Anesthesiology
2000; 92:1017–28

Investigation of Effective Anesthesia Induction Doses Using a Wide Range of Infusion Rates with Undiluted and Diluted Propofol

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Background: **The influence of infusion rate on the induction dose–response relation has not been investigated over a wide range of infusion rates. In this study, the authors defined the effect of different propofol infusion rates on the times and doses necessary to reach clinical induction of anesthesia.**

Methods: **The subjects of the study were 250 patients classified as American Society of Anesthesiologists physical status I or II aged 25–55 yr. For induction with undiluted propofol, 180 patients were allocated randomly to one of two groups of 90 patients each (A and B). Each group was further divided into nine subgroups (10 patients each) that were administered propofol infusion at rates of 10, 15, 20, 30, 40, 60, 100, 200, and 300 mg · kg^{-1} · h^{-1}. The remaining 70 patients (group C) were allocated randomly into seven subgroups (10 patients each), and these groups were induced with diluted propofol (0.5 mg/ml) at the rates of 10, 15, 30, 60, 100, 200, and 300 mg · kg^{-1} · h^{-1}. Group B was given crystalloid at the same infusion rates as group C *via* a catheter in the opposite arm. Induction time, induction dose, plasma arterial propofol concentration at loss of consciousness, and percentage decrease of systolic blood pressure were measured. A previously reported three-compartment model with an effect-site rate constant for propofol of 0.456/min was used to predict the induction time and dose at each infusion rate.**

Results: **The differences between predicted induction time and dose and the observed time and dose could be explained by factoring in the lag time from infusion site to central compartment (lag time$_{\text{circulation}}$) and the amount of propofol in transit during this time (residual dose$_{\text{circulation}}$). Residual dose$_{\text{circulation}}$ and lag time$_{\text{circulation}}$ correlated with infusion time from 20 to 60 s for undiluted and from 0 to 40 s for diluted propofol. At the infusion rates greater than 80 mg · kg^{-1} · h^{-1}, rapid circulation because of incomplete mixing in the central compartment decreased the excess induction time and dose. The use of diluted propofol significantly attenuated the decrease in systolic blood pressure provoked by the residual dose$_{\text{circulation}}$.**

Conclusions: **Induction dose and time are dependent on infusion rate in a complex manner, and residual dose$_{\text{circulation}}$ was a factor in overdose and hemodynamic depression. Hypotension during induction was attenuated by diluted propofol.** **(Key words: Overdose; residual dose; time lag; transit.)**

THE importance of injecting propofol slowly to avoid an overdose and to minimize cardiorespiratory depression is widely accepted.[1–3] However, previous reports show substantial variability in the relations among infusion rate, induction dose, and induction time. Many researchers have reported that a slower rate of propofol administration for induction of anesthesia results in smaller dose requirements and that the time necessary for induction is significantly longer at slower infusion rates.[3,4] This seems to be a straightforward simple correlation; however, it is not so simple. The relations among rate of drug administration, induction time, and dose requirement pose interesting questions that merit further consideration because of the variety of possible relations among infusion rate, induction time, and dose.[5–7] These relations have not been investigated systematically using a wide range of infusion rates.

In traditional pharmacokinetic models, an intravenously administered drug is assumed to be injected into the central compartment rather than into a stream of flowing blood. This becomes a major limitation of assumptions about the physiologic effect of a drug, especially at a high infusion rate. With administering a drug that is carried through the circulatory system to the site of drug effect, a certain amount of drug is contained in the circulation from the site of administration to the central compartment. The lag time from infusion site to central compartment (lag time$_{\text{circulation}}$) and the amount of this drug in circulation (residual dose$_{\text{circulation}}$), which

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Received from the Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, Hamamatsu, Japan. Submitted for publication December 28, 1998. Accepted for publication November 9, 1999. Support was provided solely from institutional and/or departmental sources.

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is correlated with lag $\text{time}_{\text{circulation}}$, are dependent on the infusion rate and dilution of the drug.

In addition to the lag $\text{time}_{\text{circulation}}$, there is another lag time from the central compartment to effect site that is defined as the time constant of the effect-site rate constant (k_{eO}) and the dose in the central compartment at loss of consciousness (residual $\text{dose}_{\text{central}}$) is dependent on the infusion rate of the drug.

If propofol administration is titrated with a high continuous propofol infusion rate, the anesthesiologist may administer a larger dose than is necessary to achieve loss of consciousness, and such large doses may cause a decrease in systemic arterial blood pressure. However, the relation between rate of infusion and induction dose described by previous reports is incomplete because of the small range of infusion rates used and the lack of consideration of all residual doses.

The current study was designed (1) to determine the relation between infusion rate, induction time, and induction dose using a wide range of propofol infusion rates from 10-300 mg · kg^{-1} · h^{-1}; (2) to determine whether the use of diluted propofol lessens the residual $\text{dose}_{\text{circulation}}$; (3) to compare our results with a previously published pharmacokinetic and pharmacodynamic model; and (4) to investigate the hemodynamic responses to these various infusion states.

Materials and Methods

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. The subjects selected for this study were unpremedicated patients classified as American Society of Anesthesiologists physical status I or II, aged 25-55 yr, who were scheduled for elective surgery. Exclusion criteria included a history of cardiac, pulmonary, liver, or renal disease and the presence of significant obesity (body mass index > 26). At arrival of the unpremedicated patient in the operating room, an 18-gauge cannula was inserted into a large antecubital vein during local anesthesia. Lactated Ringer's solution was infused (3 ml · kg^{-1} · h^{-1}) until the start of propofol infusion for anesthesia induction. During baseline recording, oxygen was administered with a face mask. Anesthesia was induced using a previously assigned propofol infusion rate until loss of verbal contact with the patient. The patients were asked to open their eyes or to otherwise indicate that they were still conscious. If no response to this stimulus occurred, the patients were stimulated by gently rubbing and tapping their shoulders. *Loss of consciousness* was defined as no response to these stimuli. In all patients, responses to stimuli were assessed every 20, 10, 5, and 2.5 s at the infusion rates from 10-15, from 20-30, from 40-100, and from 200-300 mg · kg^{-1} · h^{-1}, respectively, by the same attending anesthesiologist and the same assistant resident anesthesiologist, who were both blind to the assigned infusion rate or infused propofol concentration. Both anesthesiologists were completely familiar with the strict definition of response. The *induction time* was defined as the time from the start of propofol infusion to loss of consciousness, and the *induction dose* was defined as the amount of propofol administered before loss of consciousness.

Induction with Undiluted Propofol (10 mg/ml; Group A)

After 5 min preoxygenation, propofol was administered by infusion pumps through a three-way tap placed directly into the venous cannula. During propofol infusion, lactated Ringer's solution was discontinued. Ninety patients were assigned randomly to nine study groups (10 patients/group) to receive infusion of propofol at one of the following rates: 10, 15, 20, 30, 40, 60, 100, 200, or 300 mg · kg^{-1} · h^{-1} (table 1). Infusion was controlled by conventional syringe infusion pump (Graseby 3500; Graseby Medical, Colonial Way, Watford, Herts, UK), with rates of 60 mg · kg^{-1} · h^{-1} or more necessitating several infusion pumps at once because of the infusion-rate limitation of a single pump.

Induction with Undiluted Propofol Accompanied by Crystalloid Solution Infusion in the Opposite Hand (Group B)

Ninety patients were assigned randomly to one of nine study groups of different undiluted propofol infusion rates: 10, 15, 20, 30, 40, 60, 100, 200, or 300 mg · kg^{-1} · h^{-1}. Propofol administration followed the same procedures as described for group A. A second intravenous infusion catheter was placed in the opposite hand for lactated Ringer's solution infusion at rates of 20, 30, 40, 60, 80, 120, 200, 400, or 300 ml · kg^{-1} · h^{-1} at the same time as each respective propofol infusion (table 2). For infusion rates less than 40 ml · kg^{-1} · h^{-1}, lactated Ringer's solution was infused with Graseby syringe infusion pumps. At the other infusion rates, it was infused manually, and the infusion volume was checked every

Table 1. Demographic Data for Study Patients Administered Undiluted Propofol at Various Infusion Rates (Group A)

	Subgroup								
	A_{10}	A_{15}	A_{20}	A_{30}	A_{40}	A_{60}	A_{100}	A_{200}	A_{300}
Gender (M/F)	4/6	6/4	4/6	4/6	4/6	4/6	4/6	6/4	6 /4
Age (yr)	40 ± 8	42 ± 10	43 ± 9	45 ± 9	43 ± 11	44 ± 8	43 ± 10	42 ± 10	40 ± 9
Range (yr)	27–51	25–55	33–56	28–55	25–54	28–54	25–55	27–52	28–53
Height (cm)	160 ± 7	163 ± 9	158 ± 5	161 ± 7	158 ± 6	158 ± 6	161 ± 8	154 ± 5	160 ± 7
Weight (kg)	53 ± 6	56 ± 10	55 ± 3	59 ± 3	58 ± 10	53 ± 6	56 ± 8	54 ± 4	54 ± 7
LBM (kg)	42 ± 5	45 ± 7	43 ± 3	45 ± 4	44 ± 7	40 ± 4	44 ± 7	41 ± 4	43 ± 6
Propofol infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	10	15	20	30	40	60	100	200	300
Propofol infusion rate per LBM	13 ± 1	18 ± 1	26 ± 2	40 ± 3	50 ± 5	80 ± 6	128 ± 6	273 ± 42	385 ± 25
Propofol infusion concentration (mg/l)	10	10	10	10	10	10	10	10	10
Crystalloid infusion rate during induction ($ml \cdot kg^{-1} \cdot h^{-1}$)	0	0	0	0	0	0	0	0	0
Total infusion volume (ml)	9.2 ± 1.7	9.3 ± 3.3	7.8 ± 1.0	9.0 ± 1.1	10.0 ± 2.0	10.0 ± 1.7	12.2 ± 2.6	17.5 ± 2.6	24.0 ± 6.0
Induction time (s)	624 ± 60	380 ± 84	261 ± 43	184 ± 16*	156 ± 25*	116 ± 23*	79 ± 19*	51 ± 5*	45 ± 4*
Induction dose (mg)	94 ± 15	88 ± 23	78 ± 10	92 ± 12	101 ± 13	103 ± 20*	121 ± 24*	156 ± 26*	201 ± 34*
Induction dose per LBM	2.2 ± 0.1	1.8 ± 0.3	1.8 ± 0.2	2.1 ± 0.2	2.3 ± 0.2	2.6 ± 0.5	2.6 ± 0.6	3.8 ± 0.7	4.7 ± 0.5
Plasma propofol concentration at LOC (μg/ml)	5.2 ± 1.2	5.5 ± 2.0	5.8 ± 1.2	7.8 ± 1.2*	9.2 ± 3.0*	12.8 ± 2.5*	14.4 ± 2.3*	18.2 ± 3.1*	21.5 ± 2.3*
Decrease in SBP (%)	−7.6 ± 3.2	−6.8 ± 4.8	−9.1 ± 3.2	−9.5 ± 3.3	−7.8 ± 4.5	−12.3 ± 3.8*	−19.0 ± 2.8*	−30.1 ± 7.7*	−35.1 ± 3.4*

Data are mean ± SD.

*$P < 0.05$ *versus* A_{10}, A_{15}, and A_{20}.

LBM = lean body mass; LOC = loss of consciousness; SBP = systolic blood pressure.

second. After loss of consciousness, the infusion rate was adjusted again to 3 $ml \cdot kg^{-1} \cdot h^{-1}$.

Induction with Diluted Propofol (Group C)

Seventy patients were assigned randomly to one of seven groups of different diluted propofol infusion rates: 10, 15, 30, 60, 100, 200, or 300 $mg \cdot kg^{-1} \cdot h^{-1}$ (table 3). Diluted propofol at 0.5 mg/ml was used for induction except for the infusion rate of 300 $mg \cdot kg^{-1} \cdot h^{-1}$, for which diluted propofol at 1.0 mg/ml was used because of the technical limitations of infusion speed. Propofol diluted 20 times with lactated Ringer's solution was prepared just before anesthesia induction. After 5 min preoxygenation, propofol was infused at the assigned rates through the three-way tap placed directly into the venous cannula. For the infusion rates less than 15 $mg \cdot kg^{-1} \cdot h^{-1}$, diluted propofol was infused with Graseby syringe infusion pumps. For the other infusion rates, diluted propofol was infused manually as described previously.

Pain or discomfort at the site of injection during or after propofol administration was recorded and graded by the attending anesthesiologist as mild, moderate, or severe, according to patient facial expressions, arm movements, or reports of pain. Incidents of spontaneous movement and vocalization during induction were recorded. End-tidal carbon dioxide measurement was used to detect any incidence of apnea lasting more than 30 s. Spontaneous respirations were assisted manually if necessary. Heart rate, electrocardiographic data, end-tidal carbon dioxide, oxyhemoglobin saturation, and noninvasive blood pressure (1-min interval; CBM7000; Nihon Colin, Komaki, Japan) were monitored continuously throughout this study.

Immediately after loss of consciousness, infusion of undiluted propofol (10 mg/ml) was commenced at 4 $mg \cdot kg^{-1} \cdot h^{-1}$, and hemodynamic change was recorded for 20 min. Then, intubation was facilitated by fentanyl, 0.1 or 0.2 mg, and vecuronium, 0.1 mg/kg.

Cardiovascular recordings were made for 5 min at the commencement of monitoring as a baseline measurement. The minimum value of systolic blood pressure (SBP) during the 20 min after loss of consciousness and the heart rate at the minimum SBP were designated as the postinduction values. If hypotension (< 75 mmHg, or > 40% SBP decrease) persisted for 2 or 3 min, patient blood pressure was restored by ephedrine.

Although propofol was infused as a function of real body weight, the relation among induction dose, induction time, SBP decrease, propofol plasma concentration, and propofol infusion rate was investigated as a function

Table 2. Demographic Data for Study Patients Administered Undiluted Propofol and Crystalloid Solution from Different Intravenous Routes at Various Infusion Rates (Group B)

	Subgroup								
	B_{10}	B_{15}	B_{20}	B_{30}	B_{40}	B_{60}	B_{100}	B_{200}	B_{300}
Gender (M/F)	5/5	5/5	6/4	5/5	6/4	6/4	3/7	6/4	4/6
Age (yr)	42 ± 10 26–55	40 ± 11 25–55	45 ± 6 37–53	44 ± 9 32–55	45 ± 11 26–55	44 ± 12 26–55	41 ± 11 27–55	41 ± 12 26–55	43 ± 8 32–55
Height (cm)	159 ± 6	160 ± 7	162 ± 4	161 ± 8	159 ± 10	160 ± 6	156 ± 7	158 ± 8	157 ± 5
Weight (kg)	53 ± 4	58 ± 6	52 ± 3	57 ± 3	55 ± 4	55 ± 6	56 ± 5	52 ± 8	54 ± 3
LBM (kg)	42 ± 2	45 ± 6	43 ± 3	44 ± 4	44 ± 5	43 ± 3	42 ± 4	41 ± 4	42 ± 3
Propofol infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	10	15	20	30	40	60	100	200	300
Propofol infusion rate per LBM	13 ± 1	19 ± 2	24 ± 1	39 ± 4	51 ± 3	77 ± 9	134 ± 12	265 ± 36	394 ± 25
Propofol infusion concentration (mg/ml)	10	10	10	10	10	10	10	10	10
Crystalloid infusion rate during induction ($ml \cdot kg^{-1} \cdot h^{-1}$)	20	30	40	60	80	120	200	400	300
Total infusion volume (ml)	190 ± 14	189 ± 31	163 ± 23	183 ± 15	196 ± 35	223 ± 31	244 ± 46	337 ± 86	259 ± 57
Induction time (s)	625 ± 36	378 ± 78	266 ± 40	185 ± 14	151 ± 22	117 ± 22	75 ± 15	50 ± 5	44 ± 4
Induction dose (mg)	92 ± 6	90 ± 14	77 ± 11	87 ± 7	96 ± 18	106 ± 15*	116 ± 22*	149 ± 25*	195 ± 20*
Induction dose per LBM	2.2 ± 0.1	2.0 ± 0.4	1.8 ± 0.2	2.0 ± 0.2	2.2 ± 0.3	2.5 ± 0.5	2.8 ± 0.5	3.7 ± 0.7	4.7 ± 0.6
Plasma propofol concentration at LOC ($\mu g/ml$)	5.5 ± 1.3	5.3 ± 1.7	5.9 ± 1.2	7.6 ± 1.0*	8.9 ± 3.0*	12.9 ± 2.0*	14.6 ± 1.3*	18.1 ± 2.4*	21.0 ± 1.5*
Decrease in SBP (%)	−7.9 ± 3.4	−6.7 ± 5.3	−8.6 ± 2.9	−9.2 ± 2.8	−7.0 ± 3.4	−12.8 ± 5.2*	−19.6 ± 3.5*	−31.2 ± 5.5*	−33.9 ± 3.7*

Data are mean ± SD.

* $P < 0.05$ *versus.* B_{10}, B_{15}, and B_{20}.

LBM = Lean body mass; LOC = Loss of consciousness; SBP = systolic blood pressure.

of lean body mass (LBM). LBM was determined from height (cm) and weight (kg) using gender-specific formulas.[8]

$$\text{Women: LBM} = 1.07 \times \text{weight} - 148 \times (\text{weight/height})^2$$

$$\text{Men: LBM} = 1.10 \times \text{weight} - 128 \times (\text{weight/height})^2$$

At a 24-h postoperative examination, each patient was asked whether he or she recalled any event occurring after loss of consciousness. At that time, the injection site was evaluated for possible phlebitis, irritation, or thrombosis.

A femoral arterial blood sample (3 ml) was taken from each patient for analysis of plasma propofol concentration at unresponsiveness to verbal and tactile stimuli. The blood samples were immediately placed on ice, after which the plasma was separated and frozen at −70°C until it was assayed. 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). The lower limit of detection was 32 ng/ml.

Simulations of Infusion Rate versus *Propofol Induction Dose and Induction Time*

To simulate the blood concentration histories of zero-order infusions/LBM at rates from 10–450 $mg \cdot kg^{-1} \cdot h^{-1}$, previous pharmacokinetic parameters for a 42-yr-old, 57-kg, 160-cm man reported by Schnider *et al.*[9] were used. The k_{eO} for propofol equilibration of $0.456/min^{-1}$ was used to link the effect with the central compartment propofol concentrations.[10] Effect-site concentration at loss of consciousness (Ce_{LOS}) was adjusted to 3.49 $\mu g/ml$ as the simulated induction dose derived from the findings of Schnider *et al.*[9] findings became equal to our mean induction dose of group A_{10} (table 1). The infusion rate used in our group A_{10} was the same as that in the Schnider *et al.*[9] study.[9] The pharmacokinetic parameters of Schnider *et al.*[9] were derived from the data of an extremely low infusion rate, from 1.5–12 $mg \cdot kg^{-1} \cdot h^{-1}$, at which lag $time_{circulation}$ and residual $dose_{circulation}$ were negligible because lag $time_{circulation}$ is extremely small compared with induction time. Induction dose and time to reach the normalized effect-site concentration of loss of consciousness (3.49 $\mu g/ml$) were calculated at constant infusion rates/LBM from 10–450 $mg \cdot kg^{-1} \cdot$

Table 3. Demographic Data for Study Patients Administered Diluted Propofol at Various Infusion Rates (Group C)

	Subgroup						
	C_{10}	C_{15}	C_{30}	C_{60}	C_{100}	C_{200}	C_{300}
Gender (M/F)	5/5	4/6	6/4	5/5	4/6	6/4	4/6
Age (yr)	40 ± 9	42 ± 10	41 ± 9	41 ± 10	38 ± 12	42 ± 10	37 ± 12
	26–52	27–54	29–54	25–54	25–55	26–54	25–54
Height (cm)	161 ± 6	166 ± 7	165 ± 6	164 ± 6	165 ± 8	162 ± 11	159 ± 7
Weight (kg)	60 ± 11	59 ± 6	64 ± 8	59 ± 5	63 ± 8	57 ± 8	57 ± 7
LBM (kg)	48 ± 7	46 ± 6	49 ± 6	46 ± 4	47 ± 6	45 ± 8	41 ± 6
Propofol infusion rate (mg/kg/h)	10	15	30	60	100	200	300
Propofol infusion rate per LBM	13 ± 1	19 ± 1	39 ± 1	76 ± 7	145 ± 16	251 ± 16	390 ± 30
Propofol concentration (mg/ml)	0.5	0.5	0.5	0.5	0.5	0.5	1.0
Dilution ratio (×)	20	20	20	20	20	20	10
Diluted propofol infusion rate (ml · kg^{-1} · h^{-1})	20	30	60	120	200	400	300
Total infusion volume (ml)	204.9 ± 37.9	166.1 ± 27.3	174.3 ± 30.2	160.9 ± 35.0	175.7 ± 29.3	163.0 ± 27.1	140.1 ± 26.6
Induction time (s)	604.2 ± 59.5	358.3 ± 41.1	164.6 ± 15.5	81.4 ± 15.8†	50.1 ± 6.6†	34.1 ± 3.2†	27.3 ± 3.7†
Induction dose (mg)	97.3 ± 11.1	84.3 ± 15.5	85.1 ± 14.1	84.6 ± 4.8†	102.7 ± 14.7†	107.1 ± 15.4†	116.7 ± 26.4†
Induction dose per LBM	2.1 ± 0.3	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	2.2 ± 0.2	2.4 ± 0.2	2.9 ± 0.4
Plasma propofol concentration at LOC (μg/ml)	5.2 ± 1.3	5.4 ± 1.3	5.6 ± 1.4†	6.2 ± 1.9†	8 ± 1.9†	9.8 ± 1.5†	11.4 ± 1.5†
Decrease in SBP (%)	−4.2 ± 2.9	−3.8 ± 2.2	−4.2 ± 4.5	−7.2 ± 5.2	−6.4 ± 4.3†	−7.1 ± 6.6†	−6.2 ± 6†

Data are mean ± SD.

* Women, (1.07*body weight)−(148*(body weight/height)^2); Men, (1.10*body weight)−(128*(body weight/height)^2).

†P <0.05 *versus* groups A and B at same propofol infusion rates.

LBM = lean body mass; LOC = loss of consciousness; SBP = systolic blood pressure.

h^{-1} at each infusion rate in increments of 2.5 (from 10-50 mg · kg^{-1} · h^{-1}) or 10 mg · kg^{-1} · h^{-1} (from 50-450 mg · kg^{-1} · h^{-1}). If lag time$_{\text{circulation}}$ was 0, 10, 20, 40, or 60 s, induction dose was calculated by adding residual dose$_{\text{circulation}}$ to the value predicted using the pharmacokinetic parameters of Schnider *et al.*[9]

All data are presented as the mean ± SD. The data for quality of induction in each group were compared with Kruskal-Wallis tests. To compare groups A, B, and C, except for infusion volumes, one-way analysis of variance was used. *Post hoc* analysis using the Bonferroni correction of the Student *t* test would have been performed if differences had been found. $P < 0.05$ was considered statistically significant.

Results

Among the 250 patients, 10 in each infusion subgroup of groups A, B, and C, there were no statistically significant differences between the groups in gender ratio, age, height, weight, or LBM (tables 1-3). In all groups, anesthesia could be induced within 15 min with the predetermined propofol infusion rates, and no patients needed an additional propofol bolus infusion because of unsuccessful induction. The quality of anesthesia induction with propofol in all groups is summarized in table 4. Apnea occurred far more often at the faster administration rates than at the slower ones.

There was no excitatory movement. Injection pain was 5-30% in each group. In the diluted propofol group, higher propofol injection rates tended to provoke increases in the intensity of pain. Vocalization, meaning spontaneous speech, was significantly more frequent at lower infusion rates than at higher ones in groups receiving undiluted and diluted propofol both. At 24-h postoperative examinations, no patients showed complications such as persistent pain, redness, swelling, thrombophlebitis, and memory of awareness during induction. Three patients, two from group A and one from group B, were administered ephedrine because of hypotension. We recorded the lowest SBP before injection of ephedrine in these patients. In three patients from group A, blood samples could not be obtained within 10 s after loss of consciousness.

Various rates of crystalloid solution infusion in the opposite hand had no significant effect on induction

Table 4. Quality of Induction of Anesthesia

	Undiluted Propofol Infusion (Groups A and B)									Diluted Propofol Infusion (Group C)						
	A_{10} and B_{10}	A_{15} and B_{15}	A_{20} and B_{20}	A_{30} and B_{30}	A4$_{40}$ and B_{40}	A_{60} and B_{60}	A_{100} and B_{100}	A_{200} and B_{200}	A_{300} and B_{300}	C_{10}	C_{15}	C_{30}	C_{60}	C_{100}	C_{200}	C_{300}
Apnea (>30 s) (%)	0	0	0	0	5*	0	25*	30*	25*	0	0	0	0	0	10*	10*
Spontaneous movement (%)	0	0	10	5	0	5	5	0	0	0	10	0	10	10	0	0
Vocalization (%)	30*	25*	25*	20*	5*	5*	5*	0	0	30*	30*	20*	10*	0	0	0
Injection pain (%)																
Total	10	5	15	10	20	5	10	10	10	10	10	10	20	30	20	
Mild	10	0	15	10	0	5	5	5	5	10	0	0	10	10	20	10
Moderate	0	5	0	0	10	0	5	0	5	0	10	10	0	10	10	0
Severe	0	0	0	0	10	0	0	5	0	0	0	0	0	0	0	10

* Significantly different from other groups ($P < 0.05$).

time, induction dose, plasma propofol concentration at loss of consciousness, or percentage decrease in SBP (tables 1 and 3).

The induction time showed an initial steep decrease; however, it became fairly flat at infusion rates greater than 100 mg · kg^{-1} · h^{-1} (fig. 1). At all infusion rates, observed induction time necessary with undiluted propofol was an average of 21.9 s greater than that necessary with diluted propofol. In undiluted propofol, simulated induction time calculated with previously reported pharmacokinetic and pharmacodynamic parameters[9,10] was underestimated compared with the observed induction time (fig. 1). The observed mean induction times at infusion rates greater than 100 mg · kg^{-1} · h^{-1} clearly were relevant to the simulated induction time with a 20-s lag $time_{circulation}$ (fig. 1). In diluted propofol, the observed times at rates more than 100 mg · kg^{-1} · h^{-1} were relevant to the predicted line with a 0-s lag $time_{circulation}$ (fig. 1).

The relation between induction dose and infusion rate was not simple. In the simulation this relation clearly was concave when plotted (fig. 2). However, plotting the observed relation between induction dose and infusion rate did not produce a clear concave line. At infusion rates less than 80 mg · kg^{-1} · h^{-1} for undiluted propofol, the actual observed dose for induction was similar to the predicted dose combined with an additional residual $dose_{circulation}$ that corresponds with a 60-s lag $time_{circulation}$. At the infusion rates greater than 80 mg · kg^{-1} · h^{-1}, the observed dose was similar to the predicted dose combined with an additional residual $dose_{circulation}$ that corresponds with 20 s of lag $time_{circulation}$ (fig. 2). For diluted propofol, the observed dose was similar to the predicted dose combined with an additional residual $dose_{circulation}$ corresponding to 40 s of lag $time_{circulation}$ at infusion rates less than 80 mg · kg^{-1} · h^{-1}. At infusion rates greater than 80 mg · kg^{-1} · h^{-1}, the observed dose was similar to the predicted dose (fig. 2). In all infusion rates, the induction doses with undiluted propofol were greater than those with diluted propofol, and the difference corresponded to the residual $dose_{circulation}$ for approximately 20–30 s at each infusion rate (fig. 2).

The plasma propofol concentration at loss of consciousness increased with propofol infusion rate in all groups (fig. 3; tables 1-3). Although at the infusion rates less than 40 mg · kg^{-1} · h^{-1} the plasma concentrations for both undiluted and diluted propofol were similar, the concentrations for undiluted propofol were significantly higher than those for diluted propofol at higher infusion rates.

Systolic blood pressure did not change significantly at infusion rates less than approximately 80 mg · kg^{-1} · h^{-1} of undiluted and diluted propofol. At infusion rates greater than 80 mg · kg^{-1} · h^{-1}, SBP decreased significantly in the undiluted propofol groups (fig. 4; tables 1 and 2). In the diluted propofol groups, decreases in SBP were less marked, even at higher infusion rates (fig. 4; table 3).

Discussion

We evaluated the induction state from extremely low rates to extremely high rates of undiluted or diluted propofol infusion, which encompassed a much greater range than reported previously.[2,3,5,11-13] Combined pharmacokinetic-pharmacodynamic models are useful for determining the influence of administration, disposition, and effect.[6,9,11,14] These models can be used to predict the time course and intensity of drug effect if a drug is infused at various rates. When we acquired

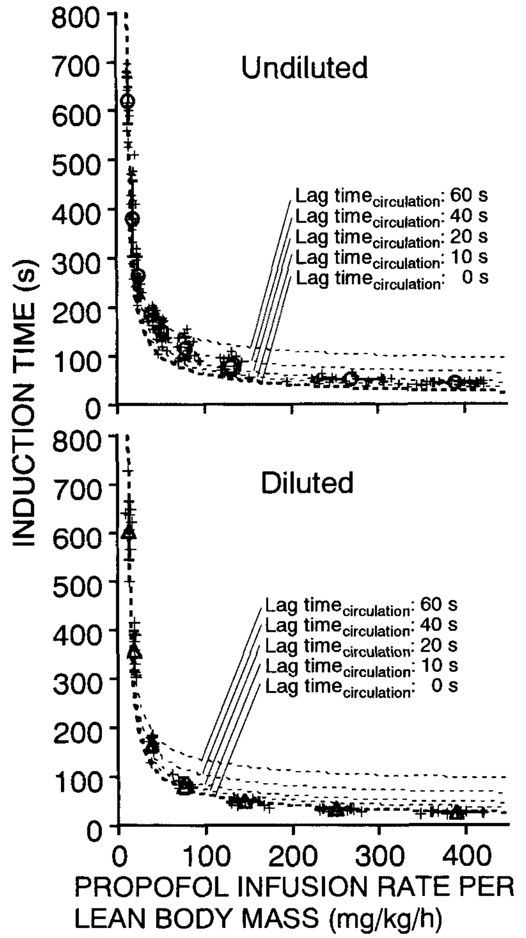

Fig. 1. Relation between propofol infusion rate and induction time. Individual induction times (+) and mean induction time of various undiluted (○) or diluted (△) propofol infusion rate subgroups are shown. Hatched lines represent predicted induction time based on the pharmacokinetic model of Schnider *et al.*[9] with additional lag time$_{circulation}$ of 0, 10, 20, 40, and 60 s (mean ± SD) and k_{eO} of 0.456/min.[10] In this model, effect-site concentration at loss of consciousness (Ce_{LOS}) was normalized to 3.49 μg/ml as simulated induction dose derived from Schnider *et al.*[9] became equal to our induction dose at a propofol infusion rate of 10 mg · kg^{-1} · h^{-1}.

curves of simulated infusion rate *versus* induction dose, the effect-site concentration at loss of consciousness in the Schnider *et al.*[9] model was adjusted as the predicted induction dose became equal to our observed induction dose at the infusion rate of 10 mg · kg^{-1} · h^{-1}. This normalization is reasonable, because the Schnider *et al.*[9] pharmacokinetic parameters used in the simulation were derived from data of a propofol infusion rate from 1.5–12 mg · kg^{-1} · h^{-1}. The simulated infusion rate *versus* induction dose indicates a concave curve. The simulation could predict propofol induction dose generally during the extreme condition of a 30-fold range of infusion rates. However, there were systematic differences between our observed induction dose and the dose predicted by this model even if we normalized this model to our data.

Previous descriptions of the relation between rate of infusion and induction dose have been incomplete because not all necessary components were evaluated.[3,4] The relation between induction dose and infusion rate can be explained with four primary factors.

First is the amount of propofol removed from the central compartment, with clearance that depends on the concentration in the central compartment. The clearance from the central compartment by metabolism and distribution is approximately 4.0–5.5 l/min.[9,15] Second is the residual dose$_{central}$. Although the plasma concentration peaks almost instantly, additional time is necessary for the drug concentration in the brain to rise and induce unconsciousness. The *time lag* is defined as time constant of k_{eO} of the effect site. Third is residual dose$_{circulation}$ that is correlated with lag time$_{circulation}$. This has not been investigated precisely. Fourth is rapid

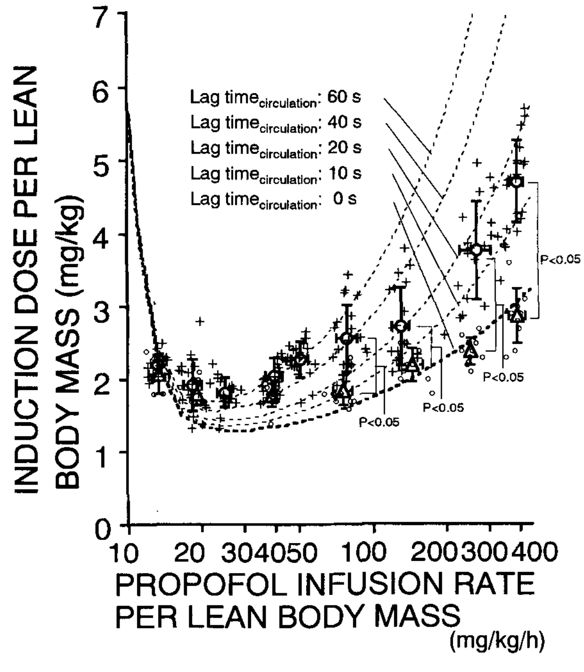

Fig. 2. Relation between propofol infusion rate and induction dose. Individual induction doses (undiluted = +; diluted = ○) and mean induction dose of various undiluted (○) or diluted (△) propofol infusion rate subgroups (mean ± SD). Hatched lines represent predicted induction dose with additional lag time$_{circulation}$ of 0, 10, 20, 40, and 60 s (k_{eO} = 0.456/min and effect-site concentration at loss of consciousness [Ce_{LOS}] = 3.49 μg/ml).

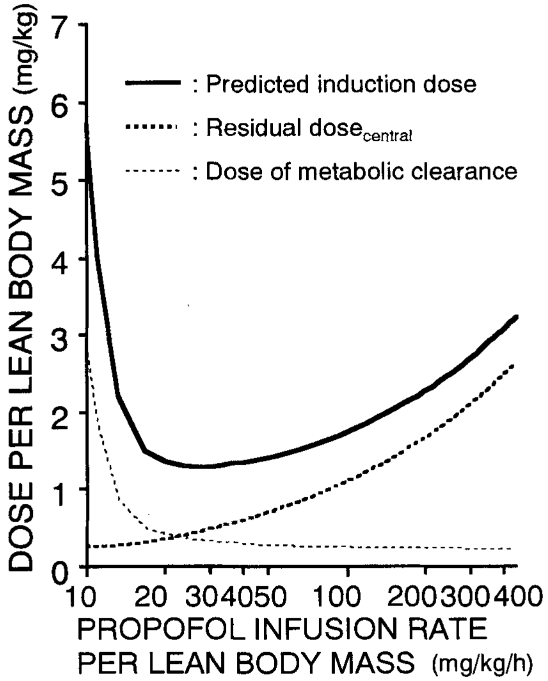

Fig. 5. Relation between propofol infusion rate *versus* residual dose$_{central}$ and dose of metabolic clearance. Simulations of infusion rate *versus* induction dose, dose for metabolic clearance, and the dose in the central compartment at loss of consciousness (residual dose$_{central}$) were calculated based on the pharmacokinetic model of Schnider *et al.*[9] (k_{eO} = 0.456/min and effect-site concentration at loss of consciousness [Ce_{LOS}] = 3.49 μg/ml).[10]

residual dose$_{circulation}$ for a 20-s lag time was necessary. For diluted propofol, 40 s for less than 80 mg · kg^{-1} · h^{-1} and 0 s for more than 80 mg · kg^{-1} · h^{-1} of additional residual dose$_{circulation}$ were necessary (fig. 2).

At all infusion rates, the difference in residual dose$_{circulation}$ between undiluted and diluted propofol can be explained by the difference of lag time$_{circulation}$ for approximately 20 s provoked by a 20-fold dilution of propofol. However, the downward change of induction dose at infusion rates greater than 80 mg · kg^{-1} · h^{-1} in undiluted and diluted propofol cannot be explained with residual dose$_{circulation}$ and has not been reported previously. In addition to the residual doses, rapid circulation resulting from incomplete mixing of the central compartment helps to explain the downward change at higher infusion rates.

The involvement of rapid circulation resulting from incomplete mixing has been ignored in conventional compartment models. However, the mechanisms of this process are well-understood and can be described by indicator dilution principles. Bolus infusion of indocyanine green can be used to define intravascular mixing transients. After central venous administration, there is a finite delay before the first indocyanine green appears at a sampling site.[16] Recirculation returns the drug through the central blood circuit to generate an oscillatory peak, which becomes damped on subsequent recirculations.[17] Roerig *et al.*[18] demonstrated in humans that indocyanine green concentration in a radial artery started to increase at approximately 15 s and peaked between 19 and 24 s after a bolus injection from a central venous catheter, with a second peak at 40–42 s representing the second circulation. Vecuronium onset time to 95% twitch depression was 21 s less during administration in the right atrium than in a peripheral vein[19]; that is, the lag time between peripheral vein and radial artery is from 36 to 45 s. Our lag time$_{circulation}$ at infusion rates less than 80 mg · kg^{-1} · h^{-1} was 60 s. Actual lag time between infusion site and radial artery may be different from our lag time$_{circulation}$ from infusion site to central compartment. In our model of low infusion rates, especially those less than 60 mg · kg^{-1} · h^{-1}, the actual observed induction dose was quite similar to the predicted dose combined with an additional residual dose$_{circulation}$ that

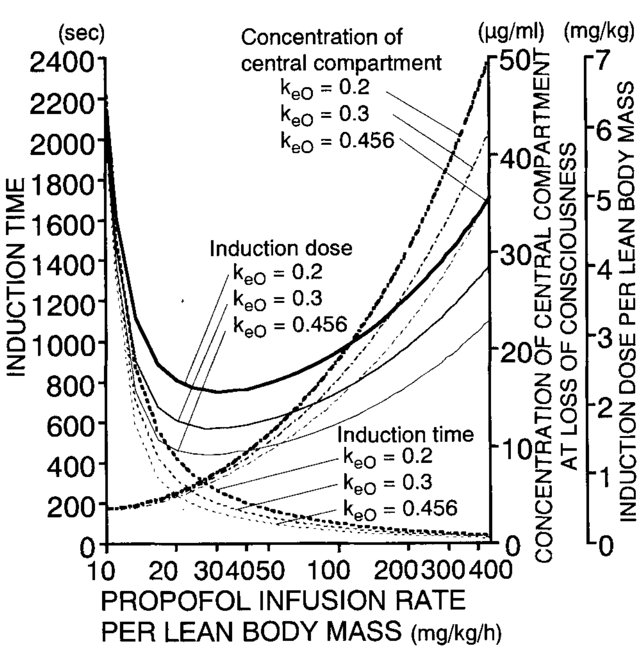

Fig. 6. Relation between infusion rate *versus* predicted induction dose, induction time, and propofol concentration in the central compartment. At various k_{eO}s of 0.2, 0.3, and 0.456/min, the relations between infusion rate and predicted induction dose, induction time, and propofol concentration in the central compartment at loss of consciousness were calculated based on the Schnider *et al.*[9] pharmacokinetic model (effect-site concentration at loss of consciousness [Ce_{LOS}] = 3.49 μg/ml).[10]

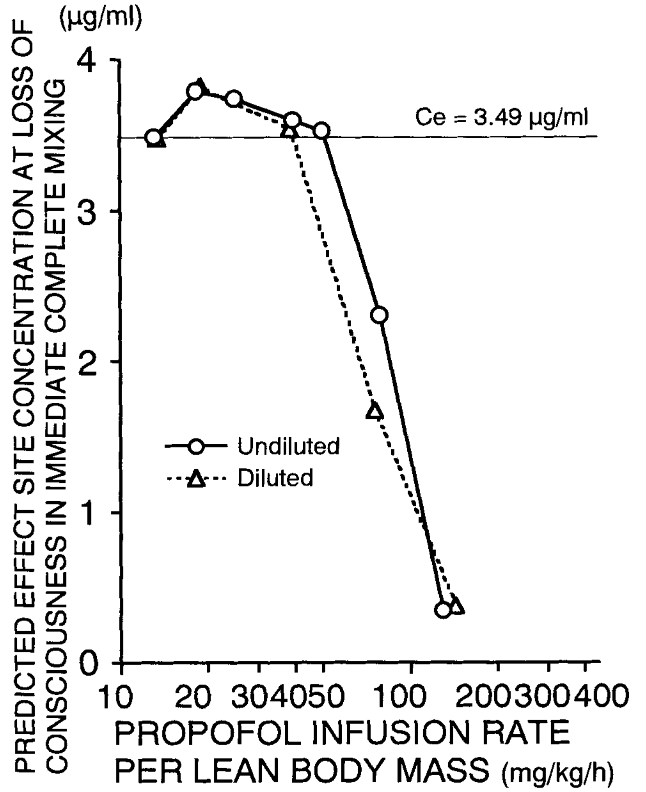

Fig. 7. During the condition of immediately complete mixing in the central compartment at a wide range of infusion rates (10–450 mg · kg^{-1} · h^{-1}), effect-site propofol concentrations at loss of consciousness at various infusion rates were calculated with effective induction dose (effective induction dose = total induction dose − 60 s for residual dose$_{\text{circulation}}$ for undiluted or 40 s for residual dose$_{\text{circulation}}$ for diluted propofol) with previous pharmacokinetic pharmacodynamic parameters.[9,10]

corresponds with 60 s of lag time$_{\text{circulation}}$, which means that the lag time$_{\text{circulation}}$ of undiluted propofol is 60 s. In the same manner, the lag time$_{\text{circulation}}$ of diluted propofol is 40 s.

If we assume that mixing in the central compartment was complete at high and low infusion rates, the predicted effect-site propofol concentrations at various infusion rates are shown in figure 7. The effect-site concentrations were calculated with effective induction dose (effective induction dose = total induction dose − 60 s residual dose$_{\text{circulation}}$ for undiluted or 40 s residual dose$_{\text{circulation}}$ for diluted propofol). At infusion rates greater than 60 mg · kg^{-1} · h^{-1}, the effect-site propofol concentration could not attain the concentration for loss of consciousness (3.49 μg/ml) if compartment mixing was completed immediately. At infusion rates greater than 150 mg · kg^{-1} · h^{-1}, the central compartment propofol concentration is zero. These results provide additional evidence that rapid circulation begins to influence the induction with continuous infusion at infusion rates more than 60 mg · kg^{-1} · h^{-1}, and that it becomes a main factor for induction at infusion rates more than 150 mg · kg^{-1} · h^{-1}.

In continuous infusion, initially, arterial propofol concentration increases more rapidly in a condition of incomplete mixing than in one of immediate complete mixing, although both conditions reach the same concentration progressively. The initial accelerative increase of propofol concentration causes a decrease of induction dose at high infusion rates. Our downward variation of residual dose$_{\text{circulation}}$ at infusion rates more than 80 mg · kg^{-1} · h^{-1} may have resulted from the decrease of induction dose provoked by the incomplete mixing.

For various lag time$_{\text{circulation}}$ values, simulation of infusion rate *versus* propofol concentration of central compartment at loss of consciousness is shown in figure 8. At lower infusion rates, predicted concentrations with measured induction doses for undiluted and diluted propofol were similar, and they were consistent with our observed propofol concentrations. However, at infusion

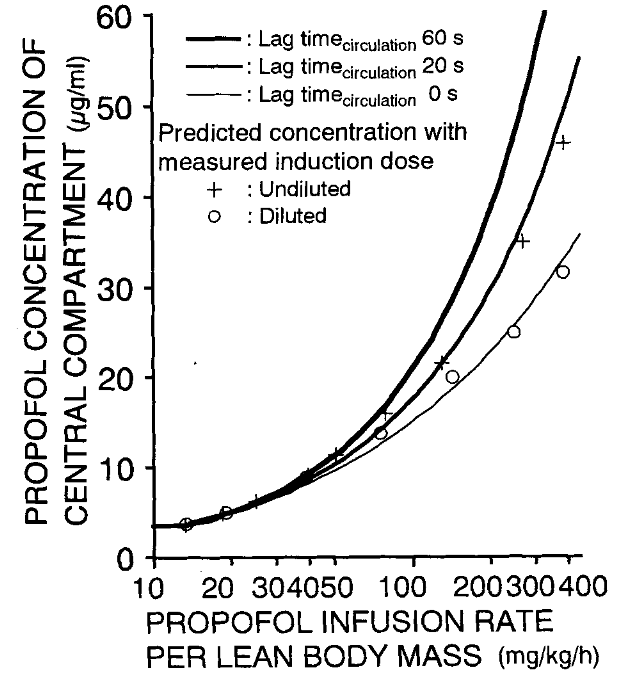

Fig. 8. Simulations of infusion rate *versus* propofol concentration of central compartment at loss of consciousness with various lag time$_{\text{circulation}}$ times of 0, 20, and 60 s were made using previously reported pharmacokinetic parameters.[9] Predicted concentration in the central compartment of our study (undiluted = +; diluted = ○) was calculated with the measured induction dose.

rates greater than 80 mg · kg^{-1} · h^{-1}, our observed plasma propofol concentrations were less than half the predicted ones (figs. 3 and 8). The predicted central concentration was obtained by measuring an induction dose that included residual $dose_{circulation}$. Blood samples were taken within 10 s after loss of consciousness, when residual $dose_{circulation}$ had not yet circulated to the artery side completely, which explains the discrepancy between predicted and measured propofol concentrations.

Upton[20,21] demonstrated that the time course of arterial concentration of drug administered in a bolus injection depends on dose rate, cardiac output, and magnitude of lung extraction. Hemodynamic depression occurs after loss of consciousness because $t_{1/2}k_{eO}$ ($t_{1/2}k_{eO} = \ln2/k_{eO}$) of SBP is 2.5 times more than that of the electroencephalographic bispectral index.[22] SBP decreased significantly more than 30% from preinduction values at high infusion rates of undiluted propofol in our study (fig. 4; tables 1-3). Cardiac output might decrease and influence induction dose; however, the maximal SBP decrease occurred after loss of consciousness. This suggests that cardiac output did not change significantly before loss of consciousness, and that it did not affect the induction dose and time in our study.

The crystalloid solution used in the dilution of propofol might change cardiac output. However, in our study, the various crystalloid infusion rates of the opposite hand in group B had no significant effects on induction time, induction dose, plasma propofol concentration at loss of consciousness, or percentage decrease in SBP (tables 1 and 3). The maximum crystalloid infusion rate was approximately 0.4 l/min. We suppose this amount of change in cardiac output would not influence the induction time, dose, or SBP depression.

For steady state lung extraction (E_{lung} [%]) of propofol against pulmonary artery concentration, Upton and Ludbrook[23] reported that the relation between the inverse of extraction ($1/E_{lung}$) and the afferent pulmonary artery concentration (C_{pa}) could be described by the following equation:

$$1/E_{lung} = 0.007\ C_{pa} + 0.013$$

According to this equation, E_{lung} values at 6.0 and 22 μg/ml of pulmonary artery concentrations are 18.2 and 6.0%. If the pulmonary artery concentration is close to the arterial concentration, infusion rates in these pulmonary artery concentrations would be approximately 26 and 385 mg · kg^{-1} · h^{-1}, respectively, in our study (tables 1-3). Consequently, doses extracted with the lung are 0.36 mg/kg at a 26-mg · kg^{-1} · h^{-1} infusion rate and 0.3 mg/kg at a 385-mg · kg^{-1} · h^{-1} infusion rate. This suggests that the dose extracted in the lung is almost constant with low and high infusion rates both, although the lung extraction might affect the induction dose.

In summary, we investigated propofol induction doses using a wide range of infusion rates with undiluted and diluted propofol. In addition to the residual $dose_{central}$ and lag time between the central compartment and effect site with increasing infusion rates, induction dose and time increased as much as residual $dose_{circulation}$ and lag $time_{circulation}$. However, at infusion rates greater than 80 mg · kg^{-1} · h^{-1}, rapid circulation resulting from incomplete mixing in the central compartment decreased induction dose and time. Overdosing related to residual $dose_{circulation}$ could be alleviated with the use of diluted propofol.

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