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Relation between Initial Blood Distribution Volume and Propofol Induction Dose Requirement

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Background: **Propofol induction dose is variable and depends on many factors, including initial volume of distribution and early disposition. The authors hypothesized that preadministration blood distribution volumes, cardiac output (CO), and hepatic blood flow (HBF) could be examined to establish a propofol induction dose.**

Methods: **Propofol dose required to reach loss of consciousness, when infused at infusion rate per lean body mass (LBM) of 40 mg · kg^{-1} · h^{-1}, was determined in 75 patients aged 11–85 yr. CO, blood volume (BV), central blood volume (CBV), and HBF were measured with indocyanine green pulse spectrophotometry. Univariate least squares linear regression analysis was used to individually analyze the relation between propofol induction dose and patient characteristics, including LBM, baseline distribution volumes, CO, and HBF. Stepwise multiple linear regression models were used to select important predictors of induction dose.**

Results: **Although there was a significant correlation between the induction dose and each of the eight variables of age, sex, LBM, hemoglobin, CO, BV, CBV, and HBF, only factors of age (partial r = −0.655), LBM (partial r = 0.325), CBV (partial r = 0.540), and HBF (partial r = 0.357) were independently associated with the induction dose (R^2 = 0.85) when all variables were included in a multivariate model.**

Conclusions: **At a constant propofol infusion rate of 40 mg · kg^{-1} · h^{-1} as a function of LBM in patients with American Society of Anesthesiologists physical status I or II, the induction dose can be determined from four variables: age, LBM, CBV, and HBF.**

DOSE requirements of propofol induction depend on patient characteristics and infusion rate.[1] Cardiac output (CO) is thought to be an important factor affecting the induction of anesthesia.[2] Particularly high concentrations could be expected if a normal dose of propofol was injected into a patient with low CO. Consistent with the experience of most anesthesiologists, critically ill patients with low CO usually require very small doses of propofol.[3] Both CO and its peripheral distribution are important determinants of the relation between early drug concentration and time in intravenously administered drugs, especially with a slow administration rate.[4] However, CO, which varies with age, does not account for age-related differences in thiopental dose requirements.[5] The safe dose of an intravenously administered drug will depend on its initial distribution volume and early disposition. Avram *et al.*[6] suggested that the central volume of a four-compartment model does not vary with age for thiopental pharmacokinetics. Central volume of a three-compartment model for propofol was also independent of age.[7]

Knowledge of a patient's characteristics of lean body mass (LBM), sex, age, hemoglobin, CO, and distribution volumes during the early infusion phase allows for the prediction of propofol induction dose requirements. The relation between these characteristics and previously reported pharmacokinetic parameters[6,7] is the basic concern of clinical anesthesia. Indocyanine green (ICG) is a useful physiologic marker because its early distribution is within the intravascular space, and it is cleared with a high extraction ratio by the liver.[8] CO, blood volume (BV), mean transit time (MTT), ICG clearance slope, and central BV (CBV; BV in the heart cavities, lungs, and central arterial tree) can be measured with pulse dye-densitometry based on the principle of pulse spectrophotometry.[9] In the present study, we evaluated these different variables as predictors for propofol induction dose at constant infusion rates per LBM of 40 mg · kg^{-1} · h^{-1}.

Materials and Methods

Seventy-five unpremedicated patients (aged 10–85 yr, with American Society of Anesthesiologists physical status I or II) who were scheduled for intravenous induction of anesthesia for elective surgery were selected as participants. Written informed consent was obtained from each patient after explanation of the study, which was approved by the District Ethics Committee of the Hamamatsu University Hospital. Exclusion criteria were a history of cardiac, pulmonary, liver, or renal disease, or significant obesity (body mass index > 30). Long-term users of central nervous system activator drugs and patients receiving either benzodiazepines or opiates were excluded from the study. Women who might be pregnant were also excluded.

Before induction, each patient was made comfortable on the operating table, routine monitoring was commenced, and during local anesthesia, a 20-gauge cannula was inserted into a forearm vein to be used for the injection of ICG and propofol infusion. A venous blood

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Table 1. Demographic Data of Study Patients

Variables	All Patients	Patients Stratified by Age						
		10–19 yr	20–29 yr	30–39 yr	40–49 yr	50–59 yr	60–69 yr	70–85 yr
Age (yr)	47.3 ± 21.5 (11–85)	15.5 ± 2.6	25.6 ± 2.8	33.5 ± 3.5	44.7 ± 3.7	56.4 ± 2.4	64.5 ± 2.7	76.3 ± 5.3
N	75	10	10	10	10	10	10	15
Sex (M/F)	34/41	5/5	4/6	5/5	3/7	5/5	5/5	7/8
Height (cm)	158.9 ± 10.0 (134–182)	165.1 ± 9.5*† (150–179)	160.3 ± 10.5 (150–182)	163.3 ± 9.1*† (149–175)	160.3 ± 10.6 (148–179)	158.4 ± 7.8 (146 –175)	154.4 ± 7.6 (144–167)	153.4 ± 10.3 (134–171)
Weight (kg)	56.6 ± 9.4 (29–73)	57.4 ± 7.0† (48–68)	53.8 ± 11.2 (43–72)	58.3 ± 6.8 (50–71)	55.7 ± 9.7 (41–68)	59.3 ± 9.6 (46 –73)	60.6 ± 6.3 (50–68)	53.2 ± 12.1 (29–72)
LBM (kg)	43.6 ± 7.6 (25–58)	45.4 ± 6.1 (37–55)	42.8 ± 9.6 (34–58)	45.7 ± 6.8 (37–55)	43.2 ± 8.4 (33–56)	45.2 ± 8.1 (35 –57)	44.1 ± 5.1 (37–53)	40.5 ± 8.4 (25–57)
Hemoglobin (mg/dl)	13.3 ± 1.7 (9.6–17.3)	14.1 ± 1.2 (12.4–15.9)	14 ± 1.3 (12–15.7)	14 ± 1.1 (12.6–15.5)	12.7 ± 2.2 (10.1–16)	13.2 ± 1.4 (10.9–14.9)	14 ± 2.1 (10.7–17.3)	12.1 ± 1.7 (9.6–14.4)
Cardiac output (l/min)	4.4 ± 1.3 (1.3–7.3)	5.6 ± 1.3*† (3.0–7.3)	4.6 ± 1.1*† (2.9–6.5)	4.8 ± 0.8* (2.9–5.9)	5 ± 1.2*† (3.1–6.6)	4.5 ± 1.2 (2.6 –6.2)	3.5 ± 1.2 (1.5–6.1)	3.4 ± 1 (1.3–5.1)
Blood volume (l)	3.9 ± 0.9 (1.8–5.9)	4.3 ± 0.8 (2.9–5.3)	3.7 ± 1.1 (2.6–5.6)	4 ± 0.3 (3.4–4.4)	4.3 ± 0.7 (3.4–5.4)	4.1 ± 1.2 (2.6 –5.9)	3.7 ± 0.7 (2.8–4.8)	3.6 ± 1.1 (1.8–5.1)
Mean transit time (s)	16.0 ± 4.4 (9.1–26.0)	15.1 ± 4.2 (9.3–21.3)	15.6 ± 3.9 (11.2–21.3)	14 ± 4* (10.9–23.4)	13.8 ± 2.4* (10.8–17.5)	16.6 ± 4.6 (11.4–25.1)	19.1 ± 5.4 (9.1–26)	17 ± 4.3 (10.9–25.3)
Central blood volume (l)	1.1 ± 0.3 (0.5–1.8)	1.3 ± 0.3† (1.0–1.8)	1.1 ± 0.2 (0.9–1.5)	1.1 ± 0.2 (0.9–1.45)	1.1 ± 0.3 (0.8–1.7)	1.2 ± 0.4 (0.5 –1.7)	1.1 ± 0.4 (0.5–1.8)	0.9 ± 0.2 (0.5–1.4)
Hepatic blood flow (l/min)	0.9 ± 0.4 (0.2–2.0)	1.1 ± 0.4 (0.6–2.0)	1.1 ± 0.4† (0.7–2.0)	0.8 ± 0.4 (0.4–1.5)	0.8 ± 0.4 (0.3–1.6)	0.8 ± 0.3 (0.5 –1.3)	0.8 ± 0.2 (0.5–1.2)	0.6 ± 0.3 (0.2–1.2)
Induction time (min)	3.0 ± 0.7 (1.5–4.4)	3.8 ± 0.3 (3.2–4.1)	3.7 ± 0.5 (3.2–4.4)	3.1 ± 0.5 (2.3–3.8)	3.0 ± 0.4 (2.7–3.9)	3.0 ± 0.3 (2.4 –3.3)	2.6 ± 0.8 (1.9–3.8)	2.2 ± 0.5 (1.5–3.3)
Induction dose (mg)	87.2 ± 25.1 (34.3–145.4)	113.5 ± 16.6 (91.6–145.4)	105.0 ± 19.1 (75.7–140)	94.2 ± 17.5 (60–121.8)	86.2 ± 22.8 (58.7–131)	88.7 ± 16.3 (60–113.7)	75.3 ± 23.5 (50.3–114.9)	60.8 ± 16.3 (34.3–86.9)

* $P < 0.05$. Significant difference from 60–69 yr. † $P < 0.05$. Significant difference from 70–86 yr.

LBM = lean body mass; women, LBM = (1.07 × body weight) − (148 × (body weight/height)^2); men, LBM = (1.10 × body weight) − (128 × (body weight/height)^2).

sample was drawn to check hemoglobin concentration before connection of a venous infusion line, and the sample 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 the patient's nostril to obtain a dye densitogram (DDG) (DDG-2001; Nihon Koden Co., Saitama, Japan). This device detects pulsatile changes of the tissue optical density of a nostril. The arterial dye concentration is continuously computed by reference to the previously measured blood hemoglobin concentration.

Patients were asked to recline on the operating table and rest until their hemodynamic parameters stabilized. A bolus injection of 0.3 mg/kg of 2.5 mg/ml ICG (Diagnogreen; Dai-ichi Pharmaceutical, Tokyo, Japan) was followed by a flush of 20 ml of lactated Ringer's solution. Plasma ICG concentrations were measured with the spectrophotometric technique.[9]

The extinction coefficients of oxygenated and reduced hemoglobin concentrations are nearly the same at 805 and 940 nm. The peak absorption for ICG is at 805 nm, and its absorption at 940 nm is negligible. The ratio of variations caused by pulse (AC) to the total transmitted light (DC) at each wavelength depends on the ratio of arterial ICG concentration to arterial hemoglobin concentration.[10] By measurement of AC:DC ratios at 805 and 940 nm and hemoglobin value, whole blood ICG concentration can be calculated. If a probe position changes during data collection, a motion artifact is easily detected in the recorded AC:DC ratio. Such problems are caused by body motion or insufficient circulation. We excluded DDGs showing these problems from the analysis.

Cardiac output, BV, MTT, CBV, and ICG clearance slope (K) were calculated with pulse dye-densitometry.[9,11] MTT was determined with the modified Stewart-Hamilton technique.[12] CO multiplied by MTT is CBV, in which ICG distributes initially. The ICG clearance slope, K, was computed *via* linear regression of the semilog plot between 2.5 and 5.5 min after MTT and extrapolated to the ICG concentration at injection time. With this method, the volume of distribution is calculated by division of the injected ICG dose by the extrapolated plasma concentration at time zero. Slope K of the log-linear dye clearance in the later phase of DDG is called the "plasma disappearance rate," and it has units of inverse time. BV multiplied by K is the effective hepatic blood flow (HBF).

After completion of these measurements with DDG, oxygen was administered with an anesthesia mask for 5 min, followed by propofol infusion through a three-way

Table 2. Correlation Coefficient and Partial Correlation Coefficient of Variables *versus* Induction Dose

	Regression Line		Correlation Coefficient (r)	Partial Correlation Coefficient
	Slope	Intercept		
Age (yr)	−0.79	125.3	−0.690*	−0.655*
Sex (0 F, 1 M)	22.8	77.8	0.492*	0.196
LBM (kg)	2.06	−2.03	0.640*	0.325*
Hemoglobin (mg/dl)	6.31	4.16	0.456*	0.117
Cardiac output (l/min)	10.71	40.73	0.581*	0.041
Blood volume (l)	13.3	36.37	0.496*	−0.073
Central blood volume (l)	54.9	26.9	0.671*	0.540*
Hepatic blood flow (l/min)	31.2	61.7	0.481*	0.357*

* $P < 0.05$.

LBM = lean body mass.

tap placed directly into the venous cannula with an infusion speed of 40 $mg \cdot kg^{-1} \cdot h^{-1}$ as a function of LBM.

All induction doses were titrated. Loss of consciousness was the induction end point. The patients were asked to open their eyes every 5 s or otherwise indicate that they were still conscious. If there was no response to verbal requests, the patients were stimulated by gentle rubbing and tapping of their shoulders. Loss of consciousness was defined as no response to these stimuli. In all patients, responses to verbal and physical stimulation were assessed by the same attending anesthesiologist and the same assistant resident anesthesiologist, who were completely familiar with the definition of response.

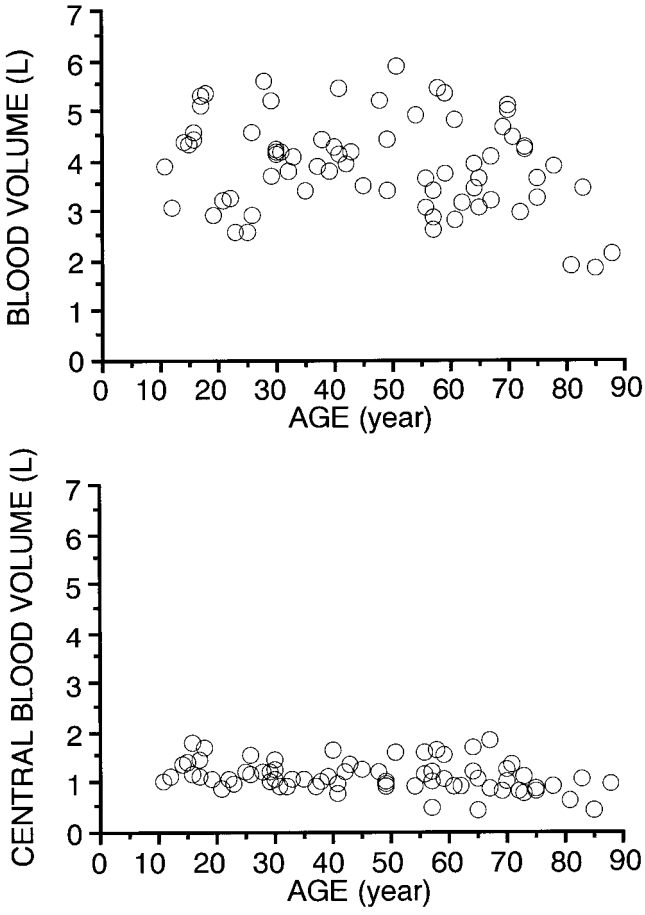

Fig. 1. There is no relation of the blood volume and the central blood volume to age.

Immediately after loss of consciousness, infusion speed of propofol was decreased to 4 $mg \cdot kg^{-1} \cdot h^{-1}$. Intubation was facilitated by 0.1 or 0.2 mg fentanyl and 0.1 mg/kg vecuronium. 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.

Lean body mass was determined from height (centimeters) and weight (kilograms) by sex-specific formulas[13]: for women, LBM = 1.07 × weight − 148 × (weight/height)^2, and for men, LBM = 1.10 × weight − 128 × (weight/height)^2.

To assure a reasonable age distribution of patients, 10 patients were included in each 10-yr range from 10–69 yr, and 15 were included in a 70–85-yr-old group. At a 24-h postoperative examination, each patient was asked about any event recall after loss of consciousness.

Statistical Analysis

Univariate least squares linear regression analysis was used to detect any relations of age, sex, LBM, hemoglobin, CO, BV, CBV, and HBF to propofol induction dose. Correlation and partial correlation coefficients were examined between each of the eight variables and the induction dose. A P value less than 0.05 was considered a significant correlation. Multiple linear regression was used to examine the relative importance of each variable to induction dose (StatView J-4.5; SAS Institute Inc., Cary, NC). Multicolinearity among the variables can hinder the interpretation of results. Forward and backward stepwise selection allowed us to identify the independently associated variables. For adding and deleting variables, the F ratio criterion was 4.0, which is the squared value obtained from a t test for the hypothesis that the coefficient of the variable in question equals zero (StatView J-4.5; SAS Institute Inc.). For the variables of demographic data, analysis of variance and the Fisher

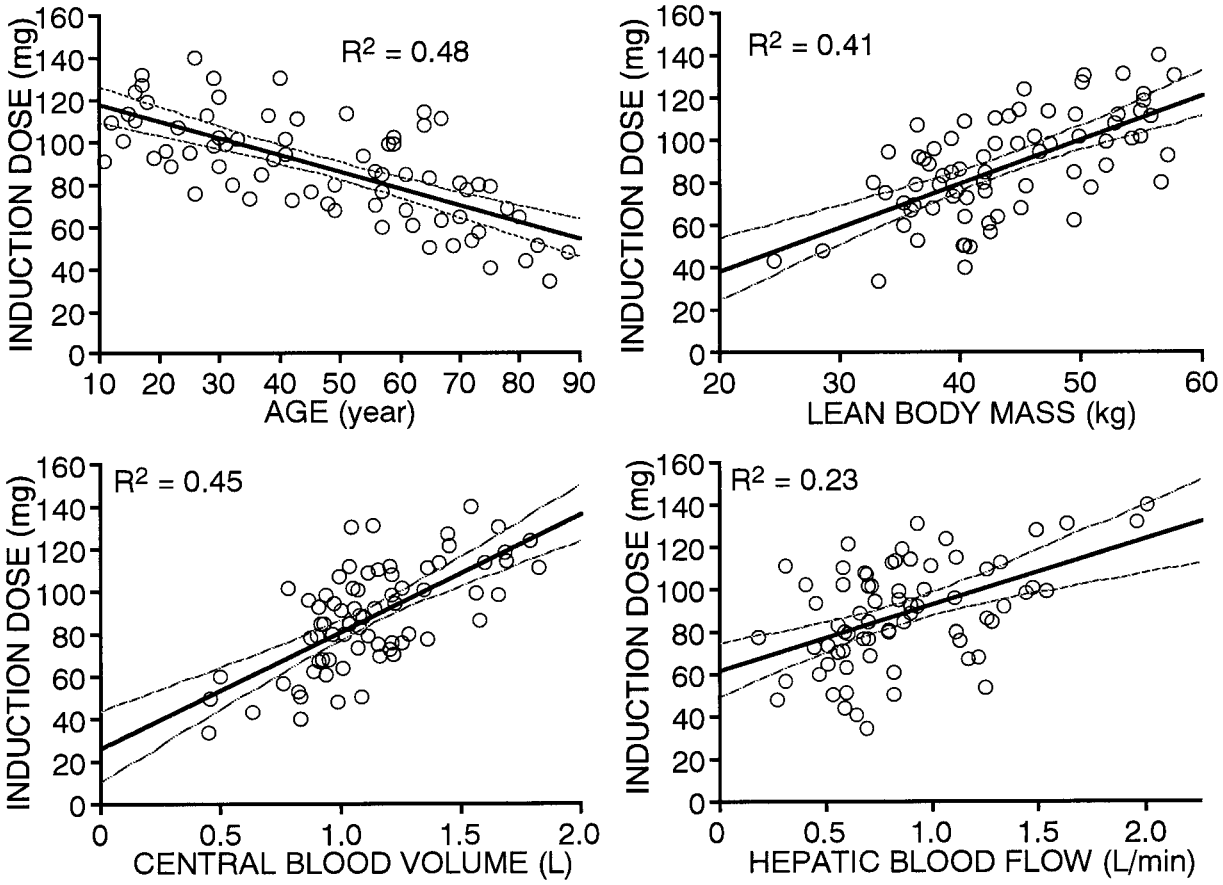

Fig. 2. The relation between propofol dose required to reach loss of consciousness and age, lean body mass, central blood volume, and hepatic blood flow. Propofol was infused at 40 mg · kg^{-1} · h^{-1} as a function of lean body mass. The lines represent least squares linear regression lines and 95% confidence intervals.

test were used for means comparison of demographic variables among each age group. A *P* value less than 0.05 was considered statistically significant.

Results

Anesthesia could be induced with propofol in all 75 patients. Two DDGs were excluded from analysis, one each from the 20–29-yr-old and 70–85-yr-old groups, because of a low AC:DC ratio, which produced a noisy DDG. In one patient each from three age groups (10–19 yr, 40–49 yr, and 70–85 yr), the DDG obtained at 2.5 min after injection of ICG was inadequate because of abrupt variation of the AC:DC ratio. We excluded these DDGs from the analysis only for BV and K.

Demographic data, stratified by age groups, are presented in table 1. CO was significantly correlated with age ($r = -0.54$; table 1). Neither CBV nor BV correlated with age (fig. 1).

Although there was a significant correlation between each of the eight variables and induction dose, only factors of age (partial $r = -0.655$), LBM (partial $r = 0.325$), CBV (partial $r = 0.54$), and HBF (partial $r = 0.357$) were independently associated with the induction dose when all variables were included in a multiple regression model (tables 2 and 3; predicted induction dose $= 17.8 - 0.5 \times$ age $+ 1.25 \times$ LBM $+ 26.9 \times$ CBV $+ 10.4 \times$ HBF; $R^2 = 0.85$). The relation between each independent variable and the induction dose are shown in figure 2. The induction dose predicted by a stepwise multiple linear regression model was closely related with measured induction dose (fig. 3).

Discussion

Plasma propofol concentration is dependent not only on LBM, total body weight, or volume of distribution, but also on other factors concerned with anthropometric variables. Because each parameter is itself an estimate with unknown variance, prediction of induction dose with parameters is fraught with error. To make matters worse, factors such as age, weight, and sex may be interrelated, so that their influences may be difficult to establish. In the present study, to identify variables that were significantly associated with induction dose, we performed all measurements with forward and backward stepwise multivariate linear regression analysis. We found that age, LBM, CBV, and HBF were significant

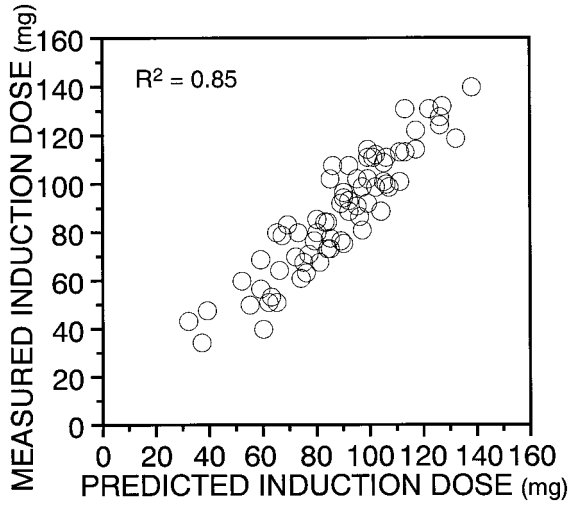

Fig. 3. Predicted induction dose by stepwise multiple linear regression modeling. The predictors are age, lean body mass (LBM), central blood volume (CBV), and hepatic blood flow (HBF). Predicted induction dose is calculated by the following formula: predicted induction dose = 17.8 − 0.5 × age + 1.25 × LBM + 26.9 × CBV + 10.4 × HBF (R^2 = 0.85).

predictors of induction dose and that the predicted induction dose was strongly correlated with measured induction dose (R^2 = 0.85; table 3 and fig. 3). The usefulness of the aforementioned parameters as significant predictors of induction dose is a basic concern of clinical anesthesia.

Relation between Induction Dose and Age

Increased reactivity of the elderly to propofol may be more severe than is readily apparent. Age influences both pharmacokinetics and pharmacodynamics of propofol.[7,14] Induction dose will be almost linearly correlated with $Cp50_{loss\ of\ consciousness}$ (the concentration that does not respond to verbal command at 50%) in identical body composition. Our regression line between age and induction dose was almost parallel to the reported relation between age and $Cp50_{loss\ of\ consciousness}$ (induction in our study = 125.3 ×(1 − 0.0063 × age), $Cp50_{loss\ of\ consciousness}$[14] = 2.9 × (1 − 0.0076 × age), which indicates that age is thought to influence mainly pharmacodynamics of propofol. Wada *et al.*[15] reported that the age-related physiologic changes have a relatively minor effect on peak plasma concentrations, with negligible differences after 2 min of thiopental infusion. In our study, the predictor with the greatest correlation coefficient for induction dose was age (table 3); this finding might be associated with $Cp50_{loss\ of\ consciousness}$. In our study, BV, which correlated weakly with induction dose, had no correlation with age (fig. 1; r = −0.24), which is consistent with reports on thiopental by Avram *et al.*[6] and on propofol by Kirkpatrick *et al.*[16] and Schnider *et al.*[7] The influence of age on propofol pharmacokinetics remains unresolved. Several studies have suggested that the pharmacokinetics of propofol are age-dependent.[17,18] Other investigators have not found an effect of age.[19,20]

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

Variable Entered in Model	Regression Coefficient	SE	Standardized Regression Coefficient
Age (yr)	−0.50	0.06	−0.43
Sex (0 F, 1 M)		*	
LBM (kg)	1.25	0.17	0.39
Hemoglobin (mg/dl)		*	
Cardiac output (l/min)		*	
Blood volume (l)		*	
Central blood volume (l)	26.9	4.6	0.33
Hepatic blood flow (l/min)	10.4	3.5	0.16
Intercept	17.8	9.3	
Adjusted R^2	0.85†		

* Not selected as a predictor variable in the multiple linear regression model. † $P < 0.05$.

LBM = lean body mass.

Relation between Induction Dose and Distribution Volumes

The compartment pharmacokinetic model provides useful information with respect to targeting blood concentrations for long-term infusion but fails to characterize the initial disposition because it is based on several assumptions.[21,22] In thiopental, serum concentration is greater in the first minute and progressively decreases until the third minute.[22] Disposition kinetics of a drug within the first few minutes after intravenous injection are often complicated. Henthorn *et al.*[8] identified early disposition of thiopental by considering the concurrent disposition of ICG. In initial volume, the drug appears to instantaneously mix before being distributed throughout the remainder of its distribution by mixing, flow, and distribution. Avram *et al.*[6] reported that the initial volume is approximately 35 ml/kg and that it did not vary with age. In our study, the CBV was 20 ml/kg, and it did not correlate with age (fig. 1). The physiologic concept of the initial distribution volume proposed by Henthorn *et al.*[8] and Avram *et al.*[6] is not yet confirmed; however, this volume should be close to our CBV that was independently associated with induction dose. According to our recent study investigating propofol anesthesia induction dose at various infusion rates,[1] the influence of rapid circulation on induction dose begins at the infusion rate per LBM of 50 $mg \cdot kg^{-1} \cdot h^{-1}$. We suppose first circulation plays a significant role in induction dose even at our slow infusion rate (40 $mg \cdot kg^{-1} \cdot h^{-1}$) because CBV was one of the significant predictors of the induction dose.

Blood Volume

Blood volume is one determinant of drug concentration in intravenously administered drugs.[4] In our study,

although BV correlated with induction dose (table 2), according to multiple linear regression modeling it was not a predictor of induction dose (table 3). For this reason, we consider BV to be strongly influenced by LBM ($r = 0.71$) and the correlation coefficient of BV to be less significant than that of LBM.

Clearance

Clearance is another determinant of drug concentration in intravenously administered drugs.[4] For drugs with flow-dependent clearance, such as propofol, changes in blood flow in the liver cause proportional changes in clearance. In our study, HBF was a significant predictor of induction dose in a multiple regression model. Avram *et al.*[6] suggested that intercompartmental clearance decreases with age in thiopental. For propofol, Schnider *et al.*[7] reported that age was a significant covariate for clearance. These are consistent with the weak correlation between HBF and age in our study ($r = -0.42$).

Relation between Induction Dose and Cardiac Output

Although CO correlated with induction dose (table 2; $r = 0.58$), according to multiple linear regression modeling it was not a predictor of induction dose (table 3). In our study, patients with American Society of Anesthesiologists physical status I or II, CO correlated with both age ($r = -0.542$) and CBV ($r = 0.548$). It was possible that CO might replace age or CBV in our multiple linear regression model. Wada *et al.*[15] performed a simulation that showed increasing peak concentrations with age to be explained by CO, which is partly consistent with our results. CO will not determine induction dose directly, but it will influence it through various ways. In our study, we defined that CBV was significantly influenced by induction dose rather than CO itself.

Dilution is the process by which increased CO decreases peak arterial concentrations. Propofol is diluted in the volume of blood entering the pulmonary artery during the infusion period; this BV is directly proportional to CO, which is same as the concept of CBV.

The present study establishes the importance of patient characteristics of age, LBM, CBV, and HBF in predicting propofol induction dose at a slow propofol infusion rate of 40 $mg \cdot kg^{-1} \cdot h^{-1}$. However, in different critical conditions such as low CO or shock, other factors may contribute to induction dose.

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