Pharmacokinetics and Distribution Properties of Pentobarbital in Humans following Oral and Intravenous Administration

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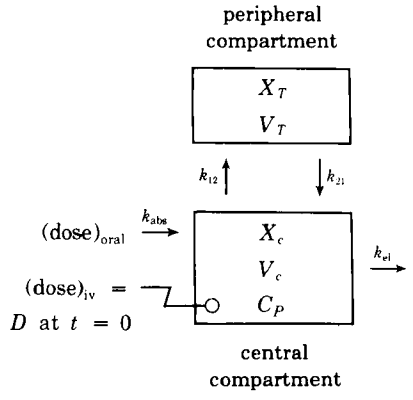
Abstract □ The pharmacokinetics of intravenously and orally administered pentobarbital (100 mg) were studied in humans by GC analysis of plasma, and the data were simulated with the aid of digital computation. The drug had an apparent disposition half-life of 22.3 ± 4.0 *(SD)* hr when administered intravenously to seven healthy subjects and after oral dosage the half-life was about the same. An examination of the individual pharmacokinetic constants showed that the volume of the peripheral compartment in the two-compartment open model appeared to increase with increased body weight in the subjects. Furthermore, this influenced the tissue to central compartment distribution of the drug. Formulas are presented which allow calculation of fractions of amount in the central compartment distributed to plasma water, plasma proteins, blood cells, and associated fluid. The application of these equations showed that of the total amount in the central compartment, about 87% was in the associated fluid; of the 13% in the systemic circulation, 4% was in plasma water, 5% was bound to plasma proteins, and the other 4% was distributed to blood cells. Analysis of the distribution volumes referenced to plasma water concentration gave volumes that considerably exceeded the total body water, so it is concluded that pentobarbital exhibits extensive tissue binding.

Keyphrases □ Pentobarbital—pharmacokinetics after intravenous and oral administration, volume of distribution □ Absorption kinetics—pentobarbital □ Bioavailability—pentobarbital, application of intravenous clearance □ Pharmacokinetics—pentobarbital after intravenous and oral administration, volume of distribution □ Drug distribution—pentobarbital, influence of body weight

Pentobarbital [5-ethyl-5-(1-methylbutyl)barbituric acid] has widespread use as a hypnotic and as a sedative and is commonly used in clinical practice. Until 1973, little information was available on the pharmacokinetics of the drug in humans following therapeutic dosage. A half-life of 35.1 ± 6.1 hr for ^{14}C-pentobarbital was reported (1) after oral administration of 6 mg/kg to four healthy subjects. The plasma levels of the drug after the intravenous injection of 750–1000 mg to six volunteers were described, but no rate constants were evaluated (2). Based on these data, Riegelman *et al.* (3) determined the half-life of the drug to be 41 hr. In the present study, 100 mg pentobarbital was given by intravenous and oral routes to seven young healthy subjects and the plasma levels were followed using a sensitive GC technique (4). Recently, Smith *et al.* (5) examined the pharmacokinetics of pentobarbital following intravenous and oral administration of 50 mg. The results of these investigators deviate to some extent from the data reported here, and the reasons behind the discrepancy will be discussed.



Scheme I

EXPERIMENTAL

Intravenous Study—Seven healthy male and female volunteers received a bolus dose of 2.2 ml of pentobarbital[1] solution equivalent to 100 mg of the acid. None of the volunteers had taken drugs regularly during the month prior to the study.

Venous blood was sampled through an indwelling catheter during the first 3 hr with the subjects lying down and thereafter by venous puncture at appropriate times. The sampling times were 6, 12, 18, 24, 30, and 45 min and 1.5, 2.0, 3.0, 6.0, 11.0, 23.0, and 47.0 hr. Each blood sample (3 ml) was centrifuged within 3 hr and the plasma was frozen (−20°).

The experiments were carried out by a surgical department with equipment for resuscitation available. No adverse effects were seen, and only three subjects fell into a light sleep for 20–30 min. The blood pressure was measured repeatedly during the first 3 hr; only a slight lowering (10–20 mm Hg) in the systolic pressure was recorded.

Oral Study—In a second experiment, the same volunteers who had participated in the intravenous test also received an oral dose of pentobarbital[2]. The subject ingested one 100-mg pentobarbital tablet on an empty stomach with approximately 100 ml water; no food was taken for at least 3 hr. Blood samples (3 ml) were drawn by venous puncture at 40 and 80 min and 2.0, 3.0, 6.0, 12.0, 24.0, and 48.0 hr after drug administration.

GC Assay of Pentobarbital—The plasma concentration of pentobarbital was determined by the method of Ehrnebo *et al.* (4) with a minor modification as follows: 500 μl of plasma was buffered to pH 5.5 with 50 μl 4 *M* NaH_2PO_4, a standard of 40 μg/ml sodium secobarbital in methanol (25 μl) was introduced, and 1.0 ml of ether was added. After mechanical agitation, the ether was separated by centrifugation, and the whole volume was transferred to another tube and shaken with an aqueous solution (25 μl) of trimethylanilinium hydroxide. To decrease the alkaline decomposition of the barbiturates in the injector, the basic extract was withdrawn and neutralized to pH 7 with 4 *M* hydrochloric acid (~1 μl). An aliquot (1.5–3.5 μl) was then injected into the chromatograph. Duplicate extractions and determinations were made on each plasma sample. This method allows the accurate determination of pentobarbital to as low as 0.25 μg/ml (4).

Calculations—The obtained plasma data indicate that the time course of the drug in the body might be properly described by assuming that the body acts as a two-compartment open model (Scheme I). Thus, in the intravenous study, the plasma concentrations (C_P) declined biexponentially with time according

[1] Nembutal, Abbott S.A., Belgium.
[2] Mebumal, Lot No. S2101, ACO Läkemedel AB, Solna, Sweden.

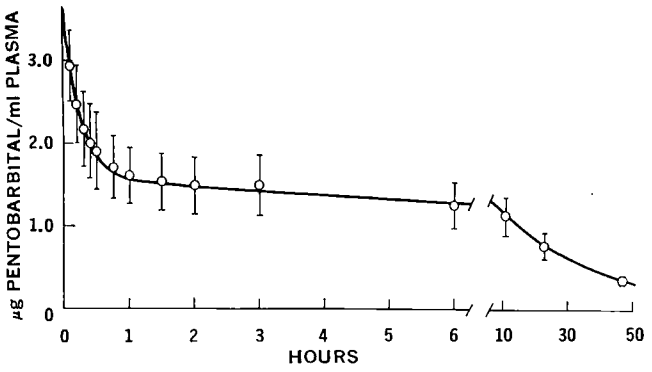


Figure 1—*Mean* (±SD) *plasma levels of pentobarbital following rapid intravenous injection of 100 mg to seven subjects. The line is drawn by an analog computer programmed with the mean constants from Table II and the mean plasma concentration at zero time,* $(C_P)_0$.

to Eq. 1:

$$C_P = Ae^{-\alpha t} + Be^{-\beta t} \quad \text{(Eq. 1)}$$

where A, B, α, and β were used to calculate the rate constants k_{12}, k_{21}, and k_{el} (Scheme I) as shown previously (6). The absorption rate constant (k_{abs}, Scheme I) and apparent absorption lag time (t_0) were evaluated using the equation for first-order absorption (7), where t_0 was included in the exponents. The various rate constants of this model and the lag time of absorption were evaluated with the aid of a digital computer[3] by a method for nonlinear least-squares fit. The plasma concentrations were given equal weights of unity.

The volumes of the central compartment (V_C) and the tissue compartment (V_T) are obtained with the expressions (8):

$$V_C = D/(C_P)_0 \quad \text{(Eq. 2)}$$

$$V_T = V_C k_{12}/k_{21} \quad \text{(Eq. 3)}$$

where D is the dose of pentobarbital (free acid) administered by rapid intravenous injection, $(C_P)_0$ is the concentration in plasma at zero time, and $V_C + V_T$ is the total distribution volume at steady state. In addition to these two volume entities, a third volume, $(Vd)_\beta$, was calculated (9):

$$(Vd)_\beta = D/\beta \int_0^\infty C_P\, dt \quad \text{(Eq. 4)}$$

where $\int_0^\infty C_P\, dt$ is the area under the plasma concentration–time curve following intravenous administration.

The ratio between the amount in the peripheral compartment (X_T) to the amount in the central compartment (X_C) during the β-phase is obtained as shown previously (10) with the expression:

$$(X_T/X_C)_\beta = k_{12}/(k_{21} - \beta) \quad \text{(Eq. 5)}$$

The bioavailability of the oral preparation ($F\%$) was determined by comparing the areas under the time–concentration curves:

$$F\% = 100(AUC_{oral}/AUC_{iv}) \quad \text{(Eq. 6)}$$

where the areas after oral and intravenous administration, AUC_{oral} and AUC_{iv}, respectively, were estimated by the trapezoidal rule including the residual area up to infinite time.

Fraction of Amount in Central Compartment Distributed to Plasma Water, Plasma Proteins, Blood Cells, and Associated Fluid—Recently, Garrett and Lambert (11) made a detailed pharmacokinetic analysis of trichloroethanol and metabolites in the dog. They presented complex formulas for the different distribution volumes of the central compartment in the three-compartment body model with reference to plasma water concentrations. The following is a simplified and condensed approach to the distribution properties of a drug in the two-compartment body model using common pharmacokinetic expressions.

[3] IBM 360; revised BMDX85 program.

Table I—Data Obtained following a Single Intravenous Injection of Pentobarbital (100 mg) to Humans; $C_P = Ae^{-\alpha t} + Be^{-\beta t}$

Subject	A, μg/ml	α, hr^{-1}	B, μg/ml	β, hr^{-1}	Area[a], (μg × hr)/ml
H.K.	2.16 (0.15)[b]	5.20 (0.50)	1.22 (0.03)	0.0293 (0.0030)	41.9
N.K.	2.07 (0.19)	4.44 (0.59)	1.39 (0.04)	0.0283 (0.0035)	49.4
L.L.	2.57 (0.16)	4.73 (0.42)	1.75 (0.03)	0.0250 (0.0020)	70.5
M.E.	1.76 (0.11)	3.60 (0.36)	1.79 (0.03)	0.0340 (0.0022)	53.0
G.P.	1.56 (0.20)	2.65 (0.61)	1.88 (0.08)	0.0309 (0.0042)	61.3
K.K.	1.95 (0.10)	4.64 (0.35)	1.16 (0.02)	0.0309 (0.0023)	37.9
U.H.	2.07 (0.14)	3.72 (0.41)	2.18 (0.04)	0.0468 (0.0031)	47.3

[a] Calculated as $A/\alpha + B/\beta$. [b] The standard deviations of the parameter (estimated by the BMDX85 program) are shown in parentheses beneath the value of the parameters.

The assumptions made are: *(a)* the drug instantaneously equilibrates between the different components in the central compartment; and *(b)* the binding capacity of both blood cells and plasma proteins is independent of concentration, *i.e.*, the dose is sufficiently low to give a linear relationship between bound and free drug with reference to plasma and whole blood. The slight difference between the corrected venous hematocrit value (blood cell volume per volume venous whole blood) and the total hematocrit value (total blood cell volume per total blood volume) is not taken into account.

As seen in the *Appendix*, the following expressions for the fraction of amount in the central compartment distributed to plasma water (F_{PW}), to plasma proteins (F_{PP}), to blood cells (F_{BC}), and to associated fluid (F_{AF}) are readily obtainable:

$$F_{PW} = \lambda_{PW}(1 - H)V_{Btrue}/(\lambda_{PW} + \lambda_{PP})V_C \quad \text{(Eq. 7)}$$

$$F_{PP} = \lambda_{PP}(1 - H)V_{Btrue}/(\lambda_{PW} + \lambda_{PP})V_C \quad \text{(Eq. 8)}$$

$$F_{BC} = \lambda_{BC}(1 - H)V_{Btrue}/(\lambda_{PW} + \lambda_{PP})V_C \quad \text{(Eq. 9)}$$

$$F_{AF} = 1 - (1 - H)V_{Btrue}/(\lambda_{PW} + \lambda_{PP})V_C \quad \text{(Eq. 10)}$$

where λ_{PW}, λ_{PP}, and λ_{BC} are the fractions of amount in whole blood distributed to plasma water, plasma proteins, and blood cells, respectively; H is the hematocrit as fraction volume blood cells per whole blood volume; and V_C is the apparent distribution volume of the central compartment (Eq. 2).

Distribution Volume of Central and Peripheral Compartment with Reference to Plasma Water Concentrations—Garrett and Lambert (11) defined the distribution volume, $V_P u$, in a formula equal to the following expression:

$$V_P u = (a_{AF} + a_{PW})/C_{PW} = [(a_{AF})_0 + (a_{PW})_0]/(C_{PW})_0 \quad \text{(Eq. 11)}$$

where $V_P u$ is the volume of distribution of associated fluid and plasma water with reference to the concentration of drug in plasma water (C_{PW}), a_{AF} is the amount of drug in associated fluid, and a_{PW} is the amount in plasma water. The 0-indexed parentheses indicate the situation at zero time in the two-compartment open model.

It is evident that:

$$a_{AF} + a_{PW} = X_C(F_{AF} + F_{PW}) = V_C C_P(F_{AF} + F_{PW}) \quad \text{(Eq. 12)}$$

which makes it possible to express $V_P u$ as:

Table II—Rates Constants and $t_{1/2}$ ($0.693/\beta$) to Fit the Plasma Pentobarbital Levels following a Single Intravenous Injection (100 mg)

Subject	Sex	Body Weight, kg	$t_{1/2}$ hr	k_{12}, hr^{-1}	k_{21}, hr^{-1}	k_{el}, hr^{-1}
H.K.	Male	82	23.6	3.26	1.89	0.0807
N.K.	Male	71	24.5	2.60	1.80	0.0700
L.L.	Female	57	27.7	2.76	1.93	0.0613
M.E.	Male	60	20.4	1.74	1.84	0.0668
G.P.	Female	50.5	22.4	1.16	1.46	0.0560
K.K.	Male	79.5	22.4	2.84	1.75	0.0820
U.H.	Female	47	14.8	1.75	1.93	0.0901
Average			22.3	2.30	1.80	0.0724
SD of averages			4.0	0.76	0.16	0.0123
Coefficient of variation, %			18	33	8.9	17

$$V_{Pu} = V_C(F_{AF} + F_{PW})/(1 - f_P) \quad \text{(Eq. 13)}$$

where f_P is the fraction of drug bound in plasma.

The distribution volume of the peripheral compartment during the β-phase referenced to plasma water concentration, $(V_Tu)_\beta$, can be defined as:

$$(V_Tu)_\beta = (X_T)_\beta/(C_{PW})_\beta \quad \text{(Eq. 14)}$$

where $(X_T)_\beta$ is the amount in the peripheral compartment of the plasma water concentration, $(C_{PW})_\beta$, during the β-phase. Since $C_{PW} = C_P(1 - f_P)$ and $(X_T)_\beta = C_P(Vd)_\beta - C_PV_C$, Eq. 14 can also be written as:

$$(V_Tu)_\beta = [(Vd)_\beta - V_C]/(1 - f_P) \quad \text{(Eq. 15)}$$

where $(Vd)_\beta$ and V_C are defined in Eqs. 4 and 2, respectively.

By relating V_Pu and $(V_Tu)_\beta$ to the volume of the body water, information is obtained concerning to what degree a drug is bound to body tissues.

RESULTS AND DISCUSSION

Intravenous Study—Figure 1 shows the mean plasma concentrations following the intravenous injection of 100 mg pentobarbital, with the standard deviation at each level indicated with bars. There was a rapid fall in the plasma levels during the 1st hr, from about 3 μg/ml at 6 min to about 1.6 μg/ml at 1 hr (mean values). The line in Fig. 1 was calculated by an analog computer using the mean values of k_{12}, k_{21}, and k_{el} in Table II. Hence, as seen in the figure, there was good agreement between predicted and observed plasma concentrations.

The plasma concentrations following the intravenous administration were found to fit very well to the biexponential function (Eq. 1) in all seven subjects; the computer solution of the parameters A, α, B, and β (Table I) gave low standard deviations of the parameters (values in parentheses). The individual and average rate constants of elimination and distribution are shown in Table II. The results indicate that both k_{12} and k_{21} are greater than k_{el} and that the ratio k_{12}/k_{21} ranged from 0.79 to 1.72 in the subjects. As indicated by the coefficient of variation, the least individual variation of the parameters in Table II was found in k_{21}, showing a coefficient of variation of only 8.9%.

The distribution volumes referenced to plasma concentrations following the 100-mg dose of pentobarbital are given in Table III. The average volume of distribution per kilogram body weight (0.990 liter/kg) showed a coefficient of variation of only 4.9%. The volume of the central compartment varied very little between the individuals (average 27.8 liters), and no significant increase in V_C with body weight was observed (Fig. 2). On the other hand, the volume of the peripheral compartment (V_T) at steady state (Eq. 3) showed an increase in volume with an increase in body weight (Fig. 2). The regression line for V_T $(= y)$ *versus* body weight $(= x)$ was $y = 0.922x - 23.1$ ($r = 0.972$). Consequently, an increase in body weight primarily seems to influence the peripheral volume of distribution, probably due to additional adipose tissue and muscles, whereas the central volume appears to be on the whole unaffected by the body weight. These findings are consonant with the proposal (6) that the main constituents of the peripheral compartment are adipose tissue, muscles, and skin tissue.

The body weight also influences the $(X_T/X_C)_\beta$ distribution ratio (Eq. 5) of pentobarbital (Fig. 3). Since $k_{21} > \beta$, this depends mainly on the ratio k_{12}/k_{21}, which increases with the body weight. This relationship is in accordance with the comparatively consistent volume of the central compartment and the increase in peripheral volume with body weight which, according to Eq. 3, should influence the ratio k_{12}/k_{21} in this way. The regression line for $(X_T/X_C)_\beta$ $(= y)$ *versus* body weight $(= x)$ was $y = 0.0243x - 0.261$ ($r = 0.885$).

As seen in Table IV, most pentobarbital in the central compartment was distributed to the associated fluid and only about 13% was present in the blood compartment where about 4% was in the plasma water, 5% was bound to plasma proteins, and 4% was distributed to blood cells. Furthermore, as seen in Table V, the value of V_Pu (distribution volume of plasma water and associated fluid referenced to plasma water concentration) far exceeded the total body water. The value of the distribution volume of peripheral compartment referenced to plasma water concentrations, $(V_Tu)_\beta$, also far exceeded total body water. Therefore, pentobar-

Table III—Distribution Volumes of Pentobarbital following Intravenous Injection of 100 mg with Reference to Plasma Concentrations

Subject	V_C, liters	V_T, liters	$V_C + V_T$, liters	$(V_C + V_T)$/body weight, liters/kg	$(Vd)\beta$, liters
H.K.	29.6	50.9	80.5	0.982	81.3
N.K.	28.9	41.9	70.8	0.997	71.5
L.L.	23.1	33.1	56.3	0.987	56.7
M.E.	28.2	26.7	54.9	0.915	55.4
G.P.	29.1	23.2	52.3	1.036	52.8
K.K.	32.1	53.3	84.4	1.061	85.4
U.H.	23.5	21.2	44.7	0.952	45.2
Average	27.8	35.6	63.4	0.990	64.0
SD of averages	3.3	12.9	15.2	0.049	15.4
Coefficient of variation, %	12	36	24	4.9	24

Table IV—Fraction of Amount in Central Compartment Distributed to Plasma Water (F_{PW}), Plasma Proteins (F_{PP}), Blood Cells (F_{BC}), and Associated Fluid (F_{AF}) following 100 mg Pentobarbital Intravenously

Subject	V_{Btrue}[a], liters	Hematocrit[b]	C_B/C_P[b]	λ_{PW}[b]	λ_{PP}[b]	λ_{BC}[b]	F_{PW} ×100	F_{PP} ×100	F_{BC} ×100	F_{AF} ×100
M.E.	3.94	0.47	0.714	0.257	0.407	0.336	2.9	4.5	3.7	88.9
H.K.	5.38	0.44	0.854	0.262	0.394	0.344	4.1	6.1	5.3	84.5
K.K.	5.22	0.42	0.833	0.279	0.417	0.304	3.8	5.7	4.1	86.4

[a] Calculated as 65.6 ml/kg body weight. [b] Unpublished data of M. Ehrnebo and I. Odar-Cederlöf.

bital shows extensive tissue binding in both the central and peripheral compartments.

Oral Study—Table VI shows that the tablet with 100 mg of pentobarbital was rapidly and almost completely absorbed from the GI tract. The half-life of the absorption process was 13 min (k_{abs} = 3.1 hr^{-1}). The lag time (t_0) until absorption began was about 30 min from the time of tablet intake (Table VI).

The average apparent biological half-life after oral administration was 25.1 ± 5.6 *(SD)* hr (n = 7) and apparently about the same as after intravenous administration (22.3 ± 4.0 hr).

The maximum availability of the 100-mg tablet was determined by the following equation (12):

$$\theta = 1 - \frac{f_m(\text{dose})_{iv}}{\dot{V}_{BL}\lambda\left(\int_0^\infty C_{\text{plasma}}\,dt\right)_{iv}} \qquad \text{(Eq. 16)}$$

where θ is the fraction of the administered dose appearing in the rest of the body, f_m is the fraction of dose metabolized in the liver, $\dot{V}_{BL}$ is the liver blood flow, λ is the ratio of the concentration of drug in blood to the concentration of the drug in plasma (C_B/C_P), and $(\int_0^\infty C_{\text{plasma}}\,dt)_{iv}$ is the area under the plasma concentration–time curve from time zero to infinity following intravenous administration of the $(\text{dose})_{iv}$. For pentobarbital, f_m approaches 1 as shown by Brodie *et al.* (2). Using 91,800 ml/hr for liver blood flow (12), values for C_B/C_P (Table IV), and areas (Table I) following intravenous administration, it can be shown that the maximum bioavailability of orally administered pentobarbital is about 97%. The average bioavailability in Table VI calculated from the ratios between areas under plasma concentration curves is in agreement with this value.

Comparison between Reported Pharmacokinetic Constants after Different Dosage Levels of Pentobarbital—Following the intravenous administration of 1000 mg of pentobarbital (2), a β-phase half-life of 41 hr (n = 6) was observed (3). With a 6-mg/kg body weight dose of oral ^{14}C-pentobarbital, half-lives of 35 hr (n = 4) were reported (1). In a recent publication (5), a mean β-phase half-life of about 50 hr was reported when 50 mg of pentobarbital was administered intravenously. A more precise value of this half-life can be obtained using the formula for the relationship between β and k_{12}, k_{21}, and k_{el} (8). This gives the mean value 60.3 hr (n = 5) for the half-life of pentobarbital in the latter study. In the present paper, the average β-phase half-life following 100 mg pentobarbital intravenously was 22.3 hr (n = 7). Accordingly, the half-life following 50 mg pentobarbital in the report of Smith *et al.* (5) gave almost three times the half-life found in the present investigation. Both Smith *et al.* (5) and the present investigator, in contrast to the other authors, used GC techniques selective for the parent drug.

The results of Smith *et al.* (5) showed deviations from the data reported here. In summary, they obtained the following values for the pharmacokinetic constants of distribution and elimination: k_{12} = 1.162 hr^{-1}, k_{21} = 0.515 hr^{-1}, k_{el} = 0.038 hr^{-1}, and V_C = 41 liters. A comparison with the data in Table II shows that the rate constants in the present report attained much higher values and that the volume of the central compartment referenced to plasma concentrations reported here is a smaller value. A minor difference in the experimental technique, disregarding the dose size, is that Smith *et al.* (5) administered the 50-mg dose by 5 min zero-order infusion compared with 30–45 sec in the present study. However, the deviations cannot solely be due to the differences in infusion time *per se* (13) and must be due to model-dependent pharmacokinetics of a more complex nature (14). This may include, among other things, the increased or decreased binding to tissues at different dose sizes, dose-induced changes in hepatic lipid–water ratios (11), or some physiological action (lowered blood pressure or decreased peripheral blood flow) that may be caused by the central effect of pentobarbital. Accordingly, a more detailed knowledge of pentobarbital pharmacokinetics will require further examinations.

The data of Smith *et al.* (5) for the oral administration of 50 mg sodium pentobarbital are, according to these investigators, as follows (mean values in five subjects): availability = 98.5%, k_{abs} = 2.00 hr^{-1}, and lag time = 0.30 hr. A comparison with the values in Table VI (100 mg pentobarbital as acid) shows that the availability and k_{abs} are about the same, whereas the lag time for the 50-mg sodium pentobarbital in capsule form appears to be shorter than that of 100 mg acid in tablet.

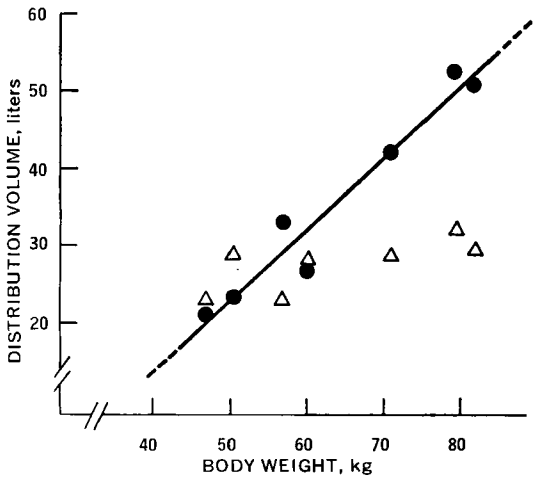


Figure 2—*Distribution volumes in liters referenced to plasma concentrations* versus *body weight in seven healthy volunteers following the administration of 100 mg pentobarbital by rapid intravenous injection. Key:* △, *central compartment; and* ●, *peripheral compartment (at steady state). The regression line* (y = 0.922x − 23.1; r = 0.972) *for peripheral volume* (= y) versus *body weight* (= x) *is drawn.*

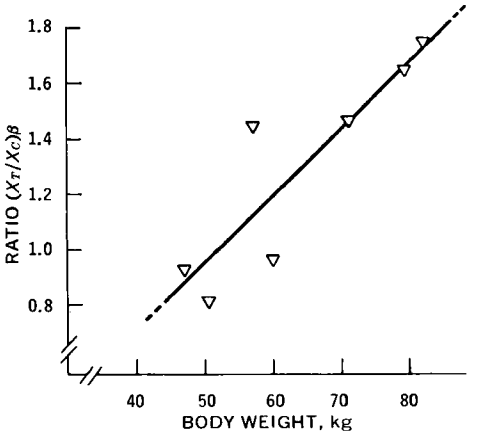


Figure 3—*Ratio of amount in peripheral compartment/amount in central compartment during the β-phase* versus *body weight in seven healthy volunteers following administration of 100 mg pentobarbital by rapid intravenous injection. The regression line* (y = 0.0243x − 0.261; r = 0.885) *is drawn.*

Table V—Distribution Volumes of Pentobarbital (100 mg) with Reference to Plasma Water Concentrations

Subject	V_C, liters	f_P[a]	V_{Pu}, liters	$(V_T u)\beta$, liters	Total Body Water, liters[b]
M.E.	28.2	0.613	66.8	70.3	36
H.K.	29.6	0.601	65.7	129.7	49
K.K.	32.1	0.600	72.4	133.3	48

[a] Fraction drug bound in plasma, unpublished data of M. Ehrnebo and I. Odar-Cederlöf. [b] Calculated as 60% of body weight (14).

CONCLUSIONS

It is concluded that pentobarbital pharmacokinetics following 100 mg administered intravenously is adequately described by the two-compartment open model. The β-phase half-life was 22 hr, and the half-life was about the same after oral dosage of 100 mg. The body weight appears to influence the peripheral to central compartment distribution ratio of the drug so that the drug is further distributed to the peripheral compartment with increased body weight. In the central compartment the drug was mainly located in the associated fluid, and only 13% of the total amount in the central compartment is present in the systemic circulation where 4% was in plasma water, 5% was bound to plasma proteins, and 4% was distributed to blood cells. Consequently, since only about 5% of the amount in the central compartment is bound to plasma proteins, the interaction of other drugs for plasma protein binding sites will have little influence on pentobarbital distribution in the body. As shown by the distribution volumes referenced to plasma water concentration, it is concluded that pentobarbital exhibits extensive tissue binding in both the central and peripheral compartments. The biological availability of the drug following oral administration was high (94%), and this value is in agreement with the calculated bioavailability of completely absorbed oral pentobarbital by application of intravenous clearance concepts.

APPENDIX

By defining λ_{PW}, λ_{PP}, and λ_{BC} as the fraction of amount in whole blood distributed to plasma water, plasma proteins, and blood cells, respectively, it is evident that $a_{PW} = \lambda_{PW}a_B$, $a_{PP} = \lambda_{PP}a_B$, and $a_{BC} = \lambda_{BC}a_B$, where a_{PW}, a_{PP}, and a_{BC} are the amounts of drug distributed to plasma water (and in the plasma), plasma proteins, and blood cells, respectively, and a_B is the amount of drug in blood.

The amount in plasma (a_P) is:

$$a_P = C_P V_{P\text{true}} = C_P(1 - H)V_{B\text{true}} \qquad \text{(Eq. A1)}$$

where $V_{P\text{true}}$ and $V_{B\text{true}}$ are the true plasma and whole blood volumes in the body, respectively. Accordingly, $a_B = C_B V_{B\text{true}}$.

It is evident that the following relationship exists between plasma and whole blood concentrations:

$$C_P = C_B(\lambda_{PW} + \lambda_{PP})/(1 - H) \qquad \text{(Eq. A2)}$$

which makes it possible to calculate the amount in blood as:

$$a_B = C_P V_{B\text{true}} = (1 - H)/(\lambda_{PW} + \lambda_{PP}) \qquad \text{(Eq. A3)}$$

Since $a_{PW} = \lambda_{PW}a_B$ and $X_C = V_C C_P$, the following expression for the fraction of amount in the central compartment distributed to plasma water (Eq. 7) is readily obtainable:

$$F_{PW} = a_{PW}/X_C = \lambda_{PW}V_{B\text{true}}(1 - H)/(\lambda_{PW} + \lambda_{PP})V_C \qquad \text{(Eq. A4)}$$

In the same way, Eqs. 8 and 9 are derived. Furthermore, $F_{AF} = 1 - (F_{PW} + F_{PP} + F_{BC})$ and $\lambda_{PW} + \lambda_{PP} + \lambda_{BC} = 1$, which allows the calculation of Eq. 10. The fraction of total drug amount in the body distributed to plasma water, *etc.*, during the β-phase can be obtained if V_C is replaced by $(Vd)_\beta$.

Table VI—Biopharmaceutical Data Obtained following an Oral Dose of Pentobarbital (100 mg in Tablet) to Humans

Subject	Availabilities, %	k_{abs}, hr^{-1}	Lag Time, hr
H.K.	95.9	4.32	0.64
		(12.01)[a]	(0.07)
N.K.	101.9	—[b]	—
L.L.	74.0	—	—
M.E.	88.7	2.72	0.56
		(0.78)	(0.04)
G.P.	93.5	5.71	0.74
		(8.36)	(0.32)
K.K.	94.0	1.82	0.64
		(0.50)	(0.04)
U.H.	107.5	0.79	0.61
		(0.08)	(0.04)
Average	93.6	3.07	0.64
SD of averages	10.6	1.96	0.07
Coefficient of variation, %	11	64	11

[a] The standard deviations of the parameter (estimated by the BMDX85 program) are shown in parentheses beneath the values of the parameters. [b] Not evaluated.

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