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Research Article

A Fractal Approach to Heterogeneous Drug Distribution: Calcium Pharmacokinetics

Panos Macheras[1,2]

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Purpose. To point out the importance of heterogeneity in drug distribution processes and develop a noncompartmental approach for the description of the distribution of drug in the body.
Methods. A dichotomous branching network of vessels for the arterial tree connected to a similar venous network was used to describe the heterogeneity of blood flow in the successive generations of the networks. The relevant kinetics of drug distribution in the well perfused and the deep tissues was considered to take place under well stirred (homogeneous) and understirred (heterogeneous) conditions, respectively.
Results. A "homogeneous model" with classical kinetics (which is mathematically equivalent with the one-compartment model) was developed for these drugs which are confined to well perfused ("well stirred") spaces. A "heterogeneous model" was proposed for the drugs reaching understirred spaces using a decreasing with time rate coefficient (fractal kinetics) to model the diffusion of drug under heterogeneous conditions. The analysis of the model equations revealed that the homogeneous model can be considered as a special case of the heterogeneous model. Concentration-time plots of multiexponential type were generated using the heterogeneous model equation. The empirically used power functions of time for the analysis of calcium clearance curves, were found to be similar to the equation adhering to the heterogeneous model. Fittings comparable to multiexponential models were obtained when the heterogeneous model equation with only one adjustable parameter was applied to six sets of long period calcium data.
Conclusions. The heterogeneous processes of drug distribution in the body can obey the principles of fractal kinetics. Calcium clearance curves were analysed with the heterogeneous model. The validity of multicompartmental models which are based on the concept of homogeneity to describe drug distribution should be reconsidered.

KEY WORDS: fractal; fractal kinetics; calcium kinetics; heterogeneity; drug distribution; pharmacokinetics.

Pharmacokinetics has been based primarily on the concept of homogeneity. The simplest model, the one-compartment model, relies on the assumption of an instantaneous distribution equilibrium reached after drug administration. In essence, the drug is considered to be distributed uniformly throughout the whole organism. Since the body is composed of a heterogeneous group of tissues, more complicated models (multicompartment models) in which various tissues with hypothetically similar distribution equilibration properties are grouped together, have been conceived (1, 2). Again, homogeneity in the drug concentration for each one of the compartments of the model is the prevailing concept.

In order to overcome some of the drawbacks of the compartment models, attempts were made to define the disposition patterns of drugs in terms of physiological principles. Thus, the distribution of drug was considered to be dependent on the perfusion of the body tissues and the physiologic pharmacokinetic models were developed (3). Once again, a homogeneous concentration-time profile is conceived for each one of the "organs or tissues" of the model during the time course of drug in the body.

All these models for the distribution of drugs are based on the concept of homogeneous, well stirred[3] compartments and are described mathematically by systems of linear differential equations which when solved result in the well known sums-of-exponentials concentration-time curves. The simplified notion of the homogeneous compartment has been questioned in literature several times and attempts have been made to describe more realistically the heterogeneous character of drug distribution in the body (4–7). Wise (4) reported a great number of concentration-time curves which can be described by negative power law models. Although his approach is empirical, the fits of these models to the data were comparable or even better than the sums of exponential model. Additionally, Wise and Borsboom (5) used power functions of time to describe

[1] Laboratory of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Athens, Panepistimiopolis, Athens 15771, Greece.
[2] To whom correspondence should be addressed.

[3] Throughout this work the concept of stirring is related exclusively to the topological constraints posed by the structure and not to external sources of mixing.

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amiodarone and calcium clearance curves. Another approach based on semi-Markov process models with Erlang transit times has been used for systems with nonhomogeneous "poorly stirred compartments"(6). Moreover, a non-Markovian model has been used to describe the complex calcium kinetics in blood plasma (7). However, these two approaches (6, 7) despite their stochastic character maintain the compartmental notion.

This paper considers a novel approach for the description of the distribution of drug in the body. The approach used, relies on fractal vascular networks models for flow heterogeneity (8, 9). This form of the microvascular network is linked with the local blood flow (8, 9); hence, homogeneous and heterogeneous conditions can be conceived for well stirred or understirred spaces, respectively. The analysis of models developed is based on classical kinetics e.g first-order for well stirred spaces and fractal kinetics (10, 11) for "poorly stirred" heterogeneous spaces.

THEORY

Standard Compartmental Modeling

In classical kinetics the interchanges of drug between compartments obey first-order kinetics and complete and instantaneous mixing within each compartment is assumed. The mathematical expression for the concentration(C)-time(t) curve in any compartment has the familiar form of the sums of exponentials:

$$C = \Sigma_i A_i e^{-\lambda_i t} \quad (1)$$

The key principle of compartmental modeling is the homogeneity throughout each of the compartments of the model.

Power Functions of Time

Several reports in literature (4, 7, 12) have shown that radiocalcium clearance curves from plasma can be described by the expression:

$$C \sim (A/t^{\gamma})e^{-\alpha t} \quad (2)$$

Calcium concentration data collected up to 200 h are nicely modeled (7) by Eq. 2 while the initial data up to 10 h can be modeled by the simplified function

$$C \sim A/t^{\gamma} \quad (3)$$

It should be noted that Eqs. 2 and 3 are not valid for $t = 0$ (7). Eq. 2 has been also shown to describe adequately a large number of clearance curves of various drugs (4). Besides, amiodarone plasma concentration data collected over a long period of time (50 days) were described by two power functions of time (5). In this article (5), radiocalcium curves exhibited the same behaviour and they were surprisingly like the amiodarone curves.

Microvascular Fractal Network

Mandelbrot (13, 14) was the first to describe and analyse the structured irregularity of the natural world. He coined the term *fractal* to denote structures in space and processes in time with multiple scale properties. The wide importance of fractals in physiology relies on the need for an understanding of many fractal objects and processes found in living things (9, 15, 16). The concept of fractals is new in the field of pharmaceutical sciences (17).

According to Mandelbrot (14) fractal bifurcating networks mimic the vascular tree. Based on this observation, van Beek et al (8) developed dichotomous branching fractal network models to explain the regional myocardium flow heterogeneity. Even though the developed models give overly simple descriptions of the fractal network, they proved to be adequate to describe the dependence of the relative dispersion of the flow distribution on the size of the supplied region of myocardium (8). These findings allow someone to infer that such fractal approaches would be useful in describing other systems with heterogeneous flow distributions.

Building on the work of van Beek et al (8) a dichotomous branching network of vessels representing the arterial tree connected to a similar venous network can be used to describe the distribution of drug in the body, Fig. 1. The key feature of the network is the continuous bifurcation of the parent vessels for many generations of branching. Each parent vessel generates two daughter branches of different sizes in which fractions g_i and $1\text{-}g_i$ of the flow entering the bifurcation are distributed to daughter branches. Thus, a distribution of flow is created down the vascular tree. Van Beek et al (8) examined different schemes for determining g_i from the experimental data of baboons and sheep myocardium. Regardless of the scheme considered (8), the average flow in the vessels of the ith generation is equal to $(1/2)^i F_0$ where F_0 is the flow at the origin of the network. This is an important finding for our purposes since it signifies the exponential reduction of flow in all successive generations down the vascular tree. For example, the flow after only 8 generations becomes $\sim 0.004F_0$. It is also interesting to note that at the terminal arteriolar endings of the heart, "arterioral bursts" or "flowers" are formed which feed a multitude of capillaries (9). The latter are not a part of the network but may be regarded as a swamp.

Other studies (18, 19) have also shown that the dimensions for vessel radii, branch length and wall thickness in the mesenteric and renal arterial beds have fractal properties. Thus, the general pattern of the distribution of flow can be also assumed for the complete vascular system of Fig.1 envisaged for the distribution of drugs in the body. The flows will diverge in the arterial tree and converge in the venous tree while at the ends of the arterial and venular ends of networks the local flow will be slow and heterogeneous.

Homogeneous-heterogeneous Distribution Models

In the light of the networks and flow considerations, the distribution of drugs in the body can be classified into two broad categories. The distribution process of the drugs of the first category takes place under homogeneous ("well stirred") conditions. For the second category of drugs a significant part of the distribution process operates under heterogeneous ("understirred") conditions. From a kinetic viewpoint, the distribution of the first category of drugs can be described with classical kinetics while fractal kinetics (10, 11) should be applied only for the heterogeneous part of the distribution processes of the second category of drugs. Drugs of the first category have physicochemical properties and permeability characteristics which allow them to leave the arteriole network

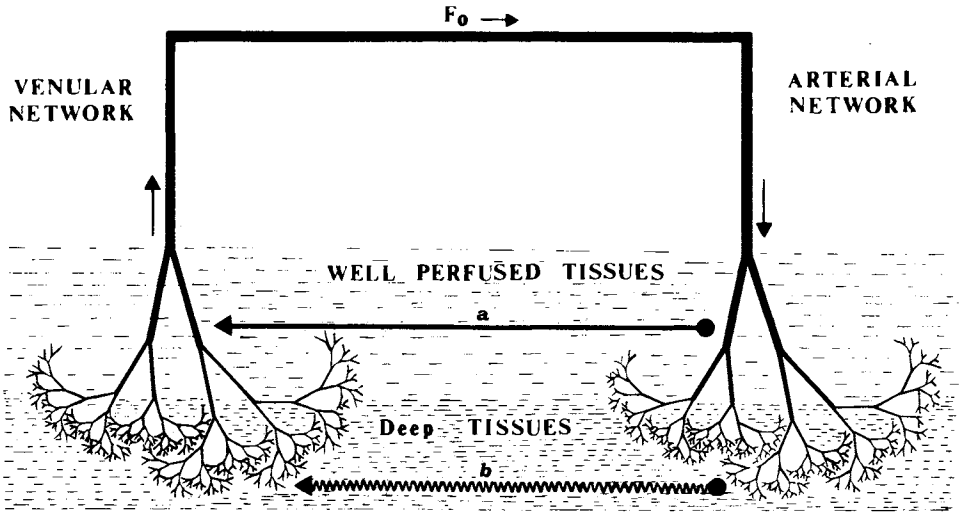

Fig. 1. A complete vascular dichotomous network used to describe the distribution of drug in the body. F_0 is the total blood flow. The black circle represents the drug. (a) The distribution of drug in well perfused tissues takes place under homogeneous (well stirred) conditions. (b) The distribution of drug in deep tissues takes place under heterogeneous (understirred) conditions. For the sake of clarity the system is oversimplified; in reality, the arterial and venular networks are scattered in three-dimensional space while venules travel with arterioles through much of the network.

and diffuse to the adjacent tissues under conditions of flow which ensure complete mixing, Fig 1a. These drugs reach only the well perfused tissues and return rapidly to the venular draining network. The disposition of this category of drugs can be modeled with the "homogeneous model" which is identical mathematically with what we call "one compartment model". Obviously, the drug molecules obeying the homogeneous model permeate the walls of vessels prior to their arrival at the hugely dense ending of networks; thus, the upper part of the vascular system and the well perfused adjacent tissues comprise a homogeneous well stirred "compartment".

Based on the considerations of flow in the network, it is reasonable to argue that in close proximity with the terminal arterioral ending, the blood flow and drug diffusion in the adjacent deep tissues will be so slow that the principle of the well mixed system will not hold any more. Consequently, if a large portion of drug is still confined in the arterial system near its ending, the drug diffusion in the deep tissues will operate under heterogeneous (understirred) conditions, Fig 1b. If such conditions prevail, the rate constant of drug movenent in the tissues is not linearly proportional to the diffusion coefficient (D) of the drug (10, 11). A better description of transport limitations can be based on the principles of diffusion in disordered media (20).

It has been shown (21) that in disordered media the value of the first-order kinetic rate constant is related to the geometry of the medium. In these media the diffusional propagation is hindered by its geometrical heterogeneity which can be expressed in terms of the fractal and fracton dimensions. For our purposes, the propagation of the drug's diffusion front in the heterogeneous space of tissues can be viewed as a diffusion process in a disordered medium. Both the diffusion coefficient of drug and the kinetic rate constant are dependent on the position of the radial coordinate of the diffusion front and therefore both parameters are time dependent. In these lower dimensional systems, diffusion is inhibited because molecules can not move in all directions and constrained to locally available sites. The result is what Kopelman has termed "fractal kinetics" where the rate constant depends on time (10, 11). In classical kinetics which is applied to homogeneous solutions (well stirred media), the rate constant is independent of time. In understirred media, where processes take place in a low dimensional space, the rate constant is time-dependent at all times (10, 11). For these heterogeneous processes, the time dependency of the rate coefficient, k, is expressed by

$$k = k_1 t^{-h} \qquad (t > 1) \tag{4}$$

where k_1 is a constant with units $(\text{time})^{h-1}$ and h is a pure number with values in the range $0 \leq h \leq 1$. According to Kopelman (10, 11), k depends on time since $h \neq 0$ in nonhomogeneous spaces; however, in three dimensional homogeneous spaces $h = 0$ and therefore $k = k_1$ i.e classical kinetics prevail and the rate constant does not depend on time. The minus sign in Equation 1 is used to mimic the decrease of the rate coefficient, k, with time as the walker (drug) has progressively less successful visits (10, 11). However, rate coefficients which monotonically increase with time have been also used (22). In recent years fractal kinetics has been applied in various fields of research (22–28).

Transport limitations of drug in tissues have been dealt with so far with the flow or membrane limited physiological models (3) which maintain compartmental and homogeneity concepts. In this work, albeit not specifying transport limitations, the approach developed relies on the more realistic heterogeneous conditions of drug diffusion. Thus, for the model depicted in Fig.1b, the diffusion of drug can become partially constrained by either the walls of the vessels at the arterial and venular endings or the phase boundaries (e.g interstitial fluid and cell membrane, liquid-solid as in the case of blood and bone). Hence, the rate "constant" of drug diffusion in the tissues, k_d, under these heterogeneous conditions, will exhibit time dependency and will in reality be a coefficient. Plausibly, this dependency is associated with the spatial arrangement and the composition of the heterogeneous

space reached by the drug. In this study, a decreasing distribution rate coefficient, k_d was postulated:

$$k_d = k_1 t^{-h} \qquad 0 \le h \le 1 \qquad (t > 1) \tag{5}$$

Eq. 5 has the classical form of Eq. 4 for fractal kinetics introduced by Kopelman (10, 11). The above considerations for the drugs following the heterogeneous route of Fig. 1b were used for the formulation of the "heterogeneous model" depicted in Fig. 2. This model describes the disposition of the second category of drugs after time τ which corresponds to the time required for the establishment of heterogeneous conditions i.e the drug has reached the heterogeneous spaces. Prior to time τ, a portion[4] of the administered dose is eliminated from the body and the kinetics of drug from time zero to time τ can be described with the homogeneous model which is mathematically equivalent to the one-compartment model since homogeneity is again the prevailing concept and classical kinetics apply, i.e.,

$$(dC/dt) = -k_{out}C \qquad 0 \le t \le \tau \tag{6}$$

After time τ, the slow diffusion of drug in the heterogeneous space becomes rate limiting to elimination, Fig. 2, and the kinetics is governed by the rate coefficient k_d:

$$(dC/dt) = -k_dC \qquad (\tau \le t) \tag{7}$$

Substituting k_d from Eq. 5 into Eq. 7 and integrating the resulting equation from $t = \tau$ to $t = t$, one has

$$\int_{C_\tau}^{C} \frac{dC}{C} = -k_1 \int_{\tau}^{t} t^{-h}dt$$

or

$$\ln C - \ln C_\tau = -k_1(t^{1-h} - \tau^{1-h})/(1 - h)$$

which can be written in exponential form

$$C = C_\tau \exp - [k_1(t^{1-h} - \tau^{1-h})/(1 - h)] \tag{8}$$

where C_τ is the drug concentration in plasma at time τ.

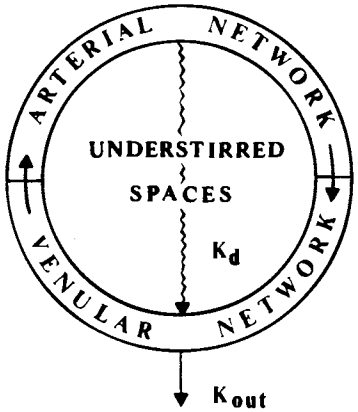

Fig. 2. The heterogeneous model. The drug diffuses to deep (understirred) spaces where heterogeneous (understirred) conditions are prevailing. The wavy arrow denotes the diffusion of drug in the heterogeneous spaces and k_d is the coefficient of fractal kinetics applied; k_{out} is the elimination rate constant.

[4] This portion depends on the amount of drug which permeates the upper part of the arterial network and the drug's elimination rate constant.

RESULTS AND DISCUSSION

The two routes of drug movement in the tissues shown in Fig. 1 provide a pictorial view of the spatial arrangement of the well perfused and the deep tissues as well as an explanation for the kinetic differences (classical versus fractal) of the two categories of drugs. For example, if the average spatial location of the well perfused and the deep tissues is in the neighbourhood of the 8th and 15th bifurcation of the model in Fig. 1, respectively, a ~100 relative reduction of the mean blood flow can be estimated from the equation $(1/2)^1F_0$ used by van Beek et al (8) for the blood flow in the dichotomous fractal network of myocardium. Similar magnitudes of relative blood flows have been used in physiological modeling (29).

The homogeneous model can also be considered as a limiting case of the heterogeneous model since for $h = 0$ in Eq. 5 the time dependency of the rate constant k_d is abolished. This can also be seen graphically in Fig. 3A where concentration versus time plots are presented for various values of the exponent h in Eq 8. The curves of Fig. 3A demonstrate that the typical monoexponential decline of concentration-time plots is observed as the value of h approaches zero. On the contrary, the shape of the curves resembles the polyexponential type of curves when the values of h deviate considerably from zero, Fig. 3A. In parallel, the corresponding log-log plots of the same data are concaving downward curves with decreasing curvature as the value of h deviates from zero, Fig. 3B. This form of log-log plots has also been generated by Wise (4) using the empirical Eqs. 2 and 3 and is the focal point for the consideration of homogeneity and heterogeneity of distribution in previous studies (4, 5). Recently, the same form of log-log plots in outflow concentration-time curves was observed after i.v bolus injection of ^{15}O-water into the arterial inflow of blood perfused rabbit hearts (30). According to the authors, these results were obtained since the vascular structures, the regional flow and the kinetics are all fractal (30).

Fig. 4 illustrates the properties of the fractal model when compared to multiexponential models using simulated data. The good fittings of multiexponentials to the three sets of theoretical data generated from Eq. 8, demonstrate that multiexponentials can describe clearance curves obeying the fractal model, Fig. 4. These findings are in full agreement with previous observations (5) in regard to the relevance of sums of exponentials and power functions of time.

Applications to Calcium Data

The analysis of calcium data (4, 5, 7) is routinely based on the empirical Eqs. 2 and 3. In fact, calcium is the classical example of "anomalous" kinetics and therefore heterogeneous kinetics is suspected (4, 5). A starting point for the consideration of calcium kinetics is Eq. 2; taking the derivative of Eq. 2 in respect to time:

$$(dC/dt) = -A\gamma(t^{-\gamma-1})e^{-\alpha t} - A\alpha(t^{-\gamma})e^{-\alpha t} \tag{9}$$
$$= -(A/t^{\gamma})e^{-\alpha t}(\alpha + \gamma t^{-1})$$

which can be written more conveniently using Eq. 2:

$$(dC/dt) = -(\alpha + \gamma t^{-1})C \tag{10}$$

This treatment reveals that the derivation of the empirical Eq.2 for calcium kinetics can be based on Eq. 10 which adhers to

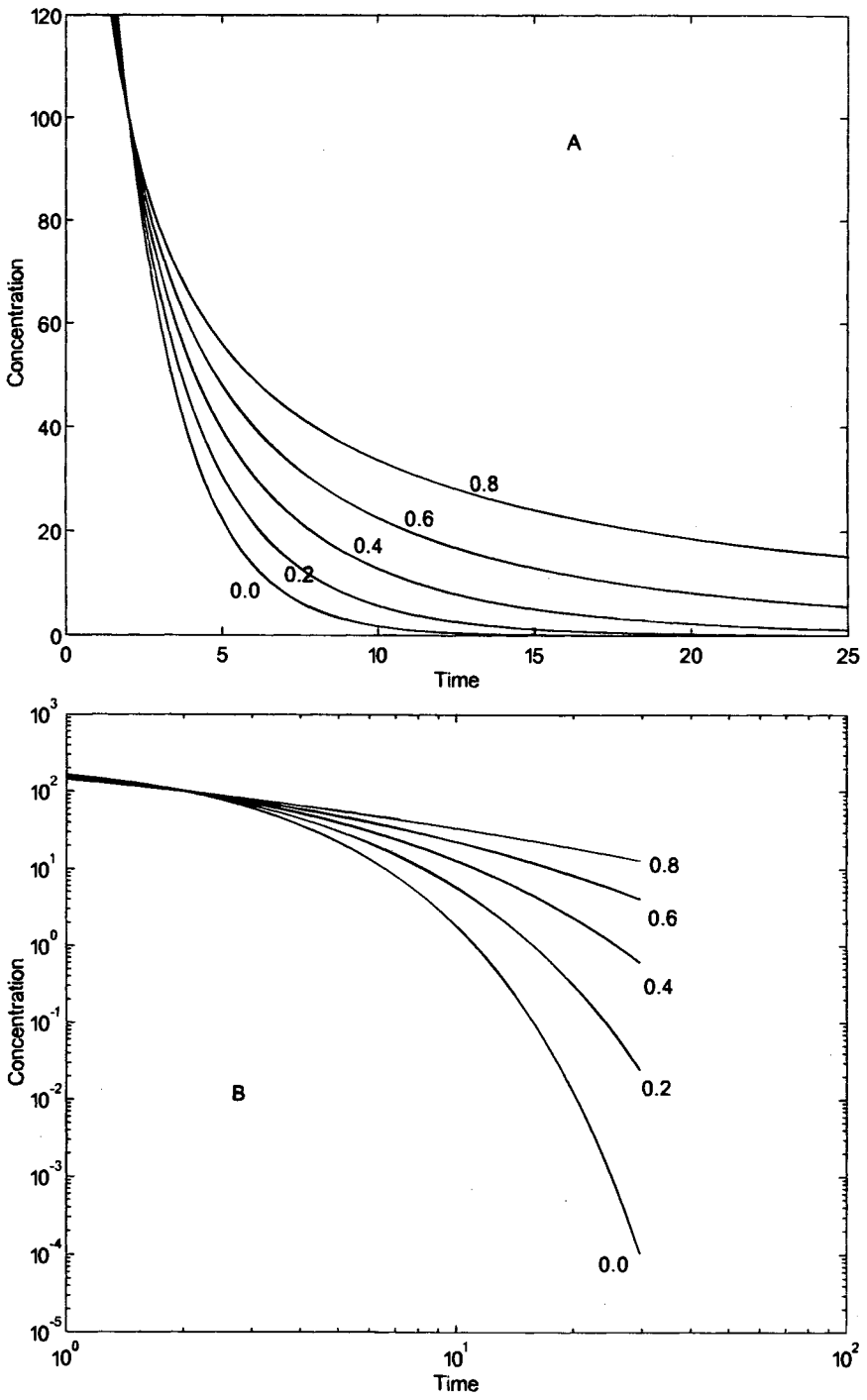

Fig. 3. (A) Concentration-time plots generated from Eq. 8 using $C_\tau = 100$, $k_1 = 0.5$, $\tau = 2$, and various values of h shown. (B) The corresponding log-log plots.

a model with i.v bolus administration and two non-reversible pathways of elimination, the first of which (the term α) obeys first-order kinetics while the second (γt^{-1}) has the features of classical fractal-like kinetics.

In a similar manner one can also prove that Eq. 3 can be derived from Eq. 11:

$$(dC/dt) = -\gamma t^{-1} C \qquad (11)$$

The only difference between Eq. 11 and Eq. 7 lies on the exponent of time (see Eq. 5). These observations allow someone to infer that the empiricaly used Eqs. 2 and 3 for the analysis of calcium clearance curves, are relevant to Eqs. 6 and 7 and the accompanying kinetic considerations of this study.

According to the theory developed, the kinetics of calcium flow out from plasma to urine is first-order when most of the calcium ions are still in the upper part of the vascular system. Subsequently, and after this initial phase, the diffusion of calcium in the deep tissues and its reversible binding to bone

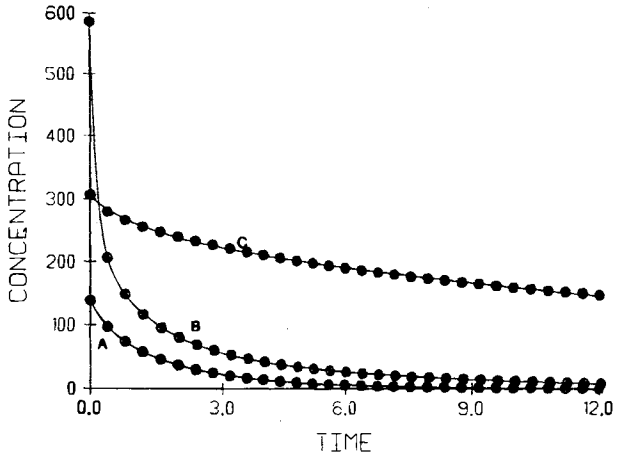

Fig. 4. Exponential fits to theoretical data generated from Eq. 8 using: (A) $C_\tau = 50$, $k_1 = 0.6$, $\tau = 1.5$, and $h = 0.2$; the fitted line corresponds to the equation:

$$C = 59.56\exp(-0.903t) + 62.75\exp(-0.395t) + 18.78\exp(-4.306t),\ r^2 = 1.0$$

(B) $C_\tau = 100$, $k_1 = 0.6$, $\tau = 1.5$, and $h = 0.6$; the fitted line corresponds to the equation:

$$C = 145.18\exp(-0.630t) + 52.86\exp(-0.136t) + 385.60\exp(-4.485t),\ r^2 = 0.99999.$$

(C) $C_\tau = 250$, $k_1 = 0.1$, $\tau = 1.5$, and $h = 0.4$; the fitted line corresponds to the equation:

$$C = 56.85\exp(-0.821t) + 248.88\exp(-0.045t),\ r^2 = 0.99999.$$

The fittings were performed with the program MINSQ (31).

Table I. Personal Details of Subjects Provided by Dr. Goans

Subject	Age-Gender-Status
1	33-Female-Normal
2A[a]	28-Female-Third semester of pregnancy
2B[a]	28-Female-Post-partum lactation
2C[a]	28-Female-Normal
3	5.9-Child-Normal
4	26-Male-Normal

[a] Subject 2 is the same in three different experiments.

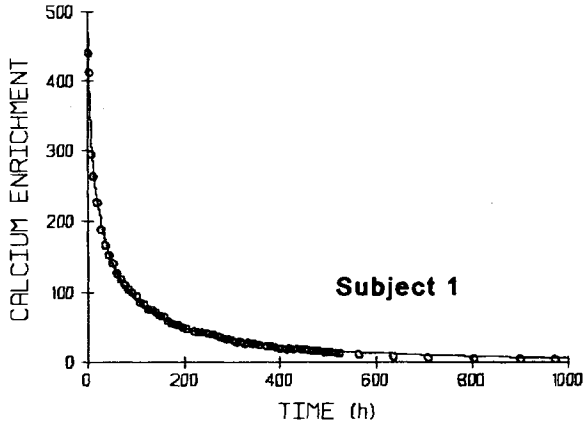

Fig. 6. The fit of Eq. 8 to the concentration-time data of calcium for the subject 1. The fitting was performed with the program MINSQ (31).

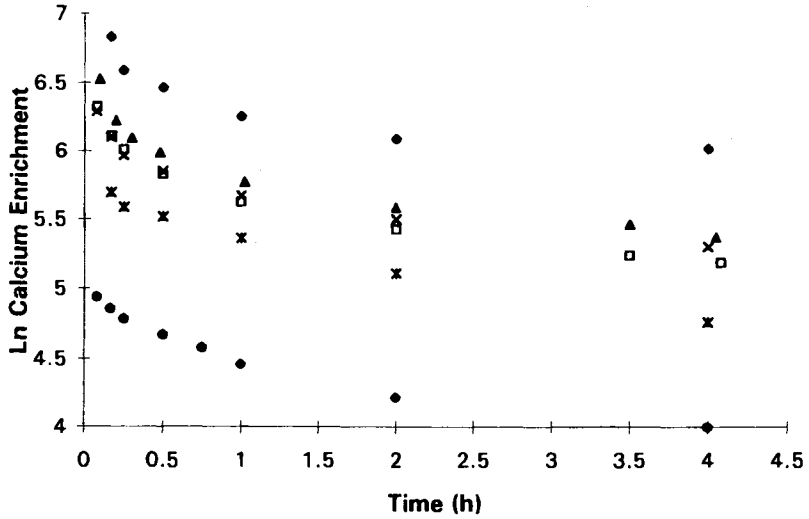

Fig. 5. Semilogarithmic plot of the initial data points of six subjects in Table I. Key (subject): ◆1, □2A, ▲2B, X2C, *3, ●4.

obeys fractal kinetics (Eq. 8) and progressively becomes rate limiting to elimination. The fractal formalism in calcium clearance can be associated with the hydrodynamics prevailing in the tissues and the reaction space, i.e., the uptake of calcium from the bone and its subsequent dissociation can be heterogeneous.

In order to verify the fitting of Eq. 8 to experimental results, the methodology was applied to six sets of long period i.v. calcium data, Table I, provided by Dr. R. E. Goans from the Oak Ridge Institute for Science and Education, USA. Firstly, a semilogarithmic plot was constructed using the data with $t \leq 4$h, Fig. 5. Linear regression analysis of the early data points with $t \leq 0.5$h resulted in the following half-life (ln2/slope) values: 0.72, 0.62, 0.52, 0.71, 1.48, and 1.13 h for subjects 1A, 2A, 2B, 2C, 3, and 4, respectively. Females (subjects 1A, 2A, 2B, and 2C) exhibit a remarkably consistent initial "homoge-

Table II. Parameter Estimates ±SD for the Curve Fitting of Eq. 8 to the Data of Table I Along with the Multiexponential Fitted Equations to the Same Data

Subject	N[a]	C_τ	h	$K_1(h)^{h-1}$	r^2	MSC[b]
1	72	502.26 ± 6.48	0.647 ± 0.011	0.150 ± 0.006	0.998	5.51
C = 38.44 ± 15.38exp(−0.002 ± 0.0007t) + 293.57 ± 8.46exp(−0.116 ± 0.007t) + 178.31 ± 12.03exp(−0.010 ± 0.001t)					0.998	5.71
2A	75	240.32 ± 2.48	0.546 ± 0.011	0.128 ± 0.005	0.998	6.06
C = 52.80 ± 3.14exp(−0.007 ± 0.0003t) + 173.28 ± 13.67exp(−0.562 ± 0.042t) + 126.81 ± 2.73exp(−0.034 ± 0.001t)					0.999	7.02
2B	66	283.65 ± 3.84	0.560 ± 0.014	0.122 ± 0.006	0.998	5.62
C = 96.08 ± 6.19exp(−0.007 ± 0.0003t) + 143.19 ± 16.47exp(−0.417 ± 0.073t) + 120.54 ± 6.67exp(−0.043 ± 0.005t)					0.998	6.01
2C	109	253.08 ± 4.56	0.542 ± 0.017	0.086 ± 0.006	0.993	4.43
C = 71.85 ± 12.53exp(−0.004 ± 0.0004t) + 131.23 ± 9.40exp(−0.188 ± 0.029t) + 90.74 ± 10.06exp(−0.015 ± 0.003t)					0.995	4.78
3	30	196.13 ± 7.45	0.607 ± 0.041	0.239 ± 0.026	0.994	4.44
C = 134.35 ± 10.64exp(−0.161 ± 0.026t) + 63.93 ± 10.14exp(−0.021 ± 0.003t)					0.992	4.13
4	8	78.28 ± 4.14	0.831 ± 0.079	0.219 ± 0.045	0.998	3.91
C = 47.22 ± 3.88exp(−0.283 ± 0.042t) + 41.48 ± 1.52exp(−0.009 ± 0.0007t)					0.999	5.20

[a] Number of observations.
[b] Model Selection Criterion (31).

neous" elimination phase with a mean half-life 0.64±0.09h while subjects 3 (child) and 4 (male) have higher half-lives i.e., 1.48 and 1.13h, respectively. These findings reveal an initial rapid "homogeneously" declining phase for all subjects. However, the visual inspection of the semilogarithmic plots in Fig. 5 indicates that this phase ceases between 0.5 and 1.0h for the majority of subjects and certainly does not last longer than 2.0h for all subjects. Based on these observations, all data points with $t \geq 2.0$h for all subjects were considered to obey the heterogeneous model while the commencement of fractal kinetics was chosen to be 1.0h as the most reasonable estimate for all subjects studied. Accordingly, the value of τ in Eq. 8 was adjusted to 1.0h and Eq. 8 was fitted to all sets of experimental data utilising all data points with $t > 1$h. A representative example of fitting is shown in Fig. 6. The fractal approach reveals a pattern in a whole set of curves and simultaneously provides physiologically meaningful estimates for the model parameters, Table II. Table II lists also the nonlinear least squares regression equations of exponential fittings to the same sets of data. Both approaches gave very good fittings. According to the values of the model selection criterion (31), Table II, the multiexponentials came out slightly better than the fractal model in the majority of cases. However, three as well as two compartment models were utilised to describe calcium kinetics in the subjects studied with four and six estimated parameters, respectively. In contrast, using the fractal model all sets of curves were fitted with three estimated parameters.

A more sophisticated analysis could be also applied for the analysis of calcium data using separate functions for each phase combined with the concept of continuity (5). In such a case, five parameters (k_{out}, τ, k_1, h, and C_0 the plasma concentration at time zero) define the curve and some of them might need to be regarded as adjustable parameters while fitting irregularities can be encountered. Instead, the approach chosen relying on simple computation requires only one adjustable parameter (τ). It can be anticipated, however, that this first application of fractal kinetics to drug distribution will be further developed in future studies depending on a drug's pharmacokinetic characteristics.

CONCLUSIONS

Based on the notion of microvascular fractal networks, a physiologically realistic model was developed for the description of drug distribution in the body. Recent studies indicate that many *in vivo* processes can be fractal (24, 26, 28, 30). In accord with these recent findings and in the same vein with previous studies (4, 5, 7), the present work strongly supports the heterogeneous character of drug disribution. The results of the present study substantiate the view that the application of fractal kinetics for the diffusion of drug in the heterogeneous spaces of the body provides a theoretical justification for the empirical mathematical relationships used for a long time to describe calcium clearance curves (4, 5). Finally, it should be emphasized that multiexponentials (Eq. 1) can be nicely fitted to data generated from Eq. 8 as shown in Fig. 4. This is again an indication as well as a warning that actual heterogeneous processes can be conceived and explained in terms of the existing theory of the homogeneous compartments.

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