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Original Article

A pharmacodynamic analysis of factors affecting recovery from anesthesia with propofol-remifentanil target controlled infusion

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Aim: To examine individual patient's demographic parameters and clinical variables related to return of consciousness (ROC) and the pharmacodynamic relationship between propofol effect-site concentration (C_e) and ROC from propofol-remifentanil anesthesia.
Methods: Ninety-four patients received propofol-remifentanil anesthesia using the effect-site target-controlled infusion (TCI) system. All clinical events were noted, and variables possibly related to propofol C_e at ROC were examined using linear correlation analyses. Pharmacodynamic modeling incorporating covariates was performed using NONMEM (Nonlinear Mixed Effects Modeling) VII software.
Results: The C_e values of propofol at loss of consciousness (LOC) and ROC were 4.4±1.1 μg/mL and 1.1±0.3 μg/mL, respectively. Age was negatively correlated with propofol C_e at ROC (r=-0.48, P<0.01). Including age as a covariate in C_{e50} (the effect-site concentration associated with 50% probability of return of consciousness) and λ (the steepness of the concentration-versus-response relationship) significantly improved the performance of the basic model based on the likelihood ratio test, with a significant decrease in the minimum value of the objective function. The C_{e50} in 25-, 50-, and 75-year-old patients was predicted to be 1.38, 1.06, and 0.74 μg/mL, respectively. The λ in 25-, 50-, and 75-year-old patients was predicted to be 12.23, 8.70, and 5.18, respectively.
Conclusion: Age significantly affects the relationship between propofol C_e and ROC, and pharmacodynamic modeling including age could lead to better predictions of ROC during emergence from propofol-remifentanil anesthesia.

Keywords: anesthesia; effect-site concentration; propofol; pharmacodynamic modeling; return of consciousness; target-controlled infusion

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Introduction

Anesthesiologists are concerned not only about inducing rapid and safe anesthesia, but also about achieving a comfortable and precise return of consciousness (ROC) after surgery[1]. To date, studies have focused mainly on individual effects of anesthesia induction. The ability to predict the individual propofol effect-site concentration (C_e) for ROC would allow the dose of propofol to be adjusted to achieve an adequate ROC. It would also reduce the anesthesiologists workload, save time and resources, and allow for safer patient recovery[2]. Some studies of ROC show large variations (0.8–2.7 μg/mL) in propofol C_e producing ROC from anesthesia[3,4], making it difficult to predict the minimum concentration for effective sedation and the concentration of propofol during emergence. In the absence of individual pharmacodynamic information, propofol is usually dosed on the basis of the average population requirement. Hence pharmacodynamic modeling incorporating a population approach with covariates could be clinically useful for describing the dose-response relationship.

The objectives of our study were: 1) to identify the clinical variables related to the propofol C_e at ROC and 2) to apply a population pharmacodynamic modeling approach to data from propofol-remifentanil anesthesia.

Materials and methods

This study was approved by the ethics committee of the Yonsei University Health System (4-2010-0580). Patients (aged ≥ 20 years, ASA I–II) scheduled for elective minor surgery at the Eye and ENT Severance Hospital were included from January 2011 to September 2011. Exclusion criteria were as follows: cardiac, pulmonary, hepatic or renal disease; hearing loss or other neurological deficit; past history of allergy or adverse

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reaction to medication; any type of medication affecting the central nervous system; or body mass index more than 30. All of the patients provided written informed consent.

Anesthesia was induced according to the same standard protocol in all patients. Patients were premedicated iv with 0.1 mg of glycopyrrolate. Anesthesia was induced by effect-site target-controlled infusion (TCI) (Orchestra® Base Primea, Fresenius Vial, France) of propofol and remifentanil after the patients anthropometric data were entered. The pump was operated according to the model for propofol developed by Schnider *et al*[5, 6] and the model for remifentanil developed by Minto *et al*[7, 8]. The initial target C_e values of propofol and remifentanil were 4 μg/mL and 2 ng/mL, respectively, for induction. Loss of consciousness (LOC) was defined as a patient's inability to open their eyes in response to their name being called loudly, *ie*, a score of 3 on the Observer's Assessment of Alertness/Sedation Scale (OAA/S)[9]. If LOC was not obtained with this initial C_e, the C_e of propofol was increased in increments of 0.5 μg/mL until LOC occurred. The remifentanil C_e was maintained at 2 ng/mL. Consciousness was assessed every 10 s. At the moment of LOC, the BIS index (BIS VISTA™, Aspect Medical System, Inc, Norwood, MA, USA) and the C_e of propofol and remifentanil were recorded. Rocuronium was given (0.6 mg/kg iv) as a neuromuscular blockade. After endotracheal intubation, ventilation was mechanically controlled with 50% oxygen in an air mixture to maintain the end-tidal carbon dioxide tension at 35 to 40 mmHg. After anesthesia was induced, the C_e of propofol was titrated to maintain BIS values between 40 and 60 throughout the intraoperative period. In addition, the C_e of remifentanil was adapted to intraoperative hemodynamics throughout the surgical procedure.

At the end of surgery, propofol and remifentanil infusion was stopped. The neuromuscular block was antagonized with 0.2 mg of glycopyrrolate and 1.0 mg of neostigmine. Return of consciousness was defined as a score of 3 on the OAA/S. At the end of surgery and at ROC, the BIS value and the C_e of propofol and remifentanil were recorded by an investigator blinded to the conditions. The total amount of propofol and remifentanil, duration of infusion, and the duration of anesthesia and surgery were also recorded. The duration of anesthesia was defined as the time from the start of propofol infusion for induction to extubation of the trachea; the duration of surgery was defined as the time from surgical incision to the application of the last suture. All of the patients were administered ramosetron (Astellas Pharma Inc, Seoul, Korea) 0.3 mg and ketorolac (Hana Pharm Co, Seoul, Korea) 60 mg iv for the prevention of postoperative nausea, vomiting and pain in the operating room before the end of surgery.

Correlations between ROC and several clinical variables were determined by linear correlation analysis. Using the observed ROC, propofol C_e in the basic pharmacodynamic model was distributed between 0 (unconscious) or 1 (conscious). The relationship between the probability of ROC and the propofol C_e was analyzed using a sigmoidal E_{max} model:

$$P=1-\frac{C_e^{\lambda}}{C_{e50}^{\lambda}+C_e^{\lambda}}$$

where P is the probability of ROC from anesthesia, C_{e50} is the C_e associated with 50% probability of ROC, and λ is the steepness of the concentration-versus-response relationship.

The likelihood, L, of the observed response, R (unconscious=0, conscious=1) is described by the following equation:

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

where P is the probability of ROC.

Model parameters were estimated using the option "LIKELIHOOD LAPLACE METHOD=conditional" in the NONMEM (Nonlinear Mixed Effects Modeling) software (version VII; GloboMax, Hanover, MD, USA). The inter-individual random variability of C_{e50} and λ was modeled using a log-normal model. For each analysis, NONMEM computes the minimum value of the objective function, a statistic that is proportional to negative twice the log likelihood of the data. To determine the relevant covariates in the final model, a forward inclusion and backward elimination approach was used in consecutive NONMEM runs. A covariate was considered significant when its inclusion lowered the minimum value of the objective function by at least 3.85 points. The difference in the minimum value of the objective function between two nested models was approximately χ^2-distributed and could therefore be used for significance tests (P<0.05, with one degree of freedom).

Results

Ninety-four patients met the selection criteria. Fifty-five patients underwent eye surgery and 39 patients underwent ENT surgery. The duration of surgery and anesthesia were 66.9±53.0 and 97.5±54.0 min. The BIS values at baseline and LOC were 92.8±4.9 and 67.0±15.1. At LOC, the effect-site concentrations (C_es) of propofol and remifentanil were 4.4±1.1 μg/mL and 2.0±0.3 ng/mL, respectively. At the end of surgery, the BIS value, the C_es of propofol and remifentanil were 43.8±10.6, 3.2±1.0 μg/mL and 2.3±0.4 ng/mL, respectively. At ROC, the BIS value, the C_es of propofol and remifentanil were 75.7±6.0, 1.1±0.3 μg/mL and 0.8±1.0 ng/mL, respectively. Table 1 shows the data and correlation coefficients between the propofol C_e at ROC and the analyzed variables. The propofol C_e at LOC had a tendency to be positively correlated with the propofol C_e at ROC, but this correlation was not statistically significant (P=0.08). With the exception of age, no other clinical variable had a significant correlation with propofol C_e at ROC (Table 1). Age was significantly correlated with the propofol C_e at ROC, with a negative slope (P<0.01, Figure 1).

Because age was the only factor that was found to be correlated with propofol C_e at ROC, we included this as a covariate in C_{e50} and λ. This pharmacodynamic modeling including age significantly improved the performance of the basic model based on the likelihood ratio test, with a decrease the minimum value of the objective function (P<0.01). Table 2 lists the model parameter estimates for the final selected model. The

Table 1. Data values and correlation coefficients between several clinical variables and propofol effect-site concentration at return of consciousness. Data are presented as mean±SD or number.

Clinical variables	Data values	Correlation coefficient	*P* value
Sex (male/female)	53/41	0.03	0.76
Age (year)	42.8±16.5	0.48	<0.0001
Height (cm)	167±10.6	0.11	0.28
Weight (kg)	71.1±14.4	0.03	0.80
Body mass index (kg/m^2)	24.8±4.4	0.02	0.86
Propofol effect-site concentration at LOC (μg/mL)	4.4±1.1	0.23	0.08
Remifentanil effect-site concentration at ROC (ng/mL)	0.7±0.8	0.02	0.88
Duration of propofol infusion (min)	79.3±51.9	0.13	0.31
Mean propofol dose during surgery (μg·kg^{-1}·min^{-1})	176.3±97.0	0.12	0.24
Mean remifentanil dose during surgery (μg·kg^{-1}·min^{-1})	0.1±0.1	0.16	0.13

LOC, loss of consciousness; ROC, return of consciousness.

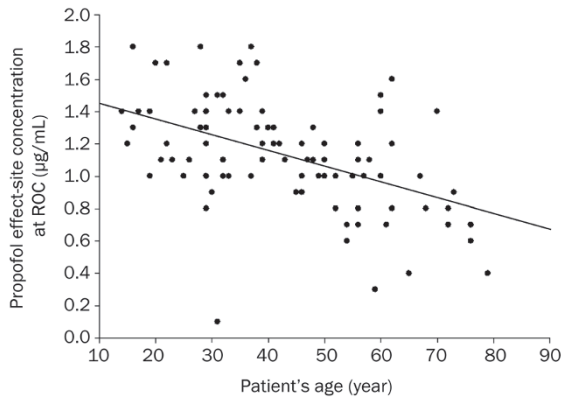

Figure 1. Linear regression between age and propofol effect-site concentration at return of consciousness (ROC). The formula of the regression is Y=-0.0097X+1.5472 (r=-0.48; P<0.01).

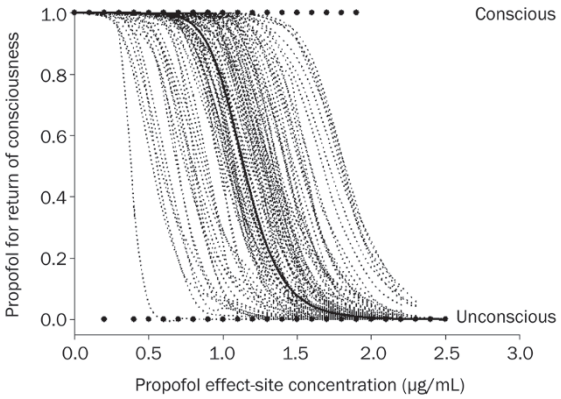

Figure 2. The relationship between the probability of return of consciousness and propofol effect-site concentration. The scattered dots are the raw data observed for all patients. The dotted lines represent individual patient fits, whereas the bold line represents the typical curve of the population data.

Table 2. Pharmacodynamic parameters.

Model	Parameter	Value	%CV	OBJF
Basic	C_{e50} (μg/mL)	1.14	32.1	643.4
	λ	9.03	–	
Final	C_{e50} (μg/mL)	1.15–0.0128×(AGE–43)	26.0	602.6
	λ	9.69–0.141×(AGE–43)	–	

AGE, age in years; CV, coefficient of variation; OBJF, minimum value of objective function; C_{e50}, effect-site concentration associated with 50% probability of return of consciousness; λ, steepness of the concentration-versus-response relationship.

relationship between the probability of ROC and propofol C_e is shown in Figure 2. The effect of age on the probability of ROC as evaluated by computed estimation is presented in Figure 3. The values of age used for the predictions correspond to the 25-, 50-, and 75-year-old patients as distributed within the studied population. The C_{e50} in 25-, 50-, and 75-year-old patients was predicted to be 1.38, 1.06, and 0.74 μg/mL, respectively. The λ in 25-, 50-, and 75-year-old patients was predicted to be 12.23, 8.70, and 5.18, respectively.

Discussion

In this study, we searched for clinical factors influencing ROC during emergence from propofol-remifentanil anesthesia and found that age was strongly correlated with ROC. In addition, upon pharmacodynamic modeling, age proved to be a significant covariate of C_{e50} and λ in the dynamic relationship between propofol C_e and ROC. This study is the first clinical investigation in which pharmacodynamic modeling of ROC has been carried out by incorporating covariates of ROC. It would be clinically advantageous if the individual propofol C_e for ROC could be predicted and applied rather than simply targeting a population-based average concentration. A nonlinear dynamic model was chosen to describe the relationship between propofol C_e and ROC, as quantal response data

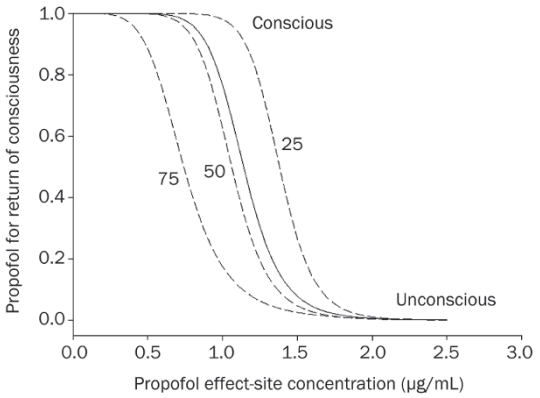

Figure 3. The fit of the logistic regression model is shown. The solid line represents the fit through the data with the age-independent model. The dotted lines are the fits predicted by the age-adjusted regression model for 25-, 50-, and 75-year-old participants.

exhibit a sigmoid relationship. A sigmoidal E_{max} model using the Hill equation provided a better model than a linear regression since this combination can estimate not only the C_{e50} value but the shape or, alternatively, the scale of the concentration-effect relationship (λ)[10]. Moreover, the C_{e50} values derived from a sigmoidal E_{max} model are not affected by extreme values to the same extent as in a linear regression model[3].

In the present study, inter-individual variability in propofol C_e at ROC could be explained by incorporating age as a covariate. Although the patients anthropometric factors except age had little influence on ROC, other potential covariates such as genetics or environmental factors might also play an important role in determining individual ROC and hence contribute to the variability of inter-individual data sets[11]. The Schnider pharmacokinetic model was developed based on data from Caucasians, so it may be necessary to examine whether the administration of propofol using a TCI technique based on the Schnider model will provide the same estimated concentration and result in the same dynamic end points in Korean patients.

According to our prediction of the probability of ROC, the propofol C_{e50} for a 25-year-old patient is around twice that for a 75-year-old patient. Younger patients may recover consciousness after receiving higher propofol concentrations than could be administered to elderly patients. The C_{e5} value, which indicates a 95% probability that a 25-year-old patient does not recover consciousness, is around 1.8 μg/mL based on our concentration-response curve. To prevent accidental awareness in young patients with propofol-remifentanil anesthesia, levels at least above this C_e should be maintained during surgery. The value of λ, representing the steepness of the dose-response curve, was greater in younger patients than in older patients. This finding suggests that younger patients may recover more abruptly than older patients, which means that young patients may be easily arousable, able to be extubated, and oriented. However, this may lead to the possibility of trauma as a result of sudden movement, and more attention should be paid to patients safety. The reverse situation could also occur. Elderly patients may experience long and more difficult recovery times. Close monitoring is necessary for elderly patients to prevent re-sedation or respiratory depression due to residual sedative effects during post-anesthetic care after initial ROC.

In older patients, a smaller propofol C_e is required at ROC for both pharmacokinetic and pharmacodynamic reasons. We used the Schnider propofol pharmacokinetic model[5, 6], which takes age into consideration, and hence the pharmacokinetic inter-patient variability caused by age would be excluded. In addition, the Schnider model, although still not perfect, has fewer limitations than the other pharmacokinetic models for propofol and therefore has the potential for being the recommended model of choice to be used for TCI[12]. The significant correlation between propofol C_e at ROC and age suggests that age has a considerable influence on the patient's sensitivity to propofol from a pharmacodynamic point of view.

When the effect of remifentanil C_e on ROC was analyzed, we did not find a significant correlation, which is consistent with previous reports[13, 14]. The C_e of remifentanil (0.7±0.8 ng/mL) at ROC was probably too low to affect ROC. However, when predicting the propofol C_e for ROC, it should be kept in mind that the C_e values of propofol might be different if another sedative, such as a benzodiazepine or a large dose of remifentanil, is also used. The type of surgery may also influence the propofol C_e at ROC. The C_e of propofol for ROC may be slightly increased in the presence of severe pain caused by major surgeries, *eg*, thoracic or abdominal surgery, compared to minor surgeries like those in our study[15]. The C_e of propofol at ROC was not correlated with the duration of propofol infusion or the mean dose of propofol during surgery, which is consistent with a previous study by Kazama *et al*[16]. These clinical contexts (duration or dose) would influence the time taken to reach an individual's propofol C_e for ROC. Current TCI devices display the time required for a calculated C_e to decline to a predetermined value of propofol C_e if the infusion is to be stopped. This allows anesthesiologists to predict the time to ROC, provided that the individual C_e at ROC is known[17].

Although not statistically significant (P=0.08), there was a tendency for the C_e of propofol for LOC to positively correlate with the propofol C_e at ROC, which suggests that patients requiring a higher propofol C_e at LOC tend to recover consciousness at a higher propofol C_e as well. We also found that the mean propofol C_e for LOC was higher than that reported in other studies (4.4±1.1 μg/mL *vs* 1.25–2.35 μg/mL)[6, 18]. One possible explanation for the higher C_e observed in our study is the use of a different pharmacokinetic model. The Schnider model predicts much faster effect-site equilibration with the blood than the Marsh model, as the equilibration constant (K_{eo}) is larger in the Schnider model than in the Marsh model (0.459 min^{-1} *vs* 0.26 min^{-1}). The predicted C_e in the Schnider model will be higher than that in the Marsh model during the induction period[19].

We note that our study has some limitations. We collected the data of dissipating propofol concentrations after stopping

infusion, which could lead to a high performance error of TCI-based predictions of propofol C_e rather than stable propofol C_e. To eliminate the confounding effects of pharmacokinetic and pharmacodynamic variability in the response of patients to a certain stimulus, constant C_e values and blood to effect-site equilibration are required[16]. However, our study design is more applicable to daily clinical practice during emergence from propofol-remifentanil anesthesia.

We conclude that age significantly affects the pharmacodynamic relationship between propofol C_e and ROC. The propofol C_e for ROC can be predicted for individual patients of different ages, and patients can be expected to require shorter recovery times and awaken quickly with early titration of propofol upon surgery completion.

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Author contribution

Dong-woo HAN and Bon-nyeo KOO designed research; Young-ran KANG and Jae-hoon LEE performed research; Dong-woo HAN, Jeong-rim LEE, Gyu-jeong NOH, and Jae-hoon LEE analyzed data; Dong-woo HAN wrote the paper.

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