Effect of a New Quinolone, Sparfloxacin, on the Pharmacokinetics of Theophylline in Asthmatic Patients

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Recently, it has become evident that some quinolones affect the processing of theophylline in the human system. The effect of a new quinolone, sparfloxacin, on the pharmacokinetics and metabolism of theophylline was investigated in six asthmatic patients receiving chronic theophylline therapy (a sustained-release theophylline tablet formulation of 200 to 300 mg twice daily at 12-h intervals). To these patients, sparfloxacin (200 mg once daily) was coadministered for 1 week. Plasma and urine samples were analyzed by high-performance liquid chromatography for theophylline and its metabolites. Plasma theophylline concentration-time curves and the urinary excretion of theophylline and its major metabolites before and after coadministration of sparfloxacin were compared. The total body clearance of theophylline after coadministration of sparfloxacin, 42.81 ± 6.64 ml/h/kg (mean ± standard error of the mean), was not significantly different from that after the administration of theophylline alone, 47.11 ± 7.61 ml/h/kg. Also, no significant change in the urinary excretion of theophylline and its metabolites was observed for subjects receiving or not receiving sparfloxacin. These findings indicate that a once-daily dose of 200 mg of sparfloxacin has no significant effect on the pharmacokinetics and metabolism of theophylline and that it would be safe to coadminister this quinolone to asthmatic patients receiving chronic theophylline therapy.

Theophylline is widely used in the treatment of patients with reversible obstructive airway diseases. In treating asthma, however, theophylline is commonly prescribed in combination with various other drugs. Many articles have been published on the interactions of theophylline with other drugs (13, 15, 17, 18, 31). Some quinolone antimicrobial drugs (ciprofloxacin, enoxacin, pefloxacin, and tosufloxacin), when coadministered with theophylline, may create clinical problems due to an inhibition of theophylline clearance, thus increasing the risk of the development of serious side effects (7, 8, 22, 24, 29, 30).

The mechanism of the decrease in theophylline clearance due to quinolones has generally been considered to be an inhibition of theophylline metabolism. However, the precise mechanism of the interaction between theophylline and quinolones is not yet fully understood. Therefore, interest remains in determining the pharmacokinetic interactions between theophylline and quinolones.

A large number of new quinolone antimicrobial drugs with broad-spectrum activity have been developed in the past few years. Sparfloxacin (Fig. 1) has broad antibacterial activity against both gram-positive and gram-negative bacteria. This study was conducted as part of a program directed to the development of guidelines for the safe use of quinolone drugs in combination with theophylline in asthmatic patients. We investigated the possibility that multiple oral doses of sparfloxacin may affect the pharmacokinetics of theophylline in asthmatic patients receiving chronic theophylline therapy.

MATERIALS AND METHODS

Patients. Six asthmatic patients participated in this study; there were three males and three females, aged 51 to 76 years

(mean, 67.7 years), with weights ranging between 34 and 57 kg (mean, 47.2 kg) and heights ranging between 151 and 163 cm (mean, 156.7 cm). All were receiving chronic theophylline therapy for asthma. Known metabolic inhibitors or inducers (15) were withheld from the subjects during the study period. Informed consent was obtained from each patient after a full explanation of the procedures.

Drugs. Theophylline tablets in a sustained-release formulation (Theo-Dur; 100 mg of theophylline per tablet; Nikken Kagaku, Tokyo, Japan) were used in this study. Likewise, the tablet form of sparfloxacin was used; each tablet contained 100 mg of 5-amino-1-cyclopropyl-6,8-difluoro-1.4-dihydro-7(cis-3,5-dimethyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid (Dainippon Pharmaceutical Co., Ltd., Osaka, Japan). The tetrabutylammonium hydrogen sulfate used for the determination of theophylline and its metabolites in urine was obtained from Aldrich Chemical Co. Inc. All other reagents used were of analytical grade.

Study design. The patients were studied during their hospitalization at Nagoya University Hospital. The study type was a single crossover with each patient serving as his own control. Each patient received theophylline at 400 to 600 mg/day twice daily at 12-h intervals (9:00 a.m. and 9:00 p.m.).

(i) **Control study.** The control study was started on the day after the patients had attained steady-state conditions. Blood samples were collected at time zero (just before the start of theophylline administration) and every 2 h from 9:00 a.m. to 9:00 p.m. after the start of theophylline administration. Urine samples were collected at the same times. Xanthine-containing foods and drinks were excluded for 48 h before the day on which sampling was begun.

(ii) **Coadministration study.** From the day after the start of the control study, 200 mg of sparfloxacin was coadministered with theophylline as a once-daily dose in the morning for 7 days. On day 8, the last morning dose of theophylline
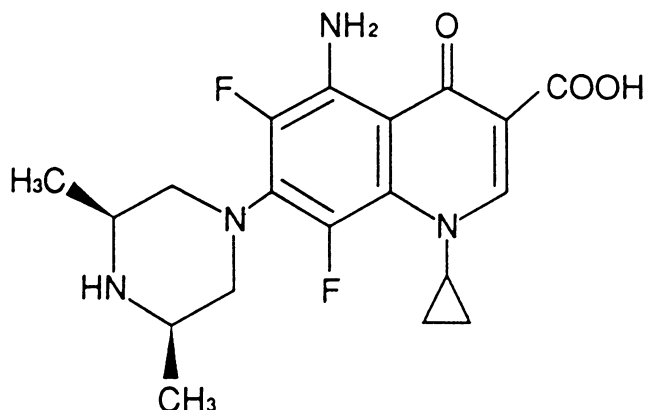
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FIG. 1. Chemical structure of sparfloxacin.

was coadministered with sparfloxacin. Blood and urine samples were collected as in the control study.

Assays. Blood samples (5 ml) were collected in glass tubes containing disodium EDTA and immediately centrifuged to yield plasma. The plasma and 10 ml of each urine sample obtained from the subjects were stored at $-40°C$ until analysis. The theophylline concentrations in the plasma were determined by high-performance liquid chromatography as previously described (21). For the analyses of theophylline and its major metabolites, 1-methyluric acid, 3-methylxanthine, and 1,3-dimethyluric acid (1,3-DMU), in urine, a Cosmosil $5C_{18}$ column (Nacalai Tesque, Kyoto, Japan) was used. The mobile phase was 10 mM CH_3COONa–5 mM tetrabutylammonium hydrogen sulfate (pH 5.0). The mobile phase was used at a flow rate of 1 ml/min. The elutions were carried out at $35°C$, and the effluent column was monitored at 278 nm. The high-performance liquid chromatography apparatus used was a Shimadzu LC-6A system (Shimadzu Co., Kyoto, Japan) with an LC-6A autoinjector.

For the analyses of theophylline and its metabolites in urine, 0.1 ml of urine and 2.0 ml of distilled water were vortexed in a 5-ml glass tube and filtered with Millipore filters (HV; 0.45 μm; Nihon Millipore Kogyo, Yonezawa, Japan). The filtrate obtained (0.1 ml) and the mobile phase (0.1 ml) were transferred to a glass tube. The mixed solution (80 μl) was injected into the column. For the calculation, standard curves for all compounds were measured over a range of 1 to 15 μg/ml and shown to be linear. Recoveries for all compounds were 95 to 101%, with intra- and interday coefficients of variation of less than 5%. Blank urine did not interfere with peaks corresponding to each compound.

Pharmacokinetic analysis. The area under the plasma concentration-time curve (AUC) of theophylline from 0 to 12 h after the last dose was calculated by the trapezoidal rule.

Total body clearance (CL) and renal clearance (CL_R) were calculated as $CL = D \cdot F/AUC$ and $CL_R = CL \cdot U$, respectively, where D is the theophylline dose adjusted by body weight (milligrams per kilogram); F is the bioavailability, assumed to be 1.0 (23, 25, 28); and U is theophylline recovered unchanged.

Datum analysis. The values in the present study are expressed as the mean ± standard error of the mean. The data were statistically analyzed by one-way analysis of variance. Statistical significance was defined as $P < 0.05$ by using Tukey's test.

RESULTS

The characteristics of the asthmatic patients studied are given in Table 1. Figure 2 shows individual plasma theophylline concentration-time data at steady state for the six patients after administration of theophylline alone and after coadministration of sparfloxacin. No significant differences in theophylline concentrations were observed for patients between study periods. Peak steady-state plasma theophylline concentration data obtained with and without coadministration of sparfloxacin are shown in Fig. 3. Three of the six patients had small increases in the peak theophylline concentration with coadministration, although the differences failed to reach the 5% level of statistical significance, as determined by one-way analysis of variance. In this study, sparfloxacin therapy was well tolerated by all patients, but three patients complained of moderate side effects in the form of gastrointestinal symptoms. These may have been attributable to sparfloxacin, since no side effects were experienced by any of the six patients receiving treatment with theophylline alone. The side effects may have resulted from the abstention from the use of antacids for gastrointestinal symptoms during the study.

The pharmacokinetic parameters of theophylline, such as time to maximum concentration, CL, and CL_R, are summarized in Table 2. No significant changes in the pharmacokinetic parameters of theophylline were observed for patients receiving or not receiving sparfloxacin, although sparfloxacin decreased slightly (approximately 20%) the CL of theophylline in two of the six patients.

Since theophylline undergoes extensive metabolism, we also investigated the influence of sparfloxacin on the hepatic metabolism of theophylline. We compared the quantities of theophylline and its major metabolites excreted in the urine after the administration of theophylline alone with those excreted after the coadministration of sparfloxacin (Table 3). The percentage of the total dose of theophylline recovered in the urine in 12 h after the coadministration of sparfloxacin was 84.95 ± 4.02, a value which did not differ significantly from the value obtained after the administration of theophylline alone (82.54 ± 3.78), indicating that there was no

TABLE 1. Characteristics of asthmatic patients in this study

| Subject	Sex	Age (yr)	Wt (kg)	Ht (cm)	Theophylline dose (mg/day)[a]	Comedication
A	Male	76	42	158	400	Isosorbide dinitrate, nifedipine
B	Male	65	45	157	600	Ubidecarenone, fenoterol
C	Male	74	54	163	400	Procaterol
D	Female	64	57	157	600	Prednisolone, ranitidine, trichlormethiazide,
E	Female	76	51	151	400	salbutamol diltiazem, fenoterol
F	Female	51	34	154	600	Ranitidine, betamethasone

[a] Maintenance dose of theophylline.
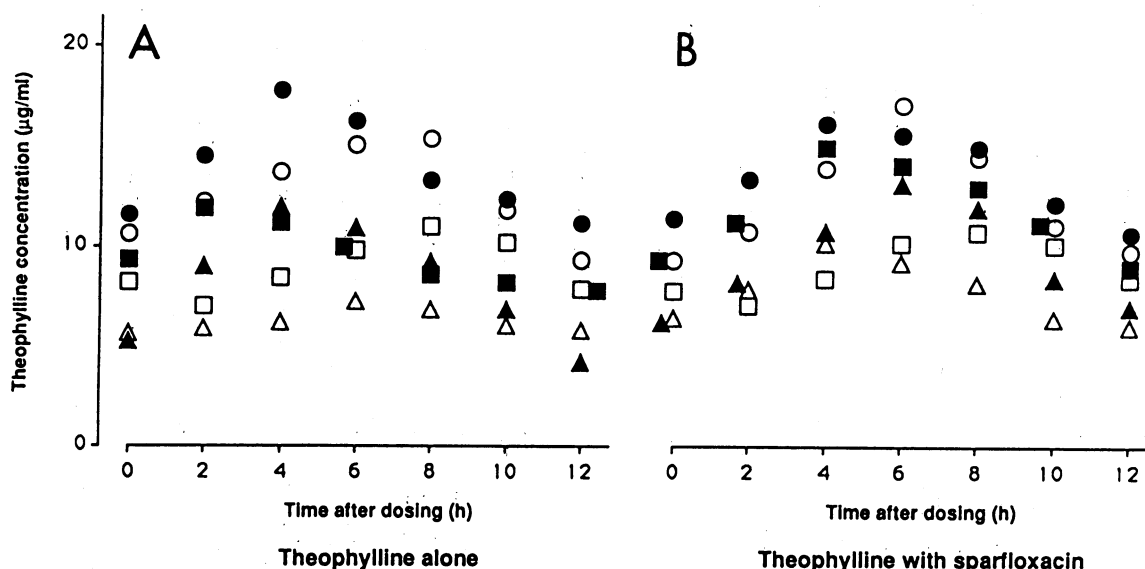
FIG. 2. Individual steady-state plasma theophylline concentration-time data for six asthmatic patients receiving or not receiving sparfloxacin. On days 1 (A) and 8 (B), plasma samples were collected every 2 h from 9:00 a.m. to 9:00 p.m. Symbols represent individual patients: □, A; ■, B; △, C; ○, D; ●, E; ▲, F.

difference in the total systemic availability (F = 1) of the two doses. Also, no significant differences in the urinary recovery of unchanged theophylline and individual metabolites were found for patients receiving or not receiving sparfloxacin, indicating that sparfloxacin has no influence on the metabolic pathway of theophylline.

DISCUSSION

The present study has shown that the new quinolone sparfloxacin, like lomefloxacin (16), has no effect on the
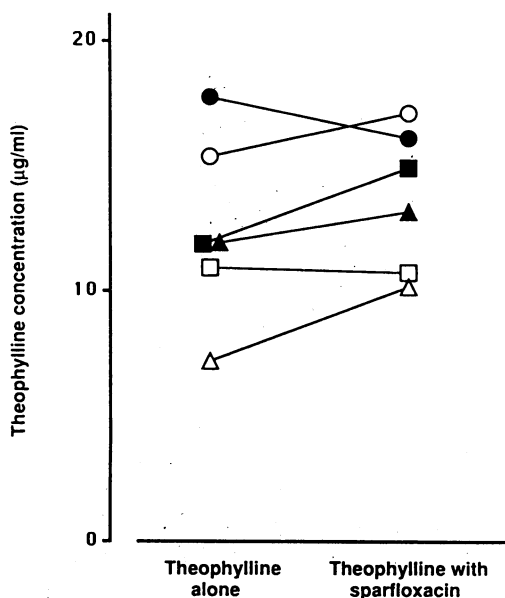

FIG. 3. Peak steady-state plasma theophylline concentration data obtained following administration of theophylline alone and theophylline with sparfloxacin in six patients. Symbols represent individual patients, as described in the legend to Fig. 2.

pharmacokinetics and metabolism of theophylline. This finding suggests that sparfloxacin would be safe to administer as a concomitant therapy for asthmatic patients receiving chronic theophylline therapy. Furthermore, no significant differences in the pharmacokinetic parameters and systemic availability (F = 1) of theophylline were observed between patients receiving or not receiving sparfloxacin. The pharmacokinetic parameters of theophylline in the elderly asthmatic patients tested in this study were similar to those observed in healthy adult volunteers (16), suggesting a lack of effect of the age of the test population on the disposition of theophylline.

We previously reported that a newly developed quinolone, lomefloxacin, which lacks 4-oxo metabolite formation, did not affect the pharmacokinetics and metabolism of theophylline in humans (16). In another previous study, we showed that tosufloxacin, which does not form a 4-oxo metabolite, unexpectedly had a moderate inhibitory effect (30%) on theophylline clearance in humans (24). The discrepancy between the findings of our previous studies could not be explained. Thereafter, Edwards et al. (5, 6) postulated that the reduction in theophylline clearance is due not to the 4-oxo metabolite but to an intermediate metabolite in the production of 4-oxo-enoxacin or to some other related metabolite which inhibits theophylline metabolism. However, there is no evidence for the formation of an intermediate metabolite or other related metabolite with the formation of the 4-oxo metabolite. Our further studies with

TABLE 2. Pharmacokinetic parameters of theophylline[a]

Drug	T_{max} (h)	CL (ml/h/kg)	CL_R (ml/h/kg)
Theophylline alone	5.33 ± 0.99	47.11 ± 7.61	4.56 ± 1.25
Theophylline with sparfloxacin	5.33 ± 0.67	4.56 ± 1.25	4.73 ± 1.15

[a] Each value represents the mean ± standard error of the mean (n = 6). T_{max}, time to maximum concentration.

TABLE 3. Mean urinary recovery of theophylline
and its metabolites

Drug or metabolite	% of drug or metabolite excreted in 12 h after administration of theophylline[a]	
	Alone	With sparfloxacin
1-Methyluric acid	21.32 ± 1.13	21.67 ± 1.76
3-Methylxanthine	15.09 ± 1.22	14.70 ± 1.66
1,3-Dimethyluric acid	36.91 ± 2.10	38.07 ± 1.28
Theophylline	9.22 ± 1.56	10.52 ± 1.24
Total	82.54 ± 3.78	84.95 ± 4.02

[a] Each value represents the mean ± standard error of the mean ($n = 6$), calculated on a molar basis. No significant difference was noted for patients receiving or not receiving sparfloxacin.

theophylline and xanthine derivatives in rats demonstrated that the reduction in theophylline clearance may be due not to an enoxacin metabolite but to enoxacin itself (12, 20). The hypothesis that the 4-oxo metabolite plays an important role in the mechanism of the inhibition of theophylline clearance remains to be conclusively proven.

Recent studies with caffeine in humans have provided further evidence that the different molecular and spatial structures of the various quinolones are responsible for differences in inhibitory potency (4, 11). Therefore, we have proposed that position 3 of the piperazinelike ring at position 7 of the quinolone molecule plays an important role in the interaction between theophylline and quinolones, since the substituent group at the 1-nitrogen atom of the quinolone molecule is not as important in the inhibition of caffeine metabolism (1).

In general, quinolones are divided into two main groups, 1,8-naphthyridine and quinoline derivatives, based on the chemical structural classification. On the basis of the relationships among the chemical structures of the quinolones and the degrees of decrease in theophylline clearance, we have proposed that the quinoline derivatives have less of an effect on theophylline disposition than have the 1,8-naphthyridine derivatives (16). This proposal is supported by the findings of the present study and previous studies (16, 20, 24). We therefore conclude not only that the interaction between theophylline and quinolones is dependent on the 4-oxo metabolite but also that the presence of substituents (methyl and amino residues, etc.) of the piperazine ring or piperazinelike ring at position 7 of the quinoline molecule, which masks the formation of the 4-oxo metabolite, plays a major role in the differences in the levels of inhibition of theophylline clearance induced by various quinolones. The latter conclusion is supported by the finding that the differences in the magnitudes of inhibition of enoxacin and its analogs relate to the substituent group at the 4'-nitrogen atom in the piperazinyl ring at position 7 of the quinolone molecule (19). Further detailed investigation is required in these respects.

Regarding the metabolism of theophylline, it is well known that approximately 90% of the CL of theophylline in humans is due to hepatic oxidative metabolism: theophylline is biotransformed by C oxidation at position 8 of the molecule to 1,3-DMU and by N demethylation at positions 1 and 3 to 3-methylxanthine and 1-methylxanthine; these processes probably involve the cytochrome P-450 system (9, 10, 14, 26). The mean urinary recoveries of theophylline and its metabolites obtained in the present study were approxi-

mately 21% for 1-methyluric acid, 15% for 3-methylxanthine, 38% for 1,3-DMU, and 10% for unchanged theophylline, values which are in agreement with other reported values (26). The present study suggests that sparfloxacin has no effect on the hepatic mixed-function oxidase system.

It has been reported that pretreatment with enoxacin does not affect the urinary excretion of the theophylline metabolite 1,3-DMU, indicating that enoxacin selectively inhibits the process of elimination of theophylline that depends on cytochrome P-450-mediated isozymes for N demethylation in humans (2). Recent studies on the metabolic inhibition of enoxacin in rats, however, suggested that quinolones may affect the pathway of theophylline metabolism for oxidation in addition to affecting N demethylation (6, 20). Further detailed studies concerning whether quinolones selectively act in the metabolic pathway of theophylline in humans are necessary, although the pathways of theophylline metabolism in humans and rats are considered to be quite similar (3, 27).

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