Site-Differential Gastrointestinal Absorption of Benazepril Hydrochloride in Healthy Volunteers

Keith K. H. Chan,[1,4] Akshay Buch,[1-3] Robert D. Glazer,[1] Vivian A. John,[1] and William H. Barr[2]

Received January 29, 1993; accepted October 5, 1993

The absorption of benazepril-HCl (BZPH), an orally active angiotensin-converting enzyme (ACE) inhibitor, in various regions of the gastrointestinal (GI) tract was investigated using an intestinal intubation technique. Thirteen subjects completed this single-dose, three-phase sequential crossover study. The drug (20 mg) was administered either as a 4-hr colonic infusion (COLON) or as a small intestinal infusion (SI) in the first two phases and as an oral bolus solution (ORAL) in the third phase, with a 2-week washout between each treatment. Serial plasma and urine samples were collected for up to 4 days after dosing. BZPH and its active metabolite benazeprilat (BZPL) were determined using a gas chromatography/mass spectrometry method. BZPH was absorbed rapidly into the bloodstream (T_{max} = 0.5 hr after ORAL). Absorption was also rapid for SI, with a postinfusion half-life (0.57 hr) nearly identical to that for ORAL (0.59 hr). The absorption rate after COLON was much slower (lower C_{max} and longer T_{max}) compared to that after SI, and the apparent half-life (1.7 hr) was prolonged. SI delivered 90%, whereas COLON delivered 23%, of the drug into the systematic circulation as compared to ORAL. BZPL was rapidly formed upon drug absorption. The metabolite-to-drug AUC ratios were comparable for SI and ORAL (8.9 vs 9.7), indicating that first-pass metabolism of BZPH was neither saturable nor input rate dependent. The metabolite-to-drug AUC ratio was reduced for COLON (5.0), indicating that the mechanism of absorption of BZPH in the colon may be different than that after SI and ORAL. Urinary recovery data were consistent with plasma data. It can be concluded that COLON delivered a smaller amount of drug at a slower absorption rate to the body than either SI or ORAL.

KEY WORDS: site-differential absorption; gastrointestinal intubation; benazepril; benazeprilat; angiotensin-converting enzyme (ACE) inhibitor.

INTRODUCTION

Benazepril hydrochloride (BZPH; Lotensin, CGS 14824A; Fig. 1) is a new oral nonsulfhydryl selective angiotensin-converting enzyme (ACE) inhibitor. The drug is rapidly absorbed into the systemic circulation and eliminated by both renal and nonrenal routes (1,2). Upon absorption, the drug is converted to benazeprilat (BZPL; CGS 14841; Fig. 1), which exerts the pharmacological activity. Only trace amounts of drug were excreted unchanged in urine and approximately 17% of the dose was excreted as BZPL after 24 hr (2). The metabolite itself is poorly absorbed when administered orally (2–4).

Based on the pharmacokinetic characteristics of the drug and active metabolite, the dosage strength and regimen for benazepril may be optimized through the use of a controlled drug delivery system. During the course of the controlled-release formulation development, evidence suggested that BZPH absorption may be site dependent. The present study is designed to investigate the absorption behavior of BZPH in various regions of the gastrointestinal (GI) tract and to explore the mechanism of any site-differential absorption behavior using an intestinal intubation technique.

EXPERIMENTAL

Clinical Procedures

Study Design. The study followed a single-dose, open-label, three-phase crossover design. In the first two phases, the drug was administered either as a 4-hr colonic infusion (COLON) or as a 4-hr small intestinal infusion (SI), depending on the position of the intestinal tube. In the third phase, the drug was administered as an oral bolus solution (ORAL) where the drug solution was swallowed.

Study Subjects. Thirteen normal healthy male subjects participated in this study. Their ages ranged from 21 to 36 (mean, 27) years, their weights from 166 to 224 (mean, 185) lb, and their height from 64 to 75 (mean, 71) in. Twelve subjects completed all phases and one subject completed only two phases of the study. Each subject gave written informed consent after being advised of the nature and risks of the study. The subjects were confirmed to be in good health by physical examination, medical history, and clinical laboratory tests. The subjects refrained from alcohol for 7 days and from caffeine-containing beverages for 3 days prior to each drug study day.

Drug Administration. The drug (20 mg) was dosed as freshly prepared solution at approximately 8:00 AM on each dosing day. A total of 60 mL of drug solution was administered as a 4-hr small intestinal infusion (SI), a 4-hr colonic infusion (COLON), and an oral bolus solution (ORAL) on three separate occasions. The washout period between successive phases was approximately 2 weeks.

Intubation. An intestinal tube (15-ft, double-lumen balloon-tipped McDowell tube, Lot 23-099, Sheridan Catheter Corporation, Rt. 4, Argyl, NY 12809) was inserted through the nostril, under light local anesthesia, approximately 12 hr (SI) or 36 hr (COLON) before drug dosing. Once the tube was in the stomach, the terminal balloon (15 mL) of the tube was then inflated and the tube was allowed to migrate to the distal gut by caudal propulsion. The position of the tip of the tube was monitored by periodic fluroscopic observation. Just prior to dosing, the position of the tip of the tube was again confirmed fluoroscopically.

The colonic intubation was considered successful only if

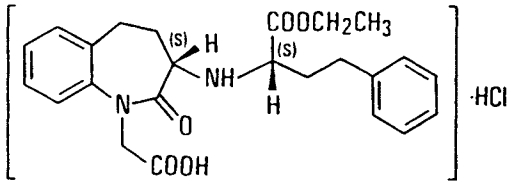
[1] Development Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Ardsley, New York 10502, and Summit, New Jersey 07901.

[2] Department of Pharmacy and Pharmaceutics, Virginia Commonwealth University, Richmond, Virginia 23298.

[3] Present address: Bristol-Meyer Squibb Inc., Syracuse, New York 13221.

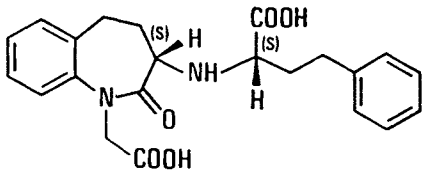
[4] To whom correspondence should be addressed at Pharmaceuticals Division, CIBA-GEIGY Corporation, Ardsley, New York 10502.

0724-8741/94/0300-0432$07.00/0



Benazepril ·HCl

(BZPH, Lotensin, CGS-14824A)



Benazeprilat

(BZPL, CGS-14841)

Fig. 1. Structures of benazepril-HCl and its active metabolite benazeprilat.

the tube reached the ascending colon or beyond. The position of the tube was determined each morning after tube insertion. A maximum of 2.5 days (2 nights after tube insertion) was allowed for the tube to reach the colon. Regardless of whether the tube reached the colon or not, the study drug was administered on the morning of Day 3 and the position of the tube recorded. Therefore, each subject had two chances (Phases 1 and 2) for their tube to reach the colon. None of the subjects was allowed to be intubated more than twice in this study.

Food. After tube insertion, subjects were allowed to eat as usual but fasted overnight after 10:00 PM on the day prior to drug administration except for water. After the start of drug administration, the subjects were permitted to have 100 mL of apple juice and two soda crackers each hour until a standard lunch was served 6 hr later.

Safety and Clinical Evaluation. Safety and tolerability were determined by physical examination including body weights, blood pressures (prior to dosing and at 4, 8, 12, and 24 hr after dosing), and pulse rates (prior to each blood pressure measurement), electrocardiograms, recording of medical problems, and clinical laboratory data.

Blood and Urine Collection. Blood specimens (10 mL) were obtained at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12, 14, 24, 34, 48, 72, and 96 hr after dosing. Plasma was harvested and frozen immediately. Urine samples were collected every 2 hr for the first 8 hr, every 4 hr for the next 4 hr, every 12 hr for the next 12 hr, and then daily for the next 3 days. All samples remained frozen until analysis.

Analytical Procedures

Plasma and urine concentrations of BZPH and BZPL were determined using an established gas chromtography/mass spectrometry (GC/MS) method (5). The method was validated with a quantitation range of 2.5 to 149 ng/mL for BZPH and 5.0 to 149 ng/mL for BZPL. Quality-control plasma samples were prepared at the beginning of the study, stored frozen, and assayed together with the subject samples.

The largest coefficient of variation for the quality-control plasma samples was 13.8% but generally smaller than 10%, indicating a good precision for the method. The largest percentage difference between measured and added concentration was 10.8%. However, the differences were generally much smaller than 10%, demonstrating a good accuracy of the assay throughout analysis of the clinical samples. Similar results were obtained from urine quality-control samples.

Pharmacokinetic Data Analysis

A noncompartmental approach was used for pharmacokinetic data analysis. Plasma concentration–time profiles for both the parent compound and the metabolite were characterized in terms of their areas under the curve (AUC), peak concentrations (C_{max}), times to peak (T_{max}), and terminal half-lives ($T_{1/2}$). C_{max} was the maximum observed level and T_{max} was the corresponding time. The AUC was calculated using the linear trapezoidal rule. Extrapolation of AUC was not needed since the levels of parent drug and metabolite were below the quantitation limit of the assay by the last sampling time. $T_{1/2}$ was determined by linear regression of the log-linear terminal phase using the last three or four time points with concentrations above the quantitation limit.

In addition, the mean residence times (MRT) for both the parent compound and the metabolite after oral administration of benazepril-HCl were calculated as follows (6):

$$MRT_{p,p}(ORAL) = \frac{AUMC_{p,p}(ORAL)}{AUC_{p,p}(ORAL)} \quad (1)$$

$$MRT_{m,p}(ORAL) = \frac{AUMC_{m,p}(ORAL)}{AUC_{m,p}(ORAL)} \quad (2)$$

where the subscripts "p" and "m" denote parent drug and metabolite, respectively. For example, $MRT_{p,p}(ORAL)$ denotes the mean residence time of the parent drug after oral bolus solution administration of the drug. AUMC is the area under the plasma concentration–time first moment curve calculated using the linear trapezoidal rule. Extrapolation of AUMC was not needed since the last sampling concentrations were below the quantitation limit of the assay. Corresponding mean residence times for SI and COLON [$MRT_{p,p}(SI)$, $MRT_{p,p}(COLON)$, $MRT_{m,p}(SI)$, and $MRT_{m,p}(COLON)$] can be calculated using equations analogous to Eqs. (1) and (2).

After adjustment for the mean infusion time (MIT), the corrected mean residence time for parent drug after the small intestinal infusions can be calculated by the following equation:

$$MRT_p(SI,corr) = MRT_{p,p}(SI) - MIT \quad (3)$$

where MIT in this study can be considered as one-half the total zero-order intestinal infusion time (4 hr/2 = 2 hr). A corresponding equation can be used to determine the corrected MRT after colon infusion. Corrected mean residence time represents the sum of the mean absorption time (MAT)

and the mean disposition residence time for the parent drug, $MDRT_p$.

The difference between the MRT of the parent drug and that of the metabolite, ΔMRT, obtained within the same treatment represent the mean disposition residence time for the metabolite (6,7) and is calculated as follows:

$$\Delta MRT = MRT_{m,p}(ORAL) - MRT_{p,p}(ORAL) \quad (4)$$

Corresponding ΔMRT values for the metabolite for SI and COLON treatments can be calculated using an equation analogous to Eq. (4).

RESULTS

All subjects received three doses except Subject 8, who refused the second intestinal infusion and consequently received only two doses of study mediation. Every subject had two chances to allow the tube to reach the colon. Seven subjects successfully had the tubes reach their colon. All subjects received drug during the small intestine phase and the oral bolus solution phase. Five subjects (1, 5, 12, 15, and 17) never had the tubes reach their colon and they were dosed twice in the small intestine. For the sake of simplicity, the resulting pharmacokinetic parameters from intestinal infusion were averaged for those subjects. The region of dosing and the exact positions of the tube in each subject are listed in Table I.

The drug was well tolerated following all three routes of administration in all subjects. There were no adverse reactions reported. There were no clinically important changes or trends in physical examination, ECG, or laboratory test findings.

Mean plasma concentrations of parent drug and metabolite for all subjects are listed in Table II and illustrated graphically in Figs. 2 and 3, while mean pharmacokinetic parameters are listed in Table III. Subject 1 had extremely low urinary excretion of BZPH and BZPL (10 and 3 times less than the average values, respectively). Therefore, his values were excluded from the calculation of the mean urinary data. Since not all subjects completed all three treatments, comparisons between treatments were appropriate only in those subjects who successfully received all treatments (Table III).

DISCUSSION

Site-specific absorption has been implicated for other ACE inhibitors as well as BZPH (8,9). However, direct evidence was lacking in support of such an implication. This study was designed to verify the existence of site-specific absorption by delivering the drug directly to various regions of the GI tract. The results provide direct evidence of differential absorption at various sites.

Rate and Extent of Absorption

When the drug was given as an oral bolus solution, the absorption of BZPH was rapid, reaching a C_{max} of 271 ng/mL, with a T_{max} of 0.54 hr. As expected, C_{max} values were lower (54 ng/mL) and T_{max} values were later (2.9 hr) after SI. The lowest C_{max} (16 ng/mL) and latest T_{max} (3.4 hr) were achieved after COLON. The $T_{1/2}$ values were comparable for ORAL and SI (0.59 vs 0.57 hr; parameter ratio, 1.0; Table III) but much longer for COLON (1.7 hr), indicating the possibility of a flip-flop model (10), where the terminal half-life represents drug absorption rather than elimination. The same behavior was observed with the metabolite data.

The data indicate that the intrinsic absorption process for parent drug after ORAL was very rapid. Similarly, the absorption process after SI was also rapid, and the postinfusion half-life was nearly identical to that after ORAL. The colonic absorption rate was much slower than that from the small intestine as indicated by the lowest C_{max} and latest

Table I. Regions of Dosing in the GI Tract

	Small intestine			Large intestine		
Subject no.	Duodenum	Jejunum	Ileum	Proximal colon	Distal colon	Oral dose
1	Vis-2 Vis-5					Vis-8
3		Vis-2		Vis-5		Vis-8
4	Vis-5				Vis-2	Vis-8
5			Vis-2 Vis-5			Vis-8
7	Vis-5			Vis-2		Vis-8
8[a]		Vis-2				Vis-8
11			Vis-2	Vis-5		Vis-8
12		Vis-5	Vis-2			Vis-8
13	Vis-5				Vis-2	Vis-8
14	Vis-5			Vis-2		Vis-8
15	Vis-5	Vis-2				Vis-8
16	Vis-5				Vis-2	Vis-8
17		Vis-5	Vis-2			Vis-8
N	8	5	5	4	3	13
TOTAL		18		7		13

[a] Subject 8 did not take part in the second intubation.

Table II. Mean (SD) Plasma Concentrations of BZPH and BZPL (ng/mL)

	Benazepril-HCl			Benzaeprilat		
Time (hr)	COLON (N = 7)	SI (N = 13)	ORAL (N = 13)	COLON (N = 7)	SI (N = 13)	ORAL (N = 13)
0.0	BQL[a]	BQL	BQL	BQL	BQL	BQL
0.5	5.0 (10.2)	25.9 (25.2)	257.5 (131.5)	BQL	8.7 (16.6)	161.8 (78.8)
1.0	10.9 (22.8)	38.8 (27.4)	96.9 (54.9)	6.5 (17.2)	34.4 (38.8)	345.2 (129.1)
1.5	11.4 (18.0)	39.1 (22.1)	40.5 (29.4)	14.2 (37.7)	66.0 (59.2)	357.0 (133.1)
2.0	10.6 (11.7)	39.5 (20.6)	19.5 (12.0)	20.1 (46.3)	97.0 (70.3)	318.7 (108.2)
3.0	9.0 (7.8)	35.2 (17.3)	5.8 (3.8)	21.6 (40.5)	145.3 (85.3)	231.9 (90.6)
4.0	7.9 (6.4)	40.5 (20.6)	BQL	25.6 (37.1)	201.6 (102.4)	174.5 (56.6)
4.5	5.3 (3.0)	20.3 (14.1)	BQL	27.4 (34.1)	198.3 (98.6)	160.6 (58.2)
5.0	4.3 (2.6)	13.6 (13.1)	BQL	27.3 (32.4)	192.4 (91.0)	139.1 (45.6)
5.5	2.7 (2.0)	7.0 (6.4)	BQL	25.9 (29.4)	171.4 (84.5)	117.8 (33.3)
6.0	BQL	3.5 (5.7)	BQL	24.9 (26.6)	144.7 (64.6)	116.7 (47.2)
8.0	BQL	BQL	BQL	15.2 (13.9)	81.4 (31.9)	73.3 (26.3)
12.0	BQL	BQL	BQL	7.5 (6.2)	38.1 (13.3)	35.0 (13.1)
14.0	BQL	BQL	BQL	BQL	27.9 (9.9)	25.5 (8.7)
24.0	BQL	BQL	BQL	BQL	8.1	7.9 (3.4)
34.0	BQL	BQL	BQL	BQL	BQL	BQL
48.0	BQL	BQL	BQL	BQL	BQL	BQL
72.0	BQL	BQL	BQL	BQL	BQL	BQL
96.0	BQL	BQL	BQL	BQL	BQL	BQL

[a] Below quantitative limit (<2.48 ng/mL for benazepril-HCl and <4.97 ng/mL for benazeprilat). A value of zero was used for the calculation of mean and standard deviation (SD).

T_{max} values, even though the same delivery rate was used for both treatments.

The extent of absorption was evaluated by comparing AUC values for either parent drug or metabolite between different treatments. SI delivered a comparable amount (90%) of drug to the systemic circulation compared to ORAL (AUC value, 179 vs 221 ng · hr/mL). Furthermore, the AUC ratio for the metabolite was 83%. On the other hand, COLON delivered a smaller amount of drug to the systemic circulation compared to ORAL (AUC ratios, 23% for the parent drug and 13% for the metabolite).

Based on AUC ratios, the relative bioavailability was comparable for SI and decreased after COLON as compared to ORAL. Urinary recovery data were consistent with the conclusions that COLON delivered a smaller amount of drug at a slower rate to the body than SI and ORAL.

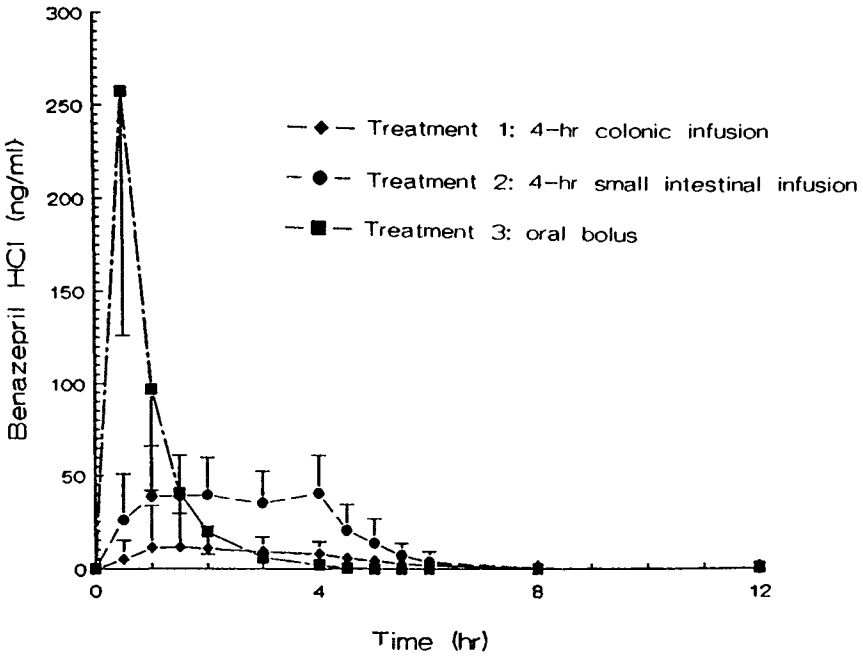


Fig. 2. Mean plasma concentration–time profiles of benazepril-HCl following administration of parent drug.

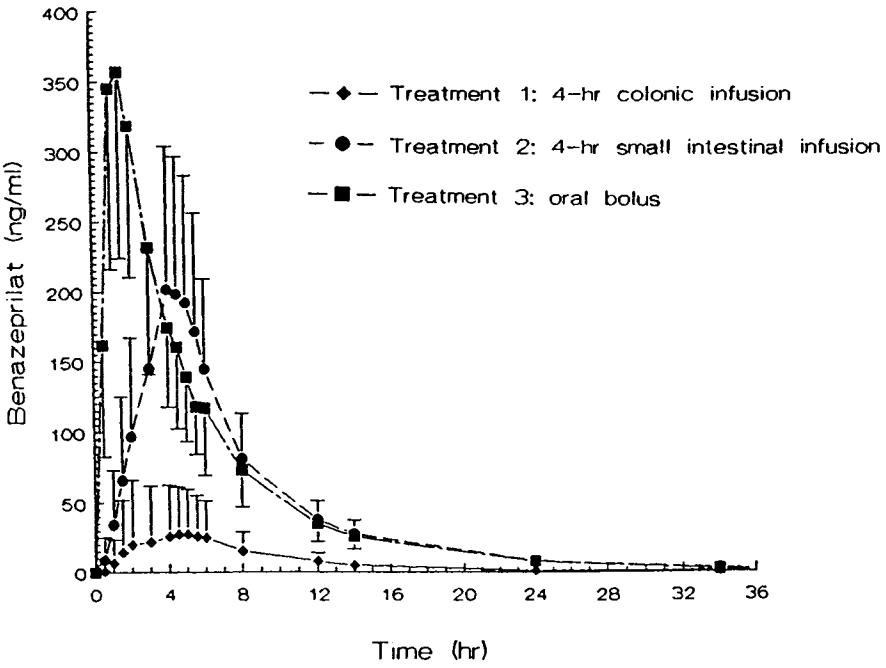


Fig. 3. Mean plasma concentration–time profiles of active metabolite, benazeprilat, following administration of parent drug.

Metabolite Pharmacokinetics After Administration of BZPH

BZPH was absorbed rapidly into the bloodstream and was converted rapidly in the body to its active metabolite. The AUC value of the metabolite was approximately 10 times higher than that of the parent drug after SI and ORAL (metabolite-to-drug AUC ratios, 8.9 and 9.7, respectively). These data are consistent with reported data after oral administration of a capsule formulation (2). COLON resulted in a lower metabolite-to-parent drug AUC ratio (5.0; approximately half that for SI and ORAL). The half-life values for the parent drug after SI (0.57 hr) and ORAL (0.59 hr) were consistent with each other and also consistent with reported data (2). However, the terminal half-life value for the metabolite (5.2 hr), while much longer than that for parent drug, was shorter than the reported value of 23 hr (2). The discrepancy is apparently due to the fact that different time points were used in the terminal half-life determination (8- to 24-hr data were used in the present study, whereas data points beyond 24 hr were used in the reported study).

Table III. Mean ± SD (*N*) Pharmacokinetic Parameters of Benazepril-HCl and Its Active Metabolite Benazeprilat

Parameter	Small intestine infusion (SI)	Colonic infusion (COLON)	Oral bolus solution (ORAL)	Parameter ratio	
				SI/ORAL	COLON/ORAL
Benazepril					
AUC (ng · hr/mL)	178.5 ± 51.5 (13)	45.0 ± 47.7 (7)	220.9 ± 97.8 (13)	0.90 ± 0.34 (13)	0.23 ± 0.25 (7)
C_{max} (ng/mL)	54.2 ± 23.4 (13)	16.1 ± 20.8 (7)	271.2 ± 114.3 (13)	0.22 ± 0.11 (13)	0.07 ± 0.08 (7)
T_{max} (hr)	2.9 ± 1.5 (13)	3.4 ± 1.6 (7)	0.54 ± 0.14(13)	5.42 ± 2.99 (13)	6.86 ± 3.24 (7)
$T_{1/2}$ (hr)	0.57 ± 0.17(12)	1.66 ± 0.29(5)	0.59 ± 0.19(13)	1.00 ± 0.33 (12)	2.93 ± 0.73 (5)
$MRT_{apparent}$ (hr)	2.9 ± 0.4 (13)	3.4 ± 1.1 (7)	0.9 ± 0.4 (13)	3.26 ± 1.19 (13)	4.14 ± 1.55 (7)
MRT_{corr} (hr)	0.9 ± 0.8 (13)	1.5 ± 1.0 (7)	0.9 ± 0.4 (13)	1.04 ± 0.93 (13)	1.81 ± 1.35 (7)
$Ae_{96\ hr}$ (μg)[a]	98.6 ± 47.2 (12)	34.4 ± 22.3 (6)	94.0 ± 48.1 (12)	1.03 ± 0.53 (11)	0.30 ± 0.24 (5)
Benazeprilat					
AUC (ng · hr/mL)	1591 ± 505 (13)	254 ± 288 (7)	2033 ± 647 (13)	0.83 ± 0.29 (13)	0.13 ± 0.17 (7)
AUC_m/AUC_p[b]	8.9 ± 1.4 (13)	5.0 ± 2.3 (7)	9.7 ± 2.3 (13)	0.96 ± 0.19 (13)	0.51 ± 0.24 (7)
C_{max} (ng/mL)	225 ± 84 (13)	34.1 ± 43.0 (7)	379 ± 126 (13)	0.62 ± 0.23 (13)	0.09 ± 0.11 (7)
T_{max} (hr)	4.4 ± 0.9 (13)	4.7 ± 1.4 (7)	1.3 ± 0.4 (13)	3.63 ± 1.28 (13)	4.31 ± 1.70 (7)
$T_{1/2}$ (hr)	6.0 ± 1.7 (13)	10.0 ± 12.7 (4)	5.2 ± 0.8 (13)	1.15 ± 0.29 (13)	2.08 ± 2.35 (3)
$MRT_{apparent}$ (hr)	8.5 ± 1.6 (13)	8.8 ± 4.4 (7)	5.9 ± 1.0 (13)	1.47 ± 0.28 (13)	1.62 ± 0.80 (7)
ΔMRT (hr)	5.7 ± 1.3 (13)	5.4 ± 4.4 (7)	4.9 ± 1.0 (13)	1.15 ± 0.20 (13)	1.16 ± 0.89 (7)
$Ae_{96\ hr}$ (μg)[a]	2135 ± 759 (12)	762 ± 509 (6)	3015 ± 1149 (12)	0.71 ± 0.28 (11)	0.28 ± 0.19 (5)

[a] Cumulative amount excreted in urine after 96 hr.
[b] Metabolite-to-drug AUC ratio.

Mechanisms of Site-Differential Absorption

Despite differences in the rate of drug delivery, the disposition pharmacokinetic parameters for BZPH and its active metabolite BZPL after SI and ORAL were remarkably similar (terminal half-live values of 0.57 vs 0.59 hr for BZPH and 6.0 vs 5.2 hr for BZPL). The mean disposition residence times for the metabolite in the body (ΔMRT), as calculated by Eq. (4), were also remarkably similar for all three treatments (5.7, 5.4, and 4.9 hr for SI, COLON, and ORAL, respectively).

The corrected MRT after the intestinal infusions represented the mean residence time of parent drug after oral administration [Eqs. (3) and (4)]. The corrected MRT values were 0.8, 1.5, and 0.9 hr for SI, COLON, and ORAL, respectively. These data imply that the intrinsic absorption process for the parent drug was rapid and probably similar for SI and ORAL but was longer for COLON.

The effects of rate of drug delivery on the extent of first-pass metabolism can be evaluated by the metabolite-to-drug AUC ratio. The metabolite-to-drug AUC ratios after SI and ORAL were similar (8.9 vs 9.7; ratio, 0.96; Table III), despite the fact that the rate of drug delivery was drastically different. These results suggest that first-pass metabolism of BZPH is not saturable under the study conditions and was not input rate dependent.

The metabolite-to-drug AUC ratio for COLON was drastically decreased compared to ORAL (5.0 vs 9.7; parameter ratio, 0.51; Table III). The reasons COLON resulted in a lower metabolite-to-drug AUC ratio is not apparent at this time. The metabolite fraction represents the portion of parent drug converted into metabolite and was governed by four possible situations: (i) metabolism by acid, enzyme, or bacteria before passing through the gut wall; (ii) gut wall metabolism; (iii) liver metabolism; and (iv) systemic metabolism after first pass. If any of the site-differential metabolism changes occurred following COLON, then the metabolite fraction would have been increased instead of decreased. The decrease in metabolite fraction after COLON indicates a different mechanism of absorption after colonic infusion, which resulted in either an increase in parent drug AUC or a decrease in metabolite AUC.

CONCLUSIONS

The results of this study demonstrate site-differential absorption of BZPH. Colonic infusion delivered a smaller amount of drug to the body at a slower absorption rate than either small intestinal infusion or oral bolus administration. In addition, the lower metabolite-to-drug AUC ratio observed after colonic infusion indicates that the drug may be absorbed from this site via a different mechanism.

REFERENCES

1. M. D. Schaller, J. Nussberger, B. Waeber, J. P. Bussien, G. A. Turini, H. Brunner, and H. R. Brunner. Hemodynamic and pharmacological effects of the converting enzyme inhibitor CGS 14824A in normal volunteers. *Eur. J. Clin. Pharmacol.* **28**:267–272 (1985).
2. G. Kaiser, R. Ackerman, S. Breckbuehler, and W. Diterle. Pharmacokinetics of the angiotensin converting enzyme inhibitor benazepril HCL (CGS 14824A) in healthy volunteers after single and repeated administration. *Biopharm. Drug Disp.* **10**:365–376 (1989).
3. D. S. Chan, R. A. Dotson, R. D. Burrell, and B. E. Watkins. Two potential angiotensin-converting enzyme (ACE) inhibitors: CGS 14824A and CGS 14831. *Pharmacologist* **25**:240 (1983).
4. S. Yee and G. Amidon. Intestinal absorption mechanism of three angiotensin-converting enzyme inhibitors: Quinapril, benazepril and CGS 16617. *Pharm. Res.* 7:S-155 (1990).
5. G. Kaiser, R. Ackerman, W. Dieterle, and J. P. Dubois. Determination of a new angiotensin converting enzyme inhibitor and its active metabolite in plasma and urine by gas chromatography-mass spectrometry. *J. Chromatogr.* **419**:123–133 (1987).
6. K. K. H. Chan and M. Gibaldi. Effects of first-pass metabolism on metabolite mean residence time determination after oral Administration of parent drugs. *Pharm. Res.* 7:59–63 (1990).
7. P. veng-Pedersen. A simple method for obtaining the mean residence time of metabolite in the body. *J. Pharm. Sci.* **75**:818–819 (1986).
8. G. M. Grass and W. T. Morehead. Evidence for site specific absorption of a novel ACE inhibitor. *Pharm. Res.* **6**:759–765 (1989).
9. Y. Seta, F. Higuchi, Y. Kawahara, N. Nishimura, and R. Ohada. Sustained release formulations resulted in decreasing bioavailability with captopril. *Int. J. Pharm.* **41**:245–254 (1988).
10. P. R. Byron and R. E. Notari. Critical analysis of "flip-flop" phenomenon in two-compartment pharmacokinetic model. *J. Pharm. Sci.* **65**:1140–1144 (1976).