International Journal of Pharmaceutics, 26 (1985) 157–164
Elsevier

IJP 00880

The absorption kinetics of barbiturates in rabbits

Nobuyoshi Kaneniwa, Mitsuru Hiura and Tomoo Funaki

School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142 (Japan)

(Received March 28th, 1984)
(Modified version received April 24th, 1985)
(Accepted May 17th, 1985)

Key words: barbiturates—absorption rate constant—partition coefficient—bioavailability—C_{max}—T_{max}

Summary

The absorption properties of six barbiturates (hexobarbital, pentobarbital, cyclobarbital, amobarbital, allobarbital and barbital) in intact rabbits were studied by means of pharmacokinetic analysis. The absorption rate constant (k_a) was calculated by the Pidgeon and Pitlick method, which does not use data points prior to the maximum plasma concentration (C_{max}) and therefore is not influenced by errors in the data before the peak concentration. A good correlation was obtained between k_a and partition coefficient, suggesting that the absorption properties of barbiturates in intact rabbits are influenced by the lipid solubility of the drugs. Relationships between k_a, elimination rate constant (k_{el}), C_{max}, time of maximum plasma concentration (T_{max}), and bioavailability (F) were also studied; F and k_{el} might be determinant factors for C_{max} and T_{max}, respectively. The highly lipid-soluble barbiturates are rapidly absorbed from the gastrointestinal tract but are also subject to a first-pass effect, and therefore the extent of absorption decreases with increasing lipid solubility.

Introduction

The disposition of drugs is predominantly influenced by the physicochemical properties of the drugs. It is convenient to clarify the relationship between physicochemical properties and drug disposition by using barbiturates as model drugs, because many barbiturate derivatives have been synthesized. Lin et al. (1973)

Correspondence: N. Kaneniwa, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo 142, Japan.

reported a good correlation between the elimination rate constant and partition coefficient for eight barbiturates. The barbiturates used by Lin et al. are mostly eliminated via metabolic pathways, except for barbital. We (Kaneniwa et al., 1979a) reported good correlations between the rate constant of in vitro metabolism and the partition coefficient, and also between the elimination rate constant and the partition coefficient.

Kakemi et al. studied the in situ absorption properties of sixteen barbiturates in rats and reported that the gastric absorption rate constant was influenced by the pH of the drug solution and was correlated to the partition coefficient (1967a), but the intestinal absorption properties could not be explained only by the pH–partition hypothesis (1967b). However, the absorption properties of barbiturates in an intact animal (in vivo) have not been studied up to the present.

The aim of the present study was to investigate the in vivo absorption kinetics of barbiturates, and to clarify the relationship between the in vivo absorption rate constant and the partition coefficient. The relationship between the absorption rate constant and bioavailability was also studied.

Materials and Methods

Materials

Six barbiturates (hexobarbital, pentobarbital, cyclobarbital, amobarbital, allobarbital and barbital) were of JP IX grade and were used without further purification. All other reagents were commercial products of special grade.

Analytical method

The concentrations of barbiturates in the plasma were determined by gas chromatography with a hydrogen flame ionization detector, as described in a previous report (Kaneniwa et al., 1979a).

Determination of partition coefficient

Phosphate buffer (1/15 M, pH 7.4) and chloroform were used as the aqueous phase and organic phase, respectively. The apparent partition coefficients were determined and corrected for the partition coefficient of non-ionic molecules as described in a previous report (Kaneniwa et al., 1979a).

Animal experiment

Groups of three male albino rabbits weighing 2.5–3.0 kg were fasted for 24 h before the experiment with water ad libitum. In the case of barbital, food was given at 12 h after drug administration because the blood sampling period extended over 30 h. In the cases of other barbiturates, no food was given throughout the experiment. For administration, each barbiturate (dose of 20 or 40 mg/kg) was dissolved in normal saline by adding equimolar NaOH shortly before each experiment. Plasma samples were collected from the congested aural vein by using a heparin-treated syringe at predetermined intervals.

Intervals of two weeks were allowed between successive experiments in each animal in order to eliminate completely the influence of the previous dose. Enzyme

induction by barbiturates was considered to be negligible under this dosage schedule, because the pharmacokinetic parameters of barbiturates were little changed by repeated administration (Hiura et al., 1984b).

As it was shown in the previous report (Hiura et al., 1984b) that the dispositions of barbiturates are linear processes, in the present study the plasma concentrations following oral administration (dose of 20 and 40 mg/kg) were normalized for unit dose, and the two dosage groups were combined into one group.

Data analysis

As the dispositions of barbiturates could be described by a one-compartment model in rabbits (Kaneniwa et al., 1979a), the absorption rate constant was calculated by the Pidgeon and Pitlick method (Pidgeon and Pitlick, 1977; Pidgeon and Pitlick, 1980) as follows:

$$k_a = \frac{C_{max}}{\int_{T_{max}}^{\infty} C\,dt - C_{max}/k_{el}} \tag{1}$$

where k_a is the absorption rate constant, C_{max} is the maximum plasma concentration, $\int_{T_{max}}^{\infty} C\,dt$ is the area under the plasma concentration–time curve from the time of maximum plasma concentration (T_{max}) to infinity (∞), and k_{el} is the elimination rate constant. The value of elimination rate constant was obtained by i.v. administration in the same rabbit. The time of maximum concentration was calculated from Eqn. 2:

$$T_{max \cdot est} = \ln(k_a/k_{el})/(k_a - k_{el}) \tag{2}$$

where $T_{max \cdot est}$ is the time of maximum plasma concentration estimated with k_a obtained from Eqn. 1. The relative error in T_{max} can be calculated as follows:

$$\text{Relative error} = T_{max \cdot est}/T_{max \cdot obs} \tag{3}$$

where $T_{max \cdot obs}$ is the observed T_{max}. The absorption rate constant obtained by Eqn. 1 was multiplied by the relative error, and then corrected for the error of determination of T_{max}. The corrected $T_{max \cdot est}$ was again calculated from Eqn. 2 using the corrected k_a. Maximum plasma concentration was calculated from Eqn. 4:

$$C_{max} = (F \cdot D/V_d)e^{-k_{el} \cdot T_{max\ est}} \tag{4}$$

where F is the bioavailability, D is the dose, and V_d is the distribution volume. Distribution volume was obtained by i.v. administration in the same rabbit. Bioavailability was calculated from Eqn. 5:

$$F = AUC_{p.o.}/AUC_{i.v.} \tag{5}$$

where $AUC_{p.o.}$ and $AUC_{i.v.}$ are the total areas under the plasma concentration–time curves after oral and intravenous administrations, respectively, in which AUC was calculated by the trapezoidal rule for major area and C_L/k_{el} for asymptotic part (C_L = last measurable plasma concentration). Calculated plasma concentrations of barbiturates following oral administration were generated at time t from Eqn. 6:

$$C_{calc} = (k_a \cdot F \cdot D/V_d(k_a - k_{el})) \cdot (e^{-k_{el} \cdot t} - e^{-k_a \cdot t}) \quad (6)$$

where C_{calc} is the calculated plasma concentration. In this equation, the values of V_d and k_{el} were also obtained by i.v. administration in the same rabbit as described above. The overall correlation (r^2) for the fits was calculated from Eqn. 7:

$$r^2 = \left(\Sigma(\overline{obs} - obs_i)^2 - \Sigma(calc_i - obs_i)^2\right)/\Sigma(\overline{obs} - obs_i)^2 \quad (7)$$

where $\overline{obs}$ is the mean of observed plasma concentrations, obs_i is the i^{th} point of observed plasma concentrations, and $calc_i$ is the i^{th} point of plasma concentration calculated from Eqn. 5.

Results and Discussion

The characteristics of barbiturates tested in the present study are outlined in Table 1. Although the numerical values of partition coefficient are different in each examined system, the relative values seem to correlate well with each other. Hexo-

TABLE 1
COMMON NAME, CHEMICAL CONSTITUTION AND SOME PHYSICAL CONSTANTS OF THE BARBITURATES TESTED

No.	Common name	Substituents	Partition coefficient				Antilog R_m [e]
			P [a]	P [b]	P [c]	P [d]	
1	Hexobarbital	1-methyl 5-methyl-cyclohexenyl				154.65	
2	Pentobarbital	5-ethyl-(1-methyl)butyl	89.1	0.927	106.00	39.77	4.88
3	Cyclobarbital	5-ethyl-cyclohexenyl	15.9	0.297	4.14	9.22	1.87
4	Amobarbital	5-ethyl-(3-methyl)butyl	89.1	0.944	113.00	43.28	4.63
5	Allobarbital	5-allyl-allyl	11.2	0.109	16.80	2.91	0.63
6	Barbital	5-ethyl-ethyl	4.47	0.035	3.82	0.79	0.18

[a] Between octanol and water. The figures are the antilogarithms of the reported values (Hansch and Anderson, 1967).
[b] Between tetrachloromethane and a pH 1.1 buffer solution (Kakemi et al., 1967).
[c] Between isoamyl acetate and a pH 1.1 buffer solution (Kakemi et al., 1967).
[d] Between chloroform and a pH 7.4 buffer solution, and corrected for the partition coefficient of non-ionic molecules (Kaneniwa et al., 1979a).
[e] Data are from Plá-Delfina et al. (1975).

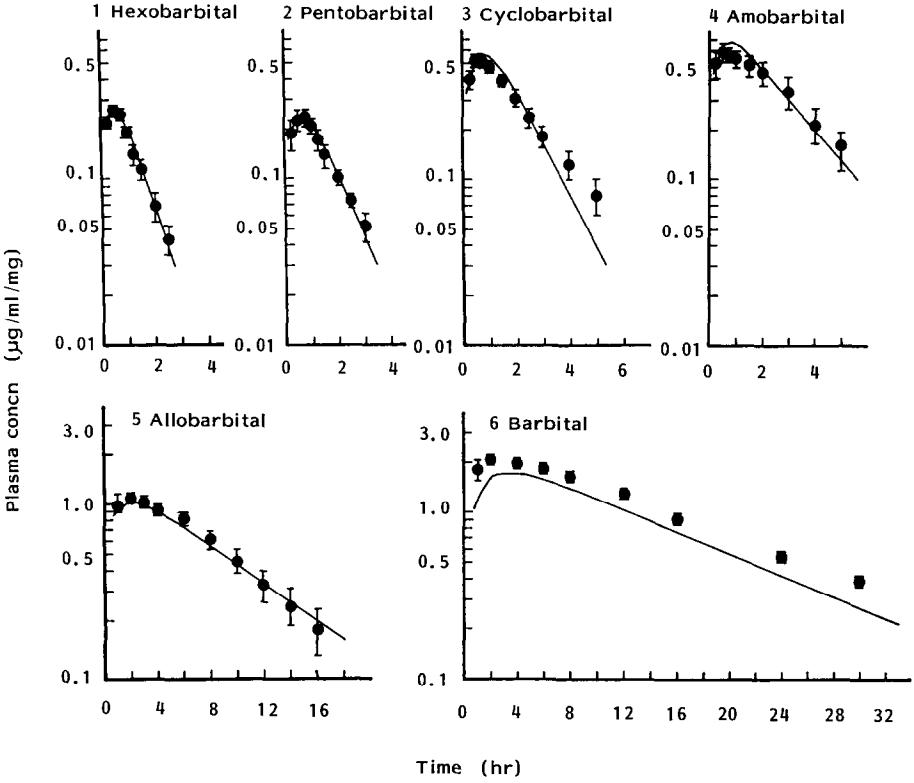

Fig. 1. Time courses of plasma concentration of six barbiturates following oral administration. The curves were calculated based on Eqn. 6. Each point is the mean ± S.E. The numbers of rabbits are shown in Table 2.

barbital, a 1-substituted barbital, was included in the present study to give a reasonably wide lipid solubility range.

Plasma concentration–time course plots following the oral administration of the six barbiturates to rabbits are shown in Fig. 1 and the pharmacokinetic parameters are shown in Table 2. As can be seen in Fig. 1, the calculated values were in good agreement with the observed values. However, when the absorption rate constants were obtained by the Wagner-Nelson method (Wagner and Nelson, 1963) or by non-linear least-squares regression analysis (Yamaoka et al., 1981), the calculated values were not in agreement with the observed values (not shown). This was due to discrepancies of k_a. The different values of k_a estimated by these methods in the present study can be attributed to the fact that there were few sample points in the absorption phase. Both the Wagner-Nelson method and non-linear least-sqaures regression analysis require large numbers of sample points in the absorption phase to permit accurate estimation of k_a. On the other hand, the Pidgeon and Pitlick method (Pidgeon and Pitlick, 1977; Pidgeon and Pitlick, 1980) does not use data points prior to C_{max} and, therefore, is not influenced by errors in the data before the

TABLE 2
PHARMACOKINETIC PARAMETERS OF BARBITURATES IN RABBITS

No.	Barbiturate	n [a]	k_a (min^{-1})	k_{el} (min^{-1})	C_{max} ($\mu g/ml/mg$)	T_{max} (min)	V_d (ml/kg)	F	r^2
1	Hexobarbital	5	0.0388 (0.0040) [b]	0.0262 (0.0023)	0.261 (0.014)	32.3 (2.9)	568 (41)	0.338 (0.029)	0.972 (0.007)
2	Pentobarbital	4	0.0406 (0.0107)	0.0164 (0.0011)	0.244 (0.035)	40.3 (5.0)	837 (62)	0.386 (0.029)	0.901 (0.039)
3	Cyclobarbital	6	0.0291 (0.0039)	0.0152 (0.0012)	0.584 (0.039)	49.0 (4.3)	529 (10)	0.633 (0.025)	0.854 (0.037)
4	Amobarbital	4	0.0420 (0.0073)	0.0087 (0.0012)	0.685 (0.089)	50.1 (5.8)	701 (18)	0.730 (0.054)	0.706 (0.099)
5	Allobarbital	4	0.0210 (0.0046)	0.0023 (0.0003)	1.068 (0.078)	133.3 (27.6)	570 (33)	0.816 (0.045)	0.917 (0.056)
6	Barbital	3	0.0151 (0.0043)	0.0013 (0.0001)	1.763 (0.208)	196.4 (37.2)	466 (38)	1.042 (0.059)	0.675 (0.125)

[a] n is the number of rabbits used.
[b] Values in parentheses represent S.E.

Fig. 2.

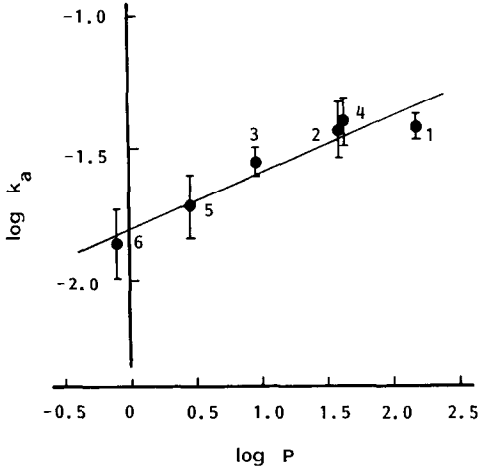

Fig. 3.

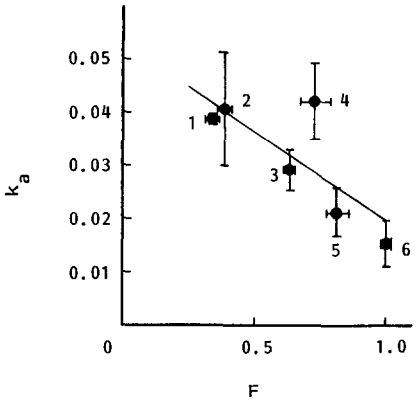

Fig. 2. Relation between the absorption rate constant and partition coefficient: 1, hexobarbital; 2, pentobarbital; 3, cyclobarbital; 4, amobarbital; 5, allobarbital; 6, barbital. Each point is the mean ± S.E. The numbers of rabbits are shown in Table 2.

Fig. 3. Relation between the absorption rate constant and bioavailability: 1, hexobarbital; 2, pentobarbital; 3, cyclobarbital; 4, amobarbital; 5, allobarbital; 6, barbital. Each point is the mean ± S.E. The numbers of rabbits are shown in Table 2.

peak concentration. As shown in Table 2, the k_{el} corresponded quite well to the previously reported values (Kaneniwa et al., 1979a). In the case of barbital, the terminal log linear portion of the time course data following intravenous administration was used for the calculation of k_{el}, because the clearance of barbital was significantly increased after food had been given (Kaneniwa et al., 1979b). On the other hand, in the previous report, all data points were used for the calculation of k_{el}, and therefore the k_{el} value obtained in the present study was about 2-fold greater than the previously reported value. Time courses of plasma concentration which showed more than one peak were omitted from the calculation of k_a. The numbers of rabbits used for each calculation are cited in Table 2.

We (Kaneniwa et al., 1979a) previously reported good correlations between the elimination rate constant and partition coefficient. The absorption rate constant (k_a) decreased with decreasing k_{el} (Table 2), and therefore it appears that k_a of barbiturates in intact rabbits is influenced by the lipid solubility. Fig. 2 shows the logarithmic relationship between k_a and partition coefficient; a good correlation ($r = 0.958$, $P < 0.01$)) was obtained. It is clear from Fig. 2 that the highly lipid-soluble barbiturates are rapidly absorbed from gastrointestinal tract. The absorption rate constant in Eqn. 1 represents an apparent k_a when incomplete absorption of barbiturates occurs. In the present study, we have assumed complete absorption of all barbiturates based on the following facts: (1) the extremely lipid-soluble barbiturates, thiopental (Goodman and Gilman, 1975) and hexobarbital (Hiura et al., 1984a), may be completely absorbed from the gastrointestinal tract; and (2) the bioavailability of the least lipid-soluble barbiturate, barbital, is 1.0.

In spite of the large k_a values of highly lipid-soluble barbiturates, C_{max} values increased with increasing F values. As the V_d values are similar to each other, F might be a determinant factor for C_{max} of barbiturates. On the other hand, T_{max} increased with decreasing k_{el} or k_a. As the decline of k_{el} values was larger than that of k_a values, k_{el} might be a determinant factor for T_{max} of barbiturates.

Fig. 3 shows the relationship between k_a and F; again, a reasonably good correlation ($r = 0.799$, statistically insignificant) was obtained. In contrast to Fig. 2, Fig. 3 indicates that the highly lipid-soluble barbiturates are subject to a marked first-pass effect, so that although k_a increases, the extent of absorption decreases with increasing partition coefficient. Consequently, it is clear that the lipid solubility affects not only the elimination properties but also the absorption properties of drugs.

References

Goodman, L.S. and Gilman, A., The Pharmacological Basic of Therapeutics, Macmillan Press, New York, 1975, p. 112.

Hansch, C. and Anderson, S.M., The structure–activity relationship in barbiturates and its similarity to that of other narcotics. J. Med. Chem., 10 (1967) 745–753.

Hiura, M., Kawashima, H. and Kaneniwa, N., Hepatic first-pass metabolism of hexobarbital in rabbits and dogs. Int. J. Pharm., 18 (1984a) 185–193.

Hiura, M., Nakagawa, S., Kawashima, H. and Kaneniwa, N., Effect of lipid solubility on hepatic first-pass metabolism of barbiturates in rabbits. Int. J. Pharm., 20 (1984b) 73–85.

Kakemi, K., Arita, T., Hori, R. and Konishi, R., Absorption and excretion of drugs. XXX. Absorption of barbituric acid derivatives from rat stomach. Chem. Pharm. Bull., 15 (1967a) 1534–1539.

Kakemi, K., Arita, T., Hori, R. and Konishi, R., Absorption and excretion of drugs. XXXII. Absorption of barbituric acid derivatives from rat small intestine. Chem. Pharm. Bull., 15 (1967b) 1883–1887.

Kaneniwa, N., Hiura, M. and Nakagawa, S., Effect of lipid solubility and dose on the elimination of barbiturates in rabbits. Chem. Pharm. Bull., 27 (1979a) 1501–1509.

Kaneniwa, N., Hiura, M. and Funaki, T., Effect of fasting on the elimination of barbital and phenobarbital in rabbits. Chem. Pharm. Bull., 27 (1979b) 2157–2162.

Lin, Y.J., Awazu, S., Hanano, M. and Nogami, H., Pharmacokinetic aspects of elimination from plasma and distribution to brain and liver of barbiturates in rats. Chem. Pharm. Bull., 21 (1973) 2749–2756.

Pidgeon, C. and Pitlick, W.H., Unique approach for calculation of absorption rate constant. Res. Comm. Chem. Pathol. Pharmacol., 18 (1977) 467–475.

Pidgeon, C. and Pitlick, W.H., Unique approach for calculation of first-order absorption rate constants from blood or urine data. J. Pharmacokin. Biopharm., 8 (1980) 203–214.

Plá-Delfina, J.M., Moreno, J., Durán, J. and del Pozo, A., Calculation of the gastric absorption rate constants of 5-substituted barbiturates through the R_m values or substituent R_m constants in reversed-phase partition chromatography. J. Pharmacokin. Biopharm., 3 (1975) 115–141.

Wagner, J.G. and Nelson, E., Per cent absorbed time plots derived from blood level and/or urinary excretion data. J. Pharm. Sci., 52 (1963) 610–611.

Yamaoka, K., Tanigawara, Y., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (multi) for microcomputer, J. Pharmacobio.-Dyn., 4 (1981) 879–885.