Absorption Differences of Ciprofloxacin along the Human Gastrointestinal Tract Determined Using a Remote-Control Drug Delivery Device (HF-capsule)

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The single-dose absorption kinetics of ciprofloxacin in different regions of the human gastrointestinal tract were investigated using a remote-control drug delivery device (HF-capsule). Doses of 180 to 200 mg ciprofloxacin (as a lactic acid solution) were placed in the HF-capsule and administered to four healthy male adults. The position of the HF-capsule in the gastrointestinal tract was checked via radiographic examination. The release of the solution from the HF-capsule was induced by a radio signal. In each volunteer, the solution was released into five different regions of the gastrointestinal tract: the stomach (B), jejunum (C_1), ileum (C_2), ascending colon (D_1), and descending colon (D_2). Two control runs (A_1, A_2), involving oral administration of the solution, were used as a reference for calculation of area under the curve. The oral administration of a conventional 250-mg tablet (A_3) was also studied. The plasma concentration of ciprofloxacin and urine concentrations of ciprofloxacin, desethylene- (M1), sulfo- (M2), and oxo-ciprofloxacin (M3) were determined fluorimetrically by high-performance liquid chromatography. Intraindividual comparisons indicated a progressive decrease in the amount of ciprofloxacin absorbed (100 percent = mean of AUC_{A1} and AUC_{A2}) from the jejunum (−61 percent, median), ileum (−75 percent), colon ascendens (−90 percent), and colon descendens (−95 percent). Absolute amounts of renally excreted ciprofloxacin and metabolites decreased due to the reduced absorption of ciprofloxacin, but the metabolite pattern was unchanged. It is concluded that the main absorption site for ciprofloxacin is the upper part of the intestinal tract (duodenum, jejunum).

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The oral bioavailability of ciprofloxacin is 55 to 85 percent in healthy subjects under normal conditions [1–5]. Drug interaction studies with butylscopolamine and metoclopramide demonstrate a rapid absorption of ciprofloxacin in the upper gastrointestinal tract [6]. No detailed information exists on possible differences in the absorption kinetics and/or presystemic elimination of ciprofloxacin in different parts of the human gastrointestinal tract.

Determination of the absorption kinetics of ciprofloxacin and the main site of this absorption was conducted using controlled bolus release of ciprofloxacin solution at selected regions of the human gastrointestinal tract. This was achieved with the aid of a special drug delivery device, the HF-capsule [7,8], in which drug release is triggered by an external high-frequency (27 MHz) radion signal (**Figure 1**).

MATERIALS AND METHODS

Single doses of ciprofloxacin (absorption kinetics as lactic acid-based solution formulations, specially prepared for use in the HF-capsule provided by Bayer AG, Leverkusen, Federal Republic of Germany and as a conventional 250-mg tablet) were investigated in four healthy male volunteers (aged 25 to 30 years). All gave their informed written consent.

The drug was released from the HF-capsule at different sites of the gastrointestinal tract (**Figure 2**). The release procedure into predetermined areas of the gastrointestinal tract (B = stomach; C1 = jejunum; C2 = ileum; D1 = ascending colon; D2 = descending colon) was executed after location of the capsule was confirmed by radiographic examination. The study design was comprised of three parts, as shown in **Figure 3**.

The runs in each volunteer followed the sequence A1, D1, C2, B, C1, D2, A3, A2, with a one week washout period between treatments. Detection of ciprofloxacin in plasma and of ciprofloxacin, desethylene- (M1), sulfo- (M2) and oxo-ciprofloxacin (M3) in urine samples was carried out by a high-performance liquid chromatography method with fluorometric detection [9,10].

Pharmacokinetic parameters of ciprofloxacin in the plasma (area under the curve [AUC], maximal concentration [C_{max}], time of C_{max} [t_{max}]) were calculated by moment analysis. The individual means for the runs A1/A2 were used as an intraindividual reference value (100 percent) for the amount absorbed (close normalized area under the curve [$AUC_{norm/0\rightarrow\infty}$]). The excretion of metabolites and unchanged ciprofloxacin in urine was calculated as molar equivalents and ex-

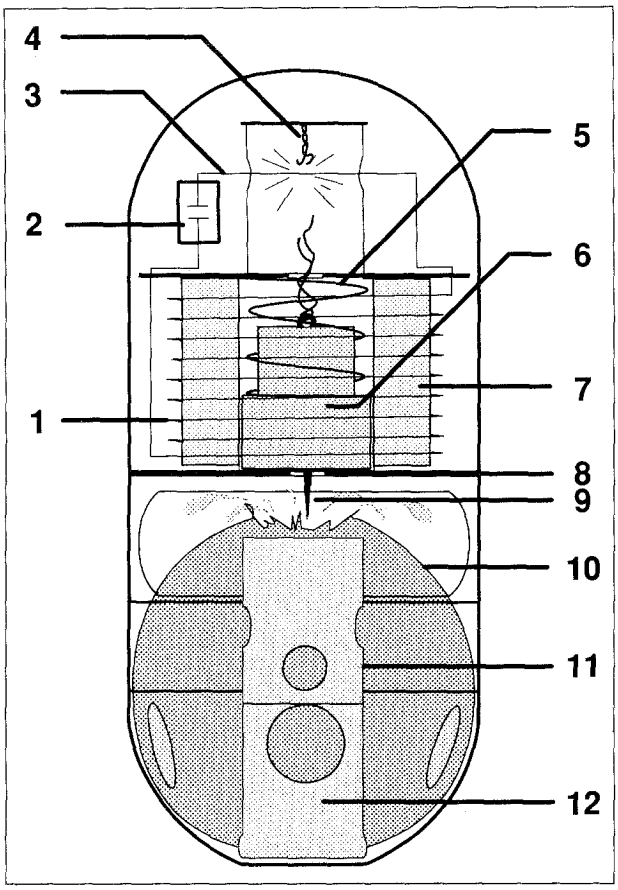

Figure 1. HF-capsule. 1 = oscillating circuit; 2 = capacitor; 3 = heating wire; 4 = nylon thread; 5 = spiral spring; 6 = piston; 7 = cylinder guide; 8 = separating membrane; 9 = needle; 10 = latex balloon (reservoir); 11 = balloon fixation; 12 = seal.

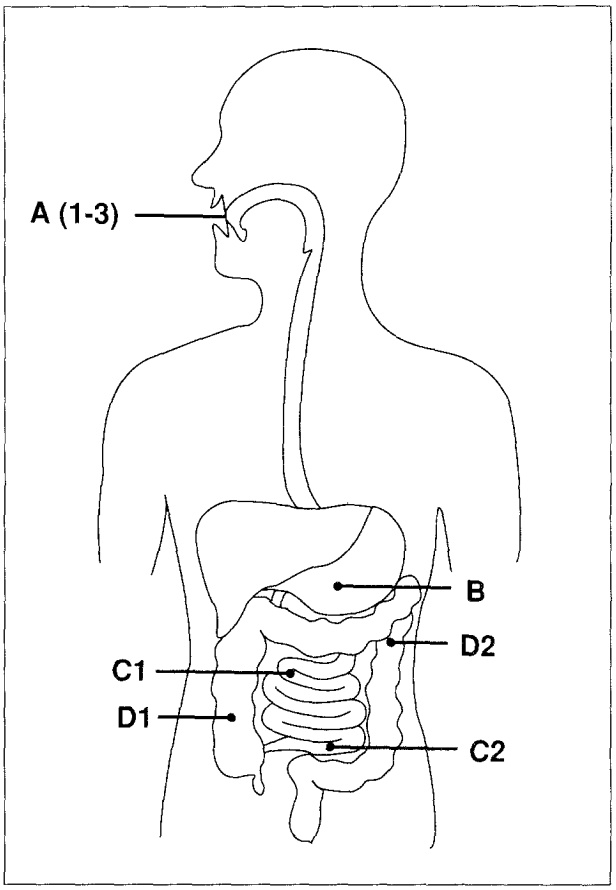

Figure 2. Release and administration sites of ciprofloxacin in the gastrointestinal tract. A(1-3) = oral administration; A1 and A2 = solution; A3 = tablet; B = stomach; C1 = jejunum; C2 = ileum; D1 = ascending colon; D2 = descending colon.

1. REFERENCE	2. HF-CAPSULE	3. CONTROL
A1/A2	B . . . D	A3
200 mg ciprofloxacin solution orally	175–180 mg CIP solution in HF-capsule	250 mg ciprofloxacin tablet (CIPROBAY(R) 250)
	1. X-ray localization after capsule-intake	
	2. radio-control release (27 MHz, ring-antenna)	

Figure 3. Plasma samples and urine collected over 24 hours immediately after administration or drug release (HF-capsule). CIP = ciprofloxacin.

pressed as a percentage of the dose given. Recovery of ciprofloxacin and its metabolites in urine was calculated as a percentage of the total amount excreted after oral intake. Because of the small number of subjects studied, statistical comparisons were made using a nonparametric Mann-Whitney U test alone. Values for $AUC_{norm/0\rightarrow\infty}$, C_{max}, and t_{max} were compared.

RESULTS

Pharmacokinetic parameters of ciprofloxacin are presented as median and range in **Tables I** to **III**. No significant differences were found (Mann-Whitney U test) for AUC, C_{max}, and t_{max} between the controls (A1, A2), HF-capsule release in the stomach, and tablet administration. However, differences in AUC and C_{max} were seen when comparing controls with the results for HF-capsule release in the jejunum, ileum, and ascending and descending colon, but t_{max} values did not differ (**Table IV**).

No significant differences in the pattern of urinary excretion of metabolites and unchanged ciprofloxacin were seen. Decreases in the urinary recovery of ciprofloxacin and its metabolites correlated with the decrease in absorbed ciprofloxacin.

COMMENTS

No significant differences in AUC, C_{max}, and t_{max} were observed when we compared the data obtained

TABLE I

Ciprofloxacin-$AUC_{norm/o\rightarrow\infty}$ at the Different Release/Administration Sites*

Subject	A1	A2	A3	B	C1	C2	D1	D2
1	1.07	1.29	1.42	1.49	ND	0.43	0.03	0.05
2	1.03	1.01	1.54	1.62	0.28	0.34	0.09	0.08
3	0.68	1.15	0.71	0.93	0.46	0.13	0.12	ND
4	0.95	1.44	1.52	2.15	0.41	0.17	0.15	0.04
Median (A1 + A2)		1.05	1.47	1.55	0.41	0.26	0.11	0.05
Maximum		1.44	1.54	2.15	0.46	0.43	0.15	0.08
Minimum		0.68	0.71	0.93	0.28	0.13	0.03	0.04

ND = not determined.
*Data are expressed in kg/hour · liter.

TABLE II

C_{max} and t_{max} of Ciprofloxacin in Plasma

Subject	A1	A2	A3	B	C1	C2	D1	D2
C_{max} (mg/liter)*								
1	0.71	0.84	1.09	1.17	ND	0.28	0.07	0.06
2	0.84	0.62	0.65	1.36	0.16	0.13	0.02	0.08
3	0.78	0.92	0.5	0.8	0.24	0.08	0.01	ND
4	0.73	1.22	1.93	1.57	0.17	0.11	0.07	0.08
Median (A_1 + A_2)		0.81	0.79	1.27	0.17	0.12	0.05	0.08
Maximum		1.22	1.09	1.57	0.24	0.28	0.07	0.08
Minimum		0.62	0.5	0.8	0.16	0.08	0.01	0.06
t_{max} (hours)								
1	1.00	1.00	1.00	0.75	ND	0.50	0.33	0.75
2	0.75	1.00	3.00	1.00	0.33	1.50	0.33	0.25
3	0.33	0.50	0.75	0.75	0.75	0.25	6.00	ND
4	0.50	0.50	1.00	0.7	0.50	0.33	0.25	0.17
Median (A_1 + A_2)		0.7	1.0	0.75	0.5	0.4	0.3	0.25
Maximum		1.0	3.0	1.0	0.75	1.5	6.0	0.75
Minimim		0.33	0.75	0.75	0.33	0.25	0.25	0.17

ND = not determined.
*Dose-corrected, 200-mg based.

TABLE III

Renally Excreted Amounts of Ciprofloxacin and Recovery of Ciprofloxacin in the Urine

	A1+2	A3	B	C1	C2	D1	D2
A_e (as % of the dose)	42	52	44	13	11	4	2
$RECOV_{rel}$	100	123	104	31	26	10	5
N	8	4	4	3	4	4	3

A_e = amount excreted (ciprofloxacin dose = 100 percent; ciprofloxacin + M1 + M2 + M3 excreted, see text); $RECOV_{rel}$ = relative recovery in the urine, with reference (A1 + A2) · 2^{-1} = 100 percent; N = runs in each release/administration site.

TABLE IV

p Values by the Mann-Whitney U Test for Ciprofloxacin Pharmacokinetic Parameters

	p Value of Compared Parameter*		
Groups Compared	AUC	C_{max}	t_{max}
A1,A2 vs B	0.149	0.248	0.655
A1,A2 vs C1	0.034	0.034	0.372
A1,A2 vs C2	0.021	0.021	0.468
A1,A2 vs D1	0.021	0.020	0.245
A1,A2 vs D2	0.034	0.034	0.147
A1,A2 vs A3	0.248	0.564	0.139

*$p < 0.05$ is considered significant.

from oral administration of ciprofloxacin as a solution, as a tablet, or as a solution released in the stomach. However, there were marked differences for AUC and C_{max} between oral administration and release of the drug in the jejunum and the distal regions of the gut. These differences were statistically significant.

Since the t_{max} of ciprofloxacin absorption is dependent on stomach emptying time [6], it can be assumed that this drug is not absorbed in the stomach. The metabolite profile in urine was unchanged, regardless of where the drug was released along the gastrointestinal tract. It would appear therefore that qualitative differences in pre-hepatic first-pass metabolism caused by differences in intestinal contents or intramural degradation can be excluded.

In vitro results with human colon tissue show both passive absorption of ciprofloxacin and a countersecretion mechanism [11]. Experiments in rats demonstrate a lack of absorption of ofloxacin, another 4-quinolone, in isolated colon segments [12]. It should be noted that the HF-capsule method involves drug absorption only at the release site and at sites distal to this [8,13,14].

CONCLUSIONS

The main absorption site of ciprofloxacin is the duodenum and the upper part of the small intestine. The amount of ciprofloxacin absorbed from the gastroin-

testinal tract progressively decreases from the upper to lower regions of the small intestine and is drastically reduced in the colon. The metabolite profile for ciprofloxacin in urine is independent of the absorption site. The reduced absorption of ciprofloxacin in the lower bowel does not appear to be due to differences in pre-hepatic metabolism along the gastrointestinal tract.

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