Effects of Aluminum Hydroxide and Famotidine on Bioavailability of Tosufloxacin in Healthy Volunteers

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Received 29 July 1996/Returned for modification 15 June 1997/Accepted 1 November 1997

This study was designed to determine the influence of aluminum hydroxide and famotidine on the bioavailability of tosufloxacin. Coadministration of aluminum hydroxide reduced the bioavailability of tosufloxacin by 31.6% (P < 0.05). Famotidine did not alter tosufloxacin absorption. To avoid potential treatment failures, the concurrent use of tosufloxacin and aluminum hydroxide should be avoided altogether.

Tosufloxacin is one of the fluoroquinolone antibacterial agents with a broad antibacterial spectrum against gram-positive and gram-negative organisms, including anaerobic bacteria. Tosufloxacin generally has greater potency in vitro than ciprofloxacin, ofloxacin, norfloxacin, and pipemidic acid. MICs of tosufloxacin against Staphylococcus aureus and Pseudomonas aeruginosa are less than or equal to 0.05 and 0.39 μg/ml, respectively (1).

Tosufloxacin absorption is about 1.4 times higher under non-fasting conditions than under fasting conditions (6). Absorbed tosufloxacin is reported to be excreted mainly in an unchanged form in urine (11). Previous studies have demonstrated that bioavailabilities of fluoroquinolones are decreased by coadministration of antacids containing aluminum (2, 7, 9, 10). Shiba et al. (9) investigated the effects of concurrent administration of aluminum hydroxide on the pharmacokinetics of fluoroquinolones, i.e., ofloxacin, enoxacin, and norfloxacin, in five healthy male volunteers. The decrease in bioavailability is attributed to interaction with metal ions, producing chelated compounds which are less able to permeate membranes (5).

This study assessed the influence of aluminum hydroxide and famotidine, a histamine H2 receptor antagonist, on the bioavailability of tosufloxacin, a new fluoroquinolone, in healthy volunteers.

Six healthy male volunteers, 24 to 39 years old, participated in a single-dose three-way randomized crossover design. Written informed consent was obtained from each volunteer before entry. Their blood urea nitrogen, serum creatinine, and other compounds which are less able to permeate membranes (5).

Six healthy male volunteers, 24 to 39 years old, participated in a single-dose three-way randomized crossover design. Written informed consent was obtained from each volunteer before entry. Their blood urea nitrogen, serum creatinine, and other laboratory test values fell within the normal range. One-half hour after a standard breakfast, two tosufloxacin tablets were orally administered, each containing approximately 300 mg of tosufloxacin tosylate (Toyama Chemical Co., Toyama, Japan), which is equivalent to 204 mg of the free base, with 100 ml of tap water. Subjects fasted for at least 4 h after administration. They were assigned to three dosage regimens, including tosufloxacin alone, tosufloxacin with 1 g of dried aluminum hydroxide gel (Chugai Pharmaceutical Co., Tokyo, Japan), and tosufloxacin with a single tablet of 20 mg of famotidine (Yamouchi Pharmaceutical Co., Tokyo, Japan) with a 2-week washout period.

After administration of tosufloxacin, 5-ml blood samples were obtained by direct venipuncture before dosing and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 h after drug ingestion. Urine samples were also collected before dosing and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 14 h after administration and were collected cumulatively thereafter for up to 24 h after administration. Blood samples were centrifuged to separate serum, and both serum and urine samples were stored at −20°C until analysis. Tosufloxacin base, supplied by Toyama Chemical Co., was used as the reference compound. Tosufloxacin concentrations in serum and urine were determined by high-performance liquid chromatography (HPLC) as described in a recent report (13), with a minor modification. Namely, tosufloxacin concentrations in serum were determined by HPLC with a column-switching technique. A L-1180 column (30-mm length by 4.0-mm inside diameter; Chemical Inspection and Testing Institute, Tokyo, Japan) with a mobile phase consisting of 0.2 M K2HPO4–10% triethylamine · CH3SO3H–H2O (36:7:960, vol/vol) was used for deproteinization, while an Inertsil ODS-2 column (150-mm length by 4.0-mm inside diameter; GL Sciences, Tokyo, Japan), with a mobile phase consisting of CH3CN-0.2 M K2HPO4–10% triethylamine · CH3SO3H–H2O (230:180:50:540, vol/vol) was used for analytical separation. The standard curves ranged from 0.1 to 1.0 μg/ml with between-days coefficients of variation of 5.0, 1.8, and 0.4% at tosufloxacin concentrations of 0.1, 0.5, and 1.0 μg/ml, respectively (n = 5 each).

Urinary samples were assayed by HPLC with a Lichrospher 100 RP-18(e) column (250-mm length by 4.0-mm inside diameter; E. Merck, Darmstadt, Germany) with a third mobile phase consisting of CH3CN-0.2 M disodium citrate–10% triethylamine · CH3SO3H–H2O (200:310:100:390, vol/vol). The standard curves ranged from 2.0 to 10.0 μg/ml. Urine samples with concentrations exceeding 10.0 μg/ml were diluted with CH3CN-0.2 M disodium citrate–10% triethylamine · CH3SO3H·H2O (230:180:50:540, vol/vol) was used for analytical separation. The standard curves ranged from 0.1 to 1.0 μg/ml with between-days coefficients of variation of 5.0, 1.8, and 0.4% at tosufloxacin concentrations of 0.1, 0.5, and 1.0 μg/ml, respectively (n = 5 each).

The maximum concentration in serum (Cmax) and the time required to reach the Cmax (Tmax) were calculated from observed data. The area under the serum concentration-time curve from 0 to 10 h (AUC0–10 h) was calculated by the trapezoidal rule. The area to time infinity (AUC) was calculated by adding to AUC0–10 h, the area obtained by dividing the concentration at the last sampling time (C10 h) by the terminal elimination rate constant estimated by least-squares regression.
analysis of three or four serum level points of the terminal concentration-time curve. Analysis using a one-compartment open model with lag time was performed by using a nonlinear regression analysis program MULTI (12) to calculate elimination rate constants ($k_{el}$). The reciprocal of the observed value was adopted as the weight to calculate pharmacokinetic parameters.

After the homoscedasticity among the three groups was checked, an analysis of variance was applied to $C_{max}$, AUC, and $k_{el}$ to determine any statistically significant differences among the treatment groups. If differences were noted, Tukey's multiple-comparison test was used to evaluate the treatments that differed from the control. The Kruskal-Wallis test was used to compare mean urinary recovery values. Results are expressed as means ± standard deviations.

All subjects completed the study. Pharmacokinetic parameters for tosufloxacin after each treatment are summarized in Table 1. Mean tosufloxacin serum concentration-time profiles after each treatment are shown in Fig. 1A. Although the average bioavailability with concomitant aluminum hydroxide administration was decreased approximately 32% compared with the control value ($P < 0.05$), the extent of the effect varied and individual subjects may be grouped into two types. As shown in Fig. 1B, tosufloxacin concentrations in serum were not affected very much by administration of aluminum hydroxide to three volunteers (in group 1, AUCs were 87.6 ± 4.5% [range, 78.9 to 93.8%] of the control values), while drug concentrations in serum were much decreased after coadministration of aluminum hydroxide to the others (in group 2, AUCs were 38.4 ± 9.8% [range, 18.8 to 49.4%] of the control values), as shown in Fig. 1C. In group 1, the $C_{max}$ of tosufloxacin was four times higher than in group 2, whereas the $T_{max}$ of group 2 was significantly longer than that of group 1 after coadministration of aluminum hydroxide. The cumulative extents of urinary

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{max}$ (µg/ml)</th>
<th>$T_{max}$ (h)</th>
<th>$k_{el}$ (h⁻¹)</th>
<th>AUC (h · µg/ml)</th>
<th>Urinary recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosufloxacin alone</td>
<td>0.88 ± 0.28</td>
<td>2.3 ± 0.8</td>
<td>0.25 ± 0.09</td>
<td>5.57 ± 1.33</td>
<td>34.0 ± 9.1</td>
</tr>
<tr>
<td>Tosufloxacin with Al(OH)₃</td>
<td>0.52 ± 0.36</td>
<td>2.2 ± 0.9</td>
<td>0.18 ± 0.04</td>
<td>3.81 ± 2.12</td>
<td>19.7 ± 9.1</td>
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<tr>
<td>Tosufloxacin with famotidine</td>
<td>0.93 ± 0.15</td>
<td>2.0 ± 0.6</td>
<td>0.20 ± 0.01</td>
<td>6.30 ± 0.98</td>
<td>32.6 ± 6.6</td>
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</tbody>
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* Values are means ± the standard deviations.
* Significantly different ($P < 0.01$) from tosufloxacin alone.
* Significantly different ($P < 0.05$) from tosufloxacin alone.
excretion of tosufloxacin after each treatment are shown in Fig. 2. Urinary recovery values were decreased significantly to 66% by concurrent administration of aluminum hydroxide but were not affected by coadministration of ranitidine.

According to Shiba et al. (9), the AUC0–24 h values of ofloxacin, enoxacin, and norfloxacin were decreased significantly to 52.1, 15.4, and 2.7%, respectively, of the control value by concurrent administration of aluminum hydroxide and tosufloxacin should be avoided.

In conclusion, since the extent of the interaction may vary and absorption can be much reduced, simultaneous administration of aluminum hydroxide and tosufloxacin should be avoided.

REFERENCES