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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Additional evidence for such site-specific absorption of chlorothiazide is presented by way of similar observations for the related drug hydrochlorothiazide in humans (7, 8).

The mechanism for the dose-dependency of hydrocortisone has been suggested to be an increased first-pass metabolism (2). By means of carefully planned studies, saturable binding and formulation factors were ruled out as determinants of the nonproportional dose–concentration relationship for hydrocortisone. Ease of absorption and linear absorption at the higher dosages used in previous studies (9, 10) were cited as the reasons for excluding saturable absorption as a contributing factor.

However, critical analysis of the two cited references (9, 10) on hydrocortisone absorption revealed the following information. First, a limited zone for absorption of hydrocortisone and hydrocortisone acetate existed in the small intestine of humans, inasmuch as the absorption from the proximal zone was nearly twice that from the distal zone. Absorption within the zones was linear. Second, the acetate ester was more efficiently absorbed than hydrocortisone. Third, both rate and extent of absorption was decreased in a malnourished patient in relapse with severe malabsorption. Last, absorption was higher when the gut was perfused under comparable conditions, using 1–5% glucose–Ringer's rather than Ringer's solution. This was probably due to the increased viscosity of the glucose–Ringer's solution and/or its energy-supplying potential as theorized previously (11). It should be mentioned that both the suspension and tablet studies (2, 4) administered the hydrocortisone dose with 180 ml of fluid, probably causing the drug to be washed past the zone of maximal absorption. The parallels between these observations for hydrocortisone and those aforementioned for chlorothiazide and hydrochlorothiazide absorption are all too obvious.

Further proof of a dose-dependent absorption phenomenon being operative for hydrocortisone is obtained by comparing the systemic availability, calculated by dividing mean AUC values after the suspension and tablet doses by those obtained after equivalent intravenous doses (2, 4, 12). The average systemic availability (F/V) of hydrocortisone was 71, 58, 56, 52, and 54% from the 5-, 10-, 20-, 30-, and 50-mg doses. In other words, there was a decrease in F, the fraction absorbed, with increasing dose, which contributed to the decrease in F/V with increasing dose seen in the tablet study (4). If, as suggested (2), there was a dose-dependent increase in the metabolism of an increased free fraction during the first pass, the systemic availability should increase, not decrease, with increasing dose. The latter would occur because of saturation of the hepatic enzymes by the increasing drug fraction. Increased systemic availability with increasing dose has been observed in the literature for propoxyphene (13) and several other drugs (14) known to undergo first-pass metabolism in humans. Additional factors that could possibly contribute to the dose-dependent bioavailability of hydrocortisone in humans include micromeritic and polymorphic effects with attendant stability and dissolution problems, as were observed with other corticosteroids (15).

In conclusion, hydrocortisone and chlorothiazide absorption after increasing, single, oral doses in humans, can be described by site-specific saturable absorption kinetics in the therapeutic dose range. The consequent dose-dependent bioavailability of these two drugs can be effectively predicted by use of the appropriate equations reported earlier (1). Use of these equations in the clinical setting should aid in the development of efficacious dosing protocols for any drug whose oral absorption is limited by the magnitude of the administered dose.

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Modified Wagner–Nelson Absorption Equations for Multiple-Dose Regimens

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To the Editor:

Equations to calculate the amount of drug absorbed per milliliter of the volume of distribution and the percent absorbed as functions of time for the one-compartment open model (1) are commonly referred to as Wagner–Nelson equations. The nature of such plots when the equations are applied to data obeying the two-compartment open model with first-order absorption was discussed by Wagner (2). In this communication modified equations

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