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Report

Effect of a Change in the Luminal Perfusion Rate on Intestinal Drug Absorption Studied by a Simple Unified Organ Clearance Approach

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A recently proposed simple, noncompartmental, unified organ clearance approach was employed to study the effect of change in luminal perfusion rate (Q) on the steady-state intestinal absorption extraction ratio (E) of drugs. The equation used for correlation or prediction is $E = H/(Q + H)$, where H is the apparent intrinsic intestinal absorption clearance of drug and assumed to be constant under linear conditions. Reported experimental data from intestinal perfusion studies in rats were used to evaluate the applicability or accuracy of the above equation. It was found that the mean difference between the predicted and the reported E values for seven steroids with a very wide range of partition coefficients between *n*-octanol and water (P) was 4.37% as Q was reduced from 0.497 to 0.247 ml/min. Reported changes in E due to multiple variation in Q (up to about 10 times) for hydrocortisone, progesterone, and iopanoic acid were satisfactorily predicted. The relationship between H and log P and the potential limitation of the present absorption approach are discussed. The present limited study also indicates that the absorption of the steroids with higher lipophilicity is usually less flow dependent.

KEY WORDS: intestinal absorption; organ clearance.

INTRODUCTION

Recently, a simple, noncompartmental, kinetic approach (1) has been used to study clearance of compounds from vastly different organs such as liver (1–3), lung (1), kidney (1,4), intestine (5), and brain (to be published), as well as from an artificial device such as a hemodialyzer (6).

In this approach, the basic assumptions are usually very few and simple and, generally, do not appear inconsistent with complex physiological reality or mechanical configuration involving removal of compounds (1–6). Furthermore, mathematical derivations and/or expressions are all very simple.

The preliminary work of application of this approach to the study of effect of change in luminal perfusion rate (Q) on the intestinal absorption of seven steroids and iopanoic acid in rats has been presented[2] and published (5). The purpose of the communication is to report in detail the findings of this preliminary study.

THEORETICAL

When this clearance approach is used to study the effect of change in Q on the absorption extraction ratio (E) of drug during passage through the intestinal lumen, the following relationship is postulated (5):

$$E = \frac{H}{Q + H} \tag{1}$$

where H is the apparent intrinsic absorption clearance of drug for the intestinal preparation studied. The value of H is simply a reflection or a relative index of the overall "force," "ability," or "efficiency" of the intestine to remove (absorb) the drug from the lumen as compared to that from the flow of the luminal perfusion medium. The above equation simply indicates that the two forces or "processes" represented by Q and H, respectively, are competing with each other for removal of drug from the lumen. There is really no prior mathematical derivations needed for developing the above relationship. Under linear conditions (i.e., the drug is absorbed by simple diffusion or the drug concentration is in the linear range of saturable absorption), the H in Eq. (1) can be considered constant for a given system. Therefore, Eq. (1) may be employed to study or predict the effect of change in Q on E under these conditions. Obviously, a sink condition for drug concentration in blood draining the intestine, the constancy of blood flow to the intestine, and the integrity of the intestine during the study are assumed.

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[2] Presented at the joint Japanese–American Pharmaceutical Association Meeting in Hawaii, November 1987.

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Table I. Summary of Relevant Steroid Data in the Absorption Study

Steroid	log P^a	$E_{0.247}{}^a$	$E_{0.494}{}^a$	H (ml/min)^b	$E_{0.247p}{}^c$	Difference^d
Hydrocortisone	1.53	0.242	0.140	0.080 (0.079)^e	0.245	+1.2
Dexamethasone	1.74	0.335	0.210	0.131 (0.124)	0.347	+3.6
Corticosterone	1.89	0.388	0.270	0.183 (0.156)	0.426	+9.8
Androstenedione	2.75	0.604	0.450	0.404 (0.377)	0.620	+2.6
Deoxycorticosterone	2.88	0.620	0.435	0.380 (0.403)	0.606	−2.3
Testosterone	3.31	0.570	0.428	0.370 (0.327)	0.600	+5.3
Progesterone	3.99	0.608	0.505	0.504 (0.383)	0.671	+10.4
Mean						+4.37

[a] Data obtained from Ref. 7.
[b] Estimated based on Eq. (2) using a Q of 0.494 ml/min and the reported E at this rate (i.e., $E_{0.494}$ in this table).
[c] Predicted E at Q = 0.247 ml/min based on Eq. (1).
[d] Percentage difference = 100 $(E_{0.247p} - E_{0.247})/E_{0.247}$.
[e] The value in parentheses was obtained using a Q of 0.247 ml/min and the reported $E_{0.247}$.

METHODS

Comparison Between Predicted and Observed E Values After a Change in O

In order to test the usefulness of Eq. (1) for predicting the effect of a change in Q on E, experimental data reported by Komiya *et al.* (7) on seven steroids with a very wide range of lipophilicity (Table I) were employed. The H value for each steroid studied with a 33.3-cm length of rat jejunum at a Q of 0.494 ml/min and with a reported E value ($E_{0.494}$) was first calculated using the rearranged equation shown below:

$$H = EQ/(1 - E) \quad (2)$$

The predicted E [$(E_{0.247p})$ based on Eq. (1) at a Q of 0.247 ml/min)] with the same calculated H value was then compared with the reported experimental value ($E_{0.247}$).

Comparison Between Predicted and Observed E Values Following Several Changes in O

Reported (7) E values obtained at four different perfusion rates for hydrocortisone (0.137 to 1.43 ml/min), as well as for progesterone (0.247 to 2.14 ml/min), were fitted to Eq. (1) using a nonlinear least-squares analysis (PCNONLIN program from Statistical Consultants, Lexington, Kentucky). In this analysis, both Q and H were independent variables and E was the dependent variable. The H was the parameter to be obtained so that it would result in a best fit between experimental and predicted E values. Additional data for iopanoic acid[3] (8) studied at eight different perfusion rates (2.1 to 20.5 μl/sec) with the perfusion fluid buffered at pH 7.8 were also similarly analyzed. In the present study the absorption clearance (CL_a), a product of E and Q, was accurately estimated from their (8) Fig. 5 with the assistance of a 0.05-mm-dial increment vernier caliper (Fisher Scientific, Chicago, IL) (4), and the E at each Q was then calculated.

[3] A compound insoluble in water and soluble in most organic solvents. Its log P (between n-octanol and water), kindly estimated by Dr. William Dunn according to the Hansch, Leo fragment method and program, CLOGP (Chemical Information Systems, Claremont, CA 91711), is 5.22.

RESULTS

The results of analysis of changes in E for the seven steroids as Q was reduced by half in the intestinal study are summarized in Table I. The mean difference between experimental and predicted E values for all the studies is 4.37%. The results for hydrocortisone and progesterone in the multiple-flow rate study are shown in Fig. 1, their correlation coefficients being 0.993 and 0.996, respectively. The relationship (r = 0.994) between the experimental and the predicted E or CL_a values at different flow rates for iopanoic acid is depicted in Fig. 2. The lesser agreements for the two lowest flow rates studied (i.e., 2.1 and 3.1 μl/sec), between the predicted and the experimental data (Fig. 2) may be attributed to a technical problem associated with the use of such low flows (personal communication from Dr. A. E. Staubus), including much higher aqueous resistance at low flow rates.

DISCUSSION

The apparent success of using Eq. (1) to study or predict the effect of change in Q on E in the present study involving eight drugs may be significant because it further supports the operational utility and generality of the unique organ clearance approach proposed earlier by this author (1,2,4–6). Simplicity in concepts, derivations, and operation appears to be a strong point in this unified organ clearance approach.

It should be noted that Eq. (1) is operationally equivalent to the one used in the well-stirred hepatic model (9,10). Unlike the liver, it seems very clear that the intestinal perfusion study (7,8) cannot be assumed to behave like a well-

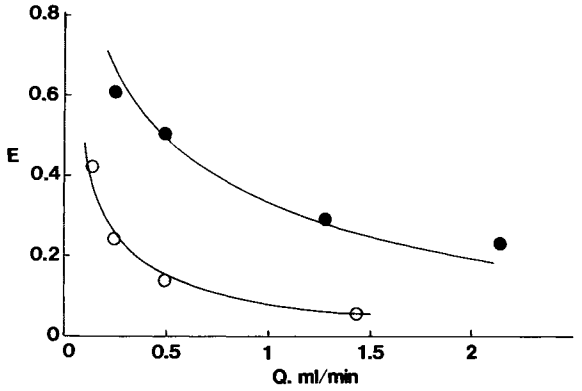

Fig. 1. Relationship between perfusion rate (Q) and intestinal absorption extraction ratio (E) for hydrocortisone (—○—) and progesterone (—●—). The curves were obtained from the nonlinear least-squares fitting of data according to Eq. (1)

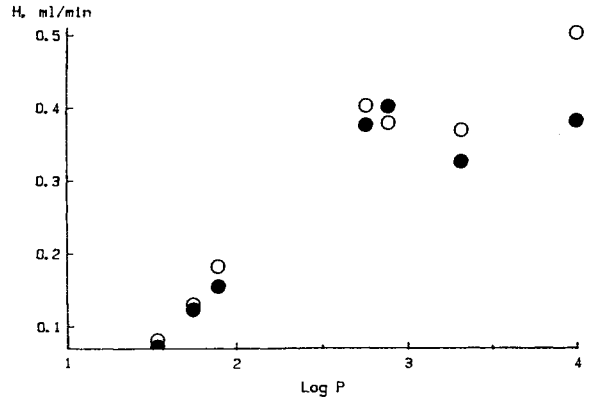

Fig. 3. Relationship between H and log P for the seven steroids studied. The H value was calculated at a Q of 0.247 ml/min (—●—) or 0.494 ml/min (—○—).

stirred homogeneous compartment. The Q and H in Eq. (1) simply reflect the relative magnitudes of the overall first-order rate constants of two very complex processes competing for removal of drug from the intestine. It should be emphasized that oftentimes an identical equation or equivalent equations can be mathematically derived with vastly different basic assumptions (2,11–13). The absorption models postulated by others (7,14) should yield similar predictions as presented in this communication.

Since H reflects the intrinsic intestinal absorbability or permeability of a compound, the magnitude of this value should be related to its partition coefficient between *n*-octanol and water (P), especially for passively absorbed compounds. The relationship between log P (7) and the H value (Table I) at a Q of 0.494 or 0.247 ml/min for the seven steroids is shown in Fig. 3.

Initially, there is a trend of increasing H as log P increases. The H values obtained at the same Q tend to level off or reach a maximum as log P further increases (e.g., greater than about 2.8 at a Q of 0.247 ml/min). This is similar to the relationship reported (Fig. 6 in Ref. 7) between the apparent permeability coefficients and log P values of these steroids. It is of interest to note that in spite of the reasonably good correlation (Table I and Fig. 1) using constant H in Eq. (1), a closer examination of the data, revealed that the H values for high-extraction drugs, such as progesterone, tend to increase to a greater extent with an increase in Q (Table I and Fig. 3). This may be attributed to the reduction in aqueous unstirred layer thickness or aqueous resistance as postulated in the early absorption model (7). The utility of the present approach for accurate prediction may thus require calculations for aqueous resistance for highly lipophilic drugs (for which clearance may be boundary layer controlled). It should be pointed out, however, that the range for normal flow rate *in vivo* may not be ascertained and some of the flow rates employed in the present study may be too high and unphysiological.

The percentage of change (increase) in E as Q was reduced from 0.494 to 0.247 ml/min for each of the seven steroids studied (Table I) was calculated by

$$\% \text{ change} = \frac{(E_{0.247} - E_{0.494})100}{E_{0.494}} \quad (3)$$

The results of this analysis are depicted in Fig. 4. They show that the intestinal absorption (i.e., E) of the more li-

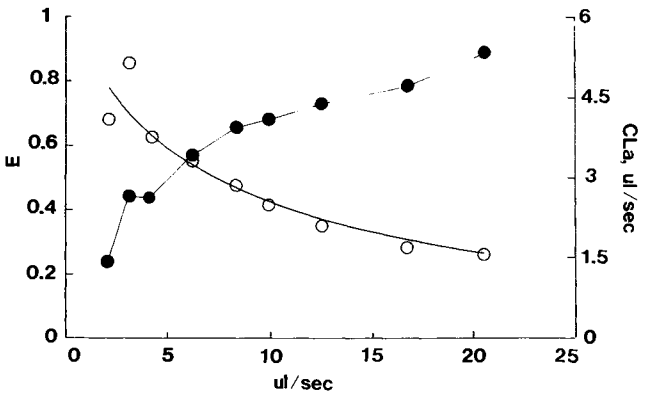

Fig. 2. Relationship between perfusion rate (Q) and intestinal absorption extraction ratio (E) for iopanoic acid (—○—). The curve was obtained from the nonlinear least-squares fitting of data according to Eq. (1). The reported intestinal absorption clearances (CL_a) as a function of Q are also shown (—●—): data points are connected with a line.

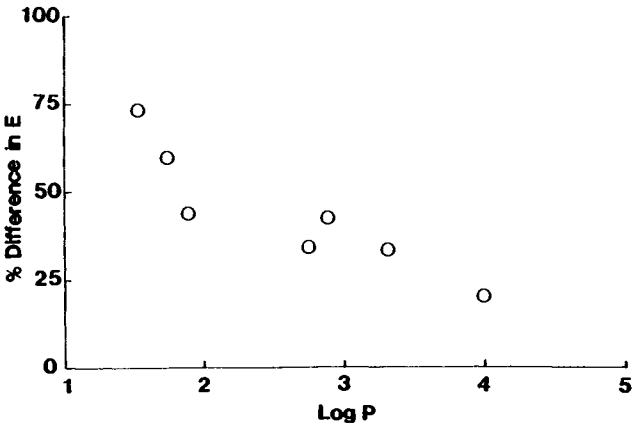

Fig. 4. Relationship between log P and percentage change in E as Q was reduced form 0.494 to 0.247 ml/min for the seven steroids studied.

pophilic steroids is less affected by change in Q (i.e., being less flow dependent). For hydrocortisone, the least lipophilic steroid studied (Table I), the change was about 73%, while for progesterone, the most lipophilic steroid studied, the change was only 20%. The absolute differences in E between a Q of 0.247 and 0.494 ml/min for the above two steroids were also practically identical (0.102 vs 0.103). This may be due to the fact that only two flow rates are considered and no highly hydrophilic compounds are studied. Thus, the apparent difference in findings between the present and previous (7,15) studies may require further investigation.

It seems of interest to point out that a simple equation, similar to Eq. (1), has been recently employed accurately to study or predict the effect of change in blood flow rate on the hemodialysis clearance (i.e., extraction ratio × blood flow rate; equivalent to CL_a shown in Fig. 2) of urea, uric acid, creatinine, and vitamin B_{12}, in patients using different types of dialyzers (6). A change in blood flow rate up to 16 times (25 to 400 ml/min) for urea and vitamin B_{12} was employed in the study (6). The E values ranged from about 0.6 to 1.0 and from 0.1 to 0.6 for these two compounds, respectively.

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REFERENCES

1. W. L. Chiou. In *Proceedings of 10th Asian Congress of Pharmaceutical Sciences,* Taipei, Taiwan, November 19–25, 1984, pp. 146–151.
2. W. L. Chiou. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **22**:577–590 (1984).
3. W. L. Chiou. *Res. Commun. Chem. Patho. Pharmacol.* **56**:121–124 (1987).
4. W. L. Chiou. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **24**:519–527 (1986).
5. W. L. Chiou. *J. Pharm. Sci.* **76**:S67 (1987).
6. W. L. Chiou and H. J. Lee. *Res. Commu. Chem. Path. Pharmacol.* **65**:393–396 (1989).
7. I. Komiya, J. Y. Park, A. Kamani, N. F. H. Ho, and W. I. Higuchi. *Int. J. Pharm.* **4**:249–262 (1980).
8. P. M. Savina, A. E. Staubus, T. S. Gaginella, and D. F. Smith. *J. Pharm. Sci.* **70**:239–243 (1981).
9. M. Rowland, L. Z. Benet, and G. G. Graham. *J. Pharmacokinet. Biopharm.* **1**:123–136 (1973).
10. G. R. Wilkinson and D. G. Shand. *Clin. Pharmacol. Ther.* **18**:377–390 (1975).
11. W. L. Chiou. *Res. Commun. Chem. Pathol. Pharmacol.* **33**:499–508 (1981).
12. M. Gibaldi and D. Perrier. *Pharmacokinetics,* 2nd ed., Marcel Dekker, New York, 1982.
13. W. L. Chiou. *J. Clin. Hosp. Pharm.* **7**:25–30 (1982).
14. P. J. Sinko, G. D. Leesman, and G. L. Amidon. Submitted for publication.
15. N. F. H. Ho, Y. Y. Park, P. F. Ni, and W. I. Higuchi. In W. Crouthamel and A. C. Sarapu (eds.), *Animal Models for Oral Drug Delivery in Man:* In Situ *and* In Vivo *Approaches,* American Pharmaceutical Association, Washington, D.C., 1983, pp. 27–106.