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 \(C_{50}\) (the effect-site concentration associated with 50% probability of return of consciousness) and \(\lambda\) (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 \(C_{50}\) in 25-, 50-, and 75-year-old patients was predicted to be 1.38, 1.06, and 0.74 μg/mL, respectively. The \(\lambda\) 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

Original Article

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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[14], 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
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, 9] and the model for remifentanil developed by Minto et al[6, 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 blind 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:

$$P=\frac{C_e^\lambda}{C_{\gamma50}^\lambda+C_e^\lambda}$$

where $P$ is the probability of ROC from anesthesia, $C_{\gamma50}$ is the $C_e$ associated with 50% probability of ROC, and $\lambda$ 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 $C_{\gamma50}$ and $\lambda$ 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 $\chi^2$-distributed and could therefore be used for a significance test ($P<0.05$, 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 ($C_s$) 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 $C_s$ 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 $C_s$ 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 $C_{\gamma50}$ and $\lambda$. 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 relationship between the probability of ROC and propofol concentration 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 \( C_{50} \) in 25-, 50-, and 75-year-old patients was predicted to be 1.38, 1.06, and 0.74 μg/mL, respectively. The \( \lambda \) 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 \( C_{50} \) and \( \lambda \) 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

| 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.

| Model  | Parameter       | Value      | %CV | OBJF  |
|--------|-----------------|------------|-----|-------|
| Basic  | \( C_{50} \) (μg/mL) | 1.14       | 32.1| 643.4 |
|        | \( \lambda \)   | 9.03       | –   | –     |
| Final  | \( C_{50} \) (μg/mL) | 1.15–0.0128×(AGE–43) | 26.0| 602.6 |
|        | \( \lambda \)   | 9.69–0.141×(AGE–43) | –   | –     |

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

![Figure 1](image1.png)

**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](image2.png)

**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 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.

Table 2. Pharmacodynamic parameters.
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 1.25–2.55 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 \( (K_{eq}) \) 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 $C_{\text{eq}}$. 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\cite{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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