Thiopental Pharmacokinetics under Conditions of Long-term Infusion

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Thiopental was used in long-term infusion (3–4.5 mg·kg⁻¹·h⁻¹ during 4–8 days) to protect the brain from injury following trauma. Thiopental plasma concentrations were measured during infusion (48 patients) and after infusion (14 patients) to determine the kinetics of the drug in continuous infusion. All mean values were mean ± SD. Steady state concentrations (C_{ss}) were 31.8 ± 10.7 mg/l for an infusion rate of 3.05 ± 0.37 mg·kg⁻¹·h⁻¹ and 48.9 ± 14.6 mg/l for a rate of 4.2 ± 0.3 mg·kg⁻¹·h⁻¹. Corresponding steady state clearance decreased when C_{ss} increased, indicating possible saturation of the metabolic enzymatic system. Michaelis-Menten kinetics were confirmed by postinfusion data that give, for higher C_{ss}, a nonlinear decay of log C versus time. First-order kinetics were only obtained with C_{ss} below 30 mg/l. The maximum rate of elimination (Vm) was 1.76 ± 1.15 mg·l⁻¹·h⁻¹ (n = 11), and the Michaelis constant (Km) was 26.7 ± 22.9 mg/l (n = 11). Hepatic enzyme saturation was between 35 and 85%. The volume of distribution at steady state was 4.35 ± 1.83 l/kg (n = 11). Apparent half-lives of elimination were between 18 and 36 h at the end of infusion, and predicted terminal half-lives were 10.15 ± 5.43 h (n = 11). Phases of burst-suppression were observed on electroencephalographic traces for concentrations greater than 40 mg/l. The authors' results suggest that a continuous infusion at a dose of 4 mg·kg⁻¹·h⁻¹ induces EEG changes consistent with a near-maximum reduction in cerebral metabolism. Because of the thiopental Michaelis-Menten kinetics at doses above 4 mg·kg⁻¹·h⁻¹, the authors suggest that thiopental plasma concentrations be measured and/or the drug effect be measured with the EEG to prevent excessive thiopental overdosage, causing a prolonged recovery time. (Key words: Anesthetics, intravenous: continuous infusion; thiopental. Brain: head injury. Pharmacokinetics: thiopental.)

THIOPENTAL INFUSIONS are used in the treatment of severe head injuries, although the effectiveness of barbiturates on the outcome of head injuries has not been clearly established. Mechanisms of repair of ischemic brain damage by barbiturates are supposed to include the following: decrease in cerebral oxidative metabolism, cerebral blood flow, and intracranial pressure together with possible scavenging of free radicals.[1-4] While the pharmacokinetics of a single bolus intravenous injection of thiopental are now well known[5-7] only few data are available for conditions of continuous infusion.[8-11] The aims of our investigations were as follows: 1) to determine the effects of a continuous infusion during 4–8 days on the pharmacokinetics of thiopental plasma concentration; 2) to study the decrease of thiopental plasma concentration after withdrawal of the infusion; 3) to determine a dose producing a near maximal decrease in cerebral metabolic rate without leading to an isoelectric electroencephalogram secondary to thiopental accumulation.

Materials and Methods

SUBJECTS

Forty-eight patients (36 male patients, 12 female patients) with severe craniocerebral trauma were included in this study. For each patient, the neurologic status was coded according to different levels of brain dysfunction. The minimum criterion was inability to obey simple commands. All patients had cranial computerized tomography (CCT) scans within 1 h following hospital entry. Age of subjects was 27.1 ± 13.3 yr (mean ± SD), ranging from 8 to 62 yr. Mean body weight was 60.4 ± 15.9 kg, ranging from 25 to 90 kg. None of the patients had hepatic or renal dysfunction: creatinine clearance, bilirubin, albumin, prothrombin times, enzymes, and alkaline phosphatases were normal. Patients with coma due to alcohol or epilepsy were excluded, as were patients suffering from a state of shock.

CLINICAL TRIAL

A preliminary bolus dose of 2 mg/kg sodium thiopental was given, followed by a continuous infusion of 3–5 mg·kg⁻¹·h⁻¹ in the antebrachial vein or by a central catheter during 4–8 days. The rate of infusion was subsequently adjusted on the basis of clinical criteria (agitation or response to nociceptive stimuli) or increased intracranial pressure (ICP) measured by means of the subarachnoid screw. The accepted normal range of ICP was 0–15 mmHg. All subjects were managed in an intensive care unit with the use of artificial ventilation. Controlled hyperventilation was used to maintain arterial P_{CO_2} between 27 and 35 mmHg and to ensure adequate oxygenation. When the ICP remained higher than 25 mmHg for 10 min, an infusion of 150 ml 20% mannitol was given.

Twenty-seven patients had electroencephalographic tracings during thiopental administration. The infusion rate was either increased from 0.5 to 1 $mg \cdot kg^{-1} \cdot h^{-1}$ if burst suppression was required or was withdrawn when the mean duration of electroencephalographic suppression was above 30 s.

Criteria for the cessation of barbiturate therapy included the following: normalization of the intracranial pressure, decrease of edema on CCT, and also signs of severe pneumonia or atelectasis.

Blood samples were collected in heparinized tubes once a day at 8 A.M. during infusion and 24, 48, and 72 h after the end of infusion. For 14 patients, blood samples were collected at 3–6-h intervals, for 72 h, after the end of infusion.

Plasma concentrations of thiopental and pentobarbital were determined respectively by high-pressure liquid chromatography[12] and gas chromatography.[13]

DATA ANALYSIS

Steady state concentrations (C_{ss}) were determined for 42 subjects by averaging daily concentrations over a period of up to 5 days. Steady state clearance (Cl_{ss}) was estimated by the ratio of the average rate of infusion Ro (mg/h) to the steady state concentration (mg/l) using the following equation.

$$Cl_{ss} \ (l/h) = \frac{Ro}{C_{ss}} \tag{1}$$

Postinfusion plasma concentration–time data were fitted to the one-compartment open model (equation [2]), using the method of least-squares for linear regression, and to the one-compartment open model with Michaelis-Menten elimination kinetics (equation [3]), using the convergent descent method for minimization[14] on a Prime 350® computer.

$$\ln C = \ln Co - kt \tag{2}$$

$$Co - C + Km \ln \frac{Co}{C} = Vm(t - to) \tag{3}$$

Vm ($mg \cdot l^{-1} \cdot h^{-1}$) is the theoretic maximum rate of drug elimination, and Km (mg/l) is the Michaelis constant defined as the thiopental plasma concentration at which the rate of drug elimination is one-half the theoretic maximum value. Volume of distribution was estimated at steady state when the rate of thiopental infusion was equal to the rate of thiopental elimination.

$$\frac{dC}{dT} = \frac{Ro}{Vd_{ss}} - \frac{VmC_{ss}}{Km + C_{ss}} \tag{4}$$

When $\frac{dC}{dT} = 0$, equation (4) gives

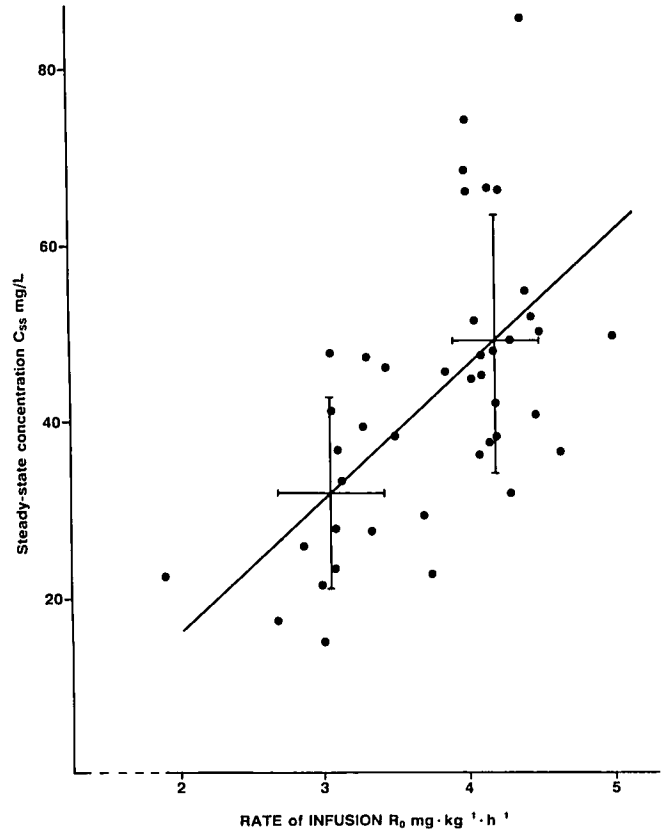$$Vd_{ss} = \frac{Ro(Km + C_{ss})}{VmC_{ss}} \tag{5}$$

FIG. 1. Variation of steady state concentrations (C_{ss}) with rate of infusion (Ro) (r = 0.58; n = 42; $P < 0.001$). Two sets of cross bars represents two groups arbitrarily defined with Ro above or below 3.5 $mg \cdot kg^{-1} \cdot h^{-1}$. Group 1: mean Ro (±SD) = 3.05 ± 0.37 $mg \cdot kg^{-1} \cdot h^{-1}$; mean C_{ss} (±SD) = 31.84 ± 10.69 mg/l. Group 2: mean Ro (±SD)= 4.2 ± 0.28 $mg \cdot kg^{-1} \cdot h^{-1}$; mean C_{ss} (±SD) = 48.93 ± 14.56 mg/l.

Initial saturation of the enzymatic system is given by equation (6).

$$\frac{-dC/dT}{Vm} \times 100 = \frac{C_{ss}}{Km + C_{ss}} \times 100 \tag{6}$$

The estimated first order rate constant, obtained when $C \ll Km$, is the ratio Vm/Km. The corresponding terminal half-life gives a good approach to the true half-life of elimination in the subject.

Results

Variations of steady-state concentrations according to the rate of infusion are shown in figure 1. All mean values are mean ± SD. The coefficient of variation (CV%) of C_{ss} was determined for each patient, and the mean CV was 8.9 ± 4%. The daily infusion rates (daily dose divided by 24 h) were constant for 21 subjects, and the CV was below 18% for other subjects. The mean duration of treatment was 6.12 ± 1.48 days, with
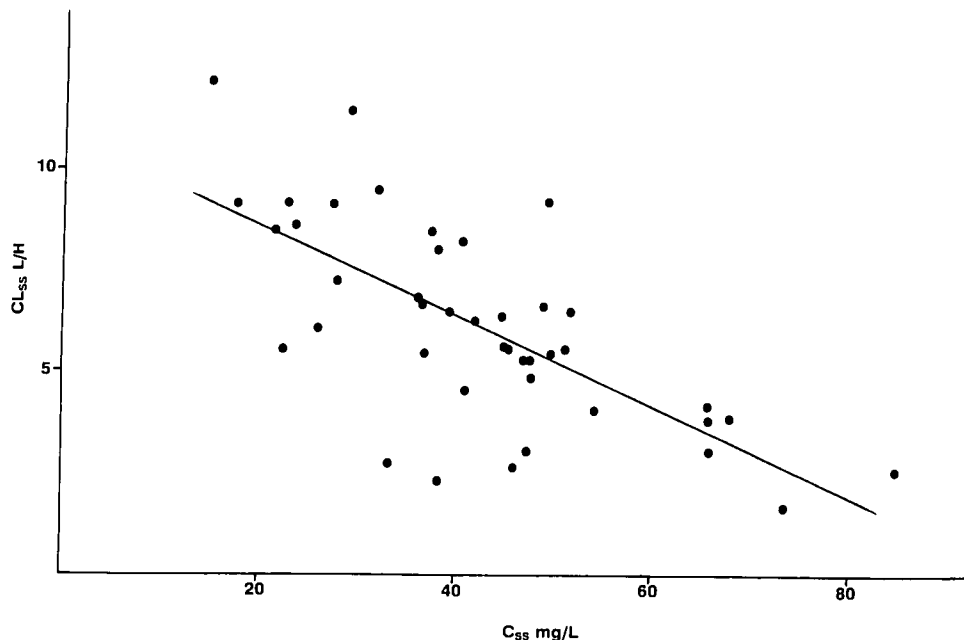
FIG. 2. Relationship between steady state clearance (Cl_{ss}) and steady state concentration (C_{ss}) (r = −0.692; n = 42; $P < 0.001$).

a mean steady state of 3.42 ± 1 days. Linear correlation exists between the rate of infusion and the resulting steady state concentration (r = 0.58, n = 42, $P < 0.001$). Mean steady state concentration was 42.4 ± 15.5 mg/l, with a mean rate of 3.76 ± 0.65 $mg \cdot kg^{-1} \cdot h^{-1}$.

Two groups have been arbitrarily defined with the mean Ro above or below 3.5 $mg \cdot kg^{-1} \cdot h^{-1}$. In Group 1 (n = 16), rate and concentration were respectively, 3.05 ± 0.37 $mg \cdot kg^{-1} \cdot h^{-1}$ and 31.84 ± 10.69 mg/l; in Group 2 (n = 26), they were 4.2 ± 0.28 $mg \cdot kg^{-1} \cdot h^{-1}$ and 48.93 ± 14.56 mg/l.

Steady state clearance, shown in figure 2, decreases when C_{ss} increases (r = 0.692, n = 42, $P < 0.001$). Because the infusion rate and C_{ss} were correlated (fig. 1) and clearance was calculated from the infusion rate and C_{ss} (equation [1]), one expects that C_{ss} and clearance will be related to one another in a significant manner.

Concentrations of pentobarbital, one of the thiopental metabolites, were approximately 10% of the concentrations of thiopental.

Decay of plasma concentrations after the end of infusion are given for three patients in figure 3. The log of concentration *versus* time can be adjusted to a straight line in one case, whereas the others give curves that become linear in the terminal part. In these cases, the rate of thiopental elimination slowly increases with time. Eleven concentration–time curves fit well with the integrated form of Michaelis-Menten equation (r = 0.995 ± 0.004). The three others give no possible fitting with equation (3) but show good first-order
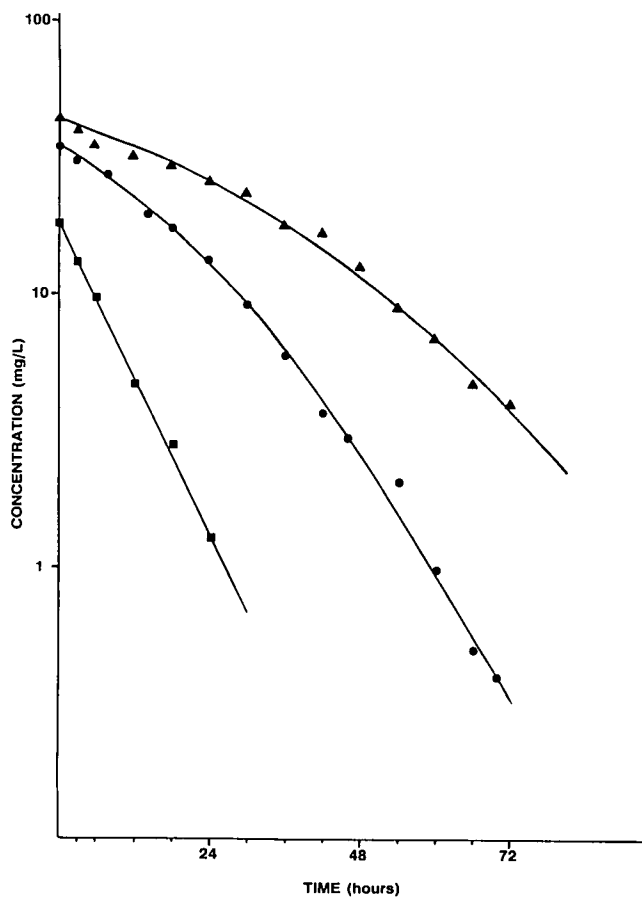

FIG. 3. Semilogarithmic plot of postinfusion plasma concentrations *versus* time in three patients. Solid lines are model-predicted concentrations based on fitting to linear kinetics (patient 13, ■) and Michaelis-Menten kinetics (patients 3, ● and 5, ▲).

TABLE 1. Pharmacokinetic Data from 14 Patients under Long-term Thiopental Infusion

Subject	Age	Weight	Ro (mg/h)	C$_{ss}$ (mg/l)	Cl$_{ss}$ (l/h)	Vm (mg·l^{-1}·h^{-1})	Km (mg/l)	Vd$_{ss}$ (l/kg)	Vm$^+$ (mg/h)	% Sat	T$_{1/2}$ Fin. (h)
1	44	65	250	45.3	5.52	1.38	11.4	3.49	313	79	5.72
2	35	75	248	47.1	5.27	0.84	8.9	4.71	295	83	7.34
3	62	76	315	37.4	8.42	1.59	17.4	3.81	460	68	7.54
4	13	35	144	47.2	3.05	1.04	8.0	4.61	168	85	5.33
5	25	75	322	48.8	6.59	1.09	16.0	5.23	427	75	10.18
6	60	70	300	31.8	9.44	1.00	36.1	9.16	641	47	25.02
7	8	30	120	73.6	1.63	1.21	16.8	4.03	147	81	9.62
8	23	50	220	54.2	4.06	1.26	14.8	4.44	280	79	8.14
9	22	65	260	68	3.82	4.29	75.6	1.97	549	47	12.22
10	19	60	245	36	6.80	3.67	64.5	3.10	684	36	12.18
11	25	75	333	51.6	6.45	1.99	24	3.27	488	68	8.36
12	23	90	333	29.2	11.40	—	—	—	—	—	19.60
13	26	60	160	17.5	9.15	—	—	—	—	—	6.41
14	19	75	250	27.5	9.08	—	—	—	—	—	5.29
Mean	28.9	64.4	250	43.9	6.48	1.76	26.68	4.35	405	68	10.2
SD	16.1	16.6	69.6	15.5	2.79	1.15	22.93	1.83	180	17	5.7

Ro = Average rate of infusion; Cl$_{ss}$ = Steady state clearance; Km = Michaelis-Menten constant; Vm$^+$ = Maximum rate of metabolism (Vm$^+$ = Vm·Vd$_{ss}$); C$_{ss}$ = average steady state concentration; Vm = theoretical maximum rate of drug elimination; Vd$_{ss}$ = steady state volume of distribution; T$_{1/2}$ Fin. = predicted final half-life $\left(T_{1/2} = \ln 2 \cdot \dfrac{Km}{Vm}\right)$.

kinetics (r = 0.998 ± 0.002). Pharmacokinetic parameters are given in table 1.

Thiopental administration on the basis of 3–4.5 mg·kg^{-1}·h^{-1} has not been associated with cardiovascular instability. During thiopental infusion, motor responses to pain stimuli were completely abolished. Flexor response recovery was studied in 14 patients in whom thiopental plasma levels were determined for 72 h after the end of infusion. Patients 6, 12, 13, 14 (table 1) had plasma concentrations of 31.8, 29.2, 17.5, and 27.5 mg/l after withdrawal of thiopental infusion; flexor responses recovered after 6–24 h. Ten other patients had thiopental plasma levels above 35 mg/l (between 36 and 73.6 mg/l); flexor responses recovered after 30–60 h in proportion to plasma levels at the end of infusion. Evidence of motor response was observed for plasma thiopental concentrations between 13 and 22 mg/l.

Among 27 patients subjected to electroencephalographic study, 19 had burst suppressions of electric activity, with thiopental plasma concentrations above 40 mg/l, while eight patients had no periods of electrical silence, with plasma concentrations below 40 mg/l.

Discussion

The steady state plasma concentrations, C$_{ss}$ of thiopental show considerable individual variations for doses between 3 and 5mg·kg^{-1}·h^{-1}. The mean steady state clearance of thiopental, Cl$_{ss}$ = 0.102 ± 0.42 l/min, is lower than the values indicated in the literature for single bolus injections of the drug.[6,7,15] The main point of interest in our work is the decrease in steady state clearance with increasing plasma concentrations of thiopental, probably linked to progressive saturation of liver metabolism. This pharmacokinetic relationship explains the rapid increase in plasma concentration for doses above 4.5 mg·kg^{-1}·h^{-1}. Levels of thiopental higher than 70 mg/l are observed to lead a total disappearance of cerebral electrical activity.

Changes in plasma concentration after withdrawal of thiopental infusion correspond to a capacity-limited model.[16,17] Patients with plasma concentrations lower than 30 mg/l show first-order kinetics while patients with plasma concentrations higher than 35 mg/l show zero-order elimination kinetics. The Vm and Km values are close to those obtained by Stanski et al.[9] The values of the elimination constant, calculated using the ratio Vm/Km, give a half-life between 5 and 12 h, similar to values reported for single bolus injections of thiopental.

In our study, the apparent initial half-life varies from 18 to 36 h for plasma concentrations between 30 and 70 mg/l, with enzyme saturation levels from 35 to 85%. Stanski et al.[9] indicates a half-life of 60 h for one patient with plasma concentrations from 60 to 70 mg/l and enzyme saturation at nearly 90%. Values of the steady state distribution volume are close to values calculated for single bolus injections of thiopental.[6,15] These results may be explained by a constant degree of protein binding of thiopental for plasma concentrations between 10 and 100 mg/l. Because the elimination half-life of thiopental increase upon terminating the thiopental infusion, the time needed for recovery of the patient's

motor response to pain will increase progressively as the thiopental plasma concentrations increase. High thiopental plasma concentrations will result in prolonged recovery times.

The doses and plasma concentrations of thiopental leading to the appearance of cerebral electrical silence were determined in our study. Cerebral protection by the drug is attributed at least in part to reduced brain metabolism, and Michenfelder[3] has demonstrated that reduction of oxygen consumption (CMR_{O_2}) is proportional to the dose of thiopental injected as long as electroencephalographic activity persists. When cerebral electrical activity is totally abolished, further injection of barbiturates leads to no further decrease of CMR_{O_2}. The doses were chosen so as to obtain short periods of electrical silence. A duration of 10–15 s of suppression, which corresponds to near maximum decrease in CMR_{O_2}, with no risk of excessive depression, was arbitrarily adopted. Periods of electrical silence (*i.e.*, suppression) appeared at plasma concentrations higher than 40 mg/l, while surgical anaesthesia corresponds to values from 39 to 42 mg/l.[18] The number of electroencephalograms recorded in our study is too small to determine the correlation between thiopental concentration and duration of electrical silence, however, in three patients the trace was flat for concentrations of 74, 75, and 90 mg/l. This was followed by total recovery of electrical activity some hours after withdrawal of thiopental infusion.

In conclusion, the variations of steady state clearance and the half-life of thiopental after the end of infusion depend on the plasma concentration and metabolism of the drug. Optimum doses of thiopental cannot be determined without taking into account the Vm and Km values. Our findings suggest that a continuous infusion at a dose of 4 $mg \cdot kg^{-1} \cdot h^{-1}$ should induce a near maximum reduction in cerebral metabolism. Doses between 4 and 5 $mg \cdot kg^{-1} \cdot h^{-1}$ for a duration of over 3 days lead to high-plasma concentrations of thiopental associated with profound coma, dilated pupils, with no reaction to light, and total electroencephalographic silence. Under these conditions of thiopental utilization, it is necessary to determine plasma concentrations and/or obtain electroencephalograms either continuously or at least several times a day, so as to avoid excessive plasma concentrations of the drug.

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