

Thiopental Disposition in Lean and Obese Patients Undergoing Surgery

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The effect of obesity on the disposition kinetics of thiopental was studied in seven morbidly obese (age 25 to 46 years) and eight age-matched lean patients (age 25 to 43 years), undergoing primarily abdominal surgery. Based upon total (bound + free) thiopental concentrations, the average (\pm SD) volumes of distribution in the terminal disposition phase and at steady-state (V_β and V_{ss}) were significantly larger in the obese (7.94 ± 4.55 l/kg and 4.72 ± 2.73 l/kg, respectively) than in the age-matched lean patients (1.95 ± 0.63 l/kg and 1.40 ± 0.46 l/kg, respectively). Clearance of total thiopental, normalized for total body weight was not significantly different between the obese (0.18 ± 0.08 l \cdot h $^{-1}$ \cdot kg $^{-1}$) and lean patients (0.21 ± 0.06 l \cdot h $^{-1}$ \cdot kg $^{-1}$). However, total body clearance not normalized for total body weight was significantly larger in the obese (24.98 ± 14.87 l/h) than in the lean patients (11.86 ± 3.66 l/h). The elimination half-life of thiopental was significantly longer in the obese (27.85 h) than in the lean patients (6.33 h) and this difference was primarily a function of the larger apparent volume of distribution for thiopental. The unbound fraction of thiopental in serum (range, 17.8 per cent to 27.6 per cent) was not correlated with the degree of obesity. The most appropriate means of comparing intrinsic metabolizing capacity (*i.e.*, normalized *vs.* non-normalized for weight) between lean and obese subjects remains unresolved. (Key words: Anesthetics, intravenous: thiopental. Induction: anesthesia. Pharmacokinetics: thiopental. Recovery.)

ALTHOUGH THIOPIENTAL is used widely and was introduced into clinical practice in 1934, little pharmacokinetic and pharmacodynamic information has been available in patients undergoing surgery until just recently.¹⁻⁵ Data concerning the influence of disease,⁶ other drugs,⁷ body weight, sex, and age⁸ on thiopental have been published. However, these studies have not attempted to quantitate rigorously the degree to which the factors mentioned contribute to the interpatient variability in thiopental disposition.

Thiopental has been known for decades to be localized in fatty tissues; there is, however, very little quantitative information available regarding the influence of obesity

on thiopental dosage requirements. Clinical observations indicate that an obese person often requires less thiopental than a thin individual.⁸ Since the duration of anesthesia after a bolus dose appears related to the amount of lean body mass, an obese person, who has a smaller ratio of lean body mass to total body weight (TBW) than an average individual, may require less drug per TBW to "fill" this smaller lean body mass. Therefore, the purpose of this investigation was to examine the disposition of the intravenous anesthetic agent, thiopental, in a group of age-matched lean and obese patients undergoing surgery.

Methods

The study group containing eight lean apparently healthy adult female patients between the ages of 25 and 43 years (34.5 ± 6.4 , mean \pm SD) and weighing 50.0–64.0 kg (57.4 ± 5.0) and seven (five females and two males) markedly obese age-matched adult patients between the ages of 25 and 46 years (33.0 ± 7.0) and weighing 84.6–215.0 kg (137.9 ± 41.3) undergoing elective primarily abdominal surgery (see table 1). Body mass index (BMI = weight [kg]/height²[m]) was used to define obesity.⁹ All obese patients were classified as being morbidly obese when the BMI exceeded a value of 30 (*i.e.*, 35–40 per cent overweight, see Table 1).⁹ A complete blood chemistry (SMA-20), urinalysis, hematocrit, and complete and differential blood counts were performed in each patient prior to the study. The study was approved by the Human Subjects Committee at the University of Arizona Health Sciences Center. Written consent to participate was obtained from each individual after the nature, purpose, and risks of the investigation were explained.

In seven of the eight lean patients premedication consisted of glycopyrrolate, 0.2–0.3 mg intramuscularly (im); diazepam, 10 mg, orally, and/or morphine sulfate, 6 to 10 mg, im. In patient 3, 75 mg meperidine was used for premedication. In five of the seven obese patients, premedication consisted of 0.3 mg glycopyrrolate, im: 10 to 15 mg diazepam, orally, and/or 10 mg morphine sulfate, im. In patients 13 and 14, premedication consisted of 15 mg diazepam, orally. All patients received gallamine (10–20 mg intravenously, iv) and were oxygenated (3–5 min) prior to induction of anesthesia. Anesthesia was induced with a bolus of thiopental at a dose selected

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Received from the Departments of Pharmaceutical Sciences and Anesthesiology and the Ruth E. Golding Clinical Pharmacokinetics Laboratory, Colleges of Pharmacy and Medicine, The University of Arizona, Tucson, Arizona 85721. Accepted for publication September 28, 1981. Supported in part by a grant from the Office of the Provost for Graduate Studies and Health Sciences, The University of Arizona.

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TABLE 1. Patient Characteristics

Subject	Sex	Age (yr)	Weight (kg)	Height (m)	BMI (kg/m ²)	Surgical Procedure*	Current Medications†
Lean Patients							
1	F	25	51.1	1.57	20.60	Tuboplasty	None
2	F	29	59.5	1.63	22.52	TAH/BSO	None
3	F	29	56.0	1.75	18.23	Metroplasty	None
4	F	36	58.7	1.61	22.56	Cholecystectomy	None
5	F	36	50.0	1.63	18.92	TAH/BSO	None
6	F	36	62.5	1.66	22.58	TAH/BSO	None
7	F	42	57.5	1.56	23.56	TAH/BSO	None
8	F	43	64.0	1.67	23.09	TAH/BSO	None
Mean ± SD		34.5 ± 6.4	57.4 ± 5.0	1.64 ± 0.06	21.51 ± 2.01		
Obese Patients							
9	F	25	84.6	1.55	35.22	Cholecystectomy	None
10	M	29	215.0	1.75	70.20	Gastric stapling	A
11	F	29	125.3	1.73	42.00	Gastric stapling	None
12	F	31	130.5	1.73	43.75	Gastric stapling	None
13	F	33	151.0	1.62	57.54	Gastric stapling	None
14	F	38	108.0	1.57	43.55	Gastric stapling	Insulin
15	M	46	151.1	1.83	45.19	Gastric stapling	B
Mean ± SD		33.0 ± 7.0	137.9 ± 41.3	1.68 ± 0.10	48.21 ± 12.56		

* TAH/BSO: total abdominal hysterectomy/bilateral salpingo-oophorectomy.

† Medication other than that associated with the anesthetic procedure.

dures: A. terbutaline, digoxin, theophylline, dexamethasone; B. isoniazid, methyldopa, ibuprofen, phenytoin, hydrochlorothiazide, Marax®.

by the anesthesiologist (2.59 to 5.98 mg/kg) and this was followed by succinylcholine (70–200 mg, iv), cricoid pressure, and placement of cuffed endotracheal tubes. Anesthesia was maintained (2–4 h) with a mixture of nitrous oxide, oxygen, and enflurane. Pancuronium bromide (2–10 mg, iv) was employed for muscle relaxation in all patients, while ventilation in the obese and lean patients was controlled to maintain arterial carbon dioxide tension (P_{aCO_2}) at 40 ± 5 mmHg, and 35 ± 5 mmHg, respectively. Arterial blood gas values were confirmed by serial determinations.

Ten-ml blood samples were obtained prior to and at 5, 10, 15, 30, 45 min and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96 h after induction of anesthesia with thiopental or until serum concentrations were less than 50 ng/ml. In the obese patients, blood samples were drawn from an arterial line in the distal arm for the first twenty-four hours. Thereafter, a heparin lock in the distal arm was used for all subsequent samples. Analysis of simultaneously collected arterial and venous samples at one and two hours after administration in one patient indicated no difference in concentration. In addition, there was no observable change in the trend of concentration-time values when sampling site was changed. In the lean patients, all blood samples were drawn from a heparin lock. One hundred units of heparin were used to flush the heparin lock after a blood sample was obtained. Serum was obtained by centrifugation of the clotted blood within 60 min of drawing the sample and kept frozen at -20° C.

All serum samples were assayed for thiopental using gas chromatography employing a nitrogen-specific detector.¹⁰ The assay was sensitive to 25 ng/ml and specific for thiopental. Diazepam, fentanyl, and morphine, drugs frequently used in conjunction with thiopental, did not interfere with the determination of thiopental.

To determine the binding of thiopental to serum proteins, pre-dose plasma samples were spiked with 250 ng/ml ¹⁴C thiopental and equilibrium dialysis performed as previously described.¹¹ These experiments were performed at 37° C with a 12-h dialysis time. In addition, the thiopental blood to plasma ratio (B/P) was determined by spiking pre-dose blood samples with 250 ng/ml ¹⁴C thiopental.

The serum concentration(C) vs. time(t) data after intravenous administration of sodium thiopental were fit to the following equation:

$$C = \sum_{i=1}^n A_i e^{-\lambda_i t} \quad (1)$$

using the nonlinear least squares regression analysis program, NONLIN.¶ In equation 1, n is the number of exponents required to describe the serum concentration-time data, A_i is a zero time intercept, and λ_i is a disposition rate constant. A weighting function of $1/C^2$ was found to provide the best fit of the data. Choice of an

¶ Metzler CM: NONLIN. A computer program for parameter estimation in nonlinear situations. Kalamazoo, The Upjohn Company, 1969.

appropriate model was determined by use of an F-test.¹² Initial estimates for A_1 and λ_1 required for input into the computer program were obtained from a plot of $\log C$ versus time and using the method of residuals to resolve the curve into its exponential components.¹³ Various pharmacokinetic parameters were calculated by conventional means¹³ as indicated in the Appendix. All results are expressed as the mean \pm standard deviation. Differences in kinetic variables between age-matched lean and obese patients were determined by Student's t test. A value of $P < 0.05$ was considered to be statistically significant.

Results

Table 2 presents pertinent clinical laboratory data for the patients in the study. Serum creatinine (except patient 13), serum albumin, SGPT (except patient 9), and SGOT (except patient 9) were within normal limits. No significant differences in any of the variables measured were detected between the lean and obese patients with the exception of weight and body mass index. On the average, the weight and body mass index were approximately 2.2 and 2.4 times larger, respectively, in the obese compared to the lean population.

Serum concentration *vs.* time plots after intravenous administration of thiopental in a typical lean and obese patient are presented in figure 1. In the age-matched lean patient, the serum concentration-time data were best described by a biexponential equation in seven patients and by a triexponential equation in one patient. However, a triexponential equation best described the disposition of thiopental in five obese patients, and a biexponential equation best described the disposition in two obese patients. Average pharmacokinetic parameters for total and unbound thiopental in the lean and obese patients are presented in Table 3. Two of the obese patients were male; however, the pharmacokinetic parameters for these two patients did not differ from those of the five female patients. The individual kinetic parameters are available from the authors upon request. In this study, where the anesthesiologist was allowed to choose the thiopental dose, the obese patient was given significantly less

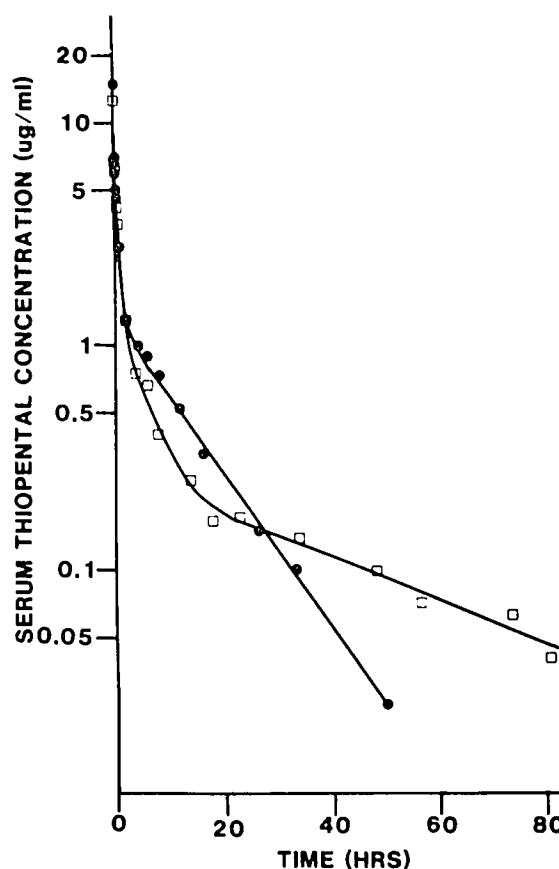


FIG. 1. Representative thiopental serum concentration-time plot for a lean (patient 6) and obese (patient 12) patient after intravenous administration of sodium thiopental. The solid line represents a non-linear regression fit of the data (●) = lean patient; (□) = obese patient.

($P < 0.02$) thiopental on a mg/kg basis (3.89 ± 0.83 mg/kg) than that given to the age-matched lean patient (5.08 ± 0.72 mg/kg).

The apparent volumes of distribution in the terminal disposition phase (V_β) and at steady-state (V_{ss}), are expressed per TBW. In the obese patients the average value for V_β is, 7.94 ± 4.55 l/kg and for V_{ss} , 4.72 ± 2.73 l/kg. These values were significantly larger than those found in the age-matched lean patient; V_β , 1.95 ± 0.63 l/kg and V_{ss} , 1.40 ± 0.45 l/kg. The systemic clearance of thiopental (Cl), which reflects the intrinsic ability of the liver to metabolize thiopental, averaged 0.21 ± 0.06 l·h⁻¹·kg⁻¹ in lean and 0.18 ± 0.08 l·h⁻¹·kg⁻¹ in the obese patients, respectively. These values were not significantly different. However, when systemic clearance of thiopental is not corrected for TBW, clearance was significantly larger in the obese (24.98 ± 14.87 l/h) compared to the age-matched lean patients (11.86 ± 3.66 l/h). The elimination half-life ($t_{1/2}$) of thiopental which is a function of both the apparent volume of distribution and clearance, was significantly longer in the obese

TABLE 2. Clinical Data for Lean and Obese Patients*

Variable	Lean	Obese	Value of Student's t
Protein (g/dl)	6.18 ± 0.65	6.21 ± 0.61	0.12 (NS)†
Albumin (g/dl)	3.79 ± 0.24	3.60 ± 0.24	1.51 (NS)
SGPT (U/l)	4.13 ± 2.64	21.57 ± 24.13	2.04 (NS)
SGOT (U/l)	12.38 ± 5.71	30.29 ± 23.38	2.11 (NS)

* Mean \pm SD

† NS = not significant.

TABLE 3. Pharmacokinetic Parameters for Total and Unbound Thiopental in Lean and Obese Patients*

	Total Thiopental			Unbound Thiopental		
	Lean (n = 8)	Obese (n = 7)	Value of Student's <i>t</i>	Lean (n = 8)	Obese (n = 7)	Value of Student's <i>t</i>
Dose (mg/kg)	5.08 ± 0.72	3.89 ± 0.83	2.98 (<i>P</i> < 0.02)	—	—	—
V_d (l/kg)	1.95 ± 0.63	7.94 ± 4.55	3.70 (<i>P</i> < 0.005)	9.85 ± 3.42	39.70 ± 21.81	3.84 (<i>P</i> < 0.005)
V_{ss} (l/kg)	1.40 ± 0.46	4.72 ± 2.73	3.40 (<i>P</i> < 0.005)	7.47 ± 2.23	23.58 ± 13.36	3.37 (<i>P</i> < 0.005)
Cl (l·h ⁻¹ ·kg ⁻¹)	0.21 ± 0.06	0.18 ± 0.08	0.82 (NS)†	1.04 ± 0.35	0.88 ± 0.38	0.82 (NS)
Cl (l/h)	11.86 ± 3.65	24.98 ± 14.87	2.42 (<i>P</i> < 0.05)	59.95 ± 20.18	125.69 ± 74.00	2.42 (<i>P</i> < 0.05)
$t_{1/2}(h)†$	6.33	27.85	5.94 (<i>P</i> < 0.001)	—	—	—
$\alpha‡$	—	—	—	0.20 ± 0.02	0.20 ± 0.02	0.30 (NS)
B/P§	0.88 ± 0.05	0.85 ± 0.07	1.01 (NS)	—	—	—

* Mean ± SD.

† Harmonic mean.

‡ α : free fraction of thiopental in serum.

§ B/P: blood/plasma concentration ratio.

¶ NS = not significant.

(27.85 h) compared to the lean patients (6.33 h). The pharmacokinetic parameters for thiopental in patient 13 who had a serum creatinine below the normal range were similar to the other patients. Patient 9 had elevated SGPT and SGOT values, but had a clearance which was well within the range of values for the seven subjects.

Thiopental was bound extensively to serum proteins in both lean and obese patients. The free fractions in serum (α) ranged between 17.9 per cent to 23.4 per cent and averaged 20 ± 2 per cent in all patients. Binding is not influenced by the *in vitro* addition of heparin.¹¹ The blood to plasma ratio (B/P) for thiopental ranged between 0.74 and 0.97 and averaged 0.88 ± 0.05 and 0.85 ± 0.07 in the lean and obese patients, respectively. No significant differences were observed in the blood to plasma ratio between lean and obese patients; nor were differences seen in the binding of thiopental to serum proteins. Thiopental blood clearances normalized for body weight were not significantly different between lean (0.24 ± 0.07 l·h⁻¹·kg⁻¹) and obese patients (0.21 ± 0.12 l·h⁻¹·kg⁻¹). Blood clearances not normalized for TBW were also not significantly different.

Average volumes of distribution based on unbound thiopental concentrations are presented in Table 3. The average values of V_d and V_{ss} in the obese were 39.70 ± 21.81 l/kg and 23.58 ± 13.36 l/kg, which were significantly larger than that found in the lean patients (9.85 ± 3.42 l/kg and 7.47 ± 2.23 l/kg, respectively). Clearance of unbound thiopental was not significantly different between the lean and obese patients (1.04 ± 0.35 l·h⁻¹·kg⁻¹ vs. 0.88 ± 0.38 l·h⁻¹·kg⁻¹) when normalized for TBW. However, when not normalized for TBW, unbound clearance was significantly larger in obese patients (125.69 ± 74.00 l/h) than in lean patients (59.95 ± 20.18 l/h).

Discussion

Bi- or triexponential equations (*i.e.*, two- or three-compartment models) describing the kinetic pattern for

thiopental in humans have been reported previously.^{1,2,4,5} The serum concentration *vs.* time data in the present study clearly demonstrated multiexponential decline. In all patients the serum thiopental concentrations declined by 50–75 per cent within thirty minutes followed by a much slower decline during the terminal phase after intravenous administration. This pattern is consistent with the initial rapid distribution of thiopental into tissues highly perfused by blood such as the brain and liver, followed by redistribution into muscle tissue. This type of profile was seen in both the lean and obese patients.

The apparent volume of distribution is a pharmacokinetic parameter that depends on the partitioning characteristics of a drug and its ability to distribute into extravascular tissue. The average value for V_d found in the lean patients (1.95 ± 0.63 l/kg) is similar to the values obtained by Andreasen *et al.*² (2.29 ± 1.10 l/kg) and Ghoneim and VanHamme¹ (1.88 ± 0.93 l/kg) in patients undergoing surgery. It is, however, smaller than that observed by Morgan *et al.*⁴ (4.16 ± 2.40 l/kg) probably because of the wider age range in this latter study. The three- to fourfold increase in apparent volumes of distribution (V_d and V_{ss}) of thiopental found in the obese compared to the lean patients may be attributed primarily to the extremely lipid-soluble nature of thiopental. Dayton *et al.*¹⁴ reported a subcutaneous fat/plasma partition ratio of 6.7 and an omental fat/plasma ratio of 8.5 after single intravenous doses of 300 to 500 mg in humans. The mean value for V_d in our obese patients (7.94 ± 4.55 l/kg) is consistent with the value of 8.4 l/kg found in an obese patient who received multiple thiopental doses to control her epilepsy.¹⁵ Similar results have been observed for diazepam,¹⁶ and theophylline.¹⁶

Since thiopental is eliminated primarily by metabolism,¹⁷ and the clearance of thiopental is low relative to liver blood flow, the clearance of thiopental reflects the

** Abernathy DR, Greenblatt DJ, Allen MD: Diazepam kinetics in obesity. Clin Res 28:233a, 1980.

intrinsic ability of the liver to metabolize the drug. When clearance was corrected for TBW, no significant difference was observed between the obese and lean patients. Therefore, if thiopental were to be administered chronically to treat seizures, particularly those refractory to more conventional therapy,¹⁸ the same daily dose on a per kg TBW basis could be administered to lean and obese patients. However, when clearance was not corrected for total body weight, a twofold increase in clearance was found in the obese patient. Similar results were reported for diazepam by Abernethy *et al.***

A question arises as to whether clearance should or should not be normalized to TBW or body mass index to provide a better estimate of the liver's intrinsic ability to metabolize a drug. Sultatos *et al.*¹⁹ review the practice of correcting clearance and volume of distribution for total body weight for antipyrine as a way to normalize the data. For antipyrine, it was found that correction of clearance for total body weight did not normalize the data. Pharmacokinetic studies with sulfisoxazole,²⁰ antipyrine and tolbutamide,²¹ indicated no difference between lean and obese subjects in drug metabolizing ability based on half-life determinations. However, half-life may not be an appropriate index of metabolism for those drugs.

Previous studies^{22,23} suggest that decreased liver function in obesity was due to fatty infiltration. Thus, for a highly lipid-soluble drug such as thiopental, which distributes into fat, one may expect that the large lipid deposits found in obese patients will result in prolonged exposure to hepatic drug metabolizing enzymes and thereby increase clearance. However, Freston and Englert²⁴ reported that the metabolism of bromsulphalein was not different in obese subjects. An attempt to determine whether obesity might influence *in vitro* hepatic drug metabolizing enzyme activities was tested in genetically obese Zucker rats.²⁵ It was shown that the cytochrome P-450-dependent microsomal enzyme system as measured by aniline hydroxylase, aminopyrine demethylase, and arylhydrocarbon hydroxylase, was dramatically deficient in the obese rats. The controversy remains as to whether clearance should or should not be normalized to TBW or body mass index and hence, whether or not obese patients metabolize thiopental at a faster rate than do lean patients.

The half-life of thiopental, which is a function of both the apparent volume of distribution and clearance, was prolonged in obese patients and was found to be primarily a function of the larger apparent volume of distribution. These findings are similar to those of Abernethy *et al.*** with diazepam. Those investigators reported a twofold increase in the half-life in obese (86.2 h) compared to lean (40.4 h) subjects receiving 0.1–0.15 mg/kg diazepam, *iv*. The apparent volume of distribution

of this fat soluble drug was 2.88 l/kg in the obese compared to 1.56 l/kg in the lean. The half-lives reported here are shorter than those reported in a previous study of a lean and an obese subject.¹⁵ This probably can be explained by the relatively short duration of sample collection in this latter study and the fact that the concentrations measured were probably in a range where non-linear metabolism occurs.²⁶

In summary, the volume of distribution of thiopental in humans is influenced by its distribution into adipose tissue and therefore is influenced by the degree of obesity. However, the question of whether metabolism, as represented by the clearance of thiopental, is altered in obese patients is not known. Further studies are necessary to answer this fundamental question.

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APPENDIX

Kinetic parameters were estimated from the following equations. The total (*i.e.*, time zero to infinity) area under the serum concentration-time curve (AUC) was determined from the following expression:

$$AUC = \sum_{i=1}^n A_i/\lambda_i \quad (1)$$

Total body clearance (Cl) was determined by

$$Cl = \frac{D_{iv}}{AUC} \quad (2)$$

where D_{iv} is the intravenous dose of thiopental. Elimination half-life ($t_{1/2}$), apparent volume of distribution (V_β), and steady-state volume of distribution (V_{ss}) were calculated using the following relationships:

$$t_{1/2} = \ln 2/\lambda_n \quad (3)$$

$$V_\beta = Cl/\lambda_n \quad (4)$$

$$V_{ss} = \frac{D_{iv}(\sum_{i=1}^n A_i/\lambda_i^2)}{AUC^2} \quad (5)$$

where λ_n is the terminal elimination rate constant. Unbound total body clearance (Cl_u) and unbound volumes of distribution ($V_{\beta u}$ and V_{ssu}) were determined as follows:

$$Cl_u = Cl/\alpha \quad (6)$$

$$V_{\beta u} = V_\beta/\alpha \quad (7)$$

$$V_{ssu} = V_{ss}/\alpha \quad (8)$$

respectively, where α is the fraction of thiopental not bound to serum proteins. Blood clearance (Cl_b) was determined from the total body clearance and the blood/plasma ratio for thiopental (B/P):

$$Cl_b = Cl/(B/P) \quad (9)$$