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Safety of Fleroxacin Coadministered with Theophylline to Young and Elderly Volunteers

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The influence of multiple doses of fleroxacin on the plasma clearance and the urinary excretion of theophylline was studied in 19 young and 18 elderly male volunteers. A theophylline dosage individualized to obtain a mean theophylline concentration in plasma of 10 ± 3 μg/ml was administered for 1 week to each subject. At week 2, oral fleroxacin (400 mg once daily) was added. Theophylline concentrations in plasma were measured with TDx (Abbott Diagnostics, Mississauga, Ontario, Canada), and urinary excretion of theophylline and its three major metabolites was measured by high-performance liquid chromatography. Total theophylline clearance remained essentially unchanged throughout the study period (3.5 and 2.9 liters/h in the young and the elderly, respectively) both after a single fleroxacin dose and after multiple doses. Although significant changes occurred in the urinary excretion of unchanged theophylline and its metabolites after a single fleroxacin dose, no changes were observed after multiple doses. Side effects consisted mainly of gastrointestinal and sleep disturbances, more related to theophylline; photosensitivity was observed in six subjects and was attributed to fleroxacin. We conclude that fleroxacin may be administered concomitantly with theophylline in either young or elderly patients. Close monitoring of theophylline concentrations in serum should be performed, particularly in patients with chronic obstructive pulmonary disease, for whom data are currently lacking.

The existence of significant drug interactions between fluoroquinolones and theophylline became evident shortly after the initiation of clinical investigations of these antibiotics (16, 32, 33). Further studies documented a wide range of effects of different fluoroquinolones on the total clearance (CL) of theophylline, ranging from a 60% decrease with enoxacin to a nonsignificant effect with ofloxacin (3, 4, 7, 9–11, 15, 18, 19, 24). Indirect evidence suggests that these results are caused by an interaction of the fluoroquinolones with the cytochrome P-450-dependent microsomal metabolism of theophylline. Besides the metabolism of methylxanthines, the metabolism of other drugs is inhibited by fluoroquinolones (antipyrine, warfarin); this inhibition may indicate that several forms of cytochrome P-450 in the liver are inhibited.

Some studies have suggested that the elderly population may be at increased risk for developing this interaction (22, 26, 34, 35). The present study was designed to evaluate the influence of fleroxacin on the steady-state CL of theophylline in normal healthy volunteers, both young and elderly.

MATERIALS AND METHODS

Nineteen young male volunteers (mean age, 23.2 years; range, 20 to 30) and 18 elderly male volunteers (mean age, 70.7 years; range, 65 to 76) gave their written consent to participate in the study. One young subject was discontinued from the study for administrative reasons, and three elderly volunteers did not complete the protocol: one because of venous access problems and two because of gastrointestinal side effects while on theophylline. All were determined to be healthy on the basis of medical history, complete physical examination, 12-lead electrocardiogram, chest X ray, and normal laboratory baseline values, including 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 aminophylline test dose.

Volunteers were asked to present to the research unit after an overnight fast. On the morning of day 1, a test dose of intravenous (i.v.) aminophylline (3 mg/kg of actual body weight) was given. This dose was administered as an i.v. perfusion over 30 min with a model 300 XL syringe-driver (Bard Medical Inc., Mississauga, Ontario, Canada). Blood samples were obtained at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, and 36 h, and urine was collected over the following intervals: 0, 0 to 2, 2 to 4, 4 to 8, 8 to 16, 16 to 24, and 24 to 36 h. Time-zero collection of urine allowed complete bladder emptying and a blank urine sample for analysis. Urine volume and pH were measured and recorded. Blood was collected in 7-ml collecting tubes with oxalate and sodium fluoride as an anticoagulant (grey stopper) (VACUTAINER; Becton Dickinson Vacutainer Systems, Rutherford, N.J.). Theophylline clearance obtained on day 1 served to determine the maintenance dosage of theophylline for each subject for the remainder of the study (12, 29). The dose was selected to aim for an average steady-state theophylline concentration of 10 ± 3 μg/ml, according to the following equation: dose = $\overline{C}_{p_{ss}} \times CL \times \tau/F$, where $\overline{C}_{p_{ss}}$ (average concentration in plasma at steady state) is 10 μg/ml, CL is dose/$AUC_{0-\infty}$ (area under the theophylline concentration-time curve [AUC] 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 the initial i.v. theophylline dose, and from day 2 until day 14, subjects received individualized doses of a theophylline oral solution (Quibron-T, 10 mg/ml; kindly provided by Bristol-Myers Pharmaceuticals, Ottawa, Ontario, Canada) in a unit-dose vial to ensure exact dose and compliance at 8 a.m., 4 p.m., and 12 midnight. Each dose had to be taken on an

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empty stomach, 1 h before or 2 h after food. Beginning 0.5 h before the theophylline dose on day 9, and daily at the same time through day 14, 400 mg of fleroxacin as two 200-mg tablets (Hoffmann-La Roche, Etobicoke, Ontario, Canada) was taken with a full glass of 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 fleroxacin. The samples were collected at 0, 0.5, 1, 2, 3, 4, 6, and 8 h for blood and over the following intervals for urine: 0, 0 to 2, 2 to 4, and 4 to 8 h. Blood and urine were again sampled on days 14 to 16 for the determination of theophylline CL once the fleroxacin steady-state was attained. During the study, subjects were asked to complete a diary, paying particular attention to the administration time of theophylline and fleroxacin doses, dose omission, and dietary deviations. In addition, the volunteers were questioned about adverse effects with open-ended questions on days 1, 8, 9, 14, and 15.

Plasma assay. Blood samples were obtained through an indwelling venous catheter placed in the antecubital vein and maintained patent with heparin (33 U/ml). All samples 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 transferred into polypropylene tubes and stored at 4°C until assayed within 5 h of collection.

Assays for theophylline were done by a polarized immunofluorescence radioassay (TDx; Abbott Diagnostics, Mississauga, Ontario, Canada). This method has been shown to be both reproducible and accurate (14, 20, 25). We obtained a coefficient of variation ranging from 1.4% for high concentrations (25 μg/ml) to 7.6% for low concentrations (1.25 μg/ml). Interday coefficients of variations were 2.0% at 26 μg/ml and 2.8% at 7 μg/ml. The limit of sensitivity was 0.51 μg/ml, with a 95% confidence interval. Fleroxacin did not interfere with the assay.

Unchanged fleroxacin was also measured in the plasma samples only of the elderly group after the last fleroxacin dose by a high-performance liquid chromatography method previously described (21). The sensitivity limit of the assay was 0.01 μg/ml. The coefficient of variation from day to day was <4.4%. Linear regression analysis of the standard calibration lines yielded a correlation coefficient of >0.999, indicating excellent linearity of the assay.

Urine assay. The reversed-phase high-performance liquid chromatography method of Kester et al. (13) for theophylline and its major metabolites was used. 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) with β-hydroxyethyltheophylline as an internal standard. Three-hundred microliters of the internal standard was added to 1.2 ml of urine diluted 1:2 to 1:10 with acetate buffer (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% water–2% methanol–tetrabutylammonium phosphate, this solution being adjusted to pH 4.5 with glacial acetic acid. The flow rate was set to 1 ml/min. A LambdaMax UV detector (Waters) was set to 280 nm. Chromatograms were recorded on a model 701 integrator (Waters).

This method showed good linearity, with a correlation coefficient of >0.99. Interday coefficients of variation of 2.25, 9.9, 18.0, and 15.1% were noted for theophylline, 1,3-DMU, 1-MU, and 3-MX, respectively. Fleroxacin was shown not to interfere with the method.

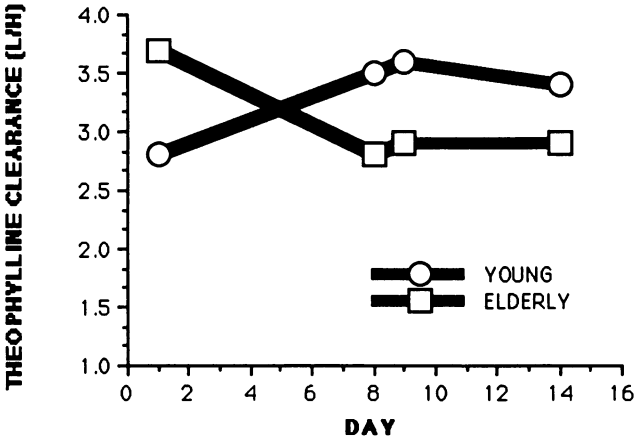

FIG. 1. Mean theophylline CL (liters per hour) in young and elderly subjects.

Pharmacokinetic analysis. Pharmacokinetic analysis was performed with a noncompartmental method. AUCs were derived from concentrations in plasma from time zero to 8 h by the linear trapezoidal method and from 8 h to infinity by extrapolation when required. The terminal elimination rate constant was estimated from the slope of a least-squares linear regression of the linear portion of the curve of the logarithm of the concentration-time curve. CL was obtained from the equation CL = dose/AUC_{0-t}, where t is infinity on day 1 and 8 h on days 8, 9, and 14. Volume of distribution was obtained from the relationship $V = CL/k_{el}$, where k_{el} is the elimination rate constant.

Statistics. The differences observed between baseline pharmacokinetic parameters (day 8) and those obtained after a single dose of fleroxacin (day 9) or multiple doses of fleroxacin (day 14) were evaluated by a paired, two-tailed Student t test. A probability of <0.05 was considered significant.

RESULTS

This study showed the lack of influence of fleroxacin on the pharmacokinetics of theophylline. In young subjects, this was exemplified by the similar values of theophylline CL on day 8 (steady-state theophylline, baseline), day 9 (after one dose of fleroxacin), and day 14 (steady-state fleroxacin): 3.5, 3.6, and 3.4 liters/h, respectively (Fig. 1). Additionally, theophylline CL values in elderly subjects remained essentially unchanged throughout the study period (2.8, 2.9, and 2.9 liters/h on days 8, 9, and 14, respectively) (Fig. 1). Figure 1 shows also the different patterns of theophylline CL in young versus elderly subjects from day 1 (single i.v. aminophylline dose) to days 8, 9, and 14 (multiple oral theophylline doses).

Other theophylline pharmacokinetic parameters are displayed in Table 1. The targeted average theophylline steady-state concentration (10 ± 3 μg/ml) was achieved on day 8 in all young volunteers but in only five elderly volunteers (Table 1). The average daily doses required to achieve these concentrations were 11.0 and 12.2 mg/kg per day in young and elderly subjects, respectively. Elderly volunteers had higher AUC than did young volunteers (96.6 to 117.3 versus 76.4 to 82.6 μg · h/ml, respectively). When compared with the baseline (day 8), the theophylline half-life was longer in both young and elderly volunteers on day 9 ($P < 0.05$). Similarly, the volume of distribution was increased by 18%

TABLE 1. Pharmacokinetic parameters of theophylline[a]

Group	Day	CL (liters/h)	$\overline{C}_{Pss}$ (μg/ml)	AUC (μg · h/ml)	$t_{1/2}$ (h)	V (liters)
Young	8	3.5 ± 0.7	10.3 ± 2.0	82.0 ± 15.7	7.6 ± 1.6	0.51 ± 0.13
	9	3.6 ± 0.8	9.6 ± 1.9	76.4 ± 15.3[b]	8.4 ± 2.0[b]	0.60 ± 0.16[b]
	14	3.4 ± 0.7	10.3 ± 2.1	82.6 ± 16.4	8.0 ± 1.5	0.53 ± 0.08
Elderly	8	2.8 ± 0.9	14.6 ± 3.6	117.3 ± 30.5	8.9 ± 1.8	0.46 ± 0.11
	9	2.9 ± 0.8	13.6 ± 2.1	109.1 ± 17.0	10.3 ± 2.2[b]	0.57 ± 0.18[b]
	14	2.9 ± 1.2	12.1 ± 4.2	96.6 ± 33.3	8.0 ± 2.4	0.48 ± 0.19
All subjects	8	3.2 ± 0.9	11.8 ± 3.8	96.2 ± 27.0	8.2 ± 1.8	0.49 ± 0.12
	9	3.3 ± 0.8	11.3 ± 2.8	89.6 ± 21.6[b]	9.2 ± 2.3[b]	0.59 ± 0.16[b]
	14	3.2 ± 0.8	11.4 ± 2.5	91.2 ± 19.8	8.0 ± 2.0	0.50 ± 0.14

[a] $\overline{C}_{Pss}$, Average concentration in plasma at steady state; $t_{1/2}$, half-life; V, volume of distribution.
[b] $P < 0.05$ (paired t test), as compared with the baseline on day 8.

on day 9 from 0.51 to 0.60 liters/kg in young subjects and from 0.46 to 0.57 liters/kg in elderly subjects ($P < 0.05$).

Table 2 displays the mean percent urinary excretion of theophylline and its metabolites. In both groups, there was an initial increase in the percentage of unchanged theophylline excreted in the urine after the first dose of fleroxacin (day 9). This change was compensated for by significant decreases in the excretion of 1,3-DMU and 1-MU. On day 14, the percentage of theophylline eliminated unchanged returned to the baseline in both groups.

The mean maximum level of fleroxacin in the elderly group was 8.5 ± 1.4 μg/ml after the last fleroxacin dose. The mean fleroxacin AUC was 100.7 ± 15.1 μg · h/ml in this group. Complete pharmacokinetic data were reported elsewhere (A. Marcotte, M. Parent, M. G. Bergeron, M. St-Laurent, and M. LeBel, Abstr. 90th Annu. Meet. Am. Soc. Clin. Pharmacol. Ther. 1989).

Table 3 lists the reported side effects as numbers of single episodes, although volunteers occasionally reported a side effect more than once. Most of the side effects presented in Table 3 were associated with theophylline administration and consisted mainly of headache, nausea, upset stomach, and insomnia. Most subjects, but more so the elderly, developed tolerance for the gastrointestinal side effects of theophylline. Six cases of photosensitivity occurred, most of them being mild but warranting skin protection for the remainder of the study. Since this side effect has not been reported with theophylline (5), the temporal relationship and recent reports (2) argue in favor of fleroxacin as the causative agent.

TABLE 2. Percent urinary excretion of theophylline and metabolites

Group	Day	% Urinary excretion of:			
		Theophylline	1,3-DMU	1-MU	3-MX
Young	8	9.5	42.3	37.3	10.8
	9	16.4[a]	38.9[a]	34.9[a]	9.7
	14	8.0	41.2	36.8	14.0[a]
Elderly	8	7.2	49.9	34.9	8.1
	9	10.3[a]	42.5	29.3[a]	9.1[a]
	14	9.2	42.9[a]	26.7[a]	14.4
All subjects	8	8.5	45.8	36.2	9.5
	9	13.7[a]	40.6[a]	32.4[a]	9.4
	14	8.5	42.0[a]	32.2[a]	14.2[a]

[a] $P < 0.05$ (paired t test), as compared with the baseline on day 8.

DISCUSSION

From the differences observed between theophylline CL after a single i.v. test dose and theophylline CL at steady state (Fig. 1), we conclude that single-dose CL values in previous nonusers of theophylline poorly predict steady-state CL values. When theophylline pharmacokinetics were compared in young and elderly volunteers, significant differences were observed during the 3 pharmacokinetic days. The magnitude of the difference in CL between young and elderly subjects (20%) is not too different from that reported by Shin et al. (15%) (28). We attribute the different patterns of alteration of theophylline CL in young and elderly subjects (Fig. 1) to the large variability in theophylline CL.

We showed that 400 mg of fleroxacin administered once a day for 7 days did not significantly alter theophylline CL in young or elderly subjects. We evaluated the largest contingent of subjects for this type of study conducted to deter-

TABLE 3. Reported side effects

Side effect	No. of the following subjects reporting each side effect after treatment with the indicated drug(s):			
	Young		Elderly	
	Theophylline	Theophylline + fleroxacin	Theophylline	Theophylline + fleroxacin
Gastrointestinal				
Nausea	5	6	5	3
Vomiting	0	1	5	0
Upset stomach	3	5	7	2
Diarrhea	0	1	1	1
Anorexia	0	2	0	0
Central nervous system				
Insomnia	4	4	8	5
Irritability	2	3	0	0
Headache	7	4	7	6
Dizziness	0	1	5	6
Tiredness	2	0	2	1
Hyperactivity	0	0	0	1
Lightheadedness	0	1	0	0
Others				
Photosensitivity	0	4	0	2
Jitters	1	3	0	0
Diaphoresis	0	0	0	3

mine an interaction between a quinolone and theophylline. Other investigations into the effects of fleroxacin on theophylline CL have yielded similar results (27a, 30).

In both studies, the theophylline dose was low (200 mg twice daily) and did not reflect clinically relevant dosages (27a, 30). Neither of these studies addressed the influence of quinolones on theophylline pharmacokinetics in elderly volunteers. Waite et al. recently studied the influence of ciprofloxacin on the disposition of the model oxidative substrate antipyrine in young and elderly subjects (N. M. Waite, D. J. Edwards, L. H. Warbasse, J. D. Steinberg, and M. J. Rybak, Pharmacotherapy **9**:42, 1989). These investigators demonstrated that the inhibition of antipyrine CL produced by ciprofloxacin was comparable in both young and elderly subjects. The elderly subjects included in that study appeared to be as unaffected by the influence of fleroxacin on theophylline pharmacokinetics as did the young subjects.

With fluroquinolones, such as enoxacin, which have demonstrated inhibition of theophylline metabolism, investigators usually observed a decreased percentage of urinary excretion of theophylline metabolites while, in turn, the percentage of unchanged theophylline excreted increased (1, 23, 27, 31). In this study, these very same changes in the urinary excretion of unchanged theophylline and its metabolites were observed only on day 9 (after the first fleroxacin dose) and were not observed after multiple fleroxacin doses. These changes in the urinary excretion of unchanged theophylline and its metabolites do not support an inhibitory effect of fleroxacin. Soejima et al. measured the urinary metabolites of theophylline and did not find any alteration in the metabolism pattern of the drug following 3 and 5 days of fleroxacin administration (200 mg twice daily) (30). In a separate but similar study design, we found that lomefloxacin had no influence on theophylline CL, and no changes could be demonstrated in the urinary excretion of theophylline metabolites (15).

The results of this study are further supported by recent in vitro work by Grech-Bélanger et al., who showed that fleroxacin does not affect the ability of the liver to oxidize xenobiotics (8). They reported a modest 10% reduction of in vitro N demethylation of aminopyrine by the N-demethylated metabolite of fleroxacin. Since N demethylation is an important pathway for theophylline biotransformation, there is little chance that the cytochrome P-450 system and thus theophylline would be significantly affected by this quinolone.

The reasons for the apparent lack of interaction between fleroxacin and theophylline are unclear. Several mechanisms have been suggested to date to explain the influence that fluoroquinolones have on the pharmacokinetics of theophylline. Wijnands et al. theorized that the 4-oxo-metabolite of fluoroquinolones such as enoxacin, ciprofloxacin, and pefloxacin acts as the inhibitor responsible for the interaction (33, 34); however, good evidence against this supposition has recently been published (2, 4, 6).

Recently, it was suggested that steric hindrance in position 8 of the quinolone nucleus could reduce the influence of the compound on the pharmacokinetics of theophylline (2, 17). Alternatively, Staib et al. proposed that the piperazine ligand may explain the affinity of the quinolone for a common binding site with methylxanthine (30a).

There is also evidence that the mechanism of the quinolone-theophylline interaction could be at least twofold: inhibition of the cytochrome P-450 system and alteration of the renal clearance. The relative magnitude of each of these alterations by individual fluoroquinolones leads to a different degree of interaction with theophylline. Fleroxacin appears devoid of any significant effect on either mechanism.

From the data generated by this study, we conclude that fleroxacin may be administered concomitantly with theophylline in either young or elderly patients. Close monitoring of theophylline concentrations in serum should be performed, particularly in patients with chronic obstructive pulmonary disease, for whom data are currently lacking.

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