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Population Pharmacokinetics and Pharmacodynamics of Thiopental: The Effect of Age Revisited

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The authors have previously attributed the mechanism for the 50–67% decrease in the required dose of thiopental for induction of anesthesia in aged human patients to a decrease in the initial distribution volume for thiopental. Using a larger group of patients and volunteers studied in the laboratory, the authors have re-examined thiopental pharmacokinetics and EEG pharmacodynamics relative to age. A population data analysis approach (NONMEM), using a three-compartment model, was used to analyze bolus and rapid iv infusion thiopental serum concentration *versus* time data from 64 subjects. A one-compartment model was also used on the first 10 min of serum concentration data to focus only on the initial distribution phase. The population pharmacokinetic analysis demonstrated that when thiopental is administered *via* an iv bolus injection, traditional pharmacokinetic models limit the accurate characterization of thiopental distribution phenomena. Using the rapid iv infusion data, the pharmacokinetic mechanism for the decreased thiopental dose requirement in the elderly was a decreased rapid intercompartment clearance. Thiopental distribution from the central compartment of the three-compartment model to the rapidly equilibrating compartment (rapid intercompartment clearance) decreased 27% between the ages of 35–80 yr and decreased 34% in the one-compartment analysis. EEG spectral edge *versus* time data from 37 subjects was analyzed with a semiparametric modelling approach to remove the disequilibrium between thiopental serum concentration and the spectral edge. A population data analysis (NONMEM) was performed with several pharmacodynamic models. There was no age-related change in brain responsiveness or pharmacodynamics when the spectral edge is used as a measure of drug effect. (Key words: Age factors. Anesthetics, intravenous: thiopental. Brain: electroencephalography. Modelling, population analysis. Pharmacodynamics: thiopental. Pharmacokinetics: thiopental.)

WE PREVIOUSLY reported that anesthetic requirements for thiopental in humans decreased 50–67% over the age range of 20–80 yr using the EEG as a measure of CNS drug effect.[1] In our previous publication we used a traditional two-stage data analysis approach to examine the effects of increasing age on thiopental pharmacokinetics and pharmacodynamics. This approach required a complete thiopental serum concentration or EEG effect *versus* time curve for each subject. These data were then fit to a three-compartment pharmacokinetic model or a pharmacodynamic effect model using nonlinear least-squares regression. Each subject generated pharmacokinetic or pharmacodynamic parameters (first stage). The effect of age on these parameters were analyzed with linear regression (second stage). The initial distribution volume of thiopental decreased from 20–25 l in the 20-yr-old subjects to 3–7 l in the elderly. Pharmacodynamic modelling of the thiopental EEG spectral edge changes could not demonstrate an age-related change in brain responsiveness.

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We have recently re-examined thiopental pharmacokinetics and pharmacodynamics relative to age for several reasons: 1) other investigators studying thiopental pharmacokinetics have described an age-related distribution phase pharmacokinetic mechanism that is different from what we reported;[2] 2) newer pharmacokinetic and pharmacodynamic data analysis techniques to examine this issue are now available;[3–7] 3) additional data on the pharmacokinetics and pharmacodynamics of thiopental have been generated in our laboratory.[8]

Using a population pharmacokinetic and pharmacodynamic analysis (NONMEM), we examined the following issues: 1) is there a difference in distribution phase pharmacokinetics between iv bolus and rapid iv infusion administration of thiopental? In our previous analysis[1] both methods of thiopental administration were used to generate pharmacokinetic data; 2) does age and weight affect thiopental distribution pharmacokinetics? 3) does age affect thiopental EEG pharmacodynamics?

Methods

Pharmacokinetic Patient Data

Thiopental serum concentration *versus* time data from 64 subjects reported by our laboratory over the past 8 yr were used in the pharmacokinetic analysis (table 1). One group included 26 surgical patients previously reported by Homer and Stanski.[1] These subjects received either an iv bolus (15 s) or rapid iv infusion of thiopental (75–100 mg/min) to a defined endpoint of 1–3 s of isoelectric EEG. An additional 13 patients originally reported in the

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pharmacodynamic section of the Homer and Stanski[1] publication were also included. These patients received a thiopental infusion (75–100 mg/min) to a defined EEG endpoint, but had arterial serum concentrations measured for only ¼ to ½ h. This short duration of blood sampling precluded pharmacokinetic analysis with conventional techniques but can be used in the NONMEM approach.

A group of 20 volunteers and patients from the study reported by Swerdlow *et al.*[8] on the effects of "heavy" alcohol intake on thiopental pharmacokinetics and pharmacodynamics was also used in this analysis. Eleven "heavy" drinkers received a thiopental infusion of 100 mg/min to a defined EEG endpoint. Five of these heavy drinkers participated in a second study approximately 1 month later. The second pharmacokinetic study data was also included in the analysis. Swerdlow *et al.*[8] also studied a control group of six volunteers and three patients who were "social" drinkers. Using a traditional two-stage data analysis approach, Swerdlow *et al.* determined that thiopental pharmacokinetics were not different between heavy drinkers and control subjects.[8]

To complete the data set for the current study, five elderly surgical patients received a iv bolus of thiopental (4 mg/kg) with serum sampling for 24–33 h. These subjects were studied by the present authors and have not been reported previously.

The pharmacokinetic data set thus involved 64 subjects, 16 receiving an iv bolus and 48 a rapid iv infusion. The iv bolus was given manually with a syringe over 15 s while a calibrated infusion pump was used for the infusion studies (75–100 mg/min). For the iv bolus studies, arterial blood was sampled at 1, 2, 3, 5, 10, 15, 30, and 45 min, then at increasing time intervals to characterize the thiopental elimination phase. For the infusion studies, arterial blood was sampled at ½–1 min intervals during the infusion, then at 1–3 min intervals for the next 20 min. For those subjects in whom elimination-phase pharmacokinetics were characterized, subsequent venous sampling occurred at appropriate intervals for 24–52 h.

For any surgical patient receiving a thiopental infusion, general anesthesia was induced 20–30 min after the initial thiopental administration. Surgical anesthesia was provided by 1–2 mg/kg of methohexital and 1 mg/kg of succinylcholine, followed by intubation of the trachea and 1–2% inspired enflurane with 70% nitrous oxide. For surgical patients receiving an iv bolus, tracheal intubation and enflurane anesthesia began 3–5 min after the initial iv bolus administration of thiopental. Heavy drinkers and volunteer controls did not receive a general anesthetic. The age range of the 64 subjects in the pharmacokinetic analysis was 23–88 yr and the weight range was 52–118 kg. Four subjects were female. Twenty-three subjects were 20–40 yr, 9 subjects 41–60 yr, and 33 subjects 61+ yr. All patients and volunteers were ASA physical status 1 or 2 without hepatic, respiratory, cardiovascular, or renal disease. Routine laboratory tests were normal in all subjects except one heavy drinker who had abnormal hepatic function tests. Protocols were approved by the Stanford Institutional Review Board and informed consent was obtained from all subjects.

Total (free and protein-bound) serum thiopental concentrations were measured using a high performance liquid chromatographic assay sensitive to 100 ng/ml.[9] The same assay was used for all of the above studies.

Pharmacodynamic Patient Data

Arterial thiopental serum concentration *versus* spectral edge data from 38 subjects in two previously reported studies were used.[1,8] Data from 18 of the surgical patients

TABLE 1. Subject Description and Source for Thiopental Population Pharmacokinetics

	Number of Patients	Subject Type	Duration of Sampling (h)	Age (yr)
Bolus administration				
n = 16 subjects	8*	Patient	24–36	20–40
382 serum samples	1*	Patient	24–36	41–60
	2*	Patient	24–36	61+
	5‡	Patient	24–36	61+
Infusion administration				
n = 48 subjects,	5*	Patient	¼–½	20–40
1943 serum samples (five subjects had two	3*,†	Patient	¼–½	41–60
separate studies)	5*	Patient	¼–½	61+
	2*	Patient	24–28	20–40
	3†	Patient	24–28	41–60
	13*	Patient	24–28	61+
	10†	Heavy drinker	25–32	20–40
	1†	Heavy drinker	25–32	41–60
	6†	Volunteer	23–28	20–40

Sources: *Homer and Stanski.[1] †Swerdlow *et al.*[8] ‡Present study.

reported by Homer and Stanski were reanalyzed. Twenty subjects involved in the study of Swerdlow *et al.* on thiopental pharmacokinetics and pharmacodynamics in heavy drinkers were included in the pharmacodynamic reanalysis. Five of the 11 heavy drinkers were studied on two occasions to generate 16 data sets while the nine control subjects increased the group size to 25 data sets. In Swerdlow's original data analysis, a parametric pharmacodynamic analysis using a traditional two-stage approach of characterizing the thiopental serum concentration *versus* spectral edge was used.[8,10,11] The heavy drinkers did not have different pharmacodynamics compared with those from the control subjects. The same EEG recording equipment and waveform analysis software were used in all subjects. The age range of the pharmacodynamic subjects was 24–88 yr and the weight range was 52–118 kg; 20 subjects were 20–40 yr, 5 subjects were 41–60 yr, and 13 subjects were 61+ yr.

Population Pharmacokinetic Data Analysis

The NONMEM nonlinear regression program‡,§ was used to derive average population pharmacokinetic parameters for thiopental and to model the influence of the following: age, bodyweight, mode of administration of the drug (bolus *vs.* infusion), and alcohol intake. The procedure was similar to that performed in our previous study regarding alfentanil.[3] A modified stepwise approach analogous to multiple stepwise linear regression was used to determine which parameters should be included in a "final," optimal model that has the best fit (lowest −2 log likelihood). To determine which factor would influence the pharmacokinetic parameters, we compared the results obtained when the factor in question was incorporated in the model and (using a value that was freely estimated by the regression program) with the results obtained when the factor was constrained to a fixed value (usually 0 or 1, depending on the model) corresponding to the null hypothesis, *i.e.*, no effect of the factor of interest. To examine the influence of an individual factor on the model fit, the following criteria were considered: the difference in −2 log likelihood (asymptotically chi-square distributed), the standard errors of the parameter estimates, the plots of the residuals, and the change in the remaining variability between patients. A conservative P value ($P < 0.005$) corresponding to a log likelihood difference of 7.8 was chosen as the limit beyond which a parameter should be included in the final model. This conservative P value was chosen because of the asymptotic nature of the chi-square test.

The data indicated in table 1, which include distribution and elimination phases, was fit to a three-compartment model with elimination from the central compartment using the same parameters as previously used for alfentanil.[3] The three-compartment model was statistically preferred over a two-compartment model. Effects of age, body weight, chronic alcohol intake, and the mode of administration (bolus *vs.* infusion) on the pharmacokinetic parameters were examined.

To focus the pharmacokinetic analysis on the period of maximal relevance for the clinical effect, a separate analysis was performed on the serum concentration data gathered between 1–10 min after the iv bolus and the serum concentration data during the 3–12-min period of thiopental infusion. The bolus and infusion data was fit to a one-compartment model¶ with two parameters: Vd, the volume of distribution that approximates the initial distribution volume of the three-compartment model; and K_e, the rate constant for drug removal, which describes distribution and elimination processes.

Population Pharmacodynamic Data Analysis

In all of the pharmacodynamic experiments, thiopental was rapidly infused to a defined endpoint evident in the EEG. Using the spectral edge as a measure of effect on the EEG, a time lag (or disequilibrium) was always observed between the measured thiopental serum concentration and the spectral edge value. Furthermore, the effect corresponding to a particular serum concentration of drug during infusion is lower than the effect corresponding to the same serum concentration after the infusion is terminated. A plot of serum concentration *versus* effect thus exhibits a hysteresis loop, indicating that the site of action of the drug is different from serum.[10] Sheiner *et al.* formalized the concept of an effect "compartment" that can be used to incorporate these observations in a "parametric" pharmacodynamic model.[11] In this approach, the serum concentration *versus* time data is first fit to a pharmacokinetic model. The effect *versus* time data is then characterized by simultaneously fitting the data to an effect compartment that estimates the degree of disequilibrium with a first order rate constant (K_{e0}) and a pharmacodynamic model that relates effect site concentrations to measured effect. This approach has been used previously to describe thiopental pharmacodynamics.[1,8,10]

Recently a "semiparametric" approach to estimating the degree of disequilibrium in drug concentration *versus* time and effect *versus* time data has been described.[5–7] The conceptual approach of this technique is described

‡ Beal SL, Sheiner LB: NONMEM User's Guide, San Francisco, University of California, 1979

§ Run on a Unix V/3 operating system with an Opus PM 350 add-in board in a generic AT-286 clone.

¶ Ebling WF, Arden JR, Holley FO, Scott JC, Stanski DR. A model of anesthetic dose requirement: Pharmacokinetic and pharmacodynamic requirements (abstract). ANESTHESIOLOGY 65:A547, 1986

in figure 1. This approach estimates K_{e0} and calculates the apparent effect-site concentration for each measured effect point without using the assumptions of a pharmacokinetic or pharmacodynamic model, hence the term "semiparametric." The apparent thiopental concentration at the effect site is equivalent to the steady-state thiopental

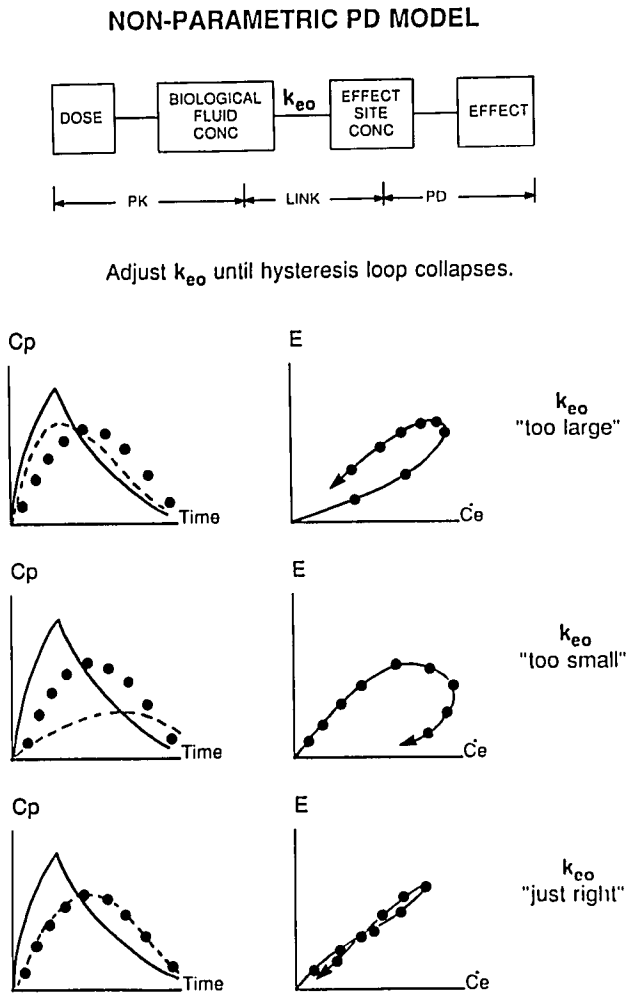

FIG. 1. Fundamental basis of semiparametric pharmacodynamic analysis. Following drug administration, the pharmacokinetic processes determine the time course of plasma drug concentration (*solid line, left panel*). The effect site is linked to the plasma with a first order rate constant, K_{e0}. The resulting effect site concentration is translated into pharmacologic effect. The theoretical time course of effect site concentrations is estimated by convolving the plasma concentration with K_{e0} (*left panels*). If K_{e0} is chosen too large the theoretical concentration (TCe, *dashed line*) are left-phase shifted from the actual effect site concentrations (Ce, symbols). In this example, plotting the TCe as Ce against effect (E) produces a counterclockwise hysteresis loop (*top right panel*). Choosing K_{e0} too small results in a clockwise hysteresis loop. When K_{e0} is chosen correctly the hysteresis loop uniquely collapses and the apparent concentration effect relationship is defined. The iterative algorithm varies K_{e0}, reducing the area inscribed by the hysteresis. (Reproduced with permission from lecture notes of Lewis B. Sheiner, M.D.)

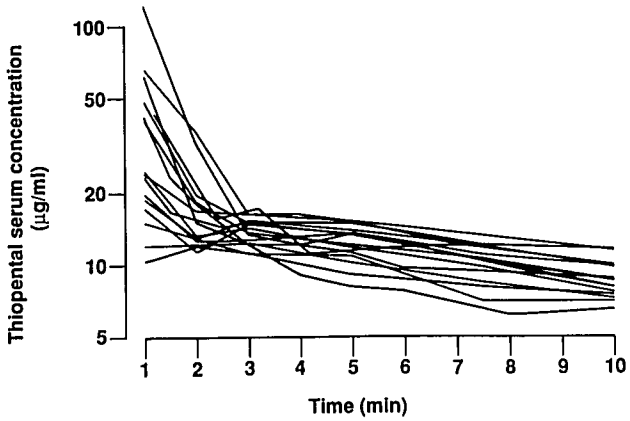

FIG. 2. The individual thiopental serum concentrations (log scale) *versus* time curves for 16 subjects who received a rapid iv bolus of thiopental. Concentrations were normalized to a thiopental bolus dose of 400 mg.

serum concentration that would result in the measured effect. For each subject, the thiopental serum concentration and spectral edge was used with the semiparametric modelling approach described above to remove the disequilibrium. The spectral edge *versus* apparent thiopental effect site concentration data was then fit to E_{max} and sigmoid E_{max} pharmacodynamic models for all of the data collectively using NONMEM. After choosing the appropriate pharmacodynamic model, the effect of age on the pharmacodynamic parameters was explored.

Results

Figure 2 displays the individual serum concentration *versus* time data during the first 10 min for all subjects who received an iv bolus injection of thiopental. Variability in the serum concentrations is greatest in the first minute and progressively decreases until the third minute. After 3 min, the serum concentration decay is relatively consistent and uniform in all subjects. Figure 3 indicates the individual thiopental serum concentration *versus* time curves for all subjects less than 60 yr during the infusion. Figure 4 indicates the same data for all subjects greater than 60 yr. In both figures 3 and 4, the thiopental infusion was terminated when the EEG in each subject was isoelectric for 1–3 s. Subjects less than 60 yr received more drug compared with subjects greater than 60 yr, reflecting the decreased dose requirement of elderly surgical patients.

Population Pharmacokinetic Analysis

Table 2A indicates the findings of the stepwise NONMEM regression performed on the bolus and infusion data using the three-compartment pharmacokinetic model. The analysis began with a three-compartment, six-

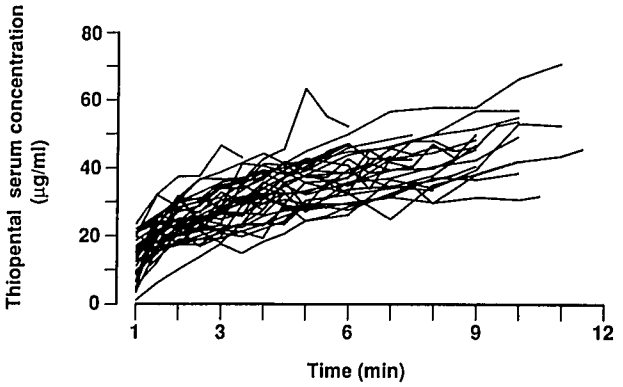

FIG. 3. The individual thiopental serum concentration (linear scale) *versus* time curves in 30 subjects less than 60 yr during a thiopental infusion normalized to a rate of 100 mg/min. Five subjects have two separate studies displayed.

parameter pharmacokinetic model with no additional factors present. Next, the initial distribution volume (V_1) and metabolic clearance (CL) were both found to be proportional to body weight. Finally, the rate constant K_{12}, which characterizes the initial distribution to the rapidly equilibrating compartment, decreased with age in a linear fashion beginning at 35 yr. This indicates that rapid intercompartment clearance ($V_1 \cdot K_{12}$) decreases with increasing age. Age did not have a statistically significant effect on the rate constant K_{13} that describes the distribution to the slowly equilibrating compartment (slow intercompartment clearance). The final model presented in table 2A includes an adjustment for the individual's weight on V_1 and CL, and an effect of age on K_{12}. There was no significant effect of alcohol intake or age on the initial distribution volume or clearance. All parameters were well estimated with relatively small standard errors. Interindividual variability (the variability in the data that can be assigned to different subjects) was assigned to four

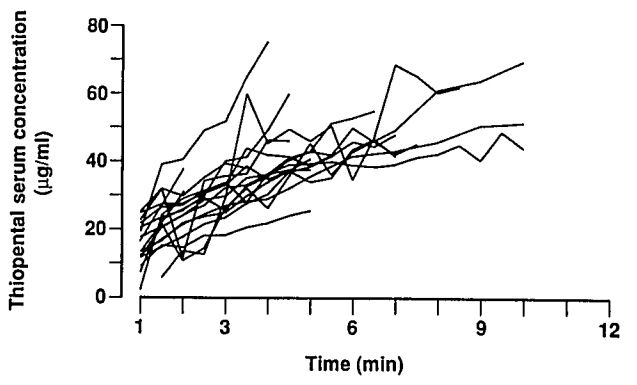

FIG. 4. The individual thiopental serum concentration *versus* time curves in the 18 subjects aged greater than 60 yr during a thiopental infusion normalized to a rate of 100 mg/min.

of the six model parameters and ranged from 50–76% for the rate constants K_{12} and K_{13} to 48% for the initial distribution volume and 30% for metabolic clearance.

When we attempted to characterize the 16 patients who received a bolus iv injection using a three-compartment pharmacokinetic model (fig. 2), we could not accurately estimate the initial distribution volume. The standard error of the initial distribution volume exceeded the value of the parameter. Inclusion of the iv infusion data with the iv bolus data reduced the standard error for the parameter, thus making it possible to use the three-compartment model. It was not possible to compare the pharmacokinetics between the bolus and infusion data for thiopental because the bolus iv pharmacokinetics could not be characterized separately with the three-compartment model and population data analysis.

Figures 2, 3, and 4 present the distribution phase data from the first 10 min after the iv bolus injection or during the 3–10 min iv infusion that was used in the one-compartment pharmacokinetic analysis. Figure 2 demonstrates the clear biexponential decay that would not be suitable for a one-compartment model and could not be characterized in the NONMEM analysis. The one-compartment model adequately characterized the thiopental infusion data of figures 3 and 4, table 2B presents the results of the data analysis. Patient weight did not affect the distribution volume (Vd) or elimination rate constant (K_e), both of which were highly correlated. K_e was found to decrease linearly after 35 yr from a value of 0.347 min^{-1} at age 35 to 0.226 min^{-1} at age 80 yr, a 34% reduction. Age did not effect Vd.

Figure 5 simulates the effect of age on thiopental serum concentrations from an infusion of 100 mg/min in 35-yr, 60-yr, and 80-yr-old subjects using the data of Table 2B. The standard deviations of the predicted serum concentrations at the end of 10 min are indicated. If the therapeutic serum concentration needed to achieve adequate induction of anesthesia is approximately 40 μg/ml, the elderly patient would reach this threshold concentration at approximately 4 min, the middle-aged patient at 5 min, and the young patient at 8 min.

Population Pharmacodynamic Analysis

Figures 6 and 7 indicate the spectral edge *versus* apparent thiopental effect-site concentration relationship estimated using the semiparametric pharmacodynamic modelling concept. An apparent effect-site concentration *versus* spectral edge curve is displayed for each subject. Figure 6 includes all of the data available for subjects less than 60 yr while figure 7 includes the data for those greater than 61 yr. Table 3 indicates the pharmacodynamic analysis obtained from this data. Using the semiparametric modelling approach, the rate constant of

TABLE 2A. Three Compartment Thiopental Population Pharmacokinetics*

Final Model	Parameters
Three-compartment model, six parameters	Cl = 0.00307 l·kg^{-1}·min^{-1}
Proportional inter-/intraindividual error model	CL interindividual variability ± 30%
Random effects on CL, V_1, K_{12}, K_{13}	V_1 = 0.0790 l/kg
No covariance on random terms	V_1 interindividual variability ± 48%
Age effect on K_{12}	If age <= 35, K_{12} = 0.48 min^{-1}
Weight effect on CL and V_1	K_{12} interindividual variability ± 51%
No effect of alcohol intake on V_1 or CL	If age > 35, K_{12} = 0.48 − (0.00288·(Age 35)) min^{-1} *
No effect of age on V_1 or K_{13}	K_{21} = 0.0787 min^{-1}
Unable to characterize iv bolus data with the model	K_{13} = 0.107 min^{-1}
	K_{13} interindividual variability ± 76%
	K_{31} = 0.00389 min^{-1}
	Residual error ± 24%

TABLE 2B. One-Compartment Thiopental Population Pharmacokinetics, Infusion Data from 1–10 min†

Final Model	Parameters
One compartment model	Vd = 6.07 l
Two parameters:	Vd interindividual variability ± 35%
Vd (distribution volume) and	If age <= 35, K_e = 0.347/min
K_e, rate constant of drug removal	If age > 35, K_e = 0.347 − (0.00268·(Age 35)) min^{-1} *
Proportional interindividual error model	K_e interindividual variability ± 50%
Additive intraindividual error model	Correlation coefficient between Vd and K_e = −0.86
Covariance between Vd and K_e	
K_e decreasing with age > 35	
No significant effect of age on Vd	
No significant effect of weight on Vd and K_e	
Unable to characterize bolus iv data with this model	

* Sixty-four subjects, 2325 data points.

† Forty-eight subjects, 578 data points.

blood:brain equilibration (K_{e0}) was estimated to be (mean ± SD) 0.58 ± 0.28 min^{-1}. This corresponds to a $T_{1/2}K_{e0}$ of 1.2 min. $T_{1/2}K_{e0}$ is linearly related to age with a slope that is statistically different than zero. However, the correlation of age to $T_{1/2}K_{e0}$ was extremely poor, with only 11% of the variability being explained by age. Although this relationship is statistically significant, we do not consider it to be clinically relevant. Table 3 presents a pharmacodynamic analysis of the spectral edge *versus* effect site concentration relationship. A sigmoid E_{max} pharmacodynamic model was found to be statistically preferable to the simpler E_{max} model that does not include a power function (γ). The pharmacodynamic parameters E_0 (spectral edge [Hz] at maximal EEG activation), E_{max} (maximal decrease of the spectral edge [Hz] by thiopental), and IC_{50} (thiopental serum concentration [μg/ml] at half of the maximal decrease (E_{max})) were estimated for the sigmoid E_{max} model with small standard errors. The interindividual variability assigned to the pharmacodynamics was moderate, ranging from 16–41%. There was no effect of age on any of the pharmacodynamic parameters.

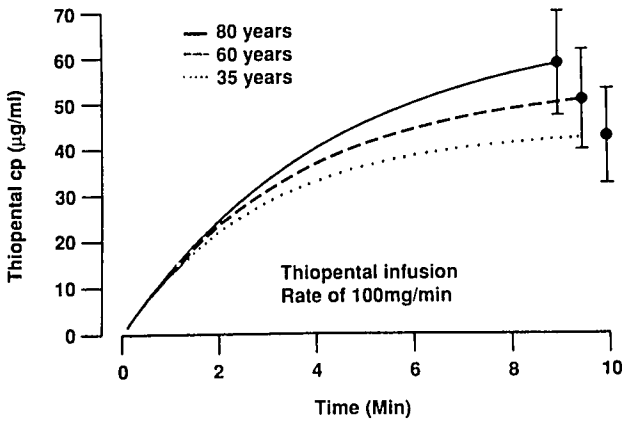

FIG. 5. The predicted thiopental serum concentration *versus* time curves for an infusion of 100 mg/min in subjects aged 80 yr (*top curve*), 60 yr (*middle curve*), and 35 yr (*lower curve*). The pharmacokinetic data from the one-compartment analysis of table 2B was used. One standard deviation of the prediction is displayed for each curve at the end of the 10-min infusion.

Discussion

We have re-examined the effect of increasing human age on thiopental pharmacokinetics and pharmacodynamics. New data analysis techniques were applied to the data we have previously reported, using population analysis approaches and semiparametric pharmacodynamic

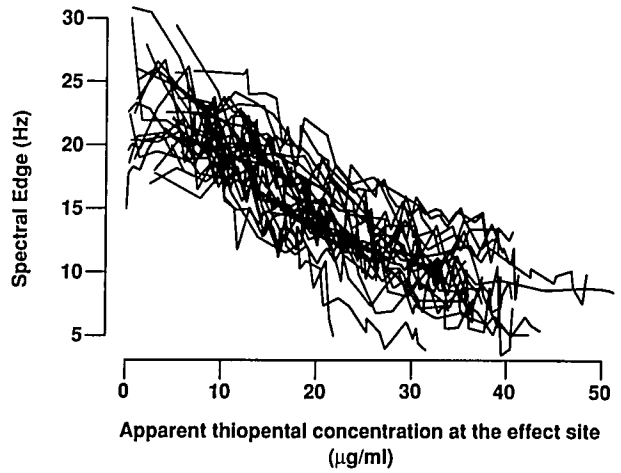

FIG. 6. The individual spectral edge *versus* apparent thiopental effect compartment concentration in 25 subjects aged less than 60 yr. Five subjects have two separate studies displayed. The semiparametric pharmacodynamic modelling approach was used to remove the disequilibrium from the measured thiopental concentrations *versus* spectral edge relationship.

modelling. We confirmed our previous report that age does not affect brain sensitivity to thiopental, using the EEG as a measure of CNS effect. The method of drug administration affected our ability to characterize thiopental's distribution phase with traditional pharmacokinetic models. When traditional pharmacokinetic models were applied to the data in subjects receiving an iv infusion of thiopental, an age-related effect on the rate of thiopental distribution from the central compartment was detected. However, the initial distribution volume could not be characterized with the three-compartment pharmacokinetic model when thiopental was given by bolus iv injection.

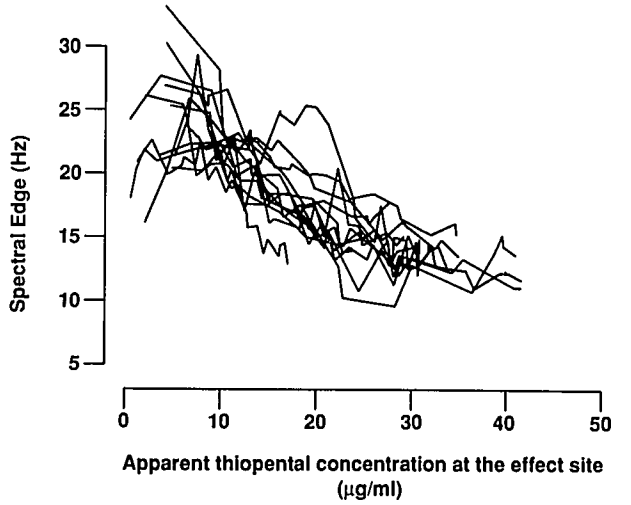

FIG. 7. The individual spectral edge *versus* apparent thiopental effect compartment concentrations in 13 subjects aged greater than 60 yr.

In reanalyzing our pharmacodynamic data, we combined the thiopental serum concentration and spectral edge data from the previously reported studies of Homer and Stanski[1] and Swerdlow *et al.*[8] Using these two data sets and the additional subjects of the current study allowed for an increased group size, specifically in the young and middle-aged subjects. Collection and measurement of the thiopental serum concentrations, EEG recording, and waveform data analysis were performed in a uniform fashion in both studies. The reanalysis involved a new conceptual approach in relating thiopental serum concentrations to the spectral edge: semiparametric effect compartment modelling.[5–7] This approach allows a more careful examination of the raw data by first removing the underlying disequilibrium in the relationship between thiopental serum concentrations and the spectral edge. One can then see the predicted effect site concentration *versus* spectral edge relationship without first applying an *a priori* pharmacodynamic model. Examining the raw data in figures 6 and 7, the apparent effect site concentration *versus* change in spectral edge relationship was similar in elderly and young subjects.

Having removed the disequilibrium from the thiopental serum concentration *versus* spectral edge data, it was possible to explore several alternative pharmacodynamic models using a population data analysis approach. We confirmed that the sigmoid E_{max} pharmacodynamic model provided the optimal characterization for this type of data. When three relevant parameters (E_0, E_{max}, and IC_{50}) were examined for age-related changes, no relationship could be detected. This confirms our previous finding that with increasing age, brain sensitivity to thiopental, as reflected by changes in the EEG, does not change.[1]

In the pharmacodynamic data, a subgroup of the subjects had a history of excessive alcohol intake. We included these subjects in the current data analysis because they had a thiopental dose requirement that was not statistically different from a control group who had only a "social" alcohol use history.[8] Additionally, the parametric pharmacodynamic modelling demonstrated that "heavy-drinking" subjects were not pharmacodynamically different from the control subjects. Removing these subjects from the data analysis did not change the conclusions of the pharmacodynamic analysis.

Complete understanding of the effect of increasing age on brain response to thiopental await the calibration of changes in the EEG to traditional clinical measures of thiopental depth of anesthesia. If the thiopental-induced changes in the EEG do correlate with clinical measures of anesthetic depth, our data predict that brain re-

TABLE 3. Thiopental Population Pharmacodynamics*

Final Model	Parameters
Sigmoid E_{max} model Spectral edge = $Eo - \frac{E_{max} \cdot Ce^{\gamma}}{IC_{50}^{\gamma} + Ce^{\gamma}}$	E_0 = 23.0 Hz Interindividual variability ± 16% E_{max} = 15.4 Hz Interindividual variability ± 24% IC_{50} = 17.9 μg/ml Interindividual variability ± 41% γ = 2.72
No effect of age on E_0, E_{max}, IC_{50}, or γ K_{e0} estimate for 38 subjects = 0.58 ± 0.28 min^{-1} (mean ± SD) Corresponding $T'_{1/2}K_{e0}$ of 1.17 min Linear regression of age *versus* $T'_{1/2}K_{e0}$ significant but the coefficient of determination (R^2 = 0.11) was very low	

* Thirty-eight subjects, 1193 measured spectral edge *versus* predicted effect compartment concentration data points, five subjects had two separate studies.

sponsiveness to thiopental does not change with increasing age.

In our thiopental pharmacokinetic analysis, our population included a group of subjects who had a history of excessive alcohol consumption. Traditional data analysis using a two-stage approach had demonstrated that the thiopental serum concentration *versus* time profiles were not significantly different in the heavy drinkers *versus* the "social" drinkers who made up the control group.[8] This finding confirmed a report by Couderc *et al.*[12] who also did not find an effect of chronic alcoholism on thiopental distribution pharmacokinetics. With this finding, we included the heavy drinkers in our data analysis.

There are two major issues in our pharmacokinetic analysis of thiopental. The first issue involves the effects of age on thiopental pharmacokinetics. The second issue involves the ability of pharmacokinetic models to characterize distribution phase pharmacokinetics relative to the method of drug administration (iv bolus *vs.* rapid infusion). We found that, following bolus iv administration of thiopental to 16 patients and with blood sampling for up to 24–48 h, population pharmacokinetic data analysis could not accurately estimate the initial distribution volume using traditional pharmacokinetic models.

This experience with characterizing thiopental distribution pharmacokinetics is typical of the problem of using pharmacokinetic models for rapid distribution phenomenon. The traditional mammillary pharmacokinetic models have numerous assumptions. These include: 1) instantaneous mixing occurs in the central compartment; 2) the pharmacokinetics are stationary (*i.e.*, volumes and clearances do not vary over time); and 3) blood samples are obtained instantaneously from the central compartment. All of these assumptions are likely to be violated during the initial distribution/phase of thiopental. Crankshaw *et al.*[13] examined the short-term distribution of thiopental in the dog, using iv bolus injections administered over 5–30 s. Frequent arterial serum concentrations were obtained at 3–5-s intervals over the first minute. They demonstrated that the peak thiopental concentrations do not occur instantaneously and will vary with the duration of injection time. There was significant variability in the peak concentrations achieved and in the rate of decline. The plots of time *versus* concentration were described as having a shape that would be anticipated for the dispersion of a rapidly administered bolus into a fast-moving circulation. The leading edges were steep while the tails are extended, suggesting some transient uptake by the pulmonary tissues. There is little evidence of recirculation, indicating a high degree of distribution into the richly perfused tissues. Crawford[14] took a more empirical anatomic and physiological approach to describing the initial distribution of injected iv bolus doses. He indicated the multiple factors governing the peak transients that occur with rapid *versus* slow iv administration of drugs. Niazi has shown, in a theoretical comparison of zero-order input relative to the generally accepted instantaneous intravascular input, that it is not possible to assume that mixing will occur instantaneously in mammillary pharmacokinetic models.[15] The assumption of instantaneous mixing will always result in an error, but this error can be corrected if the data is treated as an intravascular administration of a zero-order infusion. He recommends that all inputs be modelled as zero-input into two- and three-compartment open pharmacokinetic models. Bischoff and Brown have also created a detailed physiological model that breaks the body down into multiple small compartments, called the "minimammal."[16] They again demonstrate that there are multiple transients throughout different portions of the body when physiological models are used to predict drug concentrations over time during the initial distribution within the body. Thus it is no surprise that our attempt to use traditional pharmacokinetic models to characterize the initial distribution volume over a large group of patients using

frequent arterial sampling was not successful. Henthorn *et al.*[17] have simultaneously administered thiopental and an additional intravascular indicator, indocyanine green (ICG). They have proposed simultaneous modelling of ICG with the thiopental concentration decay that results in thiopental distribution phase pharmacokinetic parameters with more physiological constraints. Their results suggest that a 2–3 min "mixing phase" occurs during thiopental distribution. The more sophisticated pharmacokinetic modelling proposed by Henthorn *et al.* has significant promise to characterize drug distribution pharmacokinetics.

Our one-compartment analysis represents an approach of simplifying the pharmacokinetic modelling to the data maximally relevant to the clinical drug effect. For thiopental this represents the first 10–15 min following drug administration. The one-compartment modelling demonstrated that aging changes the rate of thiopental elimination in the first few minutes of drug administration and confirmed the results of the complete three-compartment modelling.

The issue of distribution pharmacokinetics for thiopental has been further confused in the literature by arterial/venous sampling differences. Numerous thiopental pharmacokinetic studies have used peripheral venous sites to sample the initial serum concentrations.[18–22] There is a large body of literature that demonstrates significant differences between the arterial and venous drug concentrations for most drugs, including thiopental. Barrett *et al.*[23,24] have demonstrated in both animals and man that thiopental concentrations from venous sites reach a peak up to 2 min after completion of the iv bolus injection. There was also a large intraindividual variability in the serum concentration *versus* time relationships when peripheral venous samples were used. Concentration differences between arterial and peripheral sampling sites were considerable in most subjects and averaged nearly 10%, up to 9 min after bolus iv administration. Chiou *et al.* have confirmed the significance of arterial/venous concentration differences impacting on pharmacokinetics.[25–29] Based upon their observation that the marked variation in initial distribution volume parameters is frequently proportional to the interval of sampling, they recommend that short iv infusions, rather than bolus iv injections, should be the preferred route for pharmacokinetic studies. The short iv infusion allows time for multiple blood samples to be drawn that will estimate the initial distribution phase. With an iv bolus, only one or two samples can be obtained to estimate the early distribution phase.

All compartmental pharmacokinetic models are based on the assumption that the parameters such as clearance and volume of distribution are constant over time, but there are several factors that might violate this assumption and alter drug distribution and elimination. For a drug such as thiopental, which is dependant on cardiac output for its distribution, any drug-induced change in cardiac output might change the distribution phase pharmacokinetics. Additionally, clinically relevant noxious stimuli (*i.e.*, laryngoscopy and intubation) can also cause profound changes in cardiovascular function, which might cause moderate changes in the rate and degree of the drug distribution. Many studies do not carefully specify whether perioperative stimuli were applied or the degree of hemodynamic response to the drug or the stimuli.

Our own approach to characterizing distribution pharmacokinetics has involved the use of a rapid iv infusion, with arterial serum concentration sampling at frequent intervals. Typically, one can obtain six to eight serum concentrations at half-minute intervals during the infusion and an equivalent number of serum concentrations during the first 3–5 min after termination of the infusion. The slower administration relative to the bolus injection tends to minimize unwanted side effects, *i.e.*, hemodynamic and respiratory depression. This should, in principle, minimize the concern of nonstationary drug kinetics. Using this approach, it is possible to obtain 12–14 data points that can then be used to characterize rapid and slow distribution phase components. These 12–14 data points are more than adequate for the estimation of the pharmacokinetic parameters (initial distribution volume, rapid and slow intercompartment clearances, metabolic clearance) that characterize the distribution phase. The data analysis in this study demonstrates that it is possible to obtain consistent and reliable pharmacokinetic data, using a rapid iv infusion with frequent arterial blood sampling. This is also compatible with the suggestions of many other theoretical and experimental studies regarding characterization of distribution phase kinetics. We would thus not recommend bolus iv injections for drug administration in pharmacokinetic studies where the distribution pharmacokinetics are of relevance and traditional pharmacokinetic modelling approaches are to be used.

In our previous publication,[1] the mode of drug administration was both iv bolus injection and rapid iv infusion. The younger subjects received an iv bolus injection, while the middle-aged and older received a rapid iv infusion. The initial distribution volumes estimated from the iv bolus studies were significantly larger, *i.e.*, 15–20 l/70-kg subject, compared with the initial distribution volumes estimated in the middle-aged to elderly subjects, 3–10 l/70 kg. The age-related change in initial distribution volume we previously reported may reflect a methodological artifact from using bolus iv and infusion data interchangeably. Also, the previously discussed inaccuracy of distribution phase pharmacokinetics obtained from rapid iv bolus dosing could also explain our previous data.

With this in mind, we have reanalyzed our data in an attempt to characterize properly the effect of age on thiopental distribution pharmacokinetics.

We have demonstrated that with increasing age there is a change of thiopental's rapid intercompartment clearance while the initial distribution volume did not change with age. Following a rapid iv bolus, the peak thiopental serum concentrations that occur within 15–30 s will be similar in the young and elderly patients because the initial distribution volume is not altered by aging. After the peak serum concentration is achieved, two pharmacokinetic factors will serve to decrease the serum concentrations: rapid and slow intercompartment clearance that represents distribution of drug into highly perfused and less well-perfused tissues, and hepatic metabolism of the drug. Thiopental serum concentrations will not decrease as rapidly in the elderly *versus* young patient because the rapid intercompartment clearance is lower in the elderly patient. The higher thiopental serum concentrations that occur in the minutes after the iv bolus will result in more thiopental being available for distribution into the biophase (brain) to create a greater anesthetic effect in the elderly. Our pharmacokinetic analysis indicates that the rapid intercompartment clearance is approximately 30% lower in the elderly (80 yr) *versus* young patient. Examining the raw serum concentration *versus* time data during the infusion of thiopental (figs. 3 and 4) one can see that the elderly subjects are consistently in the upper border of the thiopental serum concentrations relative to young and middle-aged subjects.

Using NONMEM for population pharmacokinetic data analysis, we found that the distribution pharmacokinetic parameters had significantly higher variability compared with the elimination phase parameters (*i.e.*, metabolic clearance). Given that thiopental distribution pharmacokinetics are dependant on cardiovascular function, specifically perfusion, the variability in cardiac function and cardiac output might explain in part the 30–70% variability in thiopental distribution pharmacokinetic parameters. Our ability to individualize thiopental administration will therefore be dependent upon obtaining noninvasive measures of the patient's physiological cardiovascular function prior to the administration of thiopental. At present there are no practical mechanisms for this.

In summary, we have re-examined the effect of age on thiopental pharmacokinetics and pharmacodynamics in humans. We found that iv bolus administration of thiopental did not allow accurate characterization of thiopental distribution phenomenon. Using a rapid iv infusion, we demonstrated that increasing age decreased thiopental rapid intercompartment clearance. Initial distribution volume was not age related as we previously have reported. Thiopental EEG pharmacodynamics are not altered with increasing age.

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References

1. Homer TD, Stanski DR: The effect of increasing age on thiopental anesthetic requirement and disposition. ANESTHESIOLOGY 62: 714–724, 1985
2. Avram MJ, Krejcie TC, Henthorn TK: The relationship of age to the pharmacokinetics of early drug distribution: The concurrent disposition of thiopental and indocyanine green. ANESTHESIOLOGY 72:403–411, 1990
3. Maitre PO, Vozeh S, Heykants J, Thomson DA, Stanski DR: Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. ANESTHESIOLOGY 66:3–12, 1987
4. Whiting B, Kelman AW, Grevel J: Population pharmacokinetics: Theory and clinical application. Clin Pharmacokinet 11:387–401, 1986
5. Fuseau E, Sheiner LB: Simultaneous modelling of pharmacokinetics and pharmacodynamics with a nonparametric pharmacokinetic model. Clin Pharmacol Ther 35:733–741, 1984
6. Unadkat JD, Bartha F, Sheiner LB: Simultaneous modelling of pharmacokinetics and pharmacodynamics with nonparametric kinetic and dynamic models. Clin Pharmacol Ther 40:86–93, 1986
7. Verotta D, Sheiner LB: Simultaneous modelling of pharmacokinetics and pharmacodynamics: An improved algorithm. Comp Appl Biosci 3:345–349, 1987
8. Swerdlow BN, Holley FO, Maitre PO, Stanski DR: Chronic alcohol intake does not change thiopental anesthetic requirement, pharmacokinetics, or pharmacodynamics. ANESTHESIOLOGY 72: 455–461, 1990
9. Stanski DR, Burch PG, Harapat S, Richards RK: Pharmacokinetics and anesthetic potency of a thiopental isomer. J Pharm Sci 72: 937–940, 1983
10. Stanski DR, Hudson RJ, Homer TD, Saidman LJ, Meathe E: Pharmacodynamic modelling of thiopental anesthesia. J Pharmacokinet Biopharm 12:223–240, 1984
11. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modelling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979
12. Couderc E, Ferrier C, Haberer JP, Henzel D, Duvaldestin P: Thiopentone pharmacokinetics in patients with chronic alcoholism. Br J Anaesth 56:1393–1397, 1984
13. Crankshaw DP, Rosler A, Ware M: The short-term distribution of thiopentone in the dog. Anaesth Intensive Care 7:148–151, 1979
14. Crawford JS: Speculation: The significance of varying the mode of injection of a drug. Br J Anaesth 38:628–640, 1966
15. Niazi S: Errors involved in instantaneous intravascular input assumptions. J Pharm Sci 65:750–752, 1976
16. Bischoff KB, Brown RG: Drug distribution in mammals. Chem Eng Prog Symp Ser 62:33–45, 1966
17. Henthorn TK, Avram MJ, Krejcie TC: Intravascular mixing and

drug distribution: The concurrent disposition of thiopental and indocyanine green. Clin Pharmacol Ther 45:56–65, 1989

18. Jung D, Mayersohn M, Perrier D, Calkins J, Saunders R: Thiopental disposition as a function of age in female patients undergoing surgery. ANESTHESIOLOGY 56:263–268, 1982
19. Ghoneim MM, Van Hamme MJ: Pharmacokinetics of thiopentone: Effects of enflurane and nitrous oxide anaesthesia and surgery. Br J Anaesth 50:1237–1241, 1978
20. Christensen JH, Andreasen F, Jansen JA: Pharmacokinetics and pharmacodynamics of thiopentone. Anaesthesia 37:398–404, 1982
21. Christensen JH, Andreasen F, Jansen JA: Thiopentone sensitivity in young and elderly women. Br J Anaesth 55:33–39, 1983
22. Christensen JH, Andreasen F, Jansen JA: Influence of age and sex on the pharmacokinetics of thiopentone. Br J Anaesth 53: 1189–1195, 1981
23. Barratt RL, Graham GG, Torda TA: Kinetics of thiopentone in relation to the site of sampling. Br J Anaesth 56:1385–1391, 1984
24. Barrett R, Graham GG, Torda TA: The influence of sampling site upon the distribution phase kinetics of thiopentone. Anaesth Intensive Care 12:5–9, 1984
25. Chiou WL, Lam G, Chen M-L, Lee MG: Arterial-venous plasma concentration differences of six drugs in the dog and rabbit after intravenous administration. Res Commun Chem Pathol Pharmacol 32:27–39, 1981
26. Chiou WL, Lam G, Chen M-L, Lee MG: Instantaneous input hypothesis in pharmacokinetic studies. J Pharm Sci 70:1037–1039, 1981
27. Chen M-L, Lam G, Lee MG, Chiou WL: Arterial and venous blood sampling in pharmacokinetic studies: Griseofulvin. J Pharm Sci 71:1386–1389, 1982
28. Chiou WL: Potential effect of early blood sampling schedule on calculated pharmacokinetic parameters of drugs after intravenous administration. J Pharm Sci 69:867–869, 1980
29. Chiou WL: Potential pitfalls in the conventional pharmacokinetic studies: Effects of the initial mixing of drug in blood and the pulmonary first pass elimination. J Pharmacokinet Biopharm 7: 527–536, 1979