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NOTES

Influence of Lomefloxacin on the Pharmacokinetics of Theophylline

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The effect of multiple doses of lomefloxacin (400 mg twice a day) on the clearance of theophylline and the urinary excretion of its metabolites was investigated in 15 healthy male subjects. Concentrations of theophylline in plasma were measured by TDx (Abbott Diagnostics, Mississauga, Ontario, Canada). Urinary excretion of theophylline and its three major metabolites and lomefloxacin in plasma were assayed by high-performance liquid chromatography. Total theophylline clearance remained unchanged before lomefloxacin treatment and after lomefloxacin single- and multiple-dose treatments (58.02, 56.57, 54.07 ml/min, respectively). The urinary recovery of unchanged theophylline and its major metabolites stayed stable during the study. We conclude that lomefloxacin can be added to the list of fluoroquinolones that can be administered safely with theophylline.

Certain quinolones (enoxacin, pipemidic acid, ciprofloxacin, pefloxacin, and norfloxacin) have demonstrated the ability to inhibit drug metabolism (3; M. Parent and M. LeBel, submitted for publication). Other compounds, such as ofloxacin, nalidixic acid, and fleroxacin, appear to have little or no effect (3, 6). The potential for quinolones to interact with drugs such as theophylline and cause unwanted side effects becomes an important aspect in selection among this class of drugs.

The primary objective of this study was to characterize the influence of lomefloxacin in single and multiple doses on theophylline total clearance (CL) in healthy, nonsmoking volunteers. A secondary objective was to characterize the potential influence of lomefloxacin in single and multiple doses on theophylline metabolic pathways.

Eighteen young male volunteers (mean age, 23.4 years; range, 20 to 27 years; mean weight, 74.2 ± 8.9 kg) gave their written consent to participate in the study. The protocol was approved by the Centre Hospitalier de l'Université Laval Human Research review committee. Five subjects could not complete the study because of gastrointestinal side effects during week 1 of theophylline treatment. All were determined to be healthy on the basis of medical history, complete physical examination, and normal laboratory baseline values for hematology, blood chemistry, and urinalysis. The research subjects were nonsmokers, were not taking drugs or abusing alcohol, and agreed to be kept on a xanthine- and alcohol-free diet throughout the study starting 48 h prior to the first theophylline dose. They did not have any history of seizures and they had not had an influenza vaccination in the 5 days before the study nor any acute upper respiratory tract infection in the 2 weeks preceding the study. Volunteers were asked to present to the research unit after an overnight fast. The morning of the first day, a test dose (3 mg/kg of actual body weight) of an oral solution of theophylline (Quibron T [10 mg/ml]; kindly provided by Bristol Myers Pharmaceutical, Ottawa, Canada) was given. Food was allowed 2 h after the dose. Blood samples were obtained at time zero and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, and 36 h after administration of theophylline, and urine was collected over the following intervals: 0, 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 16, 16 to 24, and 24 to 36 h after administration. The time-zero collection of urine allowed complete bladder emptying and provided a blank urine sample for analysis. Urine volume and pH were measured and recorded. Blood was collected in 7-ml collecting with red stoppers (VACUTAINER; Becton Dickinson Vacutainer Systems, Rutherford, N.J.).

Apparent clearance values for theophylline calculated from plasma data were used to determine the maintenance dose of oral theophylline. The dose was selected to aim for an average steady-state theophylline concentration of 10 ± 4 μg/ml, according to the following equation: dose = $C_{p_{22}} \times CL \times \tau/F$, where $C_{p_{ss}}$ (the average steady-state concentration in plasma) is 10 μg/ml, CL is dose/$AUC_{0-\infty}$ (area under the theophylline concentration-time curve from time zero to infinity), τ is the dosing interval (8 h), and F is the fraction of drug reaching systemic circulation (1.0 assumed). After a 1-week washout, from day 3 (of the protocol) until day 15, subjects had to take individualized doses of the theophylline oral solution in a unit dose vial to ensure exact dosage and compliance at 8 a.m., 4 p.m., and 12 a.m. (midnight). Each dose had to be taken on an empty stomach, 1 h before or 2 h after food. Beginning 0.5 h before the theophylline dose on day 9, and then twice daily at 7:30 a.m. and 7:30 p.m. throughout day 15, 400 mg of lomefloxacin as two 200-mg capsules (Searle Canada, Oakville, Ontario) was taken, preceded and followed by 200 ml of fresh water.

Blood and urine were sampled on day 8 for the determination of steady-state theophylline CL and on day 9 for the determination of theophylline CL after a single dose of lomefloxacin. Blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, and 8 h, and urine samples were collected over the following intervals: 0, 0 to 2, 2 to 4, 4 to 6, and 6 to 8 h. Blood and urine were again sampled on day 15 over 8 h for determination of theophylline CL once lomefloxacin steady state was attained.

During the study, subjects were asked to complete a diary, paying particular attention to the administration time of theophylline and lomefloxacin doses, dose omissions, and

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dietary deviations. In addition, the volunteers were closely questioned about adverse effects during the study.

Blood samples obtained through an indwelling venous catheter placed in the antecubital vein and maintained patent with heparin (33 U/ml) were kept on crushed ice for a maximum of 20 min before centrifugation at 1,000 × *g* for 20 min at 4°C. Plasma was then transferred within 5 h of collection in polypropylene tubes and stored at 4°C until assayed.

Theophylline levels were assayed by a polarized immunofluorescence radioassay (TDx; Abbott Diagnostics, Mississauga, Ontario, Canada). This method has been shown to be both reproducible and accurate: intraday coefficients of variation ranged from 1.3% for high concentrations (26 μg/ml) to 2.0% for low concentrations (7.0 μg/ml). Interday coefficients of variation were 2.0% at 26 μg/ml and 2.8% at 7 μg/ml. The limit of sensitivity was 0.05 μg/ml, with a 95% confidence interval. Lomefloxacin did not interfere with the assay. For theophylline and its metabolites in urine, we adapted the reversed-phase high-performance liquid chromatography method of Kester et al. (4). The technique was designed to simultaneously determine the concentrations of theophylline, 1,3-dimethyluric acid (1,3-DMU), 3-methylxanthine (3-MX), and 1-methyluric acid (1-MU) by using β-hydroxyethyltheophylline as an internal standard. Essentially, 300 μl of the internal standard was added to 1.2 ml of urine diluted 1:2 to 1:10 with acetate buffer (approximate pH, 4.5). Fifty microliters was injected with a WISP autoinjector into a Novapak C_{18} column (Waters Scientific, Mississauga, Ontario, Canada). The mobile phase consisted of 98% sodium acetate buffer–tetrabutylammonium phosphate–2% acetonitrile, this solution being adjusted to pH 4.5 with glacial acetic acid. The flow rate was set to 1 ml/min to optimize column efficiency. A LambdaMax UV detector (Waters) was set to 280 nm. Chromatograms were recorded on a model 745B integrator (Waters). This method showed excellent linearity ($r > 0.999$) between 0.2 to 200 μg/ml. Interday coefficients of variation of 6.4, 7.7, 8.4, and 4.6% were calculated for theophylline, 1,3-DMU, 1-MU, and 3-MX, respectively. Recovery of these four compounds varied from 72 to 86%, and the sensitivity limit was 0.2 μg/ml. Lomefloxacin was shown not to interfere with the method.

Concentrations of lomefloxacin in plasma were measured by a reversed-phase ion-pairing high-performance liquid chromatographic assay. The chromatographic system (Waters) was coupled with a fluorescence detector set at 280 and 455 nm as excitation and emission wavelengths, respectively. Separation of lomefloxacin and pipemidic acid (the internal standard) was performed with a C_{18} Novapak column at a flow rate of 1 ml/min. The sensitivity limit of the assay was 0.01 mg/ml. The mean recovery was 96.3%. The coefficients of variation for the interday specimens were less than 6.3%. Linear regression analysis yielded a correlation coefficient always >0.99, indicating excellent linearity of the assay. The plasma samples assayed for lomefloxacin were kept in their polypropylene tubes (to minimize light degradation) at −20°C.

Individual theophylline levels in serum were best described by a biexponential equation on the basis of visual inspection: $C = Ae^{-k_{el}t} - Ae^{-k_a t}$, where A is the concentration coefficient of both elimination and absorption phases and k_{el} and k_a correspond to elimination and absorption constants, respectively. An iterative polyexponential curve stripping technique was used (2). AUCs were derived from concentrations in serum from time zero to 8 h (days 8, 9, and 15) by the linear trapezoidal method and from 8 h to infinity by extrapolation (day 1, single test dose).

TABLE 1. Theophylline pharmacokinetic parameters on days 8 (steady-state theophylline), 9 (single-dose lomefloxacin), and 15 (steady-state lomefloxacin)[a]

Day	CL (ml/min)	C_{ss} (μg/ml)	AUC (μg · h/ml)	$t_{1/2}$ (h)
8	58.02 ± 16.59	14.14 ± 2.71	113.1 ± 21.7	7.0 ± 1.6
9	56.57 ± 14.32	14.32 ± 3.30	116.1 ± 26.4	7.1 ± 1.6
15	54.07 ± 16.28	15.34 ± 3.77	122.8 ± 30.2	7.5 ± 1.7

[a] Means ± standard deviation (15 subjects). C_{ss}, Average concentration; $t_{1/2}$, elimination half-life.

Theophylline CL was estimated from the model-independent pharmacokinetics equation CL = dose/$AUC_{0-\tau}$, where τ = 8 h). The bioavailability (F) of theophylline was assumed to be 1.

The differences observed between baseline pharmacokinetic parameters (day 8) and those obtained after a single dose of lomefloxacin (day 9) or multiple doses of lomefloxacin (day 15) were compared by the paired, two-tailed, Student *t* test. A probability value of <0.05 was considered significant.

This study showed the lack of influence of lomefloxacin on the pharmacokinetics of theophylline, as exemplified by similar CL values on day 8 (steady-state theophylline, baseline), day 9 (after one dose of lomefloxacin), and day 15 (steady-state lomefloxacin): 58.02, 56.57, and 54.07 ml/min, respectively (Table 1). No statistically significant differences in the half-life, AUC, peak concentration (C_{max}), and average concentration of theophylline in serum were observed between day 8 and day 9 or day 15 (Table 1). The mean theophylline C_{ss} average was 14.4 μg/ml, with only six subjects having values inside the targeted range, 10 ± 4 μg/ml. The average daily dose required to achieve these concentrations was 15.5 mg/kg.

TABLE 2. Urinary recovery of unchanged theophylline and its metabolites[a]

Day	Treatment	% Urinary excretion	Molar fraction (mM)
1	3-MX	11.0 ± 2.5	0.15 ± 0.05
	1-MU	18.6 ± 4.9	0.23 ± 0.08
	1,3-DMU	34.0 ± 4.9	0.39 ± 0.10
	Theophylline	10.8 ± 2.1	0.13 ± 0.03
	Total	74.4 ± 10.1	0.90 ± 0.22
8	3-MX	11.8 ± 3.3	0.27 ± 0.07
	1-MU	18.0 ± 4.6	0.37 ± 0.10
	1,3-DMU	37.2 ± 7.0	0.71 ± 0.13
	Theophylline	15.7 ± 4.5	0.32 ± 0.10
	Total	82.7 ± 15.2	1.67 ± 0.32
9	3-MX	11.3 ± 2.7	0.26 ± 0.08
	1-MU	18.2 ± 4.3	0.38 ± 0.11
	1,3-DMU	39.6 ± 6.6	0.77 ± 0.19
	Theophylline	15.8 ± 4.6	0.33 ± 0.10
	Total	84.9 ± 11.9	1.74 ± 0.38
15	3-MX	11.1 ± 1.7	0.25 ± 0.06
	1-MU	15.4 ± 3.1	0.30 ± 0.11
	1,3-DMU	38.6 ± 4.0	0.74 ± 0.16
	Theophylline	14.4 ± 4.0	0.30 ± 0.09
	Total	79.4 ± 7.4	1.59 ± 0.31

[a] Means ± standard deviation (15 subjects).

TABLE 3. Adverse effects probably related to study drugs

Subject no.	Side effect(s) after treatment with:	
	Theophylline	Theophylline + lomefloxacin
1	Nausea	Nausea
2	Insomnia	Headache,[b] jitters
3[a]	Nausea, tremor, stomach upset	
4	Insomnia, stomach upset	
5[a]	Flulike syndrome (nausea, vomiting, fever, etc.)	
6	Myalgia, insomnia, tremor	Nausea, tremor
7		Photosensitivity[b]
8	Vomiting	
9		Jitters
10	Headache	
11	Insomnia	
12[a]	Nausea, vomiting	
13	Nausea, vomiting	Nausea, headache[b]
14	Nausea, stomach upset	Headache[b]
15	Insomnia	
16	Headache	Headache,[b] nausea[b]
17[a]	Tachycardia, insomnia	
18[a]	Tachycardia, insomnia, nausea	

[a] Subject withdrew because of adverse experiences.
[b] Side effect(s) more related to lomefloxacin than to theophylline, according to the time sequence and nature of the side effect.

The pattern of urinary excretion of unchanged theophylline and its major metabolites 3-MX, 1-MU, and 1,3-DMU is shown in Table 2. The amount recovered in urine was expressed as the molar fraction of theophylline and its three major metabolites remained fairly stable before administration (day 8), after one dose (day 9), and after 15 doses (day 15) of lomefloxacin (400 mg twice a day).

The concentration of lomefloxacin in plasma at 0.5 and 12 h after the last dose were 4.79 ± 0.97 and 1.35 ± 0.44 μg/ml, respectively.

Table 3 shows reported adverse drug reactions probably related to drugs used in this study. The side effects characteristic of theophylline included nausea, insomnia, gastrointestinal upset, and headache. Subjects tended to develop tolerance to these side effects, since they occurred less frequently in the second half of the study when theophylline steady state was reached. Table 3 also indicates the side effects probably related to lomefloxacin. Four episodes of headache, one of nausea, and one of photosensitivity were linked to lomefloxacin intake.

The inability to meet the targeted theophylline concentration (C_{ss}) underscores the large variability of theophylline CL and the lack of precision in using a single test dose to predict steady-state theophylline pharmacokinetics in individuals who have not used theophylline. The subjects receiving multiple doses of lomefloxacin were in the upper portion of the theophylline therapeutic range (10 to 20 μg/ml), a situation that is still clinically relevant for an interaction study. This situation, however, predisposed the subjects to side effects related to theophylline.

The lack of effect of lomefloxacin on the disposition of theophylline found in this study is in agreement with recent reports showing similar results but using different designs (5, 7; W. J. A. Wijnands, J. H. Cornel, M. Martea, and T. B. Vree, Program Abstr. 16th Int. Congr. Chemother., abstr. no. 304, 1989; R. A. Robson and E. J. Begg, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 217, 1989). These investigators administered different lomefloxacin doses (400 mg once a day and twice a day) for different periods (3, 5, and 7 days) and demonstrated that under all conditions lomefloxacin did not inhibit theophylline metabolism.

There is evidence that the mechanism of quinolone-theophylline interaction could be twofold: inhibition of the cytochrome P-450 system and alteration of the renal clearance (1, 3). Staib et al. recently proposed that the piperazine ligand may explain the affinity of certain quinolones for a common binding site with methylxanthine (7).

We conclude that lomefloxacin can be added to the list of fluoroquinolones that can be administered safely with theophylline.

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