Fractal Volume of Drug Distribution: It Scales Proportionally to Body Mass

Vangelis Karalis,[1] Laurent Claret,[2] Athanassios Iliadis,[3] and Panos Macheras[1,4]

Received January 24, 2001; accepted March 21, 2001

Purpose. To develop the physiologically sound concept of fractal volume of drug distribution, v_f, and evaluate its utility and applicability in interspecies pharmacokinetic scaling.

Methods. Estimates for v_f of various drugs in different species were obtained from the relationship:

$$v_f = (v - V_{pl}) \frac{V_{ap} - V_{pl}}{V_{ap}} + V_{pl}$$

where v is the total volume of the species (equivalent to its total mass assuming a uniform density 1g/mL), V_{pl} is the plasma volume of the species and V_{ap} is the conventional volume of drug distribution. This equation was also used to calculate the fractal analogs of various volume terms of drug distribution (the volume of central compartment, V_c, the steady state volume of distribution, V_{ss}, and the volume of distribution following pseudodistribution equilibrium, V_z). The calculated fractal volumes of drug distribution were correlated with body mass of different mammalian species and allometric exponents and coefficients were determined.

Results. The calculated values of v_f for selected drugs in humans provided meaningful and physiologically sound estimates for the distribution of drugs in the human body. For all fractal volume terms utilized, the allometric exponents were found to be either one or close to unity. The estimates of the allometric coefficients were found to be in the interval (0,1). These decimal values correspond to a fixed fraction of the fractal volume term relative to body mass in each one of the species.

Conclusions. Fractal volumes of drug distribution scale proportionally to mass. This confirms the theoretically expected relationship between volume and mass in mammalian species.

KEY WORDS: drug; fractal; volume of distribution; scaling.

INTRODUCTION

The apparent volume of drug distribution, V_{ap}, is one of the most important pharmacokinetic parameters of drugs. In the context of the pharmacokinetic modeling applied to analyze plasma concentration-time data, various volume terms have been defined i.e. volume of central (V_c) and tissue (V_T) compartments, the steady state volume of distribution (V_{ss}) and the volume of distribution following pseudo-distribution equilibrium (V_z) (1). One of the major drawbacks of the calculated values of the various volume terms is their fictitious character since it is rather difficult to ascribe a physiological meaning to them. This is particular so when the volume estimate exceeds the total volume of body fluids or even the total body mass.

Due to the anatomical and physiological similarities between species, the various types of volume of drug distribution have been expressed mathematically by allometric equations (2,3). Undoubtedly, interspecies pharmacokinetic scaling has become a useful tool in drug development. However, there is an ambiguity for the value of the allometric exponent when the body mass and volumes of drug distribution are correlated among species (2). Although generally the allometric exponents of volume revolve around 1, there are several examples which deviate from unity (2,4–6). Accordingly, two types of physiological time, namely, Kallynochron (when the allometric exponent of volume is equal to 1) and Apolysichron (when the allometric exponent of volume is not equal to 1) have been used in comparative pharmacokinetics (5).

Recently, West *et al.* (7) using allometric principles presented a model which is based on the geometry of the fractal-like architecture of the interior networks (8) that distribute resources within organisms. It was shown (7) that the internal structure of the organisms which include the effective surface area is "maximally fractal" i.e., the network structure is volume filling. Since these design principles apply to mammalian species and the volume of drug distribution is inextricably related to their internal exchange surface areas, we introduce in this work the physiologically sound concept of fractal volume of drug distribution, v_f. The value of v_f can be obtained from the conventional estimate of the apparent volume of drug distribution. Moreover, we applied allometric analysis to the calculated v_f values of various drugs and demonstrated that v_f scales proportionally to body mass.

THEORY

According to West *et al.* (7) the shape and size of each mammalian species can be described by a conventional Euclidean set adhering to the external surface area, *A,* enclosing the total volume *V;* besides, a "biological - fractal" set describes the internal structure which includes the effective exchange area, *a,* and the total volume of biologically active material, *v*. Since *a* and *v* are "biological fractals" and not mathematical fractals they can only extend from a minimum to a maximum size (9). Obviously, these limits are set by the limits of the physiological object. Thus, the upper limit of the volume of drug distribution is the fractal volume *v* i.e. the body mass *M* of the species assuming a uniform constant density 1 g/mL. The conceptual and numerical equivalency between the total body mass, *M,* and the fractal volume, *v,* of the species, defines a physiological maximum for the volume of drug distribution. In reality, the volume of drug distribution should always be a part of the "biological - fractal" volume *v,* which corresponds to the total mass, *M,* of the species expressed in equivalent volume units e.g. 70 L for humans. In order to consider drug distribution, a diagrammatic description of the fractal nature of the internal structure of the mammalian species, in line with the concepts of West et al (7,8), is presented in Fig. 1.

The fractal three dimensional parallelepiped in which the circulatory system is embedded in Fig. 1 provides a pictorial view of the volume *v*. Depending on the physicochemical properties of drug, the value of the apparent volume of drug

[1] School of Pharmacy, University of Athens, Athens, Greece.
[2] Department of Population Pharmacokinetics, School of Pharmacy, University of Montreal, Canada.
[3] UPRES EA-2057, University of Mediterranee, Marseilles, France.
[4] To whom correspondence should be addressed. (e-mail: macheras@pharm.uoa.gr)

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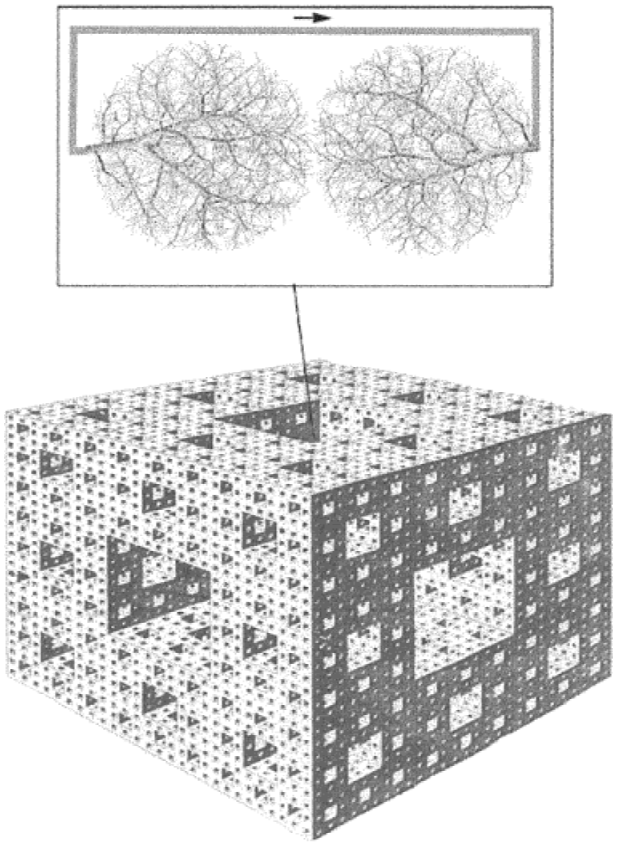

Fig. 1. A hypothetical, geometrical, fractal model of the internal structure of the organisms to exemplify drug distribution. The Menger sponge (9–11), a geometrically self-similar fractal with an infinitely high surface-to-volume ratio is used to represent the part of the non-accessible experimentally in drug distribution studies "biological-fractal" volume. The essential materials and drugs are transported through space-filling fractal networks of branching tubes of the circulatory system (8); this is shown on the top for reasons of clarity. In reality, the arterial and venular networks are scattered in three-dimensional space occupying the empty spaces of the Menger sponge. The value of v (Menger sponge plus the vascular system) for each one of the species is set equal to its body mass assuming a uniform density of 1 g/mL. The fractal volume of drug distribution, v_f, corresponds to the portion of the volume v which is accessible to the drug. The value of v_f is determined by the physicochemical properties of drug.

distribution may or may not be a true portion of the volume v. For example, if the drug at equilibrium is confined into the vascular space or is distributed throughout the total volume of body fluids, the apparent volume of drug distribution corresponds to a portion of the volume v. In contrast, for drugs distributed extensively the apparent volume of drug distribution is fictitious since it is higher than the total body mass i.e., higher than v. This paradox originates from the heterogeneous internal structure of the body since all drug measurements are applied to plasma samples.

Despite these drawbacks the apparent volume of drug distribution, V_{ap}, is used routinely to describe the volume into which a drug distributes in the body at equilibrium. Consequently, in this study the transformation of V_{ap} into meaningful values of fractal volume of drug distribution, v_f is suggested. The value of v_f represents the volume of the biological material of the body in which the drug is distributed at equilibrium; v_f should always satisfy the relationship $v_f \leq v$. According to the diagram of Fig. 1, v_f is the sum of the blood volume of the species and the portion of the parallelepiped volume visited by the drug at equilibrium. Since this portion of the volume v cannot be defined physiologically it can be characterized as the non-accessible experimentally fractal volume of distribution $v_{f,\ n\text{-}ac}$. Therefore,

$$v_f = v_{f,n-ac} + V_{pl} \tag{1}$$

where V_{pl} is the plasma volume of the species. The use of V_{pl} in Eq. 1, instead of the total blood volume of the species, is made to ensure that the plasma volume is the physiological minimum of drug's distribution in the body. In addition, the use of V_{pl} is in accord with the experimental fact that the vast majority of drug measurements are performed on plasma samples. An estimate of $v_{f,\ n\text{-}ac}$ can be obtained from Eq. 2:

$$v_{f,n-ac} = (v - V_{pl}) \frac{V_{ap} - V_{pl}}{V_{ap}} \tag{2}$$

The term in the parenthesis of Eq. 2 represents the total non-accessible experimentally fractal volume of the body of a given species; this is "corrected" by multiplying it with the unitless fraction (≤ 1) of the right-hand side of Eq. 2, which corresponds to the degree of the deviation of the experimentally determined V_{ap} from the sampled plasma volume V_{pl}. Combining Eqs. 1 and 2 we have :

$$v_f = (v - V_{pl}) \frac{V_{ap} - V_{pl}}{V_{ap}} + V_{pl} \tag{3}$$

This equation has two limiting cases. When $V_{ap} >> V_{pl}$, then $v_f = v$ which means that the fractal volume of drug distribution is equal to the "biological-fractal" volume of the species. In other words, the drug is distributed throughout the body of the species. On the other hand, when $V_{ap} \sim V_{pl}$, Eq. 3 gives $v_f = V_{pl}$. This corresponds to the lower limit of drug's distribution in the body, and indicates that the drug is confined to the plasma volume of the species. Also, the degree of drug's distribution in the body, d_d, can be calculated from Eq. 4:

$$d_d = \frac{v_f}{v} 100 \tag{4}$$

The fractal model of drug's distribution in Fig.1 is not compatible with the various volume terms of drug distribution used in pharmacokinetics. However, one can argue that the limitations imposed by the physiology (e.g., volumes for humans $\leq$ 70 L) should also apply for V_c, V_{ss}, and V_z. Hence, the fractal equivalent of these volume terms can be also derived from Eq. 3 using the estimates for V_c, V_{ss}, V_z in place of V_{ap}.

METHODS

Eqs. 3 and 4 were used to calculate the values of v_f and d_d for various drugs in humans. Also, Eq. 3 was used to calculate the values of v_f for various drugs in different species. Estimates for the volume terms V_c, V_{ss}, V_z, of different drugs were also transformed using Eq. 3 to their corresponding fractal values $(V_c)_f$, $(V_{ss})_f$, $(V_z)_f$, respectively. The available in literature (5,13–29) allometric studies involving various expressions of volume terms were re-analyzed using their fractal equivalents calculated from Eq. 3. In all cases the value of v

was set equal to the corresponding body mass of the species (12) assuming a constant density of 1 g/mL. Values for V_{pl} of the various species used in Eq. 3 were obtained from literature (12).

RESULTS AND DISCUSSION

Figure 2 shows the relationship between v_f and V_{ap} for two species, namely, human (A) and rat (B). These plots indicate that the v_f values approach asymptotically their upper limits i.e. 70 L for humans and 250 mL for rats as V_{ap} increases. Also, estimates for V_{ap} of selected drugs obtained from literature (30) were transformed to v_f values; these values along with the corresponding d_d values are quoted in Table I. All drugs listed in Table I can be classified into two categories i.e. drugs with values of the apparent volume of drug distribution higher or lower than 67 L. The values of the corresponding fractal volumes of the two categories decrease or increase, respectively. These changes become more significant as the deviation of the conventional volume from 67 L is larger. In all cases, however, the fractal volumes estimated are lower than 70 L. Overall, the estimates for v_f and d_d listed in Table I provide physiologically sound values for the degree of drug's distribution in the body.

However, caution should be exercised when Eq. 3 is used to calculate v_f for a drug exhibiting a large V_{ap} value due to its specific binding to an organ. Obviously, the corresponding v_f values for this drug will be misinterpreted as arising from extensive distribution throughout the body. It is suggested to treat the distribution of such a drug as a simple partitioning between plasma and the organ. Keeping the same terminology for reasons of uniformity, an estimate for v_f of this type of drugs can be obtained from a modified form of Eq. 3:

$$v_f = V_{org}\left(\frac{V_{ap} - V_{pl}}{V_{ap}}\right) + V_{pl} \quad (5)$$

where V_{org} is the volume of the organ exhibiting specific affinity for the drug. Again, Eq. 5 has two limiting cases. For $V_{ap} >> V_{pl}$, $v_f = V_{org} + V_{pl}$ while for $V_{ap} \sim V_{pl}$, we have $v_f = V_{pl}$. Plausibly, the size of the organ and the affinity of drug for the organ will affect the experimental value for V_{ap} and subsequently the v_f value. However, inspection of Eq. 5 reveals that whatever the value of the experimentally determined V_{ap} is, physiologically sound estimates for v_f will be derived. The use of Eq. 5 presupposes that explicit experimental evidence indicates that the drug is bound to a specific organ. For example, quinacrine is bound extensively to liver (30) having a V_{ap} value of ~40,000 L (31). Using this value for V_{ap}, assigning V_{org} = 1690 mL (12) for the human liver an estimate for v_f = 4,690 mL for quinacrine can be derived from Eq. 5. This value corresponds to the physiologically sound sum of liver and plasma volumes. Unfortunately, the lack of this kind of data in different species does not allow us to use Eq. 5 in interspecies scaling.

The results of the interspecies pharmacokinetic scaling for the fractal volumes calculated from Eq. 3 are presented in Table II. For comparative purposes the reported in literature (5,13–29) allometric equations are also listed in Table II. In all cases, the correlation coefficients of the allometric equations with the fractal volumes were found to be higher than the corresponding with the conventional volumes. This finding indicates a better correlation of the fractal volumes than the conventional volumes with body mass. In the great majority of cases the exponent of the allometric equations was found

Table I. Values of Conventional Distribution Volumes for Selected Drugs (30) and Their Corresponding Fractal Analogs in Humans (70 kgr); the Term d_d Represents the Degree of Drug Distribution in the Body

Drug	Conventional volume (L)	Fractal volume (L)	% d_d
Acetaminophen	66.5	67.0	95.7
Amiodarone	4620	70	100
Amoxicillin	14.7	56.3	80.4
Betaxolol	514.5	69.6	99.4
Bisoprolol	224	69.1	98.7
Cefazolin	9.8	49.5	70.7
Chlorpromazine	1470	69.9	99.9
Clozapin	378	69.5	99.3
Diazepam	77	67.4	96.3
Dobutamine	14	55.6	79.4
Fluconazole	42	65.2	93.1
Interferon-a	28	62.8	89.7
Imipramine	1260	69.8	99.7
Indomethacin	20.3	60.1	85.9
Isoniazid	46.9	65.7	93.9
Lidocaine	77	67.4	96.3
Omeprazole	23.8	61.6	88.0
Phenytoin	44.8	65.5	93.6
Propranolol	301	69.3	99.0
Valproic acid	15.4	56.9	81.3

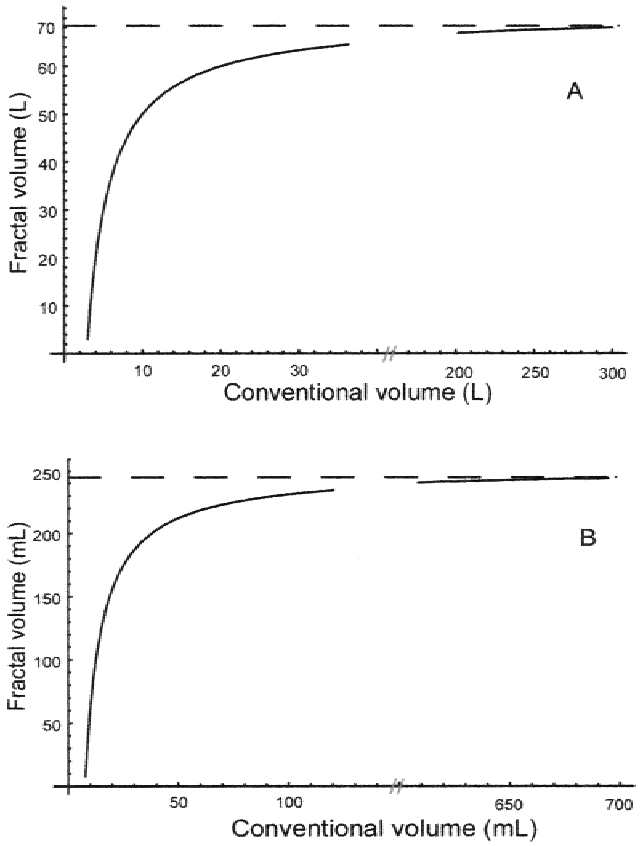

Fig. 2. Plot of v_f versus the conventional volume of drug's distribution in humans (A) and rats (B) using Eq. 3.

Table II. Allometric Equations Describing the Relationship Between Conventional or Fractal Volume and Body Mass (M) Across Species

Drug (reference)	Allometric equation with conventional volume reported[a]	R^2	Allometric equation with fractal volume calculated[b]	(exponent ± 2SE)[c]	R^2
Actisomide (13)	$V_d = 1.18M^{1.00d}$	0.992	$v_f = 0.969M^{0.998}$	(0.994, 1.002)	1.000
Amphotericin (14)	$V_{ap} = 2.79M^{0.96d}$	0.983	$v_f = 0.983M^{0.999}$	(0.996, 1.003)	1.000
Amphotericin (14)	$V_1 = 1.02M^{0.936d}$	0.961	$(v_1)_f = 0.952M^{0.995}$	(0.985, 1.005)	0.999
Amphotericin (14)	$V_{ss} = 2.82M^{0.978d}$	0.977	$(v_{ss})_f = 0.983M^{1.000}$	(0.996, 1.003)	1.000
Amsacrine (15)	$V_{ss} = 3.37M^{0.812}$	0.991	$(v_{ss})_f = 0.985M^{0.997}$	(0.996, 0.999)	1.000
BSH (16)	$V_{ap} = 1.557M^{0.865}$	0.999	$v_f = 0.972M^{0.996}$	(0.993, 0.999)	1.000
Cefazolin (17)	$V_{ss} = 0.177M^{0.931d}$	0.969	$(v_{ss})_f = 0.748M^{0.972}$	(0.934, 1.010)	0.999
Cefmetazole (17)	$V_{ss} = 0.268M^{0.851d}$	0.984	$(v_{ss})_f = 0.818M^{0.968}$	(0.940, 0.995)	0.999
Cefoperazone (17)	$V_{ss} = 0.230M^{0.913d}$	0.988	$(v_{ss})_f = 0.803M^{0.975}$	(0.944, 1.007)	0.999
Cefotetan (17)	$V_{ss} = 0.217M^{0.938d}$	0.994	$(v_{ss})_f = 0.799M^{0.980}$	(0.957, 1.004)	0.999
Cefpiramide (17)	$V_{ss} = 0.244M^{0.814d}$	0.926	$(v_{ss})_f = 0.765M^{0.951}$	(0.887, 1.014)	0.996
Chlordiazepoxide (5)	$V_1 = 1.48M^{0.54e}$	—	$(v_1)_f = 1.06M^{0.932}$	—	—
Chlordiazepoxide (5)	$V_\beta = 1.91M^{0.61e}$	—	$(v_\beta)_f = 1.02M^{0.965}$	—	—
Chlordiazepoxide (5)	$V_{ss} = 1.72M^{0.63e}$	—	$(v_{ss})_f = 1.00M^{0.970}$	—	—
CI-921 (15)	$V_{ss} = 1.22M^{0.676}$	0.943	$(v_{ss})_f = 0.942M^{0.984}$	(0.969, 0.999)	1.000
Ciprofloxacin iv (18)	$V_{ss} = 2.80M^{0.692f}$	—	$(v_{ss})_f = 0.984M^{0.994}$	—	—
Ciprofloxacin po (18)	$V_{ss} = 12.39M^{1.178f}$	—	$(v_{ss})_f = 0.997M^{1.000}$	—	—
Diazepam (19)	$V_{ssd} = 5.0M^{0.781d}$	0.876	$(v_{ss})_f = 0.993M^{0.994}$	(0.986, 1.002)	1.000
Diazepam (19)	$V_1 = 2.58M^{0.624d}$	0.922	$(v_1)_f = 0.985M^{0.980}$	(0.960, 1.000)	1.000
Diazepam (19)	$V_{darea} = 8.2M^{0.744d}$	0.775	$(v_{darea})_f = 0.996M^{0.994}$	(0.986, 1.003)	1.000
Erythromycin (20)	$V_{ss} = 3.85M^{0.823d}$	0.930	$(v_{ss})_f = 0.984M^{0.996}$	(0.992, 1.001)	1.000
Interferon-a (21)	$V_{ss} = 0.196M^{0.940d}$	0.991	$(v_{ss})_f = 0.773M^{0.980}$	(0.940, 1.020)	0.999
Lamifiban (22)	$V_{ss} = 0.295M^{1.268}$	0.987	$(v_{ss})_f = 0.876M^{1.014}$	(0.977, 1.051)	1.000
Moxalactame (17)	$V_{ss} = 0.215M^{0.921d}$	0.997	$(v_{ss})_f = 0.795M^{0.977}$	(0.956, 0.997)	1.000
Oleandomycin (20)	$V_{ss} = 2.72M^{0.752d}$	0.977	$(v_{ss})_f = 0.977M^{0.994}$	(0.990, 0.998)	1.000
Phencyclidine (23)	$V_\beta = 10M^{0.96}$	0.970	$(v_\beta)_f = 0.996M^{0.999}$	(0.998, 1.000)	1.000
Procaterol (24)	$V_c = 0.561M^{0.950d}$	0.985	$(v_c)_f = 0.930M^{0.985}$	(0.962, 1.008)	1.000
Procaterol (24)	$V_\beta = 2.812M^{1.06d}$	0.980	$(v_\beta)_f = 0.986M^{0.999}$	(0.995, 1.003)	1.000
Remoxipride (25)	$V_{ss} = 2.22M^{0.806d}$	0.983	$(v_{ss})_f = 0.975M^{0.994}$	(0.990, 0.999)	1.000
Tamsulosin (26)	$V_d = 2.54M^{0.914}$	0.994	$v_f = 0.984M^{0.997}$	(0.993, 1.000)	1.000
Theophylline (27)	$V_{ss} = 0.547M^{1.06}$	0.982	$(v_{ss})_f = 0.933M^{0.999}$	(0.990, 1.008)	1.000
Troglitazone (28)	$V_c = 0.317M^{0.999d}$	0.999	$(v_c)_f = 0.863M^{0.999}$	(0.979, 1.019)	1.000
Troglitazone (28)	$V_{ss} = 0.858M^{0.981d}$	0.995	$(v_{ss})_f = 0.948M^{0.999}$	(0.990, 1.007)	1.000
Troglitazone (28)	$V_\beta = 1.9M^{1.087d}$	0.990	$(v_\beta)_f = 0.975M^{1.002}$	(0.996, 1.008)	1.000
Valproate (29)	$V_{ss} = 0.339M^{0.896d}$	0.979	$(v_{ss})_f = 0.879M^{0.996}$	(0.955, 1.037)	1.000

[a] The symbols for the volume terms are quoted as reported in the literature.
[b] v_f is the fractal analog for V_d and V_{ap}.
[c] Confidence interval for the exponent; SE is the standard error of the exponent calculated from the slope of $\log v_f$-$\log M$ plot.
[d] Equation was derived in this study using the data of the reference.
[e] Reference data were available only for two species, human and dog.
[f] Reference data were available for two routes of drug administration, iv and oral only for two species, rat and monkey. The allometric approach was applied separately to each one of these two data sets.

equal to 1 which means that the fractal volumes of drug distribution are directly proportional to the body mass. This proportionality was observed for drugs having classical allometric exponents either close, e.g., amphotericin, phencyclidine, theophylline or smaller, larger than unity, e.g., amsacrine, cefmetazole, cefpiramide, erythromycin. Also, for drugs with classical allometric exponents deviating remarkably from one, namely, chlordiazepoxide, CI-921, ciprofloxacin, diazepam their fractal volume were found to scale proportionally to mass. Overall, only in 6 out of 35 data sets using the fractal volume as dependent variable, the estimate of the allometric exponent ± two standard errors did not overlap unity. However, even in these cases the upper limit of the confidence interval was marginally lower than one i.e., 0.995, 0.997, 0.998, 0.999. It is also worthy to mention that the coefficient (pre-exponential term) of the allometric equations listed in Table II is not simply a normalization constant which corresponds to the y-intercept of the log-log plots. Here, the value of the coefficient represents the fraction of the total body mass of each species in which the drug has distributed in all species. This is so since a proportionality between fractal volume and body mass was established.

Pharmacokinetic allometric relationships are routinely characterized as empirical. However, West *et al.* (8) have shown that allometric scaling of organisms is the result of the hierarchical branching vascular networks that distribute resources within organisms. It has also been shown (7) that the ubiquitous multiples of ¼ for the allometric exponents arise from the internal fractal geometry of species. Thus, the fundamental relationships of the geometrical variables length, area and volume associated with the biological networks of the species rely on an invariant, common, terminal unit of fixed size of the physical network (7). The data of Table II indicate that v_f follows the same scaling law as v. This is so

since v_f corresponds to the whole or a part of the fractal volume, v. The physicochemical properties of a given drug determine the degree of its access (v_f) to the available exchange surface area which is maximally fractal (7) and behaves like a conventional volume (v). Due to the internal structural and functional similarity of the mammalian species, the values of v_f which correspond to the drug partitioning in the internal fractal structure at equilibrium, scale like the fractal volume v, $v_f \propto M$. In other words, the proportionality between v_f and M is the result of the universal character of the allometric scaling laws which are so pervasive in biology (7). The data of Table II indicate that the same scaling law was also found for the various volume terms of drug distribution. In fact, these hypothetical volumes of compartmental nature can be considered as subsets of the fractal volume v. Since the estimates of these volume terms have been derived from a common pharmacokinetic modeling applied in all species, it is plausible to anticipate the same scaling law for all fractal volume terms.

Although the controversy on the validity of allometric exponents continues to be vivid (32–34), the results of the present study explicitly indicate that the fractal volume scales proportionally to mass. This verifies the theoretical expectation (7) and is in accord with a recent study (35) which compared the predictive performance of allometric models having allometric exponents estimated freely or constrained to theoretical expected values (1 for volume).

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