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

The model was proposed to relate the apparent volume of distribution (V_d') of a drug to the apparent partition coefficient (P') and the volume of blood plasma. It was found that V_d' values for basic drugs were almost constant in the region of low P' and that V_d' increases in the region of high P'.

The average V_d' value (1.47 l/kg) for basic drugs with low P' was about thirty times larger than the value of the blood plasma volume (0.05 l/kg).

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

It is well known that the apparent volume of distribution usually has no direct physiologic meaning and does not refer to a real volume.[3] However, it should also be noticed that the apparent volume of distribution (V_d') contains the blood plasma volume as a real volume and that V_d' depends on the permeability of the biological membranes such as blood capillary membranes to the drug. The apparent volume of distribution for any drug can not take a smaller value than the blood plasma volume itself, and increases as tissue distribution of drugs increases. Therefore, it is assumed that the characteristics of the drug distribution in the body would be partly clarified by investigation of factors which control the V_d' value.

Martin, *et al.* have described that acidic drugs have relative volumes of distribution less than 0.7, and basic drugs have high volumes of distribution.[4] Furthermore, it has been usually conceived that drugs with larger partition coefficients take the larger V_d' values. However, no concrete data are available to support these kinds of descriptions and concepts. In this paper, the model, which was shown in Fig. 1-a with the definition of the terms, was proposed to relate the apparent volume of distribution (V_d') of a drug to the apparent partition coefficient (P') and the volume of blood plasma, since the simplest model, which contained only plasma and lipid spaces, seemed to have a considerable discrepancy for most basic drugs. Since the apparent volume of distribution (V_d') estimated from the 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.

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

On the other hand, K_1' and K_2' are described by Eq. (2) and (3).

$$K_1' = \frac{Q_1/V_1}{(Q_{pi}+Q_{pu})/V_p} \tag{2}$$

$$K_2' = \frac{(Q_{2i}+Q_{2u})/V_2}{(Q_{pi}+Q_{pu})/V_1} \tag{3}$$

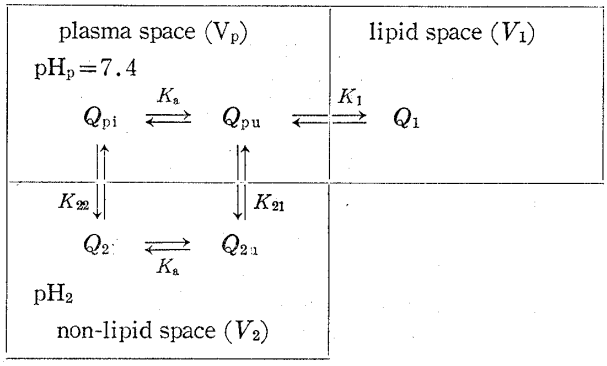
Substitution of $K_1' \cdot V_1/V_p$ in Eq. (2) and $K_2' \cdot V_2/V_p$ in Eq. (3) for $Q_1/(Q_{pi}+Q_{pu})$ and $(Q_{2i}+Q_{2u})/(Q_{pi}+Q_{pu})$ in Eq. (1), respectively, yields Eq. (4).

1) A part of this work was presented at the Meeting of Tokai Branch, Pharmaceutical Society of Japan, Nagoya, Nov. 1976.
2) This paper constitutes Part I of the series entitled "Drug Distribution in the Body"
3) M. Gibaldi and D. Perrier, "Pharmacokinetics," Marcel Dekker, Inc., New York, 1975, p. 175.
4) A.N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea and Febiger, Philadelphia, 1969, pp. 403—304.

$$V_d' = \frac{V_p}{W}\left(1+\frac{V_2}{V_p}K_2'+\frac{V_1}{V_p}K_1'\right) \quad (4)$$

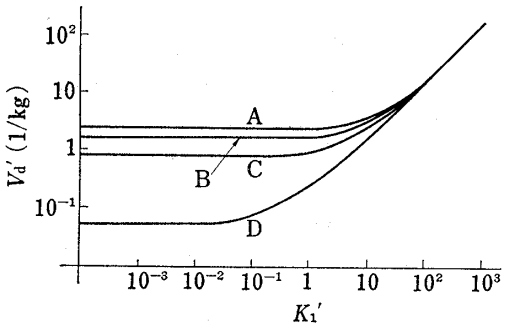
In calculation of V_d' by Eq. (4), it is assumed that $V_1/V_p=3$ and $K_2'=1$, since the blood plasma volume and the amount of fat has been reported as about 0.05 l/kg[5] and 0.15 kg/kg[6] of the whole body, respectively, and the non-lipid space in this paper can be thought to be connected to the plasma space by water-filled pores in the biological membrane. Curves in Fig. 1-b indicate that the apparent volume of distribution is almost constant in the region of low K_1', and that V_d' increases in the region of high K_1'. Besides, it should be noticed that the type of these curves is very similar to that of the curve which has been shown to relate the neurotoxicity of penicillins to the partition coefficient.[7] Furthermore, as seen from curves (A), (B), and (C), the value for V_d' in the region of low K_1' can take the larger value than the ratio of the blood plasma volume to the body-weight. Using Leo-Hansch[8]

1-a) 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.

1-b) Calculated relationship between V_d' and P' by using Eq. (4) (See text)



A: $V_2/V_p=45$, B: $V_2/V_p=30$, C: $V_2/V_p=15$, D: $V_2/V_p=0$

Fig. 1. Model for Drug Distribution and Calculated V_d'

and Henderson-Hasselbalch equations, the following equation is introduced from Eq. (4), if the lipid space of tissue in Fig. 1-a is assumed to behave as a kind of organic solvent.

$$V_d' = \frac{V_p}{W}\left[1+\frac{V_2}{V_p}K_2'+\frac{V_1}{V_p}b\{1+\text{antilog}(pK_a-7.4)\}^{a-1}(P')^a\right] \quad (5)$$

Where P' is the apparent partition coefficient in a certain organic solvent-buffer system, and a and b are parameters to relate K_1' to P'.

To prove the validity of Eq. (5), twelve basic drugs were selected, and P' values of three drugs, chlordiazepoxide,[9a] quinidine,[9b] and tolazoline,[9a] were measured at 25° in the experi-

5) *a*) R. Katori, *Kokyu to Junkan*, **14**, 968 (1966); *b*) I. Nisida, *ibid.*, **14**, 1070 (1966).
6) *a*) W.W. Mapleson, *J. Appl. Physiol.*, **18**, 197 (1961); *b*) A.W. Sloan, *J. Appl. Physiol.*, **23**, 311 (1967).
7) T.R. Weihrauch, H. Kohler, and D. Hoffer, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **239**, 55 (1975).
8) A. Leo and C. Hansch, *J. Org. Chem.*, **36**, 1539 (1971).
9) *a*) Chlordiazepoxide was kindly supplied by Takeda Chemical Industries, Ltd., and tolazoline hydrochloride by Yamanouchi Pharmaceutical Co., Ltd.; *b*) Quinidine was purchased from Tokyo Kasei Kogyo Co., Ltd., and of analytical grade. These drugs were used without further purification.

ments.[10] The observed P' values are shown in the footnote of Fig. 2. As for the three drugs, it was proved for each drug using four different levels of the concentration that there are no associated molecules in the organic solvent layer. The values of P' in *n*-heptane–water (pH 7.4) system for the other nine drugs and V_d' values for these twelve drugs were collected or calculated from the referenced data, and listed in the footnote of Fig. 2. Using these values the logarithm of V_d' was plotted against the logarithm of P' on Fig. 2. In the region of low P' ($P'<1$), the significant correlation was not observed between the log P' and log V_d' ($r=-0.307$), and V_d' values were almost constant. The geometric mean of V_d' in the region took the value of 1.47 (l/kg), which was shown by solid line in Fig. 2, and was about thirty times greater than the ratio of the blood plasma volume to body-weight, which was shown by the dotted line. The evidence suggests that there is other non-lipid space than blood plasma space for these drugs. On the other hand, the significant correlation between log V_d' and log P' was observed in the region of high P' ($P'\geqq 70$), and further investigation is now being made for other basic drugs with medium P' ($1\leqq P'<70$) experimentally and bibliographically in our laboratory.

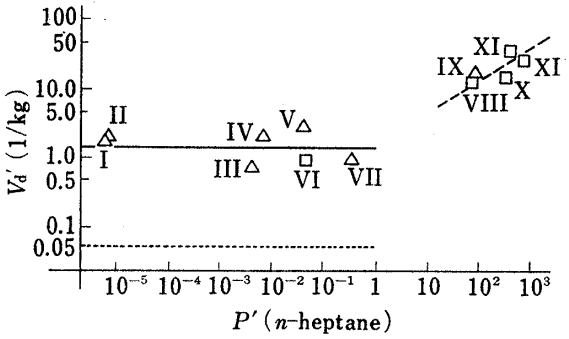


Fig. 2. Relationship between V_d' and P'

△: dogs, □: rats, (I) ephedrine: $V_d'=1.64$ (ref. 11*a*), $P'=6\times10^{-6}$ (ref. 12*a*), (II) norephedrine: $V_d'=2.15$ (ref. 11*a*), $P'=7\times10^{-6}$ (ref. 12*a*), (III) N-acetyl-4-aminoantipyrine: $V_d'=0.734$ (ref. 11*b*), $P'=4\times10^{-3}$ (ref. 12*b*), (IV) tolazoline: $V_d'=2.17$ (ref. 11*c*), $P'=6\times10^{-3}$ (determined in this paper), (V) quinidine: $V_d'=2.91$ (ref. 11*d*) $P'=3\times10^{-2}$ (determined in this paper), (VI) antipyrine: $V_d'=0.955$ (ref. 11*e*), $P'=4\times10^{-2}$ (ref. 12*b*), (VII) chlordiazepoxide: $V_d'=0.952$ (ref, 11*f*), $P'=1.6\times10^{-1}$ (determined in this paper), (VIII) promazine: $V_d'=12.6$ (ref. 12*c*), $P'=70$(ref. 12*c*), (IX) fluphenazine: $V_d'=16.8$ (ref. 11*g*), $P'=80$ (ref. 12*c*), (X) trimeprazine: $V_d'=15.1$ (ref. 12*c*), $P'=310$ (ref. 12*c*), (XI) chlorpromazine: $V_d'=37.0$ (ref. 11*h,i*), $P'=370$ (ref. 12*c*), (XII) triflupromazine: $V_d'=27.2$ (ref. 12*c*), $P'=670$ (12*c*). Values of $(V_d')_{extrap}$ were temporarily used as V_d' in this paper for tolazoline, antipyrine, fluphenazine, and chlorpromazine, which were analyzed by two-compartment open model. Other V_d' values were derived from one-compartment open model.

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10) *n*-Heptane for spectrophotometrical use was employed as the organic solvent layer, and phosphate buffer of pH 7.4 as the aqueous layer.

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