic relationship between the probability of ROR and remimazolam Ce according to age evaluated using the final population parameters is shown in Fig. 4. The age values used for the predictions correspond to the hypothetical patients aged 30-, 50-, and 80-year as distributed within the studied population. The $Ce_{50,ROR}$ and $Ce_{95,ROR}$ (effect-site concentration of remimazolam, associated with 95% probability for recovery of responsiveness) in 30-, 50-, and 80-year-old patients was predicted to be 0.52 and 0.48, 0.45 and 0.41, and

0.34 and 0.31 μg/ml, respectively.

DISCUSSION

This study is a clinical investigation quantifying the Ce of remimazolam to induce LOR to verbal commands during anesthesia induction and ROR during emergence, using the data obtained in the process of clinical practice of patients who underwent general anesthesia with remimazolam as a hypnotic component. The simulated Ce at LOR and ROR were 0.7 and 0.3 μg/ml, respectively. Moreover, we demonstrated that age was significantly related to the Ce of remim-
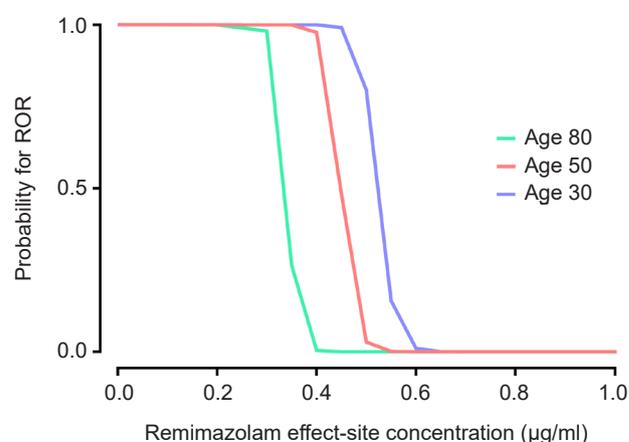
Fig. 4. The relationship between the probability of recovery of responsiveness (ROR) and effect-site concentration of remimazolam. The estimates of $Ce_{50,ROR}$ (effect-stie concentration of remimazolam, associated with 50% probability for recovery of responsiveness) and γ (steepness of the concetration-response curve) are 0.632–0.205 × (age/56) μg/ml and 32.3, respectively. $Ce_{50,ROR}$ and $Ce_{95,ROR}$ (effect-stie concentration of remimazolam, associated with 95% probability for recovery of responsiveness) are 0.34 μg/ml and 0.31 μg/ml for a hypothetical patient aged 80 year, 0.45 μg/ml and 0.41 μg/ml for a hypothetical patient aged 50 year, 0.52 μg/ml and 0.48 μg/ml for a hypothetical patient aged 30 year, respectively.

Fig. 3. Simulated effect-site concentration (Ce) at the time of recovery of responsiveness (ROR). Data are expressed as median (1Q, 3Q). Red horizontal line indicates median value.

Table 3. Population Pharmacokinetic Parameter Estimates, Inter-individual Variability, and Median Parameter Values (95% CI) of the Nonparametric Bootstrap Replicates of the Final Pharmacodynamic Model of Remimazolam

Model	Parameter		Estimate (% RSE)	CV (%)	Median (95% CI)	OFV
Basic	$Ce_{50,ROR}$ (μg/ml)		0.409 (8.7)	57.18	-	109.1
	γ		28.4 (32.9)	-	-	
Final	$Ce_{50,ROR} = \theta_1 - \theta_2 \times$ (age/56)	θ_1	0.632 (9.7)	55.86	0.637 (0.50–0.841)	102.3
	(μg/kg)	θ_2	0.205 (25.5)		0.201 (0.092–0.321)	
	γ		32.3 (33.7)	-	32.8 (3.720–120.0)	

Non-parametric bootstrap analysis was repeated 2,000 times. RSE indicates relative standard error = SE/mean × 100 (%); CV: coefficient of variation; RSE: relative standard error = SE/estimate × 100 (%), CV: coefficient of variation, OFV: objective function value, $Ce_{50,ROR}$: effect-stie concentration of remimazolam, associated with 50% probability for recovery of responsiveness; γ: steepness of the concetration-response curve, ROR: loss of responsiveness, CI: confidence interval.

azolam at ROR. These findings suggest that Ce simulations would be beneficial while administering remimazolam during anesthesia for optimal dosage adjustment, and possibly providing clinically important information for the precise dose adjustment of remimazolam to achieve rapid and safe induction and early recovery. In particular, elderly patients may recover from anesthesia at lower Ce of remimazolam; thus, timely tapering of remimazolam considering with Ce of remimazolam upon surgery completion would facilitate fast emergence from anesthesia.

This is the first research that determined the Ce of remimazolam to induce LOR and ROR to verbal commands during TIVA with remimazolam and remifentanil. Variability in the onset and offset profile of an anesthetic drug is likely due to the factors influencing the pharmacokinetics and the relationship between drug concentrations and their effect [16]. Ce rather than Cp better reflects the clinical effects of intravenous hypnotics [10,11]; however, administering remimazolam via effect-site target-controlled infusion method is still unavailable. In terms of optimal dosage adjustment, therefore, it would be clinically advantageous if the individual remimazolam Ce could be simulated and applied in clinical practice rather than simply traditional observations of autonomic response along with monitoring of depth of anesthesia. The feasibility of predicting the potential remimazolam effects by estimating the Ce of anesthetics using pharmacokinetic/pharmacodynamic simulation has also been reported [17].

A significant relationship between the simulated remimazolam Ce at ROR and age was observed in this study. We conducted population pharmacodynamic modeling, incorporating age as a covariate in Ce_{50} at ROR, and demonstrated that age plays an important role in determining inter-individual variability of remimazolam Ce_{50} at ROR. Based on our prediction of the probability of ROR according to age, elderly patients may emerge at lower remimazolam Ce than younger patients. Therefore, age has a considerable influence on the patients' sensitivity to remimazolam from a pharmacodynamic point of view. These results are consistent with the findings of the previous studies in which increased sensitivity to the sedative effects of other benzodiazepines was observed in elderly patients [18,19]. The currently reported case series suggested that adequate titration of infusion rate of remimazolam based on the patient's sedation level and general condition during maintenance of anesthesia achieved well-tolerated anesthesia with prompt emergence from anesthesia in two super-elderly patients [5]. Consequently, the ability to predict the individual remimazolam

Ce for ROR by simulation especially in elderly patients would be clinically meaningful in terms of allowing the dose of remimazolam to be adjusted to achieve fast recovery from anesthesia.

During anesthesia induction in the present study, the patients who received 12 mg/kg/h of remimazolam were unresponsive to verbal commands approximately 18 s faster than those who received 6 mg/kg/h of remimazolam. These findings are consistent with the results of the previous study, which revealed that remimazolam's induction dose had a statistically significant effect on the time to lose responsiveness to the shaking of patient's shoulder (a 13-s rapid onset with 12 mg/kg/h groups when compared with 6 mg/kg/h groups) [2]. This difference in time to LOR in our study may be explained by more cumulative doses to induce LOR and higher simulated Ce at LOR in 12 mg/kg/h group compared to that of 6 mg/kg/h group (approximately 0.14 mg/kg more for cumulative doses and 0.3 μg/ml higher for Ce, respectively). Thus, though both induction doses are suitable, 12 mg/kg/h of remimazolam is recommended in certain cases where rapid induction is needed.

In the current study, patients were unresponsive to verbal commands in median 132 and 114 s with cumulative doses of remimazolam 0.22 and 0.36 mg/kg after starting remimazolam at 6 and 12 mg/kg/h, respectively. However, a prior study reported that faster time and less cumulative doses until patients lost responsiveness to even stronger stimuli such as the shaking of their shoulder than those of the present study with equal infusion rates of remimazolam (102 s and 88.7 s for time to LOR, 0.17 and 0.29 mg/kg for cumulative doses to LOR, respectively) [2]. These different findings might result from the presence or absence of concomitantly used opioids. In a previous study, 0.25–0.5 μg/kg/min of remifentanil was infused just before remimazolam infusion to completion of tracheal intubation, whereas remifentanil infusion was commenced after confirming LOR in our study. The synergic relationship between opioids and benzodiazepine has been well-established [19]; it corresponds with the results of a recent study conducted to assess pharmacodynamic drug-drug interaction potential of remimazolam with remifentanil, which showed a high degree of synergism between two anesthetic agents [20]. In addition, the administration of remifentanil 10 min before remimazolam revealed a 20 s faster time to lose consciousness compared with when remifentanil was started 2 min before remimazolam [21].

Several limitations of this study should be considered. First, we have assumed the simulated Ce values of remima-

zolam derived from the Schüttler model to be applicable to the enrolled study population. Although the Schüttler model has drawbacks that these models have been constructed only in 20 healthy male volunteers without external validation, these can be considered reliable and unique models as they include pharmacokinetic parameters and the k_{e0} of remimazolam obtained in a single population of adults. However, the true Ce values at LOR and ROR can be more variable than presented in this study. There has been a report that the k_{e0} of remimazolam is different according to race [20]. In this study, remimazolam Ce was simulated using the k_{e0} derived from the Schüttler model which has been developed in the European population. In general, if the pharmacokinetic parameters are the same, but the k_{e0} is different, even though the same dose is administered, the time to peak effect is longer (slow onset) when the k_{e0} is small, and the Ce at that time is also low [22,23]. Accordingly, based on the facts reported in the previous study that the k_{e0} of remimazolam in the Asian race is approximately 50% low than that in the non-Asian race [20], there is possible that the Ce calculated in Koreans is lower. However, solid conclusions could be drawn by population pharmacokinetic/pharmacodynamic analysis in the Korean population. Thus, we are planning to develop a pharmacokinetic/pharmacodynamic model of remimazolam in the Korean population. Second, in this study, we investigated the simulated Ce anesthesia at the time when the patients were unresponsive to verbal commands during anesthesia induction; however, this referred to Ce only on unresponsiveness to stimuli rather than the absence of consciousness [24]. Therefore, the Ce of remimazolam to induce loss of consciousness can be different from the simulated Ce value at LOR presented in our study. Lastly, owing to the retrospective nature of the present study, LOR and ROR were not assessed in a standardized time period. Also, we did not evaluate various factors influencing LOR and ROR such as obesity, ethnicity, and co-administered drugs. Therefore, further well-designed prospective trials are warranted to quantify the exact Ce of remimazolam to induce LOR and ROR and establish thoroughly the clinical variables related to LOR and ROR during anesthesia with remimazolam.

In conclusion, the present study reports the simulated Ce of remimazolam for attaining loss and recovery of responsiveness to verbal commands in patients who underwent general anesthesia with remimazolam. Our study results suggest that it would be helpful to simulate the Ce while administering remimazolam with the conventional dosing strategy during anesthesia for optimal dosage adjustment. In particular, as there is a possibility that elderly patients may recover from anesthesia at lower Ce of remimazolam, it would be essential that remimazolam infusion should be timely ceased at the end of the surgery based on the simulated Ce of remimazolam for early recovery.

FUNDING

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Gyu-Jeong Noh, Byung-Moon Choi. Data collection: Ji-Yeon Bang, Kyung Mi Kim. Formal analysis: Kyung Mi Kim, Jong Min Lee. Writing - original draft: Kyung Mi Kim. Writing - review & editing: Hong Seuk Yang, Byung-Moon Choi.

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