Effect of Calcium Carbonate on Bioavailability of Orally Administered Gemifloxacin

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We investigated the effect of calcium carbonate on the oral bioavailability of gemifloxacin. Gemifloxacin was administered alone, 2 h before, simultaneously, or 2 h after calcium carbonate in 16 volunteers. Data for 320 mg of gemifloxacin alone were as follows: maximum concentration in serum (C_{max}), 13 μg/ml; half-life, 7.33 h; and area under the concentration-time curve from 0 h to infinity (AUC_{inf}), 6.79 μg·h/ml. Only simultaneous coadministration of calcium carbonate reduced C_{max} (−17%) and AUC_{inf} (−21%) significantly.

MATERIALS AND METHODS

Volunteers. Sixteen healthy Caucasian volunteers (10 males and 6 females; mean age, ± standard deviation, 30 ± 7.2 years; mean body weight ± standard deviation, 71.8 ± 11.3 kg; mean creatinine clearance ± standard deviation, 117 ± 11 ml/min/1.73 m²) participated in the study. The study was approved by the local ethics committee according to German law. Informed written consent was obtained from all subjects.

Study design. According to the four-way crossover design, each volunteer received the following drug combinations in a random order: (A) gemifloxacin alone, (B) gemifloxacin 2 h after calcium, (C) gemifloxacin simultaneously with calcium, and (D) gemifloxacin administered 2 h before calcium. All drugs were administered orally. The four dosing sessions were separated by washout periods of at least 6 days. Gemifloxacin was given after an overnight fast as a single oral dose of 320 mg (SB-265805). Calcium was administered as one effervescent calcium carbonate tablet containing 1,000 mg of calcium (Calcium Sandoz Fortisimum) dissolved in 200 ml of water.

Sample collection and processing. Blood samples (5 ml) were taken before drug administration and then at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 h after dosing. Plasma samples were obtained by centrifugation. Urine was collected predose and during the following periods: 0 to 6, 6 to 12, 12 to 24, and 24 to 48 h postdose. The volume of urine was measured after each collection interval, and a 5-ml aliquot of well-mixed urine was saved.

High-pressure liquid chromatography-mass spectrometry. Plasma samples were analyzed following protein precipitation with acetonitrile. The urine samples were prepared for analysis by dilution and analyzed by high-pressure liquid chromatography and mass spectrometry, using positive-ion spray ionization. The lower limits of quantification for each of the assays for gemifloxacin in plasma and urine were each 0.01 μg/ml using a 50-μl aliquot. The intra-assay and interassay coefficients of variation for determination of plasma and urine were less than 10%.

Pharmacokinetic calculations. Plasma concentration data were analyzed by standard noncompartmental methods using the software program WinNonlin-Professional Edition (version 2.1). The primary pharmacokinetic parameters to determine the effect of calcium carbonate on the bioavailability of gemifloxacin were the maximal concentration in plasma (C_{max}) and the area under the plasma concentration-time curve extrapolated to infinity (AUC_{inf}).

Primary parameters were log-transformed and compared by analysis of variance using the factor sequence, subject nested within sequence, period, and regimen. The point estimates and adjusted 95% confidence intervals for the difference between the regimens (B-A, C-A, and D-A) were constructed using the residual variance from the model, and the appropriate adjustments were made for the three multiple comparisons using Dunnett’s procedure (4). The overall significance level was maintained at 5%. The point and interval estimates on the log scale were then back-transformed to obtain the estimates of the ratios (B/A, C/A, and D/A). Within subject coefficient of variation for AUC_{inf} and C_{max} was calculated based on the log-normal distribution.

RESULTS

Pharmacokinetics. (i) Plasma. The mean plasma concentration-time profiles for gemifloxacin after administration of a 320-mg single dose either alone or at various times relative to calcium carbonate are shown in Fig. 1. Table 1 summarizes the gemifloxacin pharmacokinetics in the presence and absence of calcium carbonate. Table 2 presents the results of the statistical comparisons between the reference regimen A and the test regimens B, C, and D. Simultaneous coadministration of calcium carbonate with 320 mg of gemifloxacin significantly reduced the C_{max} by 21%, and the AUC_{inf} by 17%, compared to gemifloxacin alone (P < 0.05).

(ii) Urine. The extent of urinary excretion (Table 1) of gemifloxacin was not notably different when gemifloxacin was given 2 h before or after calcium, although there was a slight, not significant decrease when calcium was given simultaneously. There were no clear differences in renal clearance between treatments.

Safety and tolerance. The volunteers’ overall tolerance to gemifloxacin was good. No severe adverse events (AE) occurred. The most frequently reported AE was diarrhea; however there was no clear correlation between time of AE onset and gemifloxacin and calcium dosing, although diarrhea was only reported during the coadministration sessions of dosing.
There were no clinically significant changes in electrocardiogram parameters, blood pressure or pulse. Similarly, there were no clinically important findings in hematology, clinical chemistry or urinalysis following dosing gemifloxacin alone or in combination with calcium.

**DISCUSSION**

Drugs containing the multivalent cations magnesium, aluminum, and calcium have been shown to substantially interfere with the absorption of quinolones, resulting in lower plasma concentrations (1). This interaction has been attributed to the chelation by the multivalent cation to the quinolone and has been shown to be a class effect, although the interaction varies across different quinolones (6).

In the present study, simultaneously administration of calcium carbonate with 320 mg of gemifloxacin resulted in a modest reduction in bioavailability of gemifloxacin (average decrease of 21% for AUC and 17% for $C_{\text{max}}$). In contrast, administration of calcium carbonate either 2 h before or after dosing with 320 mg of gemifloxacin resulted only in a minor decrease of gemifloxacin bioavailability (average decrease of 7% for the 2 h before and 5% when gemifloxacin was administered 2 h after), compared to that observed with gemifloxacin given alone. Neither time to $C_{\text{max}}$ nor the half-life of gemifloxacin were notably affected by coadministration of calcium.

The modest reduction in gemifloxacin bioavailability seen when calcium carbonate was simultaneously administered is consistent with that seen with other quinolones but is notably less than seen for ofloxacin (5). Although the decrease in AUC

![FIG. 1. Arithmetic means of measured plasma concentration of gemifloxacin after administration of 320 mg of gemifloxacin alone (regimen A) and 2 h after 1,000 mg of calcium carbonate (regimen B), simultaneously with calcium carbonate (regimen C), and 2 h before calcium carbonate (regimen D) in 16 healthy volunteers. The direction of the error bars (standard deviation) is upwards for regimens A and D and downwards for regimens B and C.](http://aac.asm.org/)

**TABLE 1. Gemifloxacin pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>AUC$_{\text{a}}$ (µg · h/ml)</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$t_{1/2}$ (h)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$Ae_{48}$ (% of dose)</th>
<th>CL$_{\text{p}}$(liters/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.79 ± 3.13</td>
<td>1.13 ± 0.41</td>
<td>7.3 ± 2.5</td>
<td>1 (0.5–2)</td>
<td>18.1 ± 3.5</td>
<td>8.26 ± 1.88</td>
</tr>
<tr>
<td>B</td>
<td>6.12 ± 1.39</td>
<td>1.01 ± 0.26</td>
<td>6.7 ± 1.2</td>
<td>1 (0.5–2)</td>
<td>17.4 ± 4.7</td>
<td>9.09 ± 1.7</td>
</tr>
<tr>
<td>C</td>
<td>5.22 ± 1.40</td>
<td>0.90 ± 0.29</td>
<td>6.8 ± 1.3</td>
<td>1 (1–2)</td>
<td>15.1 ± 4.8</td>
<td>9.53 ± 2.6</td>
</tr>
<tr>
<td>D</td>
<td>6.34 ± 1.65</td>
<td>1.13 ± 0.39</td>
<td>6.4 ± 1.3</td>
<td>1 (0.5–2)</td>
<td>19.0 ± 4.7</td>
<td>10.4 ± 3.2</td>
</tr>
</tbody>
</table>

*a Data presented as arithmetic means ± standard deviation except for $T_{\text{max}}$, for which the median (range) is given.

*b Regimen abbreviations: A, gemifloxacin (320 mg) alone; B, gemifloxacin 2 h after calcium; C, gemifloxacin simultaneously with calcium; D, gemifloxacin 2 h before calcium.

't' $t_{1/2}$ half-life.

'd' $T_{\text{max}}$ time to $C_{\text{max}}$.

' Ae48', percentage of dose excreted in the urine over 48 h.
and $C_{\text{max}}$ is considered not to be of great clinical importance, it should be known and it should be explained to the patient when gemifloxacin is prescribed.

**Conclusions.** The results of this study demonstrate that simultaneous coadministration of 1000 mg calcium carbonate reduces the bioavailability of gemifloxacin. $C_{\text{max}}$ is reduced by 21% and $\text{AUC}_2$ is decreased by 17%. Administration of calcium either 2 h before or 2 h after administration of 320 mg of gemifloxacin has no relevant effect on the bioavailability of gemifloxacin. The effect of calcium carbonate is attributed to the chelation of the multivalent cation to the quinolone gemifloxacin.

**ACKNOWLEDGMENTS**

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**REFERENCES**


**TABLE 2. Comparison between regimens for gemifloxacin pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>Point estimate</th>
<th>95% confidence interval</th>
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</thead>
<tbody>
<tr>
<td>$\text{AUC}_2$ (µg · h/ml)</td>
<td>B:A</td>
<td>0.93</td>
<td>0.78–1.10</td>
</tr>
<tr>
<td></td>
<td>C:A</td>
<td>0.79</td>
<td>0.66–0.93</td>
</tr>
<tr>
<td></td>
<td>D:A</td>
<td>0.95</td>
<td>0.80–1.13</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>B:A</td>
<td>0.93</td>
<td>0.71–1.22</td>
</tr>
<tr>
<td></td>
<td>C:A</td>
<td>0.83</td>
<td>0.63–1.08</td>
</tr>
<tr>
<td></td>
<td>D:A</td>
<td>1.03</td>
<td>0.79–1.35</td>
</tr>
</tbody>
</table>

* Regimen abbreviations: A, gemifloxacin alone; B, gemifloxacin 2 h after calcium; C, gemifloxacin simultaneously with calcium; D, gemifloxacin 2 h before calcium.