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Comparison of Predicted Induction Dose with Predetermined Physiologic Characteristics of Patients and With Pharmacokinetic Models Incorporating those Characteristics as Covariates

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Background: **The relationship between patient characteristics and anesthesia induction dose at a high administration rate is unclear. This study was designed to investigate the relation between induction dose and patient characteristics and to compare it to the predicted induction dose using the previously reported pharmacokinetic model.**

Methods: **Diluted propofol (0.5 mg/ml) dose required to reach loss of consciousness, when infused at an infusion rate per lean body mass (LBM) of 150 mg · kg^{-1} · h^{-1} (high rate), was determined in 82 patients, ages 10–85 yr. Cardiac output, blood volume, central blood volume (CBV), and hepatic blood flow were measured with indocyanine green pulse spectrophotometry. Stepwise multiple linear regression models were used to investigate the relations between the patient characteristics and induction dose. These were compared with our previously reported parameters at the rate of 40 mg · kg^{-1} · h^{-1} (low rate) and with predicted induction doses with two previously reported pharmacokinetic models.**

Results: **Significant factors for predicting the induction dose at a high rate were age, LBM, and CBV. Induction dose with one pharmacokinetic model was 1.5 times that of the measured one and the other was half that of the measured one at a high rate. At a low rate, one pharmacokinetic model provided an accurate induction dose.**

Conclusions: **The prediction of induction dose from physiologic characteristics of patients provides reasonable accuracy at both high and low administration rates of propofol. A previously reported pharmacokinetic model that incorporated patient characteristics provides the same accurate induction dose at a low rate.**

A PHARMACOKINETIC model is a useful method of anesthesia maintenance. A pharmacokinetic model that incorporates the effects of age, weight, and height as covariates significantly improves the model.[1,2] However, there are still several assumptions of instantaneous mixing occurrence in the central compartment and stationary pharmacokinetics.[3,4] At a low propofol administration rate, the effects of these assumptions on induction dose might be quite small. At a high propofol administration rate, the effects of these assumptions might be significant because of prolonged mixing time and cardiovascular depression effects on pharmacokinetics.

We have reported the importance of the patient characteristics of age, lean body mass (LBM), central blood volume (CBV), and hepatic blood flow (HBF) in predicting the propofol induction dose at a slow propofol infusion rate of 40 mg · kg^{-1} · h^{-1} (low rate).[5] However, there are few reports on the relation between induction dose and patient characteristics at a high propofol administration rate of more than 150 mg · kg^{-1} · h^{-1} (high rate), probably because of cardiovascular depression.[6] A high administration rate of propofol provokes an increasing effect-site concentration, even after cessation of administration, because of a sustained higher blood propofol concentration than that for effect-site. The excessive residual dose of propofol also increases effect-site concentration.[6] Therefore, induction with a high propofol administration rate will sometimes be critical in elderly patients, even if the titration method is used. Recently, we reported that diluted propofol (0.5 mg/ml) has a small effect on hemodynamic depression after induction, even at a high propofol infusion rate, because of the decreasing effect on the excessive residual dose.[6]

This study was designed 1) to determine titrated induction dose with diluted propofol at a high rate as a function of LBM and to investigate the relation between induction dose with age, sex, LBM, cardiac output (CO), and initial distribution volumes; and 2) to compare the measured induction dose and the predicted induction doses using previously reported pharmacokinetic models incorporating covariates of age, weight, and height.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

Eighty-two nonpremedicated patients (ages 10–85 yr, American Society of Anesthesiologists physical status of 1 or 2) who were scheduled for intravenous induction of anesthesia for elective surgery were selected for the study. Written informed consent was obtained from each patient or a family member following an explanation of the study, which was approved by the District Ethics Committee of Hamamatsu University Hospital. Exclusion criteria were history of cardiac, pulmonary,

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liver, or renal disease; or significant obesity (body mass index >30). Patients receiving long-term treatment with central nervous system active drugs were excluded from the study, as were patients receiving either benzodiazepines or opiates. Female patients who might be pregnant were also excluded.

Before induction, each patient was made comfortable on the operating table, routine monitoring was commenced, and a 20-gauge cannula was inserted into the forearm vein of one arm during local anesthesia; this cannula was used to inject indocyanine green (ICG) and propofol infusion. A venous blood sample was drawn to measure hemoglobin concentration before connecting a venous infusion line, and was immediately analyzed with an automated blood gas analyzer (model 860, Ciba Corning Diagnostics, Medfield, MA).

A probe with two light-emitting diode infrared sources (wavelengths of 805 and 940 nm) was attached to a nostril to obtain dye densitograms (DDGs) (DDG-2001, Nihon Koden, Saitama, Japan). The details of dye-densitometry are described in our previous report.[5]

The patients were asked to lie on the operating table and rest until hemodynamic parameters became stable; 0.3 mg/kg of 2.5 mg/ml ICG (Diagno-green, Dai-ichi Pharmaceutical, Tokyo, Japan) was injected as a bolus followed by a flush of 20 ml lactate Ringer's solution. Plasma ICG concentrations were measured with a spectrophotometric technique.[7] The CO, blood volume (BV), mean transit time, CBV, ICG clearance slope (K), and HBF were calculated with pulse dye-densitometry.[7,8] After completing these measurements from a DDG, oxygen was administered for 5 min with an anesthesia mask, followed by diluted propofol infusion through a three-way tap placed directly into the venous cannula at an infusion speed of 150 $mg \cdot kg^{-1} \cdot h^{-1}$ as a function of LBM. Diluted propofol of 0.5 mg/ml was prepared in a 20-fold dilution of propofol (1% Diprivan, AstraZeneka, Osaka, Japan) with lactate Ringer's solution just before anesthesia induction. It was infused manually, and the infusion volume was checked every second. At the 24-h postoperative examination, each patient was asked about any event recalled after loss of consciousness.

In all patients, the induction doses were titrated. Loss of consciousness was chosen as the induction end-point. The patients were asked to open their eyes every 5 s or otherwise indicate they were still conscious. If no response to verbal requests occurred, the patients were stimulated by gently rubbing and tapping their shoulders. Loss of consciousness was defined as occurring when no response to these stimuli was noted. In all patients, responses to verbal commands were assessed by the same attending anesthesiologist and the same assistant resident anesthesiologist, who were completely familiar with the strict definition of response.

Immediately after loss of consciousness, administration of undiluted propofol was commenced at 4 $mg \cdot kg^{-1} \cdot h^{-1}$. Then intubation was facilitated with fentanyl, 0.1 or 0.2 mg, and vecuronium, 0.1 mg/kg. If hypotension (>30% lower than preadministration systolic blood pressure) persisted, a bolus of 4 or 8 mg of ephedrine was administered intravenously. Induction time was defined as the time from propofol administration to loss of consciousness, and induction dose was defined as the amount of propofol administered before loss of consciousness.

Infusion rate as a function of LBM was calculated for each patient. The LBM was determined from height (cm) and weight (kg) according to sex-specific formulas.[9]

Statistical Analysis

Univariate least squares linear regression was used to examine the relation between age, sex, LBM, hemoglobin, CO, BV, CBV, and HBF, and propofol induction dose. Multiple linear regression was used to examine the relation between the eight variables (age, sex, LBM, hemoglobin, CO, BV, CBV, and HBF) and the propofol induction dose (StatView J-4.5, SAS Institute, Cary, NC). Multicolinearity among variables made regression difficult to interpret. We decided to use forward and backward selection to identify the most useful variables for predicting the induction dose. The criterion for adding and deleting variables was a minimum of 4.0 for the F ratio, which is the square of the value obtained from a *t* test, with the hypothesis that the coefficient of the variable in question is equal to 0 (StatView J-4.5). To directly compare the magnitudes of independent variables in the regression model, we used standardized regression coefficients, which were calculated as if all of the independent variables had a mean of 0 and a variance of 1. For the demographic variables, ANOVA and Bonferroni *post hoc* test were applied. A P value <0.05 was considered statistically significant.

Predicting Induction Dose with Pharmacokinetic Model

Two pharmacokinetic models, previously reported by Schnider *et al.*[1] and Schuttler *et al.*,[2] which incorporated patient characteristics of age, body weight, and height as covariates, were used to predict individual induction dose. Cp50 for loss of consciousness ($Cp50_{Loss\ of\ consciousness}$) was mainly influenced by age and expressed using the following formula[10]: $Cp50_{Loss\ of\ consciousness} = 2.9 - 0.022 \times age$.

The keO values of 0.456 min^{-1} for the Schnider model[10] and of 0.239 min^{-1} for the Schuttler model were used to obtain effect site concentration. Predicted induction dose was calculated as the amount of propofol administered before attaining the effect-site concentration to the individual $Cp50_{Loss\ of\ consciousness}$ at the same administration rate of propofol of 150 $mg \cdot kg^{-1} \cdot h^{-1}$ or 40 $mg \cdot kg^{-1} \cdot h^{-1}$ as a function of LBM. Predicted blood (central compartment) and effect-site concentrations after individual measured induction dose were also calculated with both Schnider and the Schuttler models.

Table 1. Demographic Data of Study Patients

Variables	All Patients	Patients Stratified by Age, yr						
		10–19	20–29	30–39	40–49	50–59	60–69	70–85
Age, yr	47.1 ± 21.3 (11–85)	14.8 ± 2.9	25 ± 2.9	35.1 ± 3.0	46.7 ± 2.4	54.8 ± 2.7	64.8 ± 2.6	76.7 ± 5.2
N	82	11	11	11	11	11	12	15
Gender (M/F), n	44/38	5/6	6/5	6/5	5/6	7/4	7/5	8/7
Height, cm	158.5 ± 9.7 (130–177)	159.3 ± 4.8 (153–170)	165.3 ± 8.9 (152–174)	161.3 ± 10.7 (139–172)	160.7 ± 10.4 (148–177)	160.0 ± 6.2 (148–170)	155.7 ± 5.8 (147–166)	154.5 ± 11.0 (135–168)
Weight, kg	55.3 ± 11.5 (26–86)	56.4 ± 3.1 (52–61)	57.8 ± 12.5 (41–86)	57.1 ± 11.9 (38–75)	58.5 ± 10.8 (40–77)	59.8 ± 9.1 (41–71)	53.1 ± 8.0 (34–67)	54.1 ± 12.9 (35–71)
LBM, kg	43.1 ± 8.4 (22–63)	41.7 ± 2.9 (39–46)	45.1 ± 8.7 (38–63)	44.7 ± 9.3 (32–57)	45.9 ± 8.9 (32–59)	46.3 ± 6.9 (32–55)	41.6 ± 5.9 (31–52)	41.6 ± 8.9 (28–54)
BSA, m^2	1.6 ± 0.2 (1.0–2.0)	1.43 ± 0.2 (1.0–1.7)	1.6 ± 0.2 (1.4–2.0)	1.6 ± 0.2 (1.3–1.9)	1.6 ± 0.2 (1.3–1.9)	1.6 ± 0.2 (1.3–1.8)	1.5 ± 0.1 (1.3–1.7)	1.5 ± 0.2 (1.2–1.8)
Hemoglobin, mg/dl	13.4 ± 1.5 (8.8–15.8)	14.1 ± 0.9 (12.7–15.7)	13.6 ± 0.8 (12.5–15.2)	14.0 ± 1.5 (11.5–15.8)	13.8 ± 1.7 (9.6–15.4)	13.0 ± 1.8 (9.2–14.8)	13.2 ± 1.2 (11.1–14.7)	12.4 ± 1.6 (8.8–14.9)
Cardiac output, l/min	4.8 ± 1.6 (1.3–8.6)	6.0 ± 0.8†‡ (5.1–7.4)	4.7 ± 1.4 (2.5–6.8)	5.6 ± 1.5‡ (3.8–8.6)	5.2 ± 1.6 (2.7–7.4)	5.0 ± 1.1 (3.6–6.9)	4.1 ± 1.8 (2.3–7.3)	3.5 ± 1.1 (1.3–5.5)
Blood volume, l	3.8 ± 1.3 (1.2–7.0)	3.7 ± 1.6 (1.7–5.9)	4.2 ± 1.7 (1.9–7.0)	4.2 ± 1.2 (2.3–6.4)	3.9 ± 1.4 (2.4–6.1)	3.8 ± 1.0 (2.4–6.1)	3.7 ± 0.8 (1.9–4.6)	3.3 ± 0.9 (1.2–4.6)
Mean transit time, s	16.6 ± 5.1 (5.6–31.2)	13.1 ± 3.1‡ (8.8–18.6)	14.3 ± 5.8‡ (5.6–21.1)	16.8 ± 3.3 (10–21.1)	16.6 ± 3.9 (12.1–23.8)	16.8 ± 4.9 (7.9–23.1)	15.3 ± 6.1 (9.7–31.2)	21.5 ± 3.5 (16.7–28.0)
Central blood volume, l	1.3 ± 0.4 (0.5–2.6)	1.3 ± 0.3 (0.9–1.7)	1.0 ± 0.4 (0.5–1.8)	1.6 ± 0.4 (0.7–2.2)	1.5 ± 0.6 (0.7–2.6)	1.4 ± 0.4 (0.7–2.0)	1.0 ± 0.4 (0.6–1.6)	1.2 ± 0.3 (0.6–1.8)
Hepatic blood flow, l/min	0.9 ± 0.4 (0.3–2.2)	1.2 ± 0.4 (0.5–1.7)	0.9 ± 0.2 (0.6–1.2)	0.9 ± 0.3 (0.3–1.3)	0.9 ± 0.3 (0.3–1.3)	1.0 ± 0.5 (0.5–2.2)	0.7 ± 0.2 (0.4–1.1)	0.8 ± 0.4 (0.4–1.5)
Induction time, min	0.8 ± 0.2 (0.5–1.3)	1.1 ± 0.1*†‡ (1.0–1.3)	0.8 ± 0.1†‡ (0.7–1.0)	0.9 ± 0.1†‡ (0.8–1.1)	0.8 ± 0.1†‡ (0.6–1.0)	0.7 ± 0.1 (0.6–0.8)	0.7 ± 0.1 (0.5–0.8)	0.7 ± 0.1 (0.5–0.8)
Induction dose, mg	87.4 ± 24.5	113.3 ± 15.5*†‡	95.7 ± 17.1†‡	103.4 ± 21.6†‡	94.8 ± 24.2†‡	85.1 ± 16.2	68.9 ± 14.1	64.0 ± 17.1

Lean body mass (LBM) = (1.07 × body weight) − (148 × [body weight/height]^2) for women, and LBM = (1.10 × body weight) − (128 × [body weight/height]^2) for men. Body surface area (BSA) = (height in centimeters)$^{0.725}$ × (weight in kilograms)$^{0.425}$ × 0.00718.

*Significant difference from 50 to 59 yr. †Significant difference from 60 to 69 yr. ‡Significant difference from 70 to 85 yr.

Results

In all 82 patients, anesthesia could be induced with propofol. Although we asked patients to remain still, we could not obtain adequate DDGs from one patient each in the 10 - 19 and 20 - 29 age groups because of noisy DDGs resulting from a low AC:DC ratio. We excluded these DDGs from the analysis.

In Schuttler pharmacokinetic model, we could not predict induction doses for three patients of 84, 85, and 85 yr. with the rate of 150 mg · kg^{-1} · h^{-1} and for three patients of 81, 85, and 85 yr. with the rate of 40 mg · kg^{-1} · h^{-1} because of a negative calculated Cl 1 value of pharmacokinetic parameter.

No patients required ephedrine infusion due to hypotension during and after induction. At 24-h postoperative examinations, no patients reported any memory of awareness during induction. Demographic data of the 82 patients stratified by age who participated in this study are presented in table 1. These demographic data of patient characteristics were not significantly different from those for a low rate.[5]

Least squares linear regressions for patient baseline variables and propofol induction doses are shown in table 2. Age, LBM, CO, and CBV correlated with induction dose (table 2).

To identify the independent variables that are most useful for predicting induction propofol dose, all variables were subjected to a stepwise multivariate linear regression analysis using the forward and backward procedure. Age, LBM, and CBV were selected as being independently associated with the induction dose (table 3). Although the mean induction dose of 87.4 mg at a high administration rate was almost the same as 87.2 mg at a low administration rate,[5] those significant regression parameters of a high rate were different from those of the low rate. The HBF was a significant predictor with a low rate[5]; however, it was not selected as a significant

Table 2. Least-Squares Linear Regressions for Patient Baseline Variables and Propofol Induction Dose

Variable	Propofol Induction Dose, mg		
	Slope	Intercept	*R*
Age, yr	−0.8	125.8	−0.685
Sex (female = 0, male = 1)	—	—	0.285
LBM, kg	2.0	2.0	0.619
Hemoglobin, mg/dl	—	—	0.385
Cardiac output, l/min	10.3	38.1	0.646
Blood volume, l	—	—	0.390
Central blood volume, l	37.4	40.0	0.634
Hepatic blood flow, l/min	—	—	0.279

LBM = lean body mass.

Table 3. Coefficients Entered in Multiple Linear Regression Model for Patient Baseline Variables and Propofol Induction Dose

	Propofol Induction Dose, mg			
Variable Entered in Model	Regression Coefficient	Standard Error	Standardized Regression Coefficients	Partial Correlation
Age, yr	−0.7	0.05	−0.6	—
Sex (female = 0, male = 1)	*	*	*	0.1
LBM, kg	1.0	0.2	0.3	—
Hemoglobin, mg/dl	*	*	*	0.2
Cardiac output, l/min	*	*	*	0.1
Blood volume, l	*	*	*	−0.2
Central blood volume, l	23.3	2.9	0.4	—
Hepatic blood flow, l/min	*	*	*	0.1
Intercept	46.4	6.6	—	—
Adjusted R^2	0.87†	—	—	—

*Not selected as a regressor variable in the multiple linear regression model. †$P < 0.05$.
LBM = lean body mass.

predictor with high rate (table 3). Age influenced induction dose more with a high rate (standard regression coefficient, −0.6) than with a low[5] rate (standard regression coefficient, −0.4) (table 3).

Predicted induction doses obtained with the two previously reported pharmacokinetic models and with our preinduction significant physiologic parameters are shown as measured induction doses in figure 1 at the infusion rates of 150 (high rate) and 40 mg · kg^{-1} · h^{-1} (low rate). At a high rate, the predicted induction doses obtained by the Schuttler model were higher than the measured induction dose. However, at a low rate, the predicted induction dose was almost the same as the measured dose. Our predicted induction doses calculated with predetermined significant physiologic parameters were the same as the measured induction doses at every induction dose for both low[5] and high rates. Predicted induction doses obtained with the Schnider model were underpredicted by measured induction doses at both low and high rates.

Predicted effect-site concentrations calculated with the two pharmacokinetic models are shown in figure 2 when the measured induction dose was infused. The individual pharmacodynamic parameter of $Cp50_{Loss\ of\ consciousness}$ calculated with age is also shown in figure 2. At a high rate, both bunches of predicted effect-site propofol concentrations of loss of consciousness obtained by the two pharmacokinetic models were different from

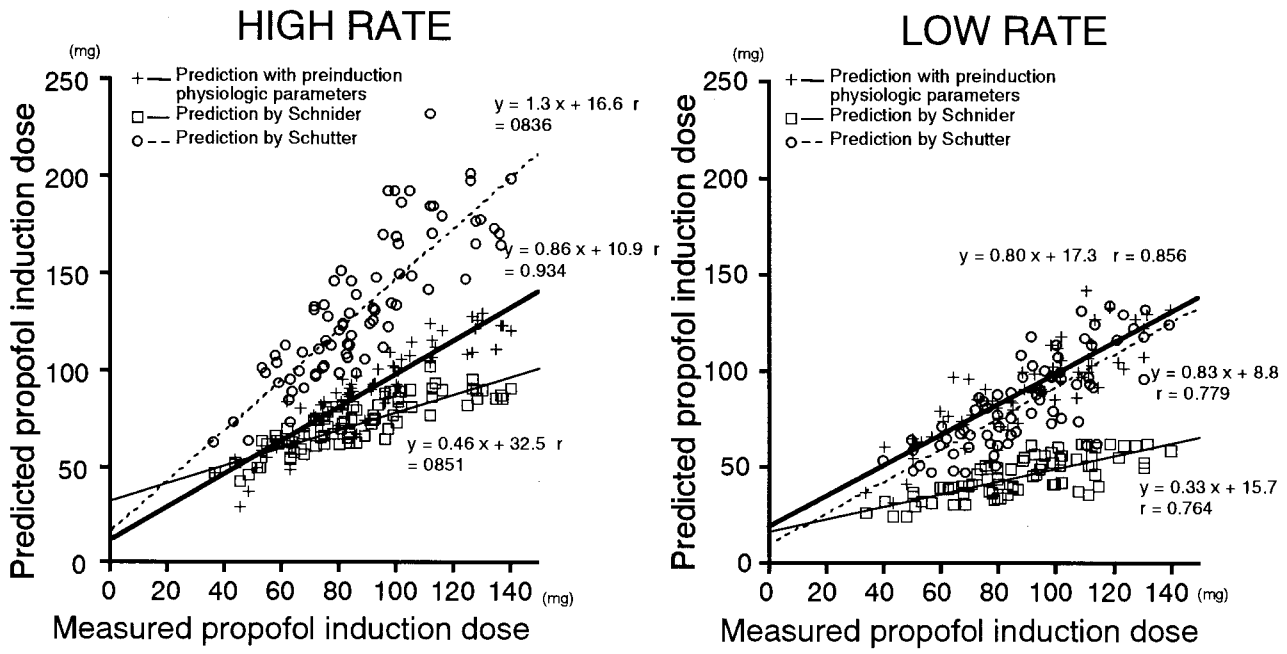

Fig. 1. Predicted propofol induction dose with Schnider (open square) and Schuttler (open circle) pharmacokinetic models were plotted. Calculated individual induction doses for significant patient characteristics (crossing) were also plotted as measured induction doses. Predicted induction doses calculated with significant parameters were the same as the measured induction doses for every induction dose at both high (150 mg · kg^{-1} · h^{-1}) and low (40 mg · kg^{-1} · h^{-1}) rates. Although predicted propofol induction dose obtained by Schuttler pharmacokinetic model was higher than the measured propofol induction dose at a high rate, it was same as the measured one at a low rate.

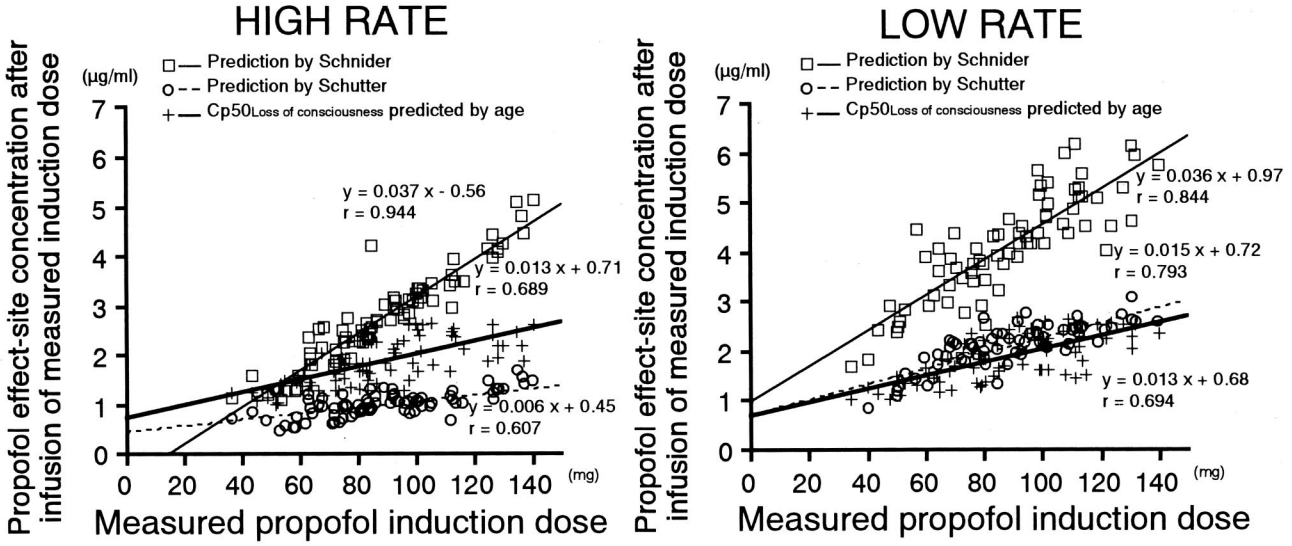

Fig. 2. Predicted propofol effect-site concentrations at loss of consciousness obtained by Schnider (open square) and Schuttler (open circle) pharmacokinetic models when measured induction dose was infused, were plotted. Individual pharmacodynamic parameters of $Cp50_{Loss\ of\ consciousness}$ (crossing) based on age were also plotted. At a high administration rate, both bunches of the predicted effect-site propofol concentrations of loss of consciousness obtained by the two pharmacokinetic models were different from $Cp50_{Loss\ of\ consciousness}$ at every measured propofol induction dose. At a low rate, the predicted propofol effect-site concentrations obtained with the Schuttler model correspond closely to pharmacodynamic parameters of $Cp50_{Loss\ of\ consciousness}$.

$Cp50_{Loss\ of\ consciousness}$ at every measured propofol induction dose. At a low rate, the predicted propofol effect-site concentrations obtained with the Schuttler model correspond closely to the pharmacodynamic parameters of $Cp50_{Loss\ of\ consciousness}$ from low to high induction doses. The predicted effect-site concentrations obtained with the Schnider model were higher than $Cp50_{Loss\ of\ consciousness}$.

Predicted propofol concentrations at central compartment after the individual measured induction dose obtained with the Schnider model were higher than those obtained with the Schuttler model at a high administration rate, whereas the difference became small at a low propofol rate (fig. 3).

Discussion

The authors previously reported induction doses for a wide range of infusion rates with undiluted and diluted propofol.[6] At the rate of 150 $mg \cdot kg^{-1} \cdot h^{-1}$ with diluted propofol, the induction dose[6] was 2.2 ± 0.2 mg/kg at the age of 38 yr, which was the same as the result of 2.3 ± 0.48 mg/kg (table 1) at 30–39 yr in the current study. They also reported that induction dose with undiluted propofol was higher by 0.6 mg/kg[6] than that with diluted propofol at the rate of 150 $mg \cdot kg^{-1} \cdot h^{-1}$. If undiluted propofol were used in the current study, the induction dose would increase, which might provoke hypotension, especially in elderly patients. In current study, no patients developed hypotension with diluted propofol. Zheng *et al.*[11] reported significantly higher arterial propofol concentrations and more profound decreases in mean arterial blood pressure with rapid injection than with slow injection of 200 mg propofol (26.9 *vs.* 11.9 μg/ml). They did not titrate the induction dose. Titrated induction with diluted propofol would not cause profound hypotension.

Although induction doses at a high rate were almost the same as those at a low rate, the HBF was not included as a significant selected parameter to determine induction dose at a high rate, and the parameter of age contributed to induction dose more at a high rate (table 3) than that at a low[5] rate.

The induction time at a low rate is 3.0 min,[5] which is four times longer than that at a high rate. As induction time becomes shorter, the effects of clearance by HBF on propofol blood concentration decrease; therefore, HBF was not included as a parameter to determine the induction dose at a high rate.

Age contributed more to induction dose at a high rate (table 3) than that at a low rate.[5] Age influences both pharmacokinetics and pharmacodynamics.[1,2,12] As for the effect of age on induction doses at low and high rates, its pharmacodynamic effect may be similar regardless of administration rates. Therefore, the potent contribution of age on induction dose at a high rate in our study has been attributed to pharmacokinetics, although its precise mechanism was not clear in our experiment.

For $Cp50_{Loss\ of\ consciousness}$ to calculate induction dose with previously reported pharmacokinetic models, we used the formula reported by Schnider *et al.*[10] The propofol $Cp50_{Loss\ of\ consciousness}$ decreases as people

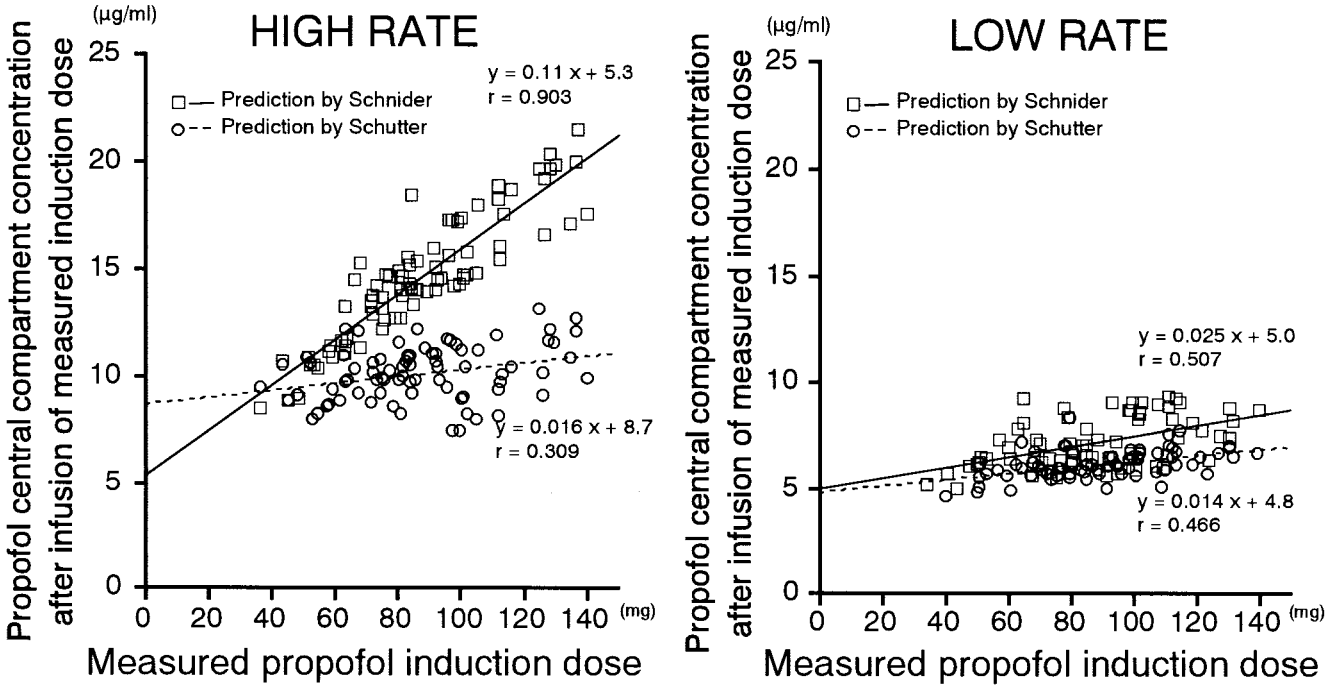

Fig. 3. Propofol central compartment concentrations at loss of consciousness were predicted by Schnider (open square) and Schuttler (open circle) pharmacokinetic models at high and low rates when the measured induction dose was infused. At a high rate, those of the Schnider model were higher than Schuttler. At low rate, those of Schnider and the Schuttler model were similar.

age[10,13] and the formula was very similar to our previously reported formula ($Cp50_{Loss\ of\ consciousness} = 2.95 - 0.021 \times age$) calculated with 69 patients from 17 to 89 yr.[12]

The predicted induction dose obtained with the Schuttler pharmacokinetic model, which incorporated age and body weight as covariates, was similar to the measured induction dose over a wide range of induction doses when propofol was infused at a low rate (fig. 1). Whereas, the predicted induction dose at a high rate was larger than the measured one (fig. 1). With induction at a high rate, blood with a high propofol concentration would be delivered to the brain before being mixed in whole circulating blood. Therefore, the measured induction dose at a high rate would be lower than the predicted induction dose obtained with the pharmacokinetic model, where the central compartment was assumed to be mixed instantly. When the measured induction dose was infused, the predicted effect-site concentrations at a high rate obtained with the Schuttler model were lower than the pharmacodynamic values of $Cp50_{Loss\ of\ consciousness}$ based on age, whereas those of a low rate were almost the same as $Cp50_{Loss\ of\ consciousness}$ (fig. 2), which is reassuring for the uncompleted mixing in the central compartment at a high rate. Moreover, the administration rate of 40 $mg \cdot kg^{-1} \cdot h^{-1}$ is thought to be slow enough for mixing in the central compartment. Major *et al.*[14] reported a significant difference of propofol concentration between venous and arterial during the first 60 s after administration of a propofol bolus dose, suggesting that instantaneous mixing does not occur.

Predicted induction doses with Schnider pharmacokinetic model were lower than the measured induction doses at both high and low rates (fig. 1). When the measured induction dose was infused, propofol concentrations at the central compartment of the Schnider model were much higher than those of the Schuttler model, especially at a high rate (fig. 3). The volume of the central compartment of the Schnider model does not include any covariates, whereas that of the Schuttler model includes age and body weight as covariates. The volume of the central compartment with The Schnider model does not increase as induction dose increases, as shown in figure 4. Consequently, blood propofol concentration increases as induction dose increases at a high rate (fig. 3), and effect-site concentrations were higher than pharmacodynamic parameter of $Cp50_{Loss\ of\ consciousness}$.

The rapidity of the emergence of drug effects is expressed by blood concentration and keO. Gentry *et al.*[15] indicated that the value of keO is highly influenced by the pharmacokinetic model and that it might be unwise to mix the keO from one study with the pharmacokinetics from a different study. However, it is still unclear which keO values should be used for predicting effect-site concentration.

When using pharmacokinetic model by Marsh *et al.*,[16] Struys *et al.*[17] adapted a keO value to 1.21/min based on the data on time-to-peak effect of 1.6 min reported by Schnider *et al.*[10] Their effect compartment target con-

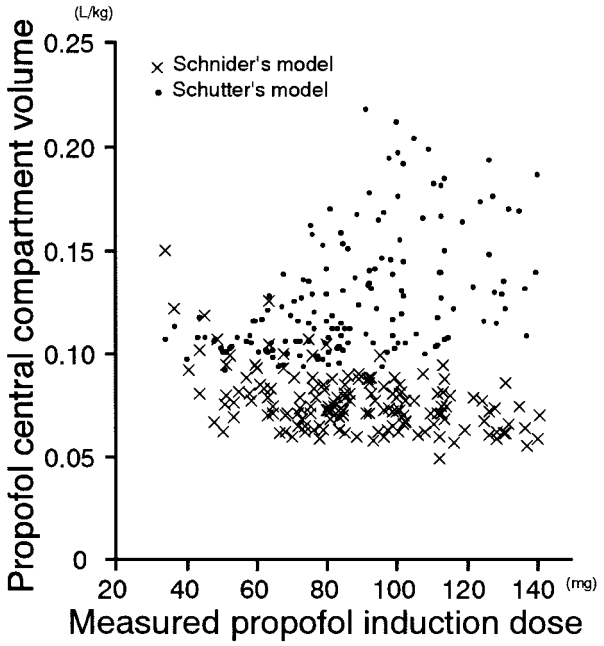

Fig. 4. Individual propofol central compartment volume calculated with Schnider (closed circle) and Schuttler (crossing) pharmacokinetic model, which incorporated patient characteristics as covariates, were plotted as measured induction dose.

trolled infusion with keO of 1.21/min produced an accurate predicted time-to-peak electroencephalography effect, lower induction dose, and lower overshoot with bispectral index (BIS) in anesthesia induction than that with the 0.2/min of keO.[18] However, their estimated effect-site concentration at loss of consciousness was 4.7 μg/ml for keO of 1.21/min.[17] Compared to the value of $Cp50_{Loss\ of\ consciousness}$ of 2.1 μg/ml for corresponding age patients, the loss of consciousness value of 4.7 μg/ml was too great. The reason for this discrepancy is still unclear.

In our study, we used the keO value for the Schnider model as 0.456/min, which was determined with the same pharmacokinetic model.[10] However, similar to the results of Struys *et al.*,[17] our predicted effect-site concentrations with the Schnider model were also higher than $Cp50_{Loss\ of\ consciousness}$ predicted by age at both low and high administration rates. In the model by Schuttler *et al.*,[2] the investigators previously determined their keO value of 0.239/min with the relation between propofol blood concentration and electroencephalography, and the predicted effect-site concentrations at loss of consciousness corresponded to the values of $Cp50_{Loss\ of\ consciousness}$ at a low rate. We previously reported that the value of keO of 0.296/min from the relation of propofol blood concentration and BIS, and that age has little effect on the keO of propofol.[19] Our reported keO value was close to the value of the Schuttler model. At a low rate, the central compartment propofol concentrations predicted with both pharmacokinetic models were similar (fig. 3), therefore, if only keO was adjusted, the predicted effect-site concentration at loss of consciousness will become the same as $Cp50_{Loss\ of\ consciousness}$ in the Schnider model as well as in the Schuttler model.

In conclusion, the prediction of induction dose using predetermined physiologic characteristics of patients provides reasonable accuracy for young, middle-aged, and elderly patients at both high and low administration rates of propofol. Significant regression parameters at a high rate were age, LBM, and CBV, which were different from those at a low rate. The pharmacokinetic model previously reported by Schuttler *et al.*,[2] which incorporated patient characteristics, provides the same accurate induction dose as predetermined physiologic characteristics at a low administration rate. However, both pharmacokinetic models reported by Schnider *et al.*[1] and by Schuttler *et al.*[2] could not predict an accurate induction dose at a high rate.

References

1. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82

2. Schuttler J, Ihmsen H: Population pharmacokinetics of propofol: a multicenter study. ANESTHESIOLOGY 2000; 92:727–38

3. Coetzee JF, Glen JB, Wium CA, Boshoff L: Pharmacokinetic model selection for target controlled infusions of propofol. Assessment of three parameter sets. ANESTHESIOLOGY 1995; 82:1328–45

4. Vuyk J, Engbers FH, Burm AG, Vletter AA, Bovill JG: Performance of computer-controlled infusion of propofol: an evaluation of five pharmacokinetic parameter sets. Anesth Analg 1995; 81:1275–82

5. Kazama T, Ikeda K, Morita K, Ikeda T, Kikura M, Sato S: Relation between initial blood distribution volume and propofol induction dose requirement. ANESTHESIOLOGY 2001; 94:205–10

6. Kazama T, Ikeda K, Morita K, Kikura M, Ikeda T, Kurita T, Sato S: Investigation of effective anesthesia induction doses using a wide range of infusion rates with undiluted and diluted propofol. ANESTHESIOLOGY 2000; 92:1017–28

7. Haruna M, Kumon K, Yahagi N, Watanabe Y, Ishida Y, Kobayashi N, Aoyagi T: Blood volume measurement at the bedside using ICG pulse spectrophotometry. ANESTHESIOLOGY 1998; 89:1322–8

8. Iijima T, Iwao Y, Sankawa H: Circulating blood volume measured by pulse dye-densitometry: comparison with (131)I-HSA analysis. ANESTHESIOLOGY 1998; 89:1329–35

9. James WPT: Research in obesity. London, Her Majesty's Printing Office, 1976

10. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502–16

11. Zheng D, Upton RN, Martinez AM, Grant C, Ludbrook GL: The influence of the bolus injection rate of propofol on its cardiovascular effects and peak blood concentrations in sheep. Anesth Analg 1998; 86:1109–15

12. Kazama T, Takeuchi K, Ikeda K, Ikeda T, Kikura M, Iida T, Suzuki S, Hanai H, Sato S: Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, middle-aged, and elderly patients. ANESTHESIOLOGY 2000; 93:662–9

13. Smith C, McEwan AI, Jhaveri R, Wilkinson M, Goodman D, Smith LR, Canada AT, Glass PS: The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. ANESTHESIOLOGY 1994; 81:820–8

14. Major E, Aun C, Yate PM, Savege TM, Verniquet AJ, Adam H, Douglas EJ: Influence of sample site on blood concentrations of ICI 35868. Br J Anaesth 1983; 55:371–5

15. Gentry WB, Krejcie TC, Henthorn TK, Shanks CA, Howard KA, Gupta DK, Avram MJ: Effect of infusion rate on thiopental dose-response relationships. Assessment of a pharmacokinetic-pharmacodynamic model. ANESTHESIOLOGY 1994; 81:316–24

16. Marsh B, White M, Morton N, Kenny GN: Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 1991; 67:41–8

17. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment versus two methods for effect compartment–controlled target-controlled infusion for propofol. ANESTHESIOLOGY 2000; 92:399–406

18. Billard v, Gambus PL, Chamoun N, Stanski DR, Shafer SL: A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. Clin Pharmacol Ther 1997; 61:45–58

19. Kazama T, Ikeda K, Morita K, Kikura M, Doi M, Ikeda T, Kurita T, Nakajima Y: Comparison of the effect-site k(eO)s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. ANESTHESIOLOGY 1999; 90:1517–27