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Research Paper

Residence Time Dispersion as a General Measure of Drug Distribution Kinetics: Estimation and Physiological Interpretation

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Purpose. To evaluate distribution kinetics of drugs by the relative dispersion of disposition residence time and demonstrate its uses, interpretation and limitations.
Materials and Methods. The relative dispersion was estimated from drug disposition data of inulin and digoxin fitted by three-exponential functions, and calculated from compartmental parameters published for fentanyl and alfentanil. An interpretation is given in terms of a lumped organs model and the distributional equilibration process in a noneliminating system.
Results. As a measure of the deviation from mono-exponential disposition (one-compartment behavior), the relative dispersion provides information on the distribution kinetics of drugs, i.e., diffusion-limited distribution or slow tissue binding, without assuming a specific structural model. It also defines the total distribution clearance which has a clear physical meaning.
Conclusion. The residence time dispersion is a model-independent measure that can be used to characterize the distribution kinetics of drugs and to reveal the influence of disease states. It can be estimated with high precision from drug disposition data.

KEY WORDS: diffusion; distribution; pharmacokinetics; residence time; tissue binding.

INTRODUCTION

The normalized variance (relative dispersion) of disposition residence time has been proposed as a measure of distribution kinetics of drugs in the body several years ago (1–3). Nonetheless, the conventional concept of intercompartmental clearances still dominates in pharmacokinetics despite the drawback that these compartments lack physiologic reality and distribution parameters cannot be interpreted in terms of underlying transport mechanisms. The reasons may be that the physiological interpretation of relative dispersion remains unclear [or is even denied (4)] and its estimation from disposition data is regarded as unreliable. The purpose of the study reported in this paper is therefore twofold: (a) to explain the information that is provided by residence time dispersion on transcapillary transport (permeation) or tissue binding kinetics, and (b) to estimate this model-independent measure from drug disposition data fitted by polyexponential functions or compartmental models. Equations relating the relative dispersion to the intrinsic parameters of tissue distribution kinetics are based on recently published lumped organ models (5, 6). The approach is applied to inulin, fentanyl, alfentanil and digoxin to illustrate the usefulness and limitations of the approach.

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THEORETICAL

Residence Time Distribution

If an amount of drug molecules (dose D_{iv}) is instantaneously injected intravenously, each molecule will spend a time t in the body until it is eliminated (the disposition residence time of that molecule). In statistical terms, the residence time distribution, $F(t)$, is defined by the fraction of molecules which have a residence time less than t. This fraction is given by

$$F(t) = A_e(t)/D \tag{1}$$

where $A_e(t)$ is the cumulative amount of drug eliminated up to time t. $F(t)$ is a monotonically increasing function with $F(0) = 0$ and $F(\infty) = 1$. Assuming that the elimination rate is proportional to the measured concentration $C(t)$,

$$dA_e(t)/dt = CL\,C(t) \tag{2}$$

we get the density of the probability distribution, $f(t) = dF(t)/dt$, as

$$f(t) = C(t)/\mathrm{AUC} \tag{3}$$

with $\mathrm{AUC} = \int_0^\infty C(t)dt$. It is important to note that the use of Eq. 3 is dependent on the validity of Eq. 2 which implies a structural assumption, namely that elimination occurs from a

well-mixed sampling compartment. Thus, in the present context, the term "model independent" will be used to indicate that the approach is independent of a specific compartmental model or empirical disposition function, while retaining the validity of Eq. 2. This does not limit the generality of the approach, in so far as Eq. 2 underlies clearance estimation in pharmacokinetics (in integrated form $CL = D_{iv}/\mathrm{AUC}$). Note further that any monotonically decreasing disposition function, $C(t)$, implies a well-mixed sampling compartment.

The mean and variance of disposition residence time, MDRT and VDRT, as the two most important measures, are defined in terms of moments of $f(t)$ as summarized in the Appendix. The normalized (dimensionless) variance

$$\mathrm{RD}_D^2 = \frac{\mathrm{VDRT}}{\mathrm{MDRT}^2} \tag{4}$$

will be called "relative dispersion."

Physiological Interpretation of Relative Dispersion

Since it is well known that the mean disposition residence time determines the steady-state distribution volume, V_{ss} = MDRT CL, it will be not surprising that higher moments provide information on the dynamics of drug distribution in the body. In a well-mixed system, the probability of leaving the system is identical for all molecules independent of their individual life times and the residence time distribution is an exponential distribution characterized by $\mathrm{RD}_D^2 = 1$. Thus, for any monotonically decreasing disposition curve, $\mathrm{RD}_D^2 - 1$ acts as a measure of deviation from the well-mixed or one-compartment behavior (7). One explanation for this departure is the influence of distribution kinetics, or multi-compartment behavior, i.e., a deviation of RD_D^2 from unity reflects non-instantaneous mixing. Intuitively, it is plausible that when drug molecules leave the initial distribution space to stay a short or long time outside (in tissues), this will increase the variance of residence time. A model-independent explanation of the role of RD_D^2 in characterizing the whole body distribution of drugs can be given in terms of the total distribution clearance.

Total Distribution Clearance

The clearance from the initial mixing space $V_0 = D_{iv}/C(0)$ into tissues of a noneliminating system, CL_M, provides a model-independent measure of the rate of drug distribution. Thus, we define a mixing or distribution clearance of drugs in the body CL_M as (8, 9)

$$V_0 \frac{\mathrm{d}C(t)}{dt} = -CL_M[(C(t) - C(\infty)] \tag{5}$$

where $C(\infty) = D_{iv}/V_{ss}$ is the concentration at distributional equilibrium in the noneliminating system ($CL = 0$ in the pharmacokinetic model). Assuming that $V_0 \ll V_{ss}$ we obtain the following relationship after substituting $AUC_M = \int_0^\infty [(C(t) - C(\infty)]\mathrm{d}t$ (3, 8)

$$CL_M = \frac{D_{iv}}{\mathrm{AUC}_M} = \frac{2Q}{\mathrm{RD}_C^2 - 1} \tag{6}$$

where Q denotes cardiac output and RD_C^2 is the relative dispersion of circulation times. The latter is related to RD_D^2 by (10)

$$\mathrm{RD}_C^2 - 1 = \frac{Q}{CL}\left(\mathrm{RD}_D^2 - 1\right) \tag{7}$$

and the total distribution clearance is obtained as

$$CL_M = \frac{2CL}{RD_D^2 - 1} \tag{8}$$

The role of RD_D^2 as a measure of distribution kinetics becomes obvious if we write Eq. 8 as ratio of the AUC*s* in the noneliminating and eliminating system

$$\frac{\mathrm{AUC}_M}{\mathrm{AUC}} = \frac{1}{2}\left(\mathrm{RD}_D^2 - 1\right) \tag{9}$$

AUC_M quantifies the transient departure of the system from equilibrium distribution; for instantaneous mixing ($\mathrm{RD}_D^2 = 1$) equilibrium, $C(\infty)$, is attained instantaneously ($\mathrm{AUC}_M = 0$) and equilibration occurs more slowly if RD_D^2 increases. As a model-independent measure, CL_M can be also derived in terms of a mammillary compartmental model (11).

Effect of Permeation, Diffusion and Binding Kinetics

The analysis presented in the following is based on a minimal circulatory model in which all organs of the systemic circulation are lumped into one heterogeneous subsystem; it accounts for transcapillary transport and tissue diffusion and binding of drugs (5, 6). The relative dispersion of circulation times is given by (12)

$$\mathrm{RD}_C^2 = \mathrm{RD}_B^2 + \left(\frac{1}{1 + V_B/V_T}\right)^2 \frac{Q}{CL_{\mathrm{BT}}}\left(\mathrm{RD}_T^2 + 1\right) \tag{10}$$

where RD_B^2 denotes the relative dispersion of vascular transit times (advective dispersion), V_T/V_B is the ratio of tissue to vascular volume, CL_{BT} is the permeation clearance (blood to tissue) and RD_T^2 is the relative dispersion of tissue residence times. The assumption of monotonically decreasing disposition curves [initial mixing volume V_0 and Eq. 2] implies instantaneous intravascular mixing ($\mathrm{RD}_B^2 = 1$ and neglecting the dispersion across the lungs). Distribution within the extravascular space is not instantaneous ($\mathrm{RD}_T^2 > 1$) and we have to distinguish two opposite extremes: (a) slowing down of intratissue diffusion by quasi-instantaneous binding to tissue constituents and (b) slow binding after quasi-instantaneous distribution within the tissue space.

The case (a), where binding is rapid compared to diffusion, holds for the overwhelming majority of drugs with unspecific tissue binding (or without extravascular binding). We have recently shown that transcapillary and intratissue diffusion can be described by the parameter PS_{diff}, the apparent permeability-surface product, assuming that both the resistance of the capillary wall and tissue determine PS_{diff} (6); using the definition PS_{diff}=V_T/d (where d is relaxation

time of the diffusional equilibration process) we obtain from Eqs. 7 and 10,

$$RD_D^2 - 1 = \frac{2}{3}\left(\frac{1}{V_B/V_T + 1}\right)^2 \frac{CL}{PS_{\text{diff}}} \tag{11}$$

where PS_{diff} represents a measure averaged over all organs. Because of slower intratissue diffusion with increasing binding (13), tissue partitioning leads to lower PS_{diff} values.

Thus far, we have only one example for the case (b), the slow binding of digoxin to skeletal Na,K-ATPase (5). Then RD_T^2 in Eq. 10 is determined by the tissue binding and unbinding rate constants k_{on} and k_{off}, respectively, and the relative dispersion is given by (13)

$$RD_D^2 - 1 = \left(\frac{1}{V_B/V_T + 1}\right)^2 \frac{CL}{V_{IS}} \frac{2k_{\text{on}}}{(k_{\text{on}} + k_{\text{off}})^2} \tag{12}$$

where V_{IS} denotes the interstitial space and V_T the tissue distribution volume, $V_T = V_{\text{IS}}\,(1 + k_{\text{on}}/k_{\text{off}})$.

Estimation of Relative Dispersion

Since any monotonically decreasing disposition function, $C(t)$, can befitted by a sum of exponentials (7)

$$C(t) = \sum_{i=1}^{n} B_i e^{-\lambda_i t} \tag{13}$$

we obtain RD_D^2 in terms of the estimated curve parameters as [cf. Eqs. 4, 18 and 19]

$$RD_D^2 = \frac{2\sum_{i=1}^{n} \frac{B_i}{\lambda_i^3} \sum_{i=1}^{n} \frac{B_i}{\lambda_i}}{\left(\sum_{i=1}^{n} \frac{B_i}{\lambda_i^2}\right)^2} - 1 \tag{14}$$

Three-exponential functions were fitted to disposition data of digoxin (14) and inulin (15) using ADAPT II (16) and maximum likelihood analysis with the variance model $\text{VAR}_i = [\sigma_0 + \sigma_1 C(t_i)]^2$, where VAR_i is the variance of the ith data point and $C(t_i)$ is the model prediction. Note that from the inulin $C(t)$-data (15) only the decreasing part was used. The quality of RD_D^2 estimates was evaluated by their approximate coefficients of variations (CVs).

Alternatively, if disposition curves have been analyzed by a mammillary compartmental model, one obtains from CL_M (11) and Eq. 8,

$$RD_D^2 = 2\sum_{i=1}^{N} \left(\frac{V_i}{V_{ss}}\right)^2 \frac{CL}{CL_{0i}} + 1 \tag{15}$$

where N is the number of peripheral compartments with volumes V_i and distribution clearances CL_{0i} (i.e., $N = 2$ for a three-compartmental model). It is important to note that in contrast to the sum of intercompartmental clearances, $\sum_{i=1}^{N} CL_{0i}$, the total distribution clearance CL_M has a definite physical meaning in terms of the distributional equilibration process in a non-eliminating system.

RESULTS AND DISCUSSION

The RD_D^2 values of inulin and digoxin were estimated with high precision by fitting Eq. 13 to disposition data as indicated by the mean coefficients of variation of 2 and 6%, respectively (Table I). This is in accordance with the results of Monte-Carlo simulations (17, 18), where the accuracy of estimates of RD_D^2 was equal to or better than that of CL and MDRT estimates.

Inulin

The RD_D^2 values obtained by fitting a three-exponential function [Eqs. 13 and 14] to disposition data (40 blood samples between 1 and 360 min after a bolus dose in normal and hypovolemic dogs) are shown in Table I together with the PS_{diff} values calculated by Eq. 11. For inulin, the tissue distribution volume V_T is identical to the interstitial volume V_{IS} and a ratio V_T/V_B of 6.0 and 4.6 is used for normovolemic and hypovolemic dogs, respectively (6). With a mean cardiac output of 7 and 4 l/min in these groups, the result $PS_{\text{diff}} \ll Q$ indicates that distribution kinetics of inulin is characterized by diffusion-limited uptake into the interstitial space. The removal of 30% blood volume led to a decrease in PS_{diff}, probably due to a decrease in the functional area (S) available for diffusion exchange following a systemic vasoconstrictor response to hypovolemia. That in contrast to the results obtained with the circulatory multiple indicator model (6) this decrease in PS_{diff} was not significant may be due to the model simplification involved in the present approach (neglect of the initial mixing process).

Digoxin

Figure 1 demonstrates the excellent correlation between the RD_D^2 values estimated directly from the disposition data as described above (20 blood samples between 2.5 min and 72 h after bolus injection) and the values predicted by Eq. 12 from the parameters CL, k_{on} and k_{off} estimated by fitting the circulatory model (5) to the same data sets. As in the latter paper, values $V_B = 0.071$ l/kg (19), and $V_{\text{IS}} = 0.277$ l/kg (20) were used. Since an upregulation or downregulation of the total content of sodium pumps in skeletal muscle under physiological or pathophysiological conditions would affect only k_{on} (which is proportional to the total number of receptors), Eq. 12 could be used to evaluate changes in skeletal muscular sodium pump capacity on the basis of RD_D^2 estimates,

$$k_{\text{on}} = \frac{2CL}{V_{IS}(RD_D^2 - 1)} - 2k_{\text{off}} \tag{16}$$

where we utilized that $k_{\text{off}}^2/k_{\text{on}} \ll k_{\text{on}}$ and $(1 + V_B/V_T)^{-2} \approx 1$ (5). This relationship illustrated in Fig. 2 reveals that an ≥1.5-fold increase in skeletal muscular sodium pump capacity, e.g., observed as an effect of thyroid or steroid hormones (21), could be detected by a decrease in RD_D^2.

Table I. Residence Time Dispersion, RD_D^2 , Estimated by Fitting a Three-exponential Function to the Data (Eqs. 13 and 14) and Derived Distribution Parameters, Apparent Permeability-surface Product, PS_{diff}, and Total Distribution Clearance, CL_M (Mean±SD)

Drug	Species	Study, N^a	RD_D^2	$CV(\%)^b$	PS_{diff} (l/min)^c	CL_M (l/min)^e	Ref.
Inulin	Dogs	Control, 4	1.68 ± 0.22	2.4 ± 1.3	0.098 ± 0.018	0.569 ± 0.106	(15)
		Shock, 4	2.04 ± 0.30	1.9 ± 0.8	0.063 ± 0.033	0.405 ± 0.213	(15)
Digoxin	Humans	5	1.57 ± 0.17	5.9 ± 4.7		0.740 ± 0.104	(14)

[a] Number of subjects
[b] Asymptotic coefficients of variation as measure of imprecision of individual RD_D^2 estimates
[c] Eq. 11
[e] Eq. 8

Fentanyl and Alfentanil

Lemmens *et al.* (22) published the parameters of three-exponential functions fitted to the disposition data of fentanyl and alfentanil in human volunteers. The RD_D^2 and PS_{diff} values calculated using Eqs. 15 and 11, respectively, are depicted in Table II. The fact that the intrinsic distribution clearance PS_{diff} for fentanyl is of the same order of magnitude as cardiac output suggests that its tissue distribution is blood flow-dependent. The fivefold lower PS_{diff} value for alfentanil indicates that the tissue diffusion limitation is significantly more pronounced. This is in reasonable agreement with the results of Bjorkman *et al.* (23), who studied the tissue distribution kinetics of these drugs in rats. As discussed below, these PS_{diff} values should be interpreted with caution, given the fact that distribution kinetics is not strictly diffusion limited. The results are well in accordance considering the different underlying models (Table II). Figure 3 shows that the total distribution clearance [Eq. 8] of alfentanil increases moderately with cardiac output, suggesting an intermediate situation between flow- and diffusion-limited distribution kinetics. This is also obvious by comparison with the CL_M-Q-relationships of antipyrine and inulin (6) as prototypes of drugs with flow- and diffusion-limited distribution, respectively. Note that in contrast to alfentanil, no correlation was found between the CL_M values (Table I) and Q values (15) of inulin. For alfentanil the differences in parameter estimates may be attributed to differences in experimental design. A short-term infusion used by Lemmens *et al.* (22) tends to hide distribution processes that occur more rapidly than drug input and thus led to a lower CL_M value of 0.86 l/min. Taking the differences in body weight into account, the PS_{diff} and CL_M values of fentanyl distribution in pigs calculated from compartmental parameters (25) are in accordance with those in humans (Table II). Hemorrhagic shock led to a significant decrease in distribution clearance CL_M, probably as a consequence of cardiac output reduction.

Limitations

The assumptions on distribution kinetics inherent in fitting polyexponential functions or conventional compartmental models to the data also define the limitations of the approach since the result cannot be better than the underlying data. The unrealistic assumption of rapid (quasi-instantaneous) drug distribution into $V_0 = D_{iv}/C(0)$ implies that the interpretation of residence time dispersion is limited to slower distribution processes occurring after initial distribution and determine the monotonically $C(t)$-curve. Thus, it is clear a priori that this approach cannot be applied to a drug with purely flow-limited distribution kinetics like antipyrine or thiopental. Circulatory modelling shows that the PS_{diff} of antipyrine is essentially determined by the initial distribution phase, i.e., $C(t)$-data of the first 2 min after bolus injection (6). As noted above, Eq. 11 is than not correct since the contribution of rapid initial distribution cannot be neglected [$RD_B^2 > 1$ in Eq. 10]: we have just the opposite situation,

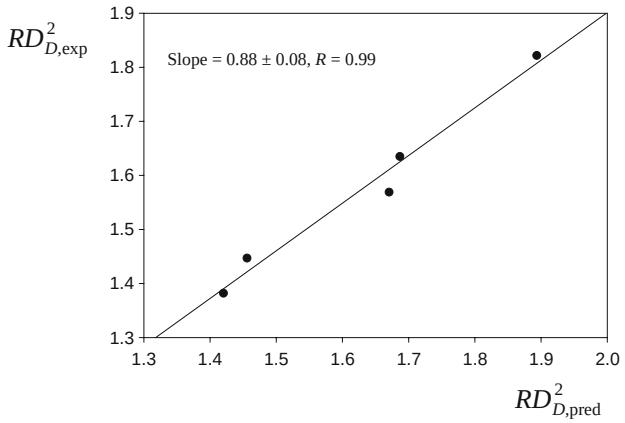

Fig. 1. Residence time dispersion of digoxin, $RD^2_{D,exp}$, estimated directly by fitting a three-exponential function to disposition data of five healthy volunteers (14) using Eqs. 13 and 14, *versus* $RD^2_{D,pred}$ predicted from the model parameters [Eq. 12] estimated by circulatory modeling (5).

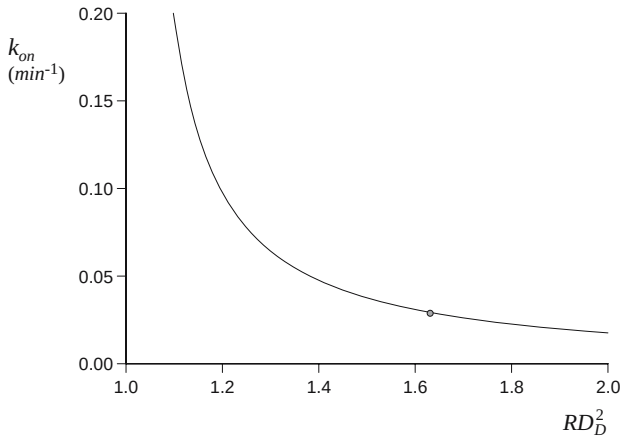

Fig. 2. Relationship between the digoxin tissue binding rate constant k_{on} and RD_D^2 [Eq. 16] for $k_{off} = 0.0012$ min^{-1}, and $CL/V_{IS} = 0.01$ min^{-1}, estimated from human data using a circulatory model (5). The point indicates the estimated k_{on} value.

Table II. Residence Time Dispersion RD_D^2 Calculated from Three Compartment Parameters (Eq. 15) and Derived Distribution Parameters, Apparent Permeability-surface Product, PS_{diff}, and Total Distribution Clearance, CL_M (Mean ± SD)

Drug	Species	Study, N^a	RD_D^2	PS_{diff} (l/min)^b	CL_M (l/min)^c	Ref.
Fentanyl	Humans	5	1.49 ± 0.22	1.05 ± 0.89	3.95 ± 3.33	(22)
	Pigs	Control, 8	2.21 ± 0.54	0.80 ± 0.33	2.90 ± 1.19	(25)
		Shock, 8	1.80 ± 0.48	0.53 ± 0.24	1.92 ± 0.80	(25)
Alfentanil	Humans	5	1.46 ± 0.11	0.23 ± 0.09	0.86 ± 0.35	(22)
		7	1.56 ± 0.29	0.32 ± 0.13	1.21 ± 0.45	(24)

[a] Number of subjects
[b] Eq. 11
[c] Eq. 8

RD_C^2 becomes quasi-independent of PS_{diff} and is nearly equal to that of the intravascular indicator. A comparison of the dispersions of circulation times estimated for antipyrine ($RD_C^2 = 3.7$) and inulin ($RD_C^2 = 17.8$) using frequent sampling within the first 3 min after bolus injection (9), shows that the RD_C^2 value of antipyrine only slightly exceeds that of the intravascular indicator ($RD_C^2 = 3.0$). For flow-limited whole body distribution, CL_M is proportional to cardiac output Q, whereas in our diffusion-limited case Eq. 11 implies that CL_M is proportional to PS_{diff} and independent of Q (6). This has to be taken into account when the approach is used in an intermediate case between flow- and diffusion-limitation, as for fentanyl and alfentanil, where CL_M is flow-dependent. In this case, the CL_M-Q relationship (Fig. 3) provides clearer information on the distributional properties of the drug since CL_M has a definite physical meaning. Blood-flow dependent distribution can be analyzed by a circulatory model applied to the drug and a simultaneously injected vascular reference indicator with frequent sampling within the first 3 min after bolus injection (6, 9). Note further that in contrast to RD_C^2 (Eq. 10), which is solely dependent on distribution kinetics, RD_D^2 is additionally dependent on the extraction ratio $E=CL/Q$ (Eq. 7). The limiting behavior $RD_D^2 \to 1$ for $E \to 0$ means that with decreasing extraction ratio more and more information on distribution kinetics gets lost, i.e., the distribution phase becomes a negligible part of the whole disposition curve, which then can be approximated by a monoexponential function. In other words, the approach fails for drugs with very low clearance, where $RD_D^2 - 1$ is near to 0. Additional information on distribution kinetics can be obtained from the third curve moment that determines the mean equilibration time MEQT (3, 11, 26).

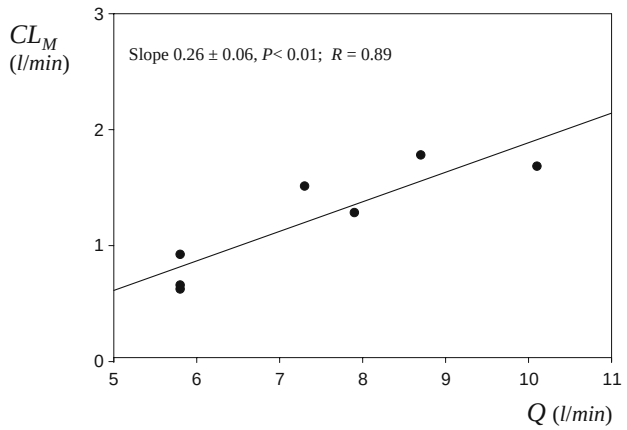

Fig. 3. Dependency of the total distribution clearance, CL_M, of alfentanil on cardiac output, Q. Eqs. 8 and 15 were used to calculate CL_M from the parameters of a three-compartment model estimated by Henthorn *et al.* (24) in human volunteers.

CONCLUSION

As an adjunct to the noncompartmental parameters CL and MDRT (or V_{ss}), the estimation of relative dispersion of disposition residence time RD_D^2 provides several useful insights into distribution kinetics of drugs. The measure RD_D^2 can be estimated with high precision from drug disposition data and represents a unifying concept by which one can compare results obtained with different models, compartmental models or polyexponential functions, irrespective of the number of compartments or exponentials, respectively. The approach clearly defines the limitations of these conventional pharmacokinetic models to describe rapid drug distribution processes.

APPENDIX

A residence time distribution can be characterized by moments of the order j of the density function [Eq. 3]: $\int_0^\infty t^j f(t)\mathrm{d}t$. For convenience, we define the moments in terms of $C(t)$ and for a polyexponential disposition curve [Eq. 14] we get

$$m_j = \int_0^\infty t^j C(t)\mathrm{d}t = j!\sum_{i=1}^{n}\frac{B_i}{\lambda^{j+1}} \tag{17}$$

The mean and relative dispersion of residence time, $\mathrm{MDRT} = \int_0^\infty tf(t)\mathrm{d}t$ and $\mathrm{VDRT} = \int_0^\infty (t-\mathrm{MDRT})^2 f(t)\mathrm{d}t$, are than obtained from Eq. 17 as

$$\mathrm{MDRT} = \frac{m_1}{m_0} = \frac{\sum_{i=1}^{n}\frac{B_i}{\lambda_i^2}}{\sum_{i=1}^{n}\frac{B_i}{\lambda_i}} \tag{18}$$

and

$$\mathrm{VDRT} = \frac{m_2}{m_0} - \left(\frac{m_1}{m_0}\right)^2 = \frac{2\sum_{i=1}^{n}\frac{B_i}{\lambda_i^3}}{\sum_{i=1}^{n}\frac{B_i}{\lambda_i}} - \mathrm{MDRT}^2 \tag{19}$$

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