Effect of Maalox and omeprazole on the bioavailability of trovafloxacin

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To determine the effect of the concurrent administration of Maalox and omeprazole in the bioavailability of trovafloxacin (CP-99,219), an open, placebo-controlled, randomized, four-way crossover study was conducted in 12 healthy male volunteers. Each received treatments of three 100 mg trovafloxacin tablets in the morning 30 min after 30 mL of Maalox (A), 30 min after placebo (B), 2 h before 30 mL of Maalox (C) and 2 h after 40 mg of omeprazole (D). For treatments A and C, Maalox was also given at 22.00 h the night before the study day, 1 and 2 h before meals and at bedtime on the study day. For B and D, placebo and omeprazole, respectively, were also given at 22.00 h the night before the study day. After treatments A and C, mean area under the curve (AUC) was reduced by 66% and 28% (14.2 and 30.2 mg.h/L), respectively, and mean $T_{1/2}$ declined by 33% and 31% (8.3 and 8.5 h), respectively, relative to the values after B (42.1 mg.h/L; 12.4 h). The mean $K_{el}$-corrected relative bioavailabilities for A and C were 50% and 104%, respectively, suggesting a large reduction in the initial absorption of trovafloxacin with A. Treatment D had no appreciable effect on mean $T_{1/2}$ but mean AUC and $C_{max}$ were reduced by 18% and 32%, respectively, relative to B. The mean relative bioavailability after D was 82%. We conclude that the concurrent administration of trovafloxacin and aluminium- and magnesium-containing antacids should be avoided but that co-administration with omeprazole is unlikely to have a clinically significant effect on the extent of absorption of the antibiotic.

Introduction

Trovafloxacin (CP-99,219) is a new synthetic fluoroquinolone antibiotic. In in-vitro susceptibility tests it was found to be 16–32 times more active than ciprofloxacin or ofloxacin against Streptococcus pneumoniae, with MIC90s ranging from 0.06 to 0.25 mg/L.1–3 Trovafloxacin also is very active in vitro against other respiratory tract pathogens, including Haemophilus influenzae, Moraxella catarrhalis and Pseudomonas aeruginosa, as well as against the important pathogens Neisseria gonorrhoeae, Chlamydia trachomatis and Bacteroides fragilis.

The results of single- and multiple-dose pharmacokinetic studies involving healthy male volunteers indicate that systemic exposure to trovafloxacin increases in a dose-related manner. The elimination half-life of the drug is about 10 h, suggesting the possibility of once-daily dosing in most clinical applications.4,5 The oral bioavailability of trovafloxacin in healthy volunteers is not altered by the presence of food in the gastrointestinal tract.6 Trovafloxacin has no effect on the steady-state pharmacokinetics of theophylline.7

The bioavailability of fluoroquinolone antibiotics is reduced by antacids containing polyvalent metal ions, such as Al3+, Mg2+ and Ca2+,11,12 and by the aluminium-containing compound sucralfate.11,13,14 Furthermore, in some studies the bioavailability of fluoroquinolones has been found to be reduced by ranitidine or other H2-receptor antagonists.8,9 The purpose of the present open-label, randomized, four-way crossover study was to determine the effect of the concomitant administration of the Al3+ and Mg2+-containing antacid Maalox and the proton pump inhibitor omeprazole on the bioavailability of trovafloxacin.

Subjects and methods

Subjects

Twelve healthy male volunteers participated in the study, all signed an informed consent form that explained the objectives and possible risks of the study. The study protocol was approved by the Pharmaco LSR Institutional Review Board, Austin, TX, USA.
The subjects were judged to be free of significant disease on the basis of a complete medical history, a full physical examination, clinical laboratory tests and a 12-lead electrocardiogram. The body weights of the subjects (mean 77.2 kg; range 64.4–87.5 kg) were within 10% of ideal for their heights and body frames as defined in actuarial tables. Their ages ranged from 19 to 43 years (mean 26 years). Subjects were excluded from the study if they had used any prescription, over-the-counter or illicit drug in the 2 weeks or any investigational drug in the 4 weeks before participation in the study. Also excluded were smokers and subjects with a known drug or alcohol dependence or drug allergy.

Drug administration

Subjects were confined to the clinic under continuous medical observation for at least 12 h before administration and for 24 h after administration of the study drug. Each subject received four open treatments separated by a 7-day washout period. To balance the study for carry-over effects, a computer-generated randomization code was used to assign the subjects in blocks of four to one of four dosing sequences in the Williams’ design.15 The four treatments were as follows: (treatment A), trovafloxacin administered 30 min after M aalox (R hône-Poulenc Rorer, Collegeville, PA, USA); (treatment B), trovafloxacin administered 30 min after a placebo; (treatment C), trovafloxacin administered 2 h before M aalox; (treatment D), trovafloxacin administered 2 h after omeprazole (Prilosec, Astra/Merck, Wayne, PA, USA). All treatments were administered in the morning. For treatments A and C, M aalox was also given at 22.00 h the night before the study day, 1 and 3 h after meals and at bedtime on the study day. For treatments B and D, placebo and omeprazole were also given at 22.00 h the night before the study day.

All trovafloxacin doses were 300 mg (three 100 mg tablets) and were taken with 150 mL of water. The M aalox formulation used was a suspension containing 600 mg of aluminium hydroxide and 300 mg of magnesium hydroxide per 5 mL. All doses of M aalox consisted of 30 mL of suspension followed by two 30 mL volumes of water to rinse the suspension from its container.

The subjects were required to fast for at least 8 h before the morning dose of trovafloxacin. They continued to fast for 4 h after the dose and then ate a standard meal. The subjects were not allowed to lie down or drink caffeine-containing beverages during the first 4 h after the administration of trovafloxacin.

Blood sampling

Blood sufficient to yield 2.5 mL of serum was drawn into evacuated tubes containing no anticoagulant just before the administration of trovafloxacin and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36 and 48 h after administration for determination of serum concentrations of trovafloxacin. Serum samples were kept frozen at −20°C until analysis.

Assay method

Serum concentrations of trovafloxacin were determined by reversed-phase HPLC with UV detection as previously described.16 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%. The lowest detectable concentration was 0.1 mg/L.

Pharmacokinetic analysis

The peak serum concentration (C max) of trovafloxacin was obtained directly from the experimental data, and the time to peak serum concentration (T max) was defined as the time of the first occurrence of C max. The terminal-phase elimination rate constant (K el) was estimated by least squares regression analysis of the concentration-time data obtained over the terminal log-linear phase. Individual trovafloxacin T 1/2 values were calculated as 0.693/K el. The area under the concentration–time curve from time zero to the time (t) of the last sampling at which a concentration was quantifiable (A U C 0–t) was calculated by the trapezoidal rule. The area under the concentration–time curve from time zero to infinity (A U C) was obtained by adding A U C 0–t and C ed(t)/K el, where C ed(t) is the estimated concentration at t. The mean A U C and C max values and standard deviations presented are geometric. The relative bioavailabilities of treatments A, C and D were determined by calculating the ratios (K el A U C) treatment A / (K el A U C) treatment B / (K el A U C) treatment C / (K el A U C) treatment D.17

Safety evaluation

All observed or volunteered adverse events, regardless of suspected causal relationship to the study drug, were recorded. Blood samples for the following laboratory tests were taken just before the administration of trovafloxacin on study day 1 and after the completion of the study: complete blood count with differential and platelet count; 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. A urinalysis with reflex microscopic evaluation also was performed at these times. Blood pressure, pulse rate and oral
temperature were measured just before and 24 h after the administration of trovafloxacin.

Statistical methods

This study was designed to have a power of at least 80% at the 5% level of significance to detect a 50% difference between treatment groups in the AUC of trovafloxacin. Analysis of variance was performed for the pharmacokinetic variables according to a model that included treatment, sequence-group, period of treatment and treatment-by-period interaction. Treatment effects on pharmacokinetic values were compared on the basis of 90% confidence intervals. Sequence, period and interaction effects were tested at the 5% level of significance.

Results

Sequence effects were statistically not significant for all pharmacokinetic variables, but period effects were significant for AUC, Cₘₐₓ, Tₘₐₓ and Kₑ₋. The treatment-by-period effects were significant for AUC and Cₘₐₓ but were not significant for the other variables. The four-period crossover design used in this study allows treatment effect to be unconfounded by period effects. Examination of 16 treatment-by-period cell means showed that the significant treatment-by-period effects for AUC and Cₘₐₓ did not alter the overall conclusion about treatment effects.

The Figure depicts the mean serum concentrations of the compound after the four treatments. The Table shows the pharmacokinetic parameters of trovafloxacin after treatments A, B, C and D. When 300 mg of trovafloxacin was administered to healthy volunteers 30 min after 30 mL of Maalox dosing (treatment A), trovafloxacin mean AUC and Cₘₐₓ were reduced by 66% (90% confidence limits, 61.7–70.2%) and 60% (90% confidence limits, 53.1–66.3%), respectively, compared with placebo (treatment B). When trovafloxacin was administered 2 h before Maalox dose (treatment C), mean AUC was reduced by about 28% but mean Cₘₐₓ was only slightly affected. Both Maalox treatments decreased the mean T₁/₂ of trovafloxacin by about 4 h. Forty milligrams of omeprazole administered the night before and 2 h before a morning dose of 300 mg of trovafloxacin (treatment D) reduced mean AUC by 18% (90% confidence limits for the ratio of treatment D and treatment B, 72.7–9.44%) and mean Cₘₐₓ by 32% (90% confidence limits, 57.8–80.5%). Omeprazole had no effect on the mean T₁/₂ of trovafloxacin.

The mean Kₑ₋-corrected relative bioavailabilities of trovafloxacin after treatments A and C were 50% and 104%, respectively, suggesting a large reduction in the initial absorption when trovafloxacin was administered 30 min after 30 mL of Maalox. The administration of trovafloxacin 2 h before 30 mL of Maalox appears not to have affected the mean initial absorption of the antibiotic. The mean Kₑ₋-corrected relative bioavailability when trovafloxacin was administered 2 h after 40 mg of omeprazole was 82%.

Discussion

A number of studies have shown that antacids containing polyvalent metal ions reduce the absorption of fluoroquinolone antibiotics.8–10,12 The potential clinical significance of this interaction is illustrated by Noyes & Polk,18

Figure. Mean serum concentrations of trovafloxacin, 300 mg, in healthy male volunteers (n = 12) receiving treatment with 30 mL of Maalox taken 30 min before trovafloxacin (▲, treatment A), placebo (●, treatment B), 30 mL of Maalox taken 2 h after trovafloxacin (□, treatment C), or 40 mg of omeprazole taken 2 h before trovafloxacin (◇, treatment D).
who report a failure of fluoroquinolone treatment resulting from concurrent treatment with an aluminium- and magnesium-containing antacid suspension.

The principal mechanism of the interaction between metal ion-containing antacids and fluoroquinolone antibiotics is thought to be chelation of the antibiotic by the ions. An increase in gastric pH may contribute to the antacid interaction of some fluoroquinolone antibiotics, as is evidenced by the significant decrease in bioavailability observed when enoxacin and ofloxacin were administered concomitantly with H₂-receptor antagonists. The bioavailability of other fluoroquinolones, on the other hand, appears not to be affected by H₂-receptor antagonists.

In the present study, the effect of aluminium- and magnesium-containing antacid Maalox on the oral absorption of the new fluoroquinolone antibiotic trovafloxacin was investigated. To determine independently the effect of an increase in gastric pH on the bioavailability of trovafloxacin, trovafloxacin was also administered 2 h after a 40 mg dose of the proton pump inhibitor omeprazole. This agent was used because it has a potent and long-lasting inhibitory effect on gastric acid secretion but does not alter gastric motility, gastric emptying or urinary acidification, actions that might obscure an effect on trovafloxacin bioavailability of an omeprazole-induced increase in gastric pH.

The administration of Maalox in treatments A (Maalox given 30 min after trovafloxacin) and C (Maalox given 2 h before trovafloxacin) reduced mean trovafloxacin AUC and Tmax by 18% and 32%, respectively. This decrease may have been the result of a decrease in the solubility of trovafloxacin caused by an omeprazole-induced increase in gastric pH.

In conclusion, the concurrent administration of trovafloxacin with aluminium- and magnesium-containing antacids should be avoided. The concurrent administration of omeprazole is unlikely to have a clinically significant effect on the systemic availability of trovafloxacin.

References


