Gastrointestinal Transit and Systemic Absorption of Captopril from a Pulsed-Release Formulation

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Captopril has been administered to eight healthy male subjects by means of a pulsatile delivery system that was designed to release the drug in the colonic region of the intestine. The gastrointestinal transit and pulsatile release were followed using gamma scintigraphy. A pulsatile capsule system with release after a nominal 5-hr period was found to perform reproducibly *in vitro* and *in vivo*. In six of the eight subjects, the drug was delivered to the colon, and in the remaining two subjects, to the terminal ileum. Measurable blood levels of free captopril were found in three subjects. Variable instability of the drug in the distal intestine is suggested as a possible reason for the lack of absorption of the drug in the majority of subjects.

KEY WORDS: captopril; pulsatile release; gamma scintigraphy; absorption.

INTRODUCTION

Captopril is an orally active angiotensin-converting enzyme (ACE) inhibitor that has been used widely for the treatment of hypertension and congestive heart failure. The drug is well absorbed from the proximal small intestine; approximately 70% is absorbed in healthy fasting subjects with an absolute bioavailability of approximately 60% compared to iv (1). Bioavailability is decreased by 25 to 50% when administered with food. Captopril is a structural derivative of the amino acid proline and it is, therefore, likely that the drug is absorbed (in part at least) from the small intestine by an active transport process (2).

The development of a once-daily captopril oral formulation would be a significant advantage for patient compliance. However, if the drug is absorbed only from the (proximal) small intestine, any form of controlled release system would display poor absorption characteristics at longer time periods when the system had passed into the distal (colonic) regions (3). The present investigation was carried out in order to determine the colonic absorption of captopril in a non-invasive manner.

The Nottingham group has considerable experience in using the technique of gamma scintigraphy to follow the transit and release characteristics of dosage forms in the human gastrointestinal (GI) tract (4–6). Osmotic pumps have been used with some success to relate position with regional drug absorption characteristics (7). However, such methodology for following the absorption of captopril was deemed inappropriate since the slow release of drug from an osmotic device could result in loss due to metabolism in the colonic environment and, more particularly, analytical problems in determining low levels of unchanged drug in the blood.

Consequently, we have utilized a new, more convenient oral pulsatile drug delivery system available from Scherer DDS Limited (8) to deliver captopril to the terminal ileum and proximal colon. Although pulsatile release systems with a range of nominal release times were available, a system with a nominal 5-hr pulse was selected on the basis of previous work that indicated that a single-unit system administered to a fasted subject should reach the colon by this time (9). The absorption of the drug has been followed by measuring free captopril levels in serial blood samples. Control experiments were performed using a conventional captopril tablet designed to release the drug in the stomach.

MATERIALS AND METHODS

Dosage Forms

Captopril [1-(D-3-mercapto-2-methyl-1-oxopropyl)-L-proline (*S,S*-isomer)] and standard captopril tablets (Capoten, 25 mg) were provided by E. R. Squibb, UK.

The oral pulsatile delivery system (Scherer DDS Limited, Clydebank, Scotland) consisted of an insoluble capsule body which contained 25 mg captopril powder and 5 mg ^{111}In (1 MBq)-labeled diethylenetriaminepentaacetic acid (DTPA). The contents were sealed into the capsule body by means of a hydrogel plug (8).

In the presence of aqueous fluids the hydrogel absorbs water and swells, and the plug is ejected from the capsule, thereby releasing the contents. The radioactive marker allowed the transit of the device in the GI tract to be determined. Ejection of the plug and release of contents were monitored by visualization of the spreading of the marker following its release from the device.

The *in vitro* release behavior of the pulsatile capsule system was confirmed using the USP dissolution test (paddle method) with 900 ml of distilled water as the release medium and a rotation speed of 50 rpm. For the *in vitro* studies the capsule contained 25 mg captopril and 5 mg unlabeled DTPA. Release of captopril was determined by continuous UV spectrophotometric analysis at 210 nm.

Subjects

The study was conducted in eight healthy male volunteers, who provided written informed consent according to an open, balanced, randomized two-way crossover design. The age range was 21–26 years and the weight range was

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63–92 kg. The study was approved by the Ethics Committee of the University of Nottingham and conformed with the Declaration of Helsinki (and subsequent revisions) and the Association of British Pharmaceutical Industry Guidelines for studies in human volunteers. Permission to administer radioactivity to human subjects was obtained from the Department of Health, London. No subject was allowed to consume caffeine- or alcohol-containing beverages or smoke before and 24 to 30 hr after each dose of captopril. The subjects refrained from strenuous exercise and received no medication other than captopril.

Procedures

Pulsed-Release Device

The volunteers were admitted to the clinical unit at 9:00 PM on the evening prior to administration and instructed to fast overnight (from 12:00 midnight). The pulsed-release formulation was administered to the volunteers with 240 ml of water at 8:00 AM. The water contained 4 MBq of $^{99}Tc^{m}$-labeled DTPA, which outlined the anatomical features of the GI tract and enabled the position of the pulsed release device to be identified accurately.

Each volunteer drank approximately 100 ml of water every hour postdose for the first 4 hr. A standard lunch and dinner were provided at 4 and 9 hr postdose, respectively. Fluid was allowed *ad libitum* after lunch.

Anatomical markers, containing 0.05 MBq of ^{111}In were taped to the skin over the liver and to the right of the stomach. Anterior scintigraphic images, each of 60-sec duration, were recorded approximately every 10 min until *in vivo* release was observed and subsequent images were acquired every 30 min. The gamma camera (General Electric Maxicamera) had a 40-cm field of view and was fitted with a medium-energy (300-Kev) parallel-hole collimator. The data were analysed to provide information on the GI transit of the device and the anatomical position of pulsatile release. The time of movement of the pulsed release device from one anatomical region to the next was taken as the midtime between recording the two images about the transition. *In vivo* release was determined in an analogous manner.

Conventional 25-mg Captopril Tablet

The volunteers were admitted to the clinical unit at 9:00 PM on the evening prior to administration and instructed to fast overnight (from 12:00 midnight). The conventional formulation, in the form of a standard 25-mg captopril tablet, was administered to the volunteers with 240 ml of water.

Food and fluid intake was identical to that detailed for the pulsed-release study.

Blood Sampling

Blood samples (12 ml) were collected either via an indwelling cannula irrigated with heparin or by direct venepuncture at the following time intervals.

(a) Pulsed-release device: 0 (predose), 2.0, and 4.0 hr and at the following times after determination of drug release; 0.17, 0.33, 0.5, 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hr. The time for *in vivo* release was determined for each subject during the actual study day and the rapid blood sampling associated with drug absorption commenced only at this time.

(b) Conventional tablet: 0 (predose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hr. The samples were collected in heparinized syringes and gently mixed several times. A 6-ml aliquot of the blood was immediately transferred into a labeled screw-top glass tube containing *N*-ethylmaleimide. The blood was vortexed and transferred to a freezer at −20°C.

Free captopril concentrations in whole blood were determined using a validated gas-chromatographic/mass spectrometric technique (10). The limit of detection for the assay was 10 ng/ml.

RESULTS AND DISCUSSION

In Vitro Release

The pulsatile drug delivery system released the drug *in vitro* in a uniform and reliable manner (Table I). These data indicated that the device should be suitable for *in vivo* evaluation in human subjects.

Gastrointestinal Transit

The transit behavior of the pulsatile delivery system following administration to subjects who had fasted overnight is shown in Table II. Emptying from the stomach occurred between 16 and 137 min, with a mean value of 61 min and a median of 46 min. These data are in line with previous reports on the emptying of large single-unit dosage forms from the fasted stomach (11). In the fasted state, the behavior of the stomach is controlled by a cyclical physiological mechanism known as the "migrating myoelectric complex" (MMC) (12), which has four phases of activity and a periodicity of about 2 hr. In phase 3, strong contractions sweep indigestible material through the open pylorus and down the small intestine. This cleansing effect has been given the title the "housekeeper wave." Thus, the time of emptying of a single-unit system from a fasted stomach will depend on the relative stage of the MMC. A dosage form administered just before a housekeeper wave will be cleared rapidly, while one administered just after such a wave will need to wait until the next cycle occurs.

In six of the subjects the device reached the colon before the drug was released. The average time of colon arrival was 235 min (Table II). The difference between the colon arrival and the gastric emptying data for these subjects allows a small intestinal transit time to be estimated. The mean value was 186 min (median, 190 min), which is in good accord with that previously reported by Davis *et al.* (9) from

Table I. *In Vitro* Release Properties of the Pulsatile Drug Delivery System (Mean Data, $n = 6$)

Captopril released (%)	Time (hr)	SD
25	5.25	0.29
50	5.29	0.34
75	5.96	0.22

Table II. Gastrointestinal Transit and Release Properties of the Pulsatile Drug Delivery System (min)

Volunteer No.	Gastric emptying	Small intestinal transit	Colon arrival	Time of drug release	Position of drug release
1	46	246	292	299	Cecum
2	16	190	206	344	Proximal colon
3	137	118	255	304	Transverse colon
4	96	—	—	373	Terminal ileum
5	26	191	217	317	Proximal colon
6	26	190	216	389	Cecum
7	46	178	224	338	Cecum
8	96	—	—	246	Terminal ileum
Mean	61	186	235	326	
SD	43	50	33	45	
Median	46	190	221	328	
Sample size	8	6	6	8	

extensive studies on the GI transit of labeled oral dosage forms in healthy subjects and patients. It confirms that the period of time a dosage form remains in what could be the optimal or only absorption site is short in comparison to the normal total transit time of 25–50 hr (13). Single-unit controlled-release dosage forms are likely to be in the colon within 4 hr following administration to a fasted stomach. Hence, the success of many "once-daily" products must depend on a sufficient degree of colonic absorption.

The time and position of drug release are recorded in Table II. Two subjects demonstrated release in the terminal ileum, three in the cecum, two in the proximal colon, and one in the transverse colon. The *in vivo* release times ranged from 246 to 389 min, with a mean of 326 min (median, 328). The mean value is in good agreement with that recorded *in vitro* and demonstrates the independent behavior of the pulsatile capsule system.

Captopril Blood Levels

Maximum drug plasma concentration (C_{max}) and the time to maximum value (T_{max}) were obtained directly from the drug plasma profile for each volunteer following administration of both the pulsed- and the conventional-release formulation. The area under the plasma concentration–time curve (AUC), up to the last measured time, was calculated using the trapezoidal rule. A summary of the pharmacokinetic parameters is provided in Table III.

In the three subjects who demonstrated measurable levels of free captopril, the pharmacokinetic profile was in good agreement with the *in vivo* release data. For one of these subjects, release took place in the terminal ileum. These data indicate that captopril is poorly absorbed from the distal bowel, and in the majority of cases no measurable amounts of drug were observed in the blood. Control parameters obtained from the conventional formulation (Table III) indicate that none of the subjects displayed atypical pharmacokinetics for the drug.

Previous studies on the absorption of captopril from the GI tract have been conducted using *in situ* animal models. Warland *et al.* (2) concluded that the absorption process for captopril appeared to be principally by passive diffusion, but more recently Hu and Amidon (14) have shown, in the rat, that the small intestine is very permeable to captopril but that this is not the case for the colon. Permeability was both pH and concentration dependent. The mechanism of captopril absorption was suggested to be mainly carrier mediated via the peptide carrier system. In addition, there was a significant passive component in the overall absorption processes.

The absorption of captopril from the large bowel has been evaluated recently via intestinal intubation with an intranasal O'Donnell tube positioned in the proximal colon

Table III. Summary Pharmacokinetic Parameters Following Administration of a Pulsed-Release and a Conventional-Release Formulation of Captopril

	Pulsed			Conventional		
Volunteer No.	C_{max} (ng/ml)	T_{max} (hr)	AUC (ng/ml hr)	C_{max} (ng/ml)	T_{max} (hr)	AUC (ng/ml hr)
1	24	6.0	24.9	215	1.0	398.8
2	0	—	0	237	0.5	358.5
3	0	—	0	224	1.0	311.0
4	23	6.5	42.0	230	1.0	383.3
5	11	6.5	5.5	234	1.0	329.5
6	0	—	0	203	1.0	314.8
7	0	—	0	225	0.5	288.0
8	0	—	0	296	0.5	415.5

(15). The mean relative bioavailability of captopril (AUC intestinal infusion/AUC oral solution) was 14%. However, the direct infusion of a drug solution into the large bowel might not be a good indicator of the behavior of dosage forms, since drug dissolution, prior to absorption, is avoided. In addition, intubation can perturb normal physiology and may alter the anaerobic colonic environment.

Colonic absorption of captopril in humans is believed to occur via passive diffusion since it seems highly unlikely that active transport processes for peptides would exist in such distal regions. The reasons why some subjects provide measurable levels and others do not is presently unclear.

It should be stressed that the combination of pulsatile release plus scintigraphy demonstrates that the drug was released *in vivo* and that failure of the delivery system is not a plausible explanation. Captopril is known to be unstable in solution and can be metabolized by the microflora present in the colon (2). *In vitro* studies in whole blood indicate that captopril is oxidized primarily to its disulfide dimer and other mixed disulfides (16,17) and that, in man, captopril is partially metabolized mainly by disulfide formation with exogenous thiol compounds including glutathione and cysteine. Since the colonic environment is anaerobic, such processes of disulfide formation seem unlikely. Intersubject differences in microbial flora and pH in the colon are known to occur. These are dependent on environment and, above all, diet (18) and could provide an explanation.

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