Introduction

Since their introduction, the fluoroquinolone antimicrobial agents have assumed a significant pharmacotherapeutic role in many infections. The class includes a variety of drugs with generally excellent in-vitro activity against most Enterobacteriaceae, fastidious Gram-negative bacilli and Gram-negative cocci. The older fluoroquinolones, especially ciprofloxacin, are less effective against streptococcal and enterococcal species.

Trovafloxacin, 7-(3-azabicyclo[3.1.0]hexyl)-naphthyridone (CP-99,219), is a new synthetic fluoroquinolone with several characteristics that distinguish it from other agents in this class. In-vitro studies have demonstrated that trovafloxacin is active against both Gram-positive and Gram-negative bacteria; its greater activity against clinically important Gram-positive organisms, most notably streptococci such as Streptococcus pneumoniae, extends the spectrum of other fluoroquinolones such as ciprofloxacin and ofloxacin. In-vivo experiments have further shown that trovafloxacin controlled systemic Gram-positive and Gram-negative infections in mice and was more active than either ciprofloxacin, ofloxacin or temafloxacin in protecting mice against lethal infections caused by S. pneumoniae or Streptococcus pyogenes.

The pharmacokinetic characteristics of trovafloxacin also differ from those of most other fluoroquinolones. In a recent study, oral doses of trovafloxacin 100-1000 mg had a mean elimination half-life of 10 h. This is considerably longer than those of many other fluoroquinolones including ciprofloxacin, and should permit once-daily dosing. Unlike most other fluoroquinolones, trovafloxacin is eliminated primarily by nonrenal excretion. The mean urinary recovery of trovafloxacin after oral doses up to 1000 mg in healthy volunteers was 7.7%.

Finally, as with most other fluoroquinolones, trovafloxacin is not readily soluble in aqueous solution and therefore not suitable for iv administration. Atratrofloxacin (CP-116,517), the L-Ala-L-Ala prodrug of trovafloxacin, was not detectable in plasma samples collected after the end of infusion, indicating rapid conversion to trovafloxacin. Maximum serum concentrations of trovafloxacin were achieved at the end of the infusions. Mean maximum plasma trovafloxacin concentrations for the four atratrofloxacin doses were 0.4, 1.8, 2.3 and 4.3 mg/L. The mean area under the concentration-time curve increased proportionally with the dose. The elimination half-life ($T_{1/2}$) for trovafloxacin was independent of the dose and the mean $T_{1/2}$s for the 100, 200 and 300 mg equivalent doses of atratrofloxacin were 10.4, 12.3 and 10.8 h. Approximately 10% of the equivalent dose was recovered as unchanged trovafloxacin in the urine. No clinical adverse or laboratory reactions were associated with iv administration of atratrofloxacin and its conversion to trovafloxacin. These results indicate that atratrofloxacin is rapidly converted to trovafloxacin and that the pharmacokinetic parameters for this new fluoroquinolone after iv administration of its parent compound are similar to those reported after oral administration of equivalent trovafloxacin doses.

Pharmacokinetics and safety of trovafloxacin in healthy male volunteers following administration of single intravenous doses of the prodrug, atratrofloxacin

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Fifteen healthy male volunteers (in four groups) received single 1 h iv infusions of atratrofloxacin (CP-116,517) equivalent to 30, 100, 200 or 300 mg of its active metabolite, trovafloxacin (CP-99,219). Blood and urine were sampled over 73 and 72 h, respectively, and plasma levels of atratrofloxacin and serum concentrations of trovafloxacin were determined by HPLC with UV detection. Atratrofloxacin was not detectable in plasma samples collected after the end of infusion, indicating rapid conversion to trovafloxacin. Maximum serum concentrations of trovafloxacin were achieved at the end of the infusions. Mean maximum plasma trovafloxacin concentrations for the four atratrofloxacin doses were 0.4, 1.8, 2.3 and 4.3 mg/L. The mean area under the concentration-time curve increased proportionally with the dose. The elimination half-life ($T_{1/2}$) for trovafloxacin was independent of the dose and the mean $T_{1/2}$s for the 100, 200 and 300 mg equivalent doses of atratrofloxacin were 10.4, 12.3 and 10.8 h. Approximately 10% of the equivalent dose was recovered as unchanged trovafloxacin in the urine. No clinical adverse or laboratory reactions were associated with iv administration of atratrofloxacin and its conversion to trovafloxacin. These results indicate that atratrofloxacin is rapidly converted to trovafloxacin and that the pharmacokinetic parameters for this new fluoroquinolone after iv administration of its parent compound are similar to those reported after oral administration of equivalent trovafloxacin doses.
trovafloxacin, has high aqueous solubility and is rapidly converted to trovafloxacin in the body. This prodrug might thus provide a practical iv dosage form that retains the favorable antimicrobial and pharmacokinetic characteristics of trovafloxacin. The study reported here was undertaken to evaluate the safety, tolerability, and pharmacokinetics of trovafloxacin after escalating single doses of alatrofloxacin in healthy male volunteers.

Subjects and methods

Subjects

Sixteen healthy male volunteers (aged 18–42 years, mean 26 years, and weighing 64.4–90.7 kg, mean 76.1 kg) were enrolled. A II volunteers were required to test negative for serological markers of previous infection with hepatitis B virus or hepatitis C virus, as well as on a urine drug screen and an ethanol breath test. Each subject provided written informed consent before entering the study, and the study was approved by the local ethics committee. Exclusion criteria included: concomitant drug therapy; a history or evidence of systemic disease; known drug or alcohol dependence, drug allergies or smoking habit; intended donation of blood or blood products during or for 1 month after completion of the study; supine blood pressure of >140/90 mm Hg or <90/60 mm Hg; heart rate of >100 or <60 beats per minute; abnormal haematological or biochemical screening tests; use of prescription drug therapy, over-the-counter medications and recreational drugs within 2 weeks and use of any investigational drug within 4 weeks before the start of the study.

Study design

In this double-blind, placebo-controlled randomized study, subjects received placebo or alatrofloxacin at doses equivalent to 30, 100, 200 or 300 mg of trovafloxacin. Each group consisted of four subjects who received alatrofloxacin and two who received placebo.

A latrofloxacin and placebo were administered as iv infusions over 1 h. Subjects fasted for at least 8 h before and 4 h after the start of the infusion. In the first six subjects alatrofloxacin was initially infused at 5 mg/mL (four at the 30 mg and two at the 100 mg dosage); however, as a result of local skin reactions, the infusate concentration was reduced to 1 mg/mL for subsequent subjects. During the infusion the ECG and EEG were monitored continuously, the ECG by telemetry, with strip chart recording every 15 min and for any observed abnormality; the EEG was continued for 1 h after infusion of the study drug. Blood pressure and heart rate were measured at frequent intervals during and immediately after the infusion and then at the times of blood sampling (see below).

Sample collection

Blood sufficient to provide 2.5 mL of serum for determination of trovafloxacin concentrations was collected before the start of the infusion and at the following times afterwards: 15, 30, 45, 55, 60, 75 and 90 min, and 2, 2.5, 3, 4, 5, 7, 9, 11, 13, 17, 25, 37, 49, 61 and 73 h. A ditional blood sufficient to provide 2.5 mL of plasma for analysis of alatrofloxacin was collected at each of the above-listed times up to 4 h after the infusion. Blood samples for determination of alatrofloxacin were immediately placed into pre-chilled (4°C) heparinized collection tubes containing 0.2 M KH₄PO₄ (pH 3) to stabilize alatrofloxacin. The ratio of buffer to whole blood was 3:1.

A II urine voided during the 72 h after the start of infusion was collected at timed intervals. For the first 24 h, urine was collected over 0–3, 3–6, 6–12 and 12–24 h. For the remaining time up to 72 h after the infusion began, urine was collected over each 24 h period. Ten millilitres of fresh urine from each collection was immediately transferred into pre-chilled (4°C) tubes containing 30 mL of 0.2 M KH₄PO₄ (pH 3). These samples were stored at −70°C until analysis for alatrofloxacin. Twenty millilitres from each urine collection was frozen at −70°C for analysis of trovafloxacin.

Analysis of alatrofloxacin in serum and urine

The concentrations of trovafloxacin, mono-AL-trovafloxacin (CP-114,099) and alatrofloxacin in serum, plasma and urine were determined by HPLC with UV detection, as described previously. After solid-phase extraction, a C₁₈ column with a phosphate mobile phase was used to extract the samples. Trovafloxacin, alatrofloxacin, CP-114,099 and internal standards were detected by UV absorbance at 275 nm. The linear dynamic range of the assay for trovafloxacin was 0.1–20.0 mg/L, that for alatrofloxacin was 0.3–20 mg/L, and that for CP-114,099 was 0.25–10 mg/L.

Pharmacokinetic analysis

A latrofloxacin and CP-114,099 are both rapidly converted to trovafloxacin in human whole blood or serum. Thus, serum concentrations of trovafloxacin determined after iv administration of alatrofloxacin are actually the sum of the concentrations of alatrofloxacin, CP-114,099 and trovafloxacin. Trovafloxacin serum concentrations presented in this report are corrected by subtraction of both alatrofloxacin and CP-114,099 concentrations.

The terminal elimination rate constant (Kₑ) for trovafloxacin was estimated by least squares regression analysis of the serum concentration–time data obtained over the terminal log-linear phase. Individual terminal phase Tₑ½S were calculated as 0.693/Kₑ.

The area under the concentration–time curve from 0 h
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to the last sampling time with a quantifiable trovafloxacin concentration \( (AUC_{0-t}) \) was calculated by the linear trapezoidal rule. The \( AUC \) from \( t \) to infinity \( (AUC_{t-\infty}) \) was estimated as \( C_{est}(t)/K_{el} \), where \( C_{est}(t) \) is the estimated serum concentration at time \( t \) based on the regression analysis described above. The total area under the concentration–time curve from zero to infinity \( (AUC_{0-\infty}) \) was estimated as the sum of \( AUC_{0-t} \) and \( AUC_{t-\infty} \).

The maximum serum concentration \( (C_{max}) \) for trovafloxacin was obtained directly from the experimental data, and its clearance \( (Cl) \) was estimated as dose/\( AUC_{0-\infty} \), assuming that alatrofloxacin was completely converted to trovafloxacin. Volume of distribution \( (V_{dss}) \) was calculated as \( (Cl)(AUMC/AUC_{0-\infty} - T/2) \), where \( AUMC \) is the area under the first moment curve from 0 h to infinity and \( T \) is the infusion time.\(^{17} \) Renal clearance \( (Clr) \) was estimated as the ratio of the amount of trovafloxacin excreted in the urine to \( AUC_{0-\infty} \).

Statistical analysis

The relationships between the dose of alatrofloxacin and \( C_{max} \), \( AUC_{0-t} \) and \( AUC_{0-\infty} \) were evaluated by linear correlation. The relationships between the dose of alatrofloxacin and \( Cl \) and \( K_{el} \) were assessed by one-way analysis of variance. The accepted significance level for all analyses was \( P < 0.05 \).

Safety evaluations

All observed or volunteered adverse reactions were recorded. Vital signs were recorded frequently before and after alatrofloxacin infusion. A physical examination and laboratory tests, including full blood count with differential and platelet counts, urinalysis and serum chemistry profile, were performed at the beginning and were repeated at the end of the study.

Results

The results from fifteen subjects were used for the pharmacokinetic analysis; one subject was excluded from the study as his baseline liver function tests did not meet the entry criteria. Four received the 30 mg equivalent dose of alatrofloxacin; four received the 100 mg dose; three received the 200 mg dose; and four were infused with the 300 mg dose.

Plasma concentrations of alatrofloxacin

Alatrofloxacin was generally not detectable in plasma except during, and up to 5 min after, the infusion in subjects given doses equivalent to either 200 or 300 mg of trovafloxacin. Plasma concentrations of alatrofloxacin were <0.5 mg/L in all cases.

Trovafloxacin pharmacokinetics

Mean concentration–time curves for trovafloxacin after administration of alatrofloxacin doses equivalent to 30, 100, 200 and 300 mg of trovafloxacin are illustrated in Figure 1. Serum concentrations of trovafloxacin reached maximum levels by the end of the 1 h infusions. The \( C_{max} \) values (geometric mean ± S.D.) for alatrofloxacin doses equivalent to 30, 100, 200 and 300 mg of trovafloxacin were 0.4 ± 0.0, 1.8 ± 0.3, 2.3 ± 0.5 and 4.3 ± 1.0 mg/L (Figure 2a). The respective values for \( AUC_{0-\infty} \) for alatrofloxacin doses equivalent to 100, 200 and 300 mg of trovafloxacin were 16.4 ± 5.2, 31.2 ± 5.2 and 43.4 ± 5.8 mg.h/L. Significant \( (P < 0.05) \) linear correlations were
J. Vincent et al. noted between the dose of alatrofloxacin and $C_{\text{max}}$ ($r^2 = 0.95$), $AUC_{0-t}$ ($r^2 = 0.98$) and $AUC_{0-\infty}$ ($r^2 = 0.98$) (Figure 2). Alatrofloxacin dose had no significant effect on $Cl$, $K_{el}$ or $T_{1/2}$ for trovafloxacin (Table).

Renal elimination of trovafloxacin

Comparison of $Cl$ and $Cl_r$ indicated that only a small portion of trovafloxacin was eliminated through the kidneys. Renal clearances of trovafloxacin after administration of the alatrofloxacin dose equivalents are listed in the Table. Therefore for the 100 mg equivalent dose of CP116,517, $Cl_r$ was $10.7 \pm 3.7\%$ of $Cl$; for the 200 mg dose, 10.5 ± 3.0% and for the 300 mg dose, 12.1 ± 2.7% (Figure 3). The average $Cl_r$ was 10.5 ± 2.5% of $Cl$ for the three doses.

Table. Pharmacokinetic parameters for trovafloxacin after administration of 30–300 mg trovafloxacin-equivalent doses of alatrofloxacin

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>30</th>
<th>100</th>
<th>200</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)$^a$</td>
<td>0.4</td>
<td>1.8</td>
<td>2.3</td>
<td>4.3</td>
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<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
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<td>$AUC_{0-t}$ (mg h/L)</td>
<td>3.1</td>
<td>13.0</td>
<td>29.2</td>
<td>40.0</td>
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<tr>
<td>$AUC_{0-\infty}$ (mg h/L)</td>
<td>ND</td>
<td>16.4</td>
<td>31.2</td>
<td>43.4</td>
</tr>
<tr>
<td>$Cl$ (mL/h/kg)</td>
<td>ND</td>
<td>85.4</td>
<td>76.3</td>
<td>96.9</td>
</tr>
<tr>
<td>$Cl_r$ (mL/h/kg)</td>
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<td>9.7</td>
<td>7.0</td>
<td>11.2</td>
</tr>
<tr>
<td>$V_{dss}$ (L/kg)</td>
<td>ND</td>
<td>12.1</td>
<td>1.30</td>
<td>1.38</td>
</tr>
<tr>
<td>$\lambda_f$ (h$^{-1}$)</td>
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<td>0.067</td>
<td>0.057</td>
<td>0.064</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)$^c$</td>
<td>ND</td>
<td>10.4</td>
<td>12.3</td>
<td>10.8</td>
</tr>
</tbody>
</table>

$^a$Values reported are mean ± s.d.; means are geometric for $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$.

$^b$Estimated as $0.693/\text{mean } \lambda_f$; thus, standard deviations are not provided.

ND, Not calculated because the assay was not sensitive enough to follow the serum profile for a sufficient interval.

Figure 2. (a) Mean $C_{\text{max}}$ values for trovafloxacin after iv infusion of 30–300 mg equivalent doses of alatrofloxacin. (b) Mean $AUC_{0-t}$ values for trovafloxacin after the 100–300 mg equivalent doses of alatrofloxacin. (c) Mean $AUC_{0-\infty}$ for the same doses.

Figure 3. Total $Cl$ (□) and percent $Cl_r$ (■), $\% Cl_r = \left(\frac{Cl_r}{Cl}\times 100\right)$ for trovafloxacin after the 100–300 mg equivalent doses of alatrofloxacin.
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Safety

A latrofloxacin was well tolerated over the dose range studied. No clinically significant abnormal vital signs or laboratory values were recorded during infusion. No EEG or ECG changes were observed in these subjects at any of the doses. A cutaneous reaction consisting of erythema around the site of the iv needle was observed, especially with the higher doses. The erythema consisted of non-confluent papular eruptions with clearly demarcated but non-palpable borders. In some subjects there was associated irritation and a burning sensation. These events occurred in two subjects at 300 mg, one subject each at 100 mg and 200 mg, and four in the pooled placebo group. They were all described as mild and usually cleared soon after discontinuation of infusion.

Discussion

The present results support several conclusions. First, alatrofloxacin is rapidly converted to trovafloxacin after iv administration. Second, the pharmacokinetic profile for trovafloxacin after iv administration of alatrofloxacin is comparable to that reported for similar doses of orally administered trovafloxacin. The pharmacokinetics of trovafloxacin are characterized by linear and dose-proportional C_max, and AUC and by dose-independent Cl and T_1/2. Finally, iv infusion of CP-116,515 is well tolerated over the dose range evaluated, as is oral administration of trovafloxacin.

The rapid conversion of alatrofloxacin to trovafloxacin is supported by the observation that it was usually undetectable by the end of the 1 h infusion. Low levels of alatrofloxacin (<0.5 mg/L) were detected in samples taken during infusion only in those subjects who received the higher doses, equivalent to 200 or 300 mg of trovafloxacin. The C_max, AUC_0-24, and AUC_0-∞ data presented here for trovafloxacin indicate linear and dose-proportional pharmacokinetics. This linear dose-proportional response is also supported by the results of Teng et al., who showed that both C_max and AUC increased linearly with dose for orally administered trovafloxacin dose between 30 and 600 mg. The linear dose-proportionality of trovafloxacin in the present study and that of Teng et al. is not the case for all fluoroquinolones. For example, Zürcher et al. reported that a single iv dose of pefloxacin 400 mg resulted in a C_max of 7.9 mg/L, which increased to only 8.0 mg/L after a 600 mg dose.

The T_1/2 of trovafloxacin remained approximately 10 h regardless of dose. This dose independence is consistent with previous findings. Dose-independent elimination appears to be a property shared by most fluoroquinolones. The T_1/2 for trovafloxacin, however, is considerably longer than those of most other agents in this class. For example, ciprofloxacin has a T_1/2 of 3.3 h and requires bd dosing with either oral or iv administration. The longer T_1/2 of trovafloxacin should permit once-daily dosing. A reduced frequency of dosing might be expected to decrease the cost of iv therapy and improve compliance with oral outpatient treatment.

The present study confirms previous results demonstrating that the route of trovafloxacin elimination was primarily nonrenal. In the present study, renal elimination accounted for only about 10% of the total trovafloxacin clearance, and this percentage did not differ significantly with dose. Teng et al. reported a mean urinary recovery for trovafloxacin of 7.7%. These results indicate dose-independent elimination of trovafloxacin.

The routes of elimination of different fluoroquinolones vary markedly. Elimination occurs by both renal and nonrenal routes for norfloxacin, ciprofloxacin, enoxacin, fleroxacin and lomefloxacin. In contrast, the elimination of ofloxacin is almost entirely renal, whereas that for pefloxacin is almost entirely nonrenal. The primarily nonrenal elimination of trovafloxacin minimizes possible alteration of its pharmacokinetic profile in patients with renal dysfunction, as has been reported for other fluoroquinolones. Nevertheless, trovafloxacin administered in oral or iv doses exceeding 100 mg achieved urinary concentrations sufficient to inhibit the Gram-negative bacteria most often responsible for urinary tract infections.

Safety data indicated that single iv doses of alatrofloxacin equivalent to up to 300 mg trovafloxacin were tolerated in a similar manner to 300 mg of orally administered trovafloxacin.

In summary, alatrofloxacin is rapidly converted to trovafloxacin, and the pharmacokinetic parameters of trovafloxacin after iv administration of its prodrug are similar to those reported after oral administration of similar doses of trovafloxacin.

References


