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

Keyphrases □ Absorption—Wagner–Nelson equations, multiple-dose regimens, one-compartment open model □ Wagner–Nelson equations—modification, multiple-dose regimens, one-compartment model □ Kinetics—absorption, Wagner–Nelson equations

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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are derived which apply to plasma, serum, or whole blood concentrations of unchanged drug during a dosage interval of any multiple-dose regimen including the steady state. As before (1) the derivation assumes applicability of the one-compartment open-disposition model but no particular kinetics of absorption need be assumed.

Let A_T represent the amount of drug which is absorbed from time zero (beginning of the dosage interval concerned) to some time T in the dosage interval (*i.e.*, $0 \leq T \leq \tau$ where τ is the time at the end of the dosage interval); A_b represent the total amount of drug remaining in the body at time T; A_b^0 be the amount of drug in the body at time zero, resulting from administration of doses previous to the one of interest; A_m be the total amount of drug metabolized between time zero and time T; A_e be the total amount of drug excreted in the urine between time zero and time T; V be the volume of distribution; C_n be the drug concentration in the interval $0 \leq T \leq \tau$; C_n^0 be the drug concentration at time zero as above; and k_e represent the elimination rate constant of the simple one-compartment open model. Then mass balance gives:

$$A_T = A_b - A_b^0 + A_m + A_e \qquad \text{(Eq. 1)}$$

Taking the derivative of Eq. 1 with respect to time gives:

$$\frac{dA}{dt} = \frac{dA_b}{dt} - \frac{dA_b^0}{dt} + \frac{d(A_m + A_e)}{dt} \qquad \text{(Eq. 2)}$$

but,

$$A_b = VC_n \qquad \text{(Eq. 3)}$$

and,

$$A_b^0 = VC_n^0 \qquad \text{(Eq. 4)}$$

and,

$$\frac{d(A_m + A_e)}{dt} = Vk_eC_n \qquad \text{(Eq. 5)}$$

Substituting from Eqs. 3–5 into Eq. 2 gives:

$$\frac{dA}{dt} = V\frac{dC_n}{dt} - V\frac{dC_n^0}{dt} + Vk_eC_n \qquad \text{(Eq. 6)}$$

Integrating Eq. 6 by term between the limits $t = 0$ and $t = T$ gives:

$$A_T = VC_n - VC_n^0 + Vk_e\int_0^T C_n dt \qquad \text{(Eq. 7)}$$

Division of both sides of Eq. 7 by V gives:

$$\frac{A_T}{V} = C_n + k_e\int_0^T C_n dt - C_n^0 \qquad \text{(Eq. 8)}$$

Equation 8 is the same as the single-dose Wagner–Nelson equation (1) except that C_n replaces C and there is the additional term $-C_n^0$ on the right-hand side. This indicates that for multiple-dose data the usual Wagner–Nelson calculation is performed, namely $C_n + k_e \int_0^T C_n dt$, then the value C_n^0 is subtracted from each value calculated. It should be noted that an incorrect set of A_T/V values would be obtained if C_n^0 was subtracted from each C_n value first, followed by the usual Wagner–Nelson calculation.

The total amount of drug absorbed per milliliter of the volume of distribution from the dose of interest A_τ/V is given by:

$$\frac{A_\tau}{V} = k_e\int_0^\tau C_n dt \qquad \text{(Eq. 9)}$$

Equation 9 gives the correct asymptotic value of A_T/V_p when the dose of interest is given at steady state and when absorption of the dose of interest is complete between the time zero and τ. If one or both of these conditions are not met and absorption is not zero order, then it is very difficult to obtain an accurate asymptotic value of the function.

The fraction absorbed (based on the amount of drug absorbed, not the dose) to time T is given by:

$$\text{Fraction absorbed} = \frac{A_T/V}{A_\tau/V} = \frac{A_T}{A\tau} \qquad \text{(Eq. 10)}$$

To appropriately apply Eqs. 8–10 the protocol for most routine multiple-dose pharmacokinetic studies will have to be modified. Modifications should include: (*a*) the dose of interest should be the last of a series of doses and preferably steady state should have been reached; (*b*) there should be intensive sampling of blood during the absorption phase; (*c*) the blood concentrations should be followed down well beyond the end of the dosage interval at τ hr to allow an estimation of k_e which is not biased by continuing absorption; and (*d*) in evaluating the integrals of Eqs. 8 and 9 it is best to use a combination such that the ordinary trapezoidal rule is used when the concentration is increasing or constant and the logarithmic trapezoidal rule when the concentration is decreasing.

Greater accuracy will be attained by determining the kinetics of absorption (if feasible at all) by resolving fraction absorbed values (Eq. 10) rather than A_T/V values (Eq. 8). If absorption is zero order then the slope of the straight line when the fraction absorbed is plotted *versus* time on reactilinear graph paper will be the correct zero-order constant even when the drug obeys two-compartment kinetics as well as one-compartment kinetics. This has been supported by simulations, and details will be published elsewhere. When absorption is first order and the one-compartment open model holds the ratio of the fraction absorbed values given by the method to the actual fraction absorbed, values will be equal to $1/(1 - e^{-k_a\tau})$ where k_a is the first-order absorption rate constant and τ is the uniform dosing interval. In almost all cases this ratio will have a numerical value between 1.001 and 1.100. An exception will be a very long half-life drug which is dosed too frequently.

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