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An Algorithm and Computer Program for Deconvolution in Linear Pharmacokinetics

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The procedure of deconvolution to evaluate the rate and the extent of input from absorption data and data from intravenous administration is the most fundamental and least assumptive method of accurately evaluating drug absorption in linear pharmacokinetics. It is shown for linear systems that if the absorption response and the response from an intravenous infusion or bolus administration are both well approximated by a polyexponential function, then the rate of absorption can be expressed as a sum of exponentials. An algorithm and computer program are presented whereby the absorption function is uniquely defined from the model-independent parameters of the polyexponential expressions fitted to the absorption data and data from intravenous administration. Fitting a sum of exponentials to data has become a routine procedure in pharmacokinetics. The method presented therefore makes the previously complex task of deconvolution a simple procedure. The deconvolution approach is discussed in relation to conventional methods of evaluating drug absorption and appears to have some distinct advantages over these methods. The method is tested using simulated data and demonstrated using pentobarbital and cimetidine data from human subjects.

KEY WORDS: bioavailability; absorption; deconvolution; computer program for deconvolution; algorithm for deconvolution; drug input evaluation; input response in linear pharmacokinetic systems; pentobarbital absorption; cimetidine absorption.

The various approaches for evaluating drug absorption have been previously discussed (1,2). An earlier paper presented the mathematical solution to the deconvolution problem of determining the rate of input when the unit impulse response function is approximated by a polyexponential expression, and the absorption response is approximated by any arbitrary function (1). The solution led to the subsequent development of a method using an adaptive least squares cubic spline function approximation of the

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absorption response (2). Although the method was tested favorably and appears to have optimal numerical and theoretical properties, it has the same disadvantage as other numerical deconvolution methods (3–6), namely, being somewhat computationally complex.

The method presented here has been developed in response to the need for a simpler approach that is easier to implement. It is based on a polyexponential approximation of the absorption response and the response from an intravenous bolus or infusion administration. Fitting a sum of exponentials to data has become a routine procedure in pharmacokinetics. The method presented therefore makes the previously complex task of deconvolution a simple procedure.

THEORY

The concentration of a drug in the blood after an intravenous (i.v.) bolus dose, D_{IV}, can often be well approximated by a (poly)exponential expression:

$$C_{IV}(t) = \sum_{i=1}^{n} a_i e^{-\alpha_i t} \qquad \alpha_i > 0 \tag{1}$$

If the system is linear with respect to drug input and response, as previously discussed (1,2), then the unit impulse response ("the characteristic response") is given by

$$C_\delta(t) = \frac{1}{D_{IV}} \sum_{i=1}^{n} a_i e^{-\alpha_i t} \tag{2}$$

and a response, $C(t)$, is the convolution between the unit impulse response, $C_\delta(t)$, and the rate of input, $F(t)$, of drug into the blood:

$$C(t) = C_\delta(t) * F(t) = \int_0^t C_\delta(t-u)F(u)\,du = \int_0^t C_\delta(u)F(t-u)\,du \tag{3}$$

The analytical deconvolution of Eq. (3) has been previously derived (1). The rate of input is given by[2]

$$F(t) = D_{IV}[K_1 C'(t) + K_2 C(t) + \varphi(t) * C(t)] \tag{4}$$

and the percent of the dose, D, absorbed at time t is

$$\mathrm{PCT}(t) = K_4\left[K_1 C(t) + K_3 \int_0^t C(u)\,du + \psi(t) * C(t)\right] \tag{5}$$

[2]The notation used in the present paper has been changed slightly to simplify the mathematical presentation.

where

$$K_1 = 1 \Big/ \sum_{i=1}^{n} a_i \tag{6}$$

$$K_2 = K_1^2 \sum_{i=1}^{n} a_i \alpha_i \tag{7}$$

$$K_3 = K_2 - \sum_{i=1}^{n-1} g_i / \gamma_i \tag{8}$$

$$K_4 = 100 D_{IV} / D \tag{9}$$

$$\varphi(t) = \sum_{i=1}^{n-1} g_i \, e^{\gamma_i t} \tag{10}$$

$$\psi(t) = \sum_{i=1}^{n-1} \frac{g_i}{\gamma_i} e^{\gamma_i t} \tag{11}$$

The parameters $\{g_i, \gamma_i\}_1^{n-1}$ of the auxiliary functions $\varphi(t)$ and $\psi(t)$ are obtained from the parameters $\{a_i, \alpha_i\}_1^n$. The γ parameters are the $(n-1)$ roots of the $(n-1)$th degree polynomial,

$$Q(x) = \sum_{i=1}^{n} a_i \prod_{\substack{j=1 \\ j \neq i}}^{n} (\alpha_j + x) \tag{12}$$

The g parameters are subsequently obtained from

$$g_i = \left[\sum_{j=1}^{n} \frac{a_j}{\gamma_i + \alpha_j} \sum_{\substack{k=1 \\ k \neq j}}^{n} \frac{1}{\gamma_i + \alpha_k} \right]^{-1} \tag{13}$$

The summation to $i = n-1$ in Eqs. (8), (10), and (11) is defined as zero for $n = 1$. Therefore, the convolution terms in Eqs. (4) and (5) vanish for $n = 1$.

The above results are valid for whatever analytical empirical function is chosen to approximate the input response, $C(t)$. It has become a routine procedure in pharmacokinetics to fit a sum of exponentials to absorption data. Several programs exist for automatically fitting such a function or for obtaining suitable initial parameter estimates for a subsequent curve fitting (7–16). It is therefore of interest to consider the following input response approximation:

$$C(t) = \sum_{i=1}^{m} b_i \, e^{-\beta_i (t - t_{lag})_+} \qquad \beta_i > 0 \tag{14}$$

where t_{lag} is the absorption lag time, provided that the b_i's satisfy the condition[3]

$$\sum_{i=1}^{m} b_i = 0 \tag{15}$$

and

$$(t - t_{lag})_+ = 0 \qquad t \leq t_{lag} \tag{16}$$

$$(t - t_{lag})_+ = t - t_{lag} \qquad t > t_{lag} \tag{17}$$

Applying Eq. (14), the following equations are needed for substitution in Eqs. (4) and (5):

$$C'(t) = -\sum_{i=1}^{m} b_i \beta_i \, e^{-\beta_i (t - t_{lag})_+} \tag{18}$$

$$\varphi(t) * C(t) = \sum_{i=1}^{n-1} g_i \sum_{j=1}^{m} \frac{b_j}{\gamma_i + \beta_j} [e^{\gamma_i (t - t_{lag})_+} - e^{-\beta_j (t - t_{lag})_+}] \tag{19}$$

$$\int_0^t C(u)\, du = \sum_{i=1}^{m} \frac{b_i}{\beta_i} [1 - e^{-\beta_i (t - t_{lag})_+}] \tag{20}$$

$$\psi(t) * C(t) = \sum_{i=1}^{n-1} \frac{g_i}{\gamma_i} \sum_{j=1}^{m} \frac{b_j}{\gamma_i + \beta_j} [e^{\gamma_i (t - t_{lag})_+} - e^{-\beta_j (t - t_{lag})_+}] \tag{21}$$

It is recognized from Eqs. (4), (5), (14) and (18)–(21) that both the rate of input, $F(t)$, and the extent of input, $\mathrm{PCT}(t)$, can be expressed simply as a sum of exponentials:

$$\mathrm{PCT}(t) = u_0 + \sum_{i=1}^{L} u_i \, e^{-v_i (t - t_{lag})_+} \tag{22}$$

$$F(t) = \frac{D}{100} \sum_{i=1}^{L} u_i (-v_i) \, e^{-v_i (t - t_{lag})_+} \tag{23}$$

where

$$L = m + n - 1 \tag{24}$$

$$v_i = \beta_i \qquad i = 1, 2, \ldots, m \tag{25}$$

$$v_i = -\gamma_{i-m} \qquad i = (m+1), (m+2), \ldots, L \tag{26}$$

$$u_i = K_4 b_i \left[K_1 - \frac{K_3}{\beta_i} - \sum_{j=1}^{n-1} \frac{g_j}{\gamma_j (\gamma_j + \beta_i)} \right] \qquad i = 1, 2, \ldots, m \tag{27}$$

[3]Equation (15) is not a requirement, but only a practical definition that simplifies the calculation of the lag time.

$$u_i = K_4 \frac{g_{i-m}}{\gamma_{i-m}} \sum_{j=1}^{m} \frac{b_j}{\gamma_{i-m} + \beta_j} \qquad i = (m+1), (m+2), \ldots, L \tag{28}$$

$$u_0 = -\sum_{i=1}^{L} u_i \tag{29}$$

The γ parameters, the roots of the polynomial $Q(x)$, Eq. (12), can be found by conventional numerical methods (11). However, the following remarkable relationship provides a basis for a more suitable method of numerically determining the roots.

Theorem 1. *If the α_i are ordered such that*

$$\alpha_i < \alpha_{i+1} \qquad i = 1, 2, \ldots, n-1 \tag{30}$$

then

$$-\alpha_{i+1} < \gamma_i < -\alpha_i \qquad i = 1, 2, \ldots, n-1 \tag{31}$$

Proof. Since

$$Q(-\alpha_i) = a_i \prod_{\substack{j=1 \\ j \neq i}}^{n} (\alpha_j - \alpha_i) \tag{32}$$

$$Q(-\alpha_{i+1}) = a_{i+1} \prod_{\substack{j=1 \\ j \neq i+1}}^{n} (\alpha_j - \alpha_{i+1}) \tag{33}$$

and the α_i are arranged in monotone order, and sign (a_i) = sign (a_{i+1}), then

$$\text{sign}\,(Q(-\alpha_{i+1})) = -\text{sign}\,(Q(-\alpha_i)) \tag{34}$$

Thus there is at least one root of $Q(x)$ between $-\alpha_{i+1}$ and $-\alpha_i$. However, since this is the case for $i = 1, 2, \ldots, n-1$, and since $Q(x)$ has $n-1$ roots, there is one and only one root between $-\alpha_{i+1}$ and $-\alpha_i$.

In summary, the above treatment presents a suitable algorithm by which the rate of input, $F(t)$, and the extent of input, PCT(t), are expressed in a simple functional form as a sum of exponentials (Eqs. 22 and 23). The parameters of the exponential functions are obtained from a poly-exponential approximation of the impulse response and the absorption response (Eqs. 1 and 14).

EXPERIMENTAL

Numerical Analysis

A routine was written (see Appendix) to carry out the deconvolution according to the algorithm presented. The parameter list of the routine

follows the mathematical notation used. The routine initially sorts the parameter pairs $\{a_i, \alpha_i\}_1^n$ in order of ascending α_i values. A root-finding algorithm proposed by Wilkinson (17) and later improved by Brent (18) was coded in line with due regard to Eq. (22) to determine the γ_i's. The algorithm is considered one of the best algorithms available for finding a zero of a function. The algorithm was further amended by the author to automatically adapt to whatever computer is used (the EPS parameter), so that the γ_i's are determined to machine precision. The parameters of the functions describing the rate of input, $F(t)$, and the extent of input PCT(t), are finally calculated according to the algorithm presented.

The routine is written in a portable subset of ANSI (1966) FORTRAN IV (19), so that it may be used without alterations on any computer with a FORTRAN compiler. The routine can be readily translated to the BASIC language to be executed on a microcomputer. A test program was written and the code (see Appendix) extensively tested with the number of exponential terms ranging from 1 to 20 (n and $m = 1$–20), which is more than the capacity needed for practical use. The test was performed successfully on two different computers using four different compilers.[4]

Pharmacokinetic Analysis

The deconvolution technique was applied to two different drugs, cimetidine (20) and pentobarbital (21), to demonstrate cases where deconvolution can (Fig. 1) and cannot (Fig. 2) be used to estimate the drug input. The curve fittings and parameter estimation (Tables I, VI, and VII) were done using the interactive nonlinear regression program FUNFIT (22). The drawings (Figs. 1 and 2) were done using a computer plotting package written by the author.

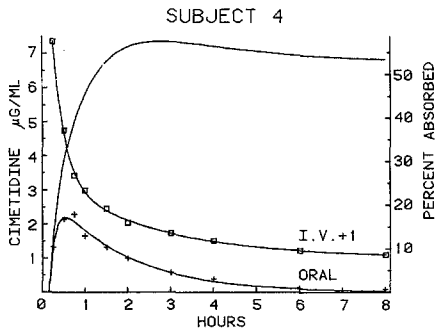

Fig. 1. Deconvolution of cimetidine data. The absorption curve is calculated according to Eq. (22). The parameters used are given in Table VI. The data from intravenous administration and the fitted curve are staggered one unit for clarity.

[4]PDP 11/70, UNIX FC compiler, and DEC FORTRAN IV PLUS. IBM 370/145, G and H compilers.

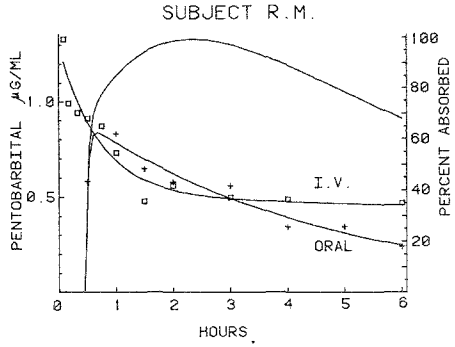

Fig. 2. Deconvolution of pentobarbital data. The absorption curve is calculated according to Eq. (22). The parameters used are given in Table VII. The strong disagreement between the terminal phases of the oral and intravenous data results in an unrealistic absorption profile.

RESULTS AND DISCUSSION

The parameters of the unit impulse response function, Eq. (2), required for the deconvolution are readily obtained directly from a bolus intravenous injection or a rapid infusion. However, several drugs are administered by a prolonged zero-order infusion due to a low solubility or due to toxicological-pharmacological reasons. Applying the fundamental convolution relationship, Eq. (3), to a zero-order infusion, the zero-order input response is obtained by a Laplace transformation:

$$C_z(t) = L^{-1}\left\{(LC_\delta(t))\left(\int_0^T e^{-st}K_z\,dt\right)\right\} = K_z L^{-1}\left\{(LC_\delta(t))\left[\frac{1}{s} - \frac{e^{-sT}}{s}\right]\right\} \tag{35}$$

$$C_z(t) = K_z\left[\int_0^t C_\delta(u)\,du - \int_0^{(t-T)_+} C_\delta(u)\,du\right] \tag{36}$$

so that

$$C_z(t) = K_z \sum_{i=1}^{n} \frac{a_i}{\alpha_i}[e^{-\alpha_i(t-T)_+} - e^{-\alpha_i t}] \tag{37}$$

where D_{IV} arbitrarily has been chosen equal to unity, and where K_z is the zero-order rate of infusion that takes place from $t = 0$ to $t = T$. Thus the parameters necessary for deconvolution $\{a_i, \alpha_i\}_1^n$ are readily obtained by fitting Eq. (37) to zero-order infusion data, treating K_z and T as constants.

Equation (37) can be readily extended to consider any number of infusion schedules.[5]

The parameters can also be obtained from data from multiple bolus input by fitting the following regression function:

$$C_b(t) = \sum_{j=1}^{J} D_j C_\delta((t - T_j)_+) \tag{38}$$

where $C_\delta(x)$ is given by Eq. (2), T_j is the time when the jth bolus dose, D_j, is given, and J is the highest value of j for which $t \geq T_j$ is satisfied. Due to the superposition principle of linear systems, Eq. (37) (or its extended form) and Eq. (38) can be combined so the required parameters can be obtained from data from a combination of bolus and zero-order infusion data. This may be of value in a clinical pharmacokinetic setting, where the therapeutical treatment takes priority over experimental design considerations.

Numerical Results

The present method was tested identically to other deconvolution methods recently proposed, using the same simulated data (2). The deconvolution of these data was done using the computer program in the appendix (Table I). The presentation of the test results in Tables II–V corresponds to the results in Tables II–V of ref. (2).

Data Set 1 (Noise Level 1%)

The method appears more accurate on this data set than the other methods (2,3), although the difference does not seem pronounced. The average percent relative error is of the same order of magnitude as the percent noise added to the data. As in the other methods, the method appears least accurate in the initial stage of the input (Table II).

Data Set 2 (Noise Level 10%)

The method determines the input to the same accuracy as the other methods (2,3). The pattern of the errors is also similar, and the average percent error is of the same order of magnitude as the noise added to the data (Table III).

Data Set 3 (Noise Level 1%)

The input is determined to the same accuracy as the other method proposed by the author (2) and is significantly better than the Cutler method

[5]For this purpose, it may be illustrative to write the expression in the brackets in Eq. (37) as $[\exp(-\alpha_i(t - T_{2j})_+) - \exp(-\alpha_i(t - T_{1j})_+)]$, where the infusion takes place from $t = T_{1j}$ to $t = T_{2j}$.

Table I. Parameters Used for Deconvolution of Simulated Data

Mathematical symbol	Program symbol	Data[a] set 1	Data[a] set 2	Data[a] set 3	Data[a] set 4
			INPUT		
a_1	A(1)	1.0427[b]	1.3377[b]	1.0308[b]	1.3377[b]
a_2	A(2)	0.97617[b]	0.52381[b]	1.0487[b]	0.5281[b]
α_1	ALPHA(1)	5.0526[b]	3.1851[b]	5.9131[b]	3.1851[b]
α_2	ALPHA(2)	0.97567[b]	0.61065[b]	1.0262[b]	0.61065[b]
n	N	2[b]	2[b]	2[b]	2[b]
D_{IV}	DIV	1.	1.	1.	1.
b_1	B(1)	−0.80547[b]	−2.2637[b]	−1.6103[b]	−5.5440[b]
b_2	B(2)	0.80547[b]	2.2637[b]	1.6103[b]	5.5440[b]
β_1	BETA(1)	3.6373[b]	2.0800[b]	3.3563[b]	2.2488[b]
β_2	BETA(2)	0.83033[b]	1.2513[b]	1.3917[b]	1.7521[b]
m	M	2[b]	2[b]	2[b]	2[b]
D	DOSE	0.6	0.6	0.6	0.6
L	L	3	3	3	3
			RESULTS		
u_0	UZ	103.38	94.012	94.363	91.159
u_1	U(1)	99.757	212.40	−1704.8	370.52
u_2	U(2)	−23.218	2395.3	73.013	−1111.2
u_3	U(3)	−179.92	−2701.7	1537.4	649.51
v_1	V(1)	3.6373	2.0800	3.3563	2.2488
v_2	V(2)	0.83033	1.2513	1.3917	1.7521
v_3	V(3)	2.9470	1.3351	3.4907	1.3351

[a] See ref. (2) for details.
[b] Values obtained using FUNFIT (22).

Table II. Input Rates Calculated from Data Set 1

Time	Exact rates	Calculated rates[a]	Percent difference[b]
0.1	0.9825	0.9625	−1.66
0.2	0.8044	0.8107	0.53
0.3	0.6586	0.6732	1.22
0.4	0.5392	0.5535	1.20
0.6	0.3614	0.3676	0.52
0.8	0.2423	0.2420	−0.02
1.0	0.1624	0.1601	−0.19
1.2	0.1089	0.1077	−0.10
1.4	0.0730	0.0742	0.10
1.6	0.0489	0.0527	0.31
2.0	0.0220	0.0292	0.61
Mean[c]			0.59
SD[c]			0.54

[a] Calculated according to Eq. (23) from the parameters given in Table I.
[b] Calculated as 100 · (calculated rate − exact rate)/1.2, where 1.2 is the initial exact input rate.
[c] The mean and the standard deviation of the absolute values of the percent difference.

Table III. Input Rates Calculated from Data Set 2

Time	Exact rates	Calculated rates[a]	Percent difference[b]
0.1	0.9825	0.9159	−5.55
0.2	0.8044	0.8199	1.29
0.3	0.6586	0.7242	5.47
0.4	0.5392	0.6319	7.73
0.6	0.3614	0.4651	8.64
0.8	0.2423	0.3269	7.05
1.0	0.1624	0.2180	4.63
1.2	0.1089	0.1355	2.22
1.4	0.0730	0.0750	0.17
1.6	0.0489	0.0324	−1.38
2.0	0.0220	−0.0152	−3.10
Mean[c]			4.29
SD[c]			2.86

[a] Calculated according to Eq. (23) from the parameters given in Table I.
[b] Calculated as 100 · (calculated rate − exact rate)/1.2, where 1.2 is the initial exact input rate.
[c] The mean and the standard deviation of the absolute values of the percent difference.

Table IV. Input Rates Calculated from Data Set 3

Time	Exact rates	Calculated rates[a]	Percent difference[b]
0.1	1.3048	1.3002	−0.30
0.2	1.0681	1.0639	−0.27
0.3	0.8551	0.8418	−0.85
0.4	0.6657	0.6473	−1.18
0.6	0.3580	0.3529	−0.33
0.8	0.1450	0.1690	1.54
1.0	0.0266	0.0639	2.38
1.2	0	0.0086	0.55
1.4	0	−0.0172	−1.10
1.6	0	−0.0269	−1.72
2.0	0	−0.0259	−1.65
Mean[c]			1.08
SD[c]			0.69

[a] Calculated according to Eq. (23) from the parameters given in Table I.
[b] Calculated as 100 · (calculated rate − exact rate)/(1.8/1.75), where 1.8/1.15 is the exact initial input rate.
[c] The mean and standard deviation of the absolute values of the percent difference.

(3). Contrary to the other methods, the input is best approximated in the initial phase. The errors are of the same magnitude as the noise added to the simulated data (Table IV).

Data Set 4 (Noise Level 10%)

The method shows the same accuracy as the other methods. The input appears to be determined best at the later sampling times (Table V).

It is not possible to differentiate between the accuracy of the present method and the other methods investigated on the basis of the above test data. The method appears to perform well considering that the average relative error in all estimations is of the same magnitude as the noise added to the simulated data.

Since the method appears as accurate as the other methods but is simpler to use, it seems to be a good first choice for deconvolution. A satisfactory performance is expected in the majority of the cases in pharmacokinetics where the drug concentration profiles are fairly regular, and a good polyexponential approximation can be provided. However, in the more irregular cases, it may be more appropriate to use a more flexible approximation, such as the adaptive least squares cubic spline approach proposed by the author (2).

Table V. Input Rates Calculated from Data Set 4

Time	Exact rates	Calculated rates[c]	Percent difference[b]
0.1	1.3048	1.2589	−2.94
0.2	1.0681	1.0562	−0.76
0.3	0.8551	0.8738	1.19
0.4	0.6657	0.7123	2.98
0.6	0.3580	0.4503	5.90
0.8	0.1450	0.2605	7.38
1.0	0.266	0.1290	6.54
1.2	0	0.0422	2.69
1.4	0	−0.0121	−0.77
1.6	0	−0.0434	−2.77
2.0	0	−0.0647	−4.13
Mean[c]			3.46
SD[c]			2.29

[a] Calculated according to Eq. (23) from the parameters given in Table I.
[b] Calculated as 100 · (calculated rate − exact rate)/(1.8/1.15), where 1.8/1.15 is the exact initial input rate.
[c] The mean and standard deviation of the absolute values of the percent difference.

Table VI. Parameters Used for Deconvolution of Cimetidine Data

Mathematical symbol	Program symbol	Value	Units
	INPUT		
i.v. administration			
a_1	A(1)	10.01[a]	μg/ml
a_2	A(2)	2.464[a]	μg/ml
α_1	ALPHA(1)	3.553[a]	h^{-1}
α_2	ALPHA(2)	0.4037[a]	h^{-1}
n	N	2	
D_{IV}	DIV	3.10^5	μg
Oral administration			
b_1	B(1)	2.964[a]	μg/ml
b_2	B(2)	−2.964[a]	μg/ml
β_1	BETA(1)	0.5798[a]	h^{-1}
β_2	BETA(2)	7.541[a]	h^{-1}
m	M	2	
D	DOSE	3.10^5	μg
L	L	3	
	RESULTS		
u_0	UZ	52.90	
u_1	U(1)	48.11	
u_2	U(2)	−13.77	
u_3	U(3)	−87.25	
v_1	V(1)	0.5798	h^{-1}
v_2	V(2)	7.541	h^{-1}
v_3	V(3)	1.026	h^{-1}

[a] Values obtained using FUNFIT (22).

Response Approximation Versus Parameter Estimation

The deconvolution is calculated from parameters obtained by fitting the sum of exponentials to absorption data and data from intravenous administration in the same subject. However, it is important not to interpret this as a standard parameter estimation problem, since the individual values of the parameters are irrelevant. It is not necessary and would be distracting to associate any kinetic significance to the parameters.

Of importance is how well the estimated parameters combined in the functional form approximate the response measured. The parameters are simply used mathematically as a way of uniquely defining a curve that approximates a measured response. This is in contrast to the classical model dependent pharmacokinetic approaches, where parameters such as "the first-order absorption rate constant," "the first-order elimination rate constant," etc., are determined.

The advantages of the "response technique" over the "parametric technique" can hardly be overemphasized. First, the pharmacokinetic

Table VII. Parameters Used for Deconvolution of Pentobarbital Data

Mathematical symbol	Program symbol	Value	Units
	INPUT		
i.v. administration			
a_1	A(1)	0.7910[a]	μg/ml
a_2	A(2)	0.5052[a]	μg/ml
α_1	ALPHA(1)	1.405[a]	h^{-1}
α_2	ALPHA(2)	1.648 $\times 10^{-2}$[a]	h^{-1}
n	N	2[a]	
D_{IV}	DIV	5×10^4	μg
Oral administration			
b_1	B(1)	0.8898[a]	μg/ml
b_2	B(2)	−0.8898[a]	μg/ml
β_1	BETA(1)	0.2304[a]	h^{-1}
β_2	BETA(2)	21.08[a]	h^{-1}
m	M	2[a]	
D	DOSE	5.10^4	μg
L	L	3	
	RESULTS		
u_0	UZ	12.24	
u_1	U(1)	228.8	
u_2	U(2)	−65.76	
u_3	U(3)	−175.2	
v_1	V(1)	0.2304	h^{-1}
v_2	V(2)	21.08	h^{-1}
v_3	V(3)	0.5577	h^{-1}

[a] Values obtained using FUNFIT (22).

model equations are nonlinear in some of the parameters, so the parameters may not be uniquely determined. Simulation studies have shown that even with excellent data several different sets of parameters may be obtained (22). The sets may differ substantially and yet give rise to nearly identical curves that fit the data well and are statistically indistinguishable (22). Furthermore, the parameters are often poorly determined, with wide confidence limits. Thus there is reason to have reservation about the significance of such parameters. This nonuniqueness and poor accuracy of the estimated parameters is not a problem in the "response technique" approach, since the only aim is a good fit to get a satisfactory approximation of the response measured. Second, if the system is linear it distracts from the fundamental properties of such a system to assume a specific pharmacokinetic model to evaluate drug absorption. Third, the graphical representation in the deconvolution approach is more meaningful than in the model dependent approach. Does a good fit to blood data alone justify the significance of the parameters of a pharmacokinetic model with intricate

assumptions such as first-order absorption, distribution, and elimination processes, etc.? Of what significance is a good fit when undoubtedly many other intricate models can be constructed that may produce just as good a fit or a better fit? However, the fit in the case of deconvolution is highly significant. Its quality directly determines the accuracy by which the input is evaluated.

The deconvolution method is an objective and "honest" method by clearly revealing its own limitation when presented graphically (Fig. 2). If PCT(t) in the postabsorptive phase deviates significantly from an asymptotic behavior, then the assumptions of a "noninteracting input" or a time invariant linear input-response relationship may be violated (1). The results would then be unreliable. However, this would also be the case if the same data were analyzed by classical linear pharmacokinetic techniques. The superimposed graphical representation of the estimated absorption and i.v. administration responses and the calculated input provided by the method (Figs. 1 and 2) is of substantial conceptual value. It enables the user to visually evaluate whether discrepancies or peculiarities found in a calculated input are due to an improper data representation, judged from the fitted curves, or whether they are due to the inherent nature of the estimated responses. For example, the pentobarbital data (Fig. 2) show an unrealistic input profile that is easily identified as being due to a substantial disagreement between the i.v. and oral curves in the postabsorptive phase. The method is therefore not used as a "black box," but enables the user to be objective and critical about the results obtained and the pharmacokinetic assumptions involved.

The deconvolution of the pentobarbital data is extremely difficult because apparently only two data points are available in the absorptive phase and because of the large errors in the data (21). Due to the low information density in the absorption phase, it is therefore not surprising that the present method (Fig. 2) and the cubic spline approach (Fig. 6 of ref. 2) differ substantially with respect to the calculation of the absorption lag time and the initial rate of input. However, the difference is not so pronounced with respect to the percent absorbed maximum and the general trend in the postabsorptive phase.

Calculation of "the first-order absorption rate constant" by model dependent approaches may seem appealing. Most pharmacokinetic textbooks deal in detail with the evaluation of k_a and its use in dosage regimen calculations and the calculation of the steady state from multiple dosing. However, the assumption of a first-order absorption may be a gross oversimplification that may lead to unrealistic calculations. The same calculations can just as well be done in a "model independent" way using "the

input function" obtained from the present method. This should lead to safer, more objective calculations.

Deconvolution Versus the AUC Approach

The use of "the area under the curve," AUC, for comparisons of the extent of drug absorption is based on the same assumptions of linearity as in deconvolution. However, the deconvolution method has some distinct advantages over the AUC approach when data from an intravenous administration are available. The difference is best explained by the following theorem deduced directly from Eq. (3).

Theorem 2. *The deconvolution calculation of the rate and the extent of input at any time* $(t = t_0)$ *does not depend on* $C_\delta(t)$ *or* $C(t)$ *beyond that time* $(t > t_0)$.

Thus if the absorption is virtually completed at $t = t_0$, then it is not necessary to sample beyond that time. In fact it is not necessary to know the characteristic response beyond that time. Also, a poor fit to the data in the postabsorptive phase does not affect the calculation of the input. Sampling beyond the absorption phase only serves the purpose of checking the assumptions of the method.

This is in strong contrast to the AUC, where a substantial number of samples must be placed in the postabsorptive phase to better estimate AUC, and in particular to get an estimate of the terminal slope for extrapolation. The extrapolation to $t = \infty$ is also very problematic and makes the AUC method in essence "model dependent." Blood sampling in human subjects is quite constrained by the number of samples that can be drawn. The experimental design aimed at the evaluation of both the rate and the extent of absorption by the quantities C_{max}, t_{max}, and AUC is complicated by conflicting demands with respect to the choice of sampling times. Compromise all too often leads to a situation where neither the rate nor the extent of absorption is appropriately determined. The deconvolution method is not faced with this dilemma. It allows a more rational sampling design. The sampling times can be concentrated in the absorption phase, where the real information about the input is present. They need not be "wasted" in the postabsorptive phase in order to estimate AUC and extrapolate to $t = \infty$.

In fact, since the method so well defines the absorption phase, it encourages a more rational sampling design in future studies. For example, if the oral cimetidine study were to be repeated for subject 4 (Fig. 1), it would be appropriate to concentrate the sampling in the first three hours with one or two "check points" in the tail region. The valuable quantities C_{max} and t_{max} are naturally available as a "byproduct" of the deconvolution method in

addition to the time for absorption. The method also provides a more detailed analysis of the absorption process than the C_{max}, t_{max}, and AUC quantities.

The method discussed appears to be a valuable tool for the evaluation of drug input and bioavailability. The easy computational implementation of the method presented should facilitate the promotion of deconvolution in pharmacokinetics. Hopefully, this may lead to a less assumptive and more critical and objective approach in drug absorption studies.

APPENDIX

```
      SUBROUTINE DECONV (A,ALPHA,N,DIV,B,BETA,M,DOSE,UZ,U,V,L)
      DIMENSION  A(N),ALPHA(N),B(M),BETA(M),U(L),V(L),G(20),GAMMA(20)
      IF (N .EQ. 1) GO TO 90
      NM1 = N - 1
      DO 5 I = 1,NM1
      IP1 = I + 1
      DO 5 J = IP1,N
      IF (ALPHA(I) .LE. ALPHA(J)) GO TO 5
      TEMP = ALPHA(I)
      ALPHA(I) = ALPHA(J)
      ALPHA(J) = TEMP
      TEMP = A(I)
      A(I) = A(J)
      A(J) = TEMP
    5 CONTINUE
      EPS = 1.0
   10 EPS = EPS/2.0
      S = 1.0 + EPS
      IF (S .GT. 1.0) GO TO 10
      DO 85 II = 1,NM1
      X1 = - ALPHA(II)
      X2 = - ALPHA(II + 1)
      QX1 = 0.0
      QX2 = 0.0
      DO 20 I = 1,N
      S1 = 1.0
      S2 = 1.0
      DO 15 J = 1,N
      IF (J .EQ. I) GO TO 15
      S1 = S1*(ALPHA(J) + X1)
      S2 = S2*(ALPHA(J) + X2)
   15 CONTINUE
      QX1 = QX1 + A(I)*S1
   20 QX2 = QX2 + A(I)*S2
   25 X3 = X1
      QX3 = QX1
      D = X2 -X1
      E = D
   30 IF (ABS(QX3) .GE. ABS(QX2)) GO TO 35
      X1 = X2
      X2 = X3
      X3 = X1
      QX1 = QX2
      QX2 = QX3
      QX3 = QX1
```

```
35 TOL = 4.Ø*EPS*ABS(X2)
   XM = Ø.5*(X3 - X2)
   IF (ABS(XM) .LE. TOL .OR. QX2 .EQ. Ø.Ø) GO TO 7Ø
   IF (ABS(E) .LT. TOL .OR. ABS(QX1) .LE. ABS(QX2)) GO TO 5Ø
   IF (X1 .NE. X3, GO TO 4Ø
   S = QX2/QX1
   P = 2.Ø*XM*S
   Q = 1.Ø - S
   GO TO 45
4Ø Q = QX1/QX3
   R = QX2/QX3
   S = QX2/QX1
   P = S*(2.Ø*XM*Q*(Q-R) - (X2-X1)*(R-1.Ø))
   Q = (Q-1.Ø)*(R-1.Ø)*(S-1.Ø)
45 IF (P .GT. Ø.Ø) Q = -Q
   P = ABS(P)
   IF ((2.Ø*P) .GE. (3.Ø*XM*Q - ABS(TOL*Q))) GO TO 5Ø
   IF (P .GE. ABS(Ø.5*E*Q)) GO TO 5Ø
   E = D
   D = P/Q
   GO TO 55
5Ø D = XM
   E = D
55 X1 = X2
   QX1 = QX2
   X2 = X2 + D
   IF (ABS(D) .LE. TOL) X2 = X2 - D + SIGN(TOL,XM)
   QX2 = Ø.Ø
   DO 65 I = 1,N
   S2 = 1.Ø
   DO 6Ø J = 1,N
6Ø IF (J .NE. I) S2 = S2*(ALPHA(J) + X2)
65 QX2 = QX2 + A(I)*S2
   IF ((QX2*(QX3/ABS(QX3))) .GT. Ø.Ø) GO TO 25
   GO TO 3Ø
7Ø GAMMA(II) = X2
   S2 = Ø.Ø
   DO 8Ø J = 1,N
   S1 = Ø.Ø
   DO 75 K = 1,N
   IF (K .EQ. J) GO TO 75
   S1 = S1 + 1.Ø/(GAMMA(II) + ALPHA(K))
75 CONTINUE
8Ø S2 = S2 + A(J)*S1/(GAMMA(II) + ALPHA(J))
85 G(II) = 1.Ø/S2
9Ø AK1 = Ø.Ø
   AK2 = Ø.Ø
   AK3 = Ø.Ø
   DO 95 I = 1,N
   AK1 = AK1 + A(I)
   AK2 = AK2 + A(I)*ALPHA(I)
95 IF (N .GT. 1 .AND. I .NE. N) AK3 = AK3 + G(I)/GAMMA(I)
   AK1 = 1.Ø/AK1
   AK2 = AK1*AK1*AK2
   AK3 = AK2 - AK3
   AK4 = 1ØØ.Ø*DIV/DOSE
   UZ = Ø.Ø
   DO 115 I = 1,L
   S = Ø.Ø
```

```
      IF (I .GT. M) GO TO 105
      V(I) = BETA(I)
      U(I) = AK4*B(I)*(AK1 - AK3/BETA(I))
      IF (N .EQ. 1) GO TO 115
      DO 100 J = 1,NM1
100   S = S + G(J)/(GAMMA(J)*(GAMMA(J) + BETA(I)))
      U(I) = U(I) - AK4*B(I)*S
      GO TO 115
105   V(I) = - GAMMA(I-M)
      DO 110 J = 1,M
110   S = S + B(J)/(GAMMA(I-M) + BETA(J))
      U(I) = AK4*G(I-M)*S/GAMMA(I-M)
115   UZ = UZ - U(I)
      RETURN
      END
```

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