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Comparison of the Effect-site k_{eO}s of Propofol for Blood Pressure and EEG Bispectral Index in Elderly and Younger Patients

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Background: **Drug effect lags behind the blood concentration. The goal of this investigation was to determine the time course of plasma concentration and the effects of propofol demonstrated by electroencephalogram or blood pressure changes and to compare them between elderly and young or middle-aged patients.**

Methods: **A target-controlled infusion was used to rapidly attain and maintain four sequentially increasing, randomly selected plasma propofol concentrations from 1 to 12 μg/ml in 41 patients aged 20–85 yr. The target concentration was maintained for about 30 min. Bispectral index (BIS), spectral edge frequency, and systolic blood pressure (SBP) were used as measures of propofol effect. Because the time courses of these measures following the started drug infusion showed an exponential pattern, the first-order rate constant for equilibration of the effect site with the plasma concentration (k_{eO}) was estimated by fitting a monoexponential model to the effect *versus* time data resulting from the pseudo–steady-state propofol plasma concentration profile.**

Results: **The half-times for the plasma-effect-site equilibration for BIS were 2.31, 2.30, 2.29, and 2.37 min in patients aged 20–39, 40–59, 60–69, and 70–85 yr, respectively (n = 10 or 11 each). The half-times for SBP were 5.68, 5.92, 8.87, and 10.22 min in the respective age groups. All were significantly longer than for BIS ($P < 0.05$). The propofol concentration at half of the maximal decrease of SBP was significantly greater ($P < 0.05$) in the elderly than in the younger patients.**

Conclusions: **The effect of propofol on BIS occurs more rapidly than its effect on SBP. Age has no effect on the rate of BIS reduction with increasing propofol concentration, whereas with increasing age, SBP decreases to a greater degree but more slowly. (Key words: Aged patients; k_{eO}; pharmacodynamics.)**

THE drug concentration time course in plasma cannot in itself predict the time course or magnitude of drug effect[1] because plasma is not the effect site for most drugs. The site at which a drug produces its effect is termed the *biophase*.[2] There is also a time lag between the blood and the actual effect-site concentrations because of the hysteresis between blood and the biophase.[2] This lag between plasma concentration and effect suggests the necessity for calculating the k_{eO} parameter, which is the rate constant describing the elimination of drug from the effect-site compartment.

Although measuring absolute effect-site concentration is not feasible, we can measure the drug effect within the central nervous system using an electroencephalogram (EEG).[3] The EEG usually exhibits a biphasic response to increasing thiopental concentration; that is, there is activation followed by slowing of the EEG waveforms.[4,5] This phenomenon has confounded attempts to predict anesthetic effect using EEGs, as one EEG variable value may be associated with two different anesthetic concentrations.[4,5] The bispectral index (BIS), which is derived from the EEG, incorporates features designed to overcome this problem.

Reductions in systolic blood pressure (SBP) often occur during induction of anesthesia with propofol.[6–8] Cardiovascular depression is rather pronounced in the elderly and is also influenced by the dose and rate of propofol administration.[9,10] However, there are few reports concerning the relationship between the time course of concentration and the effect of propofol. Furthermore, the time course of hypnotic and hemodynamic effects of propofol has not yet been investigated precisely in the elderly compared with that in younger patients.

The first part of the study was designed to determine

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the pharmacodynamics of propofol, as measured by the BIS or blood pressure. We used a target-controlled infusion system to overcome the delay and impediments arising from the rapid distribution pharmacokinetics of propofol. The second part of the study was designed to investigate k_{eO}, the rate constant describing the elimination of drug from the effect-site compartment, and to compare k_{eO} determinations in young to middle-aged and elderly patients.

Materials and Methods

The study was approved by the Hamamatsu University Hospital Ethics Committee. After obtaining written informed consent, we studied 11 patients aged 20–39 yr (group 1), 12 patients aged 40–59 yr (group 2), 12 patients aged 60–69 yr (group 3), and 12 patients aged 70–85 yr (group 4) who were undergoing elective surgery. All patients had American Society of Anesthesiologists physical status I or II, with no known or suspected cardiac, pulmonary, liver, renal, or metabolic disease. Patients with significant obesity (body mass index > 30) or with neurologic dysfunction were excluded from the study. No premedication was given prior to the experiments. After overnight fasting, the patients were brought to a quiet surgical operating room where, after the patients were given local anesthesia, a cannula was inserted into an antecubital vein for the infusion of propofol and for fluid replacement (Ringer's lactate solution of $5\ ml \cdot kg^{-1} \cdot h^{-1}$). A radial arterial catheter was inserted for measuring blood pressure and sampling blood. Heart rate, blood pressure, ECG, end-tidal carbon dioxide, rectal temperature, and oxyhemoglobin saturation were monitored continuously throughout the study. Body temperature was maintained at 36–37°C using a forced-air warming blanket (Bear Hugger, Augustine Medical, Eden Prairie, MN). Oxygen was administered through an anesthesia mask during the study, and spontaneous respirations were manually assisted when necessary to keep arterial carbon dioxide tension within physiologic range.

After skin preparation, silver/silver chloride gel-filled electrodes were secured to the left and right frontal pole regions and referenced to a central vertex electrode. Impedance was maintained at less than 3 kΩ, and EEG was recorded and analyzed using an A1000 EEG monitor (software version 3.12, Aspect Medical Systems, Natick, MA). Baseline BIS, spectral edge frequency 95% (SEF95), and SBP were recorded for at least 5 min. The subjects kept their eyes closed, and no type of stimulation, including verbal command, was permitted during the study.

Target-controlled Infusion for Propofol

Rapid attainment and maintenance of constant plasma concentrations for intravenous anesthetics can be achieved with target-controlled infusion (TCI).[11–13] Propofol was delivered using a pharmacokinetic model-driven infusion device designed for TCI. The system consisted of an NEC (Tokyo, Japan) 9821 microcomputer interfaced to an Atom (Tokyo, Japan) syringe pump (model 1235) utilizing a three-compartment model with central elimination. The control software was programmed in Turbo Pascal (Borland International, Scotts Valley, CA) by one of the authors. Details were described in our previous report.[3] The pharmacokinetic parameters used were reported by Gepts *et al.*[14] for patients aged 20–64 yr and by Oostwouder *et al.*[15] for patients older than 65 yr.

A blood sample was drawn before drug administration. After the beginning of propofol infusion, samples were collected at 0.5, 1, and 2 min. Then samples were taken every 2 min until EEG recording was terminated. Infusion time of each target concentration was about 30 min. Four sequentially increasing, randomly selected target concentrations from 1 to 12 μg/ml were studied in each patient.

TCI Pump Performance Analysis

To characterize the success in achieving the target plasma propofol concentrations, the percent performance error (PE) was defined as

$$PE = (C_M - C_T)/C_T \times 100\%$$

where C_M was the measured plasma propofol concentration from 22 to 30 min after start of infusion and C_T was the predicted target concentration. The median PE for the population was then calculated as the median of all individual median PEs. The population median PE is a measure of the systematic bias by the TCI. The median absolute PE for the population was calculated as the median of all individual median absolute PEs. To define the constant plasma concentrations, the percentage of change in individual mean stable plasma concentrations obtained from 22 to 30 min after the start of infusion was calculated. Any patients whose measured plasma propofol concentrations at 0.5 and 1.0 min after initiation of propofol infusion were not within 30% of their own individual equilibrated concentrations were excluded

from analysis of the pharmacodynamics and k_{eO}s related to EEG change or blood pressure. Patients whose propofol concentrations from 2.0 to 30 min after infusion were not within 10% of their individual mean plasma concentrations were also excluded.

Multiple Target Level Study

A TCI system was used to rapidly attain and then maintain four sequentially increasing, randomly selected propofol concentrations from 1 to 12 μg/ml. When an excessive level of anesthesia occurred, the study was terminated even if the four steps were not completed. Signs of an excessive anesthesia were defined as follows: (1) SBP less than 80 mmHg in patients aged fewer than 60 yr or less than 90 mmHg in patients aged more than 60 yr; (2) heart rate less than 50 beats/min. The target concentrations were maintained for about 30 min each to attain equilibration between blood and effect-site. If the BIS and SBP reached a constant state, they were deemed to indicate an equilibrated state between blood and effect-site. It was not possible to "step down" the concentrations because of the additional time necessary to allow the propofol concentration to decline.

Blood plasma samples were separated immediately and stored at 5°C on ice until extraction and assay. Within 12 h after sampling, plasma concentrations of propofol were determined using high-performance liquid chromatography with fluorescence detection at 310 nm after excitation at 276 nm (CTO-10A, RF550, and C-R7A, Shimadsu, Kyoto, Japan).[16] For each batch of blood samples, a standard curve was computed by adding pure propofol liquid to drug-free human plasma to achieve concentrations of 1.0, 5.0, 10.0, and 15.0 μg/ml. Linear regression (least-squares method) was used with plasma propofol concentration as the dependent variable. Propofol concentrations in this study were calculated using the obtained regression equation. The lower limit of detection was 15 ng/ml, and the coefficient of variation was 7.4%.

Intubation was facilitated by vecuronium, 6 mg, after completion of measurement of BIS, SEF95, and SBP at the individual tested highest target propofol concentration.

Propofol Pharmacodynamic Modeling

When BIS or SBP values were constant for 5 min after equilibration, we considered the plasma propofol concentration to be equivalent to that at the effect-site.

We assumed that the relationship between concentration and effects on EEG or SBP could be described with a sigmoidal E_{max} model as described by Hill:

$$\text{Effect} = E_0 - \frac{E_{max} C_e(t)^\gamma}{IC_{50}^\gamma + C_e(t)^\gamma}$$

in which E_0 was the effect with no drug, E_{max} was the maximal predicted difference from baseline effect, IC_{50} was the concentration associated with 50% of maximal effect, and γ (sometimes called the Hill coefficient) determined the steepness of the concentration *versus* response relationship. Ce(t) was the "effect-site" concentration. We expressed the effects on SBP as the percent SBP decrease from baseline to 80 mmHg:

$$\frac{SBP - 80}{SBP_{baseline} - 80} \times 100 = 100 - \frac{100 \times C_e(t)^\gamma}{IC_{50}{}^\gamma + C_e(t)^\gamma}.$$

The parameters IC_{50} and γ were fitted to the data with use of least-squares regression.

To assess the accuracy of the model, the coefficient of correlation r^2 between observed effect (E_{obs}) and predicted effect (E_{pred}) was calculated according to classic formula:

$$\text{Coefficient of correlation } (r^2) = 1 - \frac{\sum (E_{obs} - E_{pred})^2}{\sum (E_{obs} - \text{mean}(E_{obs}))^2}$$

Determination of k_{eO}

Effect-site concentration ($C_{effect}[t]$) was calculated as the convolution of the plasma concentration over time with the disposition function of the effect site.[17]

$$C_{effect}(t) = k_{eO} \int_0^t e^{-k_{eO}(t-t')} C_{plasma}(t')\, dt'$$

If plasma propofol concentration ($C_{plasma}[t]$) is constant, then the above equation can be simplified as follows:

$$C_{effect}(t) = C_{plasma}(1 - e^{-keo \cdot t})$$

And if the effect is linearly related to concentration, then the effect itself can be modeled as follows:

$$\text{Effect}(t) = a \cdot C_{plasma}(1 - e^{-keo \cdot t}) + b$$

Both BIS and SEF95 have been used as EEG measures of propofol drug effect.[18–20] SBP was used as hemodynamic effect of propofol. The parameters of k_{eO}, a and b were fitted by least-squares regression (SigmaPlot, Jandel Scientific, San Rafael, CA) to each of the decreasing time

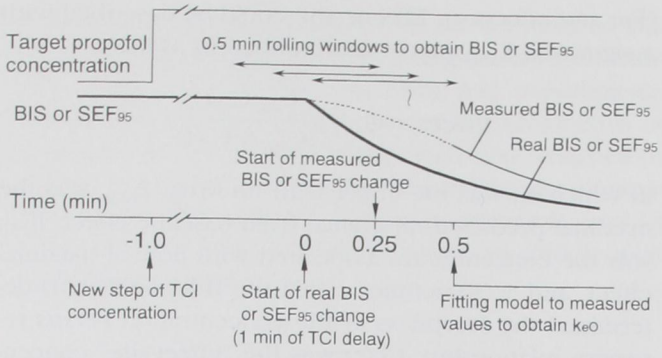

Fig. 1. Time 0 with the change of real BIS and SEF95 represents 1.0 min after making a change in target concentration, which is a lag of TCI. When estimating k_{eO} with fitting a model to measured BIS or SEF95, the data from the first 0.25 min from the start of measured BIS or SEF95 change were excluded because they contained the EEG data before the change of plasma propofol concentration.

course data of BIS, SEF95, and SBP after each multiple target propofol concentration.

There is a delay between the change of target propofol concentration and measured BIS and SEF95, which includes a lag time of about 1 min between making a change in target concentration and exposing the brain to this step change, and an inherent time delay between the actual EEG and measured BIS and SEF95 (fig. 1). Time 0 with the change of real BIS and SEF95 actually represents 1.0 min, which is the lag of TCI, after a change in target concentration. Measured BIS and SEF95 values are calculated by a 0.5-min rolling window and are displayed at the last point of the 0.5-min rolling widow. Because the measured BIS or SEF95 values should be at the midpoint of the 0.5-min rolling window, the measured BIS and SEF95 values are delayed by 0.25 min after actual EEG. Consequently, the start of measured BIS or SEF95 change was 1.25 min after each new target step (fig. 1).

To obtain k_{eO}s, the model fitting to measured BIS or SEF95 starts 0.25 min after the start of measured BIS or SEF95 change to exclude the data containing EEG effects before the change of plasma propofol concentration (fig. 1).

Propofol induced an activation in fast frequencies initially.[18,21] The existence of EEG activation at the first or second step was inspected on each patient's SEF95 data. The k_{eO}s were estimated separately with EEG activation or non-EEG activation, because the activation of EEG may influence the k_{eO} of BIS or SEF95.

The IC_{50} and mean values of the half-time of equilibration ($t_{1/2}k_{eO}$), which is $\ln(2)/k_{eO}$, were compared between all four groups. Statistical analysis included analysis of variance with Bonferroni multiple comparison tests used to assess differences between groups. A P value < 0.05 was considered statistically significant.

Results

All studies were completed without clinically significant complications. No significant differences were found between the groups with respect to sex ratio, weight, and height (table 1). Not all the patients received propofol at all four steps because of excessive anesthesia levels (fig. 2). Specifically, the patients of group 4 could not receive propofol at concentrations greater than 8 μg/ml (fig. 2).

One patient each from groups 1 and 3 and two patients each from groups 2 and 4 were excluded from the analysis of the pharmacodynamics and k_{eO}s on EEG change or blood pressure because their measured plasma propofol concentrations at 0.5 and 1.0 min after initiation of propofol infusion were not within 30% of their own individual equilibrated concentrations, or their propofol concentrations from 2.0 to 30 min after infusion were not within 10% of their individual equilibrated concentrations.

There was a strong correlation between measured equilibrated plasma propofol concentration and target concentration ($r = 0.973$). The median PE (bias) of the

Table 1. Demographic Data of Each Group

	Group 1	Group 2	Group 3	Group 4
Number of patients	11	12	12	12
Sex (M/F)	(5/6)	(5/7)	(7/5)	(6/6)
Age (yr)	27.6 ± 2.1	51.2 ± 1.1	64.3 ± 1.0	78.8 ± 1.4
	(20–39)	(46–57)	(60–69)	(73–84)
Height (cm)	163.4 ± 2.2	159.8 ± 2.9	166.4 ± 3.1	162.2 ± 3.1
	(153–175)	(149–165)	(147–168)	(141–168)
Body weight (kg)	56.1 ± 1.1	53.9 ± 3.5	54.5 ± 1.6	52.7 ± 4.0
	(51–64)	(38–79)	(42–62)	(38–78)

Data are mean ± SE (range).

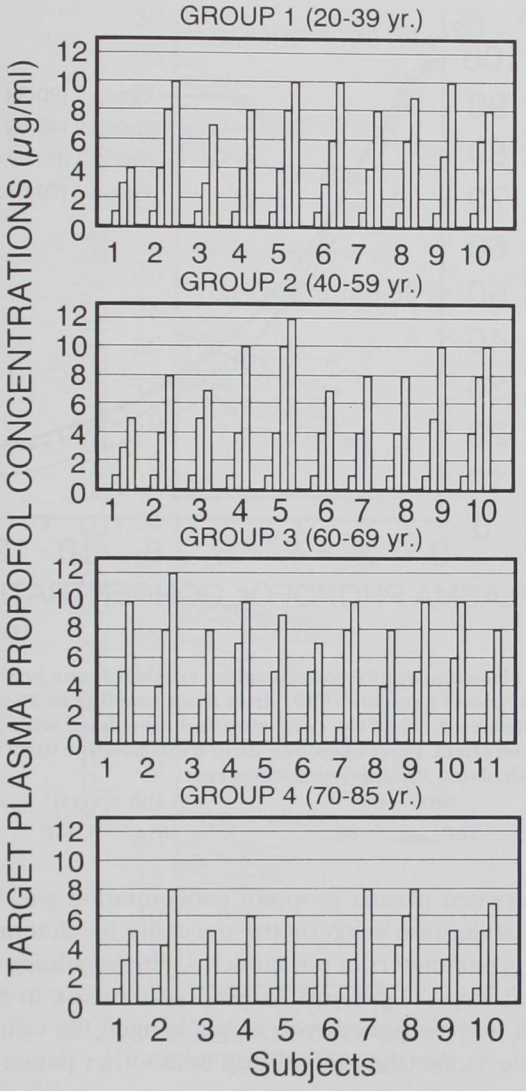

Fig. 2. Target concentrations of propofol to which patients were randomized for assessment of bispectral index and systolic blood pressure. The propofol target concentrations were achieved with sequentially increasing, randomly selected propofol concentrations from 1 to 12 μg/ml. Six patients with unstable propofol plasma concentrations were excluded. The patients of group 4 could not receive propofol at concentrations more than 7 μg/ml because of excessive anesthesia levels.

TCI in all subjects was 22.3%, and the median absolute PE (accuracy) was 22.9%. Figure 3 depicts the percent change in individual mean stable plasma concentrations versus time profiles. In each group, with the propofol pharmacokinetic parameters used in the TCI, it was possible to obtain constant plasma concentrations. Following a step change in target propofol concentration, the plasma concentration of propofol increased immediately with a slight "overshoot" to a level that is less than 30% of the final equilibrated propofol concentration, and it then remained at the pseudo-steady-state target concentration (fig. 3).

When the concentration of propofol was less than 2 μg/ml, the decrease in BIS was slight (fig. 4). In concentrations greater than 2 μg/ml, BIS decreased as propofol concentration increased (fig. 4). The IC_{50}s of BIS were

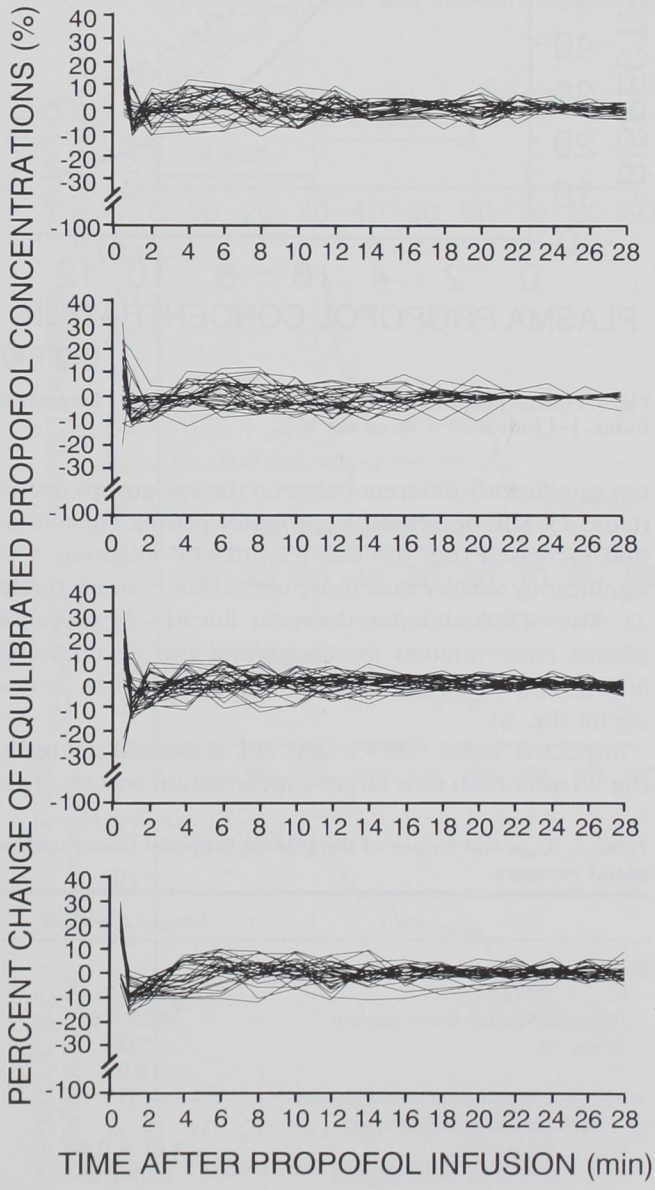

Fig. 3. Individual percentage of change in individual mean pseudoequilibrated plasma concentration obtained 22–28 min after initiation of infusion *versus* time profiles. Six patients were excluded because of "overshoot," more than ± 30% of the individual equilibrated concentration at 0.5 or 1.0 min after infusion or caused by ± 10% concentration from 2 to 30 min.

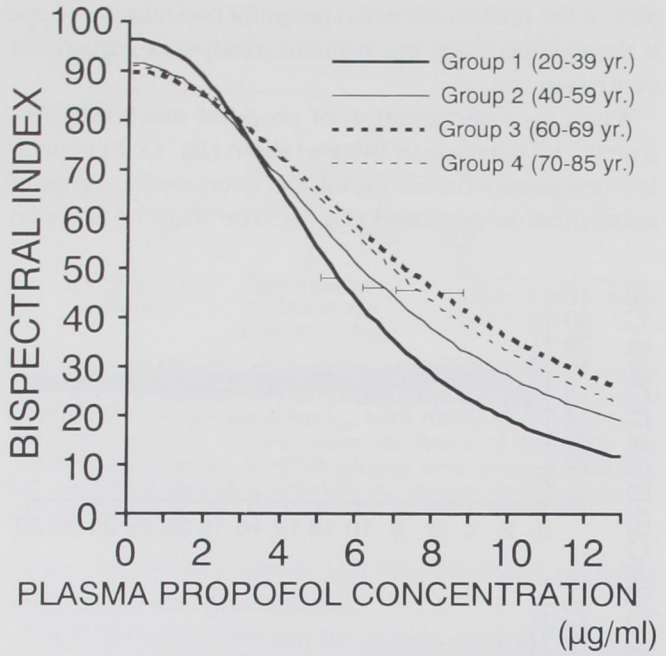

Fig. 4. Plasma propofol concentration (μg/ml) *versus* bispectral index. ⊢⊣ indicates ± SE of the IC_{50}.

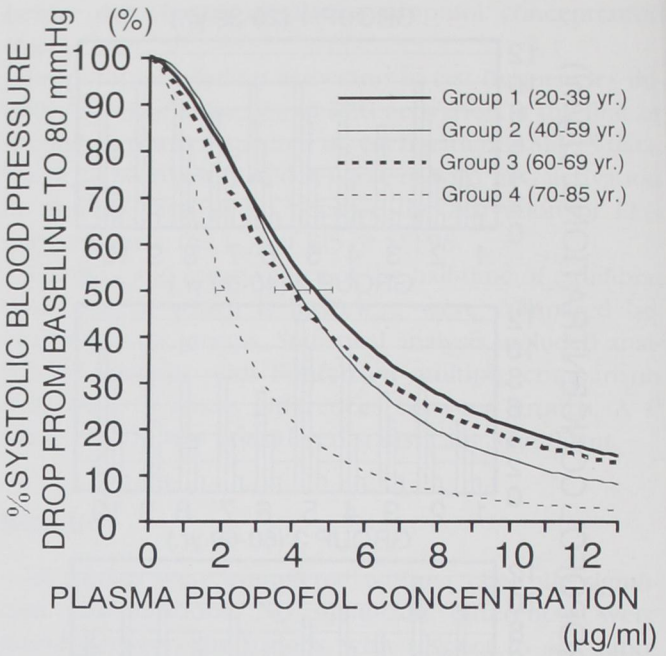

Fig. 5. Plasma propofol concentration (μ/ml) *versus* percentage systolic blood pressure (SBP) drop from baseline to 80 mmHg. ⊢⊣ indicates ± SE of the concentration associated with 50% of maximal effect. Percentage SBP drop from baseline to 80 mmHg was calculated the following equation:

$$\frac{SBP - 80}{SBP_{baseline} - 80} \times 100 = 100 - \frac{100 \times C_e(t)^{\gamma}}{IC_{50}^{\gamma} + C_e(t)^{\gamma}}$$

not significantly different between the age groups tested (table 2). SBP decreased as propofol plasma concentration increased (fig. 5). The IC_{50} of SBP in group 4 is significantly smaller than those of the other groups (table 2). The SEF95 did not decrease linearly as propofol plasma concentration increased, and the decreases in SEF95 were small in concentrations greater than 2 or 4 μg/ml (fig. 6).

Bispectral index, SEF95, and SBP stabilized gradually (fig. 7) after each new target concentration was set. This lag between plasma propofol concentration and BIS or SBP stabilization suggests the necessity for determining the k_{eO} parameters of our model. At the beginning of the second step, 21 patients showed an increase in SEF95, which was associated with an unchanged BIS value (fig. 8, table 3). For the second step in 20 other patients and

Table 2. IC_{50}s and Slopes of the Plasma Propofol Concentration–Bispectral Index and the Plasma Propofol Concentration–Systolic Blood Pressure

	Group 1 (20–39 yr)	Group 2 (40–59 yr)	Group 3 (60–69 yr)	Group 4 (70–85 yr)
Bispectral index				
IC_{50} ± SE (μg/ml)	5.60 ± 0.48	6.76 ± 0.51	8.21 ± 0.64	7.67 ± 0.58
95% confidence limits (μg/ml)	4.55–6.65	5.65–7.87	6.82–9.61	6.41–8.84
Slope (γ)	2.39	2.08	2.03	2.10
r^2	0.93	0.90	0.91	0.92
% Systolic blood pressure decrease from baseline to 80 mmHg				
IC_{50} ± SE (μg/ml)	4.61 ± 0.51	4.13 ± 0.29	3.96 ± 0.41	2.09 ± 0.19*
95% confidence limits (μg/ml)	3.51–6.05	3.50–4.86	3.08–5.09	1.67–2.61
Slope (γ)	1.75	2.12	1.64	1.98
r^2	0.83	0.92	0.87	0.80

* $P < 0.05$ *versus* groups 1, 2, and 3.

IC_{50} = propofol plasma concentration (μg/ml) at half of the maximal decrease; 95% confidence limits = defined as $IC_{50} \pm t_{0.05,n-2} \times SE$; Slope (γ) = dimensionless exponent; r^2 = coefficient of correlation between observed and predicted BIS or SBP effects.

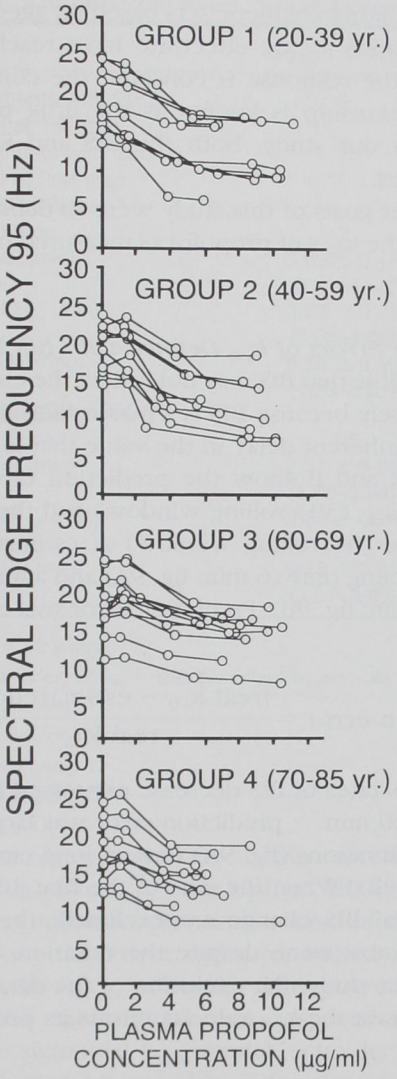

Fig. 6. Propofol plasma concentration (μg/ml) *versus* 95% spectral edge frequency (SEF95; in Hz). There was no relation between SEF95 and propofol blood concentration.

for the third or fourth step in all patients, increases in SEF95 were hard to distinguish. The $t_{1/2}k_{eO}$s of equilibration between the plasma and the site of drug effect with BIS, SEF95, and SBP, are shown in table 3. The $t_{1/2}k_{eO}$ of SEF95 in the third or fourth step could not be defined because the decreases of SEF95 values were not enough to estimate k_{eO} (fig. 6).

In elderly patients, EEG activation defined with SEF95 increase was observed more frequently in the first step than in the second step (table 3). The mean $t_{1/2}k_{eO}$ of the BIS were not significantly different between the age groups tested. The $t_{1/2}k_{eO}$s of BIS at the step with EEG activation were significantly longer, from 1.6 to 1.8 times ($P < 0.05$), than those without EEG activation. The mean $t_{1/2}k_{eO}$s of the SBP increased with age. The $t_{1/2}k_{eO}$s of SBP with or without EEG activation were the same. The mean $t_{1/2}k_{eO}$s of SBP were about 2.5 times longer than those of the BIS at the steps without EEG activation in patients younger than 60 yr. In patients more than 60 yr old, the $t_{1/2}k_{eO}$s of SBP were about four times longer than those of the BIS.

The rate of decrease of BIS was almost the same in

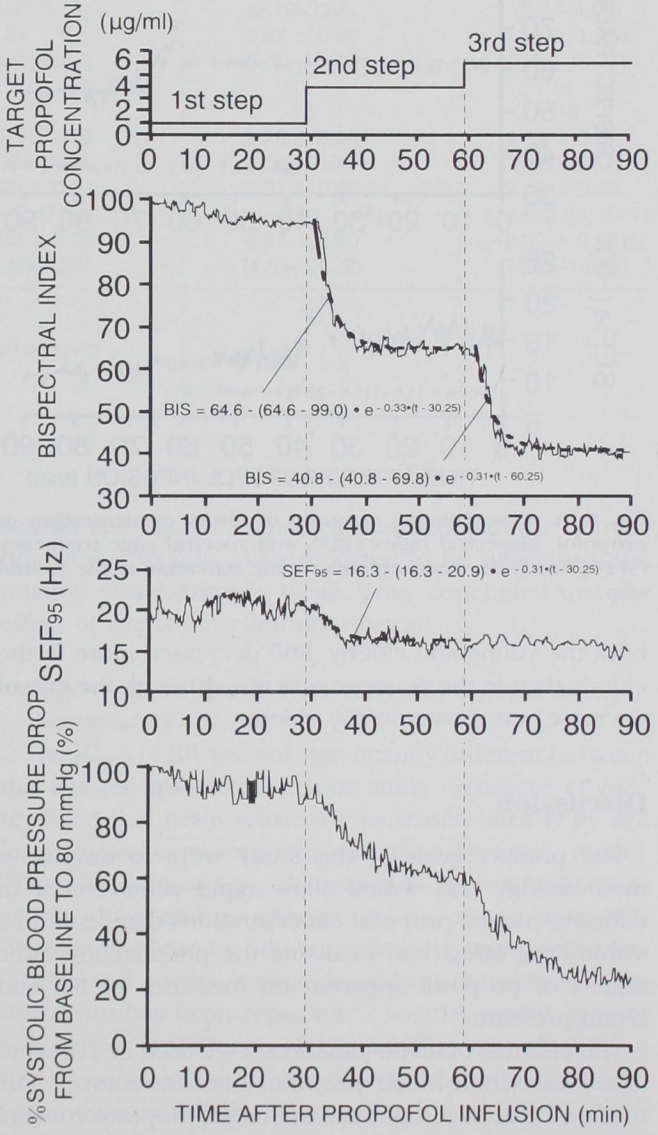

Fig. 7. A representative example of target concentration of propofol, bispectral index (BIS), spectral edge frequency (SEF95) and systolic blood pressure (SBP) without electroencephalographic activation. After the step change in propofol plasma concentration, SBP stabilized gradually following BIS stabilization.

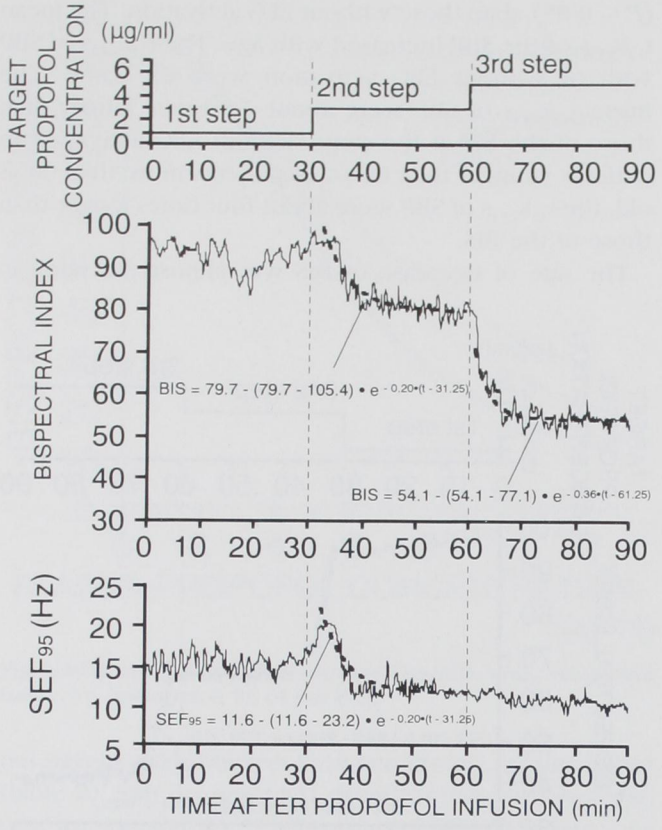

Fig. 8. A representative example of target concentration of propofol, bispectral index (BIS), and spectral edge frequency (SEF95) with electroencephalographic activation at the second step.

both the young and elderly. SBP decreased more in the elderly than in the younger patients, although the rate of decrease was slower in the elderly.

Discussion

The primary goals of this study were to develop a methodology that would allow rapid achievement of constant plasma propofol concentrations that result in a stable drug effect and to define the pharmacodynamic effects of propofol apparent on measures of BIS and blood pressure.

The pharmacokinetic parameters we used in TCI were based on whole-blood propofol concentration.[15] The median PE between plasma and target propofol concentration in our TCI was 22.3%, which may derive from the 30% difference[22] between whole-blood and plasma propofol concentration. However, the TCI in our study worked very well in maintaining stability of concentrations in both the young and the elderly by using two different pharmacokinetic sets based on age. When drug concentrations at the effect-site have reached equilibrium and the response is constant, the concentration-effect relationship is known as the drug pharmacodynamics. In our study, both the BIS and SBP reached stable states.

The other goals of this study were to define the sensitivity and the k_{eO}s of propofol as measured by the BIS or SBP.

Residual Errors of k_{eO} Defined with BIS Decrease

It is possible that BIS may not reflect the change of real EEG precisely because BIS is a 30-s rolling window providing an inherent delay in the value that is being read. Figures 9A and B show the prediction error between estimated k_{eO} (30-s rolling window) and the k_{eO} of real BIS change (0-s rolling window) at estimation from a short sampling time (6 min; fig. 9A) and a long sampling time (30 min; fig. 9B). Prediction error was calculated as follows:

$$\text{prediction error} = \frac{|\text{real } k_{eO} - \text{estimated } k_{eO}|}{\text{real } k_{eO}} \times 100$$

For various rates of BIS decrease expressed by k_{eO} from 0.05 to 2.00 min^{-1}, prediction error was larger in short-sampling durations (fig. 9A) than in long-sampling durations (fig. 9B). When the data of the first 30 s from the start of real BIS change are excluded, the prediction error is almost none despite the duration of sampling time. In our study, the exclusion of the data of the first 30 s to obtain the k_{eO} value confirms its precision.

Differences in Onset of Propofol as Measured by the BIS

Bispectral index has been shown to decrease linearly as propofol blood concentration increases.[20,23] In our study BIS was not exactly linear with increasing propofol concentration, especially in concentrations less than 2 μg/ml. We also could not calculate the k_{eO} of propofol on the BIS at concentrations between 0 and 2 μg/ml. However, BIS showed enough linearity to calculate the k_{eO} at concentrations greater than 2 μg/ml. Propofol induced an activation in fast frequencies, then a shift of the spectrum to low frequencies, and finally burst suppression.[18] Sneyd *et al.*[21] reported that β1 activity in EEG was significantly increased at the concentrations of 0.679 and 1.065 μg/ml but not in lower concentrations. Although the calculation algorithm of the BIS has been improved to account for EEG data recorded with differ-

Table 3. $t_{1/2}k_{eO}$s of Bispectral Index, Spectral Edge Frequency 95, and Systolic Blood Pressure Changes in Each Group

	Group 1 (20–39 yr)	Group 2 (40–59 yr)	Group 3 (60–69 yr)	Group 4 (70–85 yr)
Number of patients with EEG activation at 1st step	3	4	6	7
Number of patients with EEG activation at 2nd step	7	6	5	3
Step with EEG activation*				
Number of steps	7	6	5	3
$t_{1/2}k_{eO}$ of BIS (min)	3.69 ± 0.16 (3.21–4.46)	3.90 ± 0.22 (3.30–4.53)	3.65 ± 0.12 (3.23–4.08)	4.33 ± 0.30 (3.12–4.76)
$t_{1/2}k_{eO}$ of SEF_{95} (min)	3.72 ± 0.21 (3.03–4.66)	4.09 ± 0.28 (3.33–5.11)	3.52 ± 0.17 (2.79–3.88)	3.76 ± 0.31 (2.84–4.99)
$t_{1/2}k_{eO}$ of SBP (min)	6.55 ± 0.59 (4.28–8.61)	6.87 ± 0.7 (4.35–9.63)	8.97 ± 0.99 (6.10–13.86)	11.4 ± 1.96‡ (7.81–18.21)
Step without EEG activation†				
Number of steps	15	16	16	18
$t_{1/2}k_{eO}$ of BIS (min)	2.31 ± 0.06 (1.88–2.94)	2.30 ± 0.06 (1.97–2.86)	2.29 ± 0.05 (1.85–2.54)	2.37 ± 0.07 (1.86–2.87)
$t_{1/2}k_{eO}$ of SEF_{95} (min)	2.23 ± 0.14 (1.98–2.44, n=3)	2.35 ± 0.08 (2.11–2.47, n=4)	2.37 ± 0.09 (2.10–2.61, n=6)	2.18 ± 0.10 (1.96–2.43, n=7)
$t_{1/2}k_{eO}$ of SBP (min)	5.68 ± 0.31 (3.81–8.99)	5.92 ± 0.37 (3.55–8.53)	8.87 ± 0.80 (4.65–14.22)	10.22 ± 0.96‡§ (4.65–19.65)

Data are mean ± SE (range).

BIS = bispectral index; SEF_{95} = spectral edge frequency 95; SBP = systolic blood pressure.

* Included only 2nd step.

† Included 2nd, 3rd, or 4th step.

‡ $P < 0.05$ *versus* group 1.

§ $P < 0.05$ *versus* group 2.

ent anesthetic drugs and to give better correlation to the hypnotic drug effects,[23,24] the biphasic EEG response of propofol may influence the time course of drug effect. Depending on the effect measure, Billard *et al.*[18] reported that the $t_{1/2}k_{eO}$ values for delta power of EEG or BIS were 2.6 min or 3.3 min respectively using a monophasic sigmoidal E_{max} model. Schnider *et al.*[25] reported a $t_{1/2}k_{eO}$ of 2.2 min obtained with biphasic model of EEG change. We used the BIS to estimate the rate of plasma effect-site equilibration, and the EEG activation of propofol at the beginning of the second step slowed the rate of BIS decrease. The mean $t_{1/2}k_{eO}$s of BIS decrease at the steps with or without EEG activation were about 3.8 or 2.3 min respectively in our study. Schnider *et al.*[25] demonstrated that the EEG activation in older people occurs at lower concentrations but also that the transition from no effect to maximal activation is relatively gradual. These findings are consistent with ours that EEG activation in elderly was observed more frequently in the first step of target concentration than in the second step.

There was no significant relation between $t_{1/2}k_{eO}$s of BIS in the EEG depression and age in our study. As for the relation between $t_{1/2}k_{eO}$ and age, there are no other reports dealing precisely with propofol. In thiopental, Stanski and Maitre[26] reported that although the correlation of age to $t_{1/2}k_{eO}$ was reported to be significant, the relation was extremely weak. They concluded that the effect of age is not clinically relevant.

Differences in Brain Sensitivity to Propofol as Measured by the BIS

The IC_{50}s of BIS are not significantly different between the age groups tested in our study. Schnider *et al.*[25] reported that brain sensitivity increased linearly by age in a loss-of-consciousness pharmacodynamic model. They also defined Cp_{50} decreased as age with EEG activation phase and no change of Cp_{50} as age with EEG depression phase by EEG pharmacodynamic model. For inhalational agents, an age-dependent increase in brain sensitivity has been reported.[27] For thiopental, Stanski and Maitre[26] and Homer and Stanski[28] demonstrated that there was no effect of age on any of the pharmacodynamic parameters. The increased sensitivity to etomidate in the elderly was mainly accounted for by age-related pharmacokinetic changes.[29] As for the brain sensitivity to propofol in rats, Larsson and Wahlstrom[30] reported that young animals need a larger induction dose than old, but older animals had higher brain concentrations of

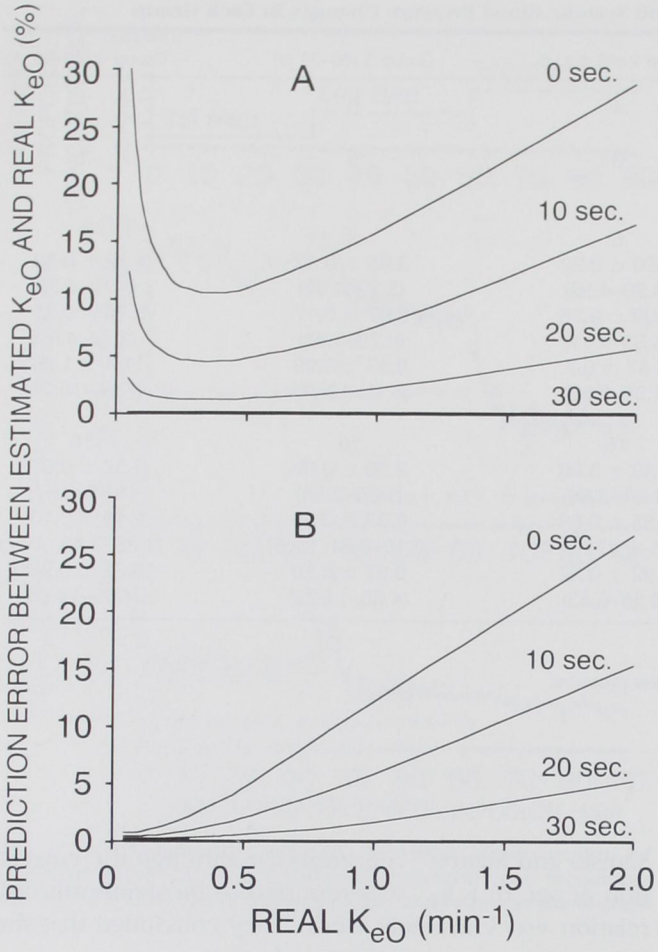

Fig. 9. Prediction error between estimated k_{eO} obtained by fitting a model to bispectral index (BIS) values calculated with 30-s rolling windows and real k_{eO} values at two sampling times of 6 min (*A*) or 30 min (*B*), after a new propofol concentration setting at target-controlled infusion. The time (labeled for each curve) showing the data-omitting interval from the start of real BIS change when fitting the model to estimated BIS to obtain k_{eO}.

$$\text{prediction error} = \frac{|\text{real } k_{eO} - \text{estimated } k_{eO}|}{\text{real } k_{eO}} \times 100$$

propofol at the EEG endpoint than young, which means young rats are more sensitive than old rats as measured by the brain concentration of propofol. It remains unresolved whether the influence of age on brain sensitivity to propofol can be mainly accounted for by pharmacodynamic changes or pharmacokinetic changes.

Differences in Onset of Propofol as Measured by SBP

In our study, propofol plasma concentration attained a target concentration within 1 min. However, SBP decreased at a slower rate than plasma concentration. Claeys *et al.*[31] reported that the arterial hypotension associated with the induction and infusion of propofol is mainly a result of a decrease in afterload without compensatory increases in heart rate or cardiac output. Ebert *et al.*[32] demonstrated that the sympathoinhibition that occurs during propofol administration importantly contributes to the subsequent hypotension. In the report of Ebert *et al.*,[32] SBP decrease and sympathetic nerve activity attained maximal effect within 3 min after a bolus injection of propofol. Billard *et al.*[6] reported that maximal predicted propofol biophase concentrations were achieved in 2.3 min. Using their unpublished data of $t_{1/2}k_{eO}$ for hemodynamic effects of propofol as 5.9 min, they predicted the time to achieve the expected maximal effect in SBP after a bolus propofol infusion as 2.8 min, which is consistent with our $t_{1/2}k_{eO}$ value in those younger than 60 yr.

Differences in Sensitivity to Propofol as Measured by SBP

There are many reports of SBP reductions greater than 25% during induction of anesthesia with propofol, an effect manifested more in elderly than in younger patients.[10,33] In addition to the already reported pharmacokinetic parameters in elderly patients,[10,15] we found significant differences in the pharmacodynamics in the IC_{50}s of pharmacodynamics on SBP between group 4 (older than 70 yr) and younger patients. This suggests that hypotension in the elderly patients younger than 69 yr is mainly a result of pharmacokinetic changes, and that hypotension in patients older than 70 yr is a result of pharmacodynamic changes in addition to pharmacokinetic changes.

The time courses of the BIS and SBP are important for understanding anesthesia status. In our study, although BIS decreased to the same degree at the same rate independent of age, SBP decreased more in elderly than in younger patients, and the rate of decrease was slower in the elderly. Considering our findings, to avoid delayed severe hypotension a lower induction dose and a slower maintenance rate of administration after loss of consciousness are suggested in the elderly than in other age groups.

In summary, we have investigated the effect of age on BIS and SBP change of propofol in humans. We found that the effect of propofol on BIS occurs more rapidly compared with the effect on SBP. The IC_{50} of BIS did not change with increasing age. Age has no effect on the rate of BIS reduction with increasing propofol concentration,

whereas with increasing age SBP decreases to a greater degree but more slowly.

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