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Effect of Lipid Solubility and Dose on the Elimination of Barbiturates in Rabbits[1]

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The elimination of seven barbiturates from plasma was studied in rabbits after intravenous administration at a dose of 20—80 mg/kg. The elimination rate constant, elimination half-life, and apparent volume of distribution of barbiturates did not depend on the dose. The area under the plasma concentration-time curve (AUC) of each barbiturate increased in proportion to the dose. Therefore, the distribution and elimination of barbiturates were considered to follow linear kinetics in rabbits. The elimination rate constant of barbiturates at a given dose was linearly related to the lipid solubility (measured as the partition coefficient between chloroform and pH 7.4 phosphate buffer).

To investigate the effect of lipid solubility on the metabolism of barbiturates, the *in vitro* rate of metabolism in rabbit liver microsomes was determined. Only barbital (having low lipid solubility) was hardly metabolized during incubation for 60 min.

A linear relationship was obtained for six barbiturates (not barbital) in a logarithmic plot of the *in vitro* metabolic rate constant *vs.* the partition coefficient. Furthermore, the *in vivo* elimination rate constant of the six barbiturates showed a good correlation with the *in vitro* metabolic rate constant in a logarithmic plot ($r=0.9670$).

These results indicate that barbital was mainly eliminated by renal excretion, while other barbiturates were mainly eliminated metabolically in the liver, depending on their lipid solubilities.

Keywords——barbiturate; elimination kinetics; dose-dependence; lipid solubility; barbiturate-metabolizing enzyme activity; elimination half-life; distribution volume; bioavailability

A drug injected or absorbed from the administration site into the blood stream will undergo simultaneous distribution and elimination. Renal excretion of highly lipid-soluble drugs is lower than that of poorly lipid-soluble drugs because increased lipid solubility facilitates reabsorption across the wall of the renal tubule, which behaves like a lipoid barrier. Therefore, the metabolic conversion of lipid-soluble drugs into more polar and relatively water-soluble derivatives is necessary if they are to be excreted readily from the kidneys.

The most important site of drug metabolism is the liver, and many of the drug-metabolizing enzymes are present in the microsomal fraction of the liver. It has also been considered that only highly lipid-soluble drugs can reach these enzymes, which are surrounded by a lipoid membrane.[3]

1) Presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977.
2) Location: *Hatanodai 1-5-8, Shinagawa-ku, Tokyo, 142, Japan.*
3) L.E. Gaudette and B.B. Brodie, *Biochem. Pharmacol.*, **2**, 89 (1959).

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Lin *et al.*[4] reported that the elimination rate constant of barbiturates in rats is significantly related to their lipid solubility. In a pharmacokinetic study of pentobarbital using normal and hepatectomized rats, the volume of distribution and elimination rate constant were found to be significantly reduced in the hepatectomized rats.[5]

Thus, it seems clear that the elimination of barbiturates involves hepatic metabolism rather than renal excretion. However, the relationship between the elimination rate constant or the elimination half-life and the *in vitro* rate constant of metabolism of barbiturates cannot be evaluated directly because the *in vitro* test conditions for metabolism of these drugs in liver were not the same in individual reports.

If drugs show capacity-limited distribution and elimination, the kinetics of disposition of these drugs in the body may be nonlinear, depending on the dose and route of administration. However, the effect of dose on the disposition of barbiturates in the body has been little studied.

The present experiments were undertaken to clarify the effect of dose on the elimination of barbiturates given intravenously to rabbits, and the relationship between the elimination rate constant and the *in vitro* rate of metabolism in rabbit liver microsomes.

Experimental

Apparent Partition Coefficient——Barbiturates were dissolved at a concentration of 100 μg/ml in $CHCl_3$ previously saturated with a buffer solution. Five ml of the $CHCl_3$ solution was added to an equal volume of 1/15 M phosphate buffer solution (pH 7.4), and equilibrated at 37° by occasional shaking for 96 hr. The concentrations of barbiturate in both phases were determined by spectrophotometry. The apparent partition coefficient of barbiturate was estimated as the ratio of drug concentration in the organic phase to that in the aqueous phase.

Drug Administration and Sampling——Adult male albino rabbits weighing 2.5—3.0 kg were used, and body weight was held constant by controlling the amount of food throughout the experimental period. The same three rabbits were used repeatedly at intervals of 2 weeks for different doses of a drug. After being fasted for 24 hr with water *ad libitum*, the rabbits were injected with 20—80 mg/kg of drug as a solution into the right aural vein. Each free barbiturate (500 mg) was dissolved in 10 ml H_2O in the form of sodium salt by adding equimolar NaOH shortly before the experiment started. Blood was withdrawn at selected intervals from the congested left aural vein, and the plasma was obtained by centrifugation at 3000 rpm for 10 min.

Assay of Barbiturate in Plasma and Urine——Each plasma or appropriately diluted urine sample (1 ml) was placed in a 15 ml glass-stoppered tube. One ml of 0.25 N HCl and 5 ml of ether containing 2 μg/ml of internal standard were added to this tube, and the mixture was shaken for 15 min. The mixture was then centrifuged at 3000 rpm for 5 min, and 4 ml of the organic phase was separated and evaporated to dryness in a water bath at 50°. The residue was dissolved in 0.2 ml of ether and a 2 μl aliquot was injected into a Simadzu GC-4CMPF gas chromatograph equipped with a hydrogen flame ionization detector. The glass

Table I. Column Conditions and Internal Standards for Measurement of Various Barbiturates

Barbiturate	Temperature (°C)		Flow rate (ml/min)			Internal standard
	Injector and detector	Column	N_2	H_2	Air	
Barbital	270	230	40	40	600	Amobarbital
Phenobarbital	270	255	40	40	700	Hexobarbital
Allobarbital	270	240	30	50	700	Hexobarbital
Amobarbital	270	250	35	50	600	Hexobarbital
Cyclobarbital	270	258	40	40	600	Hexobarbital
Pentobarbital	270	250	40	50	700	Hexobarbital
Hexobarbital	270	258	40	40	600	Cyclobarbital

4) Y.J. Lin, S. Awazu, M. Hanano, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **21**, 2749 (1973).
5) F.W. Ossenberg, M. Peignoux, D. Bourdiau, and J.P. Benhamou, *J. Pharmacol. Exp. Ther.*, **194**, 111 (1975).

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column (2 m × 5 mm (outer diam.), 3 mm (inner diam.)) was packed with 3% OV-17 on Chromosorb GHP (AW-DMCS), 100—120 mesh (Nippon Chromato Works, Ltd., Tokyo).

The column conditions and internal standards for the measurement of barbiturates are summarized in Table I. The calibration curve for each barbiturate was obtained by plotting the concentration of the drug against the peak height ratio with respect to the internal standard.

Determination of *in Vitro* Rate of Metabolism——Three male albino rabbits weighing 2.5—3.0 kg were sacrificed to obtain liver tissue. Rabbits were killed by injection of air into the aural vein. The livers were removed rapidly and homogenized with 4 volumes of 1.15% KCl—0.01 M phosphate buffer solution (pH 7.4) in a glass homogenizer. The homogenate was centrifuged at 10000 ***g*** for 20 min in a refrigerated centrifuge and the supernatant was used as the microsomal fraction.

The incubation mixture (5 ml) consisted of 3 ml of microsomal fraction, 0.1 ml of (NADP) (0.4 μmol), 0.1 ml of glucose-6-phosphate (20 μmol), 0.1 ml of magnesium chloride (37.5 μmol), 0.1 ml of nicotinamide (75 μmol), 2.3 ml of 0.2 M phosphate buffer (pH 7.4), and 0.2 ml of various substrates (4 μmol). The mixture was incubated with shaking at 37° in an atomosphere of air. One-half ml of this mixture was pippeted out at 15, 30, and 45 min after the start of incubation, and the amount of unmetabolized barbiturate was determined by the method of Brodie and Axelrod,[6] with a slight modification.

To avoid individual differences of microsomal enzyme activities among rabbits, a pooled microsomal fraction was used for determination of the *in vitro* metabolic rate for all barbiturates.

Results and Discussion

Partition Coefficient of Nonionic Molecules

Table II presents the pK_a values and partition coefficients of barbiturates used in this experiment. The pK_a values are cited from the literature.[7] The apparent partition coefficient (K_{app}) was expressed as the ratio of drug concentration in the organic phase to that in the aqueous phase at the partition equilibrium.

Since nonionic drug molecules pass preferentially through the lipoidal barrier in biological systems, the partition coefficients of nonionic molecules rather than the apparent partition coefficients may be more suitable for determining the relationship between lipid solubility and the disposition of the drug in the body.

When a weakly acidic drug is dissolved in a solution, the ratio of nonionic moleculess is given by the Henderson–Hasselbalch equation.

$$X_{wf}/X_{wi} = 10^{pK_a - pH} = F \qquad \text{Eq. (1)}$$

where X_{wf} and X_{wi} are the amounts of nonionic and ionic molecules, respectively. At the partition equilibrium, the amounts of a drug in the organic phase (X_{of}) and aqueous phase (X_w) can be calculated from Eq. (2) and Eq. (3).

$$X_w = X_{wf} + X_{wi} \qquad \text{Eq. (2)}$$

$$X_{of} = A_o - X_w \qquad \text{Eq. (3)}$$

where A_0 is the initial amount of the drug dissolved in the organic phase. By substituting Eq. (1) into Eq. (2), the following equation is obtained.

$$X_{wf} = X_w \cdot F/(F+1) \qquad \text{Eq. (4)}$$

If the total amount of the drug in the aqueous phase, the pK_a value of the drug, and the pH of the aqueous phase are known, the partition coefficients of nonionic molecules (K_p) can be calculated from Eq. (5).

$$K_p = (A_o - X_w)/X_{wf} = (A_o - X_w) \cdot (F+1)/X_w \cdot F \qquad \text{Eq. (5)}$$

These calculations are based on the assumption that only nonionic molecules are distributed in the organic phase and that the molecules exist in monomeric form in both phases. As regards the effect of concentration on the apparent partition coefficient of barbiturates, Kakemi *et al.*[8] reported that no concentration dependence was observed over

6) B.B. Brodie and J. Axelrod, *J. Pharmacol. Exp. Ther.*, **99**, 171 (1950).
7) K. Kakemi, T. Arita, R. Hori, and R. Konishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1534 (1967).
8) K. Kakemi, T. Arita, R. Hori, and R. Konishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1705 (1967).

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an initial concentration range of 50 to 500 μg/ml with chloroform, and that barbiturates existed as monomeric molecules in both phases. Therefore, the assumptions made above seem reasonable.

Values calculated according to Eq. (5) are listed in Table II. These calculated partition coefficients (K_p) of nonionic molecules were larger than the apparent partition coefficients (K_{app}).

TABLE II. pK_a and Partition Coefficients (K_{app}, and K_p) of Barbiturates

Barbiturate	pK_a	Partition coefficient	
		K_{app}	K_p[a]
Barbital	7.91	0.59	0.79
Allobarbital	7.79	2.04	2.91
Phenobarbital	7.41	2.16	4.26
Cyclobarbital	7.50	5.03	9.22
Pentobarbital	8.11	33.03	39.77
Amobarbital	7.94	33.24	43.28
Hexobarbital	8.34	138.06	154.65

a) Calculated from Eq. (5).
Each value of K_{app} and K_p represents the mean of three experiments.

Effect of Lipid Solubility on the *in Vitro* Rate of Metabolism in Rabbit Liver Microsomes

The elimination half-lives of pentobarbital and hexobarbital vary among animal species according to their drug-metabolizing enzyme activities in liver microsomes.[9] Gaudette and Brodie[3] have demonstrated that lipid solubility was the rate-limiting factor in the dealkylation of N-alkylamines by the microsomal enzymes in rabbit liver homogenate.

In order to investigate the effect of lipid solubility on the metabolism of barbiturates, the *in vitro* rate of metabolism in rabbit liver microsomes was determined. Barbital, having a low lipid solubility, was hardly metabolized during incubation for 60 min. For the other barbiturates tested, however, the amount of substrate in the *in vitro* incubation mixture decreased linearly during the first 45 min. The *in vitro* metabolic rate constant was calculated as nmoles of the substrate lost per g wet weight of liver per min, and these calculated values are listed in Table III.

TABLE III. *In Vitro* Metabolic Rate Constants of Barbiturates in Rabbit Liver Microsomes

Barbiturate	*In vitro* metabolic rate constant (nmol/min/g wet wt. liver)
Barbital	0
Phenobarbital	2.56±0.17
Allobarbital	8.95±0.55
Cyclobarbital	23.38±1.55
Amobarbital	35.01±2.98
Pentobarbital	56.02±0.67
Hexobarbital	94.54±4.38

The *in vitro* metabolic rate constant of barbiturates increased with increase in lipid solubility. As shown in Fig. 1, a linear relationship (r=0.9006) was obtained for these

9) L.C. Mark, *Clin. Pharmacol. Ther.*, 4, 504 (1963); H. Kitagawa, T. Kamataki, and S. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **16**, 2320 (1968).

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barbiturates, excluding barbital, in a logarithmic plot of the *in vitro* metabolic rate constant *vs.* the partition coefficient (K_p).

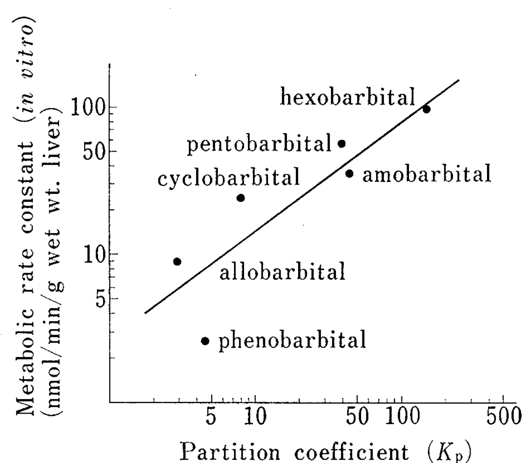

Fig. 1. Relationship between the Partition Coefficient (K_p) and *in Vitro* Metabolic Rate Constant of Barbiturates in Rabbit Liver Microsomes

Effect of Dose on the Elimination of Barbiturates

The decline of plasma concentration of seven barbiturates was determined after a single intravenous injection of 20 to 80 mg/kg in rabbits. A semilogarithmic plot of the plasma concentration *vs.* time, after injection of 20 mg/kg, is shown in Fig. 2. The decline of barbiturates (except for barbital) was linear in the plasma up to 12 hr after injection. The plasma data for these barbiturates were analyzed using a one-compartment pharmacokinetic model. However, barbital showed a biexponential decline in the plasma up to 12 hr after injection. Thus, the pharmacokinetic parameters for barbital were calculated using both a one-compartment model based on the plasma data in the linear segment and a two-compartment model with elimination occurring from the central compertment. However, the elimination rate constant and the apparent volume of distribution in the one-compartment model were nearly equal to the elimination rate constant and the total volume of the two compartments in the two-compartment model.

Therefore, the values calculated with the one-compartment model were employed as the pharmacokinetic parameters of barbital. These parameters of barbiturates at 20—80 mg/kg doses are summarized in Table IV.

The decline curves of plasma concentration of barbital and phenobarbital showed a discernible shoulder at 12 hr after injection. To determine whether feeding affected the elimination of barbiturates, the following experiments were carried out. Three rabbits were

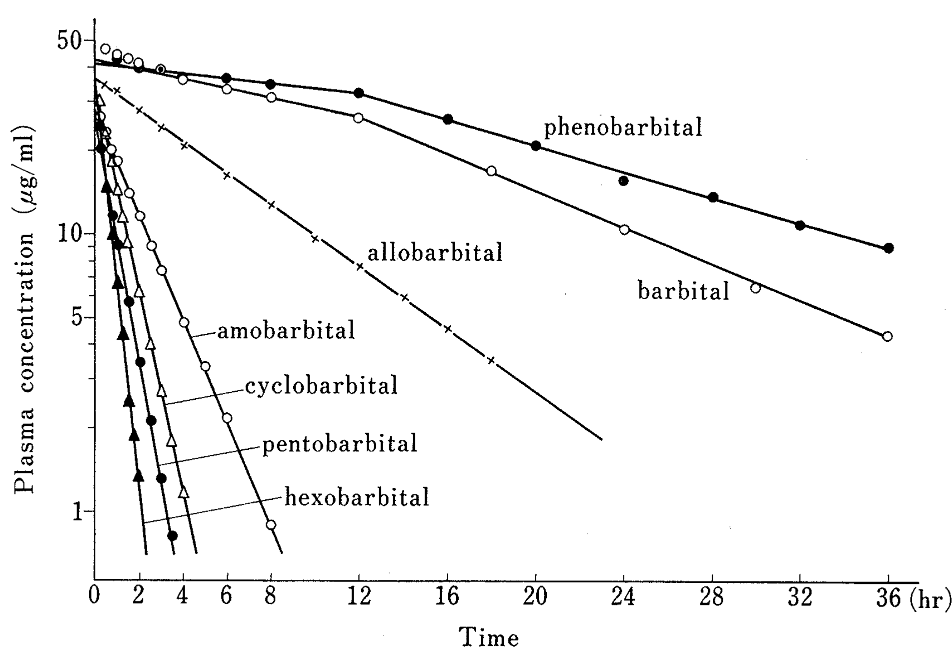

Fig. 2. Time Course of Plasma Concentrations of Barbiturates in Rabbits after Intravenous Administration (20 mg/kg)

Each plot represents the mean of three rabbits.

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TABLE IV. Elimination Rate Constant (K_{el}), Elimination Half-life ($T_{1/2}$), Apparent Volume of Distribution (V_d), and Area under the Plasma Concentration-Time Curves (AUC) for Barbiturates in Rabbits after Various Doses

Barbiturate	Dose (mg/kg)	K_{el} (hr^{-1})	$T_{1/2}$(hr)	V_d (ml)	AUC($\mu g \cdot ml^{-1} \cdot hr$)
Barbital	20	0.0422(0.0040)	16.71(1.62)	1323 (64)	765.9(32.3)
	40	0.0338(0.0031)	20.92(1.98)	1537 (98)	1508.5(20.5)
	80	0.0317(0.0043)	22.83(3.58)	1410 (88)	2983.2(21.8)
Phenobarbital	20	0.0261(0.0078)	27.37(5.99)	1392 (91)	1014.6(67.3)
	40	0.0277(0.0031)	28.58(1.19)	1310 (93)	2181.9(23.7)
	60	0.0264(0.0042)	30.25(3.52)	1355 (75)	3090.5(98.3)
Allobarbital	20	0.1371(0.0240)	5.36(0.89)	1593 (17)	283.4(41.5)
	30	0.1299(0.0215)	5.63(0.91)	1843 (32)	393.4(56.5)
	40	0.1191(0.0141)	5.97(0.64)	1598 (59)	562.2(73.0)
Amobarbital	20	0.4760(0.0904)	1.59(0.35)	1969 (20)	66.1(13.7)
	30	0.4755(0.0813)	1.62(0.30)	2050 (30)	95.8(20.1)
	40	0.4500(0.0982)	1.69(0.35)	2191 (52)	126.4(22.3)
Cyclobarbital	20	0.8681(0.0809)	0.82(0.08)	1484 (70)	41.4 (4.9)
	30	0.8603(0.0731)	0.81(0.07)	1505 (65)	64.5 (8.3)
	40	0.8585(0.0910)	0.83(0.09)	1443 (79)	92.0(13.5)
Pentobarbital	20	0.9827(0.0593)	0.71(0.05)	2222(204)	25.0 (1.1)
	30	0.9768(0.0579)	0.72(0.05)	2334(153)	36.1 (0.9)
	40	0.9776(0.0583)	0.72(0.05)	2338(167)	48.3 (1.3)
Hexobarbital	20	1.6693(0.1179)	0.42(0.03)	1752(182)	22.1 (1.1)
	30	1.4384(0.1148)	0.49(0.04)	1602(181)	35.4 (2.3)
	40	1.3164(0.0909)	0.53(0.04)	1683(196)	51.5 (2.9)

Figures in parentheses give the standard error of mean.

given food 12 hr after injection of 80 mg/kg of barbital or 20 mg/kg of phenobarbital. Two weeks later, the same three rabbits were not given food until 60 hr after injection of the drug.

As shown in Fig. 3, the rate of plasma concentration decay did not change during 60 hr in the fasted condition. In the partly fasted condition, the rate of plasma concentration decay before feeding was nearly equal to that in the fasted condition, while the slope of the

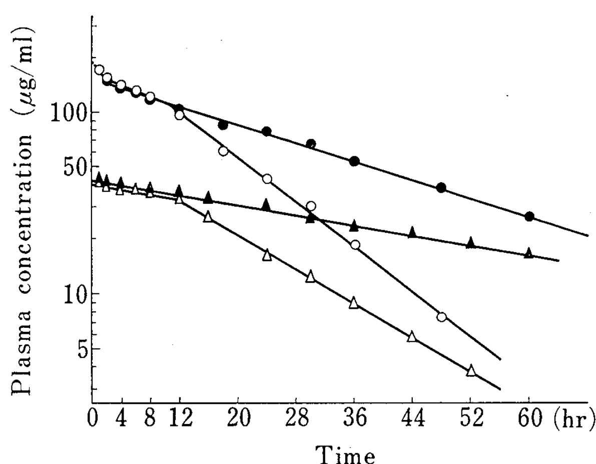

Fig. 3. Time Course of Plasma Concentrations of Barbital (○) and Phenobarbital (△) after Intravenous Administration of 80 mg/kg of Barbital or 20 mg/kg of Phenobarbital in Fasted and partly Fasted Rabbits

●, ▲: plasma concentration in the fasted condition.
○, △: plasma concentration with administration of food 12 hr after injection of the drug.
Each plot represents the mean three rabbits.

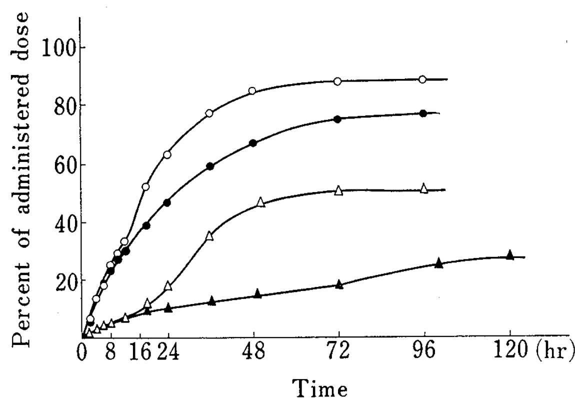

Fig. 4. Cumulative Urinary Excretion of Unmetabolized Barbital (○) and Phenobarbital (△) after Intravenous Administration of 80 mg/kg of Barbital or 20 mg/kg of Phenobarbital in Fasted and partly Fasted Rabbits

●, ▲: cumulative urinary excretion in the fasted condition.
○, △: cumulative urinary excretion with administration of food 12 hr after injection of the drug.
Each plot represents the mean of three rabbits.

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decline curve increased immediately after feeding. This result suggests an increase in the elimination of barbital and phenobarbital after feeding. Since the elimination of other barbiturates was faster than that of barbital or phenobarbital, food was not given throughout the experiment. The elimination rate constants and elimination half-lives of barbital and phenobarbital listed in Table IV show values calculated from the plasma data before administration of food for comparison with the values in the fasted condition.

The elimination rate constant and elimination half-life for each barbiturate did not alter appreciably with change in the dose. The apparent volume of distribution increased slightly with increase in lipid solubility, but did not depend on the dose. On the other hand, the area under the plasma concentration-time curve from zero to infinity (AUC) of each barbiturate was proportional to the dose. From these results, it can be considered that the distribution and elimination of barbiturates follow linear kinetics in rabbits.

Urinary Excretion of Barbiturates

Barbiturates other than barbital and phenobarbital are mostly excreted in the urine in the metabolized form. However, as shown in Fig. 4, the cumulative urinary excretions under fasted and partly fasted conditions, until no further unmetabolized drug could be detected in the urine (96 hr), were about 78 and 90% for barbital and 30 and 47% for phenobarbital, respectively. The urinary excretion rate constants were calculated by the sigma-minus method, and are listed in Table V. The difference in elimination rate constant and excretion rate constant corresponds to the metabolic rate constant (K_m), because the overall barbiturate elimination from the systemic circulation is the sum of hepatic metabolism and renal excretion.

TABLE V. Elimination Rate Constant (K_{el}), Excretion Rate Constant (K_e), and Metabolic Rate Constant (K_m) of Barbital and Phenobarbital in Rabbbits under Fasted and partly Fasted Conditions

	Phenobarbital			Barbital		
	Fasted	Partly fasted		Fasted	Partly fasted	
		Before	After[a]		Before	After[a]
K_{el} (hr^{-1})	0.0243	0.0261	0.0537	0.0354	0.0422	0.0623
K_e (hr^{-1})	0.0032	0.0058	0.0324	0.0257	0.0354	0.0526
K_m (hr^{-1})	0.0211	0.0203	0.0213	0.0097	0.0068	0.0097

a) Before and after administration of food.
Each value represents the mean of three rabbits.

Barbital shows a very low metabolic rate constant compared to the excretion rate constant in all feeding conditions, so that the elimination mainly depends on renal excretion rather than on hepatic metabolism. On the other hand, since the metabolic rate constant of phenobarbital is a considerable fraction of the elimination rate constant, especially in the fasted condition, the metabolic process in liver plays an important part in the overall elimination processes in this case.

The metabolic rate constants of barbital and phenobarbital were approximately constant regardless of feeding conditions, but the urinary excretion rate constants of both barbiturates were markedly lower during fasting than after feeding. Therefore, it should be considered that starvation tends to decrease the renal excretion of barbital and phenobarbital, though the mechanism is not clear.

Relationship between *in Vivo* Elimination Rate Constant and *in Vitro* Metabolic Rate Constant

The *in vivo* elimination rate constant of barbiturates at a given dose increased with increase in lipid solubility, and the elimination half-life showed an inverse relation to the lipid solubility, as listed in Tables II and IV. Lin *et al.*[4] reported that the intrinsic elimi-

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nation rate constant of barbiturates from the central compartment calculated by a two-compartment analysis of plasma data was significantly related to the lipid solubility. However, as shown in Table V, the elimination of barbital and phenobarbital depends not only on hepatic metabolism but also on renal excretion. Therefore, it is questionable that the *in vivo* elimination rate constants of barbital and phenobarbital adhered to the regression line between the logarithm of the elimination rate constant and the logarithm of the partition coefficient established for the other barbiturates, which are considered to involve mainly the metabolic rate constant, as reported by Lin *et al.*[4] Therefore, in correlating the lipid solubility with the rate of hepatic metabolism, the *in vivo* metabolic rate constant (K_m) should be used instead of the *in vivo* elimination rate constant (K_{el}) for barbital and phenobarbital. Thus, the *in vivo* metabolic rate constants for barbital and phenobarbital was plotted to obtain the relationship between the logarithm of the *in vivo* elimination rate constant and the logarithm of the lipid solubility (Fig. 5); there is an approximately linear relationship (r=0.8605).

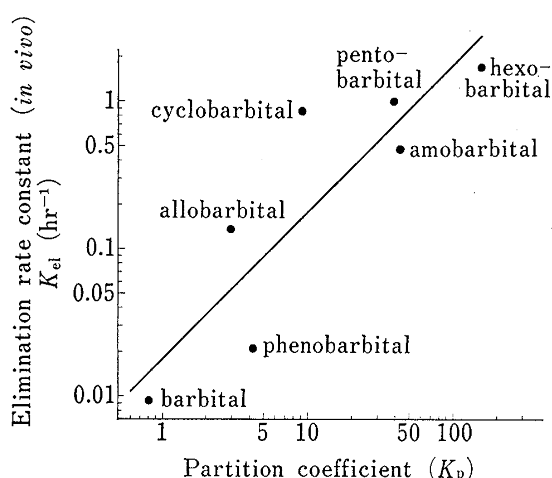

Fig. 5. Relationship between the Partition Coefficient (K_p) and *in Vivo* Elimination Rate Constant (K_{el}) of Barbiturates

In the case of barbital and phenobarbital, the *in vivo* metabolic rate constant (K_m) is plotted instead of the *in vivo* elimination rate constant (K_{el}).

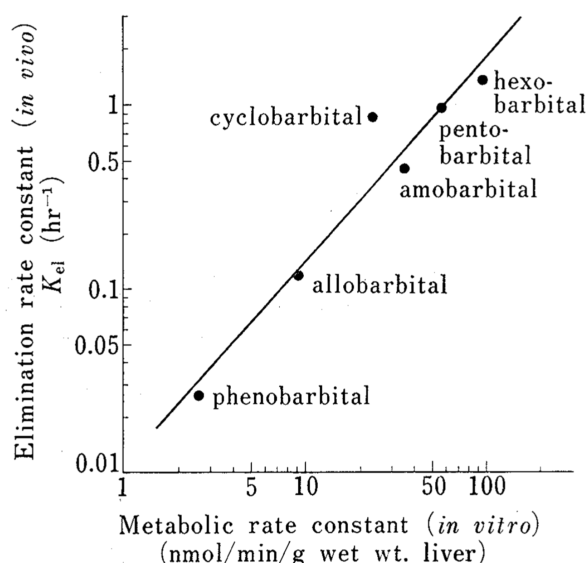

Fig. 6. Relationship between the *in Vivo* Elimination Rate Constant (K_{el}) and *in Vitro* Metabolic Rate Constant of Barbiturates in Rabbit Liver Microsomes

In the case of phenobarbital, the *in vivo* metabolic rate constant (K_m) is plotted instead of the *in vivo* elimination rate constant.

The *in vitro* metabolic rate constant increased with increase in lipid solubility as shown in Fig. 1. As might be expected, a logarithmic plot of the *in vivo* elimination rate constant *vs.* the *in vitro* metabolic rate constant showed a good linear relationship (r=0.9670) (Fig. 6); the points for barbital and phenobarbital are naturally the values of the *in vivo* metabolic rate constants.

The results presented in this study indicate that highly lipid-soluble barbiturates are mainly eliminated by hepatic metabolism, which is rate-limited by the lipid solubility. Since a poorly lipid-soluble barbiturate cannot easily reach the enzymes by passing through the lipoid membrane, the fraction of hepatic metabolism may decrease and that of renal excretion may increase with decrease in lipid solubility. The highly lipid-soluble barbiturates were hardly excreted in the urine in unmetabolized form in rabbits. Therefore, barbiturate filtering through the glomeruli must be passively reabsorbed from the tubular urine into the emergent renal vein. The highly lipid-soluble barbiturates (hexobarbital, pentobarbital,

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amobarbital, cyclobarbital, and allobarbital) were essentially metabolized and eliminated only by the liver due to complete reabsorption of the drugs in the renal tubules. However, poorly lipid-soluble barbiturates (phenobarbital and barbital), which were not reabsorbed from renal tubules, were excreted in the urine. Among barbiturates belonging to the poorly lipid-soluble class, barbital (the least lipid-soluble drug) was hardly metabolized and was mainly excreted in the urine, whereas the more lipid-soluble phenobarbital was significantly metabolized as well as excreted in the urine.

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