Effect of trovafloxacin, a new fluoroquinolone antibiotic, on the steady-state pharmacokinetics of theophylline in healthy volunteers

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Some fluoroquinolone antibiotics interfere with theophylline clearance, thereby raising concentrations of circulating theophylline and increasing the potential for toxicity. The effect of steady-state serum concentrations of the new fluoroquinolone trovafloxacin on the steady-state pharmacokinetics of theophylline was examined in 12 healthy male volunteers. For 7 days, the subjects received morning and evening theophylline doses adjusted to achieve steady-state plasma concentrations of 8–15 mg/L, the lower end of the therapeutic range. From day 8 to day 15, six volunteers received, in addition to theophylline, 200 mg of trovafloxacin in the morning and placebo in the evening (group A) and six received placebo twice daily (group B). Serial plasma samples obtained over 12 h and 60 h after the morning theophylline dose on days 7 and 14, respectively, were analysed for theophylline by HPLC with UV detection. There were no significant differences in mean \( C_{\text{max}} \) or \( \text{AUC}_{0-12} \) between the two groups on day 7 or on day 14, nor were there significant within-group differences on the two days. On day 14, mean \( C_{\text{max}}, \text{AUC}_{0-12} \) and \( T_{1/2} \) (measured on day 14 only) in group A were 10.15 mg/L, 107.32 mg·h/L and 9.0 h, respectively. In group B, the values were 10.81 mg/L, 113.73 mg·h/L and 8.3 h, respectively. The study drugs were well tolerated, and no clinically significant changes in vital signs or laboratory test values were noted. We conclude that steady-state concentrations of trovafloxacin have no clinically significant effect on the steady-state concentrations of theophylline within the therapeutic range in healthy subjects.

Introduction

Theophylline, a respiratory smooth muscle relaxant widely used to relieve the bronchospasm associated with asthma and chronic obstructive pulmonary disease, has a narrow therapeutic plasma concentration range of 10–20 mg/L (55–110 \( \mu \text{mol/L} \)). Sensitive individuals can experience serious adverse effects even when plasma theophylline concentrations are within this range\(^1,2\) and life-threatening theophylline poisoning can occur without the warning signs of milder toxicity.\(^3,4\) It is extremely important, therefore, for clinicians to be aware of drug interactions that increase plasma concentrations of theophylline.\(^5\)

Some fluoroquinolone antibiotics are known to interfere significantly with the metabolism of theophylline in the liver, thereby increasing circulating theophylline levels, while others appear to have an insignificant or no effect on theophylline clearance.\(^6-9\) The extent of the effect on theophylline pharmacokinetics, therefore, may be an important criterion in the choice among the drugs of this class.

Trovafloxacin (CP-99,219), a new fluoroquinolone with the chemical designation 7-(6-amin-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-napthyridine-3-carboxylic acid, has shown desirable characteristics in in-vitro tests and animal studies; these include a broad spectrum of activity against Gram-positive and Gram-negative bacteria, good oral bioavailability and good tissue penetration.\(^10-16\) In studies involving healthy male volunteers, the mean peak serum concentration \( (C_{\text{max}}) \) was reached after 1 h after administration, and mean terminal-phase elimination half-life \( (T_{1/2}) \) was about 10 h.\(^17\) \( C_{\text{max}} \) and area under the serum concentration–time curve \( (\text{AUC}) \) increased linearly as the trovafloxacin dose was increased.\(^17\) Multiple dosing at 100 mg and 300 mg for 14 days was well tolerated and resulted in approximately 30% accumulation.\(^18\)

In a preliminary study, we determined the effect of trovafloxacin on the pharmacokinetics of a single oral 450
mg dose of theophylline in healthy volunteers who had taken 300 mg doses of trovafloxacin od for 7 days. Mean theophylline $C_{\text{max}}$, AUC and $T_{1/2}$ before the start of trovafloxacin dosing were 6.42 mg/L, 132.36 mg·h/L and 7.9 h, respectively, and after 7 days of trovafloxacin administration the corresponding values were 6.00 mg/L, 143.45 mg·h/L and 9.1 h, respectively. These modest changes were not considered to be clinically significant.

In this double-blind, placebo-controlled, parallel-group study, we examined the effect of steady-state trovafloxacin concentrations on the steady-state pharmacokinetics of theophylline when theophylline doses were individualized to attain steady-state therapeutic concentrations in healthy male volunteers.

**Subjects and methods**

**Subjects**

Twelve healthy male subjects participated in the study. All were advised of the objectives and possible risks of the study and agreed to participate by signing an informed consent form. The study protocol was approved by the local Institutional Review Board, the Independent Investigational Review Board Inc., Plantation, FL, USA.

Subjects were judged to be free of clinically significant disease on the basis of a complete medical history, a full physical examination, clinical laboratory tests and a resting 12-lead electrocardiogram. The body weights of the volunteers (mean, 72 kg; range 66–79 kg) were within 10% of ideal for their heights and body frames as defined in actuarial tables. Their ages ranged from 28 to 45 years (mean, 34.6 years). Subjects were excluded from the study if they smoked tobacco, used drugs of any kind, or were known to have a drug allergy.

**Drug administration**

All 12 volunteers received a sustained-release theophylline preparation (Theo-Dur, Key Pharmaceuticals Inc., Kenilworth, NJ, USA) at 7.00 am and 7.00 pm daily on study days 1–13 and at 7.00 am on day 14. On days 1–13, the theophylline dose was 300 mg bd. On day 14, the theophylline dose was individually adjusted to achieve theophylline plasma concentrations of 8–15 mg/L in plasma samples taken 9 h after administration. On day 8, the subjects were randomly assigned to two groups (A and B), each consisting of six subjects. From day 8 to day 13, group A received theophylline and 200 mg (two 100 mg tablets) of trovafloxacin at 7.00 am and theophylline and placebo at 7.00 pm daily. During the same period, group B received theophylline and placebo at 7.00 am and 7.00 pm daily. On day 14, theophylline administration was discontinued after the morning dose, whereas the administration of trovafloxacin or placebo continued until day 15.

From day 6 until the end of the study, the volunteers were confined to the clinical research unit. On days 7 and 14, they were required to fast for at least 8 h before and 4 h after administration of the morning doses. For 4 h after administration, the subjects were required to refrain from drinking caffeine-containing beverages.

**Blood samples**

On days 7 and 14, blood sufficient to yield 3 mL of plasma was drawn into heparinized tubes just before the morning dose of theophylline and 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h after the morning dose for the determination of plasma concentrations of theophylline. On day 14, additional blood samples for theophylline assay were obtained 16, 24, 36 and 60 h after the morning dose. On days 5, 6, 7, 12, 13 and 14, blood samples were obtained just before the morning dose for the determination of plasma concentrations of theophylline to confirm that steady-state plasma concentrations had been achieved. To confirm that serum concentrations of trovafloxacin had reached steady state, blood samples were drawn on days 12, 13 and 14 just before the morning dose. Plasma and serum were separated from the whole blood in a refrigerated centrifuge and kept frozen at $-20^\circ$C until the time of assay.

**Assay methods**

Plasma concentrations of theophylline were determined by reversed-phase HPLC with UV detection according to a modification of the methods of Kinberger & Holmén and Wenk et al. The calibration curve of the procedure was linear over a plasma concentration range of 0.05–50 mg/L (correlation coefficient, 0.999), and the intra-assay and inter-assay coefficients of variation at the limit of quantification (0.05 mg/L) were less than 5% and 7%, respectively.

The concentrations of trovafloxacin in serum were determined by reversed-phase HPLC with UV detection as previously described. The calibration curve of the method was linear over a serum concentration range of 0.1–20.0 mg/L (correlation coefficient, 0.999), and the intra-assay and inter-assay coefficients of variation over this range were less than 10%.

**Pharmacokinetic analysis**

Values for pharmacokinetic variables were calculated by noncompartmental analysis. $C_{\text{max}}$ was obtained directly from the experimental data, and the time to peak plasma concentration ($T_{\text{max}}$) was defined as the time of the first occurrence of $C_{\text{max}}$. The terminal-phase elimination rate constant of theophylline ($K_{el}$) was estimated by the least squares regression analysis of the concentration-time data obtained over the terminal log-linear phase. Theophylline $T_{1/2}$ values were calculated as $0.693/\text{mean } K_{el}$. 

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The area under the concentration–time curve from time zero to time 12 h (AUC₀₋₁₂) for the theophylline was calculated by the linear trapezoidal rule.

Percent fluctuation of theophylline concentrations was calculated on days 7 and 14 according to the following formula:

$$\% \text{ fluctuation} = \frac{C_{\text{max}} - C_{\text{min}}}{C_{\text{min}}} \times 100$$

where $C_{\text{max}}$ is the maximum theophylline concentration and $C_{\text{min}}$ is the predose theophylline concentration.

Safety evaluation

All observed or volunteered adverse events, regardless of suspected causal relationship to either of the study drugs, were recorded. The following laboratory tests were performed just before the morning dose of theophylline on study days 1 and 14 and on day 16, after administration had ceased: complete blood count with differential and platelet count; urinalysis with reflex microscopic evaluation; measurement of serum levels of calcium, inorganic phosphorus, sodium, potassium, chloride, LDH, SGOT, SGPT, total bilirubin, alkaline phosphatase, cholesterol, triglycerides, total protein, globulin, albumin, blood urea nitrogen, creatinine, uric acid and glucose. Resting and standing blood pressure, resting and standing heart rate, and oral temperature were measured just before the morning dose of theophylline on days 1, 7, 8 and 14.

To determine whether changes in heart rate induced by theophylline were altered by the co-administration of trovafloxacin, on days 7 and 14 resting heart rate was determined just before the morning dose of theophylline and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after the morning dose. On day 14, additional measurements were made 16 and 24 h after the morning dose.

Statistical methods

The study was designed to have the power of at least 80% at the 5% level of significance to detect a difference of $\geq 30\%$ in the $C_{\text{max}}$ or $C_{\text{min}}$ of theophylline between the two study groups. The effects of trovafloxacin and placebo on the mean pharmacokinetics of theophylline and the percent fluctuation of theophylline concentration were compared by paired t-test (5% level of significance) and 95% confidence intervals. These analyses compared the mean $C_{\text{max}}$, AUC₀₋₁₂, $T_{1/2}$ and percent fluctuation values on day 14 (between-group comparisons). In addition, the mean $C_{\text{max}}$, AUC₀₋₁₂ and percent fluctuation values on day 7 were compared with those on day 14 within each of the two groups (within-group comparisons). Mean between-group heart rates were compared by one-way analysis of variance (ANOVA). The changes in heart rate from baseline in individual subjects on days 7 and 14 were compared by repeated measures analysis of variance.

Results

The mean plasma concentrations of theophylline just before the morning dose on days 5, 6, 7, 12, 13 and 14 of the mean serum concentrations of trovafloxacin on days 12, 13 and 14 (data not shown) indicated that both drugs had reached steady-state concentrations by the time

**Figure 1.** Mean plasma theophylline concentrations as a function of time after administration before (day 7) and after (day 14) the daily administration for 7 days of 200 mg of trovafloxacin (○, before trovafloxacin; ● after trovafloxacin) or placebo (▲, before placebo; ▲ after placebo).
blood samples were taken for the determination of pharmacokinetic values on days 7 and 14.

The mean plasma theophylline concentrations of the subjects in the two groups on day 7 and day 14 are plotted as a function of time in Figure 1. The steady-state theophylline pharmacokinetic values obtained in group A and B on days 7 and 14 are presented in Table. There were no significant differences in mean $C_{\text{max}}$, $AUC_{0-12}$ or $T_{1/2}$ between the two groups on day 7 or on day 14, nor were there significant within-group differences on the two days ($P > 0.42$).

On day 7, the subjects in group A and group B had geometric mean percent fluctuations of theophylline concentration of 41.49 and 37.89, respectively, a difference of 9.5%. On day 14, the mean percent fluctuations for groups A and B were 33.73 and 28.09, respectively, a difference of 20.1%. The mean percent fluctuation in both groups decreased from day 7 to day 14, but that in group A decreased more than that in group B (35% vs 23%). None of these differences in mean percent fluctuation was statistically significant ($P > 0.74$).

Figure 3 depicts the mean change in heart rate over time after theophylline administration on days 7 and 14 for the two treatment groups corrected for the baseline value. Analysis by the repeated measures (ANOVA) showed there were no significant between-group ($P > 0.73$) differences for this variable.

Trovafloxacin and theophylline administered concurrently were well tolerated by all subjects. There were no meaningful changes in any of the laboratory parameters monitored in the subjects on days 1, 14 and 16 compared with baseline.

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*Figure 2. Mean theophylline $C_{\text{max}}$ (mg/L) before (day 7) vs after (day 14) the daily administration of 200 mg of trovafloxacin (○) or placebo (●).*
trovafloxacin and theophylline

Discussion

A number of compounds, including allopurinol, cimetidine, propanolol, erythromycin and troleandomycin, are known to reduce the hepatic clearance of theophylline, thereby increasing theophylline’s potential for toxicity. The first report of an interaction between a fluoroquinolone and theophylline was published by Wijands et al. Eight patients who were receiving concomitant theophylline for asthma and enoxacin for lower respiratory tract infections experienced serious nausea and vomiting. Two patients also complained of tachycardia and headaches. To determine whether a drug interaction had taken place, the authors studied plasma theophylline concentrations in one patient while he was taking both oral enoxacin and aminophylline. By day 5, the patient’s mean daily plasma theophylline concentration had increased from 7.3 to 25.4 mg/L. This effect of enoxacin on theophylline pharmacokinetics was later confirmed by studies performed in patients and healthy subjects. Subsequently, other fluoroquinolones—notably ciprofloxacin, perofloxacin and tosufloxacin—have been found to increase significantly circulating theophylline levels.

In our study, we found no significant difference in mean theophylline $C_{\text{max}}$, AUC$_{0-12}$ or $T_{1/2}$ between trovafloxacin-treated and placebo-treated groups after co-administration of the two drugs for 7 days, nor did we observe significant differences in $C_{\text{max}}$ or AUC$_{0-12}$ within the two treatment groups over this period. Furthermore, steady-state trovafloxacin had no significant effect on the percent fluctuation of theophylline concentration, nor did theophylline have an effect on trough trovafloxacin concentrations at steady state. Theophylline is cleared through extensive oxidative hepatic metabolism in humans. The results of this study indicate that trovafloxacin does not interfere with this pathway in humans.

Recommended therapeutic doses of theophylline often transiently, but usually not substantially, increase heart rate. To determine whether changes in heart rate induced by theophylline were altered by the concomitant administration of trovafloxacin, we measured resting heart rates just before and at 12 time points after the morning dose of theophylline. Trovafloxacin did not significantly alter the mean change in heart rate of the volunteers. Concomitant administration of the two study drugs was well tolerated by the study subjects, and no clinically significant changes in vital signs or laboratory test values were noted. From these results, we conclude that steady-state trovafloxacin has no clinically significant effect on steady-state theophylline pharmacodynamics in healthy males.

References