The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin

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Aims To investigate the effect of sucralfate on sparfloxacin absorption when administered concurrently or at strategically spaced dosing times designed to avoid the potential interaction.

Methods The study was a four-way crossover design where eight healthy Japanese volunteers were randomized to one of four treatment sequences at entry. A 300 mg dose of sparfloxacin was administered alone for treatment A (control). Treatments B, C and D included sucralfate 1.5 g every 12 h for five doses. For treatment B, the fifth dose of sucralfate was administered concurrently with sparfloxacin 300 mg. For treatment C, 300 mg sparfloxacin was given 2 h prior to the fifth dose of sucralfate. Treatment D consisted of sparfloxacin 300 mg given 4 h prior to the fifth dose of sucralfate. Blood and urine samples were collected at predetermined time intervals for 72 h. Sparfloxacin concentrations in plasma and urine and the concentrations of sparfloxacin metabolite in urine were determined by high performance liquid chromatography assays.

Results Sucralfate administered concurrently with sparfloxacin decreased the mean $AUC(0, \infty)$ of sparfloxacin 2-fold ($P < 0.001$) and the mean C_{max} 2.1-fold ($P < 0.001$) compared with sparfloxacin alone. When sucralfate was administered 2 h after sparfloxacin, the mean $AUC(0, \infty)$ was decreased 1.5-fold ($P < 0.01$) and the mean C_{max} 1.4-fold ($P < 0.01$). Sucralfate did not alter the extent of absorption of sparfloxacin when it was given 4 h after the administration of sparfloxacin. The relative bioavailabilities for treatments B, C and D were 0.50 (95% CI: 0.35–0.65), 0.64 (95% CI: 0.51–0.77), and 0.92 (95% CI: 0.81–1.03), respectively, relative to sparfloxacin alone. The mean percentage of the sparfloxacin dose recovered in urine was significantly lower after sparfloxacin was administered with sucralfate than after sparfloxacin was administered alone or 2 h before the sucralfate dose ($P < 0.001$). Treatments B, C and D were demonstrated to be equivalent to treatment A in the rate of absorption. The t_{max} , CL_r and $t_{1/2}$ were not significantly affected by sucralfate. The metabolism of sparfloxacin was not altered in the presence of sucralfate.

Conclusions Oral administration of sucralfate with sparfloxacin or 2 h after sparfloxacin, decreased the extent of sparfloxacin absorption. When both drugs are to be administered together, sucralfate should be administered 4 h after sparfloxacin, allowing thus sufficient time for sparfloxacin absorption prior to the sucralfate dose and thereby minimizing the chance of a significant interaction.

Keywords: drug interaction, sparfloxacin, sucralfate

Introduction

Both laboratory and clinical studies have documented an interaction between fluoroquinolones and multivalent

metal cations, such as aluminium, magnesium, calcium, iron and zinc [1, 2]. The proposed mechanism of this interaction is chelation between the metal ion and the 4-keto oxygen 3-carboxyl group of the fluoroquinolone.

Controlled studies investigating concomitant administration of various fluoroquinolones with medications, such as antacids or sucralfate, or supplements, such as ferrous sulphate or multivitamins with zinc, have observed significant reductions in the absorption of these

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antimicrobial agents [3–7]. Therefore, therapeutic failures can be expected to occur whenever fluoroquinolones and multivalent metal cations are given together [8]. Although these various interactions are not of equal intensity for all fluoroquinolones, it is best to avoid these combinations whenever possible. If the combination of a multivalent cation and a fluoroquinolone cannot be avoided, doses should be staggered to minimize this potential drug interaction.

Recent studies have attempted to develop safe periods in which aluminium-containing antacids and quinolones can be coadministered without a significant decrease in quinolone bioavailability. It was found that when fluoroquinolones (norfloxacin, ofloxacin, and levofloxacin) were given at least 2 h prior to the administration of various antacids or sucralfate, this potential drug interaction was generally averted [9–13]. However, it is not known whether this interaction can be avoided by staggering administration for sparfloxacin, which has a relatively long process of absorption with the peak concentration of the drug usually not observed before 3–5 h postadministration [14].

The purpose of this study was to determine the effect of a 1.5-g dose of sucralfate on sparfloxacin absorption when administered concurrently or at strategically spaced dosing times designed to avoid the potential interaction.

Methods

Subjects and study design

Four male and four female healthy Japanese volunteers, aged from 21 to 42 years (mean age, 23 years) with a mean body weight of 65 kg, participated in the study after giving written informed consent. All subjects were determined to be in good health prior to the study on the basis of medical history, physical examination and laboratory tests. The subjects had not ingested any medications within 2 weeks prior to the first study period or at any time during the study. Specifically, ingestion of antacids, iron, or sucralfate was not permitted. The study protocol was approved by the Institutional Review Board of Oita Medical University Hospital, Oita, Japan.

In this four-period, randomized crossover study, the subjects were assigned at entry to one of four treatment sequences. For treatment A (control), a 300 mg oral dose of sparfloxacin was administered alone. Treatments B, C and D included sucralfate 1.5 g every 12 h for five doses. For treatment B, the fifth dose of sucralfate was administered concurrently with sparfloxacin 300 mg. For treatment C, 300 mg of sparfloxacin was given 2 h prior to the fifth dose of sucralfate. Treatment D consisted of sparfloxacin 300 mg given 4 h prior to the fifth dose of sucralfate. Each study period was separated by a wash out

period of at least 1 week. Subjects fasted for at least 8 h before and 4 h after sparfloxacin administration.

Sample collection

Blood samples (6 ml) were taken from a peripheral vein before sparfloxacin administration and then at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 h after dosing. Blood specimens were collected in heparinized tubes and were centrifuged at 3000 g for 10 min at 4°C. Plasma aliquots were frozen at –80°C until analysis, which occurred within 2 weeks. Urine was collected before dosing and from 0 to 2, 2–4, 4–8, 8–12, 12–24, 24–48, and 48–72 h after intake of sparfloxacin. Samples were frozen at –80°C as soon as each volume had been determined.

Drug analysis

Plasma samples were analysed for unchanged sparfloxacin and urine samples were analysed for sparfloxacin and its acylglucuronide metabolite by reversed-phase high performance liquid chromatography assays [15]. Because the sparfloxacin glucuronide was not available as a reference standard, the conjugated level of the drug was determined as the total drug level minus unchanged drug level, where the total drug level expressed sparfloxacin level after alkaline hydrolysis of the sample (10 min with 10 µl of 1N sodium hydroxide for 100 µl of urine sample) as described elsewhere [16].

Six concentrations (excluding blank values) defined the standard curves. The standard curves for sparfloxacin were linear within the range of 0.025–2.5 mg l^{–1} in plasma and 0.5–500 mg l^{–1} in urine and were highly reproducible. The correlation coefficients between the peak-area ratios (drug/internal standard) and the concentration of sparfloxacin were >0.999. A standard curve was generated for each analytical run and was used to calculate the concentrations of sparfloxacin in unknown samples assayed with that analytical run. The standard curves covered the entire range of concentrations in the unknown samples.

The limit of quantification for sparfloxacin as determined by precision and accuracy and where the coefficients of variation of sparfloxacin of <15% were targeted was 0.025 mg l^{–1} for plasma and 0.5 mg l^{–1} for urine. The accuracy and precision were determined with five determinations for concentration. The mean value was within 10% of the actual value. The procedure had mean intra- and interassay coefficients of variation below 10% over the concentration ranges in plasma and urine. The mean recoveries of sparfloxacin and the internal standard (IS) at concentrations ranging from 0.025 to 500 mg l^{–1} were similar and consistent and ranged from

96.7 to 97.9% for sparfloxacin and from 96.7 to 98.5% for the IS.

Pharmacokinetic/statistic analyses

Standard pharmacokinetic parameters were computed using one-compartment model. Maximum concentration ($C_{\max}$) and time to $C_{\max}$ ($t_{\max}$) were determined by observation. The area under the concentration-time curve over the dosing interval $AUC(0,72\text{ h})$ was computed using the linear trapezoidal rule and extrapolated to infinity. The extrapolation was performed by dividing the last measurable plasma concentration by the terminal elimination rate constant. The relative bioavailability was calculated by dividing $AUC(0,\infty)$ for each sparfloxacin-sucralfate treatment by $AUC(0,\infty)$ for sparfloxacin alone. Renal clearance (CL_r) was computed as the ratio of the total amount of drug excreted in the urine (A_e) and the AUC over the dosing interval. The metabolic ratio (MR) of sparfloxacin was calculated by dividing the amount excreted in urine as metabolite by the amount excreted as unchanged sparfloxacin. To describe differences in pharmacokinetic parameters between treatments, the results were evaluated by two-way analyses of variance (ANOVA) (subjects and treatments) followed by the Scheffé's multiple-range test if appropriate. Significance was defined as $P < 0.05$.

Results

All subjects completed the study and tolerated the protocol well. Sparfloxacin pharmacokinetic parameters for each treatment group are provided in Table 1. The mean plasma sparfloxacin concentration *vs* time plots for four treatment groups are shown in Figure 1. The effect

Figure 1 Mean plasma sparfloxacin concentration *vs* time curves for sparfloxacin 300 mg alone (○), sparfloxacin 300 mg administered concurrently with sucralfate 1.5 g (●), sparfloxacin 300 mg given 2 h before sucralfate 1.5 g (□), and sparfloxacin 300 mg given 4 h before sucralfate 1.5 g (■).

of sucralfate administered concurrently with sparfloxacin was very consistent on sparfloxacin absorption and produced marked changes in pharmacokinetic parameters when compared with the effects of sparfloxacin alone. All subjects had lower sparfloxacin concentrations in plasma after taking sparfloxacin with sucralfate or 2 h later than after taking sparfloxacin alone. Sucralfate administered concurrently with sparfloxacin decreased the mean $AUC(0,\infty)$ of sparfloxacin twofold ($17.65 \pm 5.86\ \mu\text{g ml}^{-1}\text{ h}$ *vs* $35.96 \pm 6.38\ \mu\text{g ml}^{-1}\text{ h}$ [mean $\pm$ s.d.]; $P < 0.001$) and decreased the mean $C_{\max}$ 2.1-fold ($0.62 \pm 0.20\ \mu\text{g ml}^{-1}$ *vs* $1.30 \pm 0.27\ \mu\text{g ml}^{-1}$; $P < 0.001$) compared with sparfloxacin alone (Figure 1 and Table 1). When sucralfate was administered 2 h after sparfloxacin, the mean $AUC(0,\infty)$ was decreased 1.5-fold ($23.82 \pm 6.70\ \mu\text{g ml}^{-1}\text{ h}$ *vs* $35.96 \pm 6.38\ \mu\text{g ml}^{-1}\text{ h}$; $P < 0.01$) and the mean $C_{\max}$ 1.4-fold ($0.91 \pm$

Table 1 Pharmacokinetic parameters (mean $\pm$ s.d. (95% CI) of sparfloxacin for the four treatment regimens.

Pharmacokinetic variables	A	B	Treatment C	D
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	1.30 ± 0.27 (1.07, 1.52)	0.62 ± 0.20 (0.45, 0.79)*	0.91 ± 0.24 (0.71, 1.12)**‡	1.34 ± 0.28 (1.11, 1.58)†§
$t_{\max}$ (h)	5.00 ± 1.07 (4.11, 5.89)	5.25 ± 1.49 (4.01, 6.49)	5.25 ± 1.83 (3.72, 6.80)	5.00 ± 1.07 (3.72, 6.78)
$AUC(0, \infty)$ ($\mu\text{g ml}^{-1}\text{ h}$)	35.96 ± 6.38 (30.63, 41.30)	17.65 ± 5.86 (12.76, 22.55)*	23.82 ± 6.70 (17.97, 29.67)**	32.87 ± 6.14 (27.74, 38.01)†¶
$t_{1/2}$ (h)	16.83 ± 2.57 (14.68, 18.99)	17.70 ± 6.88 (11.95, 23.46)	15.79 ± 4.65 (11.90, 19.68)	16.37 ± 2.94 (13.90, 18.82)
A_e/dose (% excreted)	11.56 ± 3.03 (8.91, 13.76)	6.59 ± 1.73 (4.77, 7.82)*	8.09 ± 2.47 (5.99, 9.89)*‡	11.05 ± 2.11 (8.78, 12.54)¶
CL_r (l h^{-1})	1.03 ± 0.20 (0.84, 1.21)	1.19 ± 0.20 (1.02, 1.35)	1.13 ± 0.28 (0.89, 1.37)**‡	1.03 ± 0.18 (0.88, 1.18)
MR	2.4 ± 0.3 (2.13, 2.65)	2.4 ± 0.7 (1.79, 2.92)	2.4 ± 0.7 (1.79, 2.95)	2.3 ± 0.4 (1.92, 2.63)
Relative bioavailability	1.00	0.50 ± 0.17 (0.36, 0.65)*	0.64 ± 0.15 (0.51, 0.77)*‡	0.92 ± 0.13 (0.81, 1.03)†¶

Treatment A: sparfloxacin 300 mg alone; treatment B: sparfloxacin 300 mg administered concurrently with sucralfate 1.5 g; treatment C: sparfloxacin 300 mg given 2 h before sucralfate 1.5 g; treatment D: sparfloxacin 300 mg given 4 h before sucralfate 1.5 g; $C_{\max}$, peak plasma concentration; $t_{\max}$, time to reach $C_{\max}$; $AUC(0,\infty)$, area under the concentration-time curve from 0 to ∞ ; $t_{1/2}$, half-time; A_e/dose , percentage of drug excreted in urine; CL_r , renal clearance; MR, metabolic ratio. * $P < 0.001$ *vs* A; ** $P < 0.01$ *vs* A; † $P < 0.001$ *vs* B; ‡ $P < 0.05$ *vs* B; § $P < 0.05$ *vs* C; ¶ $P < 0.01$ *vs* C. 95% CI, 95% confidence interval.

$0.24 \mu\text{g ml}^{-1}$ vs $1.30 \pm 0.27 \mu\text{g ml}^{-1}$; $P < 0.01$). There was no significant effect in the mean AUC and C_{max} values when sparfloxacin was administered 4 h before sucralfate. The relative bioavailabilities for treatments B, C and D were 0.50 (95% CI: 0.35–0.65), 0.64 (95% CI: 0.51–0.77), and 0.92 (95% CI: 0.81–1.03), respectively, relative to sparfloxacin alone. Table 2 provides the individual relative bioavailability values for the four treatments. Sucralfate administered concurrently with or 2 h after sparfloxacin decreased percentages of the sparfloxacin dose recovered in urine 1.7-fold and 1.4-fold, respectively. There was no significant difference between sparfloxacin alone and sparfloxacin administered 4 h before sucralfate in percentage of the sparfloxacin dose recovered in urine. The t_{max} , CL_r and $t_{1/2}$ were not significantly affected by sucralfate (Table 1).

The metabolism of sparfloxacin was evaluated by calculation of the MR. We found no effect of sucralfate on MRs, suggesting no alteration in the conversion of sparfloxacin to acylglucuronide metabolite. Metabolite-sparfloxacin ratio of 2.4 remained approximately constant (Table 1).

Estimated pharmacokinetic parameters (Table 1) in our subjects who took sparfloxacin alone were very similar to parameters reported by other investigators [6, 14].

Discussion

Sucralfate is a poorly absorbed complex of aluminium hydroxide and sulphated sucrose that is useful for treating peptic ulcer [17, 18]. Once solubilized in the stomach, aluminium ions are released from the sucralfate molecule

as was evidenced by an increase in aluminium concentrations in serum and urinary excretion [19, 20], while the negatively charged sulphated sucrose skeleton binds to the damaged mucosa, providing a protective barrier. It is possible that the free aluminium ions (16 per sucralfate molecule) are available to form chelation complexes with quinolones. The most likely site in the quinolone molecule for chelate formation has been proposed to be between 3-carboxyl and 4-oxo groups [21]. The resulting complex has no antimicrobial activity and it is not absorbed through intestinal mucosa, leading to a reduction in the extent of absorption.

The study presented here demonstrates that there were pronounced decreases in $\text{AUC}(0, \infty)$ and C_{max} when subjects were given sparfloxacin with sucralfate. Urinary sparfloxacin concentration decreased by about 50% when sparfloxacin was given with sucralfate. The clinical significance of these pharmacokinetic changes remains to be determined, but it seems likely that a marked decrease in AUC and peak concentrations could result in a loss of efficacy [22]. Such reduction could significantly alter the ratio of AUC to the minimum inhibitory concentration (MIC) for the target pathogen [22–24]. This ratio, otherwise referred to as the area under the inhibitory concentration–time curve, is becoming established as a useful pharmacodynamic surrogate of antibiotic efficacy [24].

The time difference in order to develop safe periods in which sucralfate and quinolones can be coadministered without a significant decrease in quinolone bioavailability is necessary to prevent a clinically important interaction. The objective of this study was to develop safe periods in which sparfloxacin and sucralfate can be administered without a significant decrease in the sparfloxacin bioavailability.

Several investigators have reported a decrease in the extent of the interaction between sucralfate and quinolones by administering the sucralfate either 2 h before or 2 h after the quinolone is administered. Parpia *et al.* [25] improved the relative bioavailability of norfloxacin from 1.8 to 56.6% by administering norfloxacin 2 h after they administered a 1 g dose of sucralfate. Ryerson *et al.* [26] reported an increase in the relative bioavailability from 12.3 to 46% if enoxacin was given 2 h after sucralfate and from 12.3 to 92% if enoxacin was given 2 h before sucralfate. Interactions with sucralfate seem to be minimized if the quinolone is administered 2 h before the sucralfate dose. This is reasonable, since the quinolones reach their maximum concentration 1–2 h after dosing. Our results demonstrate that the gastrointestinal absorption of sparfloxacin is decreased even when it is administered 2 h before sucralfate. Since the process of absorption of sparfloxacin is relatively slow (t_{max} 3–5 h), theoretically the administration of sparfloxacin 2 h before

Table 2 Individual $\text{AUC}(0, \infty)$ values for four treatment regimens.

Subject	Treatment			
	A	B	C	D
1	33.85	14.06	18.52	31.59
2	44.30	28.30	37.38	45.31
3	40.03	22.25	15.30	32.93
4	27.22	21.77	22.65	32.70
5	36.46	11.52	22.71	28.81
6	26.66	15.45	19.20	23.69
7	38.95	15.63	24.94	32.51
8	40.45	12.27	22.36	35.50
Mean	35.96	17.65	23.82	32.87
SD	6.37	5.85	6.99	6.14

*Treatment A: sparfloxacin 300 mg alone; treatment B: sparfloxacin 300 mg administered concurrently with sucralfate 1.5 g; treatment C: sparfloxacin 300 mg given 2 h before sucralfate 1.5 g; treatment D: sparfloxacin 300 mg given 4 h before sucralfate 1.5 g. AUC: area under the plasma concentration–time curve from time 0 to infinity, expressed as $\text{mg ml}^{-1} \text{h}$.

sucralfate would not allow extensive absorption to occur. Sucralfate administration 4 h after sparfloxacin administration did not decrease the oral bioavailability of sparfloxacin. In this study, multiple dose sucralfate was used so that the potential effect of residual sucralfate from the previous dose would be considered. The goal was to allow sparfloxacin to be absorbed prior to sucralfate administration and to maximize the time between the previous sucralfate dose and a sparfloxacin dose. This goal will be difficult to achieve using sucralfate dosed as 1 g four times daily since sucralfate is reported to be present in stomach for at least 6 h after dosing [17]. However, dosing sucralfate 1.5 g twice daily is a viable alternative, which appears to be therapeutically equivalent in the treatment of peptic ulcer disease and has the potential for increased patients compliance [27]. Using this dosing regimen, sucralfate should be administered 4 h after sparfloxacin to minimize the chance of a significant interaction. Since sparfloxacin has an absolute bioavailability of about 90% [28] and the relative bioavailability of 50% with the concurrent administration of sucralfate, a manipulation of the timing of the sparfloxacin dose would improve the relative bioavailability of the drug. This manipulation can be easily achieved due to the fact that sparfloxacin is administered once daily. However, administration of sparfloxacin and sucralfate to patients with decreases in gastric emptying or intestinal motility may lead to increased probability of interaction and make this interaction more difficult to avoid.

In conclusion, sparfloxacin and sucralfate should not be administered concurrently. A significant reduction in bioavailability occurs with this combination, with an increased likelihood of therapeutic failure, especially for moderately susceptible bacteria. In order to prevent a drug–drug interaction, sparfloxacin should be administered 4 h before the administration of sucralfate.

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