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Pharmacokinetics of Thiopental Enantiomers during and following Prolonged High-dose Therapy

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Background: **Thiopental is used as a racemate; however, this is not generally recognized. During conditions of prolonged high-dose therapy, the pharmacokinetics of thiopental may become nonlinear, but whether this derives from one or both enantiomers has not been evaluated. The authors determined the pharmacokinetics of *R*- and *S*-thiopental and serum concentrations of *R*- and *S*-pentobarbital from prolonged high-dose infusion of thiopental for neuroprotection.**

Methods: **Twenty patients received a mean thiopental dose of 41.2 g over a mean duration of 95 h. *R*- and *S*-thiopental enantiomer serum concentration–time data from 18 patients were fitted with two models: a linear one-compartment model with first-order output, and a nonlinear one-compartment model with Michaelis-Menten output.**

Results: **Nonlinear models were preferred in 16 of 18 patients. Paired analysis indicated that steady state clearance (Cl_{ss}) and volume of distribution (V_d) were higher for *R*-thiopental (0.108 *vs.* 0.096 l/min, $P < 0.0001$; and 313 *vs.* 273 l, $P < 0.0005$, respectively); maximal rate of metabolism (V_m) was higher for *S*- than for *R*-thiopental (1.01 *vs.* 0.86 mg · l^{-1} · h^{-1}, $P = 0.02$); elimination half-lives did not differ (14.6 *vs.* 14.7 h, $P = 0.8$); unbound fractions (f_u) of *R*- and *S*-thiopental were 0.20 and 0.18, respectively, $P < 0.0001$). The differences in mean Cl_{ss}, V_d and V_m were not significant when adjusted by f_u. Plasma concentrations of *R*- and *S*-pentobarbital were relatively small and unlikely to be of clinical significance.**

Conclusion: **The pharmacokinetics of *R*- and *S*-thiopental became nonlinear at these doses. The pharmacokinetic differences between *R*- and *S*-thiopental, although small, were statistically significant and were influenced by the higher f_u of *R*-thiopental. (Key words: Anesthetics; intravenous thiopental; enantiomers; linear pharmacokinetic models; nonlinear pharmacokinetic models; high-dose infusion.)**

PROLONGED high-dose thiopental therapy is used to reduce intracranial hypertension and protect the brain against ischemic injury in acute neurologic and neurosurgical emergencies. It is well-established that thiopental shows nonlinear Michaelis-Menten pharmacokinetics at high doses.[1–8] Commercially available thiopental, being a racemate (*rac*-thiopental), is used as an equimolar mixture of *R*- and *S*-thiopental enantiomers.‖ The pharmacokinetics[9,10] and effects[11,12] of *R*- and *S*-thiopental differ quantitatively after anesthesia induction doses. However, it is not known whether the nonlinearity of high-dose thiopental pharmacokinetics is an artifact of data analysis because of two drugs being combined or whether the component enantiomers each undergo nonlinear pharmacokinetics. Furthermore, the significance of any pharmacodynamic differences between *R*- and *S*-thiopental enantiomers, during conditions of prolonged high-dose therapy is unknown. The aims of the study were (1) to determine the pharmacokinetics of *R*- and *S*-thiopental in patients with acute neurologic and neurosurgical emergencies treated at this institution using prolonged high-dose thiopental; (2) to determine whether clinical factors (including thiopental dose, duration and dose rate, patient age, gender, and weight)

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‖ The nomenclature used in this paper is as follows: thiopental for the clinically used racemate, *i.e.*, *rac* or (*RS*)-(±)-thiopental, and for the sum of the enantiomers as would be measured, for example, in plasma and tissues by conventional achiral analyses. *R*- and *S*-thiopental are used to designate the (*R*)-(+)- and (*S*)-(−)-thiopental enantiomers. Because the optical rotations are not of significance to this article, they have been deleted for simplicity. Pentobarbital has the same configurations and optical rotations as thiopental; the same nomenclature is applied, as appropriate.

Table 1. Demographic and Relevant Clinical Summary Data for the 20 Patients Who Received Prolonged High-dose Thiopental Therapy

Parameter	Mean (SD)	95% CI‖	Range	Number of Patients
Age (yr)	40 (15)	33–47	15–69	20
Weight (kg)	72 (18)	63.8–80.4	45–105	20
Dose (g)	41.2 (19.0)	32.3–50.2	12.5–86.9	20
Duration (h)	95 (65)	65–126	31–285	20
Dose rate (g/h)*	0.50 (0.22)	0.39–0.60	0.21–1.21	20
GCS on arrival	9 (5)	6–11	3–15	20
Time to pupil recovery (h)†	22 (18)	13–32	0–69	16
Time to GCS >3 (h)‡	91 (46)	67–116	15–187	16
Median Rankin scale at 1 month§	3		1–5	20

* Average dose rate over the duration of thiopental infusion.

† Duration of pupillary unresponsiveness following completion of a thiopental infusion.

‡ Time to first GCS >3 after completion of a thiopental infusion.

§ Modified Rankin scale outcome at 1 month.

‖ 95% confidence intervals.

and pharmacokinetic parameters, including the theoretical maximum rate of metabolism (V_m), Michaelis-Menten constant (k_m), and terminal elimination half-life ($t_{\frac{1}{2}}$), are associated with the durations of pupillary and clinical unresponsiveness after cessation of an infusion; and (3) to determine the relative amount of pentobarbital, itself a potential mixture of *R*- and *S*-enantiomers, formed during an infusion of thiopental.

Materials and Methods

The Human Research and Ethics Committee at this institution approved the study. Twenty patients (13 males; 7 females) were included who received a high-dose thiopental infusion of more than 24-h duration between April 1995 and October 1997. Patients received thiopental for intracranial hypertension complicating severe head injury (nine patients), refractory vasospasm complicating subarachnoid hemorrhage (eight patients), and other diagnoses (three patients: one with sagittal sinus thrombosis, one with cerebral arteriovenous malformation complicated by intracerebral hemorrhage, and one with vasospasm complicating pituitary adenoma resection). Standard therapy was ineffective for all patients before consideration of thiopental. Patients with severe head injury, for example, were administered thiopental for treatment of persistent intracranial hypertension despite administration of mannitol, hyperventilation, sedation with midazolam–morphine, and surgical evacuation when appropriate. The demographic characteristics for the 20 patients are summarized in table 1. No patient had a history of significant hepatic, renal, or cardiac disease before hospital admission. Four patients died during or within 7 days of completion of a thiopental infusion, including two patients in whom postinfusion blood sampling could not be continued for an adequate period to determine V_m and k_m values.

Intravenous thiopental (Pentothal; Abbott Australasia, Sydney, Australia) was administered at a loading dose of 5–10 mg/kg, followed by a continuous infusion adjusted to maintain an electroencephalography (EEG) burst suppression pattern of 2–6 bursts/min. All patients were administered an infusion of norepinephrine (2–8 μg/min) to maintain a mean arterial pressure of more than 80 mmHg during thiopental therapy. Prophylactic antibiotic treatment, including second- and third-generation cephalosporins, aminoglycosides, piperacillin or imipenim, or both, was maintained during and after thiopental infusion. The only other comedication routinely administered was oral sucralfate.

All patients underwent hourly clinical neurologic assessments, including reactivity of pupillary responses to light and motor responses to verbal command and painful stimuli, during and after the course of an infusion until discharge from the intensive therapy unit. The postinfusion times to recovery of pupil reactivity to light and times to a Glasgow Coma Score (GCS)[13] of more than 3 (*i.e.*, the time when GCS was first $\geq$ 4) were documented for each patient.

A modified Rankin scale[14] outcome at 1 month after the start of thiopental therapy was used to estimate the severity of the patient's neurologic condition. Grade 0 signifies normal neurologic examination for age; Grade 1 is no significant disability despite the presence of neu-

rologic symptoms or signs; Grade 2 is mild disability but independent in activities of daily living; Grade 3 is moderate disability requiring assistance with activities of daily living but able to walk with or without assistance; Grade 4 is severe disability requiring constant nursing care and attention; and Grade 5 is death.

Arterial blood samples were collected from an indwelling cannula during and after completion of an infusion into 5-ml tubes (SST, Becton Dickinson and Co., Franklin Lakes, NJ). All samples were centrifuged at 3,000 rpm within 60 min of collection, and the sera were stored at −20°C until analysis. The mean duration of blood sample collection after commencement of thiopental for the 18 patients in whom Michaelis-Menten elimination kinetics were calculated was 219 h (SD, 66; 95% confidence interval [CI], 186–252). Blood samples were collected once to twice daily after the start of an infusion until its discontinuation, then again at 8–12 h intervals after completion of an infusion until recovery of clinical responsiveness. Thereafter, samples were drawn every 12–24 h for another 48–72 h, the actual times being noted accurately. Additional samples were collected in all surviving patients at the times of completion of a thiopental infusion and times to a GCS score of more than 3. The mean total number of blood samples collected from these patients was 14 (SD, 4; 95% CI, 11–16), including a mean of 10 (SD, 4; 95% CI, 8–12) postinfusion samples.

Thiopental enantiomer serum concentrations were determined in all patients and pentobarbital enantiomer concentrations in five patients by chiral stationary phase high-performance liquid chromatography.[15] The limits of quantitation for the *R*- and *S*-thiopental and *R*- and *S*-pentobarbital enantiomers were 10 and 100 ng/ml, respectively. Analysis of thiopental and pentobarbital enantiomer binding to serum proteins was performed in 17 and 7 patients, respectively, by equilibrium dialysis. Serial serum samples from each patient were pooled before equilibrium dialysis. Pooled serum samples were adjusted to pH 7.4 and then equilibrated at 37°C for 10 h, as previously described.[10] The fractions unbound (f_u) for the separate enantiomers were determined using the differences in postdialysis buffer and serum concentrations. The mean predialysis serum concentrations of pooled samples of *R*- and *S*-thiopental were 17 mg/l (SD, 12; 95% CI, 11–23) and 19 mg/l (SD, 13; 95% CI, 13–26), respectively. The mean predialysis serum concentrations of pooled samples of *R*- and *S*-pentobarbital for the seven patients were 4.6 mg/l (SD, 4.6; 95% CI, 3.1–6) and 3.4 mg/l (SD, 3.4; 95% CI, 1.7–5), respectively.

Pharmacokinetic Parameter Data Analysis

The doses of *R*- and *S*-thiopental enantiomers were, by definition, one half the dose of thiopental. Each set of thiopental enantiomer serum concentration (C)–time (t) data were fitted by each of two models, using the program PKAnalyst (MicroMath Scientific Software, Salt Lake City, UT): a linear one-compartment model with constant intravenous rate and first-order output and a nonlinear one-compartment model with constant intravenous rate and Michaelis-Menten output. Thiopental shows "multicompartment behavior" after intravenous bolus doses and brief infusions; however, as it approaches a steady state after a prolonged infusion, its behavior is described adequately by a single "well-mixed" compartment.[6] For both linear and nonlinear models, Cl_{ss} was defined as the ratio of average thiopental dose rate for the last 12 h of thiopental therapy to average serum concentration measured during this period, during quasi steady state conditions.

The linear model is based on the elimination constant (K_{el}) and ratio of the total dose to the volume of distribution (V_d) for the infusion time (T_{iv}) using equation (1):

$$C(t) = \frac{\text{Dose}}{V_d \times T_{iv} \times K_{el}} \times (e^{-Kel \times T} - e^{-Kel \times t}) \ldots \text{(i)} \quad (1)$$

where C(t) is the serum analyte concentration at time t; $T = t - T_{iv}$ for $t > T_{iv}$ and $T = 0$ for $t < T_{iv}$. In this model, the product of V_d and K_{el} is equal to the total body clearance (TCl).[7,8]

The nonlinear model is based on the V_m, k_m, and ratio of total dose to V_d for a given T_{iv} using the Michaelis-Menten equation (2):

$$dC/dt = \frac{\text{Dose}}{T_{iv} \times V_d} - \frac{V_m \times C}{k_m + C} \ldots \text{(ii)} \quad (2)$$

where k_m is defined as the thiopental serum concentration at which the rate of metabolism is equal to one half its theoretical maximum rate (V_m).

The model parameters V_d, V_m, k_m, and elimination $t_{\frac{1}{2}}$ were estimated separately for total and unbound *R*- and *S*-thiopental enantiomers, and for thiopental (*i.e.*, the sum of the enantiomers) so that these could be compared to values reported in the literature. C_{max} was defined as the maximum observed serum thiopental concentration during the course of an infusion. The percentage saturation (%Sat) of the enzyme system at C_{max} was

calculated from the following equation: %Sat = $[C_{max}/(k_m + C_{max})] \times 100$.

At higher concentrations, when $C \geq K_m$, the value of $t_{\frac{1}{2}}$ increases with concentration. At lower concentrations, when $C << k_m$, the elimination $t_{\frac{1}{2}}$ will be constant; the values reported, accordingly, were estimated from $\ln 2 \times k_m/V_m$ (= ln2 × the inverse of the first-order rate constant when $C << k_m$). Total clearance (TCl) for *R*- and *S*- thiopental was calculated from the ratio of the total dose to the total area under the curve (AUC), as computed by the trapezoid rule using the linear one-compartment model with extrapolation of the terminal phase. The mean residence time for the thiopental enantiomers was estimated from the ratio of the area under the moment curve (AUMC) to the total area under the curve minus one half the duration of infusion. The values of Cl_{ss}, TCl, and mean residence time, as determined, would have been subject to influence by a number of factors, including sampling frequency, variability of thiopental infusion rate caused by clinical requirements, relation of steady state concentration to dose rate at values exceeding the relevant value of k_m, and clinical condition of the patient. Hence, the primary objective of the data analysis was to provide a comparison between enantiomers because no previous studies have. The limitations of the approach are acknowledged, but the models chosen were the simplest that adequately fitted the data for the relevant time-averaged infusion rate.

Equations describing *R*-, *S*-, and (*R*- plus *S*-)-thiopental kinetics were determined by nonlinear least-squares regression analysis using weights of $1/C^2$ and the modified Powell algorithm[16] to assess the best fitting parameters. The criteria considered when choosing between models included visual inspection of the model predictions *versus* measured values, standard deviation of observed *versus* predicted concentration–time data, coefficients of determination, and correlation coefficients between observed and predicted values. The correlation coefficient between observed and predicted values exceeded 0.9 in all data sets when using the nonlinear model with values more than 0.98 for 16 of the 18 patients. A comparison between the models was also made using a modified Akaike Information Criterion[17] termed the Model Selection Criterion in the software used. One-way analysis of variance comparison of R^2 (0.97 ± 0.01 *vs.* 0.90 ± 0.08, $P = 0.0005$), correlation coefficient (0.99 ± 0.01 *vs.* 0.98 ± 0.02, $P = 0.01$), standard deviation of observed *versus* predicted concentration–time data (0.18 ± 0.06 *vs.* 0.31 ± 0.14, $P = 0.001$), and Model Selection Criterion (4.0 ± 1.2 *vs.* 3.0 ± 0.8, $P = 0.007$) values between nonlinear and linear models consistently indicated that nonlinear interpretation of the data was the preferred approach. The linear model was preferred in only two patients and, in these, the difference in the correlation coefficients between observed and predicted values was small (0.96 and 0.98, respectively) by using a nonlinear model; hence, it was decided to report the nonlinear model parameters for all 18 patients. Figure 1 shows two sets of data series from patients 4 and 11 to illustrate the linear and nonlinear model approaches.

Statistical Analysis

Because the data were derived from the same serum samples, the differences between the respective values of C_{max}, V_m, k_m, %Sat, V_d, Cl_{ss}, TCl, mean residence time, terminal $t_{\frac{1}{2}}$, and f_u for *R*- and *S*-thiopental in each patient were tested against a value of zero using the Student *t* test for paired data; the respective values of the enantiomeric ratio of the relevant pharmacokinetic parameters were tested against a value of unity using the Student single-sample *t* test.[18] Multiple linear regression analysis[18] was also performed to analyze the relation between clinical variables (total thiopental dosage, duration and dose rate, patient age, gender, and total body weight), and pharmacokinetic parameters (C_{max}, Cl_{ss}, %Sat, V_m, k_m, and elimination $t_{\frac{1}{2}}$ of thiopental) and the duration of postinfusion pupillary and clinical unresponsiveness. A *P* value of < 0.05 was significant. The analyses were performed using Statistix for Windows 1.0 (Analytical Software, Tallahassee, FL) on a personal computer.

Results

Demographic data for the patients, including age, weight, total thiopental dose, and infusion duration, are summarized in table 1. The mean times of recovery of pupillary responsiveness and times to a GCS of more than 3 after completion of a thiopental infusion and 1-month Rankin scale outcomes are also summarized in table 1. Examples showing fits of nonlinear models to the data for five patients are given in figure 2. From these cases, it can be seen that that rate of decrease of serum concentrations of both enantiomers after cessation of infusion is initially very slow.

Summary data for Cl_{ss}, C_{max}, V_d, k_m, V_m, elimination $t_{\frac{1}{2}}$, TCl, and mean residence time for *R*- and *S*-thiopental based on total serum concentrations from all patients are shown in table 2; corresponding values based on unbound serum concentrations are shown in table 3. Phar-

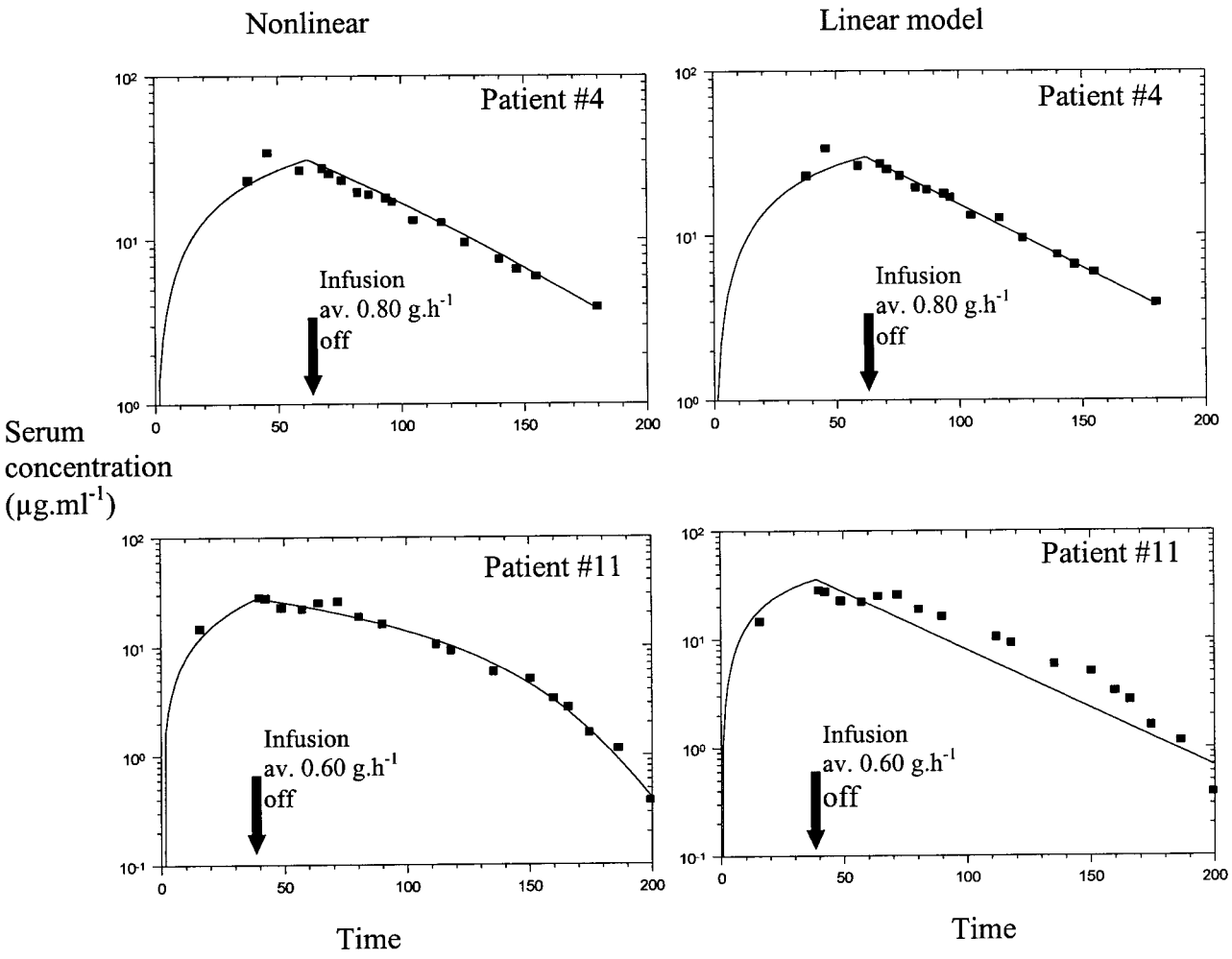

Fig. 1. Illustrative examples comparing linear (*right*) and nonlinear (*left*) approaches to pharmacokinetic modeling of thiopental. Log-linear R-thiopental serum concentration–time curves for two patients, where time 0 is time of commencement of thiopental infusion. ■ Indicates observed R-thiopental serum concentration values. – Indicates the model fitted to the serum concentration values.

macokinetic differences of approximately 10–20% were found between *R*- and *S*-thiopental, as indicated by the statistical significance of the enantiomeric ratios and the differences for the various parameters (tables 2 and 3). Although the magnitude of the differences varied among the population of subjects, the overall values were sufficiently similar that it was not possible to relate clinical events selectively to either enantiomer. Pharmacokinetic findings for the sum of enantiomers (*i.e.*, for thiopental) included the following: Cl_{ss}: 0.102 l/min (n = 20, SD = 0.05, 95% CI = 0.08–0.12); TCl: 0.094 l/min (n = 18, SD = 0.05, 95% CI = 0.07–0.12); C_{max}: 73 mg/l (n = 20, SD = 33, 95% CI = 57–89); %Sat: 68 (n = 18, SD = 16, 95% CI = 60–76); k_m: 44 mg/l (n = 18, SD = 41, 95% CI = 23–64); V_m: 1.9 mg · l^{-1} · h^{-1} (n = 18, SD = 1.2, 95% CI = 1.3–2.5); and elimination $t_{\frac{1}{2}}$: 14.6 h (n = 18, SD = 7, 95% CI = 11–18). The mean value for the maximal rate of metabolism ($V_m \times V_d$), 0.46 g/h (n = 18, SD = 334, 95% CI = 0.30–0.63), did not differ significantly from the average dose rate for the duration of a thiopental infusion, 0.50 g/h (n = 20, SD = 0.22, 95% CI = 0.39–0.60; $P = 0.7$).

The relative serum concentration–time curves of thiopental and pentobarbital formed during and after completion of a thiopental infusion is shown in figure 2 for five patients. Values of fu of *R*- and *S*-pentobarbital for the seven patients who underwent serum protein binding analysis was 32% (SD = 5, 95% CI =

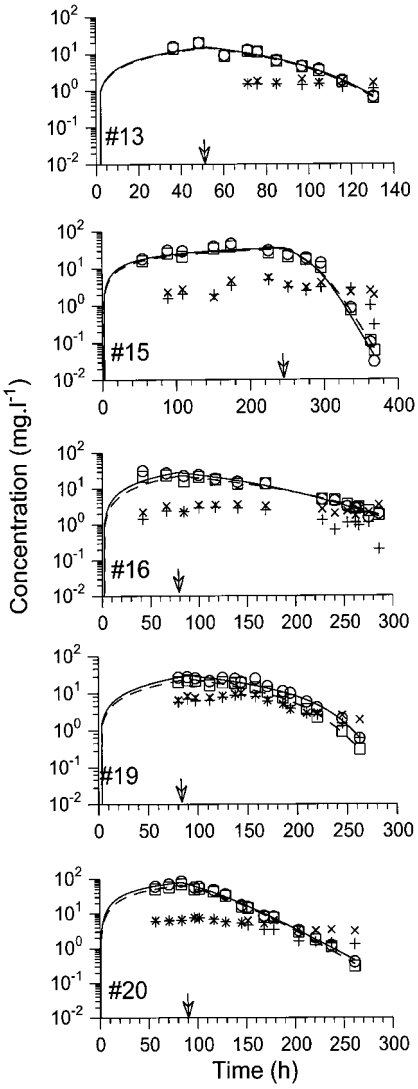

Fig. 2. Examples of log-linear serum *R*- and *S*-thiopental and *R*- and *S*-pentobarbital serum concentration–time curves shown for 5 patients. Note that the time scales are not uniform among the examples. The arrow indicates the time of completion of a thiopental infusion. □ = *R*-thiopental, o = *S*-thiopental, + = *R*-pentobarbital, x = *S*-pentobarbital. Lines are the non-linear model fits to data: - - - = *R*-thiopental, – = *S*-thiopental.

27–37) and 34% (SD = 10, 95% CI = 25–44), respectively ($P = 0.4$).

Postinfusion times of recovery of pupillary responsiveness and times to a GCS of more than 3 were significantly correlated ($P = 0.003$, n = 16, adjusted $R^2 = 0.4$); postinfusion time to GCS of more than 3 also significantly but weakly correlated with the elimination $t_{\frac{1}{2}}$ of thiopental ($P = 0.02$, n = 16, adjusted $R^2 = 0.3$). Times of onset of pupillary responsiveness or times to GCS or more than 3 after completion of a thiopental infusion were not significantly correlated with other clinical or pharmacokinetic variables, including patient age and weight, total thiopentone dose, duration or dose rate, and Cl_{ss}, C_{max}, V_m, and k_m of thiopental.

Discussion

A multitude of previous studies have described the pharmacokinetics of thiopental in linear terms. During linear conditions, a constant fraction of the thiopental body burden is eliminated per unit-time and the circulating concentration is proportional to the dose. It is well-established that thiopental can show nonlinear (Michaelis-Menten or saturable) kinetics when administered in high doses for prolonged periods.[1–8] The progression from linear to nonlinear conditions coincides with increasing body (and thus hepatic mixed-function oxidase) burden of thiopental.

Thiopental elimination becomes nonlinear when serum concentrations exceed approximately 30 mg/l.[2,19] During nonlinear conditions, a constant amount of the body burden is eliminated per unit-time and the circulating concentrations are disproportional to dose. As a general rule, if the rate of administration of a substance leads to protracted concentrations greater than the Michaelis constant (k_m) then the resultant concentrations can become substantially greater than those predicted by linear pharmacokinetic models and the elimination $t_{\frac{1}{2}}$ after cessation of administration increases with decreasing body burden until it reaches its limiting value of linear conditions. In the current study, mean k_m values of 20 and 24 mg/l were found for *R*- and *S*-thiopental, respectively; hence, it is not surprising that the pharmacokinetics of thiopental were better described by a nonlinear model in most patients. In 11 patients, the average dose rate was actually greater than the V_m, thus predisposing these patients to a phenomenon often known as "runaway accumulation," in which increasing serum thiopental concentrations (and unwanted pharmacodynamic effects) may be seen despite an essentially constant infusion rate administered per clinical requirements. This study has shown that this kind of accumulation often occurs in doses of thiopental that are typically used for neuroprotection of head-injured patients. Moreover, the $t_{\frac{1}{2}}$ shortly after cessation of infusion (as shown in figs. 1 and 2) was much greater than the late-phase (limiting) values (as given in table 2). Furthermore, with approximately a 10-fold range in thiopental

Table 2. Summary Data for the Relevant Pharmacokinetic Properties for the Thiopental Enantiomers

Parameter	*R*-thiopental [mean (SD), 95% CI]	*S*-thiopental [mean (SD), 95% CI]	Difference (*R*-*S*) [mean (SD), 95% CI, *P**]	*R*-/*S*- ratio [mean (SD), 95% CI, *P*†]
Cl_{ss} (l/min)	0.108 (0.05) 0.09–0.13	0.096 (0.04) 0.08–0.12	0.012 (0.009) 0.008–0.015 <0.0001	1.13 (0.09) 1.09–1.17 <0.0001
TCl (l/min)	0.10 (0.05) 0.07–0.13	0.08 (0.04) 0.07–0.11	0.012 (0.011) 0.007–0.017 0.0002	1.14 (0.09) 1.09–1.18 <0.0001
C_{max} (mg/l)	35 (16) 27–42	39 (18) 31–47	−4.4 (4.0) −6.1–−2.6 <0.0001	0.89 (0.07) 0.86–0.92 <0.0001
V_d (l)	313 (145) 241–385	273 (115) 216–330	39.9 (39.5) 21.6–58.1 0.0005	1.14 (0.09) 1.09–1.18 <0.0001
k_m (mg/l)	20 (19) 11–29	24 (23) 12–35	−3.8 (8.4) −7.9–0.4 0.08	0.88 (0.22) 0.78–0.99 0.03
V_m ($mg \cdot l^{-1} \cdot h^{-1}$)	0.86 (0.54) 0.59–1.13	1.01 (0.69) 0.67–1.35	−0.15 (0.25) −0.26–−0.03 0.02	0.88 (0.13) 0.81–0.93 0.0005
$t_{1/2}$ (h)	14.6 (7.0) 11.2–18.1	14.7 (7.2) 11.1–18.3	−0.1 (1.7) −0.91–0.74 0.83	1.01 (0.11) 0.95–1.06 0.74
MRT (h)	38 (16) 30–46	38 (14) 31–45	0.1 (4.6) −2.2–2.4 0.94	1.00 (0.10) 0.94–1.05 0.89
%Sat	68 (16) 60–76	67 (17) 59–75	0.83 (4.7) −1.5–3.2 0.46	1.02 (0.08) 0.98–1.05 0.34

Cl_{ss} = mean total body clearance at pseudo steady state; TCl = total body clearance (time averaged overall); C_{max} = observed maximal serum thiopental concentration during infusion; V_d = apparent volume of distribution; k_m = thiopental serum concentration at which rate of metabolism was equal to one half its theoretical maximum rate; V_m = theoretical maximal rate of thiopental metabolism; $t_{1/2}$ = elimination half-life; MRT = mean residence time; %Sat = estimated % saturation of metabolic enzyme(s).

* Tested against a difference of zero.

† Tested against a ratio of unity.

metabolic parameters, it is very difficult to predict serum concentrations from a given dose in a patient without monitoring, despite dosing to a reasonably precise pharmacodynamic end point. Within this patient group, attendant relevant pathophysiologic changes would be expected to contribute to the variability in thiopental pharmacokinetics and any thiopental serum concentration–response relation.

Recent studies have found a higher Cl_{ss} and V_d of *R*-thiopental relative to *S*-thiopental after a single intravenous bolus administration of thiopental,[9,10] but no previous study has considered the potential for nonlinear pharmacokinetic behavior of the enantiomers from a prolonged high-dose infusion. The mean values of Cl_{ss}, V_d, V_m, and $t_{\frac{1}{2}}$ for thiopental (*i.e.*, the summed enantiomers) in the current study are comparable to those previously reported in high-dose thiopental therapy.[1–4] Pseudo steady state serum concentrations of thiopental, however, in the current study (mean value 74 mg/l) were higher than in previously reported series (mean values of 31 mg/l by Russo *et al.*[4] and 49 mg/l by Turcant *et al.*[2]). This most probably reflects a higher average dose-rate requirement (0.50 ± 0.22 g/h) to achieve EEG burst suppression in our patient population. The serum thiopental concentrations at the cessation of infusion exceeded the k_m values in all but two patients (respectively, 60 *vs.* 150 mg/l; and 42 *vs.* 48 mg/l). In these two patients, concentration–time data were better fitted by a linear than a nonlinear model.

Our findings indicate that *R*- and *S*-thiopental pharmacokinetic differences, as found previously with anesthetic induction doses, are also apparent with high-dose infusions: *R*-thiopental concurrently showed a consistently greater Cl_{ss} and V_d than *S*-thiopental. Although small, the enantiomeric differences were statistically significant, supported by the enhanced power of the paired

Table 3. Summary Data for the Relevant Pharmacokinetic Properties for the Thiopental Enantiomers Based upon Unbound Serum Concentrations

Parameter	*R*-thiopental [mean (SD), 95% CI]	*S*-thiopental [mean (SD), 95% CI]	Difference (*R*-/-*S*-) [mean (SD), 95% CI, *P**]	Ratio (*R*/*S*) [mean (SD), 95% CI, *P*†]
f_u	20 (5)	18 (4)	2.2 (1.0)	1.14 (0.06)
	17–22	15–20	1.7–2.8	1.11–1.17
			<0.0001	<0.0001
$C_{max,fu}$ (mg/l)	6.5 (2.8)	6.4 (2.6)	0.1 (0.4)	1.01 (0.07)
	5.1–8.0	5.1–7.8	−0.14–0.31	0.97–1.04
			0.42	0.71
$Cl_{ss,fu}$ (l/min)	0.582 (0.26)	0.588 (0.25)	−0.01 (0.05)	0.99 (0.07)
	0.45–0.72	0.46–0.72	−0.03–0.02	0.95–1.10
			0.63	0.48
$V_{d,fu}$ (l)	1741 (817)	1688 (786)	53.1 (214)	1.03 (0.13)
	1288–2193	1252–2125	−65–172	0.96–1.10
			0.35	0.37
$k_{m,fu}$ (mg/l)	3.6 (3.7)	3.8 (3.5)	−0.2 (1.5)	1.01 (0.30)
	1.5–5.6	1.8–5.7	−1.0–0.7	0.86–1.16
			0.64	0.92
$V_{m,fu}$ ($mg \cdot l^{-1} \cdot h^{-1}$)	0.15 (0.1)	0.16 (0.1)	−0.01 (0.03)	0.98 (0.20)
	0.10–0.20	0.11–0.21	−0.02–0.01	0.84–1.18
			0.61	0.68

f_u = estimated free fraction not bound to plasma proteins; $C_{max,fu}$ = observed maximal unbound thiopental serum concentration during infusion; $Cl_{ss,fu}$ = mean total body clearance of unbound fraction at pseudo steady state; $V_{d,fu}$ = apparent volume of distribution of unbound fraction; $k_{m,fu}$ = unbound thiopental serum concentration at which the rate of metabolism was equal to one half its theoretical maximum rate; $V_{m,fu}$ = theoretical maximal rate of metabolism of unbound thiopental.

* Tested against a difference of zero.

† Tested against a ratio of unity.

analysis. In contrast, *S*-thiopental was consistently found to have a greater affinity for serum proteins, so that the enantiomeric differences in Cl_{ss} and V_d vanished when f_u of the two enantiomers were taken into account. Although thiopental undergoes nonlinear serum protein binding on increasing concentrations through the sub-to-low microgram range, it is essentially constant in the high-concentration range, as was encountered in this investigation.[20–22] We also found that *S*-thiopental has a higher theoretical maximal rate of metabolism when compared to *R*-thiopental, but this difference also vanished when the f_u were considered. Hence, the pharmacokinetic differences between *R*- and *S*-thiopental identified in our patient population appear to be strongly influenced by the higher free-fraction of *R*-thiopental. Based on mean data, the value of $C_{max} \times f_u$ for *S*-thiopental is not different than that of *R*-thiopental. Nevertheless, the contributions of both enantiomers to the pharmacodynamics and pharmacokinetics of a racemic drug need to be considered.

Previous studies indicated that the dose-derived anesthetic potency of *S*-thiopental in the mouse is approximately twice that of *R*-thiopental.[11,12] We performed studies in recombinant γ-aminobutyric acid (GABA) A receptors transfected into *Xenopus laevis* oocytes that have shown that the order of potency of GABA facilitation (mean EC_{50} for 3 μM GABA) to be *S*-thiopental (26.0 μM) more than *rac*-thiopental (35.9 μM) more than *R*-thiopental (52.5 μM) more than *rac*-pentobarbital (97.0 μM). These findings concur with the differences in potency found *in vivo*.[23] We also found, in the rat, that the distribution coefficients from plasma to central neural tissues were approximately 10–15% higher for *R*-thiopental than for *S*-thiopental.[24] Thus, in apportioning the clinical central nervous system effects between enantiomers, it appears that the higher receptor-intrinsic effectiveness of *S*-thiopental is partially offset by pharmacokinetic factors.

In the five patients for whom simultaneous serum pentobarbital and thiopental concentration measurements were taken, the ratio of *R*- to *S*-pentobarbital concentrations was the reverse of that seen for the respective parent compounds, *R*- and *S*-thiopental. During the infusion, the concurrent serum concentrations of pentobarbital were 10–30% those of thiopental, which is similar to previous findings.[1,2] After cessation of thiopental, the ratio of serum pentobarbital:thiopental concentrations increased with time, most likely because of the longer half-life of pentobarbital and its continued forma-

tion by metabolism. The potential clinical significance of the pentobarbital is therefore of interest.

The clinical and EEG effects of pentobarbital at different blood concentrations in humans are not well-defined. Animal and human studies suggest that plasma pentobarbital concentrations necessary for desired clinical and EEG effects are similar to those reported for thiopental.[25–29] For example, EEG burst suppression occurs at plasma pentobarbital concentrations ranging from 25 to 75 mg/l in patients with severe head injury,[28,29] but plasma f_u of pentobarbital would appear to be approximately twice those of thiopental at the same plasma concentrations.[30,31] However, the intrinsic potency for facilitation of GABA response *in vitro* indicates *rac*-pentobarbital to be only 40% that of *rac*-thiopental.[23] Thus, the different relative potencies from *in vitro* and *in vivo* studies support the likelihood of a similar "clinical" potency for total (bound and unbound) serum concentrations of thiopental and pentobarbital in which the potencies of the *R*-enantiomers are significantly less than the respective *S*-enantiomers.[11,12,32,33] Because the postinfusion pentobarbital serum concentrations in our patients were typically less than 10 mg/l, the amount of pentobarbital formed probably was not making a major contribution to the clinical effects observed.

The mean duration of pupillary unresponsiveness and time to first GCS of more than 3 after completion of a thiopental infusion in the current study were 22 and 91 h, respectively. Our attempt to identify factors that may have influenced the postinfusion duration of clinical and pupillary unresponsiveness was limited by the heterogeneity of the patient population and the relatively small number of patients in the study. Thus, we were unable to successfully predict the duration of clinical effect on the basis of clinical and pharmacokinetic parameters known at the time of completion of an infusion. A more detailed statistical analysis of a larger series of patients undergoing thiopental therapeutic drug monitoring has been attempted separately (Cordato *et al.,* unpublished observations). Overall, our findings indicate that an individual patient's inherent capacity to metabolize thiopental is a significant contributing factor to its postinfusion duration of effect.

In conclusion, the pharmacokinetics of both *R*- and *S*-thiopental became nonlinear at the doses infused in these head injury patient. Although significant, the pharmacokinetic differences between the thiopental enantiomers are smaller than the pharmacodynamic differences found in animal and GABA facilitation studies. The ratio of serum pentobarbital concentration relative to the serum thiopental concentration increases with time after completion of a thiopental infusion but the concentrations of pentobarbital are relatively low and, compared to the infused thiopental, may not be of clinical significance. The pharmacodynamic differences between *R*- and *S*-thiopental are unknown in humans, and future research in this area may determine whether one or another enantiomer has a clinical advantage over the racemate.

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