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Pharmacokinetic Stochastic Model with Weibull-Distributed Residence Times of Drug Molecules in the Body*

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Summary. The use of a function to fit blood concentration-time data points is equivalent, under certain assumptions, to specifying a model of the distribution of residence times of the drug molecules in the body (stochastic pharmacokinetic model).

An empirical density function of the Weibull type is offered to describe this distribution. The model gives the following disposition function describing the time course of the drug concentrations in blood after an intravenous bolus input: $C_\delta(t) = \frac{D}{CL} s\lambda t^{s-1} \exp(-\lambda t^s)$.

It contains only three parameters: λ is like an 'elimination rate constant' in the single-exponential model into which the Weibull function reduces when the shape parameters becomes equal to unity; CL is the conventional systemic drug clearance, and, D is the dose injected.

The Weibull function gives an analytical solution of the convolution integral for zero-order input, thereby permitting use of the model for intravenous infusion data and for extravascular administration, when the absorption may be considered to be zero-order.

Using examples from the literature it is shown that in some cases the Weibull function gives a better fit than may be obtained with two- and three-exponential or gamma functions.

Key words: Weibull distribution; stochastic model, pharmacokinetic modelling, distribution of residence times

The models most commonly used in pharmacokinetics - compartmental and physiological (perfusion) - may be referred to as structural models, since they tend to describe more or less accurately the real processes of mass transfer of a drug in the body, namely distribution, metabolism and excretion. Alternatively, pharmacokinetic stochastic models may be suggested, which ignore the mass transfer processes and specify a distribution function of residence times of the drug molecules in the body. The latter models are based on the concept that any disposition behaviour of a drug leads to a particular distribution of residence times which is the realization of the random variable, namely the time interval between entry of the molecule into the body and its elimination by metabolism and/or excretion; for example, one-compartment disposition produces a simple exponential distribution of residence times and a two-compartment system gives a biexponential distribution which is a mixture of two single exponential distributions. Disposition models based on the conception of circulatory drug transport (Cutler 1979; Vaughan and Hope 1979; Weiss 1979; Van Rossum 1983) in some cases lead to distributions other than polyexponential, e.g., gamma or power distributions (Weiss 1983; Wise 1985). However, the concept of the stochastic model permits use of any empirical distribution that can adequately describe the observed blood concentration - time data. There may be no supporting structural model equivalent for some of these distributions.

In the present account some general equations relating a probability density function of any distribution of residence times to the observable blood concentration - time profile are presented. A new empirical disposition stochastic model based on the Weibull distribution is also proposed. The disposition function provided is compared with polyex-

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ponential and gamma functions in fitting real kinetic data taken from literature, and some of its benefits are stressed.

Theoretical Analysis

After an intravenous (i.v.) impulse input of a drug dose D, each molecule remains within the body for a certain time and is then eliminated. This time, called the residence time of the drug molecule in the body, can be regarded as a random variable, and since the number of molecules in the dose injected is enormous, the variable may be considered to be continuously distributed within an interval from zero to infinity. A stochastic pharmacokinetic model specifies the probability density function (p.d.f.) of the residence times distribution. By definition

$$P(t_1 < t' < t_2) = \int_{t_1}^{t_2} p(t')dt' \tag{1}$$

where $P(t_1 < t' < t_2)$ is a probability that a molecule residence time t' has between t_1 and t_2. All molecules will be eliminated with time, so

$$P(0 < t' < \infty) = \int_{0}^{\infty} p(t')dt' = 1 \tag{2}$$

$P(0 < t' < t)$ will define the part of the dose already eliminated up to time t, and $P(t < t' < \infty)$ will define the amount of drug in the body at that time, A(t):

$$A(t) = D \cdot P(t < t' < \infty) = \int_{t}^{\infty} p(t')dt' \tag{3}$$

Taking into account Eq (2) the last equation can be rewritten as:

$$A(t) = D \cdot [1 - \int_{0}^{t} p(t')dt'] \tag{4}$$

Differentiating Eq. (4) by time gives the drug elimination rate:

$$-\frac{dA}{dt} = D \cdot p(t) \tag{5}$$

Assuming linear pharmacokinetics and elimination exclusively from well-perfused organs (i.e. no elimination from peripheral tissues), the elimination rate will equal to the total drug clearance, CL, multiplied by the drug concentration in blood following the i.v. impulse input, $C_\delta(t)$:

$$-\frac{dA}{dt} = CL \cdot C_\delta(t) \tag{6}$$

Combining Eqs. (5) and (6) and solving for $C_\delta(t)$ we obtain:

$$C_\delta(t) = \frac{D}{CL} p(t) \tag{7}$$

Thus, under the above mentioned conditions the drug concentration - time profile in blood reflects the form of the p.d.f. of residence times distribution (Weiss 1983).

One of the possible specific forms of the residence time distribution is a (single) exponential distribution with the following p.d.f.:

$$p(t) = \lambda \cdot e^{-\lambda t} \tag{8}$$

which leads to exponential decay of the drug level in blood after an impulse input. A one-compartment model produces the same profile, so one can say that this model results in the single-exponential distribution of residence times. However, following i.v. bolus injection of the majority of drugs, the concentration-time profiles are concave on a semilogarithmic plot. This may be described using a mixed distribution consisting of two single-exponential functions:

$$p(t) = k\lambda_1 e^{-\lambda_1 t} + (1-k)\lambda_2 e^{-\lambda_2 t} \tag{9}$$

where k represents the relative contribution of the first exponential term ($0 < k < 1$). Introducing Eq. (9) into (7) gives:

$$C_\delta(t) = L_1 e^{-\lambda_1 t} + L_2 e^{-\lambda_2 t} \tag{10}$$

where $L_1 = \frac{D}{CL} k\lambda_1$ and $L_2 = \frac{D}{CL}(1-k)\lambda_2$. Such form of the disposition function is habitual to the two-compartment model. However, there is no rigorous conjunction between the two-exponential and two-compartment models since more complex compartmental models may also give two-exponential-like dispositions curves with certain combinations of the microconstants.

In the same way one can construct mixed distributions containing three:

$$C_\delta(t) = L_1 e^{-\lambda_1 t} + L_2 e^{-\lambda_3 t} + L_3 e^{-\lambda_3 t} \tag{11}$$

or more exponential terms. However, the addition of each new term to the model adds two extra parameters to be estimated (contribution coefficient and 'rate constant').

Concave disposition curves may be also approximated by a gamma distribution of residence times:

$$p(t) = \frac{t^\alpha \exp(-t/\beta)}{\Gamma(\alpha+1)\beta^{\alpha+1}} \tag{12}$$

where $\alpha < 0$. Introducing Eq. (12) into (7) and denoting $a = -\alpha$, $A = D/[CL \cdot \Gamma(\alpha+1) \cdot \beta^{\alpha+1}]$, and $b = 1/\beta$ we have:

$$C_\delta(t) = At^{-a}e^{-bt} \tag{13}$$

Gamma-distributed residence times can be interpreted in terms of a recirculatory model (Weiss 1983). Eq. (13) contains only three parameters and seems to be applicable to many drugs (Wise 1985).

Log-concave profiles can also be described by the Weibull distribution (Johnson and Leone 1977):

$$p(t) = \frac{s}{\tau}\left(\frac{t}{\tau}\right)^{s-1}\exp\left[-\left(\frac{t}{\tau}\right)^s\right] \tag{14}$$

where $0 < s < 1$. Denoting $\lambda = 1/\tau^s$ and introducing Eq. (14) into (7) gives a disposition function of the Weibull type:

$$C_\delta(t) = Bt^{s-1}\exp(-\lambda t^s) \tag{15}$$

where $B = \frac{D}{CL} \cdot s\lambda$. The mean residence time of drug molecules in the body can be calculated in this case as

$$MRT = \Gamma\left(1+\frac{1}{s}\right) \cdot \tau = \Gamma\left(1+\frac{1}{s}\right)/\lambda^{1/s} \tag{16}$$

This may be viewed as a generalization of an exponential distribution since at $s = 1$ Eq. (15) becomes identical to Eq. (8). The lower the shape parameter s the more concave becomes the concentration-time curve. The forms of profiles simulated using Eq. (15) for s from 0.3 to 1 are plotted on a semilogarithmic scale in Fig. 1.

Like Eqs. (10), (11) and (13), Eq. (15) may be applied directly to fit concentration-time data only following i. v. impulse input. Some examples of the use of this equation are given below. It permits linearisation of data on a $\ln(C/t^{s-1})$ vs t^s scale, and this can serve as a visual check of the applicability of the Weibull function to specific data.

In the case of noninstantaneous drug input, convolution provides the best way to obtain the necessary model equations for the corresponding concentration-time profile, C(t):

$$C(t) = \int_0^t i(t')C_\delta(t-t')dt' \tag{17}$$

where i(t) is an input function representing the drug input rate into the circulation. Introducing specific forms of the disposition function $C_\delta(t)$ and of i(t) and solving the integral (17) gives an equation that describes the theoretical concentration-time profile for the assumed disposition and input models. For example, taking zero-order input which describes an i. v. infusion:

$$i(t) = \begin{cases} I & (0 < t \leqslant T) \\ 0 & (T < t < \infty) \end{cases}$$

and assuming the disposition function of the Weibull type (15) gives:

$$C(t) = \begin{cases} \frac{I}{CL}[1-\exp(-\lambda t^s)] & (0 < t \leqslant T) \\ \frac{I}{CL}\{\exp[-\lambda(t-T)^s]-\exp(-\lambda t^s)\} & (T < t) \end{cases} \tag{18}$$

where T is the duration of the infusion.

Polyexponential disposition functions also provide an analytical solution of the convolution integral with zero-order input (e. g., Wagner 1976a), but this is not the case for the gamma function. In principle, this problem may be overcome by means of a suitable numerical algorithm evaluating the integral (17). Such an algorithm is also needed to describe data after drug input of an order higher than zero, because then neither Weibull nor gamma functions give an analytical solution of the convolution integral. However, these problems, which arise mainly in case of extravascular administration, are beyond the scope of the present paper and will be discussed elsewhere.

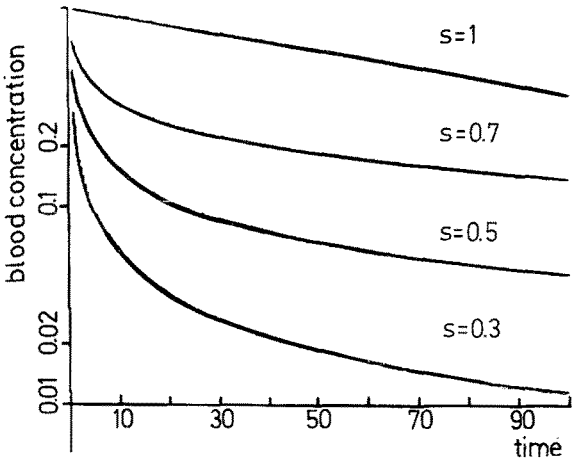

Fig. 1. Theoretical blood concentration - time profile for Weibull-distributed residence times of drug molecules in the body. Abscissa-time (conventional units); ordinate-concentration (log conventional units)

Practical Application

The disposition function of the Weibull type was compared with the other functions discussed above by fitting real drug kinetic data after i. v. injection

Table 1. Parameters of disposition functions for bishydroxycoumarin kinetics and measures of goodness of fit (data from Nagashima et al. 1968)

	2-exponential function (Eq. 10)	3-exponential function (Eq. 11)	Gamma function (Eq. 13)	Weibull function (Eq. 15)
	$L_1 = 25.6$ (8.3)[a]	$L_1 = 18.4$ (17)	$A = 22.2$ (1.6)	$B = 24.8$ (1.8)
	$\lambda_1 = 1.55$ (15.1)	$\lambda_1 = 1.20$ (31)	$a = 0.317$ (5.0)	$\lambda = 0.148$ (2.3)
	$L_2 = 16.9$ (5.4)	$L_2 = 15.8$ (8)	$b = 0.0539$ (5.3)	$s = 0.748$ (1.7)
	$\lambda_2 = 0.0905$ (6.6)	$\lambda_2 = 0.142$ (33)	$\sigma_1 = 0.026$ (66)	$\sigma_1 = 0.015$ (66)
	$\sigma_1 = -0.19$ (65)	$L_3 = 2.63$ (123)	$\sigma_2 = 2.4$ (20)	$\sigma_2 = 2.7$ (18)
	$\sigma_2 = 1.2$ (41)	$\lambda_3 = 0.0157$ (236)		
		$\sigma_1 = 0.0001$ (67)		
		$\sigma_2 = 4.8$ (10)		
r^2	0.990	0.977	0.988	0.989
SD	1.22	2.13	1.31	1.22
AIC[b]	45.0	32.6	32.2	29.5
SC[c]	50.4	35.4	35.0	32.3

[a] parameters CVs; [b] Akaike information criterion; [c] Schwarz criterion

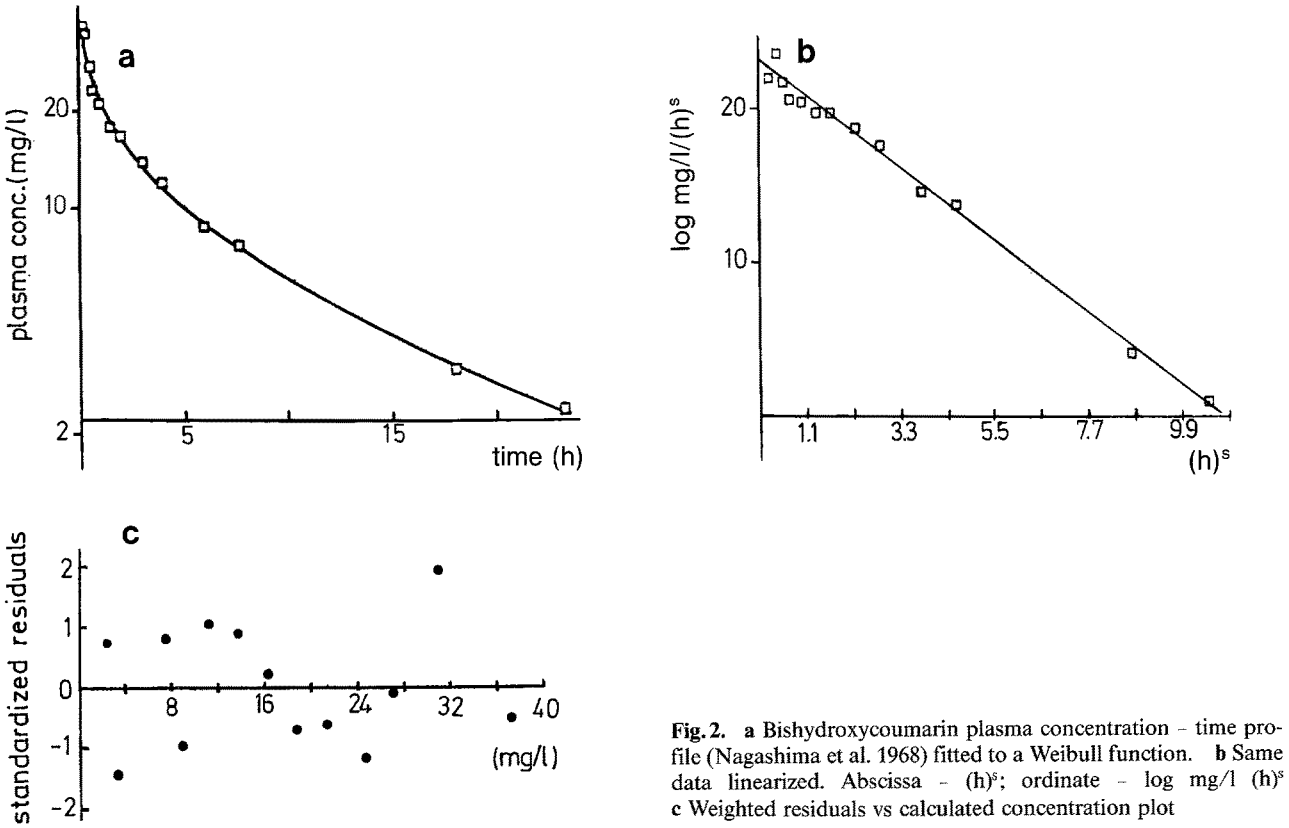

Fig. 2. **a** Bishydroxycoumarin plasma concentration – time profile (Nagashima et al. 1968) fitted to a Weibull function. **b** Same data linearized. Abscissa – $(h)^s$; ordinate – log mg/l $(h)^s$ **c** Weighted residuals vs calculated concentration plot

and, in one case, following sublingual administration. The best fits were obtained using an extended least-squares nonlinear regressional analysis program (ELSNLR; Nichols and Peck 1981) which has an important advantage over ordinary least-squares algorithms (Peck et al. 1984). In the program both pharmacokinetic and variance models are available specified. The two-parameter variance model was used, in which an error is assumed to be proportional to some power of the calculated concentration:

$$VAR = \sigma_1 C^{\sigma_2}$$

Both σ_1 and σ_2 must be estimated together with the parameters of the pharmacokinetic model from the concentration-time data points.

It should be stressed, however, that any nonlin-

Table 2. Parameters of disposition functions for lidocaine kinetics and of variance model and measures of goodness of fit (data from Supradist et al., 1984)

Dose (mg)	2-exponential function (Eq. 10)	Gamma function (Eq. 13)	Weibull function (Eq. 15)
2.5	L_1 = 2.48 (4.0)[a]	A = 5.55 (3.7)	B = 5.52 (3.3)
	λ_1 = 0.108 (9.8)	a = 0.32 (6.5)	λ = 0.036 (4.2)
	L_2 = 1.82 (6.5)	b = 0.0083 (11.3)	s = 0.73 (2.6)
	λ_2 = 0.012 (8.7)		
	σ_1 = 0.034 (25)	σ_1 = 0.041 (25)	σ_1 = 0.040 (25)
	σ_2 = −0.8 (69)	σ_2 = −0.3 (190)	σ_2 = −0.86 (73)
	r^2 = 0.999	r^2 = 0.998	r^2 = 0.998
	SD = 0.0505	SD = 0.0525	SD = 0.057
	AIC = −19.4[b]	AIC = −18.4	AIC = −18.7
	SC = −19.0[c]	SC = −18.0	SC = −18.3
5.0	L_1 = 5.48 (27)	A = 10.1 (5.0)	B = 9.87 (4.7)
	λ_1 = 0.029 (29)	a = 0.165 (15.8)	λ = 0.025 (5.9)
	L_2 = 2.34 (70)	b = 0.0125 (7.9)	s = 0.87 (2.2)
	λ_2 = 0.0085 (42)		
	σ_1 = 0.056 (36)	σ_1 = 0.098 (35)	σ_1 = 0.084 (36)
	σ_2 = 1.8 (32)	σ_2 = 0.29 (190)	σ_2 = 0.53 (108)
	r^2 = 0.994	r^2 = 0.998	r^2 = 0.998
	SD = 0.250	SD = 0.143	SD = 0.140
	AIC = 1.6	AIC = − 2.4	AIC = − 3.1
	SC = 1.9	SC = − 2.0	SC = − 2.7
10.0	L_1 = 8.33 (13)	A = 21.2 (4.2)	B = 20.2 (4.7)
	λ_1 = 0.105 (22)	a = 0.251 (8.1)	λ = 0.031 (5.9)
	L_2 = 9.06 (5.4)	b = 0.011 (5.8)	s = 0.82 (2.3)
	λ_2 = 0.0136 (3.8)		
	σ_1 = 0.055 (47)	σ_1 = 0.075 (47)	σ_1 = 0.093 (48)
	σ_2 = 1.51 (37)	σ_2 = 0.88 (64)	σ_2 = 0.81 (70)
	r^2 = 0.997	r^2 = 0.998	r^2 = 0.998
	SD = 0.321	SD = 0.210	SD = 0.250
	AIC = 5.6	AIC = 2.8	AIC = 4.1
	SC = 6.0	SC = 3.2	SC = 4.5

Footnotes as in Table 1

ear regression analysis program could be used in principle to fit models to data. Goodness of fit was assessed by the coefficient of determination (r^2) and standard deviation (SD) calculated as:

$$r^2 = 1 - \frac{\sum d^2}{S_c^2}$$

$$SD = \sqrt{\sum d^2/(N-P)}$$

where

$$\sum d^2 = \sum (C_{meas.} - C_{calc.})^2$$

$$S_c^2 = C_{meas.}^2 - \frac{(\sum C_{meas.})^2}{N}$$

N and P are points number and disposition model parameters number, respectively. Different models were compared using Akaike (Akaike 1976) and Schwarz (Schwarz 1978) criteria, by which the preferred model can be chosen according the 'principle of parsimony' (Landaw and DiStefano 1984). Coefficients of variation (CV) of parameter estimates and point deviations over model curves computed by the program were also taken into account.

Results

Example 1

The kinetic data on bishydroxycoumarin following an i.v. bolus dose (Nagashima et al. 1968) were fitted by Eqs. (10), (11), (13) and (15). The results are presented in Table 1 and Fig. 2. The concentration - time data and the best fit curve obtained with the Weibull function (semilogarithmic scale) are shown in Fig. 2a and b. Figure 2b demonstrates linearization of the data in $\ln(C/t^{s-1})$ vs t^s scale; a corresponding graph of weighted residuals is shown in Fig. 2c. By providing the lowest values of the Akaike and Schwarz criteria and the lowest SD, as well as the highest r^2, the Weibull function proved

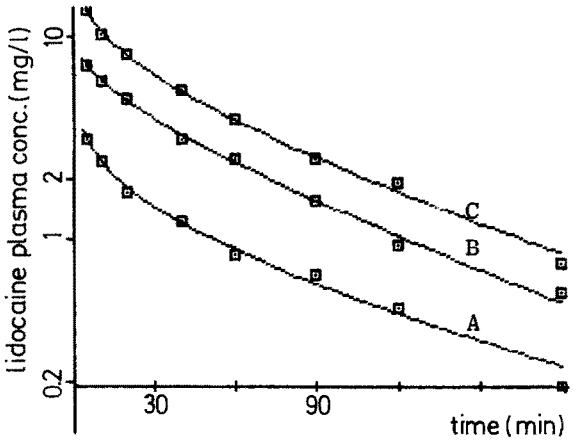

Fig. 3. Lidocaine plasma concentration – time profiles in rats following rapid i. v. injection of 2.5 mg (Curve A), 5.0 mg (B) and 10.0 mg (C; Supradist et al. 1984) fitted to a Weibull function

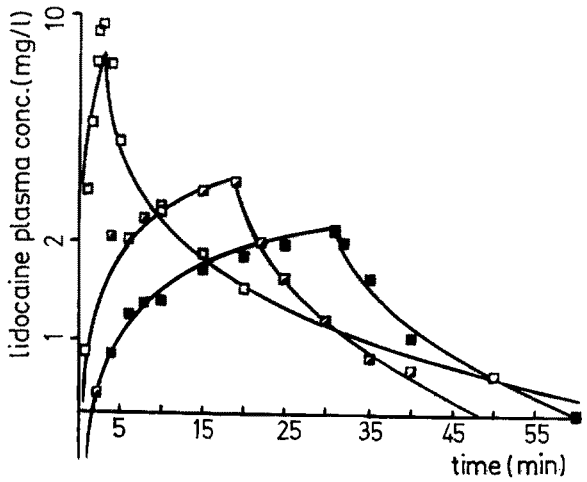

Fig. 4. Lidocaine plasma concentration – time data in man (semilogarithmic plot) during and after infusion for 3 min (□), 19 min (◪) and 31 min (■) (Tucker and Boas 1971). Curves correspond to the best fits obtained with Weibull-distributed residence times

to be superior to all other functions tested. The parameter CVs were also the lowest in the case of the Weibull function.

Example 2

The data on lidocaine kinetics by Supradist et al. (1984) obtained after the i. v. administration of three different doses to rats were fitted using Eqs. (10), (11), (13) and (15). Attempts to fit a three-exponential equation failed because the errors in the model parameters were too large. The results obtained with biexponential, gamma and Weibull functions are listed in Table 2. A semilogarithmic plot of the data from all three sets and the Weibull model best

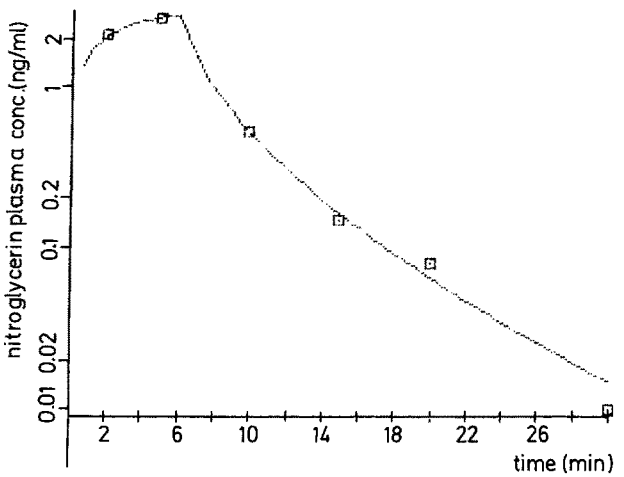

Fig. 5. Nitroglycerin plasma concentration-time data (logarithmic scale) after sublingual administration of 0.5 mg (Blagodatskikh et al. 1987). The curve represents the best fit by Eq. (17)

fit curves are shown in Fig. 3. From the comparison of criteria, in this case the Weibull function provided a better fit than the others for one of the data sets (5.0 mg dose), and for the other sets the biexponential (2.5 mg dose) and gamma (10 mg dose) functions gave better results.

Example 3

This example demonstrates the potential of the Weibull function for describing infusion data. Three data sets (Tucker and Boas 1971) obtained during and after cessation of lidocaine infusion at different constant rates in man were used. The sets were fitted by Eq. (17; see Fig. 4) and also corresponding equations for two- and three-exponential dispositions functions (Wagner 1976a). It is apparent from the results obtained (Table 3), that the Weibull function gave a better fit for the first data set, while the second set seemed to be better described by the two-exponential function according to both Akaike and Schwarz criteria. However, λ_2 in the last case appeared negative, so this function is inappropriate, and the Weibull function can be chosen as the best. For the third set the Weibull and two-exponential functions gave results close to each other. Values of criteria were slightly lower for the two-exponential function while the parameters CVs were smaller for the Weibull function.

Example 4

All the above data sets contained sufficient points to be fitted to complex disposition functions. However, in practice only a few data points may be

Table 3. Parameters of disposition functions for lidocaine kinetics and of variance model and measures of goodness of fit (infusion, data from Tucker and Boas 1971)

Infusion duration (min)	3-exponential function (Eq. 11)		2-exponential function (Eq. 10)		Weibull function (Eq. 15)	
3	L_1 = 7.42	(29)[a]	L_1 = 61.9	(13)	B = 72.3	(6.8)
	λ_1 = 0.717	(64)	λ_1 = 0.106	(9.4)	λ = 0.0544	(11)
	L_2 = 2.96	(27)	L_2 = 0.898	(5.0)	s = 0.564	(5.8)
	λ_2 = 0.0762	(19)	λ_2 = 0.00715	(4.4)		
	L_3 = 0.865	(6.8)				
	λ_3 = 0.00692	(6.0)				
	σ_1 = 0.0075	(26)	σ_1 = 0.084	(23)	σ_1 = 0.11	(23)
	σ_2 = 4.4	(10)	σ_2 = 4.7	(8.8)	σ_2 = 3.8	(11)
	r^2 = 0.802		r^2 = 0.744		r^2 = 0.800	
	SD = 1.707		SD = 1.77		SD = 1.50	
	AIC = 24.0[b]		AIC = 26.4		AIC = 26.1	
	SD = 30.2[c]		SC = 31.0		SC = 30.0	
19	L_1 = 2.43	(12900)	L_1 = 10.9	(9.6)	B = 5.98	(51)
	λ_1 = 0.342	(1470)	λ_1 = 0.268	(27)	λ = 0.150	(40)
	L_2 = 8.92	(3510)	L_2 = 0.974	(65)	s = 0.550	(23)
	λ_2 = 0.275	(381)	λ_2 = −0.035	(710)		
	L_3 = 1.05	(231)				
	λ_3 = −0.015	(500)				
	σ_1 = 0.49	(46)	σ_1 = 0.50	(44)	σ_1 = 0.35	(38)
	σ_2 = −4.8	(290)	σ_2 = −4.9	(24)	σ_2 = −2.8	(37)
	r^2 = 0.941		r^2 = 0.942		r^2 = 0.940	
	SD = 0.269		SD = 0.230		SD = 0.222	
	AIC = 1.13		AIC = −2.6		AIC = 1.0	
	SC = 5.0		SC = 0.30		SD = 3.4	
31	L_1 = 5.27	(583)	L_1 = 8.22	(11)	B = 3.97	(6.0)
	λ_1 = 0.342	(397)	λ_1 = 0.264	(28)	λ = 0.120	(3.6)
	L_2 = 3.51	(822)	L_2 = 1.70	(28)	s = 0.57	(5.0)
	λ_2 = 0.123	(615)	λ_2 0.0233	(34)		
	L_3 = 0.95	(442)				
	λ_3 = 0.00968	(869)				
	σ_1 = 0.068	(24)	σ_1 = 0.060	(24)	σ_1 = 0.040	(25)
	σ_2 = 0.65	(676)	σ_2 = 0.44	(231)	σ_2 = 4.0	(26)
	r^2 = 0.980		r^2 = 0.983		r^2 = 0.965	
	SD = 0.092		SD = 0.075		SD = 0.102	
	AIC = −17.3		AIC = −23.7		AIC = −22.0	
	SC = −12.8		SC = −20.3		SC = −19.2	

Footnotes as in Table 1

available. The fourth example is taken from a study of nitroglycerin kinetics following an 0.5 mg sublingual dose (Blagodatskikh et al. 1987). The typical plasma concentration-time data set (Fig. 5) consisted of 6 points. They were fitted by Eq. (17) assuming T to be a model parameter (not a fixed value). Thus, in this case zero-order absorption kinetics and the Weibull disposition model have been assumed. The line in Fig. 5 represents the best fit model curve, and the parameter estimates were (% CVs in parentheses): I/CL = 3.25 ng/ml (3.2); T = 6.34 min (6.0); s = 0.617 (5.8); $\lambda = 0.637\ \text{min}^{-1/s}$ (9.9). Parameters reflecting the goodness of fit were: $r^2 = 0.9999$; SD = 0.0154; AIC = −24.1; SC = −15.2. MRT of nitroglycerin calculated by Eq. (16) was 2.76 min. Mean absorption time estimated as T/2 was 3.17 min. Since the fraction of dose absorbed was not known, the systemic clearance and the steady-state volume of distribution could not be found. (This fact does not prevent proper estimation of MRT and the mean absorption time, since those parameters are not affected by the above fraction.) Polyexponential functions could not be used in this instance due to the very small number of points available.

Discussion

Models specifying the form of p.d.f. of residence times distributions represent a special class of pharmacokinetic models (stochastic models) which ac-

cording to the degree of detail provided of the drug disposition in the body, can be located between the classical structural (compartmental and physiological) models and the so-called model-independent approach (Piotrovskii 1985). The former are based on modelling mass transfer processes within the body, but the latter has a different basis and gives only an integral description of the disposition in terms of the mean residence time, its variance, clearance, volumes of distribution etc. These parameters may be computed directly from concentration-time data pairs by means of the trapezoidal rule, although, there is always the problem of extrapolation outside the sampling time interval, which requires a specific distribution, e. g. for residence times longer than the last measured time point. An exponential distribution is commonly assumed, and the corresponding 'rate constant' has to be estimated from the points referred to the terminal log-linear phase of the curve. The choice of this phase is always subjective. Furthermore, the accuracy of the drug concentration measurement at those points is usually low. All these factors together may result in biased estimation of the slope of the terminal phase, so model-independent parameters may be determined with large errors. It seems preferable to use all available data points for the extrapolation, but this forces choice of a specific function describing the data, i.e. selection of the form of the entire distribution function for all the residence times. Under assumptions formulated above (linearity of kinetics and nonperipheral elimination), the blood concentration-time profile reflects the p.d.f. of the distribution of residence times of drug molecules in the body. Those assumptions are common to linear compartmental modelling and to the model-independent approach, too. For example, if there is some elimination in peripheral tissues a reliable estimate of the model-independent parameters cannot be obtained by the statistical moments method when only blood (or urine) concentration - time data are available (see, e.g., Collier 1983).

Polyexponential functions may be regarded as p.d.f.'s of mixed distributions consisting of several exponential terms (in the sense of Eq. 9). Many pharmacokineticists consider use of these functions as equivalent to multicompartmental modeling. An alternative point of view is that the polyexponential approximation gives model-independent description of the drug kinetics (Wagner 1976a; Wagner 1976b). However, it seems more appropriate to distinguish these functions as a separate class of models, stochastic models, which include also the gamma (Weiss 1983) and Weibull functions suggested here.

The examples presented here show the potential of the Weibull function as a disposition model, which affords a good fit of data after an i.v. bolus dose, during and after zero-order infusion and even following extravascular administration (Example 4). The main advantage of the Weibull function over polyexponentials lies in the relatively small number of parameters to be estimated, and this allows its use for data sets containing only a few points, as in Example 4. The gamma function also has three parameters, but it can only be directly applied to bolus impulse injections.

Certainly, the Weibull function, as well as other functions mentioned here, is no more than an approximation to the true p.d.f. of the residence times distribution of drug molecules in the body. The former may be applied with success to profiles of relatively low curvature (on a semilogarithmic scale), as in Example 2, and in some instances to highly curvilinear profiles that lack a clear log-linear terminal phase (apparently 'polyexponential' curve) as in Example 1. Of course, since the body comprises many organs and tissues, each of which has its own distribution of residence times of drug molecules, the overall distribution will be very complex. In our opinion among simple analytical functions there is none that can be regarded as the true p.d.f. of the distribution of residence times in the body.

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