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Pharmacokinetics of Propofol in Adult Patients Undergoing Coronary Revascularization

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Background: **Propofol is increasingly used for cardiac anesthesia and for perioperative sedation. Because pharmacokinetic parameters vary among distinct patient populations, rational drug dosing in the cardiac surgery patient is dependent on characterization of the drug's pharmacokinetic parameters in patients actually undergoing cardiac procedures and cardiopulmonary bypass (CPB). In this study, the pharmacokinetics of propofol was characterized in adult patients undergoing coronary revascularization.**

Methods: **Anesthesia was induced and maintained by computer-controlled infusions of propofol and alfentanil, or sufentanil, in 41 adult patients undergoing coronary artery bypass graft surgery. Blood samples for determination of plasma propofol concentrations were collected during the predefined study periods and assayed by high-pressure liquid chromatography. Three-compartment model pharmacokinetic parameters were determined by nonlinear extended least-squares regression of pooled data from patients receiving propofol throughout the perioperative period. The effect of CPB on propofol pharmacokinetics was modeled by allowing the parameters to change with the institution and completion of extracorporeal circulation and selecting the optimal model on the basis of the logarithm of the likelihood. Predicted propofol concentrations were calculated by convolving the infusion rates with unit disposition functions using the estimated parameters. The predictive accuracy of the parameters was evaluated by cross-validation and by a prospective comparison of predicted and measured levels in a subset of patients.**

Results: **Optimal pharmacokinetic parameters were: central compartment volume = 6.0 l; second compartment volume = 49.5 l; third compartment volume = 429.3 l; Cl_1 (elimination clearance) = 0.68 l/min; Cl_2 (distribution clearance) = 1.97 l/min[1]; and Cl_3 (distribution clearance) = 0.70 l/min. The effects of CPB were optimally modeled by step changes in V_1 and Cl_1 to values of 15.9 and 1.95, respectively, with the institution of CPB. Median absolute prediction error was 18% in the cross-validation assessment and 19% in the prospective evaluation. There was no evidence for nonlinear kinetics. Previously published propofol pharmacokinetic parameter sets poorly predicted the observed concentrations in cardiac surgical patients.**

Conclusions: **The pharmacokinetics of propofol in adult patients undergoing cardiac surgery with CPB are dissimilar from those reported for other adult patient populations. The effect of CPB was best modeled by an increase in V_1 and Cl_1. Predictive accuracy of the derived pharmacokinetic parameters was excellent as measured by cross-validation and a prospective test. (Key words: Anesthetics, intravenous: pharmacokinetics, propofol. Anesthetic techniques: computer-controlled infusion. Surgery, cardiac: cardiopulmonary bypass.)**

PROPOFOL is a short-acting hypnotic that is widely used in both ambulatory and hospitalized patients. Because it permits both efficient control of anesthetic depth and a rapid, controllable recovery, propofol may be useful in the titration of anesthetic depth, including postoperative sedation, of cardiac surgical patients. Despite early concerns about the hypotensive effects of propofol during the induction of anesthesia,[1–5] several clinical studies report that propofol compares favorably to other cardiac anesthetic techniques, including high-dose opioid anesthesia,[6–9] and it may facilitate early tracheal extubation.

Rational drug dosing to minimize undesirable hemodynamic effects and hasten recovery depends on a thorough understanding of propofol pharmacokinetic parameters, especially if variable rate or computer-controlled infusions are used for titration of drug effect. Pharmacokinetic parameters vary among patient populations. The pharmacokinetics of propofol in cardiac surgical patients has been studied, but previous analysis

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has not been of sufficient detail to provide the pharmacokinetic parameters needed to guide drug dosing.[10] In this study, we analyzed the pharmacokinetics of propofol during and after variable-rate, computer-controlled infusions for adult patients undergoing cardiac surgery. Our goals were to derive pharmacokinetic parameters that describe the disposition of propofol during cardiac surgery and to evaluate the predictive accuracy of our pharmacokinetic model.

Methods

The pharmacokinetic data analyzed in this article were derived from two separate pharmacodynamic studies. Both were approved by the Human Investigations Committee of Emory University School of Medicine, and written informed consent was obtained from all patients.

Patients, Anesthetic Management, and Propofol Sampling

Both studies were restricted to patients between the ages of 21 and 80 yr with left ventricular ejection fractions greater than 30%. Patients requiring preoperative intravenous hemodynamic drug therapy (other than nitroglycerin for the treatment of angina), preoperative support by intraaortic balloon pump, or with severe or uncontrolled noncardiac disease, were excluded from the study. Patients also were excluded if they had a history or clinical evidence of renal or hepatic disease. Preoperative serum creatinine concentrations are noted in table 1. Serum glutamate-pyruvate transaminase values, a routine laboratory screen for hepatic dysfunction, were normal in all patients preoperatively. All patients in these studies underwent coronary revascularization.

Pharmacokinetic parameters were derived from a study of 11 patients receiving propofol as a primary anesthetic and for postoperative sedation. The patients in this study (the perioperative group) were premedicated with intramuscular 0.1 mg/kg midazolam and 0.1 mg/kg morphine. Anesthesia was induced with a computer-controlled infusion of propofol. Anesthesia was maintained by titrating the predicted propofol concentration from 3–10 $\mu g/kg$ to maintain the systolic blood pressure and heart rate within 20% of the average of three preoperative values. Propofol was supplemented with sufentanil infused at a constant rate of 0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the first 2 h of the study, decreased to 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the next 3 h, and then decreased to 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the remainder of surgery. Arterial blood samples for determination of propofol plasma concentrations were collected 2, 5, 10, 15, 20, and 30 min after induction of anesthesia, at skin incision and sternotomy, 2 min before cardiopulmonary bypass (CPB), 2, 5, 10, 15, and 30 min after the initiation of CPB, and at 2, 5, 10, 20, 30, 60, 120, 240, 360, 600, 900, and 1,200 min after termination of CPB.

Table 1. Patient Characteristics

	Perioperative Group	Pre-CPB Group
Age (yr)	66.4 (7.5)	63.8 (9.6)
Weight (kg)	72.9 (13.2)	78.0 (13.0)
Height (cm)	174.0 (7.6)	175.1 (8.9)
Ejection fraction (%)	57.2 (12.0)	52.9 (10.2)
Gender (M/F)	8/13	25/5
Creatinine (mg/dl)	1.1 (0.1)	1.3 (0.3)

Values are mean (SD). There were no significant differences between groups.
CPB = cardiopulmonary bypass.

Additional data were collected from a pharmacodynamic study of 30 coronary revascularization patients who were randomly assigned to receive computer-controlled propofol infusions with target plasma concentrations of 2, 4, or 6 $\mu g/ml$, respectively. These patients were not premedicated. During insertion of intravascular catheters before the induction of general anesthesia, patients received propofol for sedation, with target plasma concentrations of 0.25–0.75 $\mu g/ml$, as deemed necessary by the investigator. Induction and maintenance of general anesthesia was accomplished by a computer-controlled infusion of propofol with the target concentrations noted earlier. Propofol was supplemented by a computer-controlled infusion of alfentanil, titrated to clinical signs of depth of anesthesia by the investigator. Blood samples for determination of plasma propofol concentrations were collected at the following times:

1. entry into the operating room
2. loss of consciousness
3. tracheal intubation
4. skin incision
5. sternotomy
6. aortic cannulation
7. before making any change in the target alfentanil plasma concentration
8. 3 or 4 min after a new stable plasma alfentanil concentration was indicated by the computer

The study was terminated at the commencement of CPB. These patients are called the pre-CPB group.

Computer-controlled Infusion System and Propofol Assays

Propofol was administered with a Harvard 22 pump (South Natick, MA) driven by a Compaq 286 computer (Houston, TX). The software used to control the infusion rate was Stanpump, developed by one of the authors (SLS). This program uses a three-compartment model and derived pharmacokinetic parameters from a typical population, which are then used to calculate the infusion rates needed to achieve the target plasma concentration selected by the clinician. The pharmacokinetic parameters used during data acquisition were age- and weight-adjusted using the results of by Dyck *et al.*(table 2)‡ for adult patients. These parameters are not specific for cardiac surgical patients.

All samples were collected into heparinized tubes and centrifuged at 1,200*g* for 15 min. The plasma was then transferred to polypropylene tubes and stored at −70° until assayed.

Plasma propofol analyses were performed by ICI Pharmaceuticals Group (now Zeneca, Wilmington, Delaware) using reverse phase high-pressure liquid chromatography with fluorescence detection as described by Plummer.[11] The limits of detection of the assay was 2 ng/ml. The coefficient of variation of the assay was 7.6% for concentrations of 0.05–20 μg/ml.

Cardiopulmonary Bypass

The priming volume of the CPB circuit consisted of 1,500 ml balanced salt solution, 150 ml 25% mannitol, and 500 ml hetastarch. Mild hypothermia (23–28°C), α-stat *p*H management, and aortic cross-clamping with cold hyperkalemic cardioplegia were used in all patients. Nonpulsatile flow at a cardiac index of 2.2 $l \cdot m^{-2} \cdot min^{-1}$ was used and mean blood pressure was maintained between 50 and 90 mmHg.

Pharmacokinetic Modeling

Data acquisition produced a continuous record of the rate of propofol infusion for each individual patient as well as measured plasma propofol concentrations at the times noted earlier. Pharmacokinetic parameters were derived by the pooled data method in which the data are treated as if they were observed in a single, composite patient with the observations from each individual matched to the specific infusion that the patient received.[12–15] This was accomplished using MKMODEL (developed by Nicholas Holford, University of Auckland School of Medicine, Auckland, New Zealand), a nonlinear extended least-squares program.[16] A three-compartment structural model was assumed and a constant coefficient of variation model was used to describe the error of measured plasma concentrations. The program was modified to incorporate the iterative solution to the three-compartment model described by Bailey and Shafer.[17] This algorithm greatly facilitates the derivation of pharmacokinetic parameters when the drug input is a complicated variable infusion, as in these studies. The pharmacokinetic parameters used for regression were the compartment volumes V_1, V_2, V_3, (V_1 is the central compartment volume), and elimination and distribution clearances Cl_1, Cl_2, and Cl_3, (Cl_2 and Cl_3 are distribution clearances from the central compartment to V_2 and V_3, respectively, while Cl_1 is the elimination clearance).

The effects of CPB on pharmacokinetics were modeled by allowing each parameter (V_1, Cl_1, V_2, Cl_2, V_3, Cl_3) to change with the institution or completion of CPB. At the time of transition (pre-CPB to CPB and CPB to post-CPB) it was assumed that the amount of drug in the peripheral compartments did not change. This also was assumed for V_1 at the institution of CPB but at the completion of CPB it was assumed the concentration of drug in V_1 remained constant while the volume of the compartment changed. Thus, at the end of CPB the amount of drug in the patient could decrease if the volume of the central compartment decreased.

In the first stage of the analysis of the effects of CPB each parameter (V_1, Cl_1, V_2, Cl_2, V_3, Cl_3) was sequentially allowed to change with the institution or completion of CPB while the other parameters were held constant. When the addition of a parameter (CPB-specific or post-CPB-specific) resulted in an increase in the log likelihood of 2 or more[18] it was considered significant. This technique has been described elsewhere.[19]

After derivation of pharmacokinetic parameters, the ability of these parameters to predict both observed plasma concentrations was evaluated by two techniques. In the cross-validation procedure, model parameters were reestimated 11 times from the data from the 11 perioperative group patients. In each reestimation step, the data from a single patient were ex-

‡ Dyck JB, Varvel J, Hung O, Shafer SL: The pharmacokinetics of propofol versus age (abstract). ANESTHESIOLOGY 1991; 75:A315.

Table 2. Pharmacokinetic Parameter Estimates

	Parameter Source					
Parameter	Perioperative	Pre-CPB	Dyck	Gepts[20]	Shafer[21]	Tackley[22]
V_1	6.0	4.0	6.2	16.9	25.6	23.4
V_1-CPB	15.9					
V_2	49.5	63.9	19.4	35	142	38.3
V_3	429.3		461	215		151
Cl_1	0.67	1.19	1.73	2.01	2.19	1.93
Cl_1-CPB	1.95					
Cl_2	1.96	3.78	1.68	1.93	1.46	2.45
Cl_3	0.70		1.71	0.71		0.51

Pre-CPB and Shafer parameters are derived from two-compartment models. Dyck parameters are mean parameters for the ages and weights of the perioperative group patients.

CPB = cardiopulmonary bypass.

cluded from analysis. The accuracy with which the parameters estimated from the other ten patients' data predicted the observations in the excluded patient was assessed.[19] We also performed a prospective analysis by determining the accuracy with which the parameters derived from the perioperative group predicted the levels observed in the pre-CPB group.

The primary measure of goodness-of-fit was prediction error:

$$PE = ((C_m - C_p)/C_p) \times 100$$

where C_m is the measured plasma concentration, and C_p is the predicted plasma concentration. Median prediction error, root mean squared prediction error, and median absolute prediction error were calculated from the observed data and the results predicted by convolution of the derived unit disposition function with the infusion profiles of the individual patients. Also, the logarithm of the likelihood of the observations (log likelihood) was derived for the specific parameter estimates. Log likelihood is directly proportional to the objective function minimized in extended least-squares regression, evaluated at its minimum value.

Linearity of the relationship between C_m and C_p was assessed by linear regression of log C_m *versus* log C_p. The slope of this line should be unity if the relationship is linear. Deviation from linearity was evaluated by comparing the models log C_m = log C_p and log C_m = α log C_p + β (α is the slope and β is the intercept of the regression line) using the F statistic.

The influence of covariates was examined by plotting residual performance error *versus* weight, body surface area, age, and gender (as a categorical variable).

Pharmacokinetic parameters were also derived from the pre-CPB group data, using both two- and three-compartment models. The predictive accuracy of these parameters, as well as previously published parameter sets[20–22,‡] for data from the perioperative group were evaluated.

Results

Demographic data are presented in table 1 for the two patient groups. There were no differences among the groups ($P < 0.05$).

Pharmacokinetic parameters derived in this study are listed in table 2. When the effects of CPB were initially investigated by sequentially allowing each parameter to change in a stepwise fashion with the institution or completion of CPB, we found significant (>2 units) improvement in log likelihood only with changes in V_1 or Cl_1. We next derived pharmacokinetic parameters while allowing both V_1 and Cl_1 to undergo simultaneous changes with CPB. With this step we did not find a significant increase in log likelihood when either parameter was allowed to change again with the completion of CPB. Thus, our final model includes six parameters in the pre-CPB period (V_1, V_2, V_3, Cl_1, Cl_2, Cl_3) and two additional parameters (V_1-CPB and Cl_1-CPB) during and after CPB.

For the sake of comparison, parameters from other published studies are included in table 2. We also include a set of parameters derived from the data of the 30 patients studied only in the prebypass period. The data from these patients were best described by a two-compartment model, reflecting our inability to distinguish a third compartment with the limited duration of sampling.

Fractional coefficients and rate constants of the unit disposition function, calculated from the volumes and clearances derived in our primary analysis, were A1 = 0.957, A2 = 0.039, A3 = 0.004, $\alpha = 0.5805\ min^{-1}$, $\beta = 0.0162\ min^{-1}$, and $\gamma = 0.0008\ min^{-1}$ for the period before CPB. During and after CPB these parameters were A1 = 0.936, A2 = 0.062, A3 = 0.003, $\alpha = 0.3090$, $\beta = 0.0217$, and $\gamma = 0.0012$.

Plots of performance *versus* weight, body surface area, age, or gender did not suggest any specific influence of these covariates and further analysis of covariates was not undertaken.

Figure 1 presents a plot, on a logarithmic scale, of the measured plasma concentrations of propofol (C_m) in the perioperative group *versus* the concentrations predicted (C_p) from the pharmacokinetic parameters derived in this study. The regression equation is log Cm = 0.95log C_p + 0.0052. The slope is not significantly different from unity.

Figure 2 shows measured and predicted (by the parameters derived from the perioperative data and shown in table 2) propofol concentrations for the patients with the best, median, and worst median absolute prediction errors.

Figure 3 presents the ratio of measured to predicted propofol concentration, C_m/C_p, when the perioperative

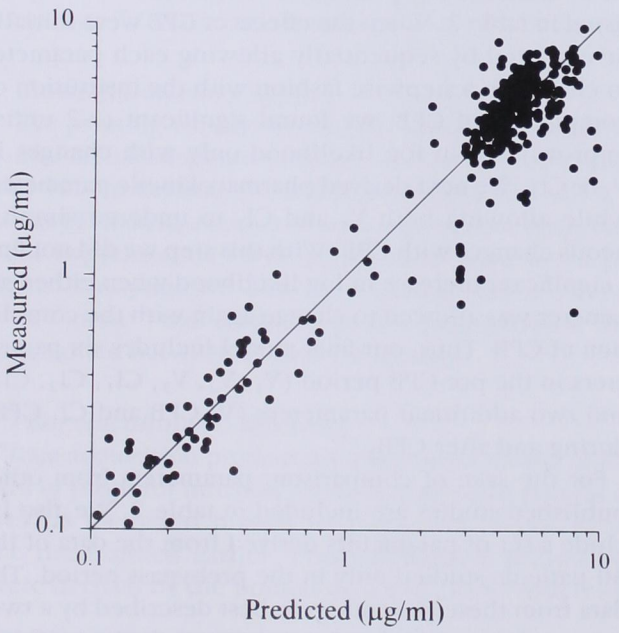

Fig. 1. Logarithmic plot of measured propofol concentrations in the perioperative group *versus* those predicted by the parameters derived from these data.

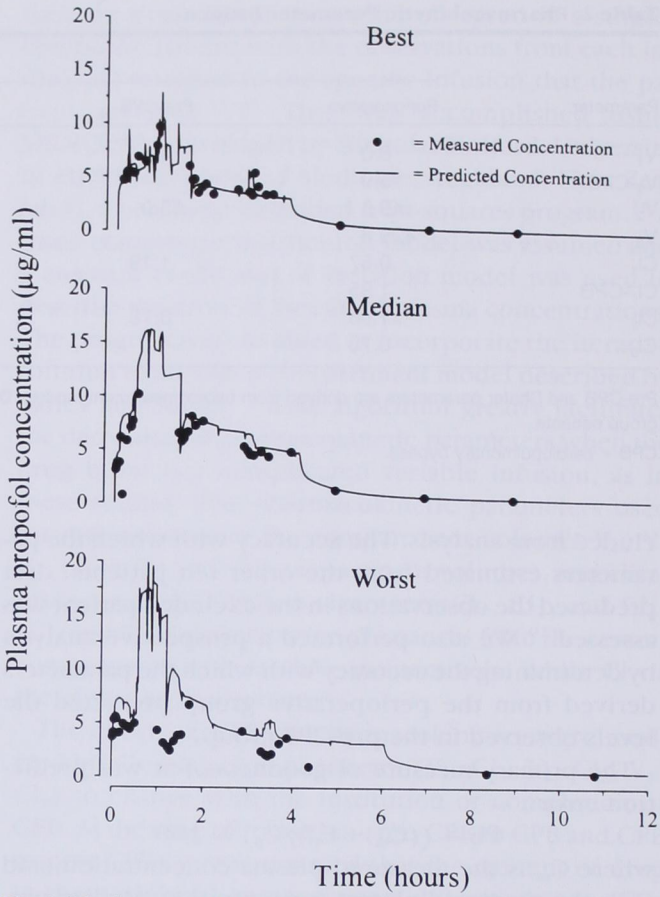

Fig. 2. The best, median, and worst predictive performance of the estimated pharmacokinetic parameters. Only the first 12 h of data are shown to provide sufficient emphasis of the intraoperative portion of the study.

group data are predicted by the parameters derived from it (retrospective error), for the cross-validation test, and when the parameters derived from the perioperative group are used to predict the observed levels in the 30 pre-CPB group patients (prospective errors). For comparison, figure 4 illustrates the C_m/C_p ratio for the prediction of perioperative group data by various other pharmacokinetic parameter sets. This includes parameters derived from the data from the pre-CPB group. Quantitative evaluations of predictive accuracy are presented in tables 3 and 4. The predictive accuracies of the parameters determined in this study in (1) predicting the data from which they were derived (retrospective), (2) the cross-validation procedure, and (3) predicting the observed results in the pre-CPB group (prospective) are shown in table 3. For comparison, table 4 presents measures of the accuracy of other parameter sets, including one derived from the

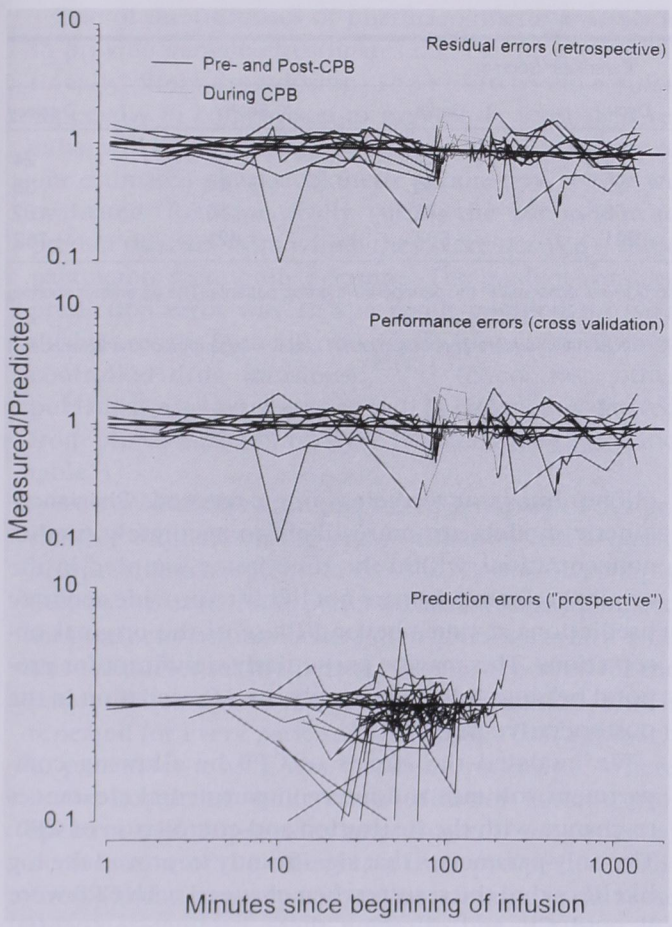

Fig. 3. The ratio of measured to predicted propofol concentrations as a function of time of infusion. The retrospective curves refer to the prediction of observed perioperative group concentrations by the parameters derived from them whereas the prospective curves refer to the prediction of the observed concentrations in the pre-CPB group by the parameters derived from the perioperative group data. The cross-validation procedure is described in the text.

pre-CPB group data, in prediction of the observed concentrations in our perioperative group.

Discussion

The results of this study are summarized in the pharmacokinetic parameter estimates presented in table 2. There are differences between our parameters and those published previously, specifically the low values of central compartment and central clearance we observe in the period before CPB. This is reflected in figure 4 where it can be seen that other parameter sets (derived from adult noncardiac surgical patients) poorly predict the plasma concentrations observed in cardiac surgical patients in the pre-CPB period. Several other published parameter sets also poorly predict the propofol levels observed during long periods (800–1,000 min). These impressions are consistent with the quantitative evaluations shown in table 3.

The parameters we derived were based on data gathered in a group of patients who received propofol throughout the perioperative period. However, we also gathered data from a group of patients who received

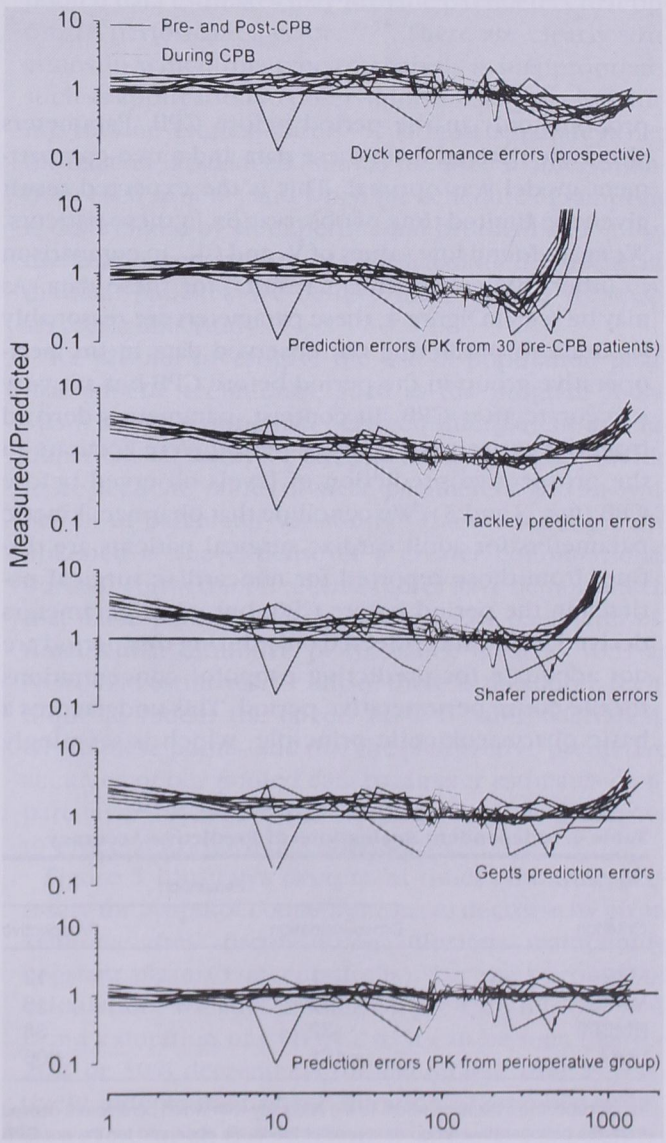

Fig. 4. The ratio of measured to predicted propofol concentrations as a function of time for various parameter sets predicting the observed concentrations in the perioperative group.

Table 3. Predictive Accuracy

Criterion	Parameter Source					
	Perioperative	Pre-CPB	Dyck	Gepts	Shafer	Tackley
MPE (%)	1	−22	21	27	37	24
MAPE (%)	16	44	35	36	44	38
RMSPE (%)	31	283	56	76	16	102
Log L	−456	−4,179	−601	−664	−1,621	−762

Data refers to the accuracy with which the various parameter sets predict the propofol levels observed in the perioperative group patients. The parameter sources are identical to those cited in table 2.

MPE = median prediction error; MAPE = median absolute prediction error; RMSPE = root mean squared prediction error; Log L = logarithm of the likelihood of the observed results; CPB = cardiopulmonary bypass.

propofol only in the period before CPB. Parameters also were derived from these data and a two-compartment model was optimal. This is the expected result given the limited time of observation in these patients. We again found low values of V_1 and Cl_1, in comparison to other two compartment results, for these data. As may be seen in figure 4, these parameters are reasonably accurate in predicting the observed data in the perioperative group in the period before CPB but are very inaccurate after CPB. In contrast, parameters derived from the entire perioperative period were accurate in the prospective prediction of levels observed before CPB (figs. 2 and 3). We conclude that pharmacokinetic parameters for adult cardiac surgical patients are distinct from those reported for noncardiac surgical patients in the period before CPB, but, also, parameters derived from data collected only during this period are not adequate for predicting propofol concentrations for the entire perioperative period. This underscores a basic pharmacokinetic principle, which is seemingly cliche, but is nevertheless often ignored. Pharmacokinetic models are more likely to accurately predict concentrations within the time frame sampled in the original research, but are not likely to provide accurate predictions at times beyond those of the original observations. This may be particularly significant for propofol because it is increasingly used for sedation in the postoperative period.

Table 4. Independent Evaluations of Predictive Accuracy

Criterion	Evaluation	
	Cross-validation	Prospective
MPE	−1	−12
MAPE	18	19
RMSPE	32	38
Log L	−471	−906

The prospective evaluation refers to the accuracy with which parameters derived from the perioperative group data predict the levels observed for the pre-CPB group.

MPE = median prediction error; MAPE = median absolute prediction error; RMSPE = root mean squared prediction error; Log L = logarithm of the likelihood of the observed results; CPB = cardiopulmonary bypass.

We modeled the effects of CPB by allowing compartment volumes and intercompartmental clearances to change with the institution and completion of CPB. The only parameters that significantly improved the log likelihood of the results when changed with CPB were V_1 and Cl_1 and allowing these parameters (central compartment volume and central clearance) to change with the institution of CPB improved log likelihood by 40 units, a large improvement. Allowing these parameters to change again with the completion of CPB did not improve log likelihood significantly. The changes in these parameters with CPB are of interest. Central compartment volume increased, as might be expected given the addition of the pump prime volume to the circulating volume of the patient. More surprisingly, central clearance also increased. This does not seem consistent with the probable decreases in hepatic blood flow during moderate hypothermic CPB.

Plots of performance error *versus* weight, body surface area, age, or gender did not suggest an influence of these covariates on the pharmacokinetics of propofol in this population. This is not surprising, because our patient population was relatively homogenous. We did not further investigate the effects of covariates. By implication, our parameter estimates should not be used for persons who do not fit the profile of the patients in this study.

One of the purposes of pharmacokinetic analysis is to provide parameter estimates that can be used to rationally direct drug dosing. The utility of the results, especially in comparison to previously published results, will be determined by the predictive accuracy of our estimated pharmacokinetic parameters, which we evaluated. Retrospectively (using the parameters to predict the data from which they were derived), these parameters were quite accurate. The median absolute prediction error was 16%, a result competitive with the best results found in other evaluations of computer-controlled drug infusions.[12–15,23] In contrast, other published parameter sets, as well as parameters derived from pre-CPB data only, were less accurate (fig. 4 and table 3).

We also evaluated the predictive accuracy of our parameter estimates using cross-validation and a quasi-prospective assessment. In cross-validation one simply deletes the data of one patient from the data pool used for parameter estimation and then determines how well this parameter set predicts the results observed for the patient deleted from the parameter estimation. This is repeated for every patient in the study. This approach to parameter testing was discussed recently,[19] where it was noted that while cross-validation is not a prospective trial, it provides an estimate of the expected performance of the model in a truly prospective trial. Cross-validation is a conservative technique in the sense that one can expect each submodel (each "leave one out" data set) to be slightly less accurate than the full model because it is based on fewer data points. In the cross-validation assessment of our parameter set, we again find excellent predictive accuracy with a median absolute prediction error of 18%. We performed a quasiprospective evaluation of predictive accuracy by determining how well our final pharmacokinetic parameters predicted the propofol concentrations observed in a separate group of patient studied only in the pre-CPB period. The median absolute prediction error in this assessment was 19%.

It has been suggested that propofol may have nonlinear kinetics.[23] We do not believe this possibility to be of significance for the results reported in this study. Figure 1 shows a plot, on a logarithmic scale, of predicted *versus* measured propofol concentrations for the 11 patients studied during the entire perioperative period. The slope of this plot is nonsignificantly different from unity, *i.e.*, the predicted concentration is a linear function of the measured concentration. If we had encountered nonlinearity one would expect the relationship between predicted and measured concentrations to vary with the measured concentration. That this plot is so highly linear with a slope of one suggests that nonlinearity was not observed.

In this study, pharmacokinetic parameters were derived by the pooled data technique. Pooled-data analysis has been the subject of considerable debate. This technique is frequently referred to as "naive pooled data" because no distinction is made between interpatient and intrapatient variability.[24,25] However, a number of recent investigations have demonstrated that pooled data estimates may provide parameters that optimize performance error.[12–15] There are clearly situations in which this type of analysis is inappropriate, such as application to observational data gathered during routine clinical care.[25] It is most accurate when the data set is balanced (similar number of observations from each patient) and when the schedule of sampling is determined by an experimental protocol and not by the pharmacodynamics or pharmacokinetics of the individual patients. We believe these caveats were observed in this study.

We did not investigate the use of population pharmacokinetic techniques, such as the program NONMEM, which distinguish between interpatient and intrapatient variability.[26] Such an analysis might provide more accurate values of mean parameters, and an evaluation of parameter variability. These advantages are obtained at the expense of a greater computational burden. Furthermore, recent studies have demonstrated that naive pooled analysis can generate parameter estimates that minimize performance error as well as NONMEM estimates.[14,15] Also, there is no simple technique to model the effects of CPB using NONMEM. Given these points, and that the prospective predictive accuracy of our pooled data parameter estimates compare favorably with other investigations, we chose not to proceed to NONMEM analysis.

Figure 5 illustrates decrement times (the time necessary for propofol concentrations to decrease by given amounts after discontinuing infusions maintaining constant plasma concentrations). For the purposes of calculation, we have assumed a pre-CPB interval of 1 h and a duration of CPB of 2 h. It can be seen that for 20% or 50% decrements the decrement time is relatively independent of the duration of administration. However, for an 80% decrement there is a substantial cost in recovery time for longer infusions.

In summary, we have analyzed the pharmacokinetics of propofol in adult patients undergoing coronary re-

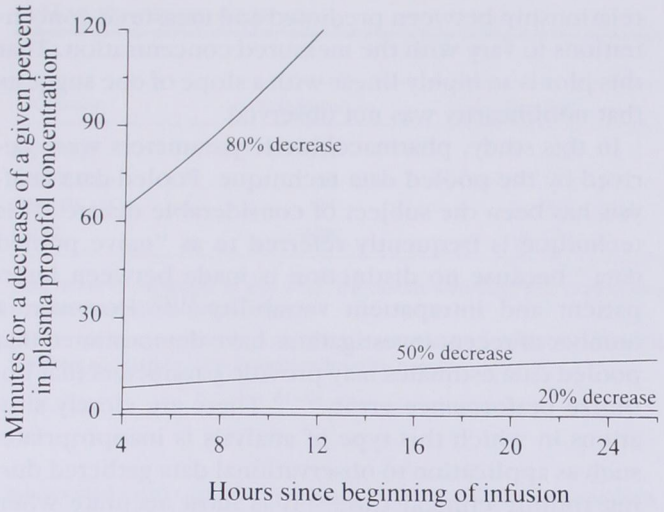

Fig. 5. Decrement times for 20%, 50%, and 80% decreases in propofol concentration as a function of the length of administration. For the sake of calculation it was assumed that propofol was administered for 1 h before CPB and that CPB required 2 h.

vascularization. We derived pharmacokinetic parameters using pooled data analysis of a CPB-adjustable model. The effects of CPB were best modeled by allowing central compartment volume and central clearance to change with the institution of CPB. The parameters derived in this study were more accurate than previously published results for the prediction of propofol concentrations throughout the perioperative period. This pharmacokinetic characterization of propofol may facilitate efficient control of anesthetic depth and a rapid, controllable recovery.

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