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Effect of lipid solubility on hepatic first-pass metabolism of barbiturates in rabbits

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Summary

The disposition of 7 barbiturates (hexobarbital, pentobarbital, cyclobarbital, amobarbital, allobarbital, phenobarbital and barbital) followed first-order kinetics after intravenous or oral administration to rabbits. The area under the plasma concentration–time curves increased in proportion to the dose after the administration of 20–80 mg/kg of barbiturates by either route. In spite of the complete absorption of barbiturates from the gastrointestinal tract as unchanged drug, the systemic availability values after oral administration were lower than unity and decreased in proportion to the *in vitro* rates of metabolism of the drugs by rabbit liver microsomes. Therefore, the reduction of systemic availability of these barbiturates is considered to be a result of first-pass metabolism through the liver before reaching the systemic circulation.

The hepatic intrinsic clearances of unbound drug for these barbiturates estimated from a simple perfusion model based on the clearance concept varied widely in the range of 0.18–132.94 ml/min per kg of body weight and increased with increase in the lipid solubilities. The rates of metabolism of barbiturates by microsomal enzymes have been reported to depend on the lipid solubility of the drugs. As might be expected from these relations, a good linear relationship was found between the *in vivo* hepatic intrinsic clearance of unbound drug and the *in vitro* rate of metabolism

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by rabbit liver microsomes. Therefore, the increased hepatic first-pass metabolism and the diminished systemic availability of orally administered barbiturates are due to the increased hepatic intrinsic clearance, which may be related to the lipid solubility, of the drugs.

Introduction

Theoretical approaches to the quantitative analysis of the hepatic first-pass effect indicate that there are two independent biological determinants of this effect, i.e. hepatic blood flow rate and intrinsic hepatic drug-metabolizing activity (Rowland, 1972; Wilkinson and Shand, 1975; Awazu et al., 1977). Since hepatic blood flow rate *in vivo* must remain within certain physiological limits, the degree of hepatic first-pass effect of a drug should depend mainly on the intrinsic ability of the liver to remove the drug metabolically. The relative rates of oxidative metabolism of various drugs have been suggested to be related to the lipophilic character of the drugs (Gaudette and Brodie, 1959; Martin and Hansch, 1971; Tong and Lien, 1976). In previous studies on the disposition of barbiturates in rabbits, highly lipid-soluble drugs were found to be mainly eliminated by hepatic metabolism with no renal excretion (Kaneniwa et al., 1979), and the highly lipid-soluble drug, hexobarbital, was shown to be subject to hepatic first-pass metabolism after oral administration (Hiura et al., 1983). The present study was therefore undertaken to clarify the influence of lipid solubility on the systemic availability and/or the hepatic first-pass metabolism of seven barbiturates (hexobarbital, pentobarbital, cyclobarbital, amobarbital, allobarbital, phenobarbital, and barbital) after oral administration.

Materials and Methods

Drug administration and sampling

Adult male albino rabbits weighing 2.5–3.0 kg were used and their body weights were held constant by controlling the amount of food throughout the experimental period. Twenty-one rabbits were divided into 7 groups of 3 animals per group, and each group was used to test one barbiturate. The 3 rabbits in each group received the same drug at 3 different doses via the intravenous and oral routes at intervals of two weeks. The rabbits were fasted for 24 h, with water *ad libitum*, then the drug was injected into the aural vein or administered orally at a dose of 20–80 mg/kg as a solution. The drug solution was prepared at concentrations of 50 mg/ml for intravenous and 10 mg/ml for oral administration by adding equimolar NaOH shortly before each experiment. In the case of barbital and phenobarbital, food was given at 12 h after administration of the drug, because the blood sampling period extended over 36 h. However, since the elimination of other barbiturates was faster than that of barbital and phenobarbital, food was not given throughout the experiment in these cases. Blood samples were collected from the congested aural

vein by using a heparin-treated syringe at predetermined intervals, and the plasma was obtained by centrifugation. Total urine collection was carried out for 96 h after administration of the drug, and fractions representing output from 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, 36–48, 48–72, and 72–96 h were obtained. Plasma and urine samples were kept frozen until analyzed. 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.

Assay of barbiturates in the plasma and urine

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

Protein binding

The binding of barbiturates to rabbit plasma proteins was determined in undiluted plasma by an ultrafiltration technique. Seven ml of plasma containing known concentrations (10 and 60 $\mu\text{g}/\text{ml}$) of drug was equilibrated for 2 h at 37°C. A 0.5 ml aliquot was removed for analysis of total drug, and the remaining plasma was introduced into a Centriflo membrane cone (Type CF50A, Amicon, Tokyo, Japan). Centrifugation for 10 min at 2000 rpm yielded 0.5–0.6 ml of plasma water (less than 10% of the total plasma volume). A 0.5 ml aliquot of plasma water was analyzed to determine the free-drug concentration. The adsorption of drug on the membrane was negligible in every case. The unbound fraction of each barbiturate is shown in Table 1. The unbound fraction of drug in the pooled plasma was similar at both concentrations tested (10 and 60 $\mu\text{g}/\text{ml}$) for each barbiturate.

Model analysis of hepatic first-pass metabolism of drugs

A simple type of perfusion model is shown in Fig. 1. It is assumed that the drug is delivered by blood flow from the blood pool to the liver, kidneys and other organs and tissues, and that the concentration of drug in emergent blood is in equilibrium

TABLE 1
UNBOUND FRACTION OF BARBITURATES IN UNDILUTED RABBIT PLASMA

Barbiturate	Plasma concentration	
	10 $\mu\text{g}/\text{ml}$	60 $\mu\text{g}/\text{ml}$
Hexobarbital	0.248 \pm 0.010	0.248 \pm 0.005
Pentobarbital	0.326 \pm 0.007	0.315 \pm 0.017
Cyclobarbital	0.343 \pm 0.008	0.340 \pm 0.003
Amobarbital	0.337 \pm 0.005	0.330 \pm 0.004
Allobarbital	0.581 \pm 0.017	0.582 \pm 0.005
Phenobarbital	0.482 \pm 0.010	0.468 \pm 0.016
Barbital	0.672 \pm 0.012	0.669 \pm 0.023

Binding activities were measured by the ultrafiltration technique. Each value represents the mean \pm S.E. of results in 3 experiments.

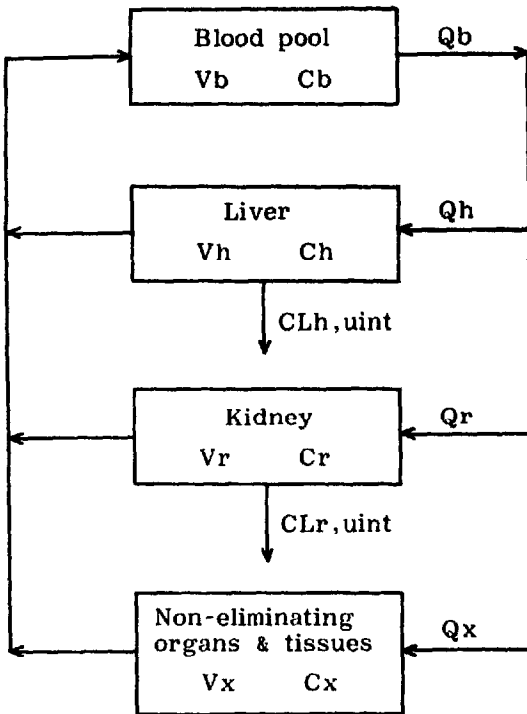


Fig. 1. Diagrammatic representation of a perfusion model containing a blood pool, eliminating organs (liver and kidney), and non-eliminating organs and tissues. The constants are described in the text.

with the organs and tissues. It is also assumed that the disposition of drug in the eliminating organs follows linear kinetics. In this model, C is the concentration of drug, V is the volume of blood pool, organs, and tissues, Q is the blood flow rate, Cl_{uint} is the intrinsic clearance of unbound drug, and the subscripts b , h , r and x denote blood, liver, kidney and non-eliminating organs and tissues, respectively.

Based on the clearance concept analysis reported by Rowland (1972), Wilkinson and Shand (1975) and Awazu et al. (1977), when the administered drug is absorbed completely and the drug is solely eliminated by hepatic metabolism, with no renal excretion ($Cl_{r, \text{uint}} = 0$), the areas under the plasma concentration-time curve after intravenous (AUC_{iv}) and after oral (AUC_{po}) administration are as follows:

$$AUC_{\text{iv}} = \frac{\text{Dose}}{\frac{Q_h \cdot Cl_{h, \text{uint}} \cdot f_p}{Q_h + Cl_{h, \text{uint}} \cdot f_p}} \quad (1)$$

$$AUC_{\text{po}} = \frac{\text{Dose}}{Cl_{h, \text{uint}} \cdot f_p} \quad (2)$$

where f_p is the fraction of unbound drug in the plasma. In this case, the hepatic intrinsic clearance of total drug ($Cl_{h, \text{uint}} \cdot f_p$), which reflects the inherent maximum drug removal ability, is equal to $\text{Dose}/AUC_{\text{po}}$. Furthermore, organ clearance is

equal to the product of the blood flow rate and the extraction ratio (E) or (1 - F). Then the hepatic clearance (Cl_h) can be defined as in Eqn. 3.

$$Cl_h = \frac{\text{Dose}}{AUC_{iv}} = \frac{Q_h \cdot Cl_{h, \text{uint}} \cdot f_p}{Q_h + Cl_{h, \text{uint}} \cdot f_p} = Q_h \cdot E = Q_h \cdot (1 - F) \quad (3)$$

On the other hand, the total body clearance (Cl) of a drug which is simultaneously subject to hepatic metabolism and renal excretion is equal to the sum of the hepatic and the renal clearance and is given by Eqn. 4.

$$Cl = \frac{\text{Dose}}{AUC_{iv}} = \frac{Q_h \cdot Cl_{h, \text{uint}} \cdot f_p}{Q_h + Cl_{h, \text{uint}} \cdot f_p} + \frac{Q_r \cdot Cl_{r, \text{uint}} \cdot f_p}{Q_r + Cl_{r, \text{uint}} \cdot f_p} \quad (4)$$

The systemic availability (F) of orally administered drug is defined by Eqn. 5.

$$F = \frac{AUC_{po}}{AUC_{iv}} = \frac{Q_h}{Q_h + Cl_{h, \text{uint}} \cdot f_p} \quad (5)$$

The mean hepatic blood flow rate (Q_h) can be estimated according to Eqn. 6 from Eqn. 3.

$$Q_h = \frac{Cl_h}{1 - F} = \frac{\text{Dose}}{AUC_{iv} - AUC_{po}} \quad (6)$$

Results and Discussion

Systemic availability of barbiturates after oral administration

The plasma concentrations of the 7 barbiturates were determined after a single intravenous or oral administration of a 20–80 mg/kg dose in rabbits. The plasma concentration–time curves after the administration of 20 mg/kg of barbiturates by both routes are shown in Fig. 2. The pharmacokinetic parameters of barbiturates after intravenous administration have been given in a previous report (Kaneniwa et al., 1979). The apparent volume of distribution and the elimination rate constant of each barbiturate were approximately constant and not dependent on the dose given to rabbits. The AUC_{iv} and AUC_{po} were calculated by means of the trapezoidal rule for the major areas and as C/K_{el} for asymptotic regions (C, last measurable plasma concentration; K_{el} , elimination rate constant of the final slope). The values of AUC_{iv} and AUC_{po} of each barbiturate increased linearly with increase in dose, as shown in Fig. 3. Therefore, it can be concluded that the dispositions of these barbiturates follow linear kinetics, at least within the range of dose levels given to rabbits in this study.

When a linear relationship exists between AUC and dose, the systemic availa-

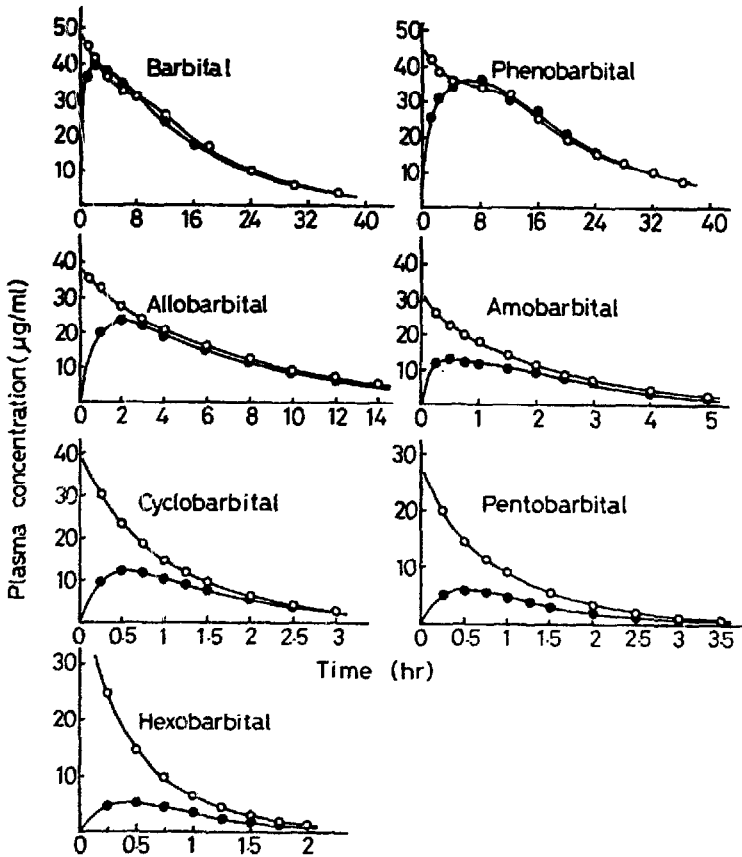


Fig. 2. Time course of plasma concentration of barbiturates after intravenous (O) or oral (●) administration at 20 mg/kg to rabbits. Each plot is the mean of results in 3 rabbits.

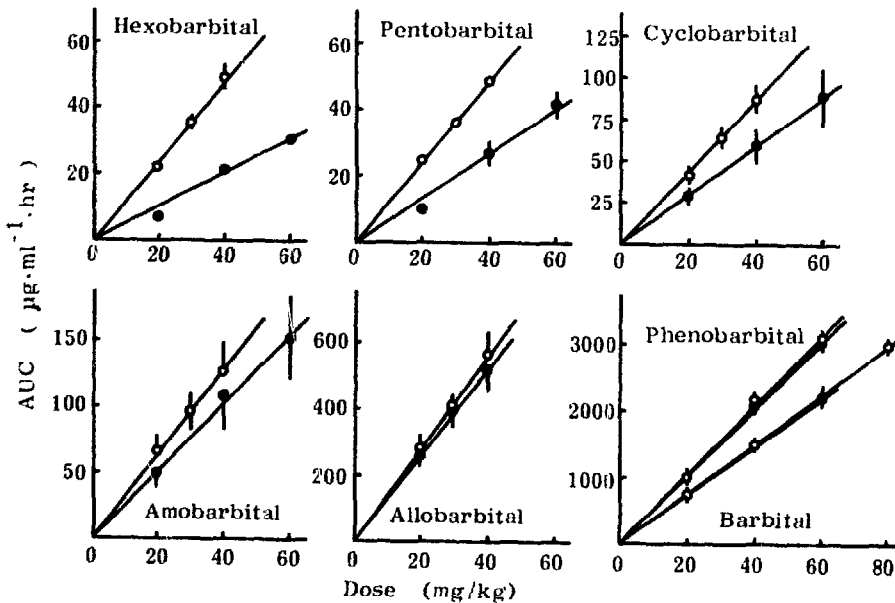


Fig. 3. Relationship between dose and the area under plasma concentration-time curve of barbiturates after intravenous (AUC_{iv} ; O) or oral (AUC_{po} ; ●) administration to rabbits. Each plot represents the mean \pm S.E. of results in 3 rabbits.

bility of orally administered drug is usually estimated as the relation of AUC_{po} to AUC_{iv} after the administration of equivalent doses by both routes. As is clear from Fig. 3, the systemic availabilities of barbital and phenobarbital were close to unity (about 0.99) at 20–80 mg/kg. Furthermore, as listed in Table 2, barbital and phenobarbital were partly excreted in the urine as the unchanged drug. The fraction of the dose excreted as the unchanged drug after oral administration was nearly equal to that after intravenous administration, and it was about 80% for barbital and about 52% for phenobarbital at every dose. It can be considered, therefore, that barbital and phenobarbital after oral administration are completely absorbed from the gastrointestinal tract as unchanged drug.

On the other hand, the systemic availability of barbiturates other than barbital and phenobarbital was lower than unity (Fig. 3), and only small amounts of these barbiturates were excreted in the urine as unchanged drug. Sjogren et al. (1965) reported that barbiturates are negligibly metabolized and degraded in the gastrointestinal tract. In a previous study, when hexobarbital, which showed the lowest systemic availability among the barbiturates tested, was directly infused into the hepato-portal vein in rabbits, the mean areas under the plasma concentration–time curves (AUC_{hp}) were directly proportional to the infused dose, and nearly equal to the mean values of AUC_{po} at corresponding doses. It was concluded that orally administered hexobarbital was completely absorbed from the gastrointestinal tract as the unchanged drug. The other barbiturates with lower systemic availability than unity should also be absorbed completely from the gastrointestinal tract, because their lipid solubilities (the rate-limiting factor for gastrointestinal absorption) are intermediate between that of hexobarbital and that of barbital or phenobarbital (Kakemi et al., 1967). Therefore, it can be concluded that the reduction of systemic availability of these barbiturates after oral administration is due to the first-pass metabolism through the liver.

Effect of lipid solubility on hepatic first-pass metabolism of barbiturates

The above discussion clearly indicates that barbiturates are completely absorbed from the gastrointestinal tract, and are subject to hepatic first-pass metabolism, and

TABLE 2
FRACTION (%) OF UNCHANGED BARBITAL AND PHENOBARBITAL EXCRETED IN THE URINE AFTER INTRAVENOUS (iv) OR ORAL (po) ADMINISTRATION AT VARIOUS DOSES TO RABBITS

Drug	Route	Dose (mg/kg)			
		20	40	60	80
Barbital	iv	82.0 ± 0.4	80.9 ± 3.8	–	80.4 ± 1.8
	po	77.6 ± 5.2	81.6 ± 6.0	81.7 ± 2.6	–
Phenobarbital	iv	51.5 ± 6.9	51.2 ± 4.3	51.6 ± 3.2	–
	po	50.3 ± 2.8	54.9 ± 2.3	52.0 ± 3.7	–

Each value represents the mean ± S.E. of results in 3 rabbits.

that their dispositions follow linear kinetics in rabbits. As the indicator of drug concentration, plasma concentration was determined in this study. Therefore, the term Q in all equations is defined as plasma flow rate. Since barbiturates other than barbital and phenobarbital are mainly eliminated by hepatic metabolism, with no renal excretion, the hepatic clearance (Cl_h), the hepatic intrinsic clearance of total drug ($Cl_{h, \text{uint}} \cdot f_p$), and the mean hepatic plasma flow rate (Q_h) can be calculated by means of Eqns. 1, 2 and 6, respectively. The hepatic clearance ($\text{Dose}/\text{AUC}_{iv}$) and the hepatic intrinsic clearance of total drug ($\text{Dose}/\text{AUC}_{po}$) were calculated from the slope of the relation between dose and AUC after intravenous and oral administration, respectively (Fig. 3). The hepatic intrinsic clearance of unbound drug ($Cl_{h, \text{uint}}$) was calculated by dividing the value of the intrinsic clearance of total drug ($Cl_{h, \text{uint}} \cdot f_p$) by the fraction of unbound drug in the plasma (f_p). In this calculation, the values of fraction of unbound drug in the plasma were those determined at the concentration of 10 $\mu\text{g}/\text{ml}$, as listed in Table 1. The calculated parameters for barbiturates are summarized in Table 3.

There is limited information about hepatic blood flow rate in rabbits. Neutze et al. (1968) reported that the flow rate was 55 ml/min per kg of body weight. A smaller value, 26 ml/min per kg of body weight, has been estimated by Dabson and Jones (1952). The estimated hepatic plasma flow rates were 19.4–28.6 ml/min per kg of body weight (Table 3). The calculated hepatic blood flow rate based on the plasma flow rate and the hematocrit¹ was about 34–50 ml/min per kg of body weight, approximately equal to the value reported by Neutze et al. (1968). Since barbiturates have a CNS depressant action, the hepatic blood flow rate immediately after the administration of barbiturates may be lower than the flow rate under normal conditions. However, the hepatic blood flow rate approaches the normal flow rate as the plasma concentration of drugs decreases. Therefore, it can be considered that the estimated flow rates in this study do not reflect the actual flow rate in the physiological state, but may be apparent mean values.

Barbital and phenobarbital were eliminated not only by hepatic metabolism but also by renal excretion. As can be seen from Eqn. 5, the systemic availability is not related to the renal clearance term (Cl_r), so that the hepatic intrinsic clearance of total drug for barbital and phenobarbital can be calculated from their systemic availability and the mean hepatic plasma flow rate. In this calculation, the hepatic plasma flow rate used was the mean value (24.3 ml/min/kg), which was estimated from the results for other barbiturates. Furthermore, putting this estimated hepatic intrinsic clearance of total drug ($Cl_{h, \text{uint}} \cdot f_p$) and other known parameters into Eqn. 4 yields the hepatic clearance (Cl_h) and the renal clearance (Cl_r) of barbital and phenobarbital. These calculated parameters for barbital and phenobarbital are also listed in Table 3.

Food was given at 12 h after the administration of barbital and phenobarbital, because the eliminations of these drugs were slow and the blood sampling period extended over 36 h. As described in our previous report (K meniwa et al., 1979), the

¹ The hematocrit value determined experimentally was 0.43 ± 0.02 (mean \pm S.E. of 5 rabbits).

TABLE 3
MEAN VALUES OF SYSTEMIC AVAILABILITY (F), HEPATIC CLEARANCE (Cl_h), RENAL CLEARANCE (Cl_r), HEPATIC INTRINSIC CLEARANCE OF TOTAL DRUG ($Cl_{h, \text{int}} \cdot f_p$), HEPATIC PLASMA FLOW RATE (Q_h), AND HEPATIC INTRINSIC CLEARANCE OF UNBOUND DRUG ($Cl_{h, \text{unt}}$) IN RABBITS

Barbiturate	F	$\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$					
		Cl_h	Cl_r	$Cl_{h, \text{int}} \cdot f_p$	Q_h	$Cl_{h, \text{unt}}$	
Hexobarbital	0.43 ± 0.03	14.2 ± 0.8	-	32.9 ± 0.6	25.2 ± 2.6	132.94 ± 2.36	
Pentobarbital	0.52 ± 0.03	13.2 ± 0.4	-	25.9 ± 3.2	28.6 ± 1.4	79.40 ± 9.66	
Cyclobarbitol	0.66 ± 0.04	7.9 ± 0.9	-	12.1 ± 2.1	23.4 ± 0.9	35.41 ± 6.17	
Amobarbital	0.78 ± 0.04	5.6 ± 1.1	-	7.4 ± 1.9	24.7 ± 1.5	21.92 ± 5.54	
Allobarbital	0.93 ± 0.02	1.2 ± 0.2	-	1.3 ± 0.2	19.4 ± 5.0	2.30 ± 0.34	
Phenobarbital	0.99 ± 0.01	0.16 ± 0.08	0.24 ± 0.07	0.16 ± 0.08	-	0.34 ± 0.17	
Barbital	0.99 ± 0.01	0.12 ± 0.07	0.43 ± 0.07	0.12 ± 0.07	-	0.18 ± 0.11	

Each value represents the mean \pm S.E. of results in 3 rabbits.

urinary excretion rate of both barbiturates increased markedly after refeeding, while the metabolic rate was little affected. This increased urinary excretion rate was due to the difference of urinary pH before and after refeeding. The feeding schedule was kept the same for both intravenous and oral administration, so that the relative systemic availability may be constant. However, it can be considered that the calculated renal clearance for barbital and phenobarbital is the mean renal clearance before and after refeeding.

Renal clearance of barbital was 3–4 times its hepatic clearance, but renal clearance of phenobarbital was of the same order as its hepatic clearance. It is thus reasonable that the cumulative amount of barbital in the urine is about 80% and that of phenobarbital is about 52%. The difference between the hepatic clearance of barbital and that of phenobarbital was not large, but the renal clearance of barbital was about twice that of phenobarbital. Therefore, it can be considered that the elimination half-life of barbital is shorter than that of phenobarbital in rabbits, as reported previously (Kaneniwa et al., 1979).

As can be clearly seen from Eqn. 3, hepatic clearances of drugs are affected not only by the hepatic blood flow rate, reflecting the drug delivery rate to the liver, but also by the hepatic intrinsic clearance, corresponding to the inherent drug-metabolizing ability of the liver. When the hepatic intrinsic clearance is much lower than the hepatic blood flow rate, the systemic availability of orally administered drugs is little reduced and is approximately equal to that after intravenous administration, because the hepatic clearance of these drugs is essentially independent of the hepatic blood flow rate and approximately equal to the hepatic intrinsic clearance of total drug. On the other hand, the contribution of the hepatic blood flow rate to the systemic availability of orally administered drugs increases with increase in their hepatic clearances. However, the hepatic blood flow rate *in vivo* must remain within certain physiological limits, so that the systemic availability (F) of orally administered drugs decreases with increase in the hepatic intrinsic clearances. Therefore, the hepatic intrinsic clearances of drugs are an important predictor of the systemic availability of orally administered drugs.

Previously, as an index of the ability of the liver to metabolize barbiturates in rabbits, the *in vitro* metabolic rate constant of barbiturates was determined by using the microsomal enzymes in rabbit liver microsomes (Kaneniwa et al., 1979). In this study, an approximately linear log–log relationship was found between the *in vitro* metabolic rate constant and the lipid solubility of the barbiturates tested (measured as the partition coefficient (K_p) between chloroform and pH 7.4 phosphate buffer). Many investigators have demonstrated the importance of lipid solubility of a drug in relation to ability to act as a substrate for the hepatic microsomal drug-metabolizing enzyme system. Gaudette and Brodie (1959) suggested that the enzyme system is protected by a lipoidal barrier, through which only lipid-soluble drugs can penetrate. In a study on the localization of cytochrome p-450 within the microsomal membrane, Cooper et al. (1965) and Ernster and Orrenius (1965) reported that the hemoprotein was most probably localized deep in the membrane, protected by lipids. Martin and Hansch (1971) reported that the relative Michaelis constants of a series of 14 drugs increased with increase in lipid solubility of the drugs. Jansson et al.

(1972) demonstrated that although a certain degree of lipid solubility is required for a substrate to be able to reach cytochrome p-450, other properties may be of major importance in deciding the affinity with which it will interact with the cytochrome. Thus, the rate-limiting factor in the metabolism of drugs by the enzyme system in the endoplasmic reticulum may be either accessibility of the drugs to the enzyme through the lipoidal barrier of the endoplasmic reticulum, or the binding affinity of the drugs to the enzyme.

As listed in Table 3, the hepatic intrinsic clearances of barbiturates varied widely in the range from 0.18 to 132.94 ml/min per kg of body weight. In the case of in vivo metabolism, a drug must penetrate various lipoidal barriers in the liver tissues to reach the enzyme from the emergent venous blood, so that the lipid solubility may be a more important factor in the in vivo metabolism of drugs than in the in vitro metabolism. As shown in Fig. 4, an approximately linear relationship ($r = 0.896$) was obtained in a logarithmic plot of the hepatic intrinsic clearance of unbound drug versus the partition coefficient for the barbiturates tested. The results reported previously and those presented in this study indicate that both the in vitro and in vivo hepatic metabolism of barbiturates are related to lipid solubility. To determine whether or not other properties than lipid solubility are involved in the hepatic metabolism of barbiturates, the relationship between the in vivo hepatic intrinsic clearance of unbound drug and the in vitro metabolic rate constant was determined. As shown in Fig. 5, a good linear relationship was obtained with a correlation coefficient of $r = 0.977$. This is better than the correlation obtained between the lipid solubility of barbiturates and the in vivo hepatic intrinsic clearance or the in vitro

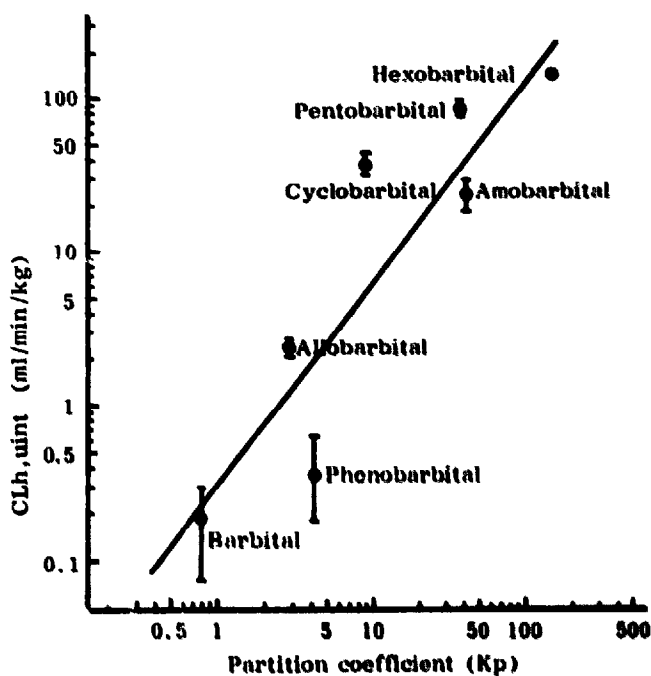


Fig. 4. Relationship between the hepatic intrinsic clearance of unbound drug ($CL_{h, \text{uint}}$) and the partition coefficient (K_p) of barbiturates.

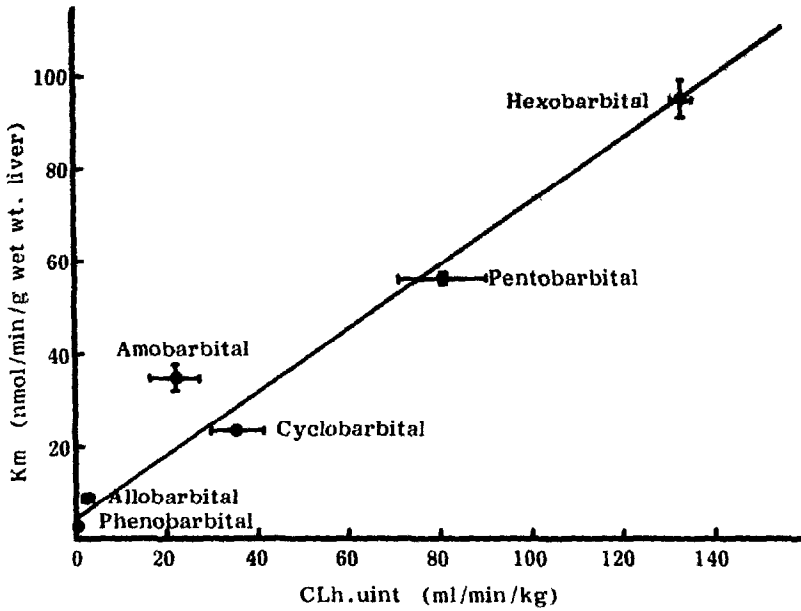


Fig. 5. Relationship between the hepatic intrinsic clearance of unbound drug ($Cl_{h,unt}$) and the in vitro metabolic rate constant (K_m) of barbiturates. Each point represents the mean \pm S.E. of results in 3 rabbits.

metabolic rate constant. Therefore, it may be concluded that although the lipid solubility is an important factor, other properties may also be significant in relation to the in vitro and in vivo metabolism of barbiturates. Although properties other than lipid solubility may act as regulating factors for the rate of metabolism of barbiturates, the drugs must first penetrate various lipid barriers prior to interaction with the enzymes in vivo. Therefore, it seems reasonable that the hepatic intrinsic clearance of barbiturates increased with increase in their lipid solubilities. Because of the low lipid solubility of barbital and phenobarbital and low partitioning to the liver tissues from emergent venous blood, large parts of these drugs pass freely through the liver without being metabolized. Thus, the poor permeability of these drugs into the liver tissues may result in an extremely reduced hepatic clearance and hepatic intrinsic clearance compared to the hepatic plasma flow rate, and thus these barbiturates are hardly subject to hepatic first-pass metabolism. On the other hand, other barbiturates may be distributed to the hepatic tissues at a concentration corresponding to the lipid solubility, so that the hepatic clearance and the hepatic intrinsic clearance increase with the lipid solubility. Therefore, the increased hepatic first-pass metabolism or the diminished systemic availability of orally administered barbiturates may be due to the increased hepatic intrinsic clearance, which may be related to the lipid solubility, though we cannot rule out a contribution by other factors.

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