Pharmacodynamics of Propofol in Female Patients

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Although the clinical properties of propofol have been studied extensively, the pharmacodynamics have not yet been described fully. We studied the propofol concentration–effect relationships for loss of eyelash reflex, loss of consciousness, and hemodynamic changes in 18 female patients, ASA physical status 1, aged 20–49 yr. Propofol was given by computer-controlled infusion. The initial target concentration of 0.5–1 µg/ml was increased every 12 min by 0.5–1 µg/ml until the patients lost consciousness. Every 3 min, loss of eyelash reflex and loss of consciousness were tested and an arterial blood sample was taken for analysis of the blood propofol concentration. The concentration–response relationships for loss of eyelash reflex and loss of consciousness were defined by fitting a sigmoid E_{max} function (where E_{max} = the maximum effect that can be reached; i.e., 100% of the patients showing loss of eyelash reflex or loss of consciousness) to the response/no response data versus the propofol concentration, using nonlinear regression. The effect of propofol on hemodynamic parameters was analyzed by linear regression. The propofol concentrations at which 50% and 90% of the patients showed loss of eyelash reflex were 2.07 and 2.78 µg/ml, respectively. The corresponding values for loss of consciousness were 3.40 and 4.34 µg/ml. The systolic and diastolic blood pressure decreased with increasing blood propofol concentration. The correlation coefficients for the decrease in systolic and diastolic blood pressure versus the blood propofol concentration were $r^2 = -0.663$ and $r^2 = -0.243$, but heart rate did not change. In conclusion, propofol concentrations inducing loss of eyelash reflex are less than those inducing loss of consciousness. (Key words: Anesthetics, intravenous: propofol. Pharmacodynamics: propofol.)

IN ADDITION to its use as an intravenous induction agent, propofol is increasingly being used for maintenance of anesthesia, and for sedation during regional anesthesia or in the intensive care unit.[1] For these purposes either manual or computer-controlled infusion pumps are used to provide adequate blood propofol concentrations continuously. To obtain optimum advantage of these techniques, both the pharmacokinetics, as well as the concentration–effect relationship (pharmacodynamics) of the agent have to be well defined.

A blood propofol concentration of about 3 µg/ml,[2,3] combined with an opioid, provides adequate anesthesia. Patients awake when the blood propofol concentration decreases to less than 1 µg/ml.[4] The propofol concentration that is associated with loss of consciousness has not yet been defined.

We designed a study to define the blood propofol concentration that causes loss of eyelash reflex and loss of consciousness in healthy female patients scheduled for general surgery. We also investigated the effect of increasing blood propofol concentrations on systolic and diastolic blood pressure and heart rate.

Materials and Methods

With approval of the local Medical Ethics Committee and informed consent, 18 female patients, ASA physical status 1, aged 20–49 yr, scheduled for general surgery, were studied. Patients with known cardiac, pulmonary, or renal disease, and patients receiving medication, including oral contraceptives, were excluded from the study. Patients consuming more than 20 g alcohol or smoking more than 10 cigarettes per day were also excluded from the study.

No preanesthetic medication was given. In the operating room an intravenous cannula was inserted into a large forearm vein for infusion of propofol, and a cannula was inserted in a radial artery for continuous measurement of arterial blood pressure and collection of blood samples. Throughout the study, patients breathed 30% oxygen in air via a face mask. The ECG, arterial blood pressure, heart rate, end-tidal carbon dioxide concentration, and oxyhemoglobin saturation (Sp_{O_2}, Nellcor N-200) were monitored continuously throughout the study.

Two different computer controlled infusion systems were used to administer propofol. In nine patients (group A) the Titration of Intravenous Agents by Computer (TIAC, Janssen Scientific Instruments, Janssen Pharmaceutica, Beerse, Belgium) was used, supplied with two-compartment pharmacokinetic data.[5] The initial target blood propofol concentration, 0.5 µg/ml, was increased every 12 min by 0.5 µg/ml, until the patients lost consciousness. In the other nine patients (group B), an Ohmeda 9000 infusion pump, controlled by an Atari

Portfolio pocket computer supplied with three-compartment pharmacokinetic data,[6] was used. In these patients, the initial target blood propofol concentration of 1 μg/ml was increased every 12 min by 1 μg/ml until loss of consciousness was induced.

The eyelash reflex was tested every 3 min. At the same time, the patients were asked to open their eyes or to otherwise indicate that they were still conscious. If no response to these stimuli occurred, the patients were stimulated by gently rubbing their shoulders, and the response was noted. Loss of consciousness was defined as unresponsiveness to both verbal and tactile stimuli. When loss of consciousness was induced, the target propofol concentration was maintained, and alfentanil 12.5 μg/kg and succinylcholine 1 mg/kg were administered intravenously, and the trachea was intubated.

Thirty minutes and 24 h after the end of surgery, the patients were questioned for any recall of events during the study up to and including intubation.

BLOOD SAMPLES AND ASSAYS

Arterial blood samples for analysis of the whole-blood propofol concentration were taken just before the start of the propofol infusion and every 3 min thereafter until the trachea was intubated. Blood samples were transferred into test tubes containing potassium oxalate and stored at 4° C. Assays were carried out within 12 weeks at the Anesthesia Research Laboratory, University Hospital Leiden, The Netherlands.

Propofol concentrations in blood were measured by reversed-phase high-performance liquid chromatography (HPLC). To blood aliquots of 0.5–1 ml in a centrifuge tube, 300 ng thymol was added as internal standard. After mixing, the sample was extracted for 2 min in a Vortex mixer with 5 ml pentane, to which 50 μl tetramethylammoniumhydroxide solution (0.1 mM in 2-propanol/methanol) was added; the sample then was centrifuged for 10 min at 2,000 × g and 4° C. The organic phase was transferred into evaporation tubes and evaporated to dryness at 10° C under a gentle stream of pure nitrogen. Finally, the residue was dissolved in 100 μl of the mobile phase, and an aliquot was injected into the HPLC column.

The HPLC system consisted of a pump (SF400); a programmer (SF450); a fluorescence detector equipped with a 5-μl flow cell (SF980) (all Applied Biosystems, Ramsey, NJ); a column thermostat (SpH99); an autoinjector, Promis II (Spark Holland B.V., Emmen, The Netherlands); and a stainless steel column, 75 × 4.6 mm, prepacked with ultrasphere C-18, 3 μm (Beckman, San Ramon, CA). For data acquisition, a SP4290 Integrator and an Epson PC-E/HD computer, with chromatographic software (Spectra-Physics, San Jose, CA) were used. The column temperature was 40° C. The excitation wavelength was 276 nm, and an emission long-pass cutoff filter of 295 nm was used. The mobile phase consisted of 16% acetonitrile (v/v), 48% methanol (v/v), and 36% water (v/v), to which 0.5 ml trifluoracetic acid per liter was added. The final pH of the mobile phase was adjusted to 3.0 with sodium hydroxide. The flow rate of the mobile phase was 1.5 ml/min.

The retention times of thymol and propofol were 2.7 min and 5.3 min, respectively. Concentrations of propofol were calculated from calibration curves, prepared by adding known quantities of propofol to blank control blood samples that were extracted according to the above procedure. The calibration curve was obtained by weighted least-squares linear regression analysis of the peak height ratio of propofol/thymol *versus* the concentration of propofol. The detection limit was approximately 5 ng propofol per milliliter blood. The coefficient of variation was ≤ 7% in the concentration range encountered in this study.

DATA ANALYSIS

The performance of the computer-controlled infusion systems was evaluated as follows. For each blood sample, the performance error was calculated as $((C_m - C_p) /C_p)$ × 100, where C_m and C_p are the measured and predicted blood propofol concentrations, respectively.[7–9] Subsequently the bias and inaccuracy of each system were assessed by determination of the median performance error and the median absolute performance error and the corresponding 95% confidence intervals. When the 95% confidence interval of the median performance error included zero, it was concluded that no significant bias had occurred. The stability of the blood propofol concentration delivered by the infusion systems was evaluated by comparing the performance errors and the absolute performance errors at the 3rd and 12th min of each target concentration, using a paired t test. Furthermore, the similarity of the infusion schemes delivered by the two infusion systems was evaluated by comparing the mean measured blood propofol concentrations at corresponding steps between the patients of group A and group B, using an unpaired t test.

The concentrations that caused loss of eyelash reflex and loss of consciousness were compared between groups A and B, using an unpaired t test. A sigmoid E_{max} function (where E_{max} = the maximum effect that can be reached, *i.e.*, 100% of the patients showing loss of eyelash reflex or loss of consciousness) was fitted to the response/no-response data *versus* the measured blood propofol concentrations obtained in the individual groups A and B, as well as to the data of the groups combined. "No response" was defined as loss of eyelash reflex or loss of consciousness; the measured blood propofol concentration at the time this occurred was used in the analysis. For the "response" value, the last measured blood propofol concen-

tration of the highest target concentration at which patients still had a positive eyelash reflex or still were conscious was used in the analysis. The sigmoid E_{max} model is described by the equation:

$$\text{Probability of no response} = \frac{C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

where C is the measured blood propofol concentration; EC_{50} is the propofol concentration at which 50% of the patients showed loss of eyelash reflex or loss of consciousness; and γ is a dimensionless parameter characterizing the slope of the curve of the concentration–effect relationship. The curve was fitted by unweighted least-squares nonlinear regression analysis, with the software package Siphar (Simed, Créteil, France).

The hemodynamic response to increasing blood propofol concentration was analyzed by linear regression of the systolic and diastolic arterial blood pressures and heart rates at 12, 24, 36, and 48 min (i.e., the times just before an increase in target concentration) versus the corresponding blood propofol concentrations. Immediate preinduction arterial blood pressure and heart rate values were used as control data. The percentage change in systolic and diastolic blood pressure and heart rate at the EC_{50} and EC_{90} for unconsciousness were derived from the regression lines.

The patient characteristics of both groups were compared using an unpaired t test.

Data are presented as mean ± SD, median and range, or percentage, unless stated otherwise. $P < 0.05$ was considered the minimum level of statistical significance.

Results

The mean age and weight of the patients in group A were 33 ± 8 yr and 68 ± 15 kg, respectively. The cor-

responding values for group B were 36 ± 8 yr and 63 ± 10 kg. Both age and weight were not significantly different between groups A and B. The age and weight of the patients of the combined groups were 35 ± 8 yr and 66 ± 13 kg, respectively.

All patients maintained spontaneous breathing and normocapnia throughout the study. Immediately before intubation, the median end-tidal carbon dioxide concentration was 4.6 vol% (3.9–5.4%). In eight patients, one or two periods of mild hypoxemia ($85\% < Sp_{O_2} < 90\%$) developed. In each case, asking the patient to take a deep breath easily restored Sp_{O_2}. At the time of loss of consciousness, all patients had an $Sp_{O_2} > 95\%$.

With increasing blood propofol concentration, patients experienced, reported, and displayed a consistent behavior pattern. At blood propofol concentrations of about 1 $\mu g/ml$ patients felt relaxed and comfortable. As the blood propofol concentration increased to 2–3 $\mu g/ml$, the patients became aroused and talkative, until eventually their speech became confused. With propofol concentrations greater than 3 $\mu g/ml$, the patients finally became quiet and lost consciousness.

Figure 1 shows the measured blood propofol concentrations versus time for the 18 patients studied. Both delivery systems showed significant bias. The median performance error (25th–75th percentile) and median absolute performance error (25th–75th percentile) in group A were both 99% (72–126%). The corresponding values for the delivery system of group B were 26% (9–40%) and 27% (14–41%), respectively. The performance errors and the absolute performance errors calculated from the first and last sample at each target concentration were not significantly different for any target concentration with either infusion system. The mean measured blood propofol concentrations at comparable steps were not sig-
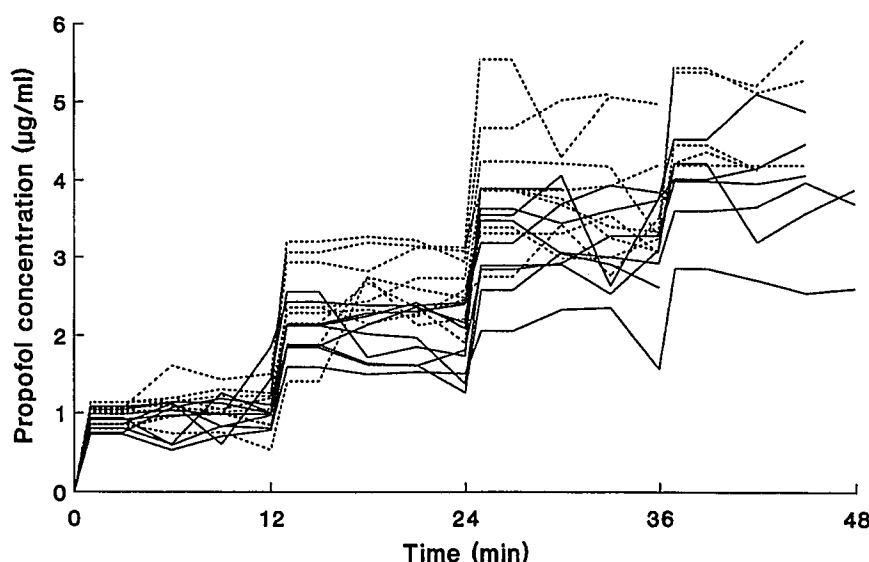

FIG. 1. The measured whole-blood propofol concentrations of the patients in group A (solid line) and group B (dashed line) over time.

TABLE 1. The Target Concentrations and Mean Measured Blood Propofol Concentrations at the Different Steps in Group A and B Patients

Step	Group A (μg/ml)		Group B (μg/ml)	
	C_T	C_M	C_T	C_M
1	0.5	1.0 ± 0.1	1	1.1 ± 0.2
2	1	2.0 ± 0.3	2	2.6 ± 0.4
3	1.5	3.1 ± 0.5	3	4.0 ± 0.7
4	2	3.9 ± 0.7	4	4.8 ± 0.7

C_T = target propofol concentration; C_M = mean measured blood propofol concentration.

No significant difference was found between the mean measured blood propofol concentrations at any of the corresponding steps between the patients of groups A and B.

nificantly different between the patients of groups A and B (table 1).

Propofol concentrations at which individual patients lost eyelash reflex and consciousness are presented in table 2. Blood propofol concentrations at which patients in group A lost eyelash reflex (2.8 ± 0.6 μg/ml) and consciousness (3.7 ± 0.6 μg/ml) did not differ from those in group B (loss of eyelash reflex 2.8 ± 0.6 μg/ml, loss of consciousness 4.3 ± 0.7 μg/ml). Figures 2 and 3 display the concentration–response curves for loss of eyelash reflex and loss of consciousness for both the individual groups and for the combined groups. The EC_{50} and EC_{90} values for the combined groups for loss of eyelash reflex were 2.07 μg/ml and 2.78 μg/ml (γ = 7.45; fig. 2). The EC_{50} and EC_{90} for loss of consciousness were 3.40 μg/ml and 4.34 μg/ml (γ = 8.97; fig. 3).

Systolic and diastolic blood pressures decreased with increasing blood propofol concentration (figs. 4 and 5). The decreases in systolic blood pressure (95% confidence

TABLE 2. Whole-blood Propofol Concentrations (nanograms per milliliter) Associated with Loss of Eyelash Reflex and Loss of Consciousness

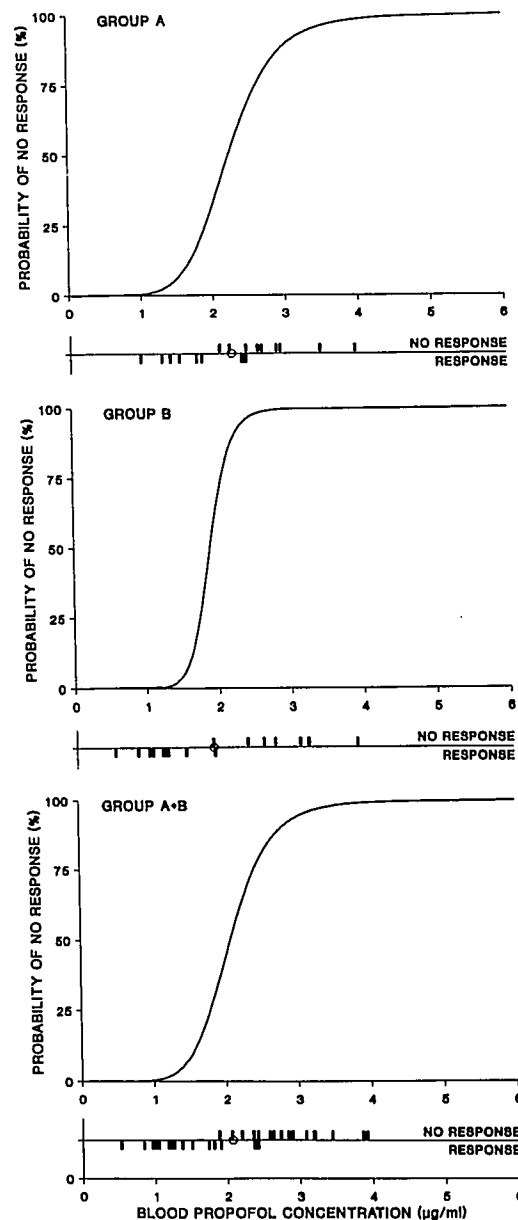| Patient	Loss of Eyelash Reflex	Loss of Consciousness
1	2,060	2,860
2	2,843	3,994
3	2,580	3,661
4	3,923	3,923
5	2,197	3,698
6	2,418	3,052
7	3,445	5,119
8	2,896	3,353
9	2,637	4,021
10	3,867	5,395
11	3,083	4,308
12	1,883	5,153
13	3,205	4,673
14	2,352	4,222
15	3,192	3,879
16	2,740	4,230
17	2,580	4,150
18	2,360	2,750

FIG. 2. The concentration–effect relationship for loss of eyelash reflex in group A, group B, and the combined groups. Beneath each curve, the response/no response data *versus* the blood propofol concentration and the EC_{50} (circle) are displayed.

interval) at the EC_{50} and EC_{90} for loss of consciousness were 30% (15–45%) and 38% (23–53%), respectively. The corresponding values for diastolic blood pressure were 28% (3–53%) and 34% (8–60%). Heart rate did not change with increasing blood propofol concentration. When asked postoperatively about the study period, the patients recalled only the first 10–15 min of the study, although the mean time they responded to verbal and tactile stimuli was 36 ± 5 min. None of the patients reported awareness during intubation.
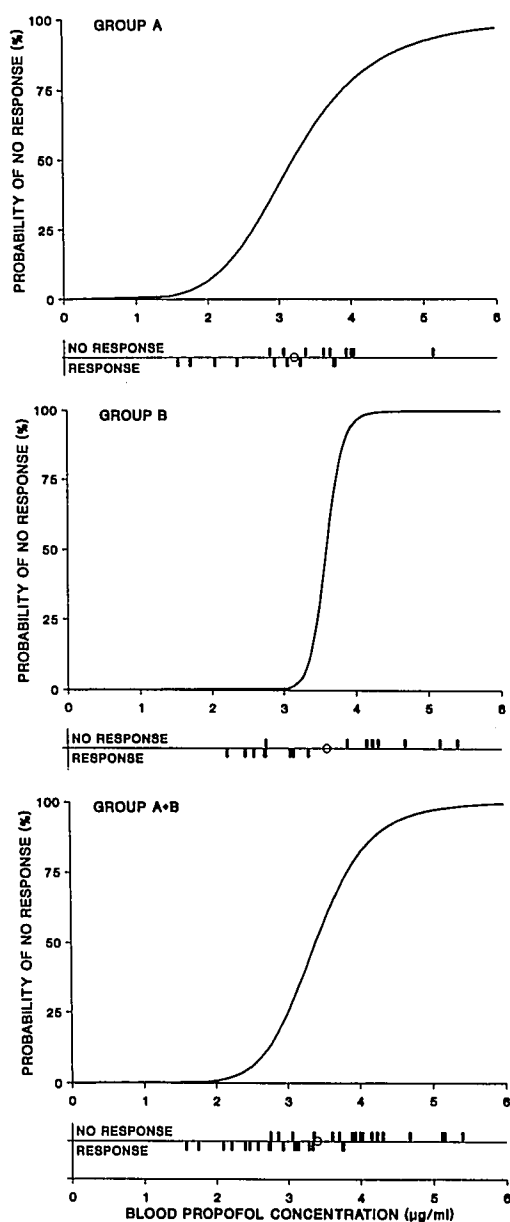
FIG. 3. The concentration–effect relationship for loss of consciousness in group A, group B, and the combined groups. Beneath each curve, the response/no response data *versus* the blood propofol concentration and the EC_{50} (circle) are displayed.

Discussion

The main objectives of this study were to determine the propofol concentration–effect relationships for loss of eyelash reflex, loss of consciousness, and hemodynamic effects. The study was performed with two different computer-controlled delivery systems, because preliminary evaluation revealed that the measured blood propofol concentrations, though stable, were approximately twice as high as those predicted on the basis of the implemented two-compartment pharmacokinetic data set. A better-performing delivery system using three-compartment pharmacokinetic data was then used, and the target concentration step size was increased from 0.5 to 1 $\mu g/ml$ to provide comparable target concentration step sizes in both groups. The data analysis proved that the effect of the difference in bias between the two infusion systems was nullified by the inverse difference in target step size, resulting in similar infusion schemes for the two groups.

The data of the two groups were pooled, both because the infusion schemes in the two groups were similar and because the concentrations that caused loss of eyelash reflex and loss of consciousness in the individual patients of group A and group B were similar. We therefore performed a regression analysis on the combined response/ no-response data *versus* the measured blood propofol concentrations.

The propofol infusion scheme was designed to allow blood–brain equilibration at each target propofol concentration (12 min is approximately four times the estimated $T^{1}/_{2Keo}$ of propofol** [where the halftime reflects the equilibration between the blood propofol concentration and the concentration in the effect compartment]). The stable blood propofol concentration at each step enabled us to study the pharmacodynamic effects of distinct blood propofol concentrations while equilibrating with the effect compartment. Nevertheless, the values of the EC_{50} and EC_{90} may be slightly overestimated as a result of two factors. First, to characterize the propofol concentration–response relationship most accurately, the ideal step size should be infinitely small, whereas in our study, for practical and ethical reasons, it was set at approximately 1 $\mu g/ml$. Second, some of the patients studied lost eyelash reflex or consciousness before the target propofol concentration was maintained for the preset 12 min. The $T^{1}/_{2Keo}$ for propofol in these patients may have been smaller than the mean 2.9 min, so that the blood equilibrated faster with the effect site. Another explanation may be that these patients lost eyelash reflex and consciousness before blood–brain equilibration had occurred, in which case the measured blood concentration still exceeded the effect site concentration, thereby contributing to the previously described overestimation.

To quantify the magnitude of the overestimation, we determined the EC_{50} and EC_{90} for loss of eyelash reflex and loss of consciousness based on calculated effect compartment concentrations. This approach assumes that the pharmacodynamic effect of a drug is closely related to the concentration in a theoretical effect compartment. The effect compartment concentration and thereby the pharmacodynamic effect lags behind the blood concen-

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** Schüttler J, Schwilden H, Stoeckel H: Pharmacokinetic-dynamic modeling of diprivan (abstract). ANESTHESIOLOGY 65:A549, 1986.
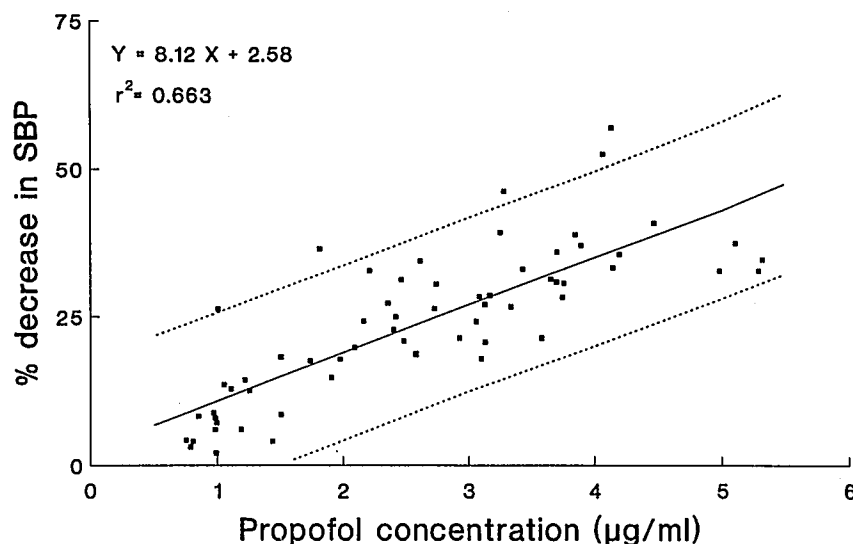
FIG. 4. The relationship between the decrease in systolic blood pressure (SBP) and whole-blood propofol concentration (solid line), with the corresponding 95% prediction intervals (dashed line).

tration.[10] Effect compartment concentrations can be calculated from the measured blood propofol concentrations using Euler's approximation technique. By this approach, the effect compartment concentrations are calculated in a stepwise manner. The accuracy of this method increases as the time step (δt) becomes small compared to the $T^{1}/_{2Keo}$ of propofol. The time step was set at 1 min, because simulation of a steady blood propofol concentration of 1 $\mu g/ml$ for 12 min revealed that using this time step resulted in an approximation error of only 5 ± 2%. Because the propofol concentrations were measured only at 3-min intervals, blood concentrations in subsequent minutes between measured blood concentrations were estimated by linear interpolation, and by extrapolation for the first 2 min after a change in target concentration. The effect

compartment concentration at each minute was then calculated by the equation:

$$Ceff_t = Ceff_{(t-1)} + \delta t \cdot k_{eo} \cdot (Cb_t - Ceff_{(t-1)})$$

where Ceff and Cb are the effect compartment and blood propofol concentrations, respectively; k_{eo} is the rate constant for drug loss from the effect site; and $\delta t = 1$ min. A sigmoid E_{max} model was then fitted to response/no-response data *versus* the corresponding calculated effect compartment propofol concentrations by unweighted least-squares nonlinear regression. The EC_{50} and EC_{90} based on effect compartment concentrations for loss of eyelash reflex were 1.85 and 2.69 $\mu g/ml$ (compared to 2.07 and 2.78 $\mu g/ml$ based on measured blood concentrations). The corresponding values for loss of conscious-
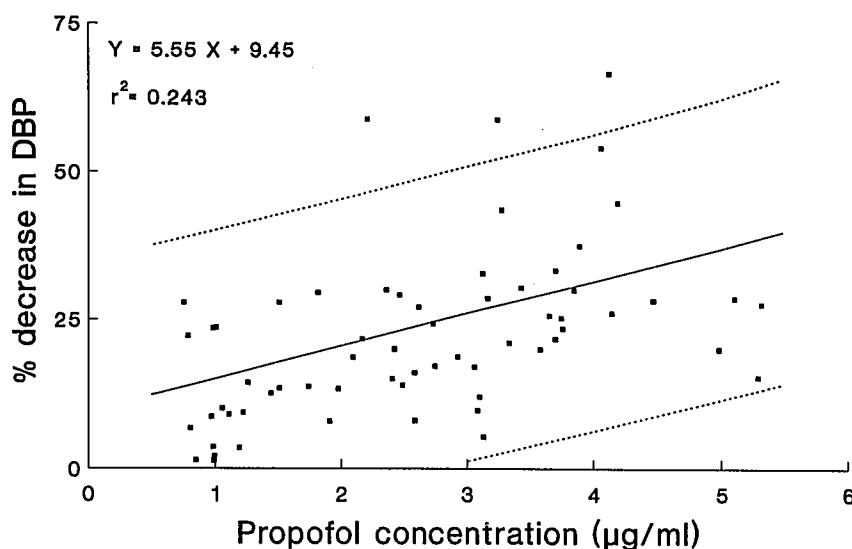

FIG. 5. The relationship between the decrease in diastolic blood pressure (DBP) and whole-blood propofol concentration (solid line), with the corresponding 95% prediction intervals (dashed line).

ness were 3.34 and 4.17 μg/ml (compared to 3.40 and 4.34 μg/ml based on measured blood concentrations). Consequently, we conclude that the overestimation is small.

The concentration–response relationship for loss of consciousness found in our study is comparable to that described by Hazeaux et al.[11] for propofol-induced changes in the EEG. They describe that the awake-type EEG changed (desynchronized, and the amplitude of the α rhythm increased) at blood propofol concentrations between 3.16 and 3.74 μg/ml, and that loss of consciousness was induced at concentrations of about 6 μg/ml.

In daily practice, anesthesiologists test the eyelash reflex as a parameter of the induction of anesthesia. Etomidate,[12] and possibly other intravenous induction agents, cause loss of consciousness at lower concentrations than those causing loss of eyelash reflex. In contrast, we found for propofol that loss of eyelash reflex occurred at concentrations less than those needed to produce loss of consciousness. This discrepancy may be related to differences in study design, in particular in the rate of drug administration. Our study design made it possible to observe the pharmacodynamic effects of propofol at different target concentrations while equilibrating with the effect compartment, whereas studies using rapid infusions or bolus administrations of intravenous agents do not allow effect compartment equilibration. This might have resulted in a finer differentiation of specific pharmacodynamic endpoints. Another explanation may be that the order of the pharmacodynamic effects for propofol differs from that of other hypnotic agents.

The hemodynamic effects of propofol in our study are similar to those described previously.[13–16] The decrease in systolic and diastolic blood pressure is concentration-dependent, and occurs in part already at concentrations that do not cause noticeable sedative or hypnotic effects. Despite an average time between starting the propofol infusion and loss of consciousness of 36 min, a substantial decrease in systolic blood pressure still occurred. This suggests that the magnitude of the hemodynamic effect is not closely related to the rate of administration. At concentrations that cause sedation, the decrease in systolic blood pressure is approximately 10–20%. Although systolic and diastolic blood pressure decreased considerably, heart rate did not change in our study. This may be due to a resetting of the baroreceptor reflex set point by propofol.[17]

In conclusion, we defined the propofol concentration–response relationships for two clinically relevant pharmacodynamic endpoints. Surprisingly, loss of eyelash reflex was induced at lower concentrations than those causing loss of consciousness. Loss of eyelash reflex may be a poor parameter for determining loss of consciousness

during induction of anesthesia with propofol. Significant hemodynamic changes also occurred before hypnotic effects were noticed.

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