Time-dependent Pharmacokinetics of High Dose Thiopental Infusion in Intensive Care Patients

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Purpose. In patients with severe head injuries receiving long-term infusion for reducing intracranial pressure, a decline in concentrations was apparent following attainment of an initial steady state. This could be explained by an increased rate of elimination. An adequate modeling of the plasma disposition curves was used to demonstrate clearly the metabolic induction.

Methods. The concentration-time data of 17 patients were fit by a one compartment pharmacokinetic model in which the decline of plasma concentration during infusion was due to an increase in the clearance rate of thiopental following a latency period. This time-dependent clearance model provided estimates of initial and final clearance rates.

Results. This study demonstrated that large interindividual variations were observed during the course of the thiopental time-dependent pharmacokinetics. Depending on the patient, one or two steps of induction occurred. The mean initial and final clearance rates were 1.22 ± 0.82 mL/min/kg and 10.5 ± 23 mL/min/kg. The latency period for the first induction averaged 69 ± 56 h. For 6 subjects, the rate of thiopental metabolism continued to change with time and there was a second step of induction.

Conclusions. Induction of thiopental metabolism occur within therapeutic ranges, but it was not established that attainment of individual limits in dosing rate, total dose, or treatment duration occur in the process. Thus, monitoring is needed for achievement of a target plasma concentration.

KEY WORDS: thiopental; long term infusion; time-dependent clearance model; critically ill patients.

INTRODUCTION

Patients with head injuries, receiving high-dose infusion of thiopental over a prolonged period to decrease elevated intracranial pressure (ICP) were studied. The pharmacokinetics of high-dose thiopental have been described using a first-order (1–3) or a Michaelis-Menten elimination.(2–6) However, for some patients these models were inappropriate, i.e., a gradual decline in plasma concentration was observed although the infusion rate was unchanged. This could be explained by an increased rate of elimination indicating that thiopental induced its own metabolism. In a previously published study, a large intraindividual variability in clearance values was observed (7). Since thiopental is completely metabolized before excretion with a low hepatic extraction ratio (8), enzyme activity is the rate limiting step of elimination.

Numerous chemical compounds and several barbiturates are well-known enzyme-inducers under a variety of input conditions (9–15). However, the assessment of hepatic enzyme activity in patients remains difficult because no routine methods are available. Enzyme induction is generally deduced from a diminished intensity of the pharmacological effect, an increase in the clearance rate, or a decrease in the terminal plasma half-life of the drug. It is known that the effects of high-dose thiopental are terminated by both metabolism and distribution into tissues. Thus, no conclusion about hepatic function can be drawn by relating duration of drug effect to drug disposition. Time-dependent pharmacokinetics of cyclophosphamide has been recently reported, declines in steady-state plasma concentrations were observed during high-dose infusion in 13 of 15 patients (16).

Adequate modeling of the plasma concentration time curves might clearly evidence metabolic induction. In the present study, we have described the pharmacokinetics of long-term infusion of thiopental by a model that incorporates the time-dependency of the clearance rate, i.e., the clearance rate increases gradually as a function of time following a latency period.

MATERIALS AND METHODS

Drug Product

Thiopental, [5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid] was supplied as the lyophilized powder of thiopental sodium (Nesdonal®, from SPECIA).

Patients

The patients, 5 women and 12 men, aged 15 to 58 years (31.5 ± 15). Weight was 55 to 90 kg (71 ± 11 kg) in males and 52 to 70 kg (56.4 ± 7.9 kg) in females. Two patients (4 and 11) were hospitalized for aneurysms while the others were hospitalized for cranial shock. All patients were free of disease before their admission for a deep coma with a Glasgow score <= 6.

Clinical Monitoring

ICP and arterial pressure were continuously measured. The infusion rate of thiopental was adjusted to maintain ICP below 20–25 mm Hg and cerebral perfusion pressure (CPP) above 50 mm Hg (CPP represents the pressure gradient across the cerebral vascular network, and can be estimated as the difference between mean arterial pressure and mean ICP or central venous pressure). Thiopental plasma levels were kept in the 15–40 mg/L range. Moreover, the drug was administered safely with colloidal fluids needed to maintain blood pressure during the loading regimen. The following examinations were performed once, or more, daily: Glasgow score, pupil reactivity test, electroencephalogram recording, and cardiovascular parameters. Renal and liver functions were assessed by blood chemistry analysis and determined to be within normal limits. The hematocrit was slightly lowered (between 32 to 44%).

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Thiopental Dosage

Thiopental was administered by long-term intravenous infusion. The infusion rate varied from 0.69 to 5.00 mg/kg/h (2.51 ± 1.03 mg/kg/h) with or without a loading dose of 20 to 40 mg/kg. Infusion rate averaged 3.00 mg/kg/h for females and 2.38 mg/kg/h for males. Five patients received a constant infusion rate while the others received two (8 patients) or three (4 patients) sequential dose regimens of thiopental. Sometimes additional doses of 10 to 50 mg/kg were allowed to keep ICP within normal ranges. Treatment duration averaged 145 ± 45 hours and the amount received during this time was 380 ± 155 mg/kg. Females received 434 ± 202 mg/kg over 138 ± 32 h while males received 358 ± 135 mg/kg over 147 ± 51 h. Cessation of thiopental treatment was determined by reduction or normalization of ICP, decrease of cerebral edema, signs of severe pneumonia, failure to control ICP or cardiovascular instability. Treatment characteristics are given in table I.

Concomitant Therapy

Other intracranial pressure-reducing drugs were dexamethasone or methylprednisolone (patient 8), with 20% mannitol as adjuncts. Ventilator-induced respiratory alcalosis was also used. Anti-infectious treatment was usually cefazolin, combined with tobramycin; other antimicrobial agents were ampicillin and ornidazole (patients 1), gentamicin (patient 8). Citocoline (patient 5), or piracetam (patients 14 and 17) were given in the acute phase of the post-traumatic cerebral ischemia. Other drugs were cimetidine (patient 3), ranitidine (patient 7), dopamine (patient 13), or cedilanide (patient 17). Ionic solutions and dextran were used to control the hemodynamic status and serum electrolytes. All drugs were administered by intravenous route.

Sample Collection

Blood samples (2 ml) were drawn into heparinized vacutainer tubes. The number of samples collected per patient averaged 15 over a period of 168 ± 39 hours. Plasma was obtained by centrifugation (3000 g for 20 minutes) and promptly analyzed. Since all blood samples were drawn for the routine therapeutic drug monitoring of patients, no informed consent or ethical approval was needed.

Drug Assay

Plasma levels of thiopental were determined in duplicate by high-pressure liquid chromatography as previously described (17).

Pharmacokinetic Analysis

Data analysis was performed covering all the doses from the commencement of the drug infusion upon the whole thiopental concentration-time curves. A one-compartment model was used to fit the data using sequentially a first-order elimination and a time-dependent clearance model. For the time-dependent pharmacokinetics, the exponential increase in clearance was defined as follows:

$$CL(t) = CL_i \qquad \text{for } 0 < t < Lag \tag{1}$$

$$CL(t) = CL_f - [CL_f - CL_i] \cdot e^{-\phi(t-Lag)} \quad \text{for } t > Lag \tag{2}$$

then the full pharmacokinetic model was

$$Vd \cdot \frac{dC}{dt} = R - CL(t) \cdot C \tag{3}$$

where C is the drug concentration at time t, dC/dt is the rate of change of drug concentration, R is the rate of infusion (t > infusion time, R = 0), Vd is the apparent volume of distribution, CL_i is the initial clearance rate, CL_f is the final clearance rate, ϕ is the rate constant for the change in clearance rate, Lag is the latency period, i.e., the time from the beginning of drug infusion to the beginning of clearance increase. The change in clearance could occur in two successive steps, with $\phi 1$, Lag1, and $\phi 2$, Lag2 defining two clearance rate change functions similar to equation 2. CL_m is then the middle value of CL reached after the first step of induction. CL_f is the final CL value reached after the second step of induction. The equations describing CL variations are then

first step of induction

$$CL(t) = CL_i \qquad \text{for } 0 < t < Lag1 \tag{4}$$

$$CL(t) = CL_m - [CL_m - CL_i] \cdot e^{-\phi 1(t-Lag1)} \quad \text{for } Lag1 < t < Lag2 \tag{5}$$

second step of induction

$$CL(t) = CL_f - [CL_f - CL_m] \cdot e^{-\phi 2(t-Lag2)} \quad \text{for } t > Lag2 \tag{6}$$

The pharmacokinetic modelling and parameter estimation were performed with the MicroPharm software (18), by nonlinear regression analysis using the weighted least squares criterion (weight, $1/C^2$). Suitable models were first assessed by visual examination of curve-fitting and residual plots. The statistical F-test was used to discriminate between models.

Statistical Analysis

Results in the text are given as mean ± standard deviation (SD). The different parameters (thiopental treatment and pharmacokinetics) were tested for normal distribution and variance homogeneity using the Kolmogorov-Smirnov test.

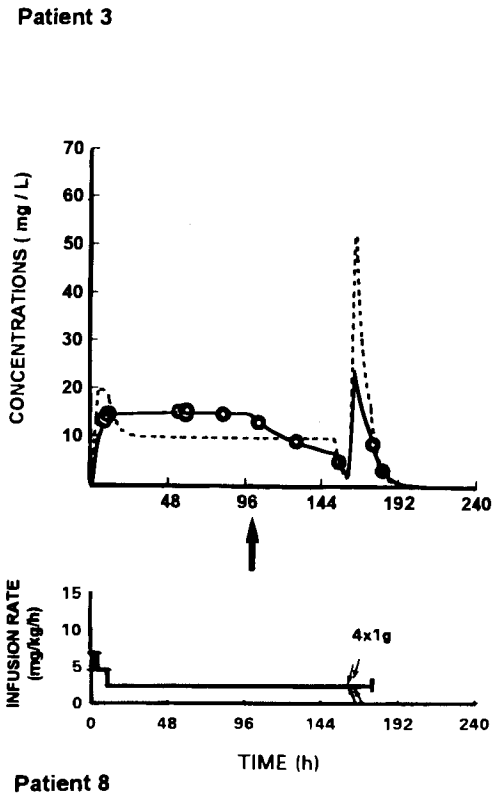
The following regression analyses were performed: i) the rise of CL expressed in percent, (CL rise = $[\langle CL_f - CL_i \rangle / CL_i] \times 100$) against the total dose and against the treatment duration of thiopental, ii) $\phi 1$ against the concentration at time Lag1 (C_{Lag1}), and against the dose of thiopental at time Lag1, $Dose_{Lag1}$.

Statistical analyses were performed using the program Statgraphics (19). Significance levels were assessed at $p < 0.05$.

RESULTS

Patients

The patients hemodynamic state was without appreciable disturbances throughout thiopental treatment except for patient 14 (severe electrolyte disturbances). Three patients died during the study from neurological (patient 3), infectious (patient 11), or cardiac (patient 16) complications. Except the above subjects, all of the other patients had a recovery without sequelae.



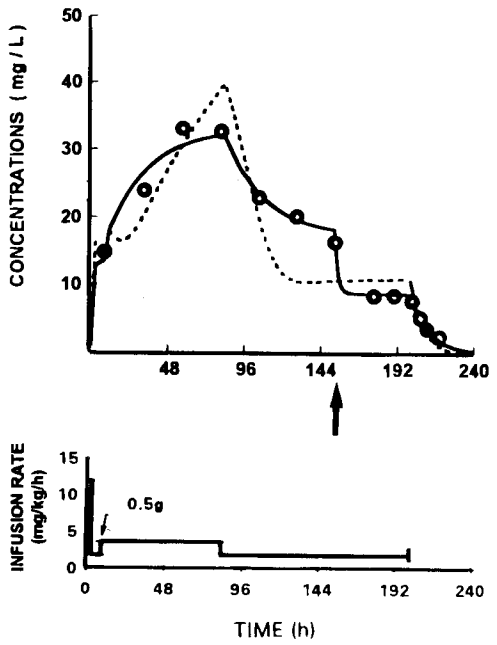


Fig. 1. Thiopental plasma concentration-time curves analized according to a one-compartment model using a time-dependent clearance with one induction step (solid lines). Dotted lines are the fits obtained with the first-order elimination model. In the bottom panels the lines depict the continuous infusion rates of thiopental, while arrows indicate bolus loading doses (↓) and Lag-time (↑).

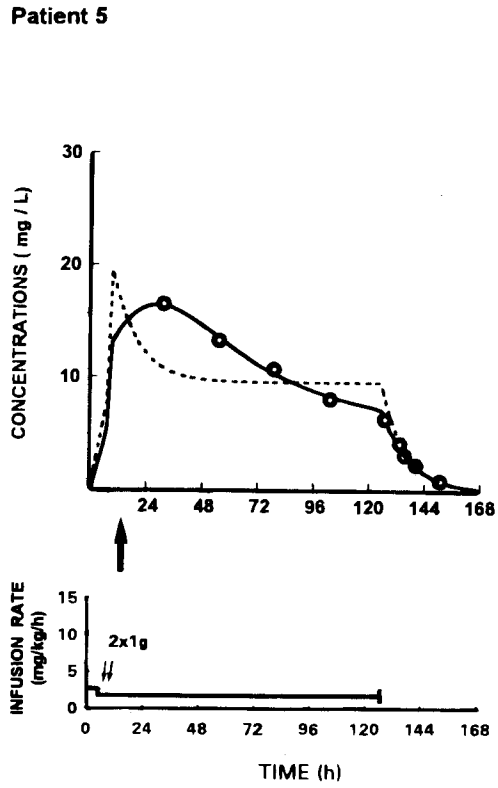


Fig. 1. Continued.

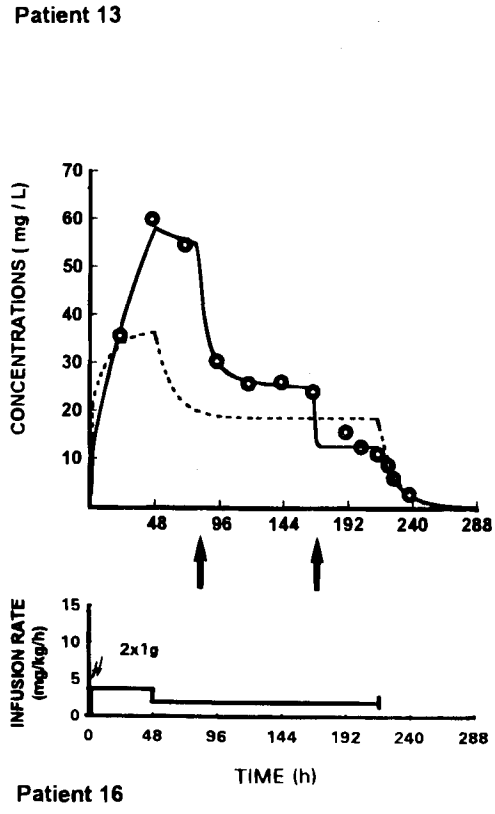
Pharmacokinetic Analysis

The model with time-dependent clearance ($r^2 = 0.974 \pm 0.041$) with one (11 patients) or two steps of induction (6 patients) adequately fitted the concentration-time curves (Figures 1 and 2). The plots obtained by using a linear kinetic model (without inducting effect) are also drawn for comparison. Pharmacokinetic parameters and the significance levels of the F-test are summarized in Table I.

The initial and final CL estimates were 1.22 ± 0.82 mL/min/kg and 10 ± 23 mL/min/kg; the CL rise averaged 755 ± 1035%. Delay of the induction process (Lag) averaged 69 ± 56 h and was quite different between subjects. For some of them, induction started soon after the initiation of thiopental treatment (2.5 to 14 h for subjects 5, 12, 15, 16, 17); for the others the Lag time was up to 156 h.

For most subjects, the CL rate variation was satisfactorily described by one induction step (equations 1 to 3). However, for 6 subjects, the rate of thiopental metabolism changed again following a first induction step and it was necessary to define a second step of induction to fit the data (equations 1 and 4–6). The second induction phase occurred just at the end of treatment duration for subject 12 and 40 h after cessation of treatment for subject 14. For the other patients, the second step occurred during the treatment. Mean $\phi 1$ value was 0.47 ± 1.14 h^{-1}, and C_{Lag1} value was 24.5 ± 14 mg/L.

There was no significant correlation between the increase in CL and thiopental treatment (total dose and treatment duration). No relationship was found between $\phi 1$ and thiopental concentration, C_{Lag1} or administered dose, $Dose_{Lag1}$.



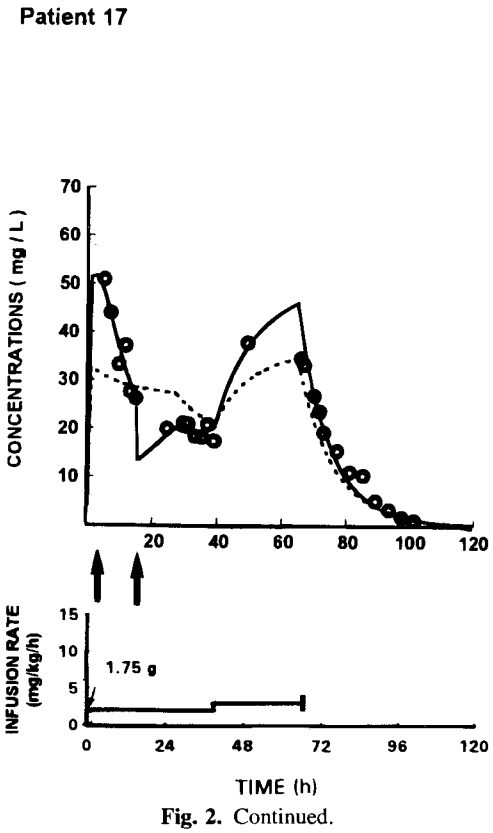


Fig. 2. Continued.

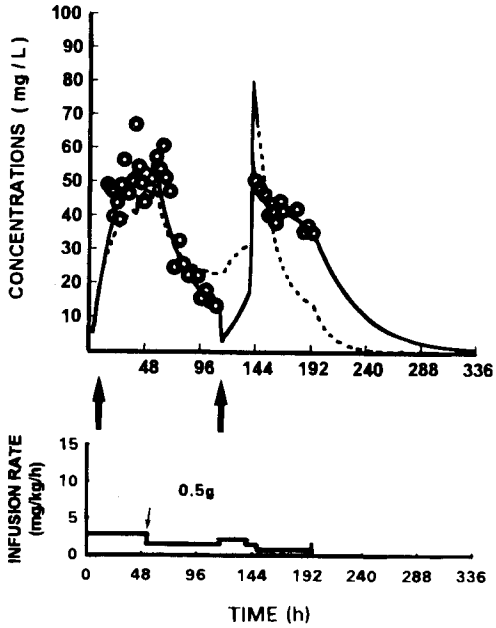


Fig. 2. Thiopental plasma concentration-time curves analized according to a one-compartment model using a time-dependent clearance model with two induction steps (solid lines). Dotted lines are the fits obtained with the first-order elimination model. In the bottom panels the lines depict the continuous infusion rates of thiopental, while arrows indicate bolus loading doses (↓) and Lag-time (↑).

DISCUSSION

In this study, during long-term constant infusion, thiopental concentrations declined after achieving an initial plateau or an initial maximal concentration, suggesting time-dependent kinetics due to enzyme induction. The time-dependency of clearance could be satisfactorily modelled according to a single exponential function in most cases, as already described for cyclophosphamide (16). However, for 6 of the 17 patients, the clearance change required two exponential functions that described two successive steps in the induction process.

Efficient doses to decrease ICP, 162 to 717 mg/Kg, were similar to those already reported (1–7). The initial clearance estimated in the present study is comparable to reported total clearance (0.6–4.7 ml/mn/kg) (1–3) but the final clearance is significantly higher. The distribution volume compared well with previous studies, 0.6 to 9.6 L/kg (1,2).

Since barbiturates are enzyme-inducing agents, it is likely that the large doses of thiopental infused over 2 weeks should stimulate its own metabolism. In addition, the autoinduction was expected as thiopental is a drug with a low hepatic extraction ratio (8) whose clearance is related to enzyme activity (20). Cytochrom P_{450} III A3 is inducible in human by barbiturates (9,21). Thiopental undergoes metabolic oxidation catalized by cytochromes P_{450}. Enzyme induction effect of thiopental has been assessed indirectly in rats (22–24). Another cause of enzyme induction following prolonged thiopental infusions is that pentobarbital is formed to a significant extent reaching 10–15% of thiopental concentrations (25,26). Pentobarbital is a potent inducer of hepatic microsomal drug metabolism.(12,15). The increase in pentobarbital clearance by autoinduction in

Table I. Infused Doses and Pharmacokinetic Parameters of Thiopental Derived from Data Modelled According to a One-Compartment Model Using a Time-Dependent Clearance with One or Two Induction Steps

Patient	Treatment duration h	Total dose mg/kg	Dose Rates[a)] mg/kg/h	$Dose_{Lag\ 1}$ mg/kg	$C_{Lag\ 1}$ mg/l	C_{stop} mg/l	Vd l/kg	$\phi 1$ h^{-1}	$\phi 2$ h^{-1}	Lag 1 h	Lag 2 h	CL_i ml/min/kg	CL_m ml/min/kg	CL_f ml/min/kg	CL rise %	F-test[b)]
1	112	259.1	2.27	104.6	32.6	19.7	1.80	0.162		45.1		0.851		1.81	112.7	<0.01
2	149	277.8	2.78-1.39	278.3	8.6	13.2	3.56	0.000937		156.5		1.84		36.2	1869.6	<0.01
3	174	500	2.27	259.1	15	8.7	3.18	0.000607		97		2.60		93.2	3486.2	<0.001
4	102.5	257.7	1.92	107.7	15.6	10.4	3.44	0.367		38.5		1.69		3.58	111.8	<0.05
5	125	243.3	1.67	56.7	14.5	6.4	3.44	0.00419		13.1		0.649		9.31	1334.5	<0.025
6	210	503.3	3.33-1.67	286.7	17.5	6.79	6.69	4.69		84		1.58		3.74	236.7	<0.05
7	114	225	3.12-1.56	100	17	6.2	4.58	0.0655		35.6		0.831		4.48	439.1	<0.05
8	199	521.4	3.57-1.79	435.7	18.2	7.7	2.61	0.416		152.7		1.75		3.49	99.4	<0.001
9	164	408.1	3.68-1.84	297.8	12	8.1	1.20	0.0258		105		2.62		4.63	76.7	<0.05
10	151	557.3	2.02-4.03	553.2	27.2	26	5.74	0.233		150.3		2.12		3.33	57.1	<0.01
11	166	720	5-2.5-5	595	47.5	21.8	2.65	0.272		137.8		1.66		2.26	36.2	<0.025
12	102.5	221.4	1.79	50	16	6	2.70	0.0247	0.0796	6.99	102.4	0.759	4.61	1.97	159.6	<0.001
13	213.5	492.9	3.57-1.79	232.1	54.6	11.2	2.21	0.139	0.666	79	165.4	0.607	1.22	2.38	292.1	<0.001
14	137	471.2	4.81-2.40	182.7	30	24.1	5.59	0.129	0.0536	41	177.1	0.146	1.89	3.63	2386.3	<0.025
15	82	237	2.78-3.7-1.55	48.6	18.2	12.3	2.97	1.37	0.159	14	28.7	0.126	1.69	2.39	1796.8	<0.05
16	193.3	385.9	2.77-1.39-0.694	27.3	21.5	35	1.21	0.00183	0.0661	9.19	111.6	0.189	8.08	0.559	195.8	<0.001
17	64.5	186.3	2.27-1.52-3.03	26.1	51.8	34.4	0.600	0.0404	0.0679	2.48	15	0.692	2.97	0.997	144	<0.001

Abbreviations: a) Thiopental was infused at one to three successive rates. b) Significance levels of the F-test between linear and time-dependent clearance models. $Dose_{Lag1}$: total dose of thiopental infused up to time Lag1; C_{Lag1}: thiopental concentration measured at time Lag1; C_{stop}: concentration at cessation of thiopental treatment; Vd: volume of distribution; $\phi 1$ and $\phi 2$: rate-constants for the changes in clearance rate; Lag1: latency period from the beginning of infusion to the beginning of clearance increase; Lag2: latency period from the beginning of infusion to the second step of clearance increase; CL_i: initial clearance; CL_m: middle clearance; CL_f: final clearance; CL rise = $[(CL_f - CL_i)/CL_i] \times 100$.

patients given a high dosage for reduction of intracranial pressure was dependent on the dose and treatment duration of pentobarbital (15).

Drug metabolism and enzyme induction exhibit large interindividual variability. Considerable differences were observed in induction onset of thiopental among these patients. Short lag times (<24 h) were observed, suggesting that enzyme induction occurred during the first exposure to thiopental. By contrast, lag-times of 5–6 days were also observed. The rate of CL change (ϕ1) was independent on the dose or the thiopental concentration measured in these patients. The increase in thiopental CL was not related with the duration of treatment or with the total dose. In the present study, a biphasic induction process was more appropriate to fit the data of six patients. The second step of induction occurring at cessation of thiopental treatment suggests that even at the end of treatment, enzyme induction cannot be assumed to have reached completion.

Thiopental appears to be a slow or a rapid metabolism inductor according to the patients. The vast difference in the induction Lag-time between patients is a known phenomenom for thiopental. Indeed, temporal differences were observed in stimulatory response of three hepatic microsomal parameters (activities of ethylmorphine N-demethylase and aniline hydroxylase and microsomal cytochrome P450 content) during, and after a daily administration of thiopental to rats. After 1 to 3 days, stimulation of at least one parameter occurred and was less than 150% of control values. After 7 days, 2 parameters were increased. After 14 days, the three microsomal parameters were increased to 160–200% of control values (24).

Studies have shown that the activity of drug-metabolizing enzymes depending on cytochrome P-450 could be influenced by genetic factors, age, sex, environmental factors such as nutritional status, disease states, alcohol consumption, smoking or the administration of various compounds (9,10). The patients in this study received numerous drugs. Cytochrome P450 III A3 is inducible by glucocorticoids (21) which were commonly administered, as opposed to cimetidine (27) and ranitidine (28) which are enzyme inhibitors and were only administered to some patients.

CONCLUSIONS

The present study shows that thiopental metabolism in man could be affected by auto induction whose degree and time-course are variable. The pharmacokinetic model applied to the data provided the optimal characterization of the time-dependent clearance. The linear model, the models with one and two induction periods were statistically hierarchical. Individuals were markedly heterogeneous with respect to the environmental factors known to influence drug metabolism. Furthermore, in critical care patients a broad spectrum can exist in severity, intensity, and duration of pathologic state. In addition, changes in disease state can occur with time. Thus, an individual can exhibit dramatic changes in thiopental elimination. In regard to drug efficiency over long-term treatment, an increased elimination may lead to underexposure to the drug. Circulating drug concentrations are sensitive to dose size and also to rate of metabolism. However, it was not established that attainment of individual limits in dosing rate, total dose or treatment duration occur during the induction process. Therefore, this study provides a basis for the long-recognized need to monitor and to individualize doses of thiopental. Because induction of thiopental metabolism can occur within the therapeutic range, the achievement of a target plasma concentration is more difficult than for a drug with linear pharmacokinetics.

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