Awakening Propofol Concentration with and without Blood–Effect Site Equilibration after Short-term and Long-term Administration of Propofol and Fentanyl Anesthesia

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Background: The propofol awakening concentration can vary. However, the effect site awakening propofol concentration will be a fixed value. The purpose of this study was to determine the awakening propofol concentrations obtained from infusion Schede using abrupt discontinuation of propofol (half-maximal effective concentration [EC_{50}]) or a descending decrease in concentration to allow blood–effect site equilibration (EC_{50}eq).

Methods: Patients undergoing short-term (group 1) and long-term (group 2) elective surgery were anesthetized with computer-assisted continuous infusion of propofol and fentanyl, with both groups receiving the same propofol (3 µg/ml) and fentanyl (1 ng/ml) concentrations 20–30 min before the end of surgery until the end. Then both groups were further divided into two subgroups: subgroup A abrupt discontinuation, and subgroup B descending concentrations of propofol (15-min duration per concentration). In the A subgroups, the response to verbal command was evaluated every 30 s. In the B subgroups, the blood propofol concentrations just permitting and just preventing response to command were averaged individually. The EC_{50} and EC_{50}eq values were determined by probit analysis.

Results: The EC_{50} of group 1A was 1 µg/ml, which was significantly less than the 1.6 µg/ml of group 2A ($P < 0.05$). The awakening time of group 1A was 5.2 ± 1.8 min, which was

significantly shorter than the 9.3 ± 3.5 min of group 2A (means ± SD). The EC_{50}eq of both groups 1B and 2B was 2.2 µg/ml.

Conclusions: The EC_{50}eq was independent of propofol infusion length, compared with the EC_{50}. Thus the potential for hysteresis during emergence from propofol anesthesia was confirmed. (Key words: Computer simulation; computers; intravenous anesthetics; pharmacodynamics; pharmacokinetics.)

IN addition to the pharmacodynamic advantages of clear-headed emergence and antiemesis, the greatest attributes of propofol are its pharmacokinetic properties, which account for rapid onset and fast awakening. Some studies have provided values for blood propofol concentrations in patients waking from anesthesia. However, these reports show substantial variability in the concentration associated with awakening.[1-6] Hysteresis is a property of the drug, and the dosing scheme might influence the amount of hysteresis. To what extent the duration of propofol infusion influences hysteresis has not yet been evaluated precisely.

This study was designed to determine the blood concentration at which 50% of patients awake by comparing two conditions: In one, propofol was abruptly discontinued at the end of surgery (half-maximal effective concentration [EC_{50}]), and in the other descending levels of propofol infusion were administered to allow equilibration between blood and the effect site (EC_{50}eq). We also compared awakening concentration after short-term propofol infusion with that after long-term infusion.

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Materials and Methods

After approval from the District Ethics Committee of Hamamatsu University Hospital, 36 patients classified as American Society of Anesthesiologists physical status I and II who were aged 20–56 yr and scheduled for

elective plastic surgery expected to last <30 min were selected for short-term propofol infusion (group 1). Sixty-four patients classified as American Society of Anesthesiologists physical status I and II who were aged 20–59 yr and scheduled for elective surgery of the extremities, neck, or body expected to last 3–4 h were selected for long-term propofol infusion (group 2). Patients with known cardiac, pulmonary, liver, renal, or metabolic disease, and those who were significantly obese (body mass index >30) or were receiving any form of medication were excluded from the study. The patients provided written informed consent after the study was explained to them. No preanesthetic medication was given. When the patient arrived in the operating room, during local anesthesia a cannula was inserted into a peripheral vein to infuse propofol and fentanyl and to replace fluids (6–8 ml·kg^{-1}·h^{-1} lactated Ringer's solution). An arterial catheter was inserted to measure blood pressure and to sample blood. Heart rate, blood pressure, electric activity of the heart, end-tidal carbon dioxide, rectal temperature, and oxyhemoglobin saturation were monitored continuously during the surgery. Body temperature was maintained at 36–37°C using a forced-air warming blanket (Bear Hugger; Augustine Medical, Eden Prairie, MN).

Clinical Protocol

Propofol and fentanyl were administered with target-controlled infusion devices. In both groups, anesthesia was induced with a target propofol concentration of 5 μg/ml and a fentanyl concentration of 3 ng/ml, and with intubation facilitated by 0.1 mg/kg vecuronium. Respiration was controlled to maintain normocarbia as measured by capnography. Vecuronium, in 1–3 mg intravenous bolus doses, was given as required by surgical conditions. At least one or two twitch responses of train-of-four stimulation were always present, as measured by a peripheral neuromuscular function monitor. At the end of the surgical procedure, 2.5 mg neostigmine and 1 mg atropine were given intravenously. Propofol and fentanyl target concentrations, which were maintained in ranges of 2.5–5 μg/ml and 2–3 ng/ml, respectively, during most of the surgery, were rigidly controlled at 3 μg/ml and 1 ng/ml, respectively, for at least the final 20–30 min of surgery. To ensure equivalent concentration sampling, target propofol and fentanyl concentrations were kept steady for at least 30 min after surgery before blood samples were obtained. The concentration-hour of propofol (integration of predicted propofol concentration) was calculated in each
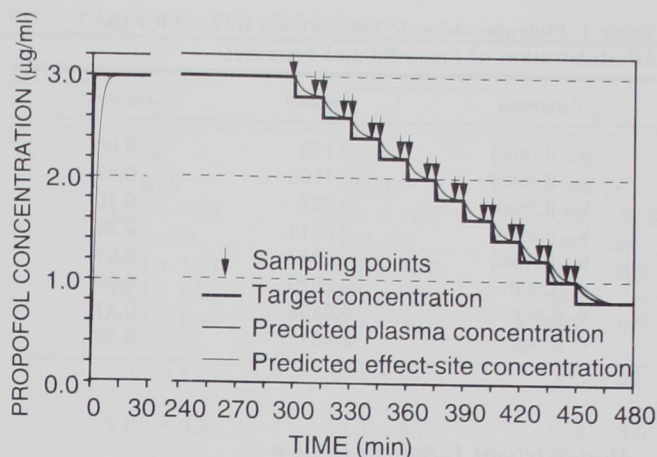

Fig. 1. Target, predicted plasma, and predicted effect site propofol concentrations after 3 μg/ml for 300 min of infusion when propofol was decreased by descending 15-min sequences are shown.

patient. The patients were further divided into two subgroups within each group: subgroup A in which abrupt discontinuation of propofol resulted in disequilibration between the blood and effect site concentrations; and subgroup B in which 0.2 μg/ml descending sequences of propofol concentrations for 15-min intervals at each concentration were used to equilibrate blood to the effect site. Arterial blood for propofol and fentanyl concentrations was sampled at discontinuation of propofol in the A subgroups and just before the descending step of propofol in the B subgroups (3 μg/ml of propofol and 1 ng of fentanyl).

In the A subgroups, the response to verbal command was evaluated every 30 s, and arterial blood samples for propofol and fentanyl concentration were taken when patients responded positively. The time from termination of propofol to a positive response to verbal command was also recorded.

In the B subgroups, each descending step of the target concentration was maintained for 15 min. Two blood samples of each step were drawn to measure propofol concentrations 10 and 15 min into each step (fig. 1). We calculated the mean value of the two samples as a step propofol concentration. The midpoint concentration between the step concentration at the first positive response and the step just before a positive response was called the awakening concentration equilibrated with the effect site for each patient. A blood sample for fentanyl concentration was also taken at the step of positive response.

Table 1. Pharmacokinetic Values Used in CaCl for the Administration of Propofol and Fentanyl

Parameter	Propofol	Fentanyl
k_{10} (L/min)	0.118	0.08
k_{12} (L/min)	0.1105	0.47
k_{21} (L/min)	0.057	0.10
k_{13} (L/min)	0.0514	0.23
k_{31} (L/min)	0.0047	0.01
v_1 (L/kg)	0.2679	0.09
v_2 (L/kg)	0.5195	0.41
v_3 (L/kg)	2.931	3.30

Model-driven Infusion Device

To maintain the blood concentration of propofol and fentanyl, we used a pharmacokinetic model-driven infusion device, such as those designed for computer-assisted continuous infusion, which consisted of a microcomputer (NEC 9821; Tokyo, Japan) interfaced to a syringe pump (model 1235; ATOM Co., Tokyo, Japan) and using a three-compartment model with central elimination. The rate of drug–mass change in the three compartments can be expressed as three simultaneous differential equations. Table 1 lists the pharmacokinetic parameters used in computer-assisted continuous infusion for fentanyl and propofol.[2,7] We solved these equations using the pharmacokinetic microconstants using the Runge-Kutta[8] method at the recursive period of 12 s. We programmed the control software ourselves in Turbo Pascal (Borland International, Scotts Valley, CA).

Assay of Propofol and Fentanyl

Blood samples were kept on ice and stored at 5°C until extraction and assay. 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).[9] For each batch of blood samples (from a single patient), a standard curve was computed by adding pure propofol liquid to drug-free human plasma to make up concentrations of 1, 5, 10, and 25 μg/ml. Linear regression (the method of least squares) was used with serum propofol concentration as the dependent variable. Propofol concentrations in this study were calculated using the obtained regression equation. The lower limit of detection was 17 ng/ml, and the coefficient of variation was 8.4%. The plasma for fentanyl concentration was separated and frozen at −70°C until assay. The plasma concentration of fentanyl was measured by a gas chromatograph mass-spectrometer (model 5989; Hewlett Packard, CA) in an outside laboratory. The lower limit of detection was 0.2 ng/ml.

Statistical Analysis

Probit analysis was used to define the probability of no response to verbal command. The EC_{50} and $EC_{50}eq$ were obtained from this analysis. All data are presented as means ± SD if not stated otherwise. Statistical analysis included analysis of variance for principal effects and Student's t test. Probability values <0.05 were considered significant.

Results

The demographic data profiles of the patients did not differ significantly between groups (table 2). Anesthesia induction and maintenance were smooth in all cases, and no excitatory movements were observed. The concentration-hour did not differ significantly between the subgroups (table 2). Recovery from anesthesia was similarly uneventful.

Fentanyl concentrations during the measurement of response to verbal command were stable and did not differ significantly between the groups (table 2). Propofol concentrations at discontinuation of the A subgroups and just before the first descending step of the B subgroups were similar (table 2). In the B subgroups, propofol blood concentrations at just one step before positive response to verbal command and the step at positive response to verbal command confirmed a stable concentration (fig. 2).

Table 2 shows the EC_{50} and $EC_{50}eq$ values of each group, and figure 3 shows the dose–response curves. The EC_{50} after the abrupt discontinuation of propofol (group 1A) was significantly lower than that after the long-term decreasing administration (group 2A). However, the $EC_{50}eq$ value obtained under the condition of equilibration between plasma and the effect site propofol concentration in group 1B was quite similar to that in group 2B. In groups 1 and 2, the EC_{50} values were lower than those for $EC_{50}eq$. The time required to respond to a verbal command was 9.3 ± 3.5 min for group 2A, which was significantly longer than the 5.2 ± 1.8 min required for group 1A (table 2).

Discussion

We observed that the EC_{50} of awakening concentration after long-term propofol infusion was greater than

Table 2. Demographic Data for Study Patients Undergoing Short-term or Long-term Propofol Infusion

	Group 1		Group 2	
	A	B	A	B
No.	18	18	32	32
Sex (M/F)	9/9	8/10	15/17	14/18
Age (yr) (range)	43.1 ± 13.4	42.9 ± 16.5	44.2 ± 18.2	43.5 ± 12.9
	(21–56)	(20–55)	(20–59)	(21–58)
Body weight (kg)	59.6 ± 9.8	58.6 ± 10.1	56.7 ± 10.9	57.5 ± 9.5
Lean body mass	43.6 ± 7.5	43.9 ± 9.0	43.3 ± 7.7	43.8 ± 7.4
Height (cm)	161.8 ± 9.9	160.0 ± 8.6	159.2 ± 10.4	159.2 ± 8.9
Duration of propofol administration before the end of surgery (min)	38 ± 12	32 ± 11	291 ± 61	305 ± 56
Concentration · hour of propofol administration before the end of surgery (hour · µg/ml)	2.1 ± 0.52	1.81 ± 0.54	16.3 ± 3.7	15.4 ± 3.9
Awakening time (min)	5.2 ± 1.8	—	9.3 ± 3.5*	—
Fentanyl concentration (ng/ml)				
At discontinuation of propofol	0.98 ± 0.19	—	0.88 ± 0.16	—
Just before first descending step of propofol	—	0.94 ± 0.16	—	0.89 ± 0.16
At awakening	0.96 ± 0.19	—	0.91 ± 0.15	—
At awakening step	—	0.96 ± 0.18	—	0.89 ± 0.14
Propofol concentration (µg/ml)				
At discontinuation	3.1 ± 0.3	—	3.0 ± 0.3	—
Just before first descending step	—	3.2 ± 0.3	—	3.1 ± 0.3
EC_{50}	1.0	—	1.6*	—
95% confidence limits	0.9–1.1		1.5–1.6	
EC_{50eq}	—	2.2	—	2.2
95% confidence limits		2.0–2.4		2.1–2.3

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).

Data are mean ± SD.

* $P < 0.05$ versus group 1A.

that after short-term infusion and entailed a longer awakening time. The blood propofol awakening concentration after short-term infusion was consistent with previously reported values obtained after repeated bolus administration (0.9–1 µg/ml).[3] Shafer et al.[1] reported that the predicted blood propofol concentration at which 50% of patients awoke after surgery was 1.07 µg/ml. They found that this value was independent of patient age, sex, weight, or type of surgery. But the patients who had major surgery took a longer time to wake (18 min compared with 9 min).[1] The EC_{50} value in our study was influenced by the length of propofol infusion, and the EC_{50} after long-term infusion of propofol in our study was higher than that reported by Shafer et al. Possible explanations for the observed higher EC_{50} in our study include a different infusion regimen, a different blood sampling site,[10] and different opiate administration. Schuttler et al.[4] reported that awakening time and propofol concentration were 7.9 min and 1.59 µg/ml after 131 min of propofol infusion, which are similar

to those of our EC_{50} of long-term propofol infusion. Wessen et al.[5] reported a 0.7 µg/ml propofol concentration for awakening and 1.8 µg/ml for arousal state after propofol infusion with an epidural block. Our criteria that the patients open their eyes after having their names called in a normal voice was comparable to Wessen's reported arousal state.

To eliminate the confounding effects of pharmacokinetic and pharmacodynamic variability in the response of patients to a stimulus, constant blood concentrations and blood to effect site equilibration are required. In our study, we determined the awakening concentration after blood–effect site equilibration, EC_{50}eq. The EC_{50}eq was independent of the duration of propofol infusion. This is in contrast to the EC_{50}, which was significantly influenced by infusion duration. To obtain the EC_{50}eq, we used descending sequences of propofol concentrations for 15-min intervals. To simulate the effect site concentration, we added a pseudocompartment of effect site to our pharmacokinetic model. The
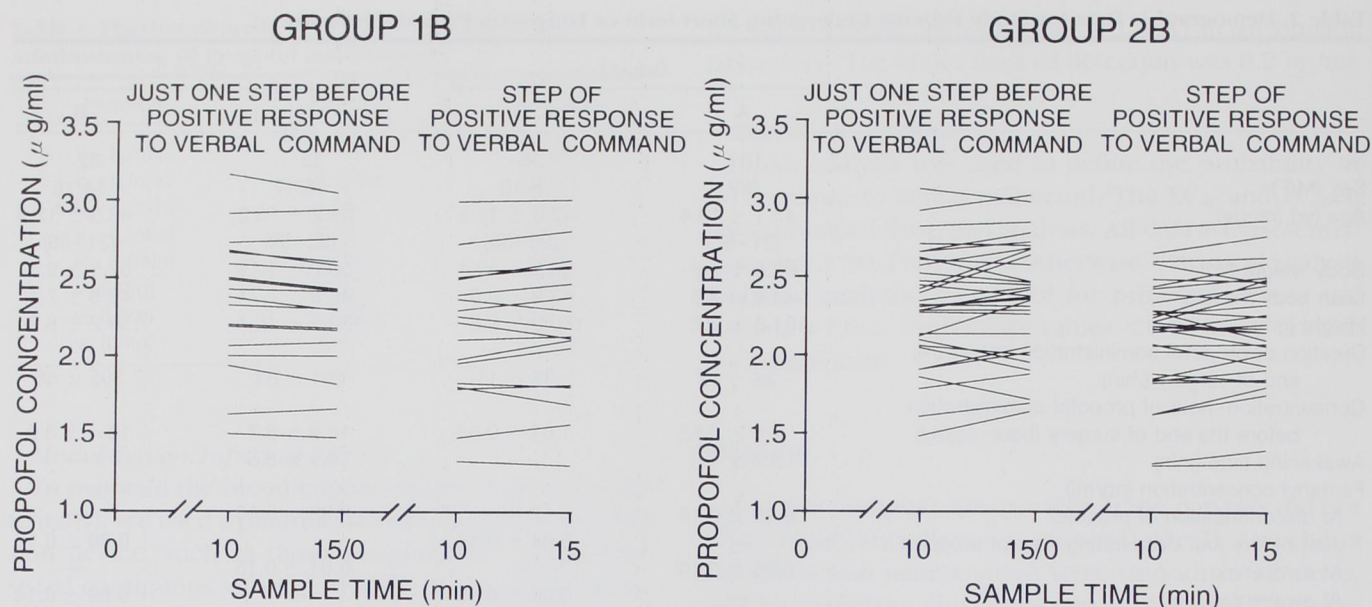
Fig. 2. The propofol concentrations for each of the 18 patients in group 1B and 32 patients in group 2B are stable at just one step before positive response to verbal command and at the step of positive response to verbal command. The average of the arterial blood propofol concentrations at 10 and 15 min of each step was defined as the individual step concentration.

concentration time course was derived from the plasma concentration by using Ke0 (the rate constant for elimination from the effect site) by solving a first-order differential equation, which was first proposed by Sheiner *et al.*[11] We used the Ke0 of propofol previously published by Schüttler *et al.*§ In figure 1, we show target plasma concentration, predicted plasma concentration, and the predicted effect site concentration of our study design with descending sequences of propofol after long infusions. The time interval that we used was long enough to allow equilibration between blood and effect site when the target propofol concentration was more than 1 μg/ml.

We used the pharmacokinetic/pharmacodynamic models to perform computer simulations of plasma and effect site concentrations *versus* infusion time (fig. 4) and probability of no response to verbal command *versus* infusion time (fig. 5) after abrupt discontinuation after various durations of propofol infusion maintained at 3 μg/ml. We assumed that the probability of no response to verbal command had a sigmoid relation with the effect site concentration, which was numerically expressed as a Hill equation.[12] We used the data from groups 1B and 2B to estimate the pharmacodynamic
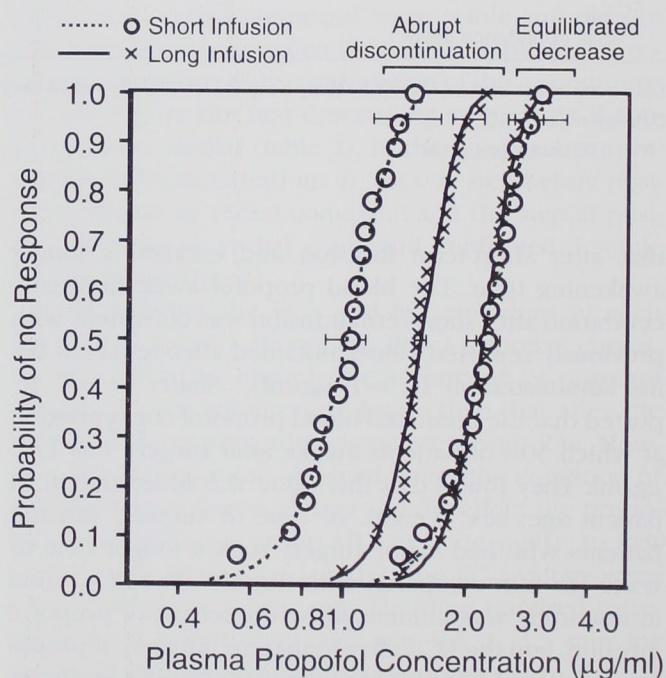

Fig. 3. The propofol concentration–response curves for awakening as a function of blood propofol level (measured in micrograms per milliliter) in the short-term (group 1) or long-term (group 2) propofol infusions. The probabilities of no response of patients who awoke after abrupt discontinuation of propofol and after the descending infusion schema to allow blood–effect site equilibration at various blood propofol levels are shown.

§ Schüttler J, Schwilden H, Stoeckel H: Pharmacokinetic-dynamic modeling of Diprivan [Abstract]. ANESTHESIOLOGY 1986; 65:A549
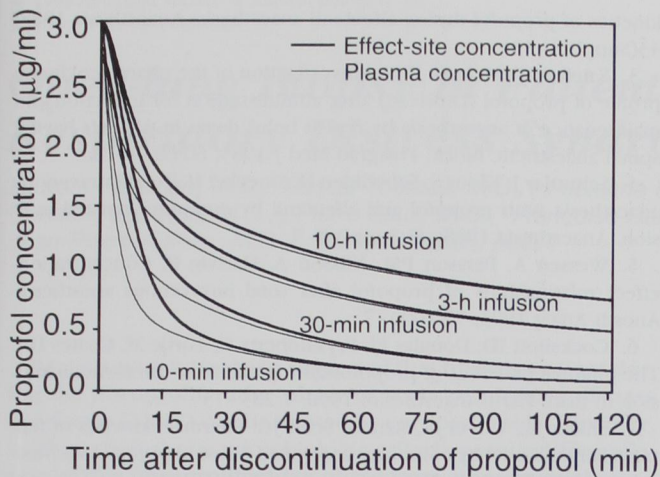
Fig. 4. Predicted plasma and effect site concentrations after various infusion times (from 10 min to 10 h) of 3 μg/ml propofol are shown. The difference between plasma and the effect site concentration is substantial, especially 3–10 min after termination of propofol infusion.

response of propofol from the effect site concentration for the constants in the equation, which were C_{50} (effect site concentration at 50% of maximum response) and r (steepness factor = EC_{95}/EC_{50}).

These simulations show that the difference between plasma and effect site concentration is significant, especially 3–10 min after termination of propofol infusion, and that the shorter the duration of propofol infusion, the faster the decrease in effect site propofol concentration; the longer the duration of propofol, the longer the awakening time. However, the time for 50% of patients to awaken is less than 10 min, even after a 10-h infusion at a 3 μg/ml propofol concentration.

Although the EC_{50}eq was independent of the duration of the propofol infusion, the EC_{50} was significantly influenced by the infusion duration in our study. Patients undergoing prolonged infusion required longer emergence times than those undergoing short infusion. Furthermore, our patients awoke at significantly higher blood propofol concentrations with prolonged infusion than with short infusion. In those who had abrupt discontinuation, the relation between the time and blood propofol concentration at emergence was influenced by the duration of propofol infusion. We assumed that the effect site propofol concentration at awakening would be the same EC_{50}eq value (2.2 μg/ml) whether the abrupt discontinuation happened after short or long propofol infusion. According to this assumption, we predicted each ke0 after short or long propofol infusion

using the least-square method by applying the following data: awakening time, awakening propofol concentration, mean propofol infusion time, mean maintenance target propofol concentration, and mean propofol blood concentration at abrupt discontinuation. The predicted ke0 values were 0.26 after short infusion and 0.21 after long infusion. Considering the use of the maintenance propofol concentration as the predicted one, the use of fentanyl with propofol during surgery, and individual pharmacokinetic deviation, these predicted Ke0 values were similar to the value of ke0 = 0.239 min − 1 (t1/2e0 = 2.9 ± 2.2 min) calculated by Schüttler *et al.*§ using the electroencephalogram median frequency.

The propofol blood concentrations at which 50% of patients did not respond to verbal command (Cp_{50}awake) determined by Smith *et al.*[13] and Chortkoff *et al.*[14] were 3.3 and 2.69 μg/ml, respectively. Vuyk *et al.*[15] reported that the propofol concentrations at which 50% of the patients showed loss of eyelash reflex and loss of consciousness were 2.07 and 3.4 μg/ml. In those studies, the propofol infusion scheme was designed to allow blood–brain equilibration at each step of the target propofol concentration (10–15 min of steady state predicted concentration with computer-assisted continuous infusion). Our EC_{50}eq was lower than that in their reports, which is consistent with differences in our study design: (1) a different endpoint for awakening, (2) a different method for defining awakening concen-
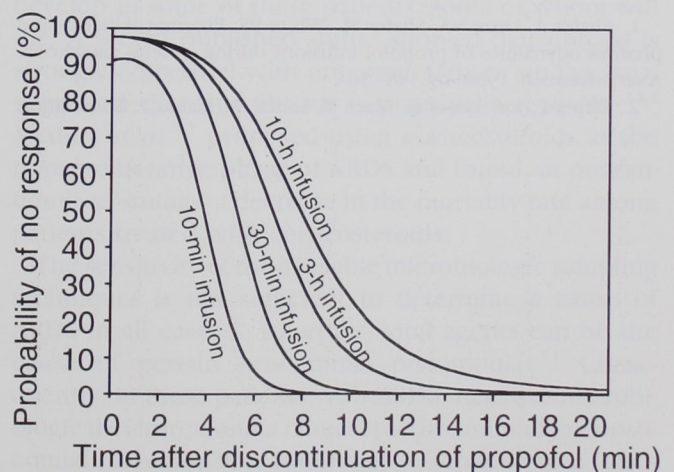

Fig. 5. Probabilities of no response to verbal command *versus* infusion time (from 10 min to 10 h) after infusion of propofol maintained at 3 μg/ml are shown. The time to 50% of patients awakening is <10 min even after a 10-h infusion at a 3 μg/ml propofol concentration.

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tration, (3) effect of fentanyl, and (4) postoperative pain. Our response criterion was the patients opening their eyes after hearing their names called twice in a normal voice, a definition of arousal state commonly used in clinical anesthesia. Although the concentration of fentanyl after surgery was <1 ng/ml, the fentanyl concentration might decrease the awakening propofol concentration. According to the report by Smith *et al.*,[13] 1 ng/ml of fentanyl concentration decreased the $EC_{50}eq$ value by approximately 1 $\mu g/ml$ compared with the Cp_{50}awake value for propofol alone. In our study, the mean fentanyl concentration of each group during all measurements was 0.88–0.98 ng/ml, and there were no significant differences between groups. Our $EC_{50}eq$ value in the presence of fentanyl thus was similar to that reported by Smith *et al.*[13] Therefore, we surmise that as the effect of fentanyl on awakening concentration was equivalent across all groups, it was not responsible for any differences seen in the EC_{50} or $EC_{50}eq$ values between the groups.

In conclusion, we confirmed the EC_{50} after abrupt discontinuation of propofol at the end of surgery and the $EC_{50}eq$ value obtained after allowing blood–brain equilibration at each decreasing target propofol concentration. Although the EC_{50} after short-term propofol infusion was less than that after long-term infusion, $EC_{50}eq$ value was independent of duration of propofol infusion time.

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