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Ciprofloxacin absorption in different regions of the human gastrointestinal tract. Investigations with the hf-capsule

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1 The absorption of ciprofloxacin from different regions of the human gastrointestinal tract was investigated in four healthy males using a remote-controlled drug delivery device (hf-capsule).

2 Significant differences in AUC were observed in the control study (oral administration of ciprofloxacin solution without the hf-capsule = 100%) and after release of ciprofloxacin in the jejunum (geometric mean: 37%), the ileum (mean: 23%), the ascending colon (mean: 7%) and the descending colon (mean: 5%), whereas t_{max} showed no difference for any of the absorption sites. Ciprofloxacin release in the stomach resulted in the greatest AUC (mean: 140%). Thus, it is concluded that the main absorption site of ciprofloxacin is the upper gastrointestinal tract, up to the jejunum.

3 Differences in presystemic metabolism of known drug metabolites along the gut could be excluded, as the pattern of urinary recovery of desethylene-, sulpho-, and oxo-ciprofloxacin and the parent compound was similar for all drug release sites.

Keywords ciprofloxacin absorption metabolism human gastrointestinal tract hf-capsule

Introduction

The fluorinated 4-quinolone ciprofloxacin has a broad antimicrobial activity and is used in the systemic therapy of infectious diseases. It is effective when given orally and may be used in out-patients. The oral bioavailability of ciprofloxacin was found to be 55–85% in healthy subjects under normal conditions (Bergan *et al.*, 1987; Höffken *et al.*, 1985; Janknegt, 1986; Neuman, 1988; Nix & Schentag, 1988) and is somewhat lower than that reported for other 4-quinolones such as ofloxacin. Possible reasons for the incomplete bioavailability after oral administration are incomplete absorption due to poor dissolution of the dosage form, an absorption window along the gastrointestinal tract, and first pass metabolism.

Interactions with butylscopolamine and metoclopramide suggest that ciprofloxacin is rapidly absorbed in the upper gastrointestinal tract (Wingender *et al.*, 1985), but no detailed information exists on the absorption and possible presystemic elimination of ciprofloxacin or any other 4-quinolone in different parts of the human gastrointestinal tract.

We have investigated the absorption of ciprofloxacin from different regions of the human gastrointestinal tract using a special drug releasing device, the hf-capsule (Hugemann & Schuster, 1982; Schuster & Hugemann, 1987; Staib *et al.*, 1986, 1989). After oral administration the progress of the polyurethane capsule (length 2.5 cm; diameter 0.7 cm) along the gastrointestinal tract can be followed by X-ray. The release of the drug is effected by a high-frequency signal which induces the opening of the drug reservoir (a latex balloon inside the capsule).

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Methods

Study design

The pharmacokinetics of a single dose of ciprofloxacin (180 mg ciprofloxacin-betaine in 0.9 ml of a liquid preparation) were investigated in four healthy male volunteers (age 23–30 years) after releasing the substance in different parts of the gastrointestinal tract. All ciprofloxacin preparations were provided by Bayer AG, Leverkusen, F.R.G. All volunteers were informed of the aims and the risks of the study and gave their written consent. The study was performed according to the Declaration of Helsinki (revised form of Tokyo and Venice) and to the German Drug Law.

After measuring the ciprofloxacin dose accurately by weighing the capsule before and after filling the reservoir, the capsule was administered orally. X-ray control was performed at subsequent times and the release procedure was executed after localisation of the capsule in the desired region (B = stomach; C1 = jejunum; C2 = ileum; D1 = ascending colon; D2 = descending colon). In addition, the same dose of the liquid preparation was administered orally with 100 ml water at the beginning (A1) and at the end (A2) of the study. A commercially available 250 mg tablet of ciprofloxacin was also administered on one occasion (A3).

Immediately before and after drug release (or oral administration) venous blood samples were taken (5, 10, 20, 30, 45, 60, 90, 120 min, 3 h, 4 h, 6 h, 9 h, 12 h, 24 h) and urine was collected for 24 h. During the 24 h before administration of the capsule, volunteers were maintained on a standard diet to reduce variability in gastrointestinal filling and motility.

Ciprofloxacin, desethylene-, sulpho-, and oxo-ciprofloxacin were measured in plasma and urine samples by h.p.l.c. (Scholl *et al.*, 1987).

Calculations

C_{max} and t_{max} were determined directly from the plasma drug concentration-time curves. AUC was calculated by using the log-linear trapezoidal rule, with extrapolation to infinity, using the terminal elimination rate constant, and was normalized to body-weight and dose.

The relative bioavailability of ciprofloxacin after hf-release and administration of the commercial tablet was calculated as a percentage (geometric mean) of the values obtained following the oral administration of ciprofloxacin solution (A1, A2). The urinary recoveries of ciprofloxacin and its metabolites were calculated as percentages of the dose. Data have been presented as the geometric means and the antilog of the standard deviations of the logarithms of the values. No detailed statistical evaluation of the data has been performed, other than use of the non-parametric Mann-Whitney U-test to compare the geometric means of normalised AUC, C_{max} and t_{max} from the two control trials (A1, A2) for each subject with the results after hf-capsule release at different locations and after tablet administration. Significant differences were assumed at a P level of < 0.05.

Results

Ciprofloxacin release in the desired regions in the gastrointestinal tract was effected successfully except in two cases: In subject 1 (site C1) the plasma concentration-time profile of ciprofloxacin indicated that the capsule had opened before the release signal. In subject 3 (site D2) the capsule was excreted before release could be induced.

Individual data, geometric means and variation of ciprofloxacin parameters are presented in Table 1. No marked differences were found in normalised AUC, C_{max} and t_{max} values between the control experiments (A1, A2) and those involving drug release in the stomach or tablet administration. However, differences in AUC and C_{max} were evident between the control values and those obtained after drug release in the jejunum, ileum, ascending and descending colon for AUC and C_{max}. The mean value of t_{max} was similar at all absorption sites. The relative bioavailability of ciprofloxacin was reduced to 37% in the jejunum, 23% in the ileum and was below 10% in the colon. The excretion of metabolites and unchanged ciprofloxacin in urine was calculated on a molar basis and has been expressed as percent of the total amount excreted (Table 2). No marked differences in the pattern of urinary excretion of ciprofloxacin or its metabolites were seen. The reduction in the overall urinary recovery of ciprofloxacin (Ae) after drug release in the lower gut was in agreement with the decrease in ciprofloxacin absorbed from this site.

Discussion

The absolute bioavailability of ciprofloxacin in humans is between 55 and 85% (Bergan *et al.*, 1987; Höffken *et al.*, 1985; Janknegt, 1986; Neuman, 1988; Nix & Schentag, 1988). Results at the lower end of this range are understandable in the light of our finding that the main absorption

Table 1 Pharmacokinetic parameters (C_{max}, t_{max} and AUC)[1] of ciprofloxacin after oral administration (A1, A2, A3) and hf-release in the stomach (B), jejunum (C1), ileum (C2), ascending colon (D1) and descending colon (D2)

	Subject	*A1*	*A2*	*A3*	*B*	*C1*	*C2*	*D1*	*D2*
C_{max}	1	0.71	0.83	1.36	1.03	—	0.24	0.06	0.05
(mg l^{-1})	2	0.84	0.62	0.81	1.19	0.14	0.11	0.02	0.07
	3	0.78	0.92	0.63	0.70	0.21	0.07	0.01	—
	4	0.73	1.19	1.17	1.37	0.15	0.10	0.06	0.07
	Mean[2]	0.76	0.86	0.95	1.04	0.16*	0.12*	0.03*	0.06*
	s.d.[2]	1.08	1.31	1.42	1.33	1.24	1.70	2.66	1.23
t_{max}	1	1.00	1.00	1.00	0.75	—	0.50	0.33	0.75
(h)	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	—
	4	0.50	0.50	1.00	0.75	0.50	0.33	0.25	0.17
	Mean[2]	0.59	0.71	1.23	0.81	0.50	0.50	0.64	0.32
	s.d.[2]	1.62	1.49	1.85	1.16	1.50	2.19	4.48	2.18
AUC	1	1.07	1.29	1.42	1.49	—	0.43	0.03	0.05
(mg l^{-1} h)				(121)	(127)		(37)	(3)	(4)
	2	1.03	1.01	1.54	1.62	0.28	0.34	0.09	0.08
				(147)	(158)	(27)	(33)	(9)	(8)
	3	0.68	1.15	0.71	0.93	0.46	0.13	0.12	—
				(91)	(105)	(52)	(15)	(14)	
	4	0.95	1.44	1.52	2.15	0.41	0.17	0.15	0.04
				(111)	(184)	(35)	(15)	(10)	(3)
	Mean[2]	0.92	1.21	1.24	1.48	0.38*	0.24*	0.08*	0.05*
				(111)	(140)	(37)	(23)	(7)	(5)
	s.d.[2]	1.23	1.16	1.45	1.42	1.30	1.77	1.97	1.38
				(1.23)	(1.28)	(1.28)	(1.65)	(2.09)	(1.53)

*Mann-Whitney-U-Test: $P < 0.05$
[1]in brackets: relative bioavailability in percent (geometric mean A1, A2 = 100%)
[2]geometric mean and antilog of s.d. of log of values

Table 2 Urinary recoveries (geometric mean % of total recovery) of ciprofloxacin (C), desethylene- (M1), sulpho- (M2), and oxo-ciprofloxacin (M3)

	A1	*A2*	*A3*	*B*	*C1*	*C2*	*D1*	*D2*
C	85.5	77.0	80.7	73.5	77.2	79.3	82.0	76.7
M1	2.0	1.8	1.8	2.2	2.0	2.2	1.5	1.7
M2	5.5	5.3	5.6	7.9	4.6	4.3	3.0	4.1
M3	6.3	14.0	10.9	15.6	15.7	13.7	11.9	17.0
Ae_C*	28.3	36.1	29.8	40.2	8.5	8.1	2.8	1.6

*total recovery of ciprofloxacin as % of the administered dose (geometric mean)

site is limited to the upper part of the gut with absorption decreasing distal to the jejunum. Therefore, an increase in the velocity of gastrointestinal passage could lead to a decrease in the amount of ciprofloxacin absorbed. The possible clinical relevance of these findings with respect to the antimicrobial efficacy of ciprofloxacin in disturbances of the gastrointestinal system (e.g. diarrhoea or after gastrectomy) should be considered.

However, in two studies (Ball & Fox, 1987; Segreti *et al.*, 1988) in volunteers and in patients with diarrhoea, plasma concentrations of ciprofloxacin after oral administration of the same dose were not significantly different between the two groups.

The extent to which oral ciprofloxacin is absorbed with and without coadministration of metoclopramide or butylscopolamine has suggested that the absorption of ciprofloxacin is extensive in the upper gastrointestinal tract, but much less in the stomach (Wingender *et al.*, 1985).

In the present study, maximum absorption occurred after ciprofloxacin release in the stomach as well as after tablet administration. Whether this was due to absorption from the gastric *and* duodenal mucosa or only from the duodenum could not be determined. It should be pointed out that although the method of release of the drug from the hf-capsule excludes absorption proximal to the release site, it includes any absorption that takes place distal to the release site, as the motility of the gut may lead to transport of drug to distal parts before absorption is complete. Thus, absorption measured by this method could be biased by the motility and filling of the gastrointestinal tract. In the present study, however, similar conditions on all occasions were ensured by administering a standard diet to the subjects.

Hf-release in the stomach led to higher AUC values than with the control preparations (oral solution and tablet intake). This might be due to wide intraindividual variability in stomach emptying and absorption in the duodenum, particularly as there were no statistically significant differences between those locations in respect of the amounts of ciprofloxacin absorbed.

As ciprofloxacin was not administered intravenously, the relative bioavailability can be compared only with the appropriate values determined by other groups. The dose-normalized AUC-value obtained in a comparable group of volunteers after intravenous ciprofloxacin administration (Bergan *et al.*, 1987) was about 1.79 mg l^{-1} h, so that our data (geometric mean A1/A2 = 1.08 mg l^{-1} h) suggest relative bioavailability of 60%, and are thus consistent with the results of other bioavailability studies.

Variations between oral and intravenous administration in the formation of sulphociprofloxacin have been reported, suggesting a small amount of first pass metabolism (pre-hepatic or hepatic) (Beermann *et al.*, 1986; Höffken *et al.*, 1985; Janknegt, 1986). However, the consistency of the urinary metabolite pattern following release at all of the sites precludes any prehepatic metabolism in the different parts of the lower gut (e.g. intraluminal or intramural degradation), so that hepatic metabolism alone appears responsible for the first pass effect.

Studies *in vitro* (Steinke, unpublished) with guinea-pig colon tissue have shown that in addition to passive absorption, there is a contrary active secretion mechanism for ciprofloxacin, the net effect of which may result in only small amounts of ciprofloxacin being available from the colon.

Comparable investigations on the absorption of other fluoroquinolones at different parts of the human gastrointestinal tract have not been performed. Studies on ofloxacin absorption in rats in defined parts of the gastrointestinal tract (isolated by ligatures) showed that there is no absorption in the stomach or the colon, the main site of absorption being along the small intestine (Japanese Society of Chemotherapy, 1982). These findings are in agreement with our results *in vivo*.

Conclusions

Despite the small number of subjects used in this investigation, the results obtained allow the following conclusions to be drawn:

1. The main site of absorption of ciprofloxacin is the upper part of the gastrointestinal tract: the duodenum and to a smaller extent the jejunum. Absorption decreases in the distal parts of the small intestine and is almost completely absent in the colon.
2. Differences in presystemic metabolism to the known metabolites along the gut could not account for these differences, as the urinary metabolite for desethylene-, sulpho-, and oxociprofloxacin and the parent compound are similar for all of the release sites investigated.
3. The hf-capsule is a suitable tool for the direct assessment of the absorption properties of a drug in different regions of the human gastrointestinal tract.

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