Effects of Sucralfate, Magnesium Oxide and Sodium Ferrous Citrate on Sparfloxacin Pharmacokinetics

Masakiyo Kudo and Kazunobu Sugawara

Department of Pharmacy, Hirosaki University Hospital

Received May 19, 2003
Accepted September 14, 2003

The effects of sucralfate, magnesium oxide and sodium ferrous citrate on the pharmacokinetics of sparfloxacin were studied in 6 healthy subjects. According to a four-way crossover design, each subject received the following drug combinations in a random order: (A) a single 200 mg dose of sparfloxacin alone; (B) a single 200 mg dose of sparfloxacin with a 900 mg dose of sucralfate; (C) a single 200 mg dose of sparfloxacin with a 1 g dose of magnesium oxide; (D) a single 200 mg dose of sparfloxacin with a 100 mg dose of sodium ferrous citrate. The four regimens were given to subjects in the fasting state. Blood samples were collected over a 24-hour period, and plasma concentrations of sparfloxacin were determined by high-performance liquid chromatography. The area under the curve from 0 to 24 hours (AUC0-24) for sparfloxacin for regimen B was significantly lower (52.9% less, p < 0.005) than that for regimen A. However, for regimens C and D, the reductions in AUC0-24 as compared with regimen A were not significant (19.4% and 28.2%, respectively). Also, the peak plasma concentrations (Cmax) of sparfloxacin for regimens B and D were significantly lower (54.7% less, p < 0.001 and 31.4% less, p < 0.05, respectively) than that for regimen A. However, the Cmax for regimen C was not significantly lower than that for regimen A (22.1% less). These results suggest that aluminum containing drugs should not be given in combination with sparfloxacin.

Key words — sparfloxacin, sucralfate, magnesium oxide, sodium ferrous citrate, interaction

Introduction

Sparfloxacin is a new fluoroquinolone that has a broad antibacterial spectrum against gram-positive and gram-negative bacteria in vitro and in vivo [1]. Compared with the other fluoroquinolones, sparfloxacin exhibits a long half-life, allowing once-daily administration [2].

There have been many reports concerning the effects of antacids, anti-ulcer agents, and other drugs or foods containing metal cations (e.g., aluminum, magnesium, iron, calcium and zinc) on the absorption of fluoroquinolones in healthy volunteers [3-23]. Previously, the interaction between the fluoroquinolones such as norfloxacin [7, 17], ofloxacin [15, 17], ciprofloxacin [3-6, 9, 10], lomefloxacin [11, 16], DR-3355 (levofloxacin) [12] and fleroxacin [14, 18] and cations has been reported. Shimada et al. [19] studied the effect of an antacid (dried aluminum hydroxide gel) on sparfloxacin gastrointestinal absorption, and found that it was the least inhibited by interaction with an antacid, compared with other new quinolones. Kanemitsu et al. [20, 21] compared the effect of concomitantly administered ferrous sulfate on the absorption of sparfloxacin and norfloxacin, and found that it was less affected by ferrous sulfate than norfloxacin. The interaction between sparfloxacin and sucralfate has been reported by Zix et al. [22] and Kanberi et al. [23]. However, there are only these reports on the interaction of sparfloxacin and sucralfate, and the interaction of sparfloxacin and sodium ferrous citrate is not reported until now.

In the present study, we describe the effects of sucralfate, magnesium oxide and sodium ferrous citrate on the pharmacokinetics of sparfloxacin.

Materials and Methods

1. Materials

Sparfloxacin tablets (Spara®), fine granules of sucralfate (Ulcemin® fine granule, 1 g per pack), magnesium oxide and sodium ferrous citrate (Ferromia®) were purchased from Dainippon Pharmaceutical Co. Ltd. (Osaka, Japan), Chugai Pharmaceutical Co. Ltd. (Tokyo, Japan), Yoshida Pharmaceutical Co. Ltd. (Tokyo) and Eisai Co. Ltd. (Tokyo), respectively. Pure sparfloxacin and 4'-oxo-enoxacin were kindly supplied by Dainippon Pharmaceutical Co. Ltd. (Osaka).

2. Subjects and Study Design

Six male subjects (age range, 24 to 41 years; weight range, 53 to 70 kg) were participated in this study. Each subject was considered to be healthy on the basis of medical
Subjects received each of four regimens in a randomized crossover design; administration of the four regimens was separated by a 7 day washout period. For regimen A, subjects were given a 200 mg dose of sparfloxacin alone. For regimen B, subjects were given a 200 mg dose of sparfloxacin and 900 mg dose of sucralfate. For regimen C, subjects were given a 200 mg dose of sparfloxacin and 1 g dose of magnesium oxide. For regimen D, subjects were given a 200 mg dose of sparfloxacin and 100 mg dose of sodium ferrous citrate. For all regimens, subjects were given drugs with 200 mL of water following an overnight fast.

Blood samples (5 mL each) were obtained by direct venipuncture at 1, 2, 3, 4, 6, 8, 10, and 24 hour postdosing. Blood samples were collected into heparinized vacuum tubes and were immediately separated by centrifugation at 1900 × g for 15 min, and plasma was stored frozen at -40°C until analysis.

3. Assay Methodology

Plasma concentrations of sparfloxacin were determined by direct injection high-performance liquid chromatography with column switching [2]. Briefly, after the plasma sample was filtrated through a Molcut II® membrane filter for deprotenization, the filtrate was loaded on the precolumn (C18 reverse-phase column, 50 × 4.6 mm, I.D.) for the elimination of interfering substances in plasma. After washing, sparfloxacin and 4’-oxo-enoxacin, as an internal standard, were eluted from the precolumn and then led to the analytical column by column-switching technique using 0.5 % sodium acetate (pH 2.5)-acetonitrile (80 : 20, v/v) as the mobile phase at a flow rate of 1.0 mL/min. Sparfloxacin was detected on an ultraviolet detector at a wavelength of 300 nm. The limit of detection was 20 ng/mL. Relative standard deviations were less than 2.2%.

4. Pharmacokinetics Analysis

The peak concentrations of sparfloxacin (Cmax) and the time to peak concentrations (Tmax) in plasma were determined from the observed concentrations. The total area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24) was calculated by using the trapezoidal rule. The elimination half-life (T1/2) in plasma was estimated by least-squares regression analysis of the terminal concentration-time curve.

5. Statistical Methods

Statistical analyses were made with the Exce® software package (Microsoft Co. Ltd., USA). Two-way analysis of variance was used for analysis of the pharmacokinetic parameters. The parameters were compared with the control values by the Fisher’s PLSD for paired values (two tailed), where appropriate. The p values <0.05 were considered to be statistically significant.

Results

The profiles of the mean plasma concentration of sparfloxacin are shown in Fig. 1 for four regimens. The observed mean Cmax (mean±S.D.) for the sparfloxacin alone (regimen A), sparfloxacin-sucralfate (regimen B), sparfloxacin-magnesium oxide (regimen C) and sparfloxacin-sodium ferrous citrate (regimen D) were 0.86±0.25, 0.39±0.15, 0.67±0.24 and 0.59±0.22 μg/mL, respectively (Table 1), while the AUC0-24 (mean±S.D.) were 12.34±3.31, 5.81±2.25, 9.95±3.88 and 8.86±3.18 μg·hr/mL, respectively (Table 1). Sucralfate reduced the Cmax of sparfloxacin by 54.7% (p<0.001) and sodium ferrous citrate by 31.4% (p<0.05). Magnesium oxide reduced the Cmax of sparfloxacin by 22.1%, but there were not significant differences. The AUC0-24 was reduced by 52.9% (p<0.005) by sucralfate. The reductions of AUC for magnesium oxide and sodium ferrous citrate were 19.4% and 28.2%, respectively, but these data were no significant differences compared with the control values. There were no statistically significant differences in the Tmax or T1/2 between the control and the other three regimens.

Discussion

The present study demonstrated the effects of sucralfate, magnesium oxide and sodium ferrous citrate on the pharmacokinetics of sparfloxacin. In this study, the relative bioavailability was considered as an amount of absorption of drug. The relative bioavailability of sparfloxacin was significantly reduced by concomitant ingestation of sucralfate. On
the other hand, the relative bioavailability of sparfloxacin af-

ter concomitant ingestion of magnesium oxide or sodium
ferrous citrate was not statistically significant difference co-
mpared with that of sparfloxacin alone. Previous studies
have demonstrated that absorption of orally administered
new quinolone antibacterial agents such as norfloxacin [7,
17], ofloxacin [15, 17], ciprofloxacin [3-6, 9, 10], lomeflox-
aclin [11, 16], DR-3355 (levofloxacin) [12], fleroxacin [14,
18], and sparfloxacin [19-23] is decreased by concomitant
administration of metal cation containing drugs. Therefore,
the interaction between sparfloxacin and sucralfate can be
explained primarily by the inhibition of absorption of spar-
floxacin.

Studies on the interaction between sucralfate and fluoro-
quinolones have been reported by a number of investigators.
Kawakami et al. [15] has reported that Cmax and AUC of
ofloxacin after co-administration with sucralfate decreased
by 70 and 61% compared with ofloxacin alone, respectively.
Lehto et al. [17] has reported that co-administration of su-
cralfate with norfloxacin and ofloxacin reduced the relative
bioavailability of these fluoroquinolones by 91 and 61%, re-
spectively. Lubowski et al. [14] has reported that the relative
bioavailability of fleroxacin given with sucralfate was 76%
compared with that of fleroxacin alone. Zix et al. [22] has
been reported that co-administration of sucralfate and spar-
floxacin leads to a 44% decrease in the relative bioavailabil-
ity of DR-3355 (levofloxacin) by 22%. In the present study,
it decreased to 19.4% in AUC as compared with sparflox-
acin alone by co-administration of sparfloxacin and magne-
sium oxide, and this result was similar with the result which
was reported by Shiba et al.

Furthermore, there have been many reports for the interac-
tion between iron containing drugs and fluoroquinolones.
Polk et al. [6] has been reported that concomitant admini-
stration of ferrous sulfate and ciprofloxacin reduced the rela-
tive bioavailability of ciprofloxacin by 64%. Shiba et al.
[12] has reported that co-administration of ferrous sulfate
and DR-3355 (levofloxacin) reduced the relative bioavail-
ability of DR-3355 by 19%. Lehto et al. [16] has reported
that ferrous sulfate reduced the Cmax and the AUG-24 of
lomefloxacin by 26 and 13%, respectively. In the present
study, it was decreased to 28.2% in AUC as compared with
sparfloxacin alone by co-administration of sparfloxacin and
sodium ferrous citrate. In the most of previous papers, it has
been reported that drugs containing aluminum were gener-
ally stronger than other cation containing drugs on the inhi-
bition of absorption of fluoroquinolones. Also, generally, it
is known that the grade of the influence of metal cation has
a difference according to the kind of new quinolones [20,
21].

It has been considered that the proposed mechanism of
this interaction of fluoroquinolones and the metal cation
containing drugs was chelation between the metal ion and
the 4-keto oxygen, 3-carboxyl group of the fluoroquinolone.
Since these groups are required for antibacterial activity, one
can anticipate that all of the quinolones will interact with
these cations, although there may be differences between the
quinolones in the extent of interaction. Mizuki et al. [24] has
reported for the relationship between the interaction and the
chemical structure on fluoroquinolone derivatives in rat.

On the other hand, decreased gastric acidity may also
contribute to reduced the oral bioavailability of fluoroqui-

Table 1. Effect of Sucralfate (900 mg), Magnesium Oxide (1 g) and Sodium Ferrous Cit-
rate (100 mg) on the Pharmacokinetic Parameters of Sparfloxacin (200 mg).

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Amax (µg/mL)</th>
<th>Bmax (µg/mL)</th>
<th>Cmax (µg/mL)</th>
<th>Dmax (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.86±0.15</td>
<td>0.49±0.22</td>
<td>0.67±0.24</td>
<td>0.59±0.22</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.33±1.02</td>
<td>3.00±0.53</td>
<td>2.17±1.12</td>
<td>2.83±0.99</td>
</tr>
<tr>
<td>AUC0-24 (µg·hr/mL)</td>
<td>12.34±3.31</td>
<td>5.81±2.25*</td>
<td>9.95±3.88</td>
<td>8.86±3.18</td>
</tr>
<tr>
<td>AUC (% of control)</td>
<td>100.0</td>
<td>47.6±12.8</td>
<td>86.4±19.0</td>
<td>78.3±35.5</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>13.7±3.6</td>
<td>15.7±2.7</td>
<td>13.9±3.0</td>
<td>14.3±4.6</td>
</tr>
</tbody>
</table>

Data are mean values ± S.D. in six subjects.
Cmax, Peak plasma concentration ; Tmax, Time to reach maximum plasma concentration ;
AUC, Area under the plasma concentration - time curve ; T1/2, Elimination half - life.
*p < 0.05 compared with control
**p < 0.005 compared with control
***p < 0.001 compared with control
acin by an average of 26%. However, Nix et al. [4] and Shiba et al. [12] have reported that ranitidine pretreatment had no significant effect on the bioavailability of ciprofloxacin and the absorption of DR-3355 (levofloxacin), respectively.

The reduction of sparfloxacin bioavailability when sucralfate and sparfloxacin were concomitantly administered to healthy subjects in the present study was similar to the results reported by Zix et al. [22] and Kamberi et al. [23]. On the other hand, no significant decrease of sparfloxacin bioavailability was demonstrated by magnesium oxide or sodium ferrous citrate. Shiba et al. [12] has reported that when aluminum hydroxide, ferrous sulfate, and magnesium oxide were co-administration with DR-3355 (levofloxacin), the relative bioavailability of DR-3355 was decreased to 56, 81, and 78%, respectively, of that for DR-3355 (100 mg) alone. These results were similar with our study result.

According to previous study, generally, the metal cation which forms more stable chelate is the order of Al$^{3+} >$ Fe$^{2+}$ $\approx$ Mg$^{2+} >$ Ca$^{2+}$[13]. In conclusion, the present results suggest that sparfloxacin and sucralfate should not be administered concurrently.

References


