Pharmacokinetics and Pharmacodynamics of Propofol Infusions during General Anesthesia

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The pharmacokinetic and pharmacodynamic properties of propofol were studied in 50 surgical patients. Propofol was administered as a bolus dose, 2 mg/kg iv, followed by a variable-rate infusion, 0–20 mg/min, and intermittent supplemental boluses, 10–20 mg iv, as part of a general anesthetic technique that included nitrous oxide, meperidine, and muscle relaxants. For a majority of the patients (n = 30), the pharmacokinetics of propofol were best described by a two-compartment model. The propofol mean total body clearance rate was 2.09 ± 0.65 l/min (mean ± SD), the volume of distribution at steady state was 159 ± 57 l, and the elimination half-life was 116 ± 34 min. Elderly patients (patients older than 60 yr vs. those younger than 60 yr) had significantly decreased clearance rates (1.58 ± 0.42 vs. 2.19 ± 0.64 l/min), whereas women (vs. men) had greater clearance rates (33 ± 8 vs. 26 ± 7 l·kg^{-1}·min^{-1}) and volumes of distribution (2.50 ± 0.81 vs. 2.05 ± 0.65 l/kg). Patients undergoing major (intraabdominal) surgery had longer elimination half-life values (136 ± 40 vs. 108 ± 29 min). Patients required an average blood propofol concentration of 4.05 ± 1.01 µg/ml for major surgery and 2.97 ± 1.07 µg/ml for nonmajor surgery. Blood propofol concentrations at which 50% of patients (EC$_{50}$) were awake and oriented after surgery were 1.07 and 0.95 µg/ml, respectively. Psychomotor performance returned to baseline at blood propofol concentrations of 0.38–0.43 µg/ml (EC$_{50}$). This clinical study demonstrates the feasibility of performing pharmacokinetic and pharmacodynamic analyses when complex infusion and bolus regimens are used for administering iv anesthetics. (Key words: Anesthesia: general. Anesthetic techniques: continuous infusion. Anesthetics, intravenous: propofol. Pharmacokinetics: continuous infusion; propofol. Pharmacodynamics: propofol.)

PROPOFOL, 2,6-diisopropylphenol, is an iv anesthetic that has been used for both induction and maintenance of general anesthesia.[1] The initial pharmacokinetic studies of propofol were performed in its original Cremophor EL formulation.[2] Reformulation of the drug in an egg–oil–glycerol emulsion has eliminated hypersensitivity reactions that occurred with the original formulation.[3] Preliminary pharmacokinetic evaluation of propofol in its current formulation has revealed a high clearance rate and relatively short elimination half-life

after bolus injections[4] or brief infusions.[5] However, some analyses have indicated a potential for accumulation of this lipophilic drug in a poorly perfused (deep) compartment,[6] which would significantly prolong its terminal elimination half-life. Prior studies involving small groups of patients have evaluated the influence of patient characteristics on propofol's pharmacokinetics.[7-9]§ None of these reports, however, have included a large enough sample size to evaluate more than one characteristic at a time.

An important advantage of using propofol for general anesthesia is rapid emergence[1]; hence the pharmacodynamics of recovery are of particular interest. Although some data are available on propofol blood concentrations at awakening after bolus doses of the original formulation,[2,10,11] only limited information is available concerning the current formulation.[12] Induction doses of propofol in the emulsion are 20–30% higher than in the original formulation,[13] secondary to an alteration in its potency.[3] Such alterations in bioavailability have been demonstrated with the newer emulsion formulations of iv diazepam.[14] It is therefore necessary to evaluate the pharmacodynamics of propofol in its currently used vehicle.

Administration of propofol by variable-rate infusion allows the anesthesiologist to titrate the propofol dose to the desired clinical effect.[1] This technique may become an important mode of administration for propofol and other iv anesthetics in clinical practice. Therefore, we analyzed the pharmacokinetics of propofol administered by variable-rate infusions to a surgical population and identified patient factors that influenced pharmacokinetic variables. In addition, we evaluated propofol's pharmacodynamic properties during and after general anesthesia.

Methods

Fifty consenting adult ASA P.S. I–III patients scheduled for elective operations were studied. The protocol was approved by the local Institutional Review Board. Demographic data included age, sex, weight, type of procedure, and baseline liver function tests (table 1). Ideal body weight (IBW) was defined using standard

TABLE 1. Demographic Data for Study Patients Undergoing Major or Nonmajor Surgical Procedures

	All Patients	Major Procedures	Nonmajor Procedures
Age (yr)*	43 ± 14	48 ± 14	41 ± 14
Sex (M/F)	22/28	4/11	18/17
Weight (kg)*	71 ± 17	69 ± 18	72 ± 16
Nonobese/obese (n)†	31/19	10/5	21/14
Type of srugery (n)		Intraabdominal (13)	Urologic (26)
		Orthopedic (1)	Laparoscopic (4)
		Other (1)	Other (5)
Liver function tests (N/Ab)‡	34/12	9/6	25/6
Duration of propofol administration* (min)	99 ± 63	175 ± 51	67 ± 32
Total dose of propofol (mg)*	915 ± 578	1605 ± 511	619 ± 272

* Data are expressed as mean values ± SD

† Obese = greater than 130% ideal body weight.

‡ No baseline liver function tests were obtained on four patients; data are expressed as number of patients with normal (N) or abnormal (Ab) values.

criteria,[15] with weight greater than 130% of IBW considered obese. Elderly patients were defined as those over 60-yr of age, as in a previous study on the effects of age on propofol pharmacodynamics.[16] Types of surgery were grouped as major (e.g., intraabdominal) or nonmajor (e.g., urologic, laparoscopic) (table 1).

General anesthesia was induced with meperidine, 1 mg/kg iv, and propofol, 2 mg/kg iv. Tracheal intubation was performed after administration of d-tubocurarine, 3 mg iv, and succinylcholine, 1.5 mg/kg iv. Anesthesia was maintained with a variable-rate propofol infusion, 0–20 mg/min (using an Autosyringe® pump), and nitrous oxide, 70% in oxygen. The propofol infusion was initiated at a rate of 10 mg/min and varied according to the presence or absence of autonomic responsiveness (e.g., diaphoresis, lacrimation, heart rate, or blood pressure changes ≥ 20% of preoperative baseline values). Small bolus doses of propofol, 10–20 mg iv, were administered for rapid control of patient responses (e.g., gross movement or hemodynamic changes exceeding 30% of baseline values) followed by an increase in the maintenance infusion rate. Supplemental meperidine, 10–20 mg iv bolus doses, was administered for persistent hypertension or tachycardia (mean arterial pressure (MAP) or heart rate (HR) changes exceeding 20% of baseline values), which was unresponsive to bolus doses of propofol and increases in the propofol infusion rate. End-tidal carbon dioxide tension was maintained between 30 and 40 mmHg during the operation using mechanical ventilation; MAP and HR were recorded at 2- to 5-min intervals using a Dinamap® monitor. Pancuronium, 1–3 mg bolus doses iv, was given as required by the surgical conditions. At least 1–2 twitch responses were always present as measured by a peripheral neuromuscular function monitor. At the end of the procedure neostigmine, 3–5 mg iv, and glycopyrrolate, 0.6–1.0 mg iv, were given (if needed) and the propofol infusion and nitrous oxide were dis-

continued. The times from termination of the propofol infusion until awakening (eyes open) and orientation to place were evaluated every 30 s and noted.

Patients were given psychometric tests to complete before the operation (baseline) and again after termination of anesthesia. Testing was done at 30-min intervals for 150 min and consisted of a Trieger test[17] (connecting a series of dots, scored as number of dots missed), a p-deletion test[18] (crossing out the letter "p" in a series of letters, scored as number of letters correctly deleted), and visual analog scales for sedation[19] (a series of five 100 mm scales, scored as the sum of the five scales). The times at which patients returned to their baseline scores were noted.

Peripheral venous blood samples were obtained from the arm contralateral to the drug infusion during and up to 10 hours following propofol administration. At 10–30 min intervals during the propofol infusion blood samples were obtained. Clinical signs of anesthetic depth, i.e., the presence (designated as inadequate anesthesia) or absence (adequate anesthesia) of autonomic responsiveness were noted at the time of blood sampling. Blood samples were kept on ice and stored at 5° C until extraction and assay (samples were stable for 18 weeks under these conditions).¶ Whole blood propofol levels were determined using high performance liquid chromatography with fluorescence detection.[20] The lower limit of detection was 0.05 μg/ml, the variability was ±7%, and the absolute recovery was 78%. Two- and three-compartment pharmacokinetic analyses were performed with Mkmodel,** an extended least squares nonlinear regression program. An iterative approach based on equations derived by Maitre et al.[21] was used to

¶ McDonald D: ICI 35-868 (Diprivan®, propofol) in whole blood by HPLC, Stuart Pharmaceuticals, Wilmington, Delaware, 1986.

** Holford N: Mkmodel Manual, version 3.13. New York, Elsevier, 1986.

estimate the disposition function based on multiple infusions and boluses.

Two-compartment modeling was done by estimating the volume of the central compartment (Vc), the distribution rate constant (α), the elimination rate constant (β), and the microconstant k_{21} for transfer from the peripheral to the central compartment. Three-compartment analysis estimated Vc, the three rate constants α, γ, and β (rapid and slow distribution and elimination, respectively), and the microconstants k_{21} and k_{31}. Standard formulae were used to calculate mean total body clearance, distribution and elimination half-lives, volume of distribution at steady state (Vd$_{ss}$), and the remaining intercompartmental microconstants.[22] The Schwartz criterion was used to compare the two models.[††]

Precision (average absolute error) and bias (average error) were calculated for each individual data set using the following equations:

$$precision = \frac{\sum_{j=1}^{n} \dfrac{|\hat{y}_j - y_j|}{y_j}}{n}$$

$$bias = \frac{\sum_{j=1}^{n} \dfrac{\hat{y}_j - y_j}{y_j}}{n}$$

where n = number of measured propofol levels for each patient, y = measured blood propofol concentration, and $\hat{y}$ = predicted blood propofol concentration. In order to evaluate the predictive value of the models when applied to an individual patient, the mean and median pharmacokinetic parameters of the population were used to simulate blood propofol levels for each patient, given the infusion and bolus regimen for that individual. The differences between the measured blood propofol levels and those estimated using mean or median values for pharmacokinetic parameters were then used to recalculate precision and bias.

Average intraoperative (from skin incision to start of wound closure) measured blood propofol concentrations at times of adequate or inadequate anesthesia were calculated for individual patients. In addition, the blood propofol level at the time the patient achieved a given stage of recovery after the operation (*i.e.*, awake, oriented, and after return to baseline psychometric scores) was estimated by interpolation. The cumulative percent of patients who achieved these stages at various blood propofol levels was then calculated. Data points consisted of the percent of patients who had achieved a

given stage of recovery at a particular blood propofol concentration. These pharmacodynamic data were analyzed with sigmoid function modeling using the Hill equation. The estimated concentration at which 50% of patients achieved a given stage of recovery (EC$_{50}$) was one of the estimated parameters; EC$_{95}$ was interpolated from the results.

Statistical analysis (Systat®[‡‡]) included multifactor ANOVA for principal effects, simple and multiple linear regression, *t* test, and Mann-Whitney rank-sum test. A value of $P < 0.05$ was considered significant. Values are expressed as mean ± SD except where noted in figure 3.

Results

Demographic data for the entire patient population, as well as the major and nonmajor subgroups, are summarized in table 1. Nineteen patients fit the criteria for obesity (151 ± 18% IBW for the obese group compared with 114 ± 9% IBW for the nonobese group). In addition, 12 patients had mildly abnormal liver function test results (*e.g.*, serum transaminase values up to two times normal), although no patient had clinical evidence of hepatic dysfunction. The propofol infusion rate was changed an average of 5 ± 3 times during surgery (range 1–14), and 2 ± 2 supplemental boluses (range 0–8) were administered.

Patients who underwent major procedures received more propofol for a longer period of time than patients in the nonmajor surgery group (table 1). The major surgery group included 13 of the 14 patients who had a prolonged duration of propofol administration (>120 min) and 13 of the 17 patients who received a high total dose of propofol (≥1,000 mg). Because of this overlap between dose, duration of administration, and type of surgery, it was not possible statistically to separate these variables when determining the influence of patient characteristics on propofol pharmacokinetics or pharmacodynamics. Among these three variables, only type of surgery is reported below. However, when patients were regrouped according to dose or duration of administration and separate analyses performed, similar results were obtained.

All patients' blood propofol levels could be described by a two-compartment model (table 2). The results of one patient who had inexplicably low intraoperative blood propofol levels (0.30–0.88 μg/ml), and hence an unusually large Vd$_{ss}$ (1,149 l) and high clearance rate (5.42 l/min), were not included in the summary data.

†† Schwartz G: Estimating the dimension of a model. Ann Stat 6:461–464, 1978.

‡‡ Wilkinson L: Systat: The System for Statistics. Evanston, Illinois, Systat, Inc., 1986.

TABLE 2. Comparison of Two- and Three-compartment Kinetic Models for Propofol Pharmacokinetic Analysis

Parameter	All Patients Two-compartment	Preferred Kinetic Model*	
		Two-compartment	Three-compartment
n	49	29	20
Clearance (l·min)	2.09 ± 0.65	2.08 ± 0.70	1.96 ± 0.57
Clearance (ml·kg^{-1}·min^{-1})	30 ± 8	29 ± 8	28 ± 8
Vc (l)	24 ± 8	24 ± 10	8 ± 5
Vc (l/kg)	0.35 ± 0.16	0.36 ± 0.19	0.12 ± 0.07
Vd$_{ss}$ (l)	159 ± 57	164 ± 64	224 ± 129
Vd$_{ss}$ (l/kg)	2.3 ± 0.8	2.3 ± 0.8	3.4 ± 2.2
t$\frac{1}{2}$ α (min)	4.6 ± 1.6	4.7 ± 1.9	1.3 ± 0.8
t$\frac{1}{2}$ γ (min)	—	—	30 ± 16
t$\frac{1}{2}$ β (min)	116 ± 34	119 ± 40	232 ± 165

Data are expressed as mean values ± SD.

Vc = volume, central compartment; Vd$_{ss}$ = volume of distribution, steady state; t$\frac{1}{2}$α = distribution half-life; t$\frac{1}{2}$γ = redistribution half-life;

t$\frac{1}{2}$ β = elimination half-life.

* Model preference as per Schwartz criterion.

Thirty-four patients' blood propofol levels could also be fit with a three-compartment model. Of these, 20 patients had data which were better described by the three-compartment model, using the Schwartz criterion for model comparison. Kinetic data for these patients are summarized in table 2. Model selection was independent of patient age, sex, weight, liver function test results, or type of surgery. The precision and bias values of the two-compartment fits were not significantly different between those data sets better fit by a two- versus a three-compartment model. Examples of individual two- and three-compartment fits are shown in figures 1 and 2. These samples were chosen because the precision and bias of the estimated blood propofol levels were approximately the mean for all individual fits (table 3). According to precision and bias calculations, use of the mean rather than the median population parameters yielded a better predictor for each individual fit. Furthermore, use of the mean parameters in the three-compartment model did not improve the prediction when compared with use of the mean two-compartment model parameters (table 3). Sampling duration was found to be unrelated to the t½β values ($r^2 = 0.10$, slope = 0.05).

Mean total body clearance was positively correlated with weight (linear regression, $P < 0.01$) and was significantly greater in obese than nonobese patients (2.48 ± 0.74 vs. 1.84 ± 0.45 l/min, $P < 0.01$). Weight-corrected clearance, however, was the same for these two groups (28 ± 7 vs. 31 ± 9 ml·kg^{-1}·min^{-1}). Elderly patients (>60 years, n = 8) had a significantly lower propofol clearance than patients under 60 years (1.58 ± 0.42 vs. 2.19 ± 0.64 l/min, $P < 0.01$), even when clearance was corrected for weight (25 ± 4 vs. 31 ± 8 l·kg^{-1}·min^{-1}, $P < 0.05$). Age was negatively correlated with weight-corrected clearance (linear regression, $P < 0.05$). Female patients had a proportionately higher weight-corrected clearance (33 ± 8 vs. 26 ± 7 l·kg^{-1}·min^{-1}, $P < 0.01$) and larger Vd$_{ss}$ (2.50 ± 0.81 vs. 2.05 ± 0.65 l/kg, $P < 0.05$) than males. Hence, elimination half-life values were not different for males and females. In addition, female patients had a larger Vc than male patients (0.39 ± 0.19 vs. 0.29 ± 0.09 l/kg, $P < 0.05$).

All pharmacokinetic parameters were independent of liver function test results. In particular, clearance rates were independent of factors that could potentially interfere with hepatic blood flow or metabolic rate, such as abnormal liver function or upper abdominal surgery. However, patients undergoing major operations had longer elimination half-life values (136 ± 40 vs. 108
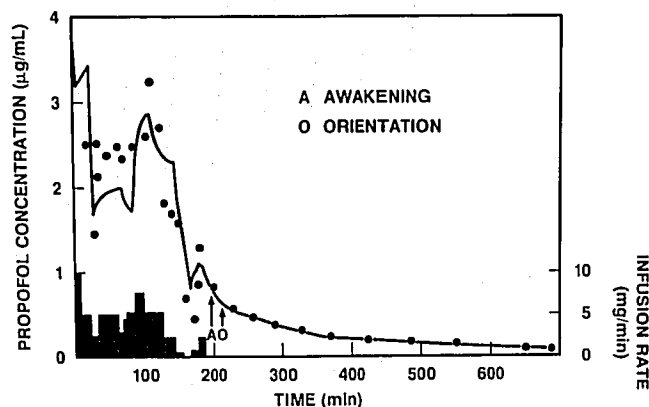

FIG. 1. Representative two-compartment pharmacokinetic analysis with propofol infusion rate and resultant measured and predicted blood propofol levels as a function of time. Type of surgery: intraabdominal. Initial propofol bolus dose = 110 mg iv. Maintenance propofol dose = 670 mg. Duration of propofol administration = 185 min. Clearance rate = 1.70 l/min. Volume of distribution at steady state = 170 l. Elimination half-life = 143 min. Symbols: (●) measured propofol concentration; (——) predicted propofol concentration, μg/ml. Precision = 17%. Bias = 5%.
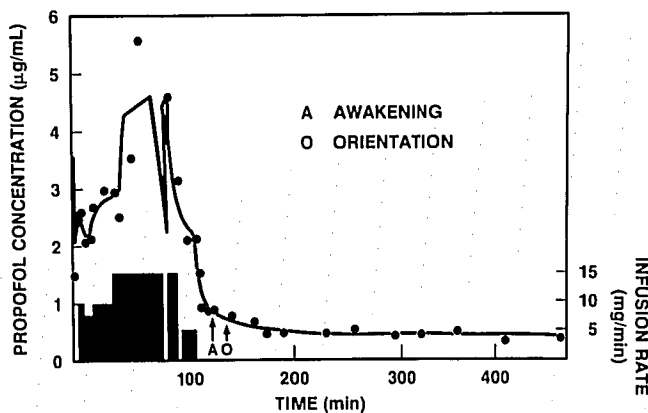
FIG. 2. Representative three-compartment pharmacokinetic analysis with propofol infusion rate and resultant measured and predicted blood propofol levels as a function of time. Type of surgery: intraabdominal. Initial propofol bolus dose = 110 mg iv. Maintenance propofol dose = 1,150 mg. Duration of propofol administration = 109 min. Clearance rate = 2.27 l/min. Volume of distribution at steady state = 321 l. Elimination half-life = 279 min. Symbols: (●) measured propofol concentration; (——) predicted propofol concentration, μg/ml. Precision = 15%. Bias = 6%.

FIG. 3. Blood propofol concentration (μg/ml) in relation to type of surgical procedure at times of absence of autonomic response (adequate) or presence of autonomic response (inadequate) to surgical stimulation. Individual and mean ± SEM values are shown. Encircled dots represent values for patients who received supplemental meperidine during the operation. *Significant differences between groups (major *vs.* nonmajor surgery), $P < 0.05$.

± 29 min, $P < 0.05$) than those patients in the nonmajor surgical group. This difference was a result of a larger Vd_{ss} (2.75 ± 0.99 *vs.* 2.12 ± 0.59 l/kg^{-1}, $P < 0.05$) in patients undergoing major (*vs.* nonmajor) procedures.

The blood propofol concentration at the time of incision averaged 3.17 ± 1.23 μg/ml (n = 46). Only seven patients were categorized as being inadequately anesthetized at the time of incision (movement and/or autonomic response), and their blood propofol levels were similar to those of patients who had no response to incision. Twenty-five patients had blood sampling for pro-
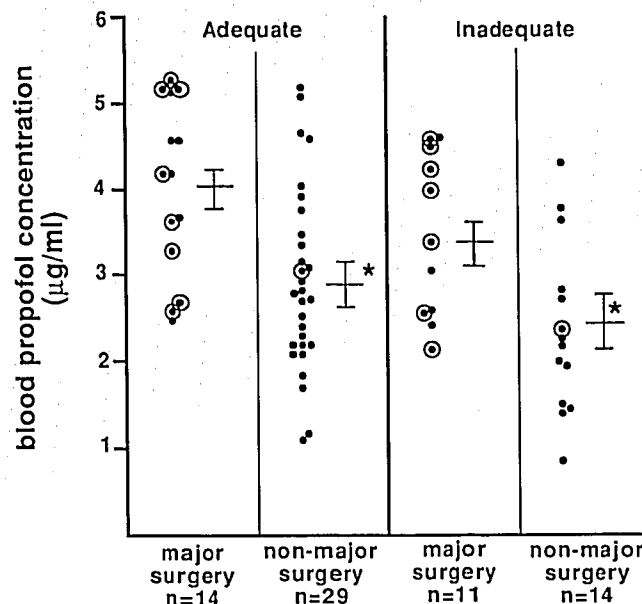
TABLE 3. Precision and Bias Data for Two- and Three-compartment Pharmacokinetic Models

	Precision	Bias
Two-compartment (n = 49)		
Individual*	18 ± 9	6 ± 6
Mean†	37 ± 29	2 ± 43
Median‡	43 ± 40	21 ± 51
Three-compartment (n = 34)§		
Individual*	13 ± 5	3 ± 3
Mean†	36 ± 31	4 ± 45
Median‡	50 ± 49	35 ± 58

Data are expressed as mean values ± SD; precision = average absolute error; bias = average error.

* Data obtained when patients' blood propofol concentration profiles were fit with each individual's pharmacokinetic parameters.

† Data obtained when all patients' blood propofol concentration profiles were fit with the mean of individual parameters.

‡ Data obtained as in (†), except the median values of the individual parameters were used.

§ Only those data sets in which a three-compartment fit was feasible are included.

pofol levels during signs of responsiveness to postincisional surgical stimulation. In spite of the fact that 53% of the patients in the major group received supplemental meperidine (15–150 mg iv, in incremental doses), higher blood propofol concentrations were required during the more stressful operations to assure autonomic nonresponsiveness compared to the drug levels required during nonmajor surgery (4.01 ± 1.01 *vs.* 2.97 ± 1.07 μg/ml, $P < 0.01$) (fig. 3). Blood propofol levels at which responses to surgical stimulation occurred were correspondingly higher in major (*vs.* nonmajor) surgical patients (3.46 ± 0.95 *vs.* 2.39 ± 0.99 μg/ml, $P < 0.05$). Nonetheless, a considerable overlap of values was present between all groups. The intraoperative blood propofol levels of the patients who received supplemental doses of meperidine did not differ significantly from the other patients having similar operations (fig. 3), nor was there a correlation between meperidine dose and intraoperative propofol blood level.

Predicted blood propofol concentrations at which 50% (EC_{50}) of patients awoke and were oriented following surgery were 1.07 ± 0.13 and 0.95 ± 0.19 μg/ml, respectively. The corresponding EC_{95} values (interpolated) were 0.52 and 0.46 μg/ml (fig. 4). These values were independent of patient age, sex, weight, liver function test results, or type of surgery. Patients who had major surgery had a longer time to awakening (18

± 15 vs. 9 ± 4 min, $P < 0.05$) and orientation (31 ± 23 vs. 11 ± 5 min, $P < 0.01$) than patients in the nonmajor surgical group. These emergence times, however, were independent of age, sex, weight, and liver function test results.

Psychometric testing was analyzed in 24 patients who returned to their preoperative baseline test scores and who received no additional intraoperative or postoperative narcotic medication. These patients were all in the nonmajor surgical group. The majority of patients (82–84%) returned to baseline Trieger and p-deletion scores within 60 minutes after surgery, whereas only 50% of patients returned to baseline on their sedation scale scores within 60 min. However, the EC_{50} values and range of blood propofol concentrations when patients returned to baseline scores were similar (EC_{50} = 0.38, 0.43, and 0.42 for sedation, p-deletion, and Trieger tests, respectively) (fig. 5).

Discussion

A continuous, variable-rate infusion can improve the anesthesiologist's ability to titrate an iv drug to the desired effect. As demonstrated with alfentanil,[23] adequate blood concentrations of a drug are dependent upon the type and severity of the surgical stimulus. Therefore, a variable-rate infusion, in which the rate is altered according to the current or anticipated stimulus, is more useful clinically than a constant-rate infusion. Although there may be a rapid termination of effect after a bolus dose of propofol due to redistribution of the drug, an initial bolus dose and subsequent supplemental boluses can be used to rapidly increase blood drug concentrations when needed.
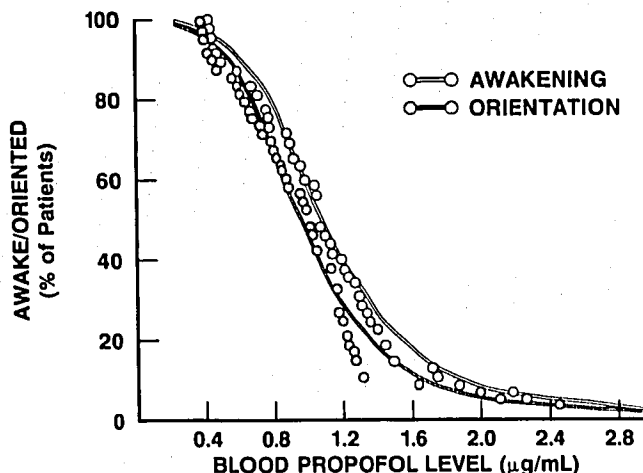

FIG. 4. Concentration–response curves for awakening and orientation as a function of blood propofol level (μg/ml). The cumulative percent of patients who awoke (O) or were oriented (◎) at various blood propofol levels are shown.

Our study evaluated the pharmacokinetics of propofol when administered in a clinically relevant manner, i.e., an induction bolus dose followed by a variable-rate infusion and supplemental boluses. No previous pharmacokinetic study of propofol has evaluated the drug using this type of administration regimen. Differences in results between studies may reflect methodologic differences. For example, Gepts et al.[24] report a longer elimination half-life (355 min with a three-compartment kinetic model) after constant-rate infusions. Furthermore, sampling site[5,25] and concomitant medications[4,6,26] are among the many factors that can affect

FIG. 5. Concentration–response curves for the return to baseline (preoperative) test scores as a function of blood propofol level (μg/ml). Each graph depicts the cumulative percent of patients who returned to baseline function for the Trieger test, p-deletion test, and sedation analog scales.
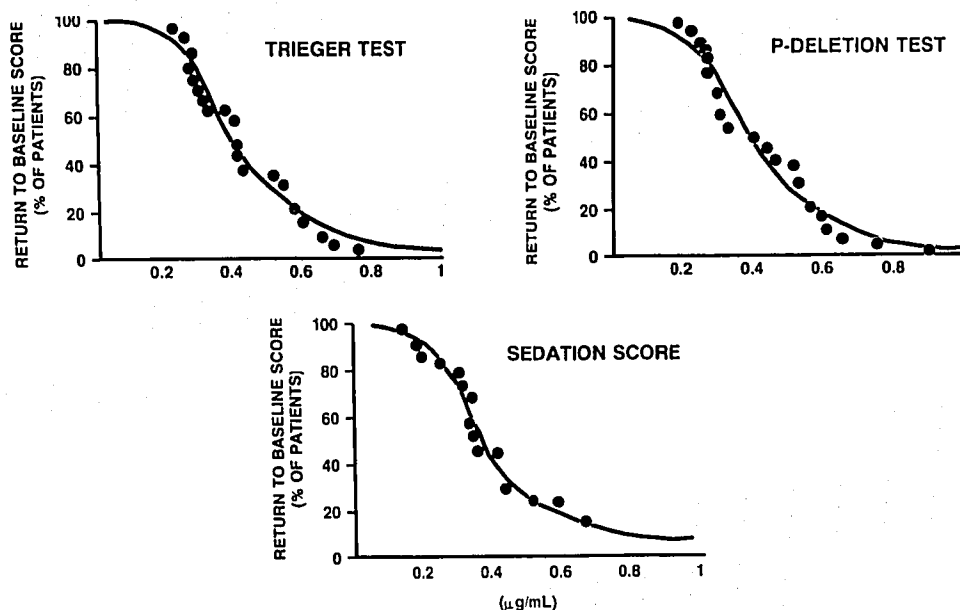
blood propofol levels and hence pharmacokinetic analysis.

Alterations in physiologic factors, such as hepatic blood flow, during intraabdominal procedures may lead to nonstationary pharmacokinetics,[27] and thus significant differences between measured and predicted blood propofol levels may be noted during surgery (fig. 1). In addition, peripheral venous blood propofol levels may not accurately reflect the acute changes in propofol levels that may be occurring in the brain. Nonetheless, the sampling site was consistent within our study, and all of the studies were conducted on patients under general anesthesia. Because the administration of the currently available emulsion formula yields lower blood propofol levels than the former cremophor formulation,[6] only pharmacokinetic studies in which the current emulsion was used will be discussed. In these studies patient age appears to be more influential in altering the pharmacokinetic profile than gender, hepatic, or renal function.[7-9]§ In our study the overlap between patients undergoing major surgery, those who received higher drug doses, and those undergoing longer operations precluded independent evaluation of these variables. The differences noted between the two surgical classifications may be related to dose, duration, and/or other factors associated with major *vs.* nonmajor surgery.

A preliminary study reported reduced propofol clearance rates in patients 65–80 yr of age.§ Our study included eight patients older than 60 years of age and also found a reduced mean total body clearance rate in these patients. Whether this effect is due to hepatic or extrahepatic mechanisms is unknown. Propofol clearance values should be weight-corrected when obese and nonobese patients are compared. Weight-correction eliminated the statistically significant greater clearance rates calculated for obese patients. No previous data exist on the effects of obesity on propofol pharmacokinetics.

The higher weight-corrected value for propofol Vd_{ss} in women may be due to the higher percentage of body fat in women.[28] The greater propofol Vd_{ss} and clearance values in women are similar to findings reported in midazolam pharmacokinetic analyses.[29] Analogous to propofol, midazolam's elimination half-life is independent of gender, as women tended to have both a higher rate of clearance and a larger volume of distribution.

Despite propofol's high clearance rate and extensive hepatic metabolism,[30] previous investigators have found no statistically significant impairment of propofol elimination in patients with cirrhosis.[8] Our study similarly demonstrated no effect of mild liver function abnormalities on propofol pharmacokinetics. In addition, patients in our study who may have had alterations in liver blood flow secondary to intraabdominal surgery did not exhibit a significant decrease in their overall systemic clearance rates. Although extrahepatic metabolism of propofol has been suggested, a preliminary study indicated that propofol's clearance rate was not significantly affected by renal failure.[9] The lung has also been proposed as a potential site of propofol metabolism.[6] The higher blood propofol levels determined from central venous as compared to peripheral arterial sampling may be due to pulmonary uptake or biotransformation as well as incomplete mixing venous.[25] A population study of pooled blood level data may be useful in more precisely defining patient characteristics that affect propofol pharmacokinetics.[31] This type of analysis may also define specific interactions within subgroups such as a comparison between obese elderly male and female patients.

We chose to present the results of both the two- and three-compartment pharmacokinetic analyses. The necessity of an additional compartment to describe the pharmacokinetics of a subset of patients has been described previously for methohexital.[32] The characterization of the elimination phase in some patients may have been affected by the lower limit of detection of our propofol assay. However, a preliminary study of six volunteers given radiolabeled propofol, in which propofol could be measured 48 h after a single bolus dose of 0.47 mg/kg, still favored a two-compartment model.[30] Nonetheless, both two-[4,5] and three-compartment[6,24] models have been described for propofol. Clearly the potential exists for accumulation of this highly lipophilic drug in fat stores (*i.e.*, a large poorly perfused third compartment). The clinical relevance of this "deep" compartment has yet to be determined. However, use of a prolonged constant-rate infusion technique might result in excessive accumulation of this lipophilic anesthetic. Indeed, one of our patients had a very large Vd_{ss}, but whether this was due to aberrancy in the assay technique or in the patient's physiology could not be determined. Interestingly, large volumes of distribution (400–1,000 l) have been previously reported.[6]

In our study use of the mean three-compartment variables did not improve the prediction of individual fits when compared to use of the mean two-compartment parameters, as determined by precision and bias calculations. In other words, blood propofol levels were estimated as accurately with mean two-compartment parameters as with mean three-compartment parameters. Use of noncompartmental analysis may remove some problems with the apparent nonstationary pharmacokinetics found in our study (fig. 1). Nevertheless, the clearance and half-life values determined in this study were similar to those previously reported following a bolus dose and analyzed by two- or three-compartment modeling.[4,6] The average volumes (central compartment and distribution at steady state) tended to be

smaller than those reported in single bolus dose studies. The values were, however, similar to those calculated after short-term infusions.[5]

Pharmacodynamic evaluation of response to surgical incision has shown EC_{50} and EC_{95} values of 1.7 μg/ml and 3.4 μg/ml, respectively, in patients given a constant-rate propofol infusion after morphine premedication and a standardized induction with propofol.[33] However, considerable interpatient variability was demonstrated in that study. Some patients exhibited response to incision with blood propofol concentrations as great as 4.0 μg/ml, whereas other patients showed no response despite a blood propofol level of only 1.2 μg/ml. Our study may not have demonstrated pharmacodynamic differences at the time of incision because of interpatient variability, nonsteady state conditions, the use of adjunctive iv drugs (meperidine, pancuronium) that could blunt responses, and the presence of a mean blood propofol concentration of 3.2 μg/ml (which approximated the EC_{95} value in the aforementioned study). Not surprisingly, a more recent study determined an even higher propofol ED_{95} for incision (5.9 μg/ml) when no opiate analgesic was administered.[34]

In a study involving volunteers, 50% of the maximal electroencephalogram (EEG) suppression, as measured by median EEG frequency, was associated with a blood propofol concentration of 2.3 μg/ml.[5] We found that blood propofol levels of 4.0 ± 1.0 and 3.0 ± 1.1 μg/ml were necessary to prevent autonomic responses during major and nonmajor surgery, respectively. Analogous to the previous studies,[33,34] we also found a high degree of interpatient variability during the intraoperative period (fig. 3). This variability may be due in part to differing degrees of surgical stimulation between patients.

The blood propofol concentration at the time of awakening (EC_{50} = 1.1 μg/ml) was similar to previously reported values for the emulsion (1.0 ± 0.2 μg/ml),[13] as well as the previous cremophor formulation (0.9–1.1 μg/ml).[2,11,12] Patients undergoing major surgical procedures required longer emergence times, although they awoke at the same blood propofol levels as other patients. Furthermore, these patients also had prolonged elimination half-life values. Although supplemental meperidine may also have influenced emergence times, our data suggest that pharmacokinetic alterations may be more important than pharmacodynamic effects in determining emergence from propofol anesthesia. Similarly, the reported sensitivity to propofol in the elderly[16] may be secondary to pharmacokinetic changes because propofol concentrations at emergence appeared to be independent of age in our study.

Pharmacodynamic analyses of the three psychometric tests were similar, with a range of blood propofol concentrations from 0.17 to 0.90 μg/ml at the time patients returned to their baseline scores (fig. 5). Use of a more sensitive tests, such as a driving simulator,[35] may result in a greater distinction between EC_{50} values for recovery tests. Pharmacodynamic analyses of the psychometric testing could only be performed on the results from patients in the nonmajor surgical group. Postoperative pain, supplemental centrally active medications, and side effects (e.g., nausea and vomiting) precluded patients undergoing major surgery from returning to their baseline scores. Full recovery of preoperative psychomotor skills in these patients would appear to be less dependent on anesthetic blood levels than on other factors in the early postoperative period.

In conclusion, propofol's pharmacokinetic profile is suited to administration via a combination bolus and variable-rate infusion technique. Propofol's high clearance rate exceeds hepatic blood flow.[36] A prolonged elimination half-life can occur following major (e.g., intraabdominal) operations (or the use of long infusions) and may contribute to a delayed emergence. Elderly patients may exhibit reduced clearance that could decrease the maintenance propofol requirement and prolong recovery. Considerable interpatient pharmacokinetic and pharmacodynamic variability exists. Thus, as with any anesthetic, drug dosages should be carefully titrated depending on the clinical response of the individual patient.

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