Inhibition of Theophylline Clearance by Coadministered Ofloxacin without Alteration of Theophylline Effects

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The influence of multiple doses of ofloxacin (ORF 18489) on the disposition of theophylline was studied in 15 male volunteers. Subjects were confined in the Clinical Research Unit for 13 days and given a xanthine-free diet. A single dose (3 mg/kg) of theophylline was given orally, and blood samples were collected at fixed time intervals for 36 h. The concentrations of theophylline were measured with TDX (Abbott Diagnostics, Irving, Tex.), and clearance was calculated. Theophylline clearance was used to individualize subsequent doses to achieve average steady-state theophylline concentrations in plasma of 10 mg/liter. Individualized theophylline doses were administered every 8 h until steady-state conditions were reached. Theophylline clearance was determined again at steady state and on days 7 and 8. On day 8, ofloxacin (400 mg every 12 h) was given concomitantly with theophylline. Theophylline clearance was measured again on day 12, after the last theophylline dose. Administration of ofloxacin for 1 day did not change theophylline clearance, but coadministration for 4 days significantly decreased theophylline clearance by 12.1% (P < 0.05). The area under the concentration-time curve for theophylline increased 9.9% (P < 0.05), and average steady-state concentrations in plasma increased 10.3% (P < 0.05). Despite changes in clearance, adverse effects of theophylline did not increase during coadministration of ofloxacin. Although statistically significant, the interaction between ofloxacin and theophylline is unlikely to be of major clinical importance.

Oflaxocin (ORF 18489) is a synthetic, carboxyquinolone antibacterial agent which has potent bactericidal activity against a wide spectrum of bacteria both in vitro and in vivo (8). This spectrum includes most bacteria responsible for pulmonary infections (14). Interestingly, ofloxacin has been effective against Mycobacterium tuberculosis both in vitro and in humans (16, 17). Legionella pneumophila is also eradicated by ofloxacin both in vitro and in the animal model (13).

Asthma and other chronic obstructive pulmonary diseases predispose patients to bronchopulmonary infections (1, 2). Thus, it is likely that ofloxacin and theophylline will be given concomitantly to patients with exacerbations of chronic obstructive pulmonary diseases. Theophylline is extensively metabolized in the liver by dealkylation and hydroxylation. Drugs which interfere with the cytochrome P-450 or P-448 system may alter the clearance of theophylline and have the potential to increase theophylline toxicity (7, 11, 12).

Anecdotal reports suggest that at least some of the fluoroquinolone antimicrobial agents can reduce the hepatic clearance of theophylline (9, 18). Maesen et al. (9) and Wijand and Herwaarden (18) reported adverse effects suggestive of theophylline toxicity when patients received enoxacin administered with theophylline. However, clinical symptoms of theophylline toxicity were not observed with concomitant administration of ciprofloxacin or pefloxacin (9). Wijand and Herwaarden also demonstrated an increase in concentration of theophylline in serum with coadministration of enoxacin (18). Ofloxacin had not been studied, so we recruited normal volunteers for a study of the effects of regular administration of ofloxacin on steady-state theophylline concentrations and its adverse effects on patients.

MATERIALS AND METHODS

Fifteen male volunteers were studied (mean age, 23 years; range 18 to 34). Before initiation of the study, the protocol was approved by the Human Research Committee, and written informed consent was obtained from each volunteer. All subjects (mean weight, 72.9 kg; range, 61 to 94.4 kg) were in good health as determined by medical histories, complete physical examinations, 12-lead electrocardiograms, and normal base-line values for hematology, serum chemistry, urinalysis, ophthalmology, and audiometry testing.

The volunteers were nonsmokers, had no history of drug abuse, and denied hypersensitivity to theophylline or quinolone antibiotics. Subjects were instructed to abstain from xanthine-containing substances, alcohol, and any drugs for 48 h before confinement and for the duration of the study. Volunteers were confined in the Millard Fillmore Hospital Clinical Research Unit from 12 h before the first dose of theophylline until the completion of all study procedures, i.e., for a total of 13 days. A xanthine-free diet was administered for the duration of the study. Every day of the study, subjects fasted for 8 h before the morning dose of drug(s). Water was permitted ad libitum until 2 h before dosing. A standard breakfast was served 2 h after the morning dose of theophylline. On day 1, a single dose (3 mg/kg) of theophylline syrup (Slo-Phyllin [William H. Rorer, Inc., Fort Washington, Pa.]; 80 mg/15 ml) was administered. Blood samples were collected before theophylline dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, and 36 h after dosing. This initial clearance study served to determine the maintenance dosage of theophylline for each subject for the remainder of the study. The following equation was used to determine individualized doses: dose = Cpss × CL × r/F, where F is the fraction of drug systemically available (1.0 assumed), Cpss is the aver-

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age steady-state concentration in plasma sought (i.e., 10 mg/liter), CL is the clearance determined by dose/AUC_{0-\infty}(area under the theophylline concentration-time curve from time zero to infinity), and \( \tau \) is the dosing interval (8 h).

Beginning on day 3, individualized theophylline (SloPhyllin) doses calculated to achieve a \( C_{p,s} \), of 10 mg/liter were administered at 8 a.m., 4 p.m., and 12 a.m. Starting on the morning of day 8 and continuing throughout day 13, 400 mg of ofloxacin (two doses of 200 mg each) was given 30 min before the morning dose of theophylline and every 12 h thereafter.

Theophylline clearance was measured on four occasions during the study. On days 1 and 12 of the study, serial blood samples (5 ml each) were obtained from an indwelling venous catheter maintained patent with heparin (4.0 U/ml) at the following times: predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, and 36 h after theophylline dosing. On days 7 and 8 of the study, serial blood samples were obtained to determine steady-state theophylline clearance; samples were taken predose and at 0.5, 1, 2, 3, 4, 6, and 8 h after the morning dose of theophylline.

Assay. All blood samples were centrifuged at 2,000 rpm for 10 min, and plasma samples were assayed for theophylline within 2 h. Theophylline concentrations in plasma were determined by TDX (Abbott Diagnostics, Irving, Tex.). This method has been shown to be accurate and reproducible (6, 12).

Analysis. Pharmacokinetic analysis of theophylline concentration in plasma was done with a noncompartmental model. AUC was determined by the LaGrange approximation method. Clearance was calculated by the equation CL_{T} = (F \times dose)/AUC_{0-\infty}, where CL_{T} is the total body clearance, AUC_{0-\infty} is the AUC from 0 to 8 h, and \( F \) is the fraction of dose systemically available. Theophylline syrup was assumed to be 100% bioavailable. \( C_{p,s} \) was calculated by the equation \( C_{p,s} = AUC_{0-\infty}/\tau \).

Statistics. The differences observed between the pharmacokinetics parameters of single-dose and steady-state theophylline and the differences between theophylline parameters preofloxacin and after multiple doses of ofloxacin were evaluated by paired, two-tailed Student’s \( t \) test. A probability value of less than 0.05 was used to define significant difference.

RESULTS

All 15 volunteers completed the study. Their mean weight was 72.9 kg (range, 61 to 94.4 kg).

Theophylline concentrations in plasma from the volunteers were determined daily. In the TDX assay, the average coefficient of variation of all three of the quality controls assayed with every batch was 4.3% within day and 4.5% between days.

The purpose of the theophylline clearance study on day 1 was to individualize the dosing of each volunteer to a target steady-state concentration of 10 mg/liter. The actual steady-state concentration on day 7 averaged 10.7 mg/liter (Table 1). The average 8-h dose required to reach this concentration was 3.85 mg/kg. Table 1 also provides theophylline pharmacokinetic parameters obtained on four occasions: after single dose, at steady state, on day 8 after the first dose of ofloxacin, and after 4 days of regular administration of ofloxacin. The profiles of \( C_{p,s} \) versus time at steady state during an 8-h dosing interval with and without chronic ofloxacin treatment are illustrated in Fig. 1.

Theophylline pharmacokinetic parameters were linear in this study in that single-dose parameters accurately predicted steady-state concentrations. The mean clearance after a single dose was 3.5 liters/h and was not significantly different from the mean steady-state clearance (3.3 liters/h). After a single dose of 400 mg of ofloxacin, clearance was 3.4 liters/h and was not significantly different from the steady-state mean. However, theophylline clearance after multiple ofloxacin doses (3.0 liters/h) showed a significant decrease (12.1%) when compared with the steady-state clearance before ofloxacin.

Theophylline AUC_{0-\infty} also showed a significant change when the steady-state value was compared with that measured postofloxacin. Theophylline AUC_{0-\infty} was 85.1 mg · h/liter preofloxacin and was not significantly different at 83.0 mg · h/liter after one dose of ofloxacin. Postofloxacin, the average increase in AUC_{0-\infty} was 9.9% with a value of 93.6 mg · h/liter, which was significantly different (\( P = 0.002 \)) from the preofloxacin value.

The \( C_{p,s} \) achieved preofloxacin and that achieved after one dose of ofloxacin were not significantly different and were 10.7 and 10.4 mg/liter, respectively. Multiple doses of ofloxacin caused an increase in theophylline \( C_{p,s} \) to 11.7 mg/liter, which was 10.3% higher and statistically (\( P = 0.002 \)) different from the \( C_{p,s} \) preofloxacin.

The volunteers were closely questioned about adverse effects throughout the study (Table 2). Table 2 lists the number of single episodes, although volunteers occasionally reported a side effect more than once. The most common adverse effects reported during theophylline administration were headache, insomnia, and jitters. Most subjects develop-
oped tolerance to the insomnia and jitteriness by the time they reached steady-state concentrations of theophylline.

After the introduction of ofloxacin, the most commonly reported adverse effects were nausea and upset stomach. Anorexia, palpitations, and light-headedness were reported by one patient each (Table 2) but did not occur together. Postofloxacin audimetric and ophthalmologic examinations revealed no differences from preofloxacin base-line values.

**DISCUSSION**

These data show that ofloxacin at a dosage of 400 mg every 12 h for 4 days resulted in a significant decrease in theophylline clearance. Also, AUC for theophylline in plasma increased by 9.9%, and C_{pmax} increased significantly by 10.3%.

Several mechanisms could account for the relatively minor interaction between ofloxacin and theophylline compared with the marked effects of other quinolone antibiotics. Enoxacin interacts with theophylline when the two drugs are coadministered, but ciprofloxacin and pefloxacin apparently do not interact (9, 18). Structural differences are a likely explanation. Enoxacin, like nalidixic acid, has a naphthyridine ring with nitrogen atoms at positions 1 and 8. Ciprofloxacin, pefloxacin, and ofloxacin are quinolones lacking the nitrogen at position 8. Further study of nalidixic acid interaction with theophylline may reveal the naphthyridine ring to be the important structural component of metabolic inhibition. Other possible mechanisms include differences between quinolones in the amount of the dose metabolized or in the amount of quinolone which reaches the site of theophylline metabolism.

Recently, Fourtillan and co-workers examined the differences in theophylline disposition in 12 volunteers after regular dosing (5 days) with ofloxacin at 200 mg every 12 h (3). These workers found a slight increase in AUC_{pmax}, but this increase did not reach statistical significance. The authors gave a theophylline dose of 200 mg every 8 h to all volunteers, and this dosage yielded theophylline concentrations in serum well below 10 mg/liter. As dosages of both ofloxacin and theophylline were lower in the Fourtillan study, the lack of interaction may have been due to insufficient substrate to uncover a dose-related competitive metabolic inhibition. Alternatively, the interaction may have occurred even at these lower dosages, but there may not have been a large enough number of subjects to show the small degree of interaction statistically significant.

In clinical studies, Maesen et al. reported an epileptiform seizure, along with other signs of theophylline toxicity such as nausea and hallucinations, in a patient who received enoxacin and theophylline (9). However, Simpson and Brodie reported convulsions secondary to enoxacin administered alone (15). Convulsions related to nalidixic acid have also been reported (4). It is possible that these adverse effects on the central nervous system are caused by the quinolones, but it is also possible that theophylline augments the neurological actions of the carboxyquinoles or that these adverse effects are due to theophylline independent of the quinolone.

In our volunteers, most of the adverse events occurred before ofloxacin was administered and consisted mainly of insomnia, headache, and jitters. Our volunteers were xantheine free when the first dose of theophylline was administered and developed tolerance to these effects by day 4, as has been observed in other studies of chronic theophylline administration (6).

The addition of ofloxacin to the regimen did not cause the effects of theophylline on the central nervous system to reoccur. In fact, there was further reduction in adverse effects after the introduction of ofloxacin. Also, the adverse effects reported with ofloxacin, consisting primarily of nausea and upset stomach, were different from preofloxacin complaints. These adverse effects are the most frequently reported with quinolones and ofloxacin (5, 10). Thus, the slight increase in theophylline concentration in plasma did not increase or cause recurrence of the theophylline-related adverse effects seen at the beginning of the study, and ofloxacin itself caused only minor and transient adverse reactions.

While the safety of concomitantly administered ofloxacin and theophylline should be closely monitored, it appears that ofloxacin and theophylline can be safely coadministered to patients.

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**LITERATURE CITED**


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**TABLE 2. Reported adverse effects of theophylline administered alone or with ofloxacin**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>No. of episodes with</th>
<th>AUC_{pmax}</th>
<th>C_{pmax}</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>theophylline</td>
<td>Alone</td>
<td>With</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Nausea and upset stomach</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Jitters</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Palpitations</td>
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<td>1</td>
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</table>

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Quinolones and raised plasma concentration of theophylline. Lancet ii:530.