[Chem. Pharm. Bull. 26(11)3463—3470(1978)]

UDC 615.453.2.011.3.014.21 : 539.215

Relationship between Partition Coefficients and Apparent Volumes of Distribution for Basic Drugs. II[1,2]

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(Received June 1, 1978)

According to the previously proposed model for drug distribution in the body, the apparent volumes of distribution (V_d') of basic drugs with high apparent partition coefficients (P') were related to the blood plasma volume, the other non-lipid space, and the lipid space. The logarithm of V_d' values for basic drugs with P' of $3.2\times10^0-6.7\times10^2$ had good correlation ($r=0.937$) with the logarithm of P' values.

The relationship between V_d' and P' was estimated in the region of both low and high P'. The comparison of the result with the observed values indicated that the proposed model was considerably satisfactory, but that there were some other factors which fluctuated the values of V_d'.

Keywords——pharmacokinetic constant; apparent volume of distribution; basic drugs; high partition coefficient; blood plasma volume; drug distribution model

In the preceding short communication,[1] it was reported that apparent volumes of distribution (V_d') for basic drugs with low apparent partition coefficients ($P'<0.16$) had an almost constant value, and that the value was about thirty times greater than plasma volume. At the same time, the proposed model for drug distribution in the body and the derived equation implied that V_d' would increase with the increment in P' of basic drugs only in the region of considerably high P'.

In the present paper, apparent and true partition coefficients of two basic compounds, 3,4-xylidine and *o*-chloroaniline, were determined, and apparent volumes of distribution of these two compounds and *p*-toluidine were estimated from respective plasma levels following intravenous administration of them to rabbits. These results together with bibliographically collected values for other five basic drugs were employed to confirm the previously expected relationship[1] between P' and V_d' in the region of high P' which ranged from 3.23 to 670. Then, these observed V_d' values for basic drugs both with low and high P' were compared with V_d' values calculated from the proposed model in the preceding paper.[1] The comparison indicated that the proposed model was considerably satisfactory, but suggested that there would be some other factors which fluctuated the values of V_d'.

The main purpose of this paper is to relate physicochemical properties of drugs with parameters in classical pharmacokinetics. The similar investigation has been done by Lin *et al.*,[4] who found a significant correlation between the elimination rate constants for seven barbiturates and their partition coefficients. These approaches may be referred to as physicochemical pharmacokinetics, and will give a useful information to drug design work in the future.

Experimental

Materials——*p*-Toluidine was purchased from Katayama Chemical Industries Co., Ltd., and recrystalized from water. 3,4-Xylidine and *o*-chloroaniline, which were purchased from Tokyo Chemical Industry Co.,

1) Part I: J. Watanabe and A. Kozaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 665 (1978). A part of this work was presented at the 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, Apr. 1977.
2) This paper constitutes Part II of the series entitled "Drug Distribution in the Body."
3) Location: *3-1, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan.*
4) Yi-Jong Lin, S. Awazu, M. Hanano, and H. Nogami, *Chem. Pharm. Bull.* (Tokyo), **21**, 2749 (1973).

Ltd., were of reagent grade and used without further purification. All other reagents were commercially available and of analytical grade.

Animals——Male albino rabbits weighing 2.7—4.9 kg were used without fasting.

Experimental Procedures——(1) Determination of Partition Coefficients of 3,4-Xylidine and *o*-Chloroaniline: For determination of apparent partition coefficient (P'), a drug solution of 73.9—6.14 mg/l was made using pH 7.4 phosphate buffer solution which was previously saturated with *n*-heptane. Ten ml of the drug solution was added to an equal volume of *n*-heptane which was also previously saturated with pH 7.4 phosphate buffer solution. After shaking for 90 min at 25° to attain the equilibrium, both the separated buffer layer and organic solvent layer were spectrophotometrically analyzed for 3,4-xylidine at 287 and 293 nm, respectively, and the separated buffer layer for *o*-chloroaniline at 290 nm. The apparent partition coefficient of 3,4-xylidine was directly estimated from both concentrations in aqueous and organic layers, and that for *o*-chloroaniline was calculated from the decrease of concentration in the buffer layer. As for the determination of true partition coefficient (P) and the number of associated molecules of 3,4-xylidine in *n*-heptane, the drug solutions in eight concentration levels were made using 0.1 N NaOH and employed as aqueous layers. The absorbance of the separated aqueous layer and organic solvent layer was determined at 289 and 295 nm, respectively, using a spectrophotometer. The other condition was exactly the same as that in the experiment for determination of the apparent partition coefficient. The true partition coefficient of *o*-chloroaniline was assumed to be equal to the apparent partition coefficient at pH 7.4, since its pK_a is 2.64.[5]

(2) Estimation of Pharmacokinetic Parameters: In order to estimate the apparent volumes of distribution and the other pharmacokinetic parameters for these basic drugs, 5 mg/ml of *p*-toluidine, 10 mg/ml of 3,4-xylidine, and 10 mg/ml of *o*-chloroaniline were dissolved in water and adjusted to be isotonic with NaCl. *p*-Toluidine, 3,4-xylidine, and *o*-chloroaniline in these solutions were administered to rabbits through ear-vein at doses of 10, 10, and 8 mg/kg, respectively. Blood samples were taken from ear-vein, and centrifuged for 15 min at 3000 rpm. Blood plasma samples obtained were analyzed for unchanged drugs. According to two-compartment open model, blood plasma levels of these three drugs were analyzed to estimate pharmacokinetic parameters by the least-squares fitting of them using a digital computer, HITAC 5020 (Hitachi, Ltd.).

Analytical Methods for *p*-Toluidine, 3,4-Xylidine, and *o*-Chloroaniline in Blood Plasma——One ml of blood plasma was added to an equal volume of isotonic phosphate buffer solution of pH 7.4, and the subsequent assay procedure was carried out according to the similar method for aniline by Brodie and Axelrod.[6] However, the final test solutions were measured spectrophotometrically at 584 nm 25 min after the color reaction for *p*-toluidine, at 588 nm 8 min after for 3,4-xylidine, and at 559 nm 1.5 min after for *o*-chloroaniline, since the rates of the color development for three drugs were not similar and the resulted colors were rather unstable after these time-points.

Results and Discussion

Partition Coefficients

Apparent partition coefficients (P') for basic compounds, 3,4-xylidine and *o*-chloroaniline, were determined, and the values are listed in Table I. These two compounds have larger apparent partition coefficients (P') at pH 7.4 than unity, *i.e.* 8.28±0.32 for 3,4-xylidine and 12.3±0.80 for *o*-chloroaniline. The true partition coefficient (P) determined at the condition where each compound exists mostly as unionized form in the aqueous layer, was almost constant when the initial concentration of each basic compound in aqueous layer was varied. Hence, there seemed to be no association of each compound at least in the organic solvent.

Blood Plasma Levels and Pharmacokinetic Parameters for *p*-Toluidine, 3,4-Xylidine, and *o*-Chloroaniline

The plasma levels of the unchanged drugs were measured after bolus intravenous administration in rabbits. These levels for *p*-toluidine, 3,4-xylidine, and *o*-chloroaniline were shown in Fig. 1, Fig. 2, and Fig. 3, respectively. Fairly good reproducibility of the plasma levels was obtained for each drug in three or four rabbits, though some fluctuation was observed in the region of low plasma levels. It was confirmed by TLC technique[7] that each plasma

5) M. Kilpatrick and C.A. Arenberg, *J. Am. Chem. Soc.*, **75**, 3812 (1953).
6) B.B. Brodie and J. Axelrod, *J. Pharmacol. Exp. Ther.*, **94**, 22 (1948).
7) TLC glass plates pre-coated with 0.25 mm of Silica Gel 60 F_{254} (Merck) were used. Solvent systems employed were methanol-benzene (1:9) and *n*-butanol-acetic acid-water (4:1:5). Compounds were detected on the plates with iodine vapour.

TABLE I. Partition Coefficients for 3,4-Xylidine and *o*-Chloroaniline in *n*-Heptane/Phosphate Buffer or *n*-Heptane/0.1 N NaOH System

Basic compound	Aqueous phase: Type	Aqueous phase: Initial concn. (mg/l)		Partition coefficient ± S.D.[a]	Number of experiments (*n*)
3,4-Xylidine	A[b]	73.9		8.28±0.32 (P')[d]	6
	B[c]	26.5		7.34±0.41 (P)[e]	4
	B	35.4		7.09±0.65 (P)	4
	B	36.0		8.80±0.20 (P)	3
	B	47.5		7.98±0.68 (P)	3
	B	48.1		8.87±0.10 (P)	4
	B	58.6		8.16±0.45 (P)	4
	B	60.0		8.66±0.05 (P)	4
	B	71.2		8.03±0.20 (P)	4
			Mean	8.06±0.72 (P)	30
o-Chloroaniline	A	6.14		11.7±0.52 ($P'=P$)	3
	A	9.21		12.3±0.89 ($P'=P$)	3
	A	12.3		13.0±0.46 ($P'=P$)	3
			Mean	12.3±0.80 ($P'=P$)	9

a) S.D.: standard deviation,
b) A: phosphate buffer of pH 7.4,
c) B: 0.1 N NaOH solution,
d) P': apparent partition coefficient,
e) P: true partition coefficient.

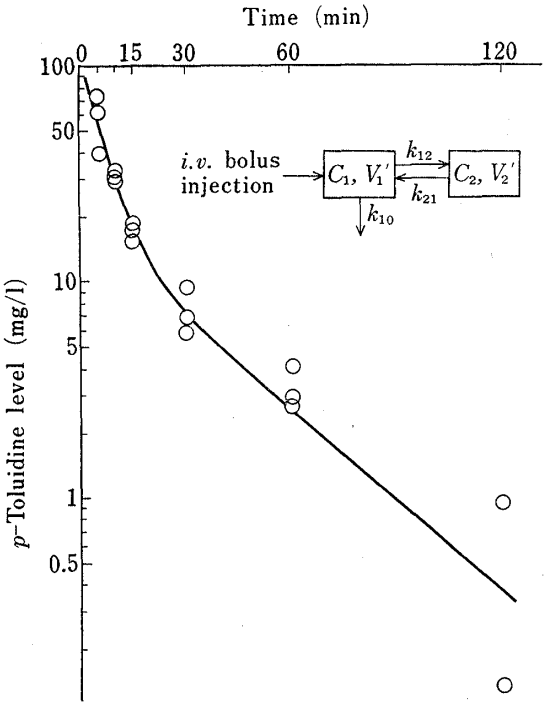

Fig. 1. Blood Plasma Concentration of *p*-Toluidine after Bolus Intravenous Administration (10 mg/kg) in Rabbits

○: observed in three rabbits. Total number of the observed points is 17. ——: calculated according to two compartment open model illustrated above. (Weight (i)=$1/C_{11}$, where C_t is the blood plasma concentration.)

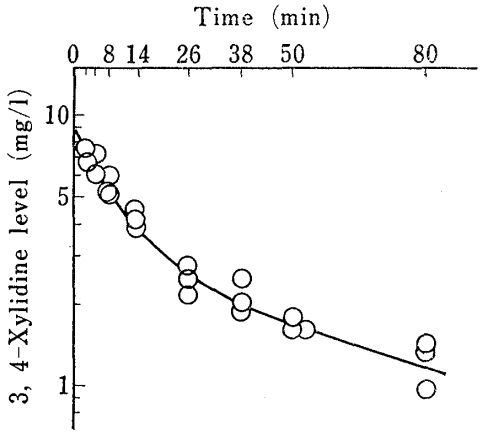

Fig. 2. Blood Plasma Concentration of 3,4-Xylidine after Bolus Intravenous Administration (10 mg/kg) in Rabbits

○: observed in three rabbits. Total number of the observed points is 22.
——: calculated according to two compartment open model illustrated in Fig. 1. (Weight (i)=$1/C_{11}^2$).

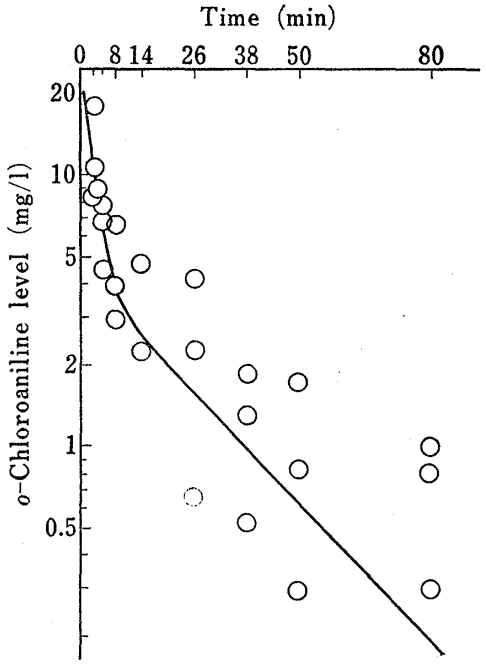

Fig. 3. Blood Plasma Concentration of *o*-Chloroaniline after Bolus Intravenous Administration (8 mg/kg) in Rabbits

○: observed in four rabbits. Total number of the observed points is 24.
——: calculated according to two compartment open model illustrated in Fig. 1. (Weight (i)= $1/C_{1i}$).

level determined did not contain any other compound such as the metabolite than the unchanged drug itself. As indicated in Fig. 1, Fig. 2, and Fig. 3, the plasma levels decreased biexponentially with time. All the observed points for each drug were analyzed according to the two-compartment open model of which scheme is shown in Fig. 1. Parameters were estimated by the least-squares fitting[8] of the blood plasma concentrations to the following equation, $C_1=A\exp(-\alpha t)+B\exp(-\beta t)$, where C_1 is plasma concentration, and A, B, α, β, are hybrid parameters. The most probable regression curves calculated are shown by solid lines in Fig. 1, Fig. 2, and Fig. 3, and the estimated parameters in Table II. Volume terms were calculated by the following equations, $(V_d')_{extrap}=\text{Dose}/B$ and $V_{d'\beta}=V_1k_{10}/\beta$.

Relationship between Partition Coefficients (P') and Apparent Volumes of Distribution ($(V_d')_{extrap}$) for Basic Drugs

The observed and bibliographically collected values of apparent partition coefficients (P') are listed in Table III. All of the P' values were determined in *n*-heptane/water (pH 7.4) system. *n*-Heptane was selected as a model solvent layer, because drugs were assumed to be less influenced by hydrogen bonding in *n*-heptane than in *n*-octanol.[9]

Table II. Pharmacokinetic Parameters for *p*-Toluidine, 3,4-Xylidine, and *o*-Chloroaniline following Bolus Intravenous Administration in Rabbits

Parameters	Drug (Dose)		
	p-Toluidine (10 mg/kg) (17)[a]	3,4-Xylidine (10 mg/kg) (22)[a]	*o*-Chloroaniline (8 mg/kg) (24)[a]
A, mg/l	93.5 ±22.2[b]	6.17 ±0.749[b]	30.5 ±25.3[b]
B, mg/l	17.5 ±10.0	2.87 ±0.615	4.33 ± 2.06
α, min^{-1}	0.172 ± 0.056	0.103 ±0.028	0.482 ± 0.270
β, min^{-1}	0.0320± 0.0107	0.0110±0.0031	0.0384± 0.0150
k_{10}, min^{-1}	0.102 ± 0.020	0.0281±0.0049	0.198 ± 0.123
k_{12}, min^{-1}	0.0483± 0.0267	0.0454±0.0129	0.229 ± 0.160
k_{21}, min^{-1}	0.0541± 0.0255	0.0401±0.0145	0.0937± 0.0426
V_1', l/kg	0.0901± 0.0212	1.11 ±0.11	0.230 ± 0.175
V_2', l/kg	0.0804± 0.0614	1.25 ±0.59	0.563 ± 0.635
[AUC], mg·min/l	1090	322	176
$V_{d'ss}$, l/kg	0.171	2.36	0.793
$V_{d'\beta}$, l/kg	0.287	2.83	1.18
$(V_d')_{extrap}$, l/kg	0.572	3.48	1.85

a) The number in parenthesis indicates the number of observed points.
b) S.E.: standard error.

8) W.E. Deming, "Statistical Adjustment of Data," John Wily and Sons, Inc., New York, 1946.
9) C. Hansch and W.J. Dunn, III, *J. Pharm. Sci.*, **61**, 1 (1972).

Table III. Apparent Partition Coefficients (P') and Apparant Volumes of Distribution [$(V_d')_{extrap}$] for Basic Drugs

Drug	Molecular weight	P'	$(V_d')_{extrap}$, l/kg	Species
p-Toluidine	107.15	3.23[a]	0.572	rabbit[b]
3,4-Xylidine	121.18	8.28[b]	3.48	rabbit[b]
o-Chloroaniline	127.57	12.3[b]	1.85	rabbit[b]
Promazine	284.41	70[c]	12.6	rat[c]
Fluphenazine	437.52	80[c]	16.8	dog[d]
Trimeprazine	298.44	310[c]	15.1	rat[c]
Chlorpromazine	318.88	370[c]	37.0	rat[e]
Triflupromazine	352.43	670[c]	27.2	rat[e]

a) From ref. 10, *b*) determined in this paper, *c*) from ref. 11, *d*) from ref. 12, *e*) from ref. 13.

The extrapolated volumes of distribution for these eight basic drugs are also shown in Table III. For a drug that confers the characteristics of a one-compartment model on the body, the apparent volume of distribution does not change with time. On the other hand the volume can be assumed as a function of time for a drug that confers the characteristics of a multiple-compartment model on the body[14]. In this paper the relationship between partition coefficients and apparent volumes of distribution will be discussed in the region of pseudo-distribution equilibrium. Therefore, $V_d'_\beta$ or $(V_d')_{AUC}$ should be used instead of $(V_d')_{extrap}$ in the case of a drug which has been analyzed according to a two-compartment model. The values of $(V_d')_{extrap}$, however, are more readily available in literatures than those of $V_d'_\beta$. Furthermore, the difference between $(V_d')_{extrap}$ and $V_d'_\beta$ for a drug is not so great when they are expressed in the logarithmic scale. Thus, it is assumed to be not inadequate to employ $(V_d')_{extrap}$ instead of $V_d'_\beta$ for an approximate estimation of the relationship between partition coefficients and apparent volumes of distribution.

It has been known that there are species differences in the volume of distribution for some drugs, *e.g.*, for amphetamine,[15] quinidine,[16] chlorpromazine,[17] and tetraethylammonium.[18] To strictly relate partition coefficients to the volumes of distribution, it is desirable to use the values of $(V_d')_{extrap}$ obtained in the same species. But the number of $(V_d')_{extrap}$ values collected bibliographically is so few that only those values in small or medium animals, rats or dogs, are listed in Table III and employed to draw Fig. 5.

The logarithm of $(V_d')_{extrap}$ in Table III was plotted against the logalithm of P' as shown in Fig. 4. The fairly good correlation ($r=0.939$) between $\log\{(V_d')_{extrap}\}$ and $\log P'$ was observed in the region of medium ($1 \leqq P' < 70$) and high P' ($P' \geqq 70$). This result agrees qualitatively with the relationship proposed in the preceding paper,[1] which has suggested that V_d' values for basic drugs are almost constant in the region of low P' and increase in the region of high P'. The proposed relationship between V_d' and P' has been expressed by the following equation.

$$V_d' = \frac{V_p}{W}\left[1+\frac{V_2}{V_p}K_2'+\frac{V_1}{V_p}b\{1+\text{antilog}\,(pK_a-7.4)\}^{a-1}(P')^a\right] \quad (1)$$

10) C.A.M. Hogben, D.J. Tocco, B.B. Brodie, and L.S. Schanker, *J. Pharmacol. Exp. Ther.*, **125**, 275 (1959).
11) M.A. Mahju and R.P. Maickel, *Biochem. Pharmacol.*, **18**, 2701 (1969).
12) J. Dreyfuss, J.M. Shaw, and J.J. Ross, Jr., *J. Pharm. Sci.*, **65**, 1310 (1976).
13) *a*) S.H. Curry, J.E. Derr, and H.M. Mailing, *Proc. Soc. Exp. Biol. Med.*, **134**, 314 (1970); *b*) S.H. Curry, A. D'Mello, and G.P. Mould, *Br. J. Pharmacol.*, **42**, 403 (1971).
14) S. Niazi, *J. Pharm. Sci.*, **65**, 452 (1976).
15) J.D. Baggot, *Diss. Abstr. Int. B*, **32**, 2897 (1971).
16) C.A. Neff, L.E. Davis, and J.D. Baggot, *Am. J. Vet. Res.*, **33**, 1521 (1972).
17) S.H. Curry, *J. Pharm. Pharmacol.*, **24**, 818 (1972).
18) C.A.N. Davis, L.E. Davis, and J.D. Baggot, *Am. J. Vet. Res.*, **34**, 425 (1973).

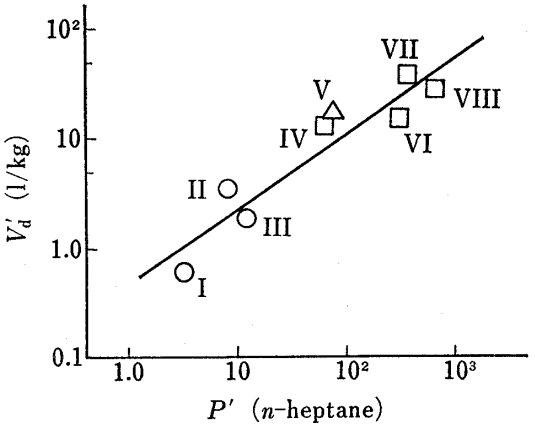

Fig. 4. Relationship between V_d' and P' for Basic Drugs with High Partition Coefficients

○: rabbits, □: rats, △: dogs, I: *p*-toluidine, II: 3,4-xylidine, III: *o*-chloroaniline, IV: promazine, V: fluphenazine, VI: trimeprazine, VII: chlorpromazine, VIII: triflupromazine. Values of $(V_d')_{extrap}$ were temporarily used as V_d' in this paper for *p*-toluidine, 3,4-xylidine, *o*-chloroaniline, fluphenazine, and chlorpromazine, which were analyzed by two-compartment open model. Other V_d' values were derived from one-compartment open model.

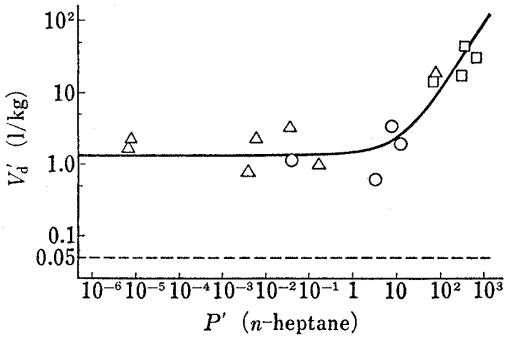

Fig. 5. Relationship between V_d' and P' in the Region of Both Low and High Partition Coefficients for Basic Drugs

○: rabbits, □: rats, △: dogs. For further details, see the text.

The definition of terms and the derivation of Eq. 1 together with the model scheme for the distribution of basic drugs are shown in the appendix of this paper.

In the region of low P', Eq. 1 is simplified to Eq. 2.

$$V_d' = \frac{V_p}{W}\left(1+\frac{V_2}{V_p}K_2'\right) \tag{2}$$

Though the exact region of P' where Eq. 2 holds approximately has not yet been determined, the temporary boundary was set at $P'=5$ in order to include the low $(V_d')_{extrap}$ value for *p*-toluidine in that region. The geometric mean of V_d' or $(V_d')_{extrap}$ for eight basic drugs took the value of 1.32 l/kg, when the pata for *p*-toluidine, those for six drugs shown in the preceding paper,[1] and that for antipyrine in rabbits[19] were used as V_d' values in the region of low P'. Therefore, Eq. 2 became,

$$\frac{V_p}{W}\left(1+\frac{V_2}{V_p}K_2'\right) = 1.32 \tag{3}$$

In the region of high P', Eq. 1 is approximately reduced to Eq. 4 assuming $a=1$, since Leo and Hansch[20] has reported that "a" takes the value of around unity in most cases. To estimate the value

$$V_d' = \frac{V_p}{W}\left(1+\frac{V_2}{V_p}K_2'+\frac{V_1}{V_p}bP'\right) \tag{4}$$

for V_1b/W, Eq. 5 was derived from Eq. 3 and Eq. 4.

$$V_d' - 1.32 = \frac{V_1}{W}bP' \tag{5}$$

Taking the logarithm of both sides of the equation, the least-squares fitting was carried out using V_d' or $(V_d')_{extrap}$ and P' values for other seven basic drugs than *p*-toluidine in Table III.

19) H.M. Solomon and J.J. Schrodie, *J. Pharmacol. Exp. Ther.*, **154**, 660 (1966).
20) A. Leo and C. Hansch, *J. Org. Chem.*, **36**, 1539 (1971).

Then, the value of -1.04 was obtained for log (V_1b/W), *i.e.* the value of 0.0912 for V_1b/W. As V_1 represents the volume of lipid space in this paper and the amount of fat has been reported as 0.15 kg/kg[21] of the whole body, "b" in this case would take the value of 0.608 from $b=0.0912\cdot W/V_1\fallingdotseq 0.0912/0.15$ approximately.

The relationship between V_d' and P' in the region of both low and high P' was estimated by Eq. 4 employing those values estimated above for (V_p/W) $(1+V_2K_2'/V_p)$ and V_1b/W. The result is shown with a solid line in Fig. 5. The observed values for V_d' or $(V_d')_{extrap}$ scattered near along the solid line, indicating that the proposed model for distribution of basic drugs was considerably satisfactory. In this paper, however, it was assumed that extents of protein binding of those basic drugs would be comparable to one another and that molar volume or molecular weight of those drugs would have little influence on drug distribution in the body. These assumptions may cause a fluctuation of some V_d' values from the calculated line in Fig. 5. It is considered that the further study should be necessary to establish an exact relationship between V_d' and P' values for many basic drugs, and the influence of protein binding on V_d' for a basic drug is now being investigated in this laboratory.

Appendix

The model for drug distribution at pseudo-distribution equilibrium has been proposed in the preceding paper.[1] The model and the definition of terms are shown in Fig. 6. Since the apparent volume of distribution (V_d') estimated from blood plasma concentration of a drug is defined as a proportional constant that relates the plasma concentration of a drug to the total amount of drug in the body, the following equation is obtained.

$$V_d' = \frac{1}{W}\cdot\frac{Q_{pi}+Q_{pu}+Q_{2i}+Q_{2u}+Q_1}{(Q_{pi}+Q_{pu})/V_p} \qquad (A1)$$

On the other hand, K_1' and K_2' are described by Eq. (A2) and Eq. (A3).

$$K_1' = \frac{Q_1/V_1}{(Q_{pi}+Q_{pu})/V_p} \qquad (A2)$$

$$K_2' = \frac{(Q_{2i}+Q_{2u})/V_2}{(Q_{pi}+Q_{pu})/V_p} \qquad (A3)$$

Substitution of $K_1'\cdot V_1/V_p$ in Eq. (A2) and $K_2'\cdot V_2/V_p$ in Eq. (A3) for $Q_1/(Q_{pi}+Q_{pu})$ and $(Q_{2i}+Q_{2u})/(Q_{pi}+Q_{pu})$ in Eq. (A1), respectively, yields Eq. (A4).

$$V_d' = \frac{V_p}{W}\left(1+\frac{V_2}{V_p}K_2'+\frac{V_1}{V_p}K_1'\right) \qquad (A4)$$

To derive the relationship between V_d' and the true partition coefficient in blood plasma–lipid system, the following equation is introduced by using Henderson–Hasselbalch equation.

$$K_1' = \frac{K_1}{1+\text{antilog}\,(pK_a-7.4)} \qquad (A5)$$

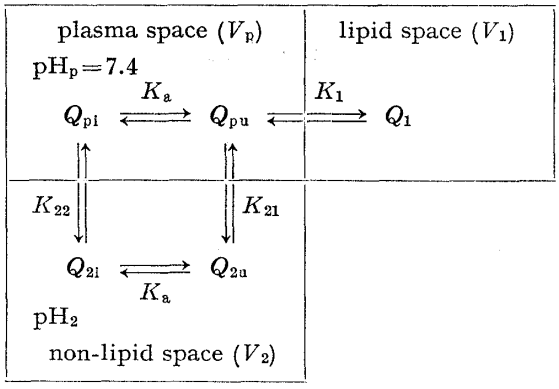

Fig. 6. Model for Drug Distribution

Q_{pi}: amount of ionized drug in blood plasma, Q_{pu}: amount of unionized drug in blood plasma, Q_1: amount of drug in lipid space of tissue, Q_{2i}: amount of ionized drug in non-lipid space, Q_{2u}: amount of unionized drug in non-lipid space, V_p: volume of blood plasma (l), V_1: volume of lipid space of tissue (l), V_2: volume of non-lipid space of tissue (l), V_d': apparent volume of distribution (l/kg) based on blood plasma concentration, W: body weight (kg), K_1: true partition coefficient in lipid-plasma system, K_1': apparent partition coefficient in lipid-plasma system, K_{21}: partition coefficient of unionized drug in non-lipid-plasma space system, K_{22}: partition coefficient of ionized drug in non-lipid-plasma system, K_2': apparent partition coefficient in non-lipid-plasma space system.

21) *a*) W.W. Mapleson, *J. Appl. Physiol.*, **18**, 197 (1961); *b*) A.W. Sloan, *J. Appl. Physiol.*, **23**, 311 (1967).

Substitution for K_1' in Eq. (A4) from Eq. (A5) yields,

$$V_d' = \frac{V_p}{W}\left[1+\frac{V_2}{V_p}K_2' + \frac{V_1}{V_p}\{1+\text{antilog}\,(pK_a-7.4)\}^{-1}K_1\right] \quad (A6)$$

Leo and Hansch[20] developed the relationship existed between partition coefficients in one system (P_1) and those in a second system (P_2) by deriving a similar equation as follows,

$$\log P_2 = a \log P_1 + \log b \quad (A7)$$

where "a" and "b" are parameters for a certain pair of solvent systems. If the lipid space of tissue in Fig. 6 is considered to behave as a kind of organic solvent, the true partition coefficient of a drug in a blood plasma–lipid system (K_1) may be related to the true partition coefficient in a buffer–organic solvent system (P) according to the similar viewpoint to Eq. (A7), and is written as Eq. (A8).

$$K_1 = b \cdot P^a \quad (A8)$$

Therefore, K_1 in Eq. (A6) is replaced by $b \cdot P^a$ in Eq. (A8), yielding,

$$V_d' = \frac{V_p}{W}\left[1+\frac{V_2}{V_p}K_2' + \frac{V_1}{V_p}b\{1+\text{antilog}\,(pK_a-7.4)\}^{-1}P^a\right] \quad (A9)$$

The relationship between P and P' of a basic drug in buffer-organic solvent system is generally expressed as follows,

$$P = 1 + \{\text{antilog}\,(pK_a-pH_b)\}P' \quad (A10)$$

where pH_b is the pH of buffer solution and takes a value of 7.4 in this paper. Substitution for P in Eq. (A9) from Eq. (A10) gives the Eq. (A11).

$$V_d' = \frac{V_p}{W}\left[1+\frac{V_2}{V_p}K_2' + \frac{V_1}{V_p}b\{1+\text{antilog}\,(pK_a-7.4)\}^{a-1}(P')^a\right] \quad (A11)$$

Acknowledgement The authors thank Dr. Kikuo Iwamoto for his critical reading of the manuscript. The authors also wish to express their gratitude to Miss Reiko Namba and Miss Yoshiko Sudo for their technical assistance.