Absorptive Clearance of Carbamazepine and Selected Metabolites in Rabbit Intestine

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Received June 12, 1990; accepted February 20, 1991

The intestinal permeability of carbamazepine, an antiepileptic drug, was examined as a function of intestinal site (duodenojejunum vs colon). A "through-and-through" *in situ* intestinal perfusion technique was adopted using the rabbit as an animal model. Coperfusion of the 10,11-epoxide and the 10,11-*trans*dihydrodiol metabolites along with carbamazepine allowed for an examination of the effect of lipophilicity on intestinal permeability when molecular weight differences are negligible. Our results showed that carbamazepine is absorbed from rabbit duodenojejunum as well as the colon, which may explain the prolonged absorption behavior observed in humans. Also, the absorptive clearance of compounds having similar molecular weights is dependent not only on the lipophilicity but also on the extent of solvent drag during the course of the perfusion.

KEY WORDS: lipophilicity; *in situ* perfusion; absorptive clearance; solvent drag; sieving coefficient.

INTRODUCTION

Carbamazepine (CBZ; 5-carbamyl-5H-dibenzo[b,f] azepine), an oral anticonvulsant, is used in the treatment of epilepsy (1) and trigeminal neuralgia (2). Practically insoluble in water, CBZ is a model compound for drugs whose absorption is dissolution rate limited. Previous work done in our laboratory (3) shows that a conventional tablet formulation of CBZ, Tegretol, exhibits sustained-release absorption in humans. This is manifested by prolonged absorption as a result of the continued delivery of CBZ during its transit through the gastrointestinal tract. Also, it has been shown in humans that CBZ is absorbed in the rectum (4).

One objective of this research was to examine the intestinal permeability of CBZ as a function of site (duodenojejunum vs colon). For this purpose, a constant-rate *in situ* "through-and-through" intestinal perfusion technique (5–8) in the rabbit (9,10) was adopted. This method offers the advantages of maintaining intact blood supply, accessing a specific intestinal region, and controlling input into the segment.

Another objective was to compare the intestinal permeability of compounds having similar molecular weights but differing in their degree of lipophilicity. CBZ (MW 236) and its two major metabolites, carbamazepine-10,11-epoxide (CBZE; MW 252) and *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine (CBZD; MW 270), were chosen as model compounds for this purpose, using simultaneous *in situ* intestinal perfusion of these compounds to allow for comparison of absorptive clearances under identical conditions in the duodenojejunum and colon.

MATERIALS AND METHODS

Segment Preparation

Male New Zealand White rabbits (Birchwood Farm Rabbitry, Grantsburg, WI) weighing 2.8–3.1 kg were used. Prior to surgery, the rabbit was fasted for 16–18 hr in a restraining cage to prevent coprophagy (11), and water was allowed *ad libitum*. Anesthesia was achieved by intramuscular injections of 45 mg/kg ketamine (Parke-Davis, Morris Plains, NJ; 100 mg/ml) and 2 mg/kg acepromazine (Butler, Columbus, OH; 10 mg/ml) for muscle relaxation. A second dose of 25 mg/kg of ketamine and 2 mg/kg of acepromazine was given 15 min later. The animal was laid in a supine position on an underpad (American Hospital Supply Co., McGaw Park, IL) which was placed over a heating pad to maintain body temperature throughout the experiment. After the abdominal area was shaved and cleaned, a longitudinal midline incision, 8–10 cm in length, was made. The intestinal segment of interest was exposed and isolated carefully to avoid any mechanical disruption of the circulatory system perfusing the intestine.

To cannulate the duodenojejunal segment, the proximal end was ligated below the bile duct and 2 cm from the pyloric sphincter, using surgical silk. An incision was made, and a Color-Course four-way stopcock and its extension tubing (Travenol Laboratories, Inc., Morton Grove, IL) were secured in place, serving as the cannula through which solutions were to be perfused. The desired length of the intestinal segment was measured using surgical silk, and the distal end was cannulated using an L-shaped glass cannula.

For the colon, the proximal end was ligated immediately after the *ampulla coli,* the desired length measured, and finally, the distal end tied off. Incisions were made at each end, and solid fecal debris was expelled by gentle manipulation of the segment. The remaining fecal debris was removed by gently infusing 37°C normal saline through the proximal end. Finally, both the proximal and the distal ends were cannulated as mentioned earlier.

For additional cleaning of the segment, 37°C normal saline was infused at a constant rate of 1.1 ml/min until the effluent was clear. The remaining saline in the segment was cleared by carefully infusing air so as not to cause excessive intraluminal pressure. The intestinal segment under study was carefully arranged in a uniform S to multi-S pattern to avoid kinks and ensure a certain degree of uniformity in the perfusion fluid flow pattern. The isolated segment was kept warm and moist through frequent application of 37°C normal saline to a gauze covering.

Preparation of the Perfusing Solutions

To prepare the perfusing solution, a 500-μl aliquot of each of CBZ, CBZE, and CBZD standard solutions in methanol (1 μg/μl) was transferred to a 100-ml volumetric flask. The methanol was evaporated on an N-EVAP evaporator (Organomation Associates Inc., South Berlin, MA) at 45°C

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0724-8741/91/0800-1050$06.50/0

under nitrogen. The solid residue was dissolved in normal saline using a sonicator (Bransonic 52, Branson Instruments Co., Shelton, CT). Prior to the experiment, 1 μCi of [^{14}C]polyethylene glycol 4000 (PEG-4000; Amersham Corp., Arlington Heights, IL; sp act, 60 mCi/mmol) was added as a nonabsorbable marker to monitor water transport across the intestinal segment.

Perfusions

For the intestinal perfusions, a dilute solution of 5 μg/ml of each of CBZ, CBZE, and CBZD in normal saline was perfused at a constant rate of 0.27 ml/min through a 50-cm duodenojejunal or a 30-cm colon segment. The lag time was noted as the time when drug solution appeared at the distal end of the intestinal segment. The timer was reset, and effluent perfusate samples were collected every 10 min for 160 min in tared 5-ml glass Vacutainers (Beckton Dickinson & Co., Rutherford, NJ). The sample weight was calculated by difference.

At the end of the experiment, a second measurement of the length of the intestinal segment was made by dissecting the mesentery and blood vessels and placing the segment flat over a ruler whose surface was wetted with saline to prevent segment elongation. This second measurement was used in the calculations.

Analytical Methods

To quantitate CBZ, CBZE, and CBZD in the effluent perfusate samples and the original solution, a sensitive microbore HPLC method developed in our laboratory (12) was used with the following modifications. Standard-curve as well as perfusate-sample tubes were spiked with 10 μl of 0.03 μg/μl of cyheptamide in methanol as an internal standard. Appropriate volumes of standard solutions of CBZ, CBZE, and CBZD in methanol were added to the standard-curve tubes to provide concentrations ranging from 0.01 to 4.0 μg/ml. The methanol was evaporated, and 0.5-ml aliquots of normal saline were added to the standard-curve tubes prior to extraction. For the sample tubes, 0.5-ml aliquots of the effluent samples or the original perfusing solution were used for extraction. The volumes of the 0.2 *M* phosphate buffer (pH 11.2) and the organic extracting solvent (5% *t*-butyl alcohol in chloroform) were adjusted to 1 and 10 ml, respectively. The high-pressure liquid chromatograph used was a Hewlett–Packard, Model 1090L (Hewlett-Packard, Palo Alto, CA). The eluting peaks were monitored at 212 nm using a variable-wavelength UV detector (Shimadzu, Model SPD-6A; Shimadzu Corp., Kyoto, Japan), and the peak heights were measured with an electronic integrator (Hewlett-Packard, Model 3390A).

The original solution and the effluent perfusate samples were also analyzed for [^{14}C]PEG-4000. A 200-μl sample aliquot was mixed with 10 ml of scintillation fluid, Ecolume (ICN Biomedicals, Inc., Irvine, CA). Samples were counted using a scintillation counter (Beckman LS-3801, Beckman Instruments, Inc., Fullerton, CA) with automatic quench correction.

Data Analysis

Estimation of Absorptive Clearance

The fraction of drug remaining to be absorbed at steady state within a cylindrical intestinal segment during perfusion is described by the following equation:

$$\{C(l)/C(0)\}_{ss} = \exp(-A \cdot P_e/Q) \quad (1)$$

where $C(0)$ is the drug concentration entering the intestinal segment, $C(l)$ is the drug concentration leaving the intestinal segment, A is the effective surface area (cm^2), P_e is the effective permeability coefficient (cm/min), and Q is the bulk flow rate through the segment in ml/min.

Since there are segmental differences in transmucosal fluid movement along the intestinal tract (13), the $C(l)/C(0)$ term may be corrected for net water flux. The corresponding fraction of drug absorbed (F_a) is a function of the ratio of the rate of exit, R(e), to the input rate, R(i), if it is assumed that disappearance from the lumen represents absorption:

$$F_a = 1 - \{R(e)/R(i)\}_{ss} \quad (2)$$

where

$$\{R(e)/R(i)\}_{ss} = \exp(-A \cdot P_e/Q) \quad (3)$$

To compare among compounds simultaneously perfused through an intestinal segment, Eq. (3) may be solved for an area–permeability product. This product, which represents an absorptive clearance (ml/min), makes no assumption about the anatomical nature of the absorbing surface:

$$A \cdot P_e = -Q \cdot \ln\{R(e)/R(i)\}_{ss} \quad (4)$$

Absorptive clearances in the duodenojejunum and the colon were normalized to segment length and compared.

Effect of Solvent Drag on Absorptive Clearance

Several reports (14–20) have indicated that net water flux influences intestinal drug absorption. This phenomenon has been explained through a model that involves simultaneous diffusive and convective terms, with the latter accounting for the effect of solvent drag. Therefore, the rate of absorption of a solute (J) is equal to its rate of disappearance from the lumen as described by

$$J = K(C - C_p) + \Phi J_w C \quad (5)$$

in which the first term is the diffusive component to membrane transport and the second term is the convective component. In this model, K is a diffusive clearance, given by $DAK_p/\Delta x$, in which D is the diffusion coefficient, A is the membrane surface area, K_p is the partition coefficient, Δx is the path length, and C and C_p are the concentrations of the solute in the lumenal fluid and plasma, respectively. J_w, the volumetric rate of water absorption, depends on the nature and composition of the perfusing medium and can, therefore, be positive or negative. Φ is a sieving coefficient, equal to the ratio of the solute concentration in the convective stream to that in the lumenal fluid. $\Phi = 1 - \sigma$, where σ is the reflection coefficient. Both coefficients are a measure of the interaction between solvent and solute molecules entrained in the convective stream (14).

Due to sink conditions in the blood, C_p approaches zero, and when lumen concentrations of drug are at steady state, Eq. (5) reduces to

$$J_{ss} = DAK_p/\Delta x\langle C_{ss}\rangle + \Phi J_w\langle C_{ss}\rangle \quad (6)$$

where J_{ss} is the steady-state flux and $\langle C_{ss} \rangle$ is the length-averaged steady-state concentration of the solute in the lumen and is given by

$$\langle C_{ss} \rangle = [C(0) - C(l)]/\ln\{C(0)/C(l)\}_{ss} \quad (7)$$

Dividing the steady-state flux by $\langle C_{ss} \rangle$ gives

$$J_{ss}/\langle C_{ss} \rangle = DAK_p/\Delta x + \Phi J_w \quad (8)$$

This is an expression for the overall absorptive clearance (in units of ml/min), which may be estimated experimentally as the area–permeability product, $A \cdot P_e$.

The overall absorptive clearance of lipophilic compounds would be expected to be mainly diffusive and, thus, less dependent on net water flux. Therefore, Eq. (8) reduces to

$$J_{ss}/\langle C_{ss} \rangle \approx DAK_p/\Delta x \quad (9)$$

On the other hand, for hydrophilic compounds, the overall absorptive clearance would be primarily convective and therefore highly dependent on net water flux, as follows:

$$J_{ss}/\langle C_{ss} \rangle \approx \Phi J_w \quad (10)$$

RESULTS

Corrections for net water flux, assuming that PEG-4000 was not absorbed from the lumen, did not coincide with those obtained using gravimetric correction. During one collection interval, up to 45% of the perfused [^{14}C]PEG-4000 disappeared from the perfusing solution, suggesting that it was absorbed or bound to lumenal components. For this reason, the gravimetric correction factor for water flux was used in calculating $R(e)/R(i)$.

Permeability of CBZ as a Function of Intestinal Site

To examine the permeability of CBZ as a function of intestinal site, a normalized absorptive clearance, $(A \cdot P_e/l)$, was calculated for the duodenojejunum and colon. The corresponding mean values were 0.0127 and 0.0196 ml/min · cm for the duodenojejunum and the colon, respectively. This length-normalized intestinal permeability for CBZ was greater in the colon than in the duodenojejunum (one-tailed Student t test; $0.01 > P > 0.005$). A summary of the data for both segments is given in Table I.

The lag time, which is taken as the time required for the perfusing solution to first appear at the distal end of the segment, may be used as an estimate of the mean residence time, $\langle t \rangle$, of the solution. The average lag time for the colon (42.9 min) was significantly longer than that for the duodenojejunum (14.7 min) (one-tailed Student t test; $0.005 > P > 0.0005$).

Effect of Lipophilicity on the Permeability of Intestinal Barriers

To examine the effect of lipophilicity on intestinal permeability, the area–permeability products for compounds of similar molecular weights were normalized to length and compared. The mean values in the duodenojejunum were 0.0127, 0.00933, and 0.00202 ml/min · cm for CBZ, CBZE, and CBZD, respectively, and the corresponding mean values in the colon were 0.0196, 0.00877, and 0.00264 ml/min · cm. In both intestinal sites, the mean absorptive clearances of the three compounds were significantly different (Scheffe F test; $\alpha = 0.05$).

Table I. *In Situ* Perfusion Data of CBZ, CBZE, and CBZD in the Duodenojejunum and Colon

	Duodenojejunum (mean ± SD)[a]	Colon (mean ± SD)[a]
Carbamazepine		
Body weight (kg)	2.96 ± 0.125	3.05 ± 0.0756
$C(0)$ (μg/ml)	4.64 ± 0.403	4.67 ± 0.422
Segment length (cm)	49.3 ± 1.53	28.7 ± 0.577
Lag time (min)	14.7 ± 1.10	42.9 ± 7.17
$\{R(e)/R(i)\}_{ss}$	0.100 ± 0.0251	0.127 ± 0.0232
$A \cdot P_e$ (ml/min)	0.572 ± 0.0787	0.560 ± 0.0511
$A \cdot P_e/l$ (ml/min · cm)	0.0127 ± 0.00145*	0.0196 ± 0.00218*
Carbamazepine-10,11-epoxide		
$C(0)$ (μg/ml)	5.03 ± 0.182	4.83 ± 0.485
$\{R(e)/R(i)\}_{ss}$	0.183 ± 0.0296	0.396 ± 0.0408
$A \cdot P_e$ (ml/min)	0.461 ± 0.0453	0.251 ± 0.0270
$A \cdot P_e/l$ (ml/min · cm)	0.00933 ± 0.00093**	0.00877 ± 0.00107**
Carbamazepine-10,11-*trans*diol		
$C(0)$ (μg/ml)	4.45 ± 0.631	4.96 ± 0.546
$\{R(e)/R(i)\}_{ss}$	0.694 ± 0.069	0.755 ± 0.0274
$A \cdot P_e$ (ml/min)	0.0993 ± 0.269	0.0759 ± 0.00982
$A \cdot P_e/l$ (ml/min · cm)	0.00202 ± 0.000586***	0.00264 ± 0.000297***

[a] $n = 3$ for each intestinal segment.
* $A \cdot P_e/l$ in colon significantly greater than that in duodenojejunum (one-tailed Student t test; $0.01 > P > 0.005$).
** Not significantly different (unpaired Student t test; $P = 0.53$).
*** Not significantly different (unpaired Student t test; $P = 0.18$).

The mean (±SD) $R(e)/R(i)$ versus t_{mid} plots for the three compounds in duodenojejunum and colon are given in Figs. 1 and 2, respectively. Steady states were reached in 25–35 min of perfusion. Table I summarizes the data for CBZ, CBZE, and CBZD.

In a given intestinal segment where the surface area is common, the ratios of the absorptive clearances of two com-

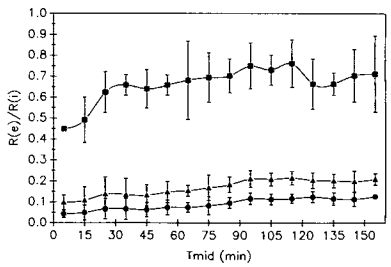

Fig. 1. Mean (±SD) $R(e)/R(i)$ versus time profile during duodenojejunal perfusion of CBZ, CBZE, and CBZD in normal saline ($n = 3$). (●——●) CBZ; (▲——▲) CBZE; (■——■) CBZD.

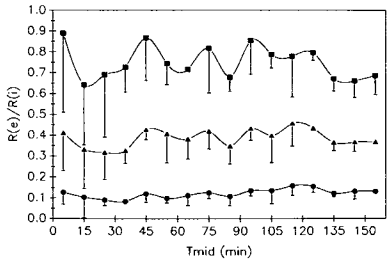

Fig. 2. Mean (±SD) $R(e)/R(i)$ versus time profile during colon perfusion of CBZ, CBZE, and CBZD in normal saline (n = 3). (●——●) CBZ; (▲——▲) CBZE; (■——■) CBZD.

pounds would represent the ratios of their corresponding permeability coefficients:

$$A \cdot P_{e(CBZE)}/A \cdot P_{e(CBZ)} = P_{e(CBZE)}/P_{e(CBZ)} \quad (11)$$

In the duodenojejunum, the mean (±SD) of the ratios of absorptive clearance of CBZE to CBZ and CBZD to CBZ were 0.734 (±0.0117) and 0.163 (±0.060), respectively (n = 3). For the colon, the corresponding ratios were 0.448 (±0.0297) and 0.137 (±0.0293), respectively (n = 3).

DISCUSSION

Intestinal Permeability of CBZ and Selected Metabolites

CBZ is a neutral lipophilic compound that is practically insoluble in water, its solubility in phosphate buffer (pH 7.4) at 23°C being 0.072 g/L (21). Thus, a dilute solution of CBZ in physiological saline (5 μg/ml) was used in the perfusion studies. At this concentration, solubilizing agents that may alter the intestinal permeability of CBZ were not required. One limitation of using such dilute solutions is that systemic plasma levels of CBZ and its metabolites are nonquantifiable for mass balance purposes. Therefore, only the perfusate concentrations of CBZ were determined here as an index of drug absorption from the lumen.

No conversion of CBZ to its epoxide and *trans*-dihydrodiol metabolites was detected when perfusion experiments were conducted with only CBZ. In work previously done in our laboratory, CBZD was not detected in the plasma or urine upon systemic administration of CBZ or CBZE to the rabbit. Also, no CBZD was detected when perfusion experiments were conducted with CBZE alone. Therefore, the effect of the degree of lipophilicity on intestinal permeability was examined by coperfusing CBZ, CBZE, and CBZD as model compounds with similar molecular weights but varying lipophilicity. As such, these compounds were studied under identical hydrodynamic and anatomic conditions (e.g., bulk fluid flow rate, net water flux and effective surface area) that may influence their intestinal permeabilities.

A plot of the log of the duodenojejunal area–permeability products normalized to length versus lipophilicity, expressed as log of partition coefficient (K_p) of CBZ, CBZE, and CBZD either experimentally determined at 37°C or reported in the literature (22), was nonlinear (Fig. 3). This is in agreement with earlier work conducted with a series of steroids of varying lipophilicity (6). The authors were able to show that for compounds with higher partition coefficients,

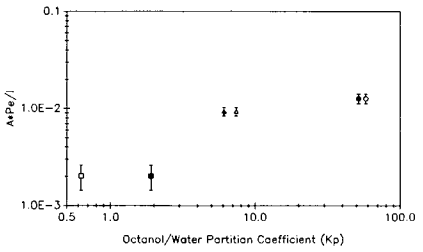

Fig. 3. Relationship between the permeability of CBZ, CBZE, and CBZD in the duodenojejunum and lipophilicity. Measured partition coefficients at 37°C: (●) CBZ; (▲) CBZE; (■) CBZD; Literature values (22) of the partition coefficients determined at 25°C: (○) CBZ; (△) CBZE; (□) CBZD.

the effective permeability coefficient (P_e) approaches a plateau which represents the aqueous boundary-controlled region for lipophilic compounds. However, our results do not agree with those recently reported (23), where the log permeabilities of CBZ, CBZE, and CBZD in the renal tubule were linearly correlated with the corresponding log octanol/water partition coefficients. One explanation may be differences in the nature of the surface epithelium of the renal tubule and the intestine. Also, the effective thickness of the aqueous boundary layer may be greater in the intestine due to a slower linear velocity in the lumen than in the renal tubule under the stated experimental conditions, increasing the resistance to diffusion of lipophilic compounds.

Effect of Solvent Drag on Absorptive Clearance

The dependence of absorptive clearance of CBZ, CBZE, and CBZD on net water flux was examined in the duodenojejunum and colon. Plots showing the steady-state area–permeability products of CBZ versus net water flux are given in Figs. 4A and B for the duodenojejunum and colon, respectively (n = 3). Figures 5A and B show the same relationship for CBZE (n = 3). Similar plots for CBZD (n = 3) are given in Figs. 6A and B.

Equation (8) was fitted to the data by linear regression,

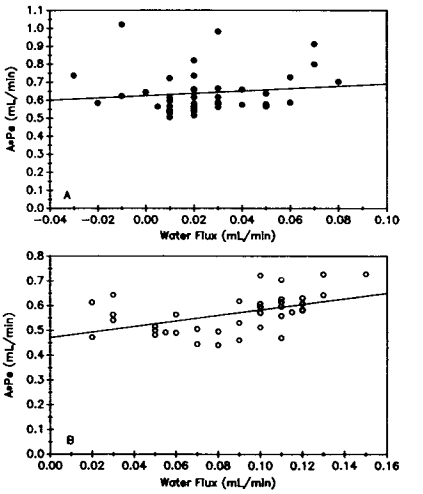

Fig. 4. Absorptive clearance of CBZ and water flux. (A) (●) Duodenojejunum; $y = 0.642x + 0.629$ (n = 3). (B) (○) Colon; $y = 1.07x + 0.478$ (n = 3).

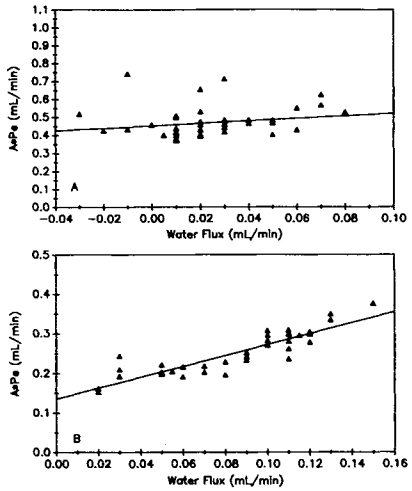

Fig. 5. Absorptive clearance of CBZE and water flux. (A) (▲) Duodenojejunum; $y = 0.687x + 0.453$ ($n = 3$). (B) (△) Colon; $y = 1.25x + 0.148$ ($n = 3$).

and the estimates of the regression parameters for CBZ, CBZE, and CBZD in both segments are given in Table II. For CBZ, the absorptive clearance was independent of net water flux in the duodenojejunum. This suggests that the overall absorptive clearance of CBZ in this segment may be described by Eq. (9), i.e., predominantly transcellular diffusion. In the colon, however, a positive slope significantly different from zero was observed ($P < 0.005$), suggesting that convective paracellular transport of CBZ is important in this region.

The absorptive clearance of CBZE in the duodenojejunum was also independent of net water flux ($R^2 = 0.036$). On the other hand, it was highly correlated with net water flux in the colon ($R^2 = 0.75$).

However, the absorptive clearance of CBZD was moderately well correlated with net water flux in both intestinal segments ($R^2 = 0.30$ and 0.53 for the duodenojejunum and colon, respectively). This apparent dependence of absorptive clearance on water flux in both segments may be attributed to the hydrophilic nature of CBZD.

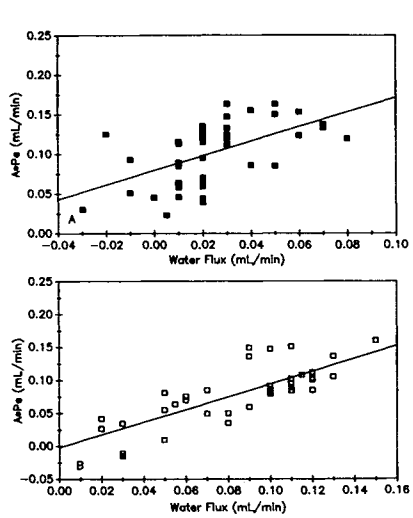

Fig. 6. Absorptive clearance of CBZD and water flux. (A) (■) Duodenojejunum; $y = 0.908x + 0.080$ ($n = 3$). (B) (□) Colon; $y = 0.845x + 0.010$ ($n = 3$).

Table II. Effect of Water Flux (ml/min) on the Overall Absorptive Clearance (ml/min): Regression Parameters Obtained from Fitting Eq. (8)

	Duodenojejunum[a]		Colon[a]	
Carbamazepine				
Intercept ($DAK_p/\Delta x$)	0.629*	(0.027)[b]	0.478*	(0.029)
Slope (Φ)	0.642**	(0.821)	1.07*-*****	(0.318)
Coefficient of determination (R^2)	0.015		0.24	
Carbamazepine-10,11-epoxide				
Intercept ($DAK_p/\Delta x$)	0.453*	(0.018)	0.148*	(0.011)
Slope (Φ)	0.687***	(0.558)	1.25*-******	(0.121)
Coefficient of determination (R^2)	0.036		0.75	
Carbamazepine-10,11-*trans*diol				
Intercept ($DAK_p/\Delta x$)	0.080*	(0.007)	0.010****	(0.012)
Slope (Φ)	0.908*	(0.216)	0.845*	(0.135)
Coefficient of determination (R^2)	0.30		0.53	

[a] $n = 3$ for each intestinal segment.
[b] Standard error of the parameter estimate in parentheses.
* Significantly different from zero ($P < 0.005$).
** Not significantly different from zero ($P = 0.44$).
*** Not significantly different from zero ($P = 0.56$).
**** Not significantly different from zero ($P = 0.43$).
***** Not significantly different from unity ($\alpha = 0.05$).
****** Significantly different from unity ($\alpha = 0.05$).

The positive intercepts resulting from the fitted lines provide estimates of the diffusive component of the overall absorptive clearances for CBZ, CBZE, and CBZD. For both segments, CBZ showed the largest diffusive permeability, which is in agreement with its highest lipophilicity of the three compounds under examination.

In the colon, the dependence of absorptive clearance of CBZ, CBZE, and CBZD on solvent drag suggests that convective diffusion through the paracellular route significantly contributes to the overall transport process.

The slope of the fitted line is an estimate of the sieving coefficient (Φ), which depends on the degree of interaction between solute and water molecules. Although Φ normally ranges between 0 and 1, a value of Φ for CBZE significantly greater than unity ($\alpha = 0.05$) was calculated for the colon. Sieving coefficients greater than unity (i.e., $\sigma < 0$) were calculated (16) when absorption of aminopyrine and antipyrine from rat jejunum was examined. The authors attributed this to an interaction between the drug and the water molecules in the lipid part of the cell membrane, in addition to solvent drag via the paracellular pathway.

Clearance of [^{14}C]PEG-4000

The results demonstrate that [^{14}C]PEG-4000 disappeared from the perfusate, and the fraction disappearing at steady state was dependent on the extent of water absorption, as observed in previous work (24). These results are in

agreement with those of others (25,26), where it was shown that [^{14}C]PEG-4000 was absorbed through paracellular routes, and its absorptive clearance increased with fluid absorption. This route has been shown to allow the passage of molecules as large as PEG-4000 and inulin across the intestinal epithelium (27,28). The conditions used in our studies (0.27 ml/min flow rate and 30- to 50-cm segment length) provide a longer residence time and a larger surface area for absorption than was operative in similar studies in the rat reported recently (29).

During the course of the studies, the viability of the segment was confirmed by its pink color and the pulsating arcades of blood vessels perfusing the segment. Although the fraction of the marker disappearing was water flux dependent, it was not time dependent, indicating segment viability throughout the experiment.

In conclusion, the results of this study show that CBZ is absorbed not only from the small intestine, but also from the colon. This finding is consistent with the prolonged absorption profiles observed in humans, where CBZ is absorbed over a period longer than usual transit times through the small intestine (3). Also, the absorptive clearance of compounds having similar molecular weights (CBZ, CBZE, and CBZD) not only was dependent on the degree of lipophilicity but also was affected by solvent drag occurring during the course of absorption.

ACKNOWLEDGMENTS

This research was supported by the Egyptian Government and a Graduate School Dissertation Fellowship from the University of Minnesota. The authors wish to thank Dr. Keith Chan, Pharmaceuticals Division, CIBA-GEIGY Corp., Ardsley, NY 10502, for supplying carbamazepine, carbamazepine-10,11-epoxide, and *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine.

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