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RESEARCH AND REPORTS

Effect of famotidine on ciprofloxacin pharmacokinetics after single intravenous and oral doses in rats

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SUMMARY

The effect of intravenous (3·5 mg/kg) and oral (5 mg/kg) famotidine on ciprofloxacin pharmacokinetics after single (i.v.) intravenous (5 mg/kg) and oral (20 mg/kg) doses were examined in the rat. Famotidine co-administration significantly increased the terminal elimination half-life of ciprofloxacin (54% and 29% following i.v. and oral administration, respectively) and tended to reduce the total body clearance by 27% and 34% following i.v. and oral routes, respectively. The area under the plasma concentration–time curve and the mean residence time in the body after i.v. and oral doses were significantly increased following famotidine co-administration. No changes in the steady-state apparent volume of distribution was observed after i.v. administration. The maximum plasma concentration and the time to peak concentration after oral dosing were also unaffected. These results suggest a possible reduction in the total clearance of ciprofloxacin, owing to inhibition of its renal tubular excretion by famotidine. Further studies are warranted to determine whether this interaction occurs in humans.

INTRODUCTION

Ciprofloxacin is a fluoroquinolone antibacterial agent with excellent activity against Gram-negative and Gram-positive pathogens (1). The volume distribution of ciprofloxacin is large, reflecting an excellent penetration of the drug into most tissues, including the central nervous system (CNS). The drug is eliminated predominantly unchanged in urine by glomerular filtration and active tubular secretion. In addition, metabolic degradation, biliary excretion and transluminal secretion across the enteric mucosa account for approximately one-third of the total plasma clearance of ciprofloxacin (2). Recently, it has been reported that reduced ciprofloxacin clearance by inhibition of its renal excretion by fenbufen gave rise to serious convulsions in both humans and laboratory animals (3–5).

Famotidine is a potent histamine H_2-receptor antagonist widely used in the treatment and prevention of peptic ulcer disease. The drug has a small volume of distribution, is minimally metabolized in the body and is mainly excreted unchanged in the urine by glomerular filtration and active tubular secretion (6).

The purpose of this study was to examine the effects of intravenous and oral famotidine on the single-dose pharmacokinetics of intravenous and oral ciprofloxacin using the rat as an animal model.

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MATERIALS AND METHODS

Chemicals

Ciprofloxacin hydrochloride was kindly supplied by Bayer AG (Leverkusen, Germany) and famotidine was obtained from Merck Sharp and Dohme Ltd. (U.S.A.). All other reagents were commercially available and of analytical grade.

Animals

Sixteen male Sprague–Dawley rats (250–300 g) were randomly assigned to two treatment groups for i.v. dosing (eight rats per group). The rats were lightly anaesthetized with ether prior to the insertion of a silastic catheter (silastic tubing, 0·02 in. [0·51 mm] i.d., Dow Corning, Midland, MI, U.S.A.) into the jugular vein, which was then exteriorized to the back of the

neck. The same catheter was used for drug administration and for blood sampling. All rats were alert at the time of dosing. Food and water were denied during the study period. Each rat in group A received a 5 mg/kg i.v. bolus dose of ciprofloxacin in normal saline (total volume 1·2 ml). Blood samples (0·3 ml) were taken just prior to dosing and at 5, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240 and 300 min following drug administration. Each rat in group B received a 3·5 mg/kg i.v. dose of famotidine followed (after 5 min) by a 5 mg/kg i.v. dose of ciprofloxacin. Blood samples were obtained at the same time as those outlined for group A. For oral dosing another group of Sprague–Dawley rats were used. Ciprofloxacin (20 mg/kg) alone or in combination with famotidine (5 mg/kg), was orally administered, at random, by gastric intubation. The rats were fasted overnight but allowed free access to water. Each treatment group consisted of eight rats. Blood samples were obtained just prior to dosing and at 5, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360 and 420 min after oral dosing. Blood was collected in heparinized polypropylene tubes and immediately centrifuged. The plasma was harvested and stored at $-20°C$ pending analysis.

Analysis of plasma samples

Plasma concentrations of ciprofloxacin were quantified by a sensitive and validated high-performance liquid chromatographic procedure (7). This assay involves simple protein precipitation of plasma samples, with acetonitrile enriched with quinine as the internal standard. After mixing and centrifugation, the drug and the internal standard were eluted from a 10 μm μ-Bondapak C-18 cartridge at ambient temperature with a mobile phase consisting of acetonitrile:0·1 M sodium dihydrogen phosphate (20:80%, v/v) at a flow rate of 2·5 ml/min. The effluent was monitored on a fluorescence detector using excitation and emission wavelengths of 280 and 455 nm, respectively. Each analysis required no longer than 6 min. The minimum detectable drug concentration in plasma was 25 ng/ml. The test samples from the dosed rats were always analysed along with a standard and a control sample. Standard curves for the analyte in plasma were generated daily and were linear ($r>0·999$) in the range 50–4,000 ng/ml over the entire period of the study. The intra-day coefficient of variation (CV) ranged from 0·4 to 5·8%, and inter-day CV from 4·6 to 8·8% at three different concentrations (150, 500 and 3,000 ng/ml). Relative recovery ranged from 98·0 to 100·2% at the three concentrations.

Pharmacokinetic analysis

A non-linear regression computer program PCNONLIN (version 4·2, Statistical Consultants Inc., Lexington, KY, U.S.A.) was used to fit the individual plasma ciprofloxacin concentrations to a first order, two-compartment open model. Selection of the most appropriate model was based upon the application of Akaike's Criterion (8). Initial estimates of the coefficients and exponentials required by PCNONLIN was obtained from exponential curves by the use of the stripping technique (9). Other pharmacokinetic parameters were calculated from the fitted parameters, including the terminal elimination rate constant (β), the terminal elimination half-life ($t_{\frac{1}{2}\beta}$), and the area under the plasma concentration–time curve (AUC).

Model-independent parameters were also computed. These include the total body clearance of ciprofloxacin (Cl), the steady-state volume of distribution (Vd_{ss}) (10), the mean residence time of the drug in the body (MRTB) (11), the mean residence of the drug in the peripheral tissue (MRTP) and the intrinsic mean residence time in the peripheral tissue (IMRTP) (12, 13).

Following oral administration, the maximum plasma concentration (C_{max}) and the corresponding time (T_{max}) were obtained directly from the plasma concentration–time profiles. The total body clearance (Cl/F) was calculated from the dose divided by the area under the plasma concentration–time curve.

Statistical analysis

Statistical comparisons of the pharmacokinetic parameters were made using analysis-of-variance and the unpaired Student's t-test, between both the with and without famotidine groups, on a microcomputer statistical package (SAS, Statistical Analysis System). Statistical differences were considered significant at the level of 0·05. Pharmacokinetic parameters are presented as mean ± SD.

RESULTS

The mean plasma concentration–time profiles of ciprofloxacin after intravenous bolus and oral

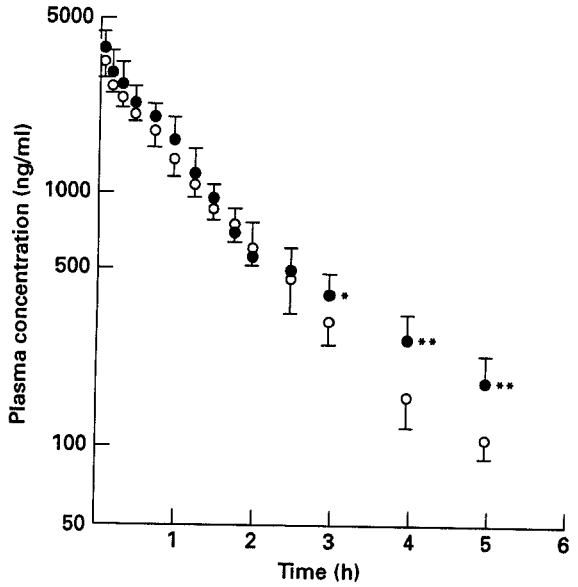

Fig. 1. Mean plasma concentrations of ciprofloxacin with (●) and without (○) famotidine co-administration following i.v. dosing.

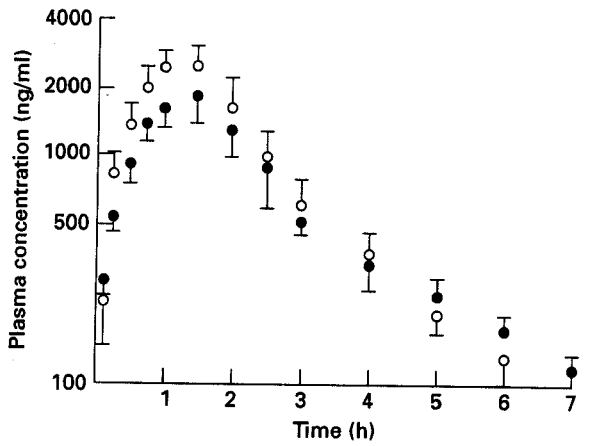

Fig. 2. Mean plasma concentrations of ciprofloxacin with (●) and without (○) famotidine co-administration following oral dosing.

Table 1. Pharmacokinetic parameters of ciprofloxacin after administration of a single i.v. bolus dose of 5 mg/kg, with and without famotidine (i.v., 3·5 mg/kg) co-administration to rats

Parameter	Control	With famotidine
AUC (μg.min/ml)	251·80 ± 41·60	331·80 ± 45·50*
Cl (ml/min/kg)	21·64 ± 4·18	15·80 ± 1·90*
Vd_{ss} (ml/kg)	1709·90 ± 193·70	1698·30 ± 216·80
α (h^{-1})	2·28 ± 1·20	1·60 ± 0·67
$t_{\frac{1}{2}\alpha}$ (h)	0·39 ± 0·19	0·50 ± 0·15
β (h^{-1})	0·61 ± 0·08	0·40 ± 0·06*
$t_{\frac{1}{2}\beta}$ (h)	1·16 ± 0·16	1·79 ± 0·26*
MRTB (h)	1·42 ± 0·14	1·87 ± 0·23*
MRTP (h)	0·30 ± 0·21	0·59 ± 0·27**
IMRTP (h)	1·13 ± 0·31	2·01 ± 0·34*

Each value represents the mean ± SD of eight rats.
*$P<0.005$. **$P<0.05$.

Table 2. Pharmacokinetic parameters of ciprofloxacin after oral administration of a single dose (20 mg/kg) with and without famotidine (5 mg/kg) co-administration to rats

Parameter	Control	With famotidine
AUC (μg.min/ml)	404·96 ± 76·55	595·15 ± 52·78*
C_{max} (μg/ml)	3·55 ± 1·01	3·97 ± 0·42
T_{max} (h)	0·94 ± 0·12	1·16 ± 0·30
Cl/F (ml/min/kg)	51·04 ± 10·16	33·81 ± 2·77*
MRTB (h)	2·09 ± 0·24	2·71 ± 0·20*
β (h^{-1})	0·492 ± 0·11	0·380 ± 0·07**
$t_{\frac{1}{2}\beta}$ (h)	1·47 ± 0·35	1·90 ± 0·40**

Each value represents the mean ± SD of eight rats.
*$P<0.005$. **$P<0.05$.

administration, both with and without famotidine, are presented in Figs 1 and 2, respectively. In both treatments, the plasma concentration of ciprofloxacin was found to decline bi-exponentially with time. A significant elevation of the plasma concentration in the terminal phase occurred after famotidine co-administration. The calculated compartmental and non-compartmental pharmacokinetic parameters following both routes of administration are shown in Tables 1 and 2. The terminal elimination half-life ($t_{\frac{1}{2}\beta}$) of ciprofloxacin with famotidine administration was significantly longer ($P<0.001$ and $P<0.05$ for i.v. and oral treatments, respectively) than in the control groups. The total body clearance (*Cl*) following i.v. administration and the ratio *Cl/F* following oral administration, were significantly reduced ($P<0.005$) with famotidine administration resulting in a higher plasma concentration and an increase in the area under the plasma concentration–time curve (*AUC*) ($P<0.005$ for both i.v. and oral administration). The mean residence time in the body (MRTB) was significantly increased with famotidine, following both routes of

administration. Furthermore, following i.v. administration of ciprofloxacin the mean residence time in the peripheral tissue (MRTP), and the intrinsic mean residence time in the peripheral tissue (IMRTP) were dramatically increased after famotidine administration. There were no significant differences in the distribution half-life ($t_{\frac{1}{2}\alpha}$) and in the apparent volume of distribution at steady-state (Vd_{ss}) between the control and famotidine-treated rats following i.v. administration (Table 1). After oral administration, no significant differences between the two groups in the maximum plasma concentration (C_{max}) and the time to maximum plasma concentration (T_{max}) were observed (Table 2).

DISCUSSION

The results of the present study indicate that famotidine significantly decreases the clearance of ciprofloxacin (27% and 34% for i.v. and oral administration, respectively) in the rat. As a consequence, the terminal elimination half-life ($t_{\frac{1}{2}\beta}$), the area under the plasma concentration-time curve (*AUC*) and the mean residence-time in the body (MRTB), were dramatically increased (54%, 32% and 32% for the $t_{\frac{1}{2}\beta}$), *AUC* and MRTB, respectively following i.v. administration and 29%, 47% and 30% for $t_{\frac{1}{2}\beta}$, *AUC* and MRTB, respectively following oral administration). The lack of significant changes in the volume of distribution at steady-state (Vd_{ss}) and the distribution half-life ($t_{\frac{1}{2}\alpha}$) suggest that the elevation in the plasma concentration of ciprofloxacin is not related to an alteration in the plasma protein binding of ciprofloxacin.

Ciprofloxacin, like other quinolones, is predominantly excreted unchanged in the urine, and glomerular filtration and active tubular secretion account for approximately 66% of the total plasma clearance of ciprofloxacin (2). Famotidine is also mainly eliminated (70%) unchanged in the urine by both glomerular filtration and active tubular secretion. It is suggested, therefore, that the apparent reduction in the plasma clearance of ciprofloxacin by the co-administration of famotidine may be due to competitive inhibition for renal tubular secretion. The possibility of a decreased elimination of ciprofloxacin as a result of metabolic inhibition is remote.

The possibility of decreased transluminal secretion of ciprofloxacin across the enteric mucosa as a consequence of famotidine co-administration cannot be ruled out and remains to be investigated.

It has been reported that the concomitant administration of ciprofloxacin and fenbufen induced severe convulsion in both humans and experimental animals (3–5). This resulted from an increase in the plasma concentrations of ciprofloxacin, a reduction in the total clearance as a consequence of inhibition of its renal excretion by fenbufen and an enhancement of ciprofloxacin permeability into the CNS (4, 5).

The calculated mean time parameters relating to the tissue distribution of ciprofloxacin following i.v. administration are of considerable importance from the toxico-kinetic point of view. The mean residence time in the peripheral tissue (MRTP) and the intrinsic mean residence time in the peripheral tissue (IMRTP), increased dramatically (97% and 78% for MRTP and IMRTP, respectively) following famotidine co-administration. The MRTP is the mean total time the drug molecules spend in the peripheral tissue, and the IMRTP is the mean total time for the drug molecules spend in the peripheral tissue before being eliminated (centrally or peripherally) from the body (12, 13). Therefore, it is possible that the elevation in the plasma concentration of ciprofloxacin by co-administration of famotidine may raise the concentration and prolong the transient time in the central nervous system, leading to the induction of neurotoxic side-effects.

In conclusion, this study demonstrates a possible interaction between famotidine and ciprofloxacin. Alteration in the renal excretion of ciprofloxacin is the most plausible explanation. Nevertheless, future studies are warranted to assess the existence and relevant clinical significance of this interaction in humans.

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