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

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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-cyclopenta-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...
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 containing disodium EDTA and immediately centrifuged and thylxanthine, samples used. filters carried ratus used 278 vortexed in (0.1 ml) all of the last dose standard curves of concentration-time curve coefficients of variation of less than 5%. Blank urine did not reach the peak theophylline concentration with and without coadministration of sparfloxacin were 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 abstinence from the use of antacids for gastrointestinal symptoms during the study.

The pharmacokinetic parameters of theophylline, such as time to maximum concentration, CL, and CLR, 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

Total body clearance (CL) and renal clearance (CLR) were calculated as CL = D ∙ F/AUC and CLR = CL ∙ 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.

**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. The 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 abstinence from the use of antacids for gastrointestinal symptoms during the study.

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**TABLE 1. Characteristics of asthmatic patients in this study**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>Theophylline dose (mg/day)*</th>
<th>Comedication</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Male</td>
<td>76</td>
<td>42</td>
<td>158</td>
<td>400</td>
<td>Isosorbide dinitrate, nifedipine</td>
</tr>
<tr>
<td>B</td>
<td>Male</td>
<td>63</td>
<td>45</td>
<td>157</td>
<td>600</td>
<td>Ubidecarenone, fenoterol</td>
</tr>
<tr>
<td>C</td>
<td>Male</td>
<td>74</td>
<td>54</td>
<td>163</td>
<td>400</td>
<td>Procaterol</td>
</tr>
<tr>
<td>D</td>
<td>Female</td>
<td>64</td>
<td>57</td>
<td>157</td>
<td>600</td>
<td>Prednisolone, ranitidine, trichlormethiazide, salbutamol diltiazem, fenoterol</td>
</tr>
<tr>
<td>E</td>
<td>Female</td>
<td>76</td>
<td>51</td>
<td>151</td>
<td>400</td>
<td>Ranitidine, betamethasone</td>
</tr>
<tr>
<td>F</td>
<td>Female</td>
<td>51</td>
<td>34</td>
<td>154</td>
<td>600</td>
<td></td>
</tr>
</tbody>
</table>

* Maintenance dose of theophylline.
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 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

![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.](image)

![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.](image)

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$\text{CL}$ (ml/h/kg)</th>
<th>$\text{CL}_{\text{xy}}$ (ml/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline alone</td>
<td>5.33 ± 0.99</td>
<td>47.11 ± 7.61</td>
<td>4.56 ± 1.25</td>
</tr>
<tr>
<td>Theophylline with sparfloxacin</td>
<td>5.33 ± 0.67</td>
<td>4.56 ± 1.25</td>
<td>4.73 ± 1.15</td>
</tr>
</tbody>
</table>

* Each value represents the mean ± standard error of the mean ($n = 6$). $T_{\text{max}}$, time to maximum concentration.
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 quinolines are responsible for differences in inhibitory potency (4, 11). Therefore, we have proposed that position 3 of the piperazineline ring at position 7 of the quinolone molecule plays an important role in the interaction between theophylline and quinolines, since the substituent group at the 1-nitrogen atom of the quinoline 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 quinolines is dependent on the 4-oxo metabolite but also that the presence of substituents (methyl and amino residues, etc.) of the piperazine ring or piperazineline 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 quinoline 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 approximately 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 is considered to be quite similar (3, 27).

**REFERENCES**


