most routine procedures for determining model rate constants. The first three methods are obviously bad choices when $k_a = k_e$. A nonlinear regression analysis program such as NONLIN, with the simplest model, successfully revealed the real values of k_a and k_e. Bialer's criteria (1) can serve as additional proof of the NONLIN output.

It should be emphasized that although nonlinear regression techniques successfully converged to the real rate constants used to generate the data in the example, this does not imply that Eq. 1 is the only model which can be fitted to the data. The problems associated with obtaining a reliable value for a pharmacokinetic parameter, such as absorption rate constants after oral administration, have been previously identified. For example, a multiple-compartment open model may also be collapsed to a one-compartment open model under certain conditions (7). In reality, the true model is rarely known, and in most cases one can not distinguish one model from another. However, this study demonstrated that if Eq. 1 represents a true model, nonlinear regression analysis separates the rate constants where other methods can not.

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Kinetic Interpretation of the Microparameters in Compartmental Modeling When Adjoining Compartments are Sampled

Keyphrases □ Pharmacokinetic analysis—compartmental modeling □ Compartmental modeling—kinetic interpretation of microparameters □ Diffusional transport hypothesis—compartmental modeling

To The Editor:

In linear compartmental modeling, the rate of mass transfer of drug from compartment i to compartment j is $k_{ij}x_i$, and for the reverse transfer $k_{ji}x_j$, where the k's are constant microparameters and the x's stand for the amounts in the compartments (1). It appears tempting to justify compartmental pharmacokinetic analysis by attaching special kinetic significance to the microparameters. However, it is well recognized that this type of modeling is merely an abstract mathematical way of accounting for the combined effect of many complex disposition processes, which are too difficult or impossible to consider individually, in order to explain the concentration profile in a sampled compartment; typically the blood. It is also recognized that in pharmacokinetic practice when dealing with prediction and adjustment of blood levels, in the calculation of dosage regimens and in the evaluation of drug input, there is no need for compartmental modeling. It would be irrational to do so, because the required calculations can (at least for dose-linear systems) be done simply on the basis of the principles of superposition, convolution, or deconvolution. However, there are cases in pharmacokinetics where more than one tissue compartment is sampled for the drug. A compartmental type of kinetic analysis is then definitely justified. The blood–brain barrier (BBB) transfer kinetics of theophylline in dogs has recently been investigated. In the analysis, the classical linear compartmental approach was avoided because it appears completely irrational to assume that the transfer across a membrane is proportional to amounts and not to a concentration differential. A model-independent approach combined with a more rational compartmental transport mechanism was applied instead. In analyzing the equations resulting from this approach an interesting relationship was discovered between the diffusion and binding parameters and the microparameters in a classical compartmental approach. It is of interest to communicate these findings which bring the classical compartmental modeling into a different perspective.

The Diffusion Approach: The diffusion rate of the drug across the BBB is proportional to the difference between the free drug concentrations on the two sides of the barrier:

$$\frac{d}{dt}[V_cC_c(t)] = K_1[F_sC_s(t) - F_cC_c(t)] \quad \text{(Eq. 1)}$$

Subscripts c and s denote cerebrospinal fluid (CSF) and serum, respectively; V, C, and F stand for volume, total drug concentration, and free (unbound) fraction, respectively; while K_1 is a positive diffusion constant. Equation 1 assumes that the drug is not metabolized in the CSF, which is consistent with our current knowledge about the metabolic systems present on the CNS side of the BBB (2). The equation can readily be solved by Laplace transforms to give the following expression relating the total concentration of the drug in the CSF to the total concentration in the serum:

$$C_c(t) = \left(\frac{F_cK_1}{V_c}\frac{F_s}{F_c}\right) C_s(t) * e^{(F_cK_1/V_c)t} \quad \text{(Eq. 2)}$$

where * denotes convolution.

The derivation of Eq. 2 assumes that F_c and F_s do not depend significantly on the drug concentration. The free fractions depend on the unbound protein concentration as well as on the affinity of the protein for the drug. Usually only a small fraction of the available binding sites is occupied at therapeutic drug concentrations; therefore, the

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free fraction is relatively constant and independent of the drug concentration (3).

The diffusional transport hypothesis (Eq. 1) was verified kinetically in the following manner according to Eq. 2: A suitable arbitrary function was chosen to approximate the $C_s(t)$ response. (The fitting of a two-exponential expression to the C_s, t data appeared to give an excellent approximation.) The fitting of the arbitrary function to the serum data was done simultaneously with the fitting to the CSF data of a second function resulting from convoluting the first function according to Eq. 2. Good correlations to the CSF and serum data were observed.

The Classical Compartmental Approach: The rate of change of the amount, x_c, of drug in the CSF is

$$\frac{dx_c}{dt} = k_{sc}x_s - k_{cs}x_c \qquad \text{(Eq. 3)}$$

where k_{sc} and k_{cs} are the first-order rate constants for the transfer of drug from serum to CSF and reverse, respectively. Solving Eq. 3 through Laplace transforms gives:

$$x_c(t) = k_{sc}x_s(t)*e^{-k_{cs}t} \qquad \text{(Eq. 4)}$$

so that

$$C_c(t) = k_{sc}\left(\frac{V_s}{V_c}\right)C_s(t)*e^{-k_{cs}t} \qquad \text{(Eq. 5)}$$

By comparing Eqs. 5 and 2 the following relations are obtained:

$$V_c k_{cs} = F_c K_1 \qquad \text{(Eq. 6)}$$

$$V_s k_{sc} = F_s K_1 \qquad \text{(Eq. 7)}$$

One can, therefore, in this case of compartmental analysis with data available from adjoining compartments, relate the microparameters of the abstract mass transfer of classical compartmental modeling to the more meaningful parameters of a rational, diffusional-based transport mechanism (Eq. 1).

The relationships (Eqs. 6 and 7) may be stated simply as follows: The intercompartmental clearances are equal to the intercompartmental diffusion rate constant multiplied by the free fraction of the drug in the respective compartment.

The above analysis is valid for any complexity of the compartmental system as long as one of the two sampled, adjoining compartments is not connected to other compartments.

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Predicting the Dose-Dependent Bioavailability of Hydrocortisone and Chlorothiazide in Humans

Keyphrases □ Bioavailability—dose dependency, hydrocortisone, chlorothiazide □ Hydrocortisone—dose-dependent bioavailability, saturable absorption kinetics □ Chlorothiazide—dose-dependent bioavailability, saturable absorption kinetics

To the Editor:

A recent report (1) described the occurrence and mechanisms of dose-dependent saturable absorption kinetics for several commonly used drugs. Equations were also derived, on the basis of the classical Michaelis–Menten approach, to predict such dose-dependent absorption kinetics (1). In the present communication, these equations are applied, in an effort to predict the recently reported, nonproportional dose bioavailability data on hydrocortisone (2) and chlorothiazide (3).

Predicted values for hydrocortisone plasma levels (C_{max}), area under the curve (AUC) and AUC corrected for variance in the first-order rate constant for drug elimination (AUC_{kel}) as well as chlorothiazide urine recovery were calculated using the parameters obtained from the derived equations reported earlier (1). Tables I and II list these calculated parameters and compare the observed values with the predicted values for each dose of hydrocortisone and chlorothiazide, respectively. The excellent correlations between the observed and predicted values attest to the validity of the saturable absorption predictive model for those two drugs. It should be noted that the dose-dependent hydrocortisone tablet data (4) also can be treated in a similar manner with good predictability.

The saturable absorption of chlorothiazide is probably related to the existence of an absorption window (1), inasmuch as the average urinary recovery of chlorothiazide is increased in humans in the presence of food (5) and in dogs following propantheline bromide administration (6).

Table I—Comparison of Observed and Predicted Values for Hydrocortisone

Dose, mg	C_{max}[a], ng/ml		AUC[b], ng·hr/ml		$AUC_{\cdot k_{el}}$[c], ng/ml	
	Obs[d]	Pred[e]	Obs	Pred	Obs	Pred
5	119	114	293	278	171	162
10	175	188	447	502	248	267
20	263	278	835	838	377	396
40	389	366	1340	1259	553	521
r value	0.990		0.996		0.991	

[a] C_{max} = 533 ng/ml when the Michaelis constant (K_m) is 18.2 mg. [b] AUC_{max} = 2531 ng·hr/ml when K_m = 40.4 mg. [c] $(AUC \cdot k_{el})_{max}$ = 763 ng/ml when K_m = 18.5 mg. [d] Observed values (Obs) from previously published work (2). [e] Predicted values (Pred) calculated using previously derived equations (1).

Table II—Comparison of Observed and Predicted Urine Recovery for Chlorothiazide

Dose, mg	Recovery, mg[a]	
	Obs[b]	Pred[c]
50	28.3	28.0
100	47.0	47.8
250	83.3	82.7
r value	0.999	

[a] $Recovery_{max}$ = 161.6 mg when K_m = 238.2 mg. [b] Observed values (Obs) from previously published work (3). [c] Predicted values (Pred) calculated using previously derived equations (1).

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