

Pharmacokinetics of Sparfloxacin and Interaction with Cisapride and Sucralfate

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In an open, randomized, triple crossover study, the effects of cisapride and sucralfate on the pharmacokinetics of sparfloxacin were assessed. Fifteen healthy volunteers received 400 mg of sparfloxacin as a single oral dose on day 0. In a random order, concomitant doses of 10 mg of cisapride three times daily from day -2 to day 2 and 1 g of sucralfate four times daily from day -2 to day 0 were administered. Sparfloxacin concentrations were measured by bioassay and high-performance liquid chromatography. Pharmacokinetic parameters for sparfloxacin alone were as follows (mean ± standard deviation): maximum concentration of drug in serum (C_{max}), $1.27 \pm 0.39 \mu\text{g/ml}$; time to C_{max} (T_{max}), $4.1 \pm 1.9 \text{ h}$; area under the concentration-time curve (AUC), $35.0 \pm 9.7 \mu\text{g} \cdot \text{h/ml}$; mean residence time, $28.5 \pm 5.7 \text{ h}$; half-life ($t_{1/2}$), $20 \pm 4 \text{ h}$; urinary recovery ($\text{UR} \cdot f$), $11.0\% \pm 2.7\%$; and metabolite-sparfloxacin ratio in urine, 2.6. For the cisapride group there was a significant decrease in the sparfloxacin T_{max} ($1.9 \pm 2.1 \text{ h}$) and a significant increase in C_{max} ($1.74 \pm 0.73 \mu\text{g/ml}$). The QTc interval for patients receiving sparfloxacin and cisapride was prolonged by 7.7% compared to the QTc interval during medication-free periods. Significant differences in the values for the group receiving sucralfate compared to the values for the group receiving sparfloxacin alone were found: C_{max} , $0.77 \pm 0.31 \mu\text{g/ml}$; AUC, $18.6 \pm 5.8 \mu\text{g} \cdot \text{h/ml}$; $t_{1/2}$, $26 \pm 10 \text{ h}$; and $\text{UR} \cdot f$, $5.8 \pm 1.8\%$. Concomitant administration of cisapride accelerates the absorption and increases the peak concentration of sparfloxacin without having a significant effect on the extent of bioavailability. Coadministration of sucralfate leads to a 44% decrease in the bioavailability of sparfloxacin.

Most quinolones exhibit their greatest activity against aerobic gram-negative pathogens. Sparfloxacin is a new broad-spectrum amino-fluoroquinolone. Retaining good activity against gram-negative bacteria (4, 22, 30, 42), it offers increased antimicrobial activity against gram-positive organisms. In comparison to ciprofloxacin, it has higher levels of activity against staphylococci, streptococci, and enterococci (4, 22, 34, 42) and against atypical bacteria such as *Mycoplasma*, *Chlamydia*, and *Rickettsia* spp. (2, 25, 30, 42). With MICs at which 90% of isolates are inhibited ($\text{MIC}_{90\text{s}}$) of less than $0.2 \mu\text{g/ml}$, it also has good in vitro activity against *Mycobacterium tuberculosis* (20, 30, 36). Fluoroquinolones are known to have numerous interactions with agents that are active in the gastrointestinal system (10). Since they are used for the treatment of severe infections, the knowledge of drug interactions is of clinical importance and may help to prevent therapeutic failures.

Cisapride is a prokinetic drug which restores or increases motility throughout the length of the gastrointestinal tract by enhancing cholinergic neurotransmitter release selectively in the myenteric plexus (26, 43). We assumed that the acceleration of the gastrointestinal transit reduces the absorption time of sparfloxacin, thus possibly leading to a reduction in bioavailability.

Under certain conditions a prolongation of the QTc interval can be observed after the administration of cisapride. Such conditions are preexisting cardiac disease, increased risk for arrhythmias, renal insufficiency, electrolyte imbalance, or the

simultaneous use of medications associated with prolongation of the QTc interval or arrhythmia such as macrolides, imidazole antimycotic agents, tricyclic antidepressants, phenothiazines, and antiarrhythmic agents (9, 24, 44). Since sparfloxacin is also known to prolong the QTc interval (18), we wanted to investigate whether the coadministration of both drugs is associated with adverse cardiovascular events.

Sucralfate is a nonsystemic antulcer drug which mainly protects the stomach and the duodenum by lining the gastroduodenal mucosa. The adsorption of pepsin and bile acids, the stimulation of bicarbonate and mucus secretion, and the stimulation of prostaglandin synthesis are additional protective characteristics (16). Sucralfate reduces the bioavailability of ciprofloxacin significantly by chelation with aluminum and magnesium ions (13). Our hypothesis was that sparfloxacin might be influenced in the same way.

MATERIALS AND METHODS

Volunteers. Fifteen healthy male volunteers participated in the study. Physical examinations, electrocardiograms, and laboratory screening including testing for use of illicit drugs and hematological and biochemical parameters as well as urinalysis were all normal before and after the study. Further criteria for inclusion were as follows: no blood donation 8 weeks prior to the study; negative serology for human immunodeficiency virus and hepatitis; Caucasian race; and negative medical histories concerning drug, alcohol, and nicotine abuse as well as allergies or intolerance to any drugs, in particular to quinolones. The use of any additional medication 2 weeks prior to or during the study was not allowed. After approval by the local ethics committee according to German law, informed written consent was obtained from all subjects.

Study design. According to the three-way crossover design, each volunteer received the following drug combinations in a random order: (i) sparfloxacin alone, (ii) sparfloxacin and cisapride, and (iii) sparfloxacin and sucralfate. The study consisted of three study periods, which were separated from each other by 1-week washout periods. Sparfloxacin (RP 64206; batch CB 06077; Rhône-Poulenc Rorer, Antony Cedex, France) was given after overnight fasting as a single

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oral dose of 400 mg on the first profiling day of each study period with 100 ml of tap water. Ten milligrams of cisapride (batch 94G16-46093; Janssen, Neuss, Germany) was administered three times per day from day -2 to day 2. One gram of sucralfate (batch 30432103; Lipha/Merck, Essen/Darmstadt, Germany) was administered four times daily from day -2 to the first profiling day. Sparfloxacin was given 15 min after cisapride administration and 30 min after sucralfate intake. Drinking was allowed 2 h after sparfloxacin administration, and eating was allowed 4 h after sparfloxacin administration.

Subjects abstained from alcoholic beverages and nicotine use from 24 h before to 3 days after sparfloxacin administration. During the complete time of the study, the intake of additional medication was prohibited. In the cisapride group an electrocardiogram was recorded 5 h after sparfloxacin administration.

Sample collection and processing. Blood samples (10 ml) were taken from a peripheral vein before sparfloxacin administration and then at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, and 96 h after dosing. Blood specimens were collected in heparinized tubes and were subsequently centrifuged at $1,300 \times g$ for 10 min at 4°C. Plasma and standard solutions were stored at -80°C until analysis.

Urine was collected over the following intervals: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 h after dosing. The volume of urine was measured after each collection interval, and two 5-ml aliquots were saved. The samples were stored without the use of preservatives in sterile tubes at -80°C until they were analyzed.

All specimens were protected against light and heat during collection, storage, and pretreatment.

Microbiological assay. Sparfloxacin concentrations in plasma and urine were measured by an agar diffusion method previously described in detail by Reeves and Bywater (35). Four plasma or urine samples, one control sample, and five standard samples were assayed for sparfloxacin concentrations in triplicate on each agar plate. The test organism was *Bacillus subtilis* (ATCC 6633; Difco Laboratories, Detroit, Mich.), and N-agar medium (pH 7.4) was used. Standards were prepared by using pooled human serum for plasma samples and phosphate buffer (pH 7.0) for urine samples. The agar plates were incubated for 18 h at 30°C. Neither the blood samples taken before sparfloxacin administration nor the pooled serum used in the assays for standard concentrations showed any detectable antimicrobial activity. The detection limits were 0.06 µg/ml in plasma and 0.03 µg/ml in urine. The coefficient of variation, determined on 3 different days between concentrations of 0.1 and 11 µg/ml, was 3.8% for plasma and 3.9% for urine.

HPLC. In all samples from the group receiving sparfloxacin, the concentrations of sparfloxacin and its inactive metabolite were also measured by a modified high-performance liquid chromatography (HPLC) method. The method was previously described in detail by Borner et al. (6, 7). It involved a deproteinization of the plasma samples, a separation by reversed-phase chromatography, and two different detection methods: UV absorbance detection for the metabolite and fluorescence detection for the parent compound. The lower limit of quantification was 0.03 µg/ml in plasma and 0.7 µg/ml in urine. Concentrations versus peak area curves were linear in the following ranges: 0.03 to 2.0 µg/ml for plasma and 0.7 to 52.2 µg/ml for urine. The day-to-day coefficients of variation (precision between series) were 4.1% for sparfloxacin in serum, 1.9% for sparfloxacin in urine, and 0.7% for the metabolite in urine.

Pharmacokinetic calculations. The pharmacokinetic parameters of sparfloxacin were evaluated on the basis of an open one-compartment model (elimination half-life $t_{1/2\beta}$, mean area under the concentration-time curve [AUC] absorption rate constant $[k_a]$, elimination rate constant $[k_{el}]$, and the time between drug administration and the beginning of absorption [lag time; in minutes; t_{lag}]) as well as noncompartmentally (all other parameters). The decision to use an open one-compartment model was based on the criterion of Schwarz (37). The model equation for the concentrations in plasma is

$$C(t) = f \cdot D / V \cdot k_a / (k_a - k_{el}) \cdot [e^{-k_{el} \cdot (t-t_{lag})} - e^{-k_a \cdot (t-t_{lag})}]$$

where $C(t)$ is the concentration in plasma at time t (in minutes), f is the absolute bioavailability, D is the administered dose, and V is the volume of distribution.

An iterative least-squares method was used to fit the regression curve to the experimentally obtained values after normalization of the concentrations in plasma to a mean body weight of 70 kg. Nonlinear regression analysis was performed to minimize the following objective function:

$$\sum_{i=1}^n [C(t_i) - C_i]^2 / C(t_i)$$

where C_i is the concentration measured at time t_i ($i = 1, \dots, n$). This weighting scheme ($\alpha = 1$ according to Peck et al. [33]) was chosen because the coefficient of variation was not constant in the domain of the measured values but increased with lower concentrations. In addition, iterative reweighting was applied.

Individual regression curves and a mean regression curve were constructed for each combination of study drugs. The mean maximum concentration of drug in serum (C_{max}) and the mean time to C_{max} (T_{max}) were calculated as the means from the C_{max} and the T_{max} of the individual regression curves. The $t_{1/2\beta}$ in plasma was determined by division of $\ln 2$ by k_{el} . The plasma AUC was determined as the integral of the area under the regression curve, with the results

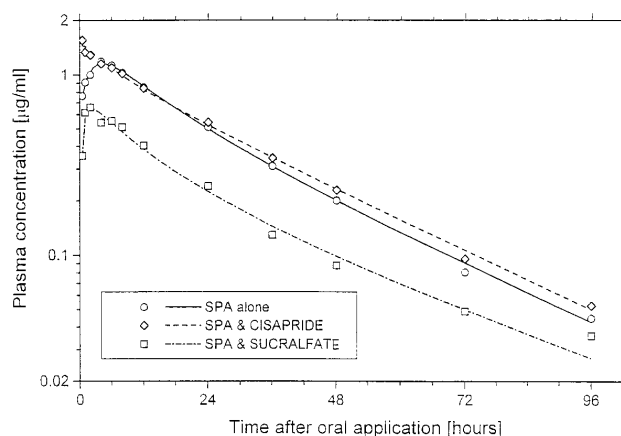


FIG. 1. Measured mean concentrations of sparfloxacin in plasma after administration of sparfloxacin (SPA) alone and with sucralfate or cisapride.

showing excellent concordance with those obtained by the noncompartmental technique (data not shown).

Since the expression of clearance of orally administered drug from plasma (CL/F) should be adjusted to body surface (like creatinine clearance), the AUC from time zero to infinity ($AUC_{0-\infty}$) was recalculated on the basis of the non-weight-normalized, raw concentrations in plasma. CL/F was then obtained by division of the sparfloxacin dose by $AUC_{0-\infty}$ and adjustment of the result to a body surface area (BSA) of 1.73 m². The individual's BSA was calculated by the equation $BSA = a_1 \cdot L^{a_2} \cdot W^{a_3}$, where L is body length (in centimeters) and M is body mass (in kilograms) with the following parameters proposed by Gehan and George (14) for individuals of older than 20 years of age $a_1 = 0.01545$, $a_2 = 0.54468$, and $a_3 = 0.46336$ (a_1 to a_3 are experimental parameters).

Statistical analysis. Differences in the pharmacokinetic parameters between the groups were identified by the Student-Newman-Keuls procedure for multiple comparisons of sample means, with significance defined as a P value of <0.05.

RESULTS

Volunteers. The mean \pm standard deviation age of the volunteers was 28 ± 5 years, the mean body weight was 77 ± 8 kg, the mean height was 183 ± 4 cm, and the mean creatinine clearance was 109 ± 16 ml/min/1.73m².

Safety and tolerance. The volunteers' overall tolerance of sparfloxacin was good. No severe adverse events occurred. No significant differences in the values of clinical parameters and laboratory test results were found before and after the study. Adverse drug reactions reported in the cisapride group were three cases of cephalalgia, one case of soft stool, and one case of fatigue lasting from day -2 to day 1. No side effects were noted in the sucralfate group. One volunteer in the group treated with sparfloxacin alone showed a skin irritation at the puncture site of the cannula. All adverse effects were self-limiting and required no therapy. None of the subjects had to be excluded from the study.

Comparison of analysis methods. The correlation between the results of bioassay and those of HPLC was excellent. The methods were compared by bivariate analysis of regression (3), which is described by the following equations: C (bioassay) = $1.066 \cdot C$ (HPLC) + 0.07 for plasma and C (bioassay) = $0.968 \cdot C$ (HPLC) + 0.03 for urine, where C indicates concentration. The coefficient of correlation was 0.98 for plasma and 0.94 for urine.

Pharmacokinetics. The mean concentrations of sparfloxacin alone and together with concomitant administration of cisapride or sucralfate in plasma are presented in Fig. 1. The pharmacokinetic data are listed in Table 1. Except for the metabolite-sparfloxacin ratio and the recovery of the metabolite in urine, the following data are the values obtained by the

TABLE 1. Pharmacokinetic parameters as determined by bioassay after the administration of sparfloxacin alone and with concomitant administration of sucralfate and cisapride^a

Drug(s)	C_{\max} ($\mu\text{g/ml}$)	T_{\max} (h)	T_{lag} (h)	$t_{1/2}$ (h)	MRT (h)	AUC ($\mu\text{g} \cdot \text{h/ml}$)	CL (ml/min/ 1.73m ²)	Urinary recovery (% of dose)	V (liters/ 70 kg)	Relative bioavailability
Sparfloxacin	1.27 \pm 0.39	4.1 \pm 1.9	0.11 \pm 0.16	20 \pm 4	28.5 \pm 5.7	35.0 \pm 9.7	193 \pm 49	11 \pm 2.7	326 \pm 104	1.00
Sparfloxacin + cisapride	1.74 \pm 0.73 ^{b,c}	1.9 \pm 2.1 ^b	0.05 \pm 0.12	21 \pm 5 ^c	29.3 \pm 6.6	37.6 \pm 8.4 ^c	200.6 \pm 43.3 ^d	12.2 \pm 1.8 ^c	357 \pm 121 ^d	1.14 \pm 0.36 ^c
Sparfloxacin + sucralfate	0.77 \pm 0.31 ^b	3.2 \pm 2.2	0.15 \pm 0.14	26 \pm 10 ^b	32.3 \pm 10	18.6 \pm 5.8 ^b	203.9 \pm 48.2 ^d	5.8 \pm 1.8 ^b	403 \pm 158 ^d	0.56 \pm 0.23 ^b

^a Data are means + standard deviations.

^b Significant in comparison to sparfloxacin alone ($P < 0.05$).

^c Significant in comparison to sparfloxacin plus sucralfate ($P < 0.05$).

^d In reference to the relative bioavailability.

bioassay method. Sparfloxacin absorption started after a mean T_{lag} of 6.6 \pm 9.6 min and reached a C_{\max} of 1.27 \pm 0.39 $\mu\text{g/ml}$ after 4.1 \pm 1.9 h (T_{\max}). T_{\max} showed a broad interindividual variability in all treatment groups, ranging from 30 min to 6 h. A wide range of variation was also found for the calculated T_{lag} values. The AUC for sparfloxacin alone was 35.7 \pm 9.8 $\mu\text{g} \cdot \text{h/ml}$. The volume of distribution at steady state (V_{ss}) was 326 \pm 104 liters/70 kg. The mean $t_{1/2\beta}$ was 20 \pm 4 h, and the mean residence time (MRT) was 28.5 \pm 5.7 h. As measured by bioassay, 11% \pm 2.7% of the administered dose was recovered from urine as unchanged sparfloxacin. The value obtained by HPLC was 10.6% \pm 3% for the parent compound and 28% \pm 7.2% for the metabolite (Fig. 2). The metabolite-sparfloxacin ratio of 2.6 remained approximately constant over the entire profiling period.

Concomitant administration of cisapride decreased the T_{\max} significantly to 1.9 \pm 2.1 h compared to the T_{\max} after the administration of only sparfloxacin. Although the C_{\max} of 1.74 \pm 0.73 $\mu\text{g/ml}$ was significantly higher than that after the administration of sparfloxacin alone, the AUC (37.6 \pm 8.4 $\mu\text{g} \cdot \text{h/ml}$) was not significantly altered. All other parameters showed no significant differences compared with the values obtained after the administration of sparfloxacin alone.

In combination with sucralfate, C_{\max} was significantly reduced to 0.77 \pm 0.31 $\mu\text{g/ml}$ and AUC was significantly decreased to 18.9 \pm 5.8 $\mu\text{g} \cdot \text{h/ml}$ compared to the values for the sparfloxacin group. Hence, the relative bioavailability (0.56% \pm 0.23%) and the recovery in urine ($\text{UR} \cdot f = 5.8\% \pm 1.8\%$) were found to be significantly lower. $t_{1/2\beta}$ (26 \pm 10 h) was significantly longer with coadministration of sucralfate. The

values of none of the other parameters were significantly different compared with the values obtained for the group receiving sparfloxacin alone.

The evaluation of the electrocardiograms showed a highly significant prolongation ($P < 0.01$) of the QTc interval with the concomitant administration of cisapride compared to the QTc interval during medication-free periods, from 376 \pm 21 to 405 \pm 25 ms.

DISCUSSION

Compared to ciprofloxacin (400 mg), the most widely used quinolone, the process of absorption of sparfloxacin is relatively slow (4.1 versus 1.07 h) and the C_{\max} is lower (1.27 versus 1.5 $\mu\text{g/ml}$) (8). Our results are similar to those of other studies which found T_{\max} values of 2.7 to 5 h and C_{\max} values of 1.18 to 1.6 $\mu\text{g/ml}$ (19, 29, 38, 40). The great variability of T_{\max} , with values ranging from 0.5 to 6 h, has already been noted by Johnson et al. (19) and Thebault et al. (40).

Due to the extended $t_{1/2\beta}$ of sparfloxacin, with a value of 20 h on average, once-a-day administration is possible. At 24 h after the intake of 400 mg of sparfloxacin, which is the recommended loading dose for most therapeutic regimens, the concentration in plasma of about 0.48 $\mu\text{g/ml}$ exceeds the MIC_{90s} for the majority of susceptible pathogens (30, 34).

The apparent V_{ss} (V_{ss}/f) is 4.7-fold the normal body volume and reflects the accumulation of sparfloxacin in certain tissues, cells, or fluids, as shown, for example, in macrophages (ratio of the concentration at a particular site to the concentration in serum, 48.2) and bile (ratio of the concentration at a particular site to the concentration in serum, 11) (17, 39).

The AUC is an important pharmacokinetic parameter for the bioavailability of sparfloxacin. In previous studies, the AUCs ranged from 32.2 to 41.6 $\mu\text{g} \cdot \text{h/ml}$ and therefore confirm our value of 35.0 $\mu\text{g} \cdot \text{h/ml}$ (19, 40). Compared to the AUC of ciprofloxacin (5.76 $\mu\text{g} \cdot \text{h/ml}$), the AUC of sparfloxacin is exceedingly higher due to its longer $t_{1/2}$ (8).

The elimination of sparfloxacin is mainly extrarenal. Less than 40% of the antibiotic is excreted via urine; roughly 11% is excreted as unchanged drug and 28% is excreted as an acylglucuronide conjugate. The fact that the metabolite-sparfloxacin ratio in urine of 2.6 remained constant over the sampling time indicates that the metabolism is not saturable. It is notable that the metabolite is only found in urine (7). The attempt to measure the glucuronide concentration in plasma was not successful. This may be partly explained by a high clearance of the metabolite or by an insufficient sensitivity of the HPLC-UV method. The absence of the metabolite in feces can be explained by the deglucuronization by bacterial enzymes in stool

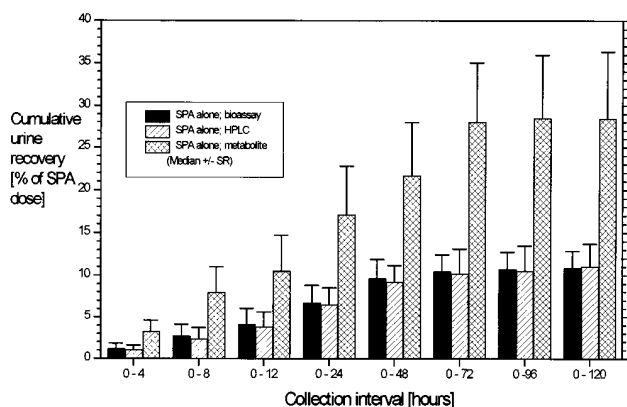


FIG. 2. Cumulative urine recovery measured by bioassay and HPLC after intake of 400 mg of sparfloxacin (SPA). SR, standard range.

(7). Since the metabolite was only detected by HPLC and not by bioassay, the metabolite must be biologically inactive.

The acceleration of gastrointestinal motility induced by cisapride may affect the absorption rates and, in some cases, even the bioavailabilities of other drugs. For example, an increased C_{max} without a change in bioavailability has been demonstrated for two cephalosporins and diazepam (5, 11, 15). On the other hand, coadministered cisapride may also reduce the C_{max} as well as the AUC, as shown for digoxin (21).

In the case of sparfloxacin, concomitant cisapride administration resulted in a significantly accelerated absorption of the quinolone. C_{max} was reached more than 2 h earlier compared with that after the administration of sparfloxacin alone. The peak concentration of sparfloxacin increased when cisapride was given concomitantly. We assume that this increase is due to a faster transport of the more concentrated drug to the site of absorption. However, the AUC and therefore the relative bioavailability, the most important pharmacokinetic parameters, were not significantly modified.

In our study, no cardiovascular side effects could be noted. The evaluation of the electrocardiograms showed that compared to the QTc intervals in the medication-free state, coadministration of sparfloxacin and cisapride led to a prolongation of the QTc interval of from 376 ± 21 to 405 ± 25 msec. This is equivalent to a 7.7% increase. According to data provided by the manufacturer, sparfloxacin alone leads to a prolongation of only less than 3% (18). A possible interaction should be kept in mind in patients with risk factors such as preexisting cardiac disease, arrhythmias, or electrolyte imbalance.

Most adverse drug reactions in our study occurred with the coadministration of cisapride and sparfloxacin. Since the adverse drug reactions were rather unspecific, it is not possible to differentiate between the side effects caused by sparfloxacin and the side effects caused by cisapride or eventually by the combination of the two.

Sucralfate is one of the first-line drugs used in the prophylaxis of stress bleeding in patients in intensive care, because it does not modify the gastric pH and therefore is not associated with an increased risk of nosocomial pneumonia (41). Additionally, it has the advantage that its use results in a very low rate of side effects, because it acts as a topical, nonsystemic agent (12).

A possible interaction of sucralfate and sparfloxacin was assumed because the absorption of fluoroquinolones is decreased by Mg^{2+} and Al^{2+} ions, which are also contained in sucralfate. This hypothesis was confirmed by the results of our study, which showed a significant decrease in the C_{max} , the AUC, and the relative bioavailability.

So far, norfloxacin and ciprofloxacin have been tested in combination with sucralfate. The use of both quinolones resulted in significant reductions in bioavailability. According to Garrelts et al. (13), sucralfate reduces the AUC of ciprofloxacin to 12.5% of the AUC for the control group when the drugs are coadministered. The administration of sucralfate 2 and 6 h prior to the administration of ciprofloxacin reduces the AUC by 30% (31). In the study of Parpia et al. (32), norfloxacin was administered with sucralfate and 2 h after the administration of sucralfate. The AUC after coadministration was 2% of the value obtained after the administration of norfloxacin alone, and the AUC after administration of the sucralfate after a 2-h interval was 57% of the value obtained after the administration of norfloxacin alone.

So far, all published studies investigated the effect of sucralfate administered prior to quinolone application. That the administration of a quinolone prior to the administration of a cation-containing drug is also associated with a decrease in

bioavailability was demonstrated by Mignot et al. (28). Administration of the antacid Maalox (800 mg) 30 min after sparfloxacin administration resulted in a decrease of the AUC to 56% of the value obtained after the administration of sparfloxacin alone (28).

This extent of reduction in sparfloxacin bioavailability (53% reduction in AUC) is similar to the results obtained in our study when sparfloxacin was administered 30 min after the administration of sucralfate.

The underlying reason for the malabsorption might be that quinolones form chelation complexes in the presence of multivalent cations, which are hardly soluble. Besides their effect on the absorption process, it has also been described that the presence of cations reduces the antimicrobial activity and the accumulation of quinolones in bacteria (23, 27). Because the increase in aluminum and magnesium concentrations in serum with sucralfate administration is negligible in patients with normal renal function (1), we do not expect this to have an influence on the antimicrobial efficacy of sparfloxacin.

In conclusion, a possible prolongation of the QTc interval with the coadministration of cisapride and sparfloxacin should be kept in mind, especially when treating patients with cardiac disease and arrhythmia. Since cisapride has no pharmacologically important influence on the pharmacokinetics of sparfloxacin, it is not expected to have an impact on the efficacy of this antibiotic when the drugs are coadministered.

Sucralfate significantly reduces the bioavailability of sparfloxacin. It is recommended that the interval between sucralfate and sparfloxacin administration be at least 2 h.

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