Pharmacokinetics and absolute bioavailability of sitafloxacin, a new fluoroquinolone antibiotic, in healthy male and female Caucasian subjects

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1. The aim was to compare the pharmacokinetics of sitafloxacin from a capsule formulation (dose of 500 mg sitafloxacin) and an intravenous (i.v.) formulation infused over 1 h (dose of 400 mg sitafloxacin) in healthy male and female subjects and to estimate the absolute bioavailability of sitafloxacin from the capsule formulation.

2. Following oral administration, sitafloxacin was rapidly absorbed, with a mean maximum concentration in plasma ($C_{\text{max}}$) of 4.65 mg ml$^{-1}$ occurring at a median $t_{\text{max}}$ of 1.25 h giving a mean AUC(0→28) = 28.1 μg h ml$^{-1}$. For the i.v. administration, a mean $C_{\text{max}}$ = 5.53 μg ml$^{-1}$ occurred at the end of the 1-h infusion with a mean AUC(0→25) = 25.4 μg h ml$^{-1}$. The mean terminal elimination half-life was 7.0 h (oral) and 6.6 h (i.v.). For the oral and i.v. formulations, the mean total plasma clearance was 296 and 263 ml min$^{-1}$, respectively and the mean volume of distribution was 180 and 150 litres, respectively.

3. Within 48 h post-dose, ~61% (range 26–86%) of the administered dose was excreted unchanged in urine following capsule administration, compared with ~75% (range 42–101%) following the i.v. formulation. For both formulations, the renal clearance of sitafloxacin (means of 181 and 198 ml min$^{-1}$ for the capsule and i.v. doses, respectively) implies active tubular secretion of the drug.

4. The absolute bioavailability of sitafloxacin from the capsule formulation was high at 89%, with a 95% CI of 84–94%. The intersubject variability (CV%) in the sitafloxacin AUC(0→∞) for the capsule was low at 18.6%.

5. Gender differences in the pharmacokinetics of sitafloxacin were small and would not warrant dose adjustment.

6. The findings show that the capsule formulation offers good oral bioavailability and merits further clinical evaluation of sitafloxacin as an orally effective fluoroquinolone antibacterial.

Introduction

Sitafloxacin, (−)-7-[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinoxaline-carboxylic acid (figure 1) is a new fluoroquinolone antibacterial agent undergoing clinical development (as the sequihydrate form) for the treatment of systemic bacterial infections. It exhibits high activity against Gram-positive,
-negative and anaerobic organisms (Milatovic et al. 2000) and is effective against resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) (Shetty and Wilson 2000). Its mechanism of action involves inhibition of bacterial DNA-gyrase (topoisomerase II), an enzyme required for DNA replication.

Several early pilot studies showed that orally administered sitafloxacim, given to healthy subjects (volunteers), was rapidly and extensively absorbed and that elimination of the drug was largely by renal excretion, which could account for some 50–70% of the dose. Metabolism is only a relatively minor pathway of elimination for this drug; urinary and plasma metabolites of sitafloxacim that have been identified include the acyl glucuronic acid conjugate of the parent drug, N-acetylsitafoxacin and the two metabolites arising from the oxidative deamination and consequent reduction of the ketone metabolite to the hydroxy form (Daiichi 2000, unpublished data). Although some of these metabolites have antibacterial properties in vitro they probably contribute little, if any, to the overall systemic antibacterial properties of sitafloxacim itself.

Sitafloxacim has the properties of an ampholytic electrolyte due to the presence of a carboxyl and an amino group in its molecular structure; it shows a relatively low aqueous solubility (100 μg ml⁻¹), but higher solubilities in organic solvents such as chloroform (3000 μg ml⁻¹). In view of these solubility characteristics it became of obvious importance to develop and evaluate an oral formulation of sitafloxacim which could provide adequate oral bioavailability and plasma level profiles compatible with providing effective plasma antibacterial concentrations.

This paper describes the pharmacokinetics of intravenously and orally administered (capsule formulation) sitafloxacim given to healthy male and female subjects in an open, randomized, balanced, two-period crossover study.

**Materials and methods**

**Test compounds**

Daiichi Pharmaceutical Co. Ltd. (Tokyo, Japan) supplied hard, yellow capsules containing 250 mg sitafloxacim and an intravenous (i.v.) solution of 2 mg ml⁻¹ sitafloxacim. The doses were expressed as the equivalents of the anhydrate of sitafloxacim.
Subjects

Twenty-four healthy Caucasian subjects (twelve males, twelve females) participated in this study. Before commencement, ethical approval of the study was obtained from the Covance Clinical Research Unit (Leeds, UK) Independent Review Board and, prior to participation in the study, each subject provided their written informed consent. The subjects were aged between 21 and 52 years. Body weights ranged between 69.4 and 101.3 kg for males and 55.8 and 82.2 kg for females. Subjects were healthy as assessed by physical examination, standard biochemical, haematological and urinalysis screening, vital signs and 12-lead electrocardiography. The subjects had taken no prescribed medications for 14 days before dosing and no over-the-counter medications had been taken by the subjects for 7 days before dosing. Alcohol, caffeine-containing food and beverages, grapefruit and grapefruit juice were prohibited during the study. Treatment randomization to the sequence of oral and i.v. treatments was performed using a computer-generated pseudo-random permutation procedure.

Dosing and sample collection

An oral formulation (capsule) and an i.v. formulation (1 h constant rate infusion) of sitafloxacin, at dose levels of 500 and 400 mg, respectively, were administered to the subjects in a two-period crossover design. There was an interval of at least 7 days between treatments. Subjects were studied in two groups, each comprising of six males and six females. Each treatment period comprised of day −1 and days 1–3; dosing occurred on the morning of day 1. For each group, in each treatment period, six subjects received the oral formulation and six subjects received the i.v. formulation such that overall each subject received a single oral and a single i.v. dose of sitafloxacin. Breakfast was not permitted on the day of dosing. Lunch, an afternoon snack and an evening meal were provided at ∼4.5, 7.5 and 10.5 h, respectively, after dosing. Water consumption was restricted from 1 h pre-dose up to 2 h post-dose.

Blood samples for the determination of plasma concentrations of sitafloxacin were collected from each subject in each treatment period pre-dose and at 30, 45, 60, 75, 90 min, 2, 3, 4, 6, 12, 18, 24, 36 and 48 h post-dose following oral dosing and pre-dose, 30, 60 (end of infusion), 65, 70, 80, 90, 105 min, 2, 3, 4, 6, 8, 12, 18, 24, 36 and 48 h after the start of the infusion. The sampling times were selected from previous pharmacokinetic studies with sitafloxacin to give a reliable measure of the extent of bioavailability. The samples were centrifuged within 1 h of collection, at ∼1500 g for 10 min at ∼4°C. For each sample, the separated plasma was transferred into two 5 ml polypropylene tubes and stored at approximately −20°C, pending analysis. Urine samples were collected from pre-dose (−12 to 0 h) and 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36 and 36–48 h after oral dosing or the start of the infusion. Two subsamples (each ∼10 ml) were removed into polypropylene tubes and stored at about −20°C, pending analysis.

Quantification of sitafloxacin in plasma and urine

The concentrations of sitafloxacin in plasma and urine were determined using a validated method incorporating solid-phase extraction for sample preparation and high-performance liquid chromatography (HPLC) with post-column photolysis.
and fluorescence detection. A post-column photolysis procedure was used as it has been found that it produces a marked enhancement of the fluorescent intensity of halogenated quinolones through the elimination of halogen substituents (Aoki et al. 1994) and structural rearrangements (Matsumoto et al. 1992).

Briefly, plasma and urine study samples, quality control (QC) samples and control matrix were thawed at room temperature and each tube was then vortex mixed and centrifuged at a nominal 4°C for 5 min at 3500 rpm. A 200-μl aliquot of sample was then transferred into glass tubes, to which 400μl 50μM potassium dihydrogen orthophosphate was added, followed by 200μl (1.25 μlml⁻¹ solution for plasma and 10μgml⁻¹ solution for urine) of a structurally related internal standard (7-[8S]-8-amino-6-azaspiro[3,4]octan-6-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid). All tubes were then vortex mixed.

Before loading with sample, each solid-phase extraction cartridge (C8 Isolute, Jones Chromatography, Hengoed, UK) was primed with 3 ml methanol followed by 2 ml water and finally 3 ml 50μM potassium dihydrogen orthophosphate. The sample solutions (800μl) were then individually transferred to the cartridges. Each solid-phase cartridge was washed with 3 ml 50μM potassium dihydrogen orthophosphate followed by 2 ml of a solution of tetrahydrofuran (THF)/water (20:80 v/v). Sitafoxacin and the internal standard were then eluted from each solid-phase extraction cartridge into glass tubes with 2 ml of a solution of THF/0.15% orthophosphoric acid (30:70 v/v). The resulting eluate was mixed thoroughly and transferred into amber microvials.

Chromatography was achieved using an Inertsil ODS2-150 (5μm) analytical column (15×4.6 mm i.d., Hichrom, Reading, UK) together with an Inertsil ODS2-10C (5 μm) guard column (10 × 3.2 mm i.d.; Hichrom) at room temperature. An injection volume of 50–100 μl was used. The mobile phase was potassium dihydrogen orthophosphate (50 μM, pH 2.0)/THF/ammonium acetate solution (1 μM) (3240:760:40 v/v/v) at a flow rate of 1.0 ml min⁻¹. The analytical instrumentation consisted of a PU-980 pump (Jasco UK, Great Dunmow, UK) with a Gilson 231XL autosampler (Anachem, Luton, UK). The post-column photolysis was achieved using a Beam Boost system incorporating a Beam Boost lamp (IC89500) together with a Beam Boost reaction coil (5 m × 0.3 mm i.d.) supplied by Technicol (Congleton, UK). Sitafoxacin and the internal standard were detected using a FP-920 fluorescence detector (Jasco) with an excitation wavelength of 280 nm and an emission wavelength of 430 nm.

The signal from the fluorescence detector was integrated to produce peak height. Concentrations in calibration standards, QC samples and study samples were obtained by interpolation of their peak height ratios (sitafoxacin/internal standard) from the calibration curves. Chromatography showed the sitafoxacin and internal standard peaks at retention times of ~10 and 15 min, respectively, with a run time of 20 min.

The lower limit of quantification of sitafoxacin in plasma was 10 ng ml⁻¹ and the interassay precision of the QC samples analysed throughout the study ranged between 6.2 and 7.1% at concentrations of 30–1500 ng ml⁻¹ (analysed after dilution with control human plasma), with the interassay accuracy between 104.5 and 112.4%. The lower limit of quantification of sitafoxacin in urine was 0.1 μg ml⁻¹ and the interassay precision of QC samples analysed throughout the study ranged between 3.1 and 7.6% at concentrations of 0.3–15.0 μg ml μ (analysed after dilution...
with control human urine), with the interassay accuracy between 104.5 and 112.4%.

**Pharmacokinetic calculations and statistical analysis**

The software used for the pharmacokinetic analyses was SAS v.6.12 (SAS Institute, Inc., Cary, NC, USA). Pharmacokinetic parameters were calculated using non-compartmental procedures from the bioanalytical data. Maximum plasma concentrations ($C_{\text{max}}$) and time to maximum concentration ($t_{\text{max}}$) were determined by examination of the plasma concentration-time profiles. The apparent terminal elimination rate constant, $\lambda_z$, was determined by linear regression of the logarithm of plasma concentration-time curve over the terminal linear disposition phase. The start points of the elimination phase for each subject were defined by visual inspection of the profiles of logarithmic plasma concentrations. The terminal elimination half-life ($t_{1/2}$) was calculated from $\ln(2)/\lambda_z$. The areas under the curve for plasma concentrations were calculated using linear trapezoids from pre-dose to $t_{\text{max}}$ and log-linear trapezoids from $t_{\text{max}}$ to 24 h post-dose for AUC(0-24 h) and to the last quantifiable plasma concentration ($C_z$ at time $t_z$) for AUC(0-$t_z$). Extrapolation to infinity from the last quantifiable plasma concentration ($C_z/\lambda_z$) was performed to estimate AUC(0-$\infty$). Mean residence time (MRT) was calculated for the oral dose as the ratio of the area under the first moment curve to infinity [($\text{AUMC}(0-\infty)$)] to AUC(0-$\infty$). The intrinsic MRT (MRT$_{\text{int}}$) for the i.v. dose was calculated as for the oral dose, but with a correction of minus half the infusion time. Total plasma clearance of sitafloxacin, $\text{CL}/F$ for the oral dose and $\text{CL}$ for the i.v. dose, were calculated from the dose divided by AUC(0-$\infty$). During the elimination phase, the volume of distribution, $V_z/F$ and $V_z$ for the oral and i.v. doses, respectively, was calculated from ($\text{CL}/F$)/$\lambda_z$ and $\text{CL}/\lambda_z$, respectively. The amount of sitafloxacin excreted in the urine ($A_e$) was calculated for each collection period and then combined over 0–48 h post-dose. The percentage of the dose excreted, $f_e$, was calculated as the ratio of $A_e$ to the dose for each collection interval and over 0–48 h post-dose. Renal clearance, $\text{CL}_R$, was calculated over 0–48 h post-dose as the ratio of $A_e$ to AUC. The absolute bioavailability of sitafloxacin was calculated as the ratios of AUC(0-$\infty$) (primary variable) and $A_e$(0–48 h) (secondary variable), between the oral and i.v. doses, corrected for the dose level administered.

Statistical analyses of the pharmacokinetic data were performed for all subjects with the exception of three females (subjects 12, 19, 23). For Subjects 12 and 19, there were practical problems obtaining some blood samples for the analysis of sitafloxacin following the i.v. treatment. For subject 23, data following the i.v. treatment only were obtained as the subject was withdrawn from study after completing treatment period 1.

The pharmacokinetic parameters (including dose and body weight normalized variables (norm)), with the exception of $t_{\text{max}}$, were analysed by analysis of variance. Least squares (LS) means were calculated for the capsule and i.v. formulations of sitafloxacin for males, females and both sexes combined (overall). Ratios and 95% CI were calculated for the comparisons of the capsule formulation relative to the i.v. formulation for all subjects and male and female subjects separately for AUC(0-$\infty$) (norm) and $f_e$(0–48 h). Ratios and 95% CI were calculated for the comparison of females relative to males for each formulation separately for all
parameters analysed. For $t_{\text{max}}$, median differences and 95% CI for the gender comparisons were performed using non-parametric methods.

**Results**

*Safety and tolerability*

Twenty-four subjects (12 males, 12 females) entered the study of which 23 completed as planned. One female was withdrawn due to concerns about rechallenge with sitafloxacin, following an urticarial rash during the i.v. dosing in the first treatment period, which resolved after 2 h 40 min. The urticaria was mild in severity and considered as probably treatment-related. Overall, sitafloxacin was generally well tolerated following administration of the capsule and i.v. formulations. There were no severe, serious or life-threatening adverse events during the study. The incidence of treatment-emergent adverse events was low following the capsule and i.v. formulations with most subjects not reporting any drug-related adverse events. The majority of drug-related adverse events were mild in severity. The most frequently reported adverse event for both oral (capsule) and i.v. dosing was mild diarrhoea, reflecting the results of previous studies with sitafloxacin. There were no clinically significant findings in the vital signs or 12-lead ECG parameters for each formulation, and there were no changes in any of the laboratory safety parameters during the study considered to be of clinical significance. In addition, there were no clinically significant changes in the physical examination or the dermatological examination findings during the study and no trends in body weight.

*Pharmacokinetic parameters of sitafloxacin*

Following i.v. administration of a single 400 mg dose of sitafloxacin, plasma concentrations of sitafloxacin were maximal at the end of the 1 h infusion (figure 2). Following oral administration of a single 500 mg dose of sitafloxacin as the capsule
formulation, plasma concentrations of sitafloxacin were above the lower limit of quantification (10 ng ml\(^{-1}\)) at 30 min post-dose (the first blood sampling time) for all subjects (figure 3). After reaching \(C_{\text{\text{\footnotesize max}}}\), the semilogarithmic concentration-time curves revealed that the plasma concentrations of sitafloxacin declined in a biphasic manner for both formulations. Sita\text{f}loxacin concentrations were quantifiable in plasma for at least 36 h post-dose in all subjects and up to 48 h post-dose in the majority of subjects, following administration of both formulations.

The pharmacokinetic parameters for the i.v. and oral doses of sitafloxacin are given in tables 1 and 2. The mean plasma concentration-time curves showed sitafloxacin was rapidly absorbed from the oral capsule formulation with median \(t_{\text{\text{\footnotesize max}}}\) occurring at 75 min post-dose. Comparison of the pharmacokinetics of sitafloxacin in males and females showed that AUC(0–24 h) and AUC(0–\(\infty\)) were \(\sim 14\%\) higher in females than in males for the capsule formulation and \(\sim 15\%\) higher for females for the i.v. formulation. These differences were essentially accounted for by the differences in body weight between the two genders. Following the i.v. formulation, mean total plasma clearance in females and males was 243 and 278 ml min\(^{-1}\), respectively, with corresponding volumes of distribution during the terminal phase (\(V_z\)) of 137 and 160 litres. These small differences between males and females were again reduced following correction for body weight. For both the i.v. and capsule formulation, the terminal elimination half-life of sitafloxacin was similar for both genders, at \(\sim 7\) h.

The rate of urinary excretion of sitafloxacin, following both the i.v. and capsule formulations was greatest during the 0–2 h period post-dose, with means of 20.7 and 10.6\% of the dose being excreted for the two treatments, respectively. The fraction excreted then became progressively less with time. The fraction of the administered dose renally excreted as sitafloxacin over the 48 h post-dose was \(\sim 75\%\) for the i.v. formulation and 61\% for the capsule. For both formulations, the fraction excreted over 48 h post-dose was lower for females than males (by \(\sim 14\) and 24\% for the i.v. and capsule formulations, respectively). The renal clearance (CLR) of sitafloxacin gave means of 198 and 181 ml min\(^{-1}\) for the i.v. and capsule formulations, respectively.
Absolute bioavailability of sitafloxacin from the capsule formulation

The absolute bioavailability [F(AUC)(%)] of sitafloxacin for the capsule formulation, based on a statistical analysis of AUC(0–∞), was 89% (95% CI of 84–94%) for males and females overall, and was very similar in males compared with females (89.4 and 88.3%, respectively). For individual subjects, the absolute bioavailability based on AUC(0–∞) ranged from 70.2 to 106% for males and 74.9 to 103% for females. The absolute bioavailability based on a statistical analysis of $f_e(0–48h)$, for males and females overall, at 80% (95% CI of 74–87%), was less than that based on AUC(0–∞) and was lower for females (75.6%) compared with males (84.7%). For individual subjects, the absolute bioavailability based on $f_e(0–48h)$ ranged from 68.9 to 100% for males and 57.7 to 103% for females.
The between-subject coefficient of variation (CV\%) for the bioavailability of sitafloxac in based on the primary variable, AUC(0\text{–}\infty), was shown to be low at 18.6\% for the capsule, only slightly higher than that for the i.v. infusion (CV\% = 17.3\%). Based on the secondary parameter, $f_e(0\text{–}48\text{ h})$, CV\% = 34.3 and 25.3\% for the capsule and i.v., respectively.
Discussion

This Phase I, open, randomized, balanced, two-period, single-dose crossover study showed sitafloxacin was generally well tolerated in male and female subjects receiving 500 mg sitafloxacin as a solid oral capsule formulation and 400 mg sitafloxacin as a 1 h constant rate i.v. infusion. The most frequently reported drug-related adverse event following both oral (capsule) and i.v. dosing was mild diarrhoea, reflecting the results of previous studies with sitafloxacin. There were no findings in the safety data of clinical significance.

The mean plasma concentration-time curves showed sitafloxacin was rapidly absorbed from the oral capsule formulation with median $t_{max}$ occurring at 75 min post-dose. Comparison of the pharmacokinetics of sitafloxacin in males and females showed only small differences between genders and these were essentially accounted for by the lower body weight of females compared with males. These small gender differences would not warrant any dose adjustment for sitafloxacin when administered to males and females.

The absolute bioavailability of sitafloxacin from the capsule formulation was high with a mean (95% CI) of 89% (84–94%) when based on AUC(0–$\infty$) data. This high bioavailability was associated with a low between-subject variability in AUC(0–$\infty$), with the between-subject coefficient of variation (CV%) being 18.6% for the capsule, only slightly higher than that for the i.v. infusion (CV% = 17.3%). Based on $f_{a}(0–48\ h)$, the absolute bioavailability determined for the capsule formulation was slightly less at 80%. The reason for the differences in absolute bioavailability between the AUC(0–$\infty$) and $f_{a}(0–48\ h)$ may demonstrate a small dose-route related difference in the urinary excretion of sitafloxacin. Based on the secondary parameter, $f_{a}(0–48\ h)$, the CV% were higher than those based on AUC(0–$\infty$), but showed a similar trend for the two formulations (CV% = 34.3 and 25.3% for capsule and i.v., respectively).

The fraction of the administered dose renally excreted as sitafloxacin over the 48 h post-dose was $\sim$75% for the i.v. formulation and 61% for the capsule. The renal clearance of sitafloxacin was higher than the glomerular filtration rate, implying active tubular secretion of sitafloxacin. The high urinary concentrations of sitafloxacin may be beneficial in the treatment of urinary tract infections.

Sitafloxacin has a high in vitro activity against Gram-positive and -negative bacteria and anaerobes (Milatovic et al. 2000). Integration of pharmacokinetics and antibacterial activity in vitro or in vivo provides important information about the pharmacodynamic properties of an antibacterial agent. For the fluoroquinolones the AUC(0–24 h) minimum inhibitory concentration (MIC) ratio has been identified as the pharmacokinetic/pharmacodynamic parameter best correlating with the microbiological and clinical efficacy (Craig 1998).

In the case of sitafloxacin (based on a mean AUC(0–24 h) = 25 $\mu$g.h.ml$^{-1}$), such AUC/MIC ratios would be achieved by MIC $\leq$ 0.25 $\mu$g.ml$^{-1}$ for Gram-negative and $\leq$ 0.5 $\mu$g.ml$^{-1}$ for Gram-positive bacteria. Thus, combining the pharmacokinetic results of the present study with the MIC data from a recently published large European surveillance study (Milatovic et al. 2000) and applying the above-mentioned pharmacodynamic breakpoints, sitafloxacin appears to be active against 100% of the three major respiratory tract pathogens ($S.\ pneumoniae$, $H.\ influenzae$, $M.\ catharrhalis$), 96% of staphylococci including methicillin-resistant strains, 90% of the enterobacterial strains, 70% of the enterococci including vancomycin-resistant strains and 63% of $Pseudomonas$ strains (table 3).
Clinical studies evaluating the pharmacodynamics of sitafloxacin would have to prove this efficacy assumption, although Phase II clinical studies in Europe and South Africa with sitafloxacin (400 mg i.v., once daily) have shown bacteriological efficacy. In randomized studies, satisfactory bacteriological responses were obtained in all 24 (100%) of patients with intra-abdominal infections treated with sitafloxacin (Dâuchi 1999, unpublished data); and in patients with pneumonia (Feldman et al. 2001), 19 of the 20 (95%) bacteriologically evaluable patients in the sitafloxacin treatment group had a satisfactory bacteriological response 21–35 days post-treatment. In an open study with resistant organisms, six of nine (67%) patients with vancomycin-resistant enterococci and four of 11 (36%) patients with methicillin-resistant Staphylococcus aureus treated with sitafloxacin achieved a satisfactory bacteriological assessment at the first evaluation (2–5 days post-treatment) (Shetty and Wilson 2000).

In conclusion, this study has shown the capsule formulation of sitafloxacin to offer excellent bioavailability with plasma levels compatible with providing effective antibacterial concentrations with no marked gender differences, a low variability between subjects and a high renal excretion of unchanged drug. These characteristics merit further clinical evaluation of this drug as an orally effective quinolone antibacterial.

References


