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Pharmacokinetics of Hexobarbital in Man After Intravenous Infusion

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The plasma levels of hexobarbital in humans were determined during and after a 30-min or 60-min zero-order intravenous infusion. Hexobarbital kinetics could be described by conceiving the body to exhibit two compartments. The plasma concentrations were fitted to the postinfusion equation and the parameters intrinsic to the two-compartment open model were estimated. The elimination half-life varied considerably among the 14 individuals (160–441 min), which could mainly be explained by the greatly varying metabolic clearance of the compound (123–360 ml/min). The apparent volume of distribution per kilogram of body weight was relatively constant (1.10 ± 0.12 liters/kg).

KEY WORDS: hexobarbital pharmacokinetics; intravenous infusion; healthy volunteers.

INTRODUCTION

Even though hexobarbital has been widely used in intravenous anesthesia and also in hypnotic drug therapy, its pharmacokinetics have not been well defined. Bush and Weller (1) have recently reviewed the fate of hexobarbital in several species. The compound is completely metabolized in the liver and has been used as a model substrate in hundreds of studies concerning the activity of the mixed-function oxygenase system. In such studies, sleeping time is considered as a measure for oxidative enzyme activity, rather than the elimination half-life or the metabolic clearance constant. Brodie in

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1952 (2) measured blood levels of hexobarbital in one human volunteer after intravenous administration of 3 g hexobarbital sodium. It can be deduced from the blood concentration curve obtained that the elimination half-life after this extremely high dose was about 5 hr. Sjögren *et al.* (3) and Bush *et al.* (4) have determined blood levels after oral administration of hexobarbital sodium to healthy subjects. However, concentrations could be followed only for a few hours and consequently the estimation of pharmacokinetic parameters was impossible. Improvements in the sensitivity of the assay for hexobarbital, using gas chromatography with a nitrogen selective detector (5), now make it feasible to study the pharmacokinetics after therapeutic doses to man. Preliminary results have already been published (6) on the elimination half-lives of racemic hexobarbital and its optical antipodes after oral administration to man.

It was the purpose of the present investigation to determine a pharmacokinetic model for hexobarbital after intravenous administration and to assess the pharmacokinetic parameters describing distribution and elimination. This will further allow a study of the influence of pathological conditions (liver disease) on the parameters of the model. In previous studies, we found that patients with acute hepatitis show a decreased tolerance to hexobarbital after intravenous infusion (7,8). In a separate study, we tried to correlate these findings with alterations in hexobarbital pharmacokinetics, especially with respect to the metabolic clearance (9).

MATERIALS AND METHODS

Racemic hexobarbital sodium for intravenous injection was used.[4] Solutions were prepared by dissolving the sterile contents of an ampule in sterile water (100 mg/ml) immediately before use.

Fourteen healthy male volunteers, ranging in age from 20 to 25 years and in body weight from 50 to 83 kg, participated in the study. They had received no regular medication during the 4 weeks preceding initiation of the experiments. After an overnight fast, the subjects received hexobarbital sodium intravenously at 9 A.M. by 30-min or 60-min zero-order infusion. The doses applied (calculated as hexobarbital free acid) were in the range of 6.85–8.82 mg/kg (see Table II). A relatively slow infusion procedure for intravenous drug administration was preferred in order not to make the volunteers uncomfortable and to avoid systemic reactions which often follow rapid intravenous administration of short-acting barbiturates (10). The volunteers remained prone for about 3 hr after drug infusion. Blood samples (5 ml) were taken from a forearm vein at the following times during

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a 30-min infusion: 5, 10, 15, 20, 25, and 30 min. Samples were taken at 10, 20, 30, 40, 50, and 60 min in the case of a 60-min infusion. Blood sampling was continued usually at 10, 20, and 30 min and 1, 2, 4, 6, 8, 10, 12, 18, and 24 hr postinfusion. The blood was heparinized and centrifuged, and plasma was separated and frozen until assayed. The hexobarbital plasma concentrations were determined by gas chromatography with nitrogen selective detection, as described previously by Breimer and van Rossum (5).

RESULTS AND DISCUSSION

During intravenous infusion of hexobarbital sodium, a rapid rise in the hexobarbital plasma concentration occurred until the zero-order infusion was terminated. After this event, the plasma concentration–time curve exhibited two distinct phases, an early phase with a relatively steep slope and a latter phase with a more gradual slope (see Fig. 1). This suggests that the early rapid drop in hexobarbital plasma concentration is dictated by rapid tissue localization, whereas the subsequent more gradual slope is a reflection of the elimination of the drug. This kinetic behavior is consistent with the conception that for hexobarbital the body consists of two kinetically distinct compartments: a central compartment and a peripheral compartment (11). The postinfusion plasma concentration curve can be represented mathematically as a sum of two exponentials according to Loo and Riegelman (12):

$$C_{p(\text{post})} = A_1^* \cdot e^{-\alpha t^*} + A_2^* \cdot e^{-\beta t^*} \tag{1}$$

where $C_{p(\text{post})}$ is the postinfusion plasma concentration, A_1^* and A_2^* are the coefficients (concentration intercepts of the exponential terms at $t^* = 0$), α and β are the rate constants (reciprocal time constants), and t^* is the time after the end of the infusion, i.e., $t^* = t - T$, where T is the infusion time.

During infusion, the plasma concentration, based on two-compartment kinetics, can be described by the following equation:

$$C_p = A_1 \cdot \frac{1}{\alpha T}(1 - e^{-\alpha t}) + A_2 \cdot \frac{1}{\beta T}(1 - e^{-\beta t}) \tag{2}$$

where A_1 and A_2 are the hypothetical intercepts with the ordinate for an intravenous bolus injection of the same amount of drug (i.e., $T = 0$). It is evident that A_1 and A_2 are equal to A_1^* and A_2^* if T is very short, but the difference increases as the infusion time increases. The relationship between A_1^* and A_1 and A_2^* and A_2 is shown by the following equations (12):

$$A_1^* = A_1 \cdot \frac{1}{\alpha T}(1 - e^{-\alpha T}) \tag{3}$$

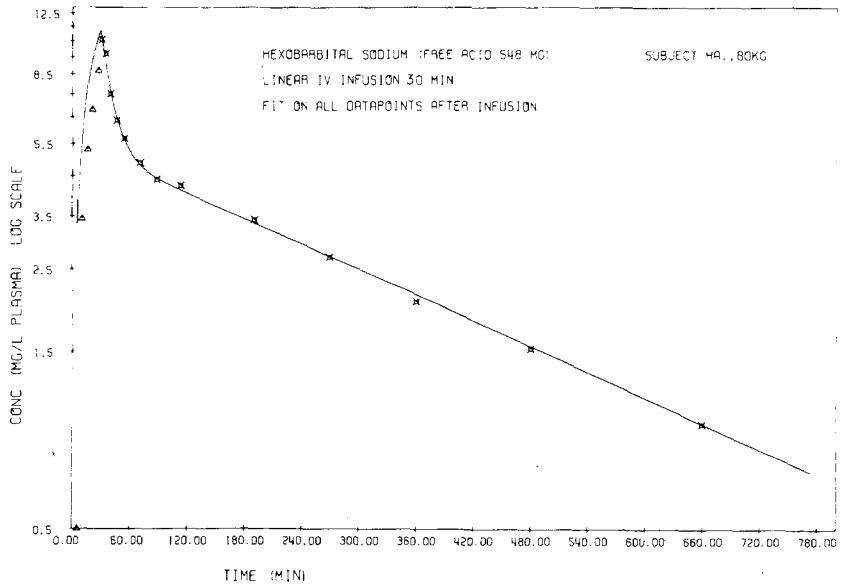

Fig. 1. Hexobarbital plasma concentration curve on semilogarithmic scale during and after a 30-min zero-order intravenous infusion of hexobarbital sodium into a healthy volunteer. The postinfusion concentrations were fitted according to equation 5. The curve during infusion was calculated on basis of the parameters of the postinfusion curve; the concentrations during this phase (triangles) were not used in the fitting procedure. The picture has been taken direct from a computer plot.

$$A_2^* = A_2 \cdot \frac{1}{\beta T}(1 - e^{-\beta T}) \tag{4}$$

Once the hypothetical intercepts A_1 and A_2 together with the time constants have been determined, the pharmacokinetic parameters intrinsic to a two-compartment open model can be calculated (13).

In the present investigation with hexobarbital, use was made of the FARMFIT computer program[5] and the postinfusion plasma concentrations were fitted according to the following general equation:

$$C_{p(\text{post})} = \sum_{i=1}^{n} A_i \cdot \frac{1}{k_i T}(1 - e^{-k_i T}) \cdot e^{k_i(T-t)} \tag{5}$$

where k_i is the ith rate constant.

A two-term exponential is assumed to describe the curve adequately (two-compartment model, $n = 2$). The initial graphic estimates of α and β

[5]FARMFIT, a non-linear curve fitting program, in use at the Computer Centre of the University of Nijmegen. Details available on request.

Table I. Estimated and Fitted Two-Compartment Open Model Parameters of Hexobarbital for Subject H. A. (Relative Errors in Parentheses)

	Initial estimates	Only postinfusion data included in the fitting procedure (see Fig. 1)		All data included in the fitting procedure (see Fig. 2)	
α (min^{-1})	0.0694	0.0855	(8.4%)	0.0378	(34.9%)
β (min^{-1})	0.00248	0.00271	(2.1%)	0.00223	(37.1%)
A_1 (mg · liter^{-1})		17.1	(10.1%)	8.41	(13.6%)
A_2 (mg · liter^{-1})		5.41	(2.0%)	4.63	(22.5%)

were used as preliminary estimates. A relative error of 5% was taken into account (weighting factor inversely proportional to the concentration), since this was the standard deviation found in the assay procedure (5). An example of a fitted and directly plotted curve is given in Fig. 1 and it illustrates the agreement between the plasma levels and the two-compartment open model. In Table I the preliminary estimates and the fitted parameter values are given.

The curve shown during the infusion period was simulated on the basis of the postinfusion parameters. It may be noticed that the experimental data points obtained for this subject during this period are somewhat lower than theoretically expected. Initially these data points were included for the computation of the best-fitted total curve and were fitted according to equation 2, which is valid during infusion. The results of the combined fitting according to equations 2 and 5 are given in Fig. 2 for the same experiment as in Fig. 1. It can be observed that now there is less agreement between the experimental data and the computed curve, which also became apparent in the higher estimated relative errors of the fitted parameters (Table I). Although it is unlikely that the kinetic behavior of hexobarbital during infusion is fundamentally different from the behavior after infusion, it may be expected that the plasma concentration during the relatively rapid infusion period does not always follow two-compartment kinetics exactly. Since we are dealing with racemic hexobarbital, this may be explained by the following. In a previous investigation, it was found that the optical isomers of hexobarbital are eliminated with different rates in man (6). The (+)-isomer showed an average half-life of 276 min and the (−)-isomer of 84 min. As a consequence, two different rate constants underlie the elimination phase for the racemate. However, it may be argued that if a drug with a half-life of 84 min is infused in a time period of 30 or 60 min, then a great deal has already been eliminated during infusion and during the so-called distribution phase. When the terminal log linear phase is reached, the contribution of the (−)-isomer may be almost negligible and one rate constant may well be adequate to describe this phase. This is in agreement with the fact that the

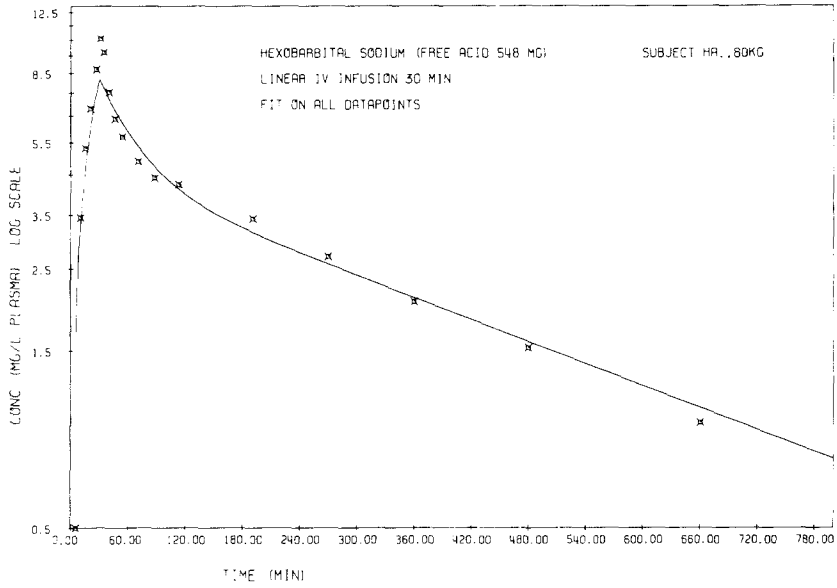

Fig. 2. The same experiment as in Fig. 1, but with the concentrations during infusion included in the fitting procedure according to equation 2. There is less agreement between the experimental data and the computed curve than in the case of Fig. 1. The picture has been taken direct from a computer plot.

estimated half-life of the racemate is almost equal to the half-life of the (+)-isomer: 261 vs. 276 min (6). In the present experiments, the infusion phase and the so-called distribution phase are in fact complex functions of the rapid elimination of (−)-hexobarbital, the slower elimination of (+)-hexobarbital, and the distribution of the two compounds into extravascular tissues. If the plasma concentrations during infusion are nevertheless included in the fitting procedure for the two-compartment model, relatively large errors may be induced. It was therefore decided to use concentrations after infusion only, in order to obtain the more accurate model parameters.

In Table II the pharmacokinetic parameters of hexobarbital in each of the 14 volunteers are given, as well as the mean values. All the values for each individual are reported since it is considered important to present the degree of variability of the kinetics of a drug in man and also to examine the validity of the model for each individual. For the fitted parameters (α, β, A_1, and A_2), the estimated relative errors are given and it is evident that these are usually substantial with respect to α and A_1. These parameters are associated with the rapid initial drop in plasma concentration after termination of the infusion, due to the distribution of the drug into the peripheral compartment. Only a limited number of plasma samples can be obtained

Table II. Two-Compartment Open Model Parameters of Hexobarbital for 14 Healthy Male Volunteers (Relative Errors in Parentheses)

	Subject									
	K. H.		H. A.		B. W.		E. R.		K. B.	
Age (yr)	22		23		23		24		25	
Body weight (kg)	73		80		80		74		63	
Dose (free acid, mg)	548		548		548		548		461	
Dose/kg (mg)	7.51		6.85		6.85		7.41		7.32	
Infusion time (min)	60		30		60		30		60	
α (min^{-1})	0.0662	(43.1%)	0.0855	(8.4%)	0.1163	(39.0%)	0.1681	(19.2%)	0.0439	(8.4%)
β (min^{-1})	0.00273	(7.4%)	0.00271	(2.1%)	0.00344	(6.2%)	0.00273	(5.5%)	0.00434	(3.3%)
Half-life (min)	254		256		201		253		160	
A_1 (mg · liter^{-1})	13.7	(51.3%)	17.1	(10.1%)	30.2	(54.1%)	54.4	(30.3%)	8.70	(9.4%)
A_2 (mg · liter^{-1})	4.94	(8.0%)	5.41	(2.0%)	4.94	(7.1%)	5.63	(4.5%)	5.30	(3.0%)
V_1(liters)	29.5		24.3		15.6		9.13		32.9	
V_1/kg (liters)	0.40		0.30		0.20		0.12		0.52	
V_d (liters)	89.8		83.9		80.0		72.9		65.3	
V_d/kg (liters)	1.23		1.05		1.00		0.99		1.03	
Clearance (ml · min^{-1})	272.2		249.5		323.9		230.5		326	
Clearance/kg (ml · min^{-1})	3.73		3.12		4.05		3.11		5.17	
k_{12} (min^{-1})	0.040		0.055		0.080		0.127		0.019	
k_{21} (min^{-1})	0.020		0.022		0.019		0.018		0.019	

Table II. Continued

	Subject									
	B. E.		F. B.		M. K.		B. B.		D. A.	
Age (yr)	23		25		24		22		24	
Body weight (kg)	69		77		70		73		69	
Dose (free acid, mg)	505.1		563.5		512.5		534.4		505.1	
Dose/kg (mg)	7.32		7.32		7.32		7.32		7.32	
Infusion time (min)	60		60		60		60		60	
α (min^{-1})	0.0323	(37.2 %)	0.0510	(31.9 %)	0.0352	(32.6 %)	0.0299	(49.2 %)	0.0355	(25.9 %)
β (min^{-1})	0.00226	(6.1 %)	0.00291	(6.6 %)	0.00257	(4.6 %)	0.00271	(6.4 %)	0.00334	(9.3 %)
Half-life (min)	306		238		270		256		208	
A_1 (mg · $liter^{-1}$)	9.05	(16.8 %)	18.1	(40.8 %)	9.95	(31.1 %)	9.96	(49.3 %)	17.0	(28.6 %)
A_2 (mg · $liter^{-1}$)	6.20	(10.2 %)	3.90	(11.3 %)	5.56	(8.0 %)	4.20	(13.6 %)	3.86	(16.3 %)
V_1 (liters)	33.1		25.6		33.0		37.7		24.2	
V_1/kg (liters)	0.48		0.33		0.47		0.52		0.35	
V_d (liters)	67.5		91.6		72.7		87.8		67.9	
V_d/kg (liters)	0.98		1.19		1.03		1.20		0.98	
Clearance (ml · min^{-1})	167.5		332.6		209.2		284.5		308.8	
Clearance/kg (ml · min^{-1})	2.43		4.32		2.99		3.90		4.48	
k_{12} (min^{-1})	0.015		0.030		0.017		0.014		0.017	
k_{21} (min^{-1})	0.014		0.011		0.014		0.011		0.009	

Table II. Continued

	Subject								Mean ± SD	
	S. G.		W. G.		P. F.		S. M.			
Age (yr)	22		23		20		21		22.9	± 1.4
Body weight (kg)	50		80		83		68		71.6	± 8.2
Dose (free acid, mg)	366.0		585.6		600		600		530.4	±61.1
Dose/kg (mg)	7.32		7.32		7.23		8.82		7.37	± 0.46
Infusion time (min)	60		60		60		60			--
α (min^{-1})	0.0123	(21.4 %)	0.0235	(19.5 %)	0.0253	(35.0 %)	0.0205	(35.1 %)	0.0533	± 0.0434
β (min^{-1})	0.00198	(4.0 %)	0.00157	(6.6 %)	0.00328	(8.7 %)	0.00273	(8.2 %)	0.00281	± 0.00067
Half-life (min)	351		441		211		254		261	±69
A_1 (mg · liter^{-1})	6.79	(11.4 %)	13.2	(18.8 %)	6.52	(23.9 %)	6.70	(19.5 %)		
A_2 (mg · liter^{-1})	4.79	(7.9 %)	3.33	(8.6 %)	4.64	(12.9 %)	6.82	(10.8 %)		--
V_1 (liters)	31.6		35.5		53.8		44.4		30.7	±11.1
V_1/kg (liters)	0.63		0.44		0.65		0.65		0.43	± 0.16
V_d (liters)	52.5		111.9		94.5		70.0		79.2	±15.2
V_d/kg (liters)	1.05		1.40		1.18		1.03		1.10	± 0.12
Clearance (ml · min^{-1})	123.1		219.3		359.3		212.6		259	±69
Clearance/kg (ml · min^{-1})	2.46		2.74		4.33		3.13		3.57	± 0.83
k_{12} (min^{-1})	0.004		0.013		0.009		0.007		0.032	± 0.034
k_{21} (min^{-1})	0.006		0.006		0.012		0.012		0.014	± 0.005

during this short period of time. Consequently, this is the main explanation for the relatively large error in the parameters describing this phase. Usually, the errors in A_2 and β were much smaller and substantiated the evidence for the single first-order kinetics of the elimination phase. The plasma half-life of hexobarbital in man is seen to vary from 160 to 441 min, with a mean value of 261 min. The main factors governing the rate of elimination of the drug in the body are the metabolic clearance (ml/min) and the apparent volume of distribution (V_{dss}). These parameters were calculated according to van Rossum (13) by the following equations:

$$\text{Clearance} = D/(A_1/\alpha + A_2/\beta) \tag{6}$$

$$\text{Steady-state volume of distribution} = \frac{D(A_1/\alpha^2 + A_2/\beta^2)}{(A_1/\alpha + A_2/\beta)^2} \tag{7}$$

The volume of distribution per kilogram of body weight is relatively constant in these subjects, whereas there is a substantial variability in the metabolic clearance constant (Table II). It can therefore be concluded that the observed differences in half-life are mainly due to individual differences in the hexobarbital-metabolizing ability of the liver. Siegert *et al.* (14) also found a substantial individual variability of $t_{1/2}$ in dogs for hexobarbital, which they attributed to fluctuations in the amount of metabolizing microsomal protein.

The calculated parameters V_1 (the volume of the central compartment, also called the initial dilution space) and k_{12} (the distribution rate constant from the central to the peripheral compartment) vary considerably due to the fact that their calculation is strongly dependent on A_1 and α, respectively. It is clear, however, that the volume of the central compartment is two- to threefold smaller than the overall apparent volume of distribution (V_{dss}). This indicates extensive tissue distribution of the drug, which may be explained by its relatively high lipophilicity. The smaller distribution rate constant from the tissues to the plasma compartment (k_{21}), compared to k_{12}, is a consequence of the apparent large volume of the tissue compartment.

All of the volunteers displayed typical signs of central nervous system depression during infusion (drowsiness, incoherent speech, and sometimes sleep). These effects, which varied considerably in intensity from one person to the other, became more pronounced as the infusion proceeded. This was evident especially in the case of a 30-min infusion. Obviously, when infusion proceeds more rapidly the plasma concentration and also the brain concentration for this lipophilic drug rise more rapidly. The peak plasma concentrations were approximately 1.5-fold higher with a 30-min infusion than with a 60-min infusion. After infusion, recovery occurred relatively rapidly and all the subjects were able to go out for lunch within 4 hr after drug

administration. The plasma levels attained at this time were usually in the range of 2–4 mg/liter.

Finally, the excretion of unchanged drug in five subjects was measured (urine, 24 hr). It appeared that less than 0.5% of the dose administered was excreted as unchanged hexobarbital.

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