The Effect of Multiple-Dose Oral Lomefloxacin on Theophylline Metabolism in Man

Giel J. A. Wijnands, M.D., Ph.D.; Jan H. Cornel, M.D.; Magdalena Martea, Pharm.D.; and Tom B. Vree, Ph.D.

Single-dose plasma pharmacokinetics of theophylline (6 mg/kg intravenously) and renal excretion of theophylline and its metabolites, resulting from 8-oxidation and N-demethylation, were investigated in eight healthy volunteers before and at day 3 of concomitant oral administration of the quinolone derivative lomefloxacin (400 mg twice daily). Plasma samples were collected until 24.5 h, and urine samples were collected until 72 h after theophylline administration. The concentrations of theophylline and the major metabolites, resulting from N-demethylation and 8-oxidation, were measured utilizing a high-pressure liquid chromatography (HPLC) technique. No significant changes in theophylline half-life, volume of distribution, protein binding, total body clearance, or renal clearance were noted. In addition, renal excretion of unchanged theophylline, the products of the N-demethylation, 3-methylxanthine, and 1-methyluric acid, and the product of the 8-oxidation, 1,3-dimethyluric acid, were not altered by simultaneous administration of lomefloxacin. Orally admin-

istered lomefloxacin is absorbed quickly and to a high extent. During administration of 400 mg twice daily, plasma concentrations reached are well above minimum inhibitory concentration (MIC) values of pathogens that are frequently isolated in lower respiratory tract infections. This study shows that lomefloxacin in a twice daily dose of 400 mg does not effect theophylline metabolism. Lomefloxacin and theophylline can be coadministered without concern about effects of lomefloxacin on theophylline pharmacokinetics.

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Lomefloxacin (SC-47111) is a recently developed broad-spectrum antibacterial agent, belonging to the fluoroquinolone class. The in vitro activity of lomefloxacin against Gram-positive and Gram-negative bacteria is comparable to the activity of ofloxacin.1 A clinically important interaction with the bronchodilator theophylline has been demonstrated for the quinolone derivatives enoxacin,24 ciprofloxacin,43 per-

floxacin,4 and pipemidic acid.3,7 These compounds decrease liver microsomal N-demethylation of theophylline, resulting in increased plasma theophylline concentrations.6,9 Because of the clinical importance of this interaction, it is necessary to study all fluoro-

quinolones with respect to an effect on theophylline pharmacokinetics.

This study was aimed at evaluating a potential effect of lomefloxacin at steady state on the pharmacokinetics of theophylline. For reason of completeness, not only plasma pharmacokinetics of theophylline were stud-

ied, but also the different metabolic pathways of theophylline, as reflected by the renal excretion of the three major metabolites: 1, 3-dimethyluric acid (1,3-DMU), 1-methyluric acid (1-MU), and 3-methylxan-

thine (3-MX).

METHODS AND MATERIALS

Subjects

Eight healthy subjects, seven men and one woman, aged 24 to 37 years (mean age, 28.9 ± 4.0 years) gave their written informed consent to be included in this study, which had the approval of the Hospital Ethics Committee. Prior to the study, all volunteers had a baseline evaluation, including medical history, physical examination, and laboratory evaluation. For all subjects, renal and liver function test results were within normal ranges. None of them used medications. Three days prior to the start of the trial and during the entire study period, all subjects abstained from xanthine-containing food and alcoholic beverages. All volunteers were nonsmokers. Adverse reactions occurring during the measurement periods were registered by the volunteers in a diary.

Drugs

Theophylline solutions were prepared by the pharmacy of the Deventer Hospitals. Theophylline, 6 mg/kg of body weight, was dissolved in 100 ml of 0.9 percent NaCl, immediately before administration.

Lomefloxacin capsules, containing 200 mg of lomefloxacin, were obtained (Searle Nederland B.V., Maarsen, The Netherlands). Two capsules were ingested twice daily at 9 AM and 9 PM for a six-day period (800 mg/day).

*From the Department of Pulmonary Diseases, Foundation of Deventer Hospitals, Deventer, The Netherlands (Drs. Wijnands and Cornel), and the Department of Clinical Pharmacy, St Radboud Hospital, University of Nijmegen, Nijmegen, The Netherlands (Drs. Martea and Vree).

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Reprint requests: Dr. Wijnands, PO Box 50-01, 7400 GC Deventer, The Netherlands

HPLC = high-pressure liquid chromatography; 3-MX = 3-
methylxanthine; 1-MU = 1-methyluric acid; 1,3-DMU = 1,3-
dimethyluric acid; Cmax = maximum concentration; T1/2 = time to Cmax; Ctrough = trough concentration; AUC(0-∞) = area under the plasma concentration time curve from 0 to infinity; T1/2 = elimination half-life; Cl = total body clearance = dose/

AUC; Clrenal = renal clearance = mg excreted/AUC; k10 = elimination rate constant = 0.693/T1/2; Vd = volume of distribution = Cl/k10.
Sampling Procedure

The study had a parallel nonrandomized design. The pharmacokinetics of theophylline were assessed after a single intravenous (IV) theophylline dose, when the drug was administered alone, and seven days later, during comedication with lomefloxacin, 400 mg twice daily (bid). Lomefloxacin therapy was started 72 hours prior to theophylline infusion and continued until 72 hours after theophylline infusion to ensure the presence of lomefloxacin in the blood at steady-state concentrations during the whole period (72 hours) in which the urinary excretion of theophylline and its metabolites were measured.

During the period in which lomefloxacin was administered, the sampling protocol was as described above. Lomefloxacin was administered in an oral 400-mg dose at 9 AM and 9 PM for a six-day period. At day 3 of lomefloxacin administration, theophylline was infused IV as described below. Lomefloxacin renal excretion was measured to prove that lomefloxacin was present during the whole sampling period in sufficiently high and stable concentrations.

At day 1 of the first study period, at 8:30 AM, an indwelling cannula was inserted in a forearm vein. Prior to theophylline administration, a blood and a urine sample were taken to check for the presence of xanthines. At 9 AM, a single 6 mg/kg body weight theophylline dose was infused IV in 20 minutes. After the infusion, the cannula was removed. Blood samples were taken at 0, 1, 2, 6, 8, 10, 12, 24, and 24.5 hours after the completion of theophylline infusion. Plasma was separated immediately by centrifugation. Spontaneously voided urine was collected until 72 hours after theophylline infusion. Plasma and urine samples were kept at -18°C pending analysis.

Analytic Methods

Theophylline and its metabolites were measured by a high-pressure liquid chromatography (HPLC) method.10

Precision: Duplicate assays were performed in 20 percent of all plasma and urine samples (three urine samples of each volunteer in both study periods; n = 48). In urine, the precision is as follows: for theophylline, 2.82 ± 0.06 percent (SD); for 1, 3-MU, 2.74 ± 0.61 percent; for 1-MU, 2.92 ± 1.67 percent; and for 3-MX, 3.47 ± 0.02 percent. In plasma, the precision is as follows: for theophylline, 1.85 ± 1.52 percent; for 1, 3-MU, 3.85 ± 2.87 percent; for 1-MU, 4.75 ± 3.37 percent; and for 3-MX, 3.85 ± 2.87 percent.

Lomefloxacin Concentrations in Plasma and Urine Were Measured by HPLC: A Spectra Physics high performance liquid chromatograph 3500 B was used, equipped with a Kratos 703 UV spectrophotometric detector. The column was Spherisorb 5 ODS 100 mm × 4.6 mm ID (Chrompack, Middelburg, The Netherlands) with a guard column 10 mm × 4.6 mm 10 μM. The mobile phase was a mixture of 300 ml of dimethylformamide, 300 ml of acetonitrile, 500 ml of water, and 25 ml of a cocktail of 36 g of orthophosphoric acid and 10 g of tetramethylammonium chloride in 1 L of water. The flow rate was 1.2 ml/min. Detection was achieved at 285 nm. The detection limit for lomefloxacin in plasma was 0.1 mg/L and in urine it was 0.5 mg/L. The capacity factor of lomefloxacin is 3.20.

Sample Preparation: Plasma: Plasma, 100 μl, was vortexed with 400 μl of 5 percent trichloroacetic acid and centrifuged for 5 minutes at 11,000 g. Supernatant, 100 μl, was injected onto the column. A calibration curve was constructed (r = .9999 in the

-18°C pending analysis.

![Graph](http://journal.publications.chest.net/pdfaccess.ashx?url=/data/journals/chest/21622/)

**Figure 1.** The plasma concentration time curve and the renal excretion rate profile of theophylline (T) and its metabolites 1, 3-dimethyluric acid (1, 3-MU), 3-methylxanthine (3-MX), and 1-methyluric acid (1-MU) for one subject after an intravenous 6.0 mg/kg of body weight theophylline dose.
concentration range 0.6 to 6 mg/L. Precision was 1.4 percent (n = 6) and accuracy was 2.03 ± 1.68 percent (n = 16). Urine: Urine, 100 µL was diluted 100 times with the mobile phase, and 100 µL was injected onto the column. A calibration curve was constructed (r = .9999) in the concentration range 30 to 1,200 mg/L. Precision was 1.29 percent (n = 6) and accuracy was 2.87 ± 2.26 percent (n = 16).

**Protein Binding**

The protein binding of theophylline and its metabolites was measured by the "Amicon" micropartition system-1 (Amicon, Danvers, Mass).

**Pharmacokinetics**

AUC \( \text{inf} \) was calculated with the trapezoidal rule, with \( T = 0 \) at the start of the infusion. Ti/2 was calculated by semilogarithmic regression of the elimination phase. Total body clearance (CI) = dose/AUC. Renal clearance (CLR) = milligram of excreted/AUC. Volume of distribution (Vd) = CI/\( k_a = 0.693/Ti/2 \).

**Statistical Calculations**

Statistical calculations were carried out using a statistic package (SAS Institute Inc, Cary, NC), providing Wilcoxon test for paired observations. The pharmacokinetic parameters of theophylline obtained during lomefloxacin comedication were compared with those acquired when theophylline was administered alone. Results are expressed as mean values ± SD. Differences were considered significant at the \( p < 0.05 \) level.

**RESULTS**

**Theophylline**

As an example of the individual data, Figures 1 and 2 show the plasma concentration time curves and the renal excretion rate time profiles of theophylline and its metabolites 1, 3-MU, 3-MX, and 1-MU for one subject after an IV 6.0 mg/kg body weight theophylline dose, with and without concomitant lomefloxacin administration. Table 1 summarizes the mean pharmacokinetic parameters of theophylline when administered alone and during comedication of lomefloxacin. The AUC values and the elimination half-life of theophylline were not affected by concomitant lomefloxacin administration. The plasma concentrations of the metabolites were low and showed elimination phases similar to those of the parent drug. The Vd of theophylline was not affected by lomefloxacin. No change in protein binding of theophylline occurred. Plasma albumin concentration was the same in the two study periods (50.9 ± 3.2 and 50.1 ± 4.0 g/L⁻¹, respectively). Total body clearance of theophylline was

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**Figure 2.** The theophylline plasma concentration time curve of theophylline (T) and the renal excretion rate time profiles of both lomefloxacin (L) and theophylline with its metabolites 1, 3-dimethyluric acid (1, 3-MU), 3-methylxanthine (3-MX), and 1-methyluric acid (1-MU) for one subject after an intravenous 6.0 mg/kg of body weight theophylline dose, during lomefloxacin coadministration.
not affected by concomitant lomefloxacin administration (p = 0.688). Renal clearance of theophylline was not affected by lomefloxacin (p = 0.625).

Table 2 summarizes the renal excretion of theophylline and its metabolites for both study periods for 72 hours after administration, expressed as percentage of the administered theophylline dose. In both periods, about 90 percent of the administered theophylline dose was recovered in the urine. Comparing the excretion of theophylline and the metabolites with and without lomefloxacin comedication showed no significant differences.

Lomefloxacin

The pharmacokinetic parameters of lomefloxacin after five dosages are summarized in Table 3. After oral administration of lomefloxacin 400 mg bid, a mean peak plasma concentration of 3.9 mg/L was reached after 1.7 hours. The decline of the plasma concentration time curve is represented by a T½ of 9.0 hours. The protein binding of lomefloxacin appeared to be negligible. Over 155 hours, more than 70 percent of the total administered dose was excreted unchanged in the urine. Lomefloxacin is mainly eliminated by renal excretion. The high renal clearance of 177 ml/min indicates that the drug is excreted both by glomerular filtration and active tubular secretion.

**Adverse Reactions**

Seven volunteers complained of nervousness and had a tremor after theophylline infusion; these reactions were the same in both study periods. The reactions, which disappeared completely within two hours after the end of theophylline infusion, were clearly related to quick increase in theophylline plasma concentrations. One volunteer had development of a mild headache at day 2 of lomefloxacin medication. This reaction disappeared spontaneously during continued lomefloxacin administration.

**Discussion**

Fluoroquinolones will influence the metabolic clearance of theophylline to a variable extent. Enoxacin reduces total body clearance of theophylline over 60 percent, whereas ciprofloxacin and peflouxacin have been shown to decrease theophylline clearance about 30 percent. Recently, Staib and coworkers demonstrated a similar effect by pipemidic acid. The effect results from a decreased N-demethylation of theophylline.

This study demonstrates that three days pretreatment with lomefloxacin, 400 mg bid, does not influence theophylline metabolism, when administered to healthy volunteers. The duration of pretreatment with lomefloxacin can be considered to be long enough since a highly significant effect on theophylline elimination has been demonstrated to occur at day 2 of comedication with enoxacin and at day 3 of comedication with ciprofloxacin and peflouxacin. In 1986, the hypothesis was raised that not the parent quinolones, but one of the metabolites, the 3'-oxo-quinolone, interacts with theophylline N-demethylation. This 3'-oxo-metabolite is formed from enoxacin, ciprofloxacin, peflouxacin, and pipemidic acid, but not from nalidixic acid and ofloxacin. No interaction with theophylline was measured when nalidixic acid or ofloxacin was coadministered. In lomefloxacin, the 3'-oxo-metabolite is not formed because of methylsubstitution at the 3' position. The fact that lomefloxacin lacks an interaction with xanthine metabolism seems to provide

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**Table 1 — Some Pharmacokinetic Parameters of Theophylline after a Single 6 mg/kg Intravenous Dose When Administered Alone and during Comedication with Lomefloxacin (n = 8; mean ± SD)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Theophylline</th>
<th>Lomefloxacin + Theophylline</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T½, h</td>
<td>6.0 ± 1.6</td>
<td>6.2 ± 2.1</td>
<td>0.672</td>
</tr>
<tr>
<td>AUC∞-∞, (mg·h·L⁻¹)</td>
<td>96.9 ± 35.5</td>
<td>98.5 ± 32.0</td>
<td>0.641</td>
</tr>
<tr>
<td>Vd, L·kg⁻¹</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.297</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>61.4 ± 4.0</td>
<td>63.1 ± 7.8</td>
<td>0.183</td>
</tr>
<tr>
<td>Cl, L·h⁻¹</td>
<td>4.4 ± 1.4</td>
<td>4.7 ± 1.1</td>
<td>0.688</td>
</tr>
<tr>
<td>Clr, ml/min</td>
<td>6.7 ± 2.2</td>
<td>7.8 ± 3.0</td>
<td>0.625</td>
</tr>
</tbody>
</table>

*Abbreviations are explained in text.

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**Table 2 — Renal Excretion of Theophylline and Its Metabolites after a Single 6 mg/kg of Body Weight Intravenous Dose, When Administered Alone and during Comedication with Lomefloxacin (Percentage Theophylline Dose Excreted) (n = 8; mean ± SD)**

<table>
<thead>
<tr>
<th>Theophylline</th>
<th>Theophylline + Lomefloxacin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>9.5 ± 1.7</td>
<td>9.7 ± 2.7</td>
</tr>
<tr>
<td>1, 3-dimethyluric acid</td>
<td>36.0 ± 4.6</td>
<td>33.3 ± 6.4</td>
</tr>
<tr>
<td>1-methyluric acid</td>
<td>27.3 ± 4.1</td>
<td>25.9 ± 4.7</td>
</tr>
<tr>
<td>3-methylxanthine</td>
<td>19.7 ± 3.7</td>
<td>22.2 ± 2.3</td>
</tr>
<tr>
<td>Total excreted</td>
<td>92.5 ± 6.2</td>
<td>90.2 ± 12.5</td>
</tr>
</tbody>
</table>

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**Table 3 — Some Steady-State Pharmacokinetic Parameters of Lomefloxacin, When Administered 400 mg Twice Daily for 6 Days (n = 8; mean ± SD)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀, mg·L⁻¹</td>
<td>3.9 ± 0.9</td>
</tr>
<tr>
<td>Tₘ, h</td>
<td>1.7 ± 0.4</td>
</tr>
<tr>
<td>C₀, mg·L⁻¹</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>T½, h</td>
<td>9.0 ± 3.7</td>
</tr>
<tr>
<td>AUC₀-∞, mg·h·L⁻¹</td>
<td>27.7 ± 6.9</td>
</tr>
<tr>
<td>Vₘ, L·kg⁻¹</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>Cl, L·h⁻¹</td>
<td>9.4 ± 3.3</td>
</tr>
<tr>
<td>Clᵅ, ml·min⁻¹</td>
<td>177 ± 32</td>
</tr>
<tr>
<td>Urinary excretion, %</td>
<td>72.0 ± 10.2</td>
</tr>
</tbody>
</table>

*Vₘ and Cl are calculated with dose 400 mg (administered over a period of 12 h, and assuming 100 percent absorption). Cl = dose/AUC₀-∞. Other abbreviations are explained in text.
further evidence for the above-mentioned hypothesis. Pipemidic acid shows an inhibition of theophylline metabolism that is comparable to that of enoxacin. In pipemidic acid, the 3'oxo-metabolite is the main metabolite found in the urine. Enoxacin and pipemidic acid have an alternating N-C=N-C-N-C moiety of the naphthyridine ring in common. Harder and coworkers suggested this sequence to be responsible for the influence on the N-demethylation of the methylxanthine metabolism. However, ciprofloxacin and pefloxacin lack this moiety, and they do interact with methylxanthines. The urine recovery data in this study show that orally administered lomefloxacin is absorbed very well from the intestinal tract. Using the same lomefloxacin dose (400 mg bid), higher steady-state peak plasma concentrations have been reported. The lower peak plasma concentration of lomefloxacin in this study may be a result of the diuretic action of theophylline. The long elimination half-life permits once or twice daily dosing of the drug.

Theophylline is prescribed frequently in patients with exacerbated chronic obstructive lung disease, a clinical condition in which lower respiratory tract infections occur recurrently. The fluoroquinolones are effective in these kinds of infections. Because of the small therapeutically range of theophylline and the risk of theophylline toxicity, fluoroquinolones that interact with theophylline metabolism should preferably be avoided in these clinical situations. Because of the absence of an interaction between lomefloxacin and theophylline, both drugs can be coadministered safely without precautions.

REFERENCES
5 Raoof S, Wollschläger C, Khan F. Serum theophylline levels are increased by ciprofloxacin (Bay 9867), a new quinolone antibiotic. Chest 1985; 88:32-8