unless reference is made to the exact pH, buffer, and buffer concentrations used in the dissolution medium. Inclusion of the pKa of the buffer and acid, together with the intrinsic solubility of the acid, also is of use in interpretation of such dissolution data.

The relevance of the model presented here to the dissolution of acidic drugs from buffered tablet formulations is that, since the dissolution rate of an acidic drug is affected by the buffering effect and pH of its immediate surroundings, the incorporation of suitable buffering agents directly in tablet formulations should facilitate the release of the acidic drug from the tablet. The model certainly may assist the formulator in the choice of a buffering agent in the tablet relative to the pKa and solubility of the dissolving acid. However, direct application of the model to buffered dosage forms is difficult since the buffer must dissolve from the tablet simultaneously with the acidic drug. Furthermore, the surface area from which the dissolution occurs obviously changes during dissolution, and hydrodynamic conditions between an experiment and the *in vivo* situation are likely to differ markedly.

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Pharmacokinetic Analysis by Linear System Approach I: Cimetidine Bioavailability and Second Peak Phenomenon

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Abstract □ The pharmacokinetics of cimetidine were evaluated using a linear system analysis that was formulated specifically to resolve the second peak in the blood drug concentration profile after oral dosing. The analysis exemplifies a new approach to pharmacokinetic modeling, which appears to be a valuable alternative to linear compartmental or physiological modeling. The formulation of linear system analysis according to a certain interpretation of a pharmacokinetic phenomenon avoids the complexity of conventional modeling, which often obscures the significance of the kinetic parameters. The new approach should result in a more rational analysis of pharmacokinetic phenomena because the less important pharmacokinetic processes are not specifically modeled but are still accounted for in the mathematical treatment. The bioavailability of cimetidine calculated by deconvolution agrees with previous findings. The model proposed to describe the second peak after oral absorption appears to agree well with the data and the hepatic recycling reported for cimetidine.

Keyphrases □ Linear system approach—evaluation of pharmacokinetics of cimetidine □ Pharmacokinetics—cimetidine, evaluation by linear system approach □ Cimetidine—evaluation of pharmacokinetics by linear system approach

Pharmacokinetic phenomena have been modeled and analyzed primarily according to two classes of models: linear compartmental models and physiological models. The classical linear compartmental models frequently provide a good fit to pharmacokinetic data. However, due to the fictitious structure of these models, which often bears little relation to the true nature of the pharmacokinetic processes, the parameters estimated from such models often have no real kinetic significance. The physiological models that attempt to be more realistic by considering such factors as blood flow and elimination and distribution in various organs and tissues may provide more meaningful results. However, the great number of physiological parameters and the difficulty of obtaining accurate and reliable estimates of these parameters make this approach very difficult. Both approaches to modeling

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are faced with a statistical and numerical dilemma: the more complex a model becomes to consider the many kinetic factors involved and/or to get a better fit to the data, the less significant the individual parameters become.

This report discusses how linear system analysis may be applied as an alternative to other modeling approaches and how the described problems can be overcome, to some extent, by the new approach. Linear system analysis apparently has not been used in pharmacokinetic modeling because the analysis is considered and treated basically as a model-independent procedure. It is demonstrated that the linear system approach may be formulated according to a specific pharmacokinetic interpretation, without having to rely on complex pharmacokinetic or mathematical models. The formulation should result in a more rational analysis of the pharmacokinetic phenomena of interest because the pharmacokinetic processes of minor interest are not specifically modeled but are still accounted for in the mathematical treatment.

The new type of modeling is demonstrated using the pharmacokinetics of cimetidine. Since its peculiar kinetic behavior was discussed and analyzed recently using linear compartmental principles (1, 2), there should be a good basis for comparison with this conventional type of analysis.

THEORETICAL

Derivation—The mathematical derivation is based on a linear system approach that involves the following basic assumptions:

1. The pharmacokinetic system is linear and time invariant (3) in the sense that the drug concentration response in the sampling region, S (the blood), behaves linearly with respect to direct (intravenous) drug input (Fig. 1, part 1) and to indirect (absorption) input (Fig. 1, part 2) independent of time.
2. The characteristic response (the unit impulse response) of the sampling region is the same for direct and indirect input.

Under Assumption 1, the concentration response, $c(t)$, in S is the convolution of the characteristic response, $c_\delta(t)$, and the rate of direct input, $f(t)$, into S:

$$c(t) = c_s(t)*f(t) = \int_0^t c_\delta(t-u)f(u)du = \int_0^t c_\delta(u)f(t-u)du \qquad \text{(Eq. 1)}$$

The characteristic response, $c_s(t)$, is determined by the transfer of drug between the sampling region, S, and the peripheral region, P[1], and by the elimination from S (Fig. 1, parts 1 and 2). If the $S \leftrightarrow P$ transfer kinetics and the drug elimination kinetics do not change significantly between the direct (intravenous) input and the indirect (absorption) input, then Assumption 2 will be valid. In that case, Eq. 1 can be used to evaluate the input–response relationship in the absorption case. The vital link in this relationship, the characteristic response, $c_\delta(t)$, then can be evaluated from a direct (intravenous) drug administration (4, 5).

The current definition of bioavailability is based on the rate and extent of input into the systemic circulation (6–8). In mathematical terms, these parameters are equivalent to $f(t)$ and $\int_0^t f(t)dt$ or $\int_0^\infty f(t)dt$. The various deconvolution methods proposed to evaluate $f(t)$ from Eq. 1 were discussed previously (9–11). These methods are either inaccurate and particularly sensitive to errors in the data[2] (12) or computationally complex (9, 13, 14). However, a recently proposed deconvolution method appears to be accurate, error stable, and simple to use (5).

This method is based on an approximation (*e.g.*, least squares) of the absorption response, $c(t)$, by a sum of exponentials:

$$c(t) = \sum_{i=1}^{m} b_i e^{-\beta_i t_+} \quad \beta_i > 0 \qquad \text{(Eq. 2)}$$

where $t_+ = (t - t_{lag})_+$ and $c(0) = 0$. The characteristic response, $c_\delta(t)$, is obtained from a polyexponential approximation of the intravenous bolus response[3]:

$$c_{iv}(t) = \sum_{i=1}^{n} a_i e^{-\alpha_i t} \quad \alpha_i > 0 \qquad \text{(Eq. 3)}$$

according to:

$$c_\delta(t) = c_{iv}(t)/D_{iv} \qquad \text{(Eq. 4)}$$

where D_{iv} is the intravenous bolus dose.

The cumulative amount of drug absorbed, expressed as a percentage of the dose (D), was derived previously (5) as:

$$PCT(t) = \frac{100}{D}\int_0^t f(t)dt = u_0 + \sum_{i=1}^{m+n-1} u_i e^{-v_i t_+} \qquad \text{(Eq. 5)}$$

and the absorption rate was derived as:

$$f(t) = \frac{D}{100}\sum_{i=1}^{m+n-1} u_i(-v_i)e^{-v_i t_+} \qquad \text{(Eq. 6)}$$

The parameters $u_0, \{u_i\}_1^{m+n-1}$ that define the input function are calculated from $\{b_i,\beta_i\}_1^m$ (Eq. 2) and $\{a_i,\alpha_i\}_1^n$ (Eq. 3) and the doses (5).

Second Peak Phenomenon—A previous investigation strongly suggested that the second peak observed in the oral absorption curve of cimetidine is due to a discontinuous recycling phenomenon (1). Thus, it seems appropriate to consider the oral absorption input of this drug as consisting of two components: an input, $f_A(t)$, of drug that has not been recycled and an input, $f_B(t)$, of recycled drug:

$$f(t) = f_A(t) + f_B(t) \qquad \text{(Eq. 7)}$$

This corresponds, according to the fundamental superposition principle of linear systems (3, 15), to an equivalent partitioning of the response:

$$c(t) = c_A(t) + c_B(t) \qquad \text{(Eq. 8)}$$

The input components, $f_A(t)$ and $f_B(t)$, may be estimated individually from the response components, $c_A(t)$ and $c_B(t)$, by deconvolution if these response components can be properly resolved. This seems to be the case for the oral cimetidine data because of the substantial delay in the recycling and because of the substantial magnitude of the second peak that is superimposed at the end of the primary (A) absorption response.

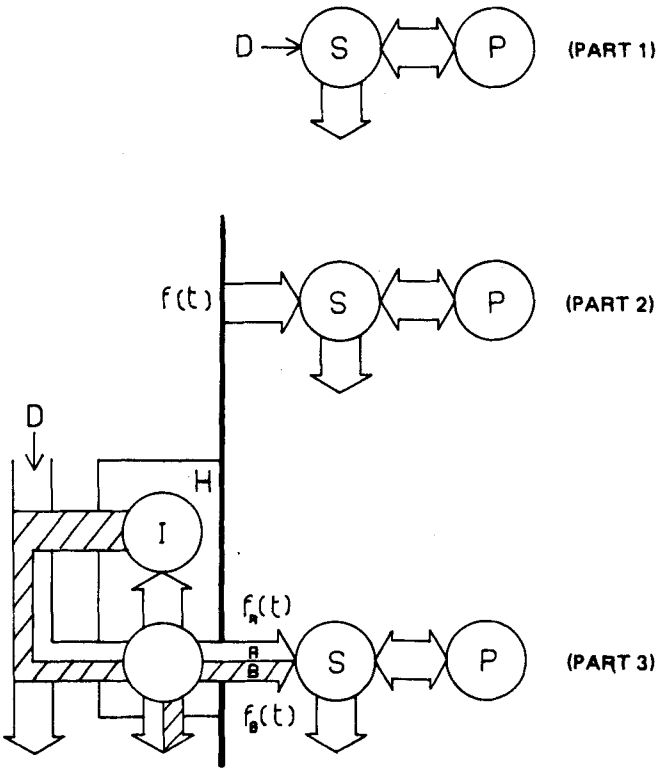

Figure 1—*Proposed pharmacokinetic model for cimetidine.*

[1] The treatment also is valid if the drug is eliminated from P.

[2] L. Z. Benet and C. W. N. Chiang, presented at the APhA Academy of Pharmaceutical Sciences, Chicago meeting, November 1977.

[3] The characteristic response can be determined readily from other types of intravenous input (5).

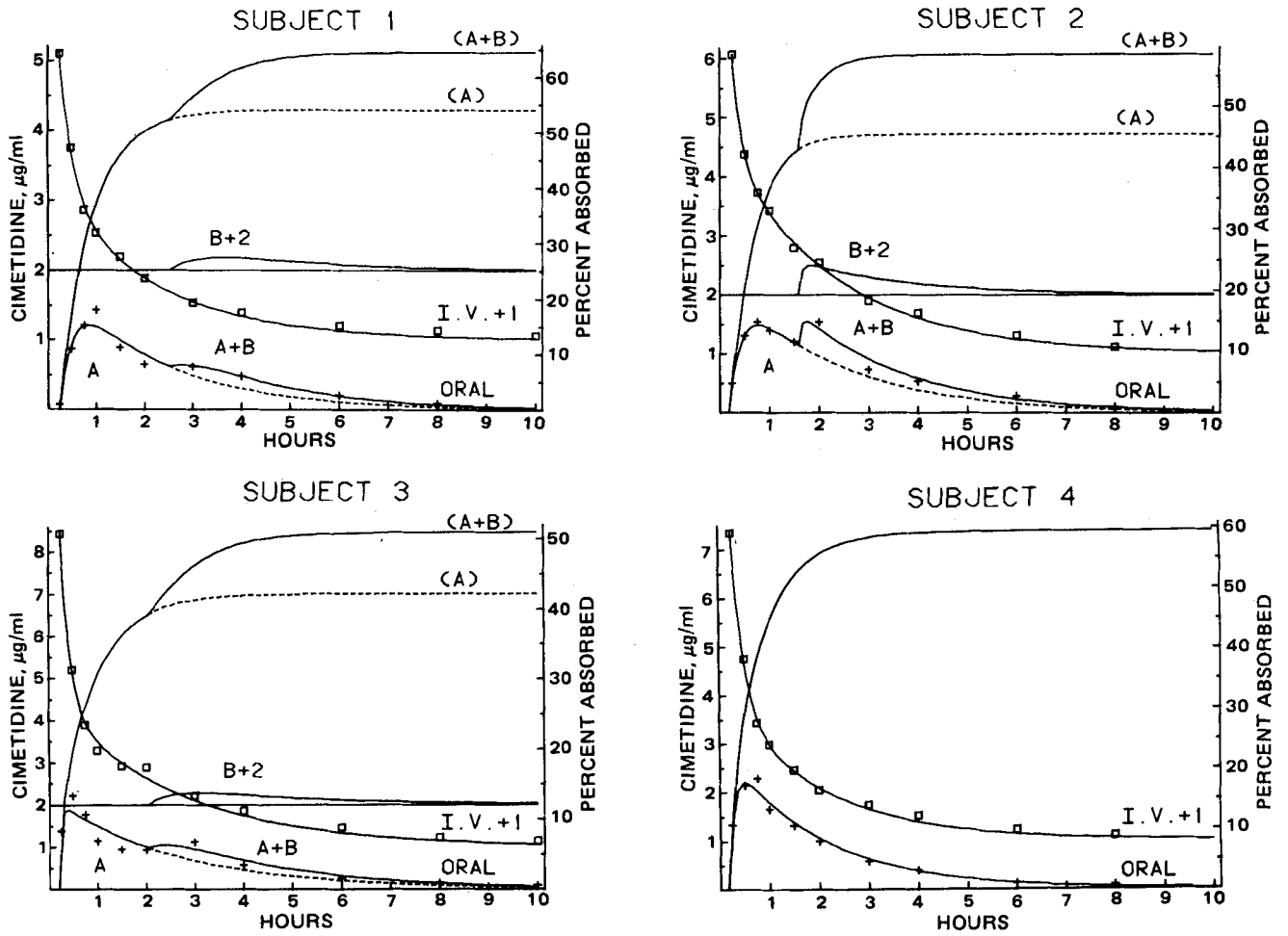

Figure 2—*Deconvolution of cimetidine data for Subjects 1–4. The monotonically increasing curve is the cumulative amount of input expressed as percent of the dose. The oral drug concentration–response approximation and input have been resolved into two components,* A *and* B, *where* A *is the primary input (or response) and* B *is a reabsorption component proposed according to the model in Fig. 1. The intravenous curve and data are staggered vertically one unit for clarity (I.V. + 1). The response component* B *is extracted from the oral curve and is staggered two units (*B + 2*).*

The pharmacokinetic literature has demonstrated the great utility of Eq. 2 in approximating oral absorption responses. For this reason and because of the smooth and asymptotic behavior of Eq. 2, it seems appropriate to apply Eq. 2 to resolve the absorption response in two polyexponential components:

$$c(t) = \left(\sum_{i=1}^{r} b_i e^{-\beta_i t+}\right)_A + \left(\sum_{j=1}^{s} b_j e^{-\beta_j t+}\right)_B \qquad \text{(Eq. 9)}$$

and to estimate these components by fitting their sum (Eq. 9) to the oral cimetidine data. The corresponding input components, $f_A(t)$ and $f_B(t)$, subsequently can be estimated individually by the deconvolution method, where the characteristic response is determined from the intravenous bolus data.

According to Assumption 2, the asymptotic terminal phases of the responses from the intravenous and oral administrations should agree within each subject. This specification requires that:

$$\min_i \alpha_i = \min_i (\beta_i)_A = \min_j (\beta_j)_B \qquad \text{(Eq. 10)}$$

To enforce this restriction, it is necessary to fit Eqs. 3 and 9 simultaneously to the data because of the shared parameter (Eq. 10).

The deconvolution method allows any number of exponential terms in the approximation of the characteristic response and the absorption input response. However, two exponential terms ($n = 2, r = 2, s = 2$) gave a satisfactory approximation to the data in all 12 cases (Figs. 2–4). Thus, the following equations were fitted simultaneously to the cimetidine data:

$$c_{iv}(t) = a_1 e^{-\alpha_1 t} + a_2 e^{-\alpha_2 t} \qquad \text{(Eq. 11)}$$

$$c(t) = (b_1 e^{-\beta_1 t+} + b_2 e^{-\beta_2 t+})_A + (b_1 e^{-\beta_1 t+} + b_2 e^{-\beta_2 t+})_B \qquad \text{(Eq. 12)}$$

with due consideration of the boundary conditions, $c_A(0) = 0$ and $c_B(0) = 0$:

$$(b_1 + b_2)_A = 0 \qquad \text{(Eq. 13)}$$

$$(b_1 + b_2)_B = 0 \qquad \text{(Eq. 14)}$$

If b_1 is defined as positive in Eq. 12, then $\beta_1 < \beta_2$ and the restriction in Eq. 10 becomes:

$$(\beta_1)_A = (\beta_1)_B = \min(\alpha_1, \alpha_2) \qquad \text{(Eq. 15)}$$

which is readily considered in the simultaneous curve fitting.

The theory (5) predicts that if m exponential terms are used for the approximation of the absorption response and n terms are used for the characteristic response, then the input function will consist of $m + n - 1$ exponential terms (Eqs. 5 and 6). Of these $m + n - 1$ exponential terms, m has exponents (time coefficients) identical to those used in the absorption response approximation (Eq. 2). If any exponent in the absorption response approximation coincides with an exponent for the characteristic response, then the corresponding exponential term of the input function vanishes ($u \to 0$). There is one common exponent parameter (Eq. 15) in the simultaneous fitting of Eqs. 11 and 12. Thus, the number of exponential terms in the input function is $(m + n - 1) - 1 = (2 + 2 - 1) - 1 = 2$ for components A and B[4].

In addition to a graphical presentation (Figs. 2–4) that provides the most informative picture of the absorption process, it is valuable to

[4] The u values corresponding to the common exponents calculated by the computer program in Ref. 5 were zero within the accuracy of the computer computations.

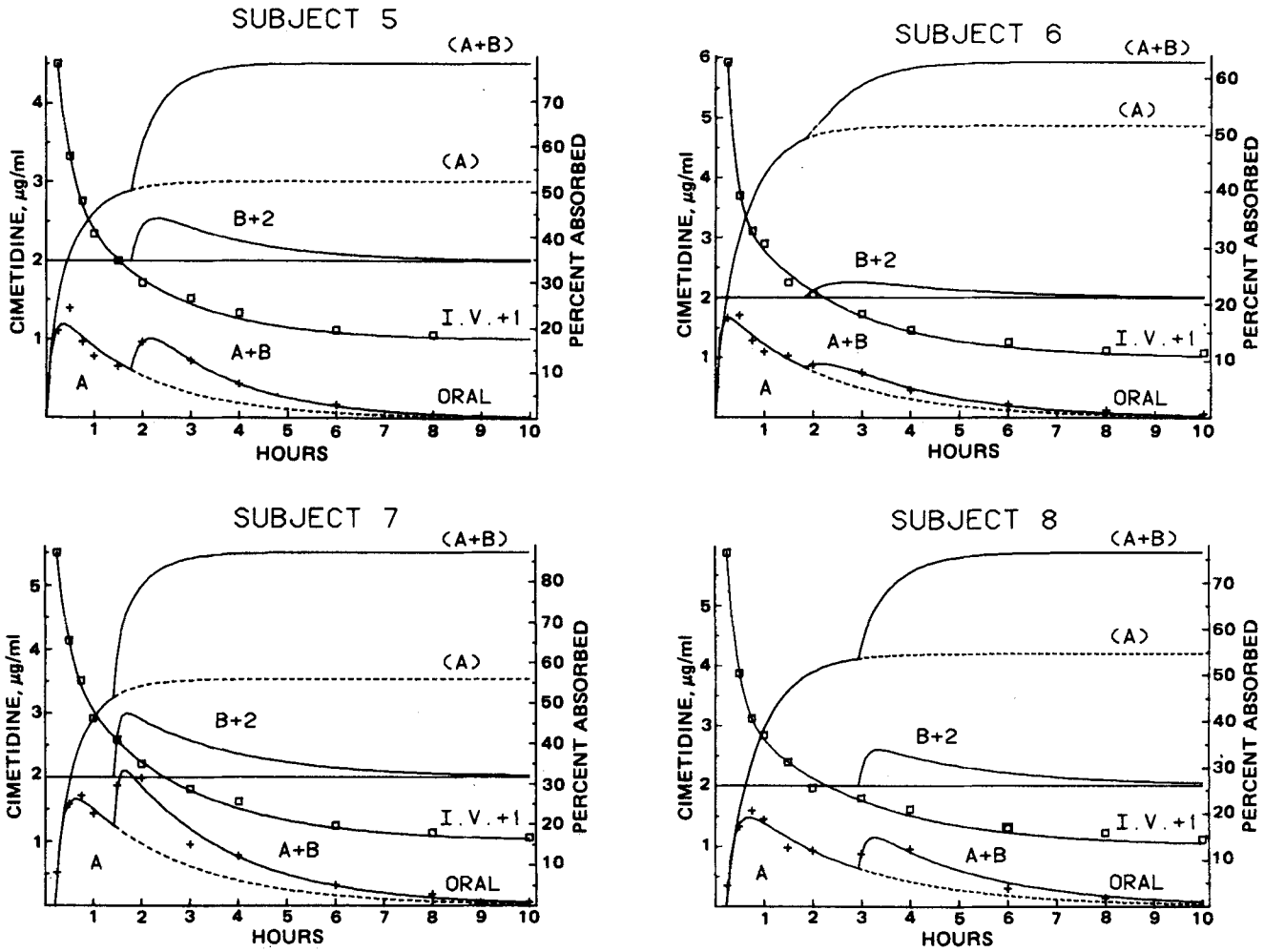

Figure 3—*Deconvolution of cimetidine data for Subjects 5–8. (See legend to Fig. 2.)*

quantify the rate and extent of drug input in simple terms. When Eq. 15 is satisfied, then $f(t) > 0$ for $0 < t < \infty$. Consequently, $PCT(t)$ is monotonically increasing, and the total bioavailability, expressed as percent of the dose, is ($v_i > 0$):

$$F = \lim_{t \to \infty} PCT(t) = (u_0)_A + (u_0)_B \qquad \text{(Eq. 16)}$$

The time, t_x (corrected for the lag time), for a given fraction, x, of the total amount absorbed to be absorbed is obtained from:

$$xF - PCT(t_x + t_{lag}) = 0 \qquad \text{(Eq. 17)}$$

where $PCT(t)$ is given by Eq. 5. The absorption times, $t_{1/2}$ and $t_{0.9}$, obtained in this way are useful measures of the absorption rate.

EXPERIMENTAL

The simultaneous fittings of Eqs. 11 and 12 to the cimetidine data were obtained using the general nonlinear regression program FUNFIT (16). The deconvolutions were done according to the algorithm and the computer program listed in Ref. 5. The absorption times, $t_{1/2}$ and $t_{0.9}$, were obtained by solving Eq. 17 using a root-finding algorithm proposed by Wilkinson (17) and improved by Brent (18). Figures 2–4 were drawn by a penplotter using computer graphics software written by the author[5].

RESULTS AND DISCUSSION

Since the deconvolution approach makes no assumptions about the mechanism and kinetics of drug absorption or the elimination and distribution kinetics, it is a particularly powerful method. It is versatile in that it is not limited to a particular pharmacokinetic model. It is well known from the theory of linear differential equations that the input–response relationship of classical linear compartmental models can be described by the convolution integral, Eq. 1. Therefore, the deconvolution approach can be thought of as a generalization of the linear compartmental approaches in drug absorption studies. However, it is not limited to this family of models described by first-order linear differential equations. It generalizes the families of models described by linear differential equations of any kind. In fact, the convolution integral relationship (Eq. 1) can be derived for a linear response system without reference to pharmacokinetic processes modeled in differential form (3, 19). Because of the nonspecificity of the deconvolution approach, there are no restrictions, other than the basic assumptions (Assumptions 1 and 2), with respect to the interpretation or modeling of the pharmacokinetic system. The deconvolution approach should stimulate a more rational and objective evaluation of pharmacokinetics.

In the case of cimetidine, one may assume a simple pharmacokinetic model as in Fig. 1, parts 1 and 2. In the intravenous bolus administration (Fig. 1, part 1), the drug input is directly into the sampling region, S (the blood). The change in the amount or concentration of drug in S is due to two basic processes, elimination and reversible distribution. This change is considered in the simplest form in the model in Fig. 1, part 1, where no specific assumptions are made about the distribution kinetics ($S \leftrightarrow P$) or the elimination kinetics ($S \rightarrow$ out). In the oral administration (Fig. 1, part 2), the drug input is not directly into the sampling region. In the first-pass process, the drug is exposed to the complex kinetic mechanism of the hepatic system before it reaches S. However, under Assumptions 1 and 2, if the first-pass process does not significantly change the drug distribution kinetics ($S \leftrightarrow P$) or elimination kinetics from S, then the input can be evaluated without considering the first-pass kinetics (Fig. 1, part 2). The present deconvolution calculations of cimetidine absorption can be interpreted in this simple way (Fig. 1, parts 1 and 2).

[5] An IBM 370/148 computer was used for the calculations and the plotting.

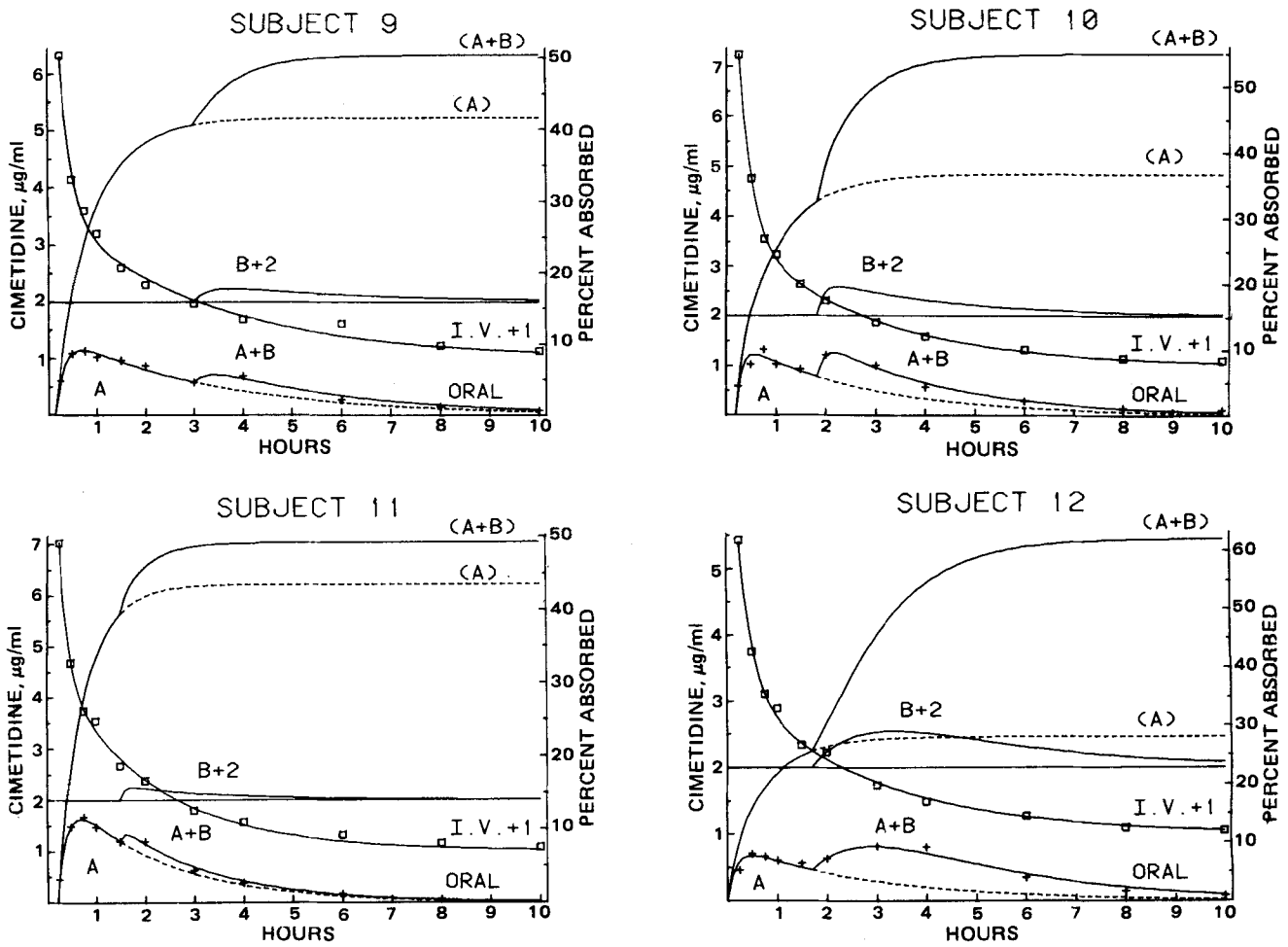

Figure 4—*Deconvolution of cimetidine data for Subjects 9–12. (See legend to Fig. 2.)*

The oral data show a pronounced secondary peak that a previous analysis (1) strongly suggests is a first-pass phenomenon. The following interpretation was proposed. The drug accumulates in a tissue or organ that is well perfused in the first-pass transfer. The hepatic parenchymal tissue and the bile phase appear to be the most likely storage areas. The rate of accumulation is much higher in the first-pass transfer than from the systemic circulation. The accumulation occurs by a competitive process, and absorbed elements of food seem to compete in this process. The second peak appears to be the result of a rapid release of drug and bioreversible drug compounds from the hepatic biliary system with subsequent reabsorption. This release may occur spontaneously but appears to be triggered by the intake of food.

It is of interest to quantify this proposed hepatic recycling. The pharmacokinetic model in Fig. 1, part 3, was constructed in agreement with this interpretation. This extension of the simpler model in Fig. 1, part 2, is not needed for the deconvolution calculations but is constructed to resolve the proposed drug absorption mechanism. Most of the drug (D) is absorbed from the GI system and is transferred to the hepatic system (H), where some of it is metabolized and accumulated (I) or passed on to the general systemic circulation (S) (Fig. 1, part 3). The drug accumulated in the hepatic system is released after some delay and then is reabsorbed and transferred to the systemic circulation (the shaded pathway in Fig. 1, part 3).

The extent of reaccumulation from the reabsorbed drug probably is not very significant because reabsorption appears to coincide with the intake of food (2 hr after dosing), and food apparently inhibits the hepatic drug accumulation (1). Even if the drug accumulates to the same extent after being reabsorbed, the compounded total amount (*e.g.*, 20% × 20% = 4%) most likely will not be detectable, considering the limited information density of the data. It apparently is not possible to detect any tertiary peaks in the oral data. Thus, the analysis can be appropriately limited to the primary input (A) and the reabsorption component (B) (Fig. 1, part 3), as discussed under *Theoretical*.

The simultaneous fitting of Eqs. 11 and 12 to the cimetidine data appears to give a good response approximation for all 12 subjects (Tables I and II and Figs. 2–4). The fit in the terminal phases of the oral and intravenous data is excellent for each subject, which is in agreement with Assumption 2 and Eq. 15. The cumulative input profiles for components A and B show asymptotic behavior, in agreement with the theory, and give a well-defined graphical representation of the extent of absorption due to A and B (Figs. 2–4). There is no secondary peak for Subject 4, perhaps because of a particularly slow or inhibited (nonfasting state?) hepatic drug accumulation in this subject. The good similarity between the oral response profile of Subject 4 and the A response profiles of the other subjects indicates that the particular A/B partitioning of the responses is a valid approach.

The average extent of primary absorption $(u_0)_A$ and reabsorption $(u_0)_B$ is 47 and 17%, respectively (Table III). The average total availability,

Table I—Least-Squares Polyexponential Approximation of Intravenous Bolus Response (Eq. 11) [a]

Subject	α_1, μg/ml	α_2, μg/ml	α_1, hr^{-1}	α_2, hr^{-1}	$RSS^b \times 10^2$, $(\mu g/ml)^2$
1	2.30	5.07	0.479	3.56	3.96
2	3.69	7.20	0.449	5.60	2.54
3	3.60	15.3	0.395	5.19	19.1
4	3.08	10.3	0.523	4.15	7.92
5	2.18	3.95	0.531	3.64	1.67
6	2.78	11.4	0.464	6.18	5.37
7	3.05	4.59	0.449	3.79	4.11
8	2.55	8.31	0.407	4.69	7.15
9	2.66	7.99	0.318	4.13	13.6
10	2.87	9.73	0.388	3.94	2.64
11	3.83	9.97	0.506	5.29	8.74
12	2.31	5.68	0.365	3.64	4.76

[a] Fitted simultaneously with the oral absorption data (Eq. 12). [b] Residual sum of squares.

Table II—Least-Squares Polyexponential Approximation of Absorption Response (Eq. 12) [a]

Subject	Component A			Component B			$RSS^b \times 10^2$, $(\mu g/ml)^2$
	b_1, $\mu g/ml$	β_2, hr^{-1}	t_{lag}, hr	b_1, $\mu g/ml$	β_2, hr^{-1}	t_{lag}, hr	
1	1.82	4.09	0.25	0.453	1.53	2.51	10.3
2	2.16	4.34	0.18	0.571	17.1	1.58	5.84
3	2.04	30.0	0.21	0.521	16.3	2.05	40.7
4	2.76	9.29	0.17	—	—	—	10.1
5	1.54	8.46	0	0.817	4.48	1.76	7.81
6	1.95	13.7	0	0.540	1.90	1.82	6.38
7	2.15	6.92	0.21	1.16	13.5	1.43	8.30
8	1.92	6.13	0.22	0.756	7.55	2.94	5.65
9	1.45	5.57	0.14	0.316	3.47	2.99	1.73
10	1.47	8.93	0.19	0.737	7.36	1.83	5.99
11	2.30	5.37	0.20	0.285	13.3	1.50	1.10
12	0.860	6.04	0	1.58	0.955	1.71	4.11

[a] Fitted simultaneously with the intravenous bolus data; $b_2 = -b_1$ and $\beta_1 = \alpha_1$ (Table I). [b] Residual sum of squares.

Table III—Parameters Defining the Input Function (Eqs. 5 and 6) [a]

Subject	Component A					Component B					Total Availability, *PCT* %
	u_0, %	u_1, %	u_2, %	v_1, hr^{-1}	v_2, hr^{-1}	u_0, %	u_1, %	u_2, %	v_1, hr^{-1}	v_2, hr^{-1}	
1	54.0	−4.31	−49.7	4.09	1.44	10.4	102.7	−113.1	1.53	1.44	64.4
2	45.5	10.5	−56.0	4.34	2.19	13.1	−3.95	−9.10	17.1	2.19	58.6
3	42.3	−9.19	−33.1	30.0	1.31	8.76	10.4	−19.1	1.99	1.31	51.1
4	59.6	−12.7	−46.9	9.29	1.36	—	—	—	—	—	59.6
5	52.2	−16.6	−35.6	8.46	1.64	26.1	−3.47	−22.6	4.49	1.64	78.3
6	51.6	−8.22	−43.4	13.7	1.59	11.2	39.0	−50.2	1.90	1.59	62.8
7	55.9	−16.0	−39.9	6.92	1.78	31.3	−12.2	−19.1	13.5	1.78	87.2
8	54.7	−5.02	−49.7	6.13	1.41	21.9	−3.07	−18.8	7.55	1.41	76.6
9	41.7	−4.29	−37.4	5.57	1.27	8.76	0.812	−9.57	3.47	1.27	50.5
10	36.8	−7.21	−29.6	8.94	1.20	18.2	−3.07	−15.1	7.36	1.20	55.0
11	43.5	−0.360	−43.1	5.37	1.83	5.74	−1.39	−4.35	13.3	1.83	49.2
12	28.0	−5.13	−22.9	6.04	1.31	34.0	−92.4	58.4	0.955	1.31	62.0
Mean	47.15					17.2					62.9
CV, %	19.4					56.8					19.1

[a] These parameters correspond to the absorption curves in Figs. 2–4.

Table IV—Absorption Times [a]

Subject	Component A		Component B		A + B	
	$t_{1/2}$, hr	$t_{0.9}$, hr	$t_{1/2}$, hr	$t_{0.9}$, hr	$t_{1/2}$, hr	$t_{0.9}$, hr
1	0.442	1.54	0.835	2.29	0.585	2.99
2	0.370	1.14	0.168	0.885	0.537	1.72
3	0.343	1.58	0.851	2.27	0.521	2.74
4	0.347	1.52	—	—	0.347	1.52
5	0.242	1.17	0.367	1.32	0.614	2.47
6	0.330	1.34	0.799	2.07	0.482	2.62
7	0.257	1.10	0.163	1.02	0.668	1.78
8	0.432	1.56	0.394	1.52	0.785	3.40
9	0.472	1.73	0.598	1.88	0.652	3.42
10	0.405	1.74	0.436	1.77	0.968	2.69
11	0.375	1.25	0.238	1.11	0.452	1.59
12	0.400	1.60	1.22	3.22	2.04	4.23
Mean	0.368	1.44	0.552	1.76	0.721	2.60
CV, %	19.0	15.9	61.4	39.3	61.8	32.4

[a] Defined by Eq. 17.

$(u_0)_A + (u_0)_B$, is 63%, which agrees closely with the availability of 61% calculated previously by the area under the curve approach (1). Cimetidine is eliminated mainly *via* the kidneys (20). This agrees closely with the 50% recovery reported previously (21), which indicates that the calculated extent of bioavailability appears to be physiologically meaningful.

A statistical comparison of the absorption rates of input components *A* and *B* on the basis of $t_{1/2}$ and $t_{0.9}$ (Table IV) indicates that *B* is significantly slower than *A* (one-tailed, paired *t* test, $\alpha < 0.05$). The drug accumulated in the hepatic system appears to be secreted as conjugates or complexes (1). The reabsorption of the drug from these forms may involve deconjugation and decomplexation, which may explain the slower absorption than from the oral solution.

The present method of analyzing the pharmacokinetics of cimetidine and resolving the second peak phenomenon is radically different from the approach presented previously (1) and from classical linear compartmental approaches in general. The deconvolution approach has several advantages.

1. The method is more general since it does not make specific kinetic assumptions such as first-order absorption, first-order compartmental transfer, and first-order elimination processes.

2. The method is basically model independent since it does not assume a specific pharmacokinetic model with a certain compartmental structure, nor does it make specific assumptions about the nature of the kinetic processes involved.

3. Because of this model independence, the method allows a more free and rational analysis of the pharmacokinetics. The method does not postulate a specific pharmacokinetic interpretation or attempt to justify a particular model; instead, it allows a great degree of freedom in the interpretation. This approach should stimulate a more specific and rational experimental design in a future study.

4. As demonstrated for cimetidine, the deconvolution approach can

be formulated according to a specific pharmacokinetic interpretation without relying on a complex pharmacokinetic or mathematical model as in the previous study (1).

5. The deconvolution approach is computationally easier than the often complex equations of compartmental models. Considerable effort may be necessary to derive and check the equations of such models and to obtain suitable initial estimates of the often numerous microparameters for curve fitting. However, the simplicity of the equations in the deconvolution approach and the few parameters involved virtually eliminate such problems.

6. In the deconvolution approach, the input is presented in a clear comprehensible manner in terms of an input profile (Figs. 2–4), which appears to be more descriptive and detailed than classical measures of absorption such as k_a and $t_{1/2(abs)}$.

7. The deconvolution approach has the important property of not requiring an extrapolation to time infinity, as required by the AUC_0^∞ approach for the evaluation of the extent of bioavailability (11). In that sense, it makes fewer assumptions than the AUC_0^∞ approach. It also allows a more rational and intelligent sampling design (5, 11).

The main disadvantage of the linear system approach is that it is limited to linear response systems. However, this limitation does not mean that the basic kinetic processes, such as distribution, metabolism, glomerular filtration, and drug binding that determine pharmacokinetics, need to be linear or first order. These processes most likely are of a nonlinear nature instead of the pseudolinear nature that often is assumed. However, the overall effect of the individual kinetic processes may result in a system that is well approximated linearly, so that the fundamental convolution integral relationship (Eq. 1) applies (5, 11).

The modelless nature of the linear system approach may not seem appealing if the objective of a study is to model the kinetics of specific pharmacokinetic processes. However, with some ingenuity, it may be possible to adapt the linear system approach to model and analyze a specific pharmacokinetic phenomenon, similar to what is done in this work. The linear system approach also may be combined with conventional models to simplify systems that otherwise would be rather complex. Such limited modeling approaches should be more appropriate because fewer assumptions are involved and they should lead to models of a more general nature.

The most rational approach is, if possible, not to model peripheral kinetic aspects that cannot be experimentally verified but to focus the modeling on the pharmacokinetic aspects of particular interest. If the objective is to elucidate drug input kinetics, then this can be readily accomplished using the deconvolution approach by plotting the input function according to the models considered. For example, if a plot of ln $[f(t)]$ *versus* t is approximately linear, then it indicates a first-order input. Different mathematical models for the input can be considered quickly in this way. This approach is obviously more rational than is mathematical derivation with subsequent fitting of the regression equation specifically for each input model.

The equations fitted to approximate the concentration–time response in the linear system approach are empirical. There is no need to attach any specific kinetic significance to their parameters. Model-dependent approaches, however, often attempt to be kinetically significant by considering many pharmacokinetic factors. Complex models often result where the parameters of particular interest lose their practical significance because of the large total number of parameters and the low information density frequently found in pharmacokinetic data. The linear system approach is not faced with this dilemma. There is no loss in kinetic significance when the number of parameters is increased to get a more appropriate approximation of the concentration–time response.

The linear system analysis approach to evaluate pharmacokinetic phenomena seems promising. A careful formulation of this approach may offer a valuable alternative to conventional modeling. Considering the great complexity of the biological processes that determine a drug's pharmacokinetics and the often limited information density of pharmacokinetic data, it seems irrational to derive complex models to consider the many factors involved, particularly when the mechanism of many of these factors cannot be verified. It seems more rational, if possible, not to model unknown processes that are not of primary interest but instead to consider their total effect and to focus the modeling on the pharmacokinetic aspect of real concern. The linear system analysis approach offers this possibility. These principles have been exemplified in analyzing the second peak phenomenon of cimetidine.

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