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Pharmacokinetic Profile of Levofloxacin following Once-Daily 500-Milligram Oral or Intravenous Doses

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The pharmacokinetics of once-daily oral levofloxacin (study A) or intravenous levofloxacin (study B) in 40 healthy male volunteers were investigated in two separate randomized, double-blind, parallel-design, placebo-controlled studies. Levofloxacin at 500 mg or placebo was administered orally or intravenously as a single dose on day 1; daily oral or intravenous dosing resumed on days 4 to 10. In a third study (study C), the comparability of the bioavailabilities of two oral and one intravenous levofloxacin formulations were investigated with 24 healthy male subjects in an open-label, randomized, three-way crossover study. Levofloxacin at 500 mg as a single tablet or an intravenous infusion was administered on day 1; following a 1-week washout period, subjects received the second regimen (i.e., the other oral formulation or the intravenous infusion); the third and final regimen was administered following a 1-week washout period. The concentrations of drug in plasma and urine were measured by validated high-pressure liquid chromatography methods. Pharmacokinetic parameters were estimated by noncompartmental methods. In both study A (oral levofloxacin) and study B (intravenous levofloxacin), steady state was attained within 48 h after the start of the multiple dosing on day 4. Levofloxacin pharmacokinetics were linear and predictable for the single and multiple 500-mg, once-daily oral and intravenous dosing regimens, and the values of the pharmacokinetic parameters for the oral and intravenous administrations were similar. Study C indicated that levofloxacin was rapidly and completely absorbed from the oral tablets, with mean times to the maximum concentration of drug in serum of approximately 1.5 h and mean absolute bioavailability of ≥99%. These results support the interchangeability of the oral and intravenous routes of levofloxacin administration.

Fluoroquinolone antimicrobial agents are broad-spectrum antibacterial agents with excellent in vitro activity against gram-negative organisms and variable activity against gram-positive cocci and anaerobes (7). Levofloxacin, the active component of the racemate ofloxacin (Floxin), has been studied for a variety of clinical conditions including acute sinusitis, lower respiratory tract infections, uncomplicated skin and soft-tissue infections, and complicated urinary tract infections and has been shown to be effective against a variety of pathogens such as members of the family *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and commonly isolated gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus pneumoniae*. The in vitro activity of levofloxacin is approximately twofold greater than that reported for ofloxacin against members of the family *Enterobacteriaceae*, *P. aeruginosa*, and gram-positive organisms (3, 4, 13). As a single isomer, levofloxacin appears to possess more potent microbiologic activity than other currently marketed quinolones, while it preserves the pharmacokinetic and safety profiles of its racemic predecessor, ofloxacin (3).

The primary purpose of these investigations was to evaluate the pharmacokinetics of oral and intravenous levofloxacin following the administration of single and multiple 500-mg doses once daily to healthy male volunteers and to determine the absolute bioavailability of the oral formulation.

(This study was presented, in part, at the 4th International Symposium on New Quinolones, 27 to 29 August 1992, Munich, Germany [1a] and at the 5th International Symposium on New Quinolones, Singapore, 1994 [6a, 6b].)

MATERIALS AND METHODS

Subjects. Healthy male subjects between the ages of 18 and 55 years were eligible for entry into the studies. Subjects qualified for the studies if they had normal findings following a prestudy medical history and physical examination, performed within the 3 weeks before entry into the study. Subject eligibility was also restricted to those with no evidence of clinically significant abnormal values in hematologic, serum chemistry, or urinalysis studies, subjects who were human immunodeficiency virus seronegative, and, for the oral studies, subjects who had no history of a significant gastrointestinal condition that could interfere with the absorption or disposition of the study medication. Additionally, subjects had to have normal ophthalmology examinations (funduscopy, slit lamp, visual acuity, and color tests) and electroencephalograms prior to entry into the study. Key exclusion criteria were a previous history of allergy to a fluoroquinolone, alcohol or controlled substance abuse, use of an investigational agent within 30 to 60 days of entry into the study, use of any medication within 3 days prior to administration of the first study dose, or an acute illness within 1 week of entry into the study. Prior to receiving any study drug, all subjects signed an informed consent form approved by the institutional review board.

Study design and drug administration. Studies A and B consisted of two separate randomized, double-blind, placebo-controlled, parallel-design studies. Subjects in study A were randomly assigned to one of two treatment regimens: levofloxacin hemihydrate at 500 mg (five 100-mg tablets [equivalent to 97.6 mg of anhydrous levofloxacin]; R. W. Johnson Pharmaceutical Research Institute) or identically appearing placebo tablets (R. W. Johnson Pharmaceutical Research Institute). Subjects in study B were randomly assigned to one of two intravenous treatment regimens: levofloxacin (500 mg; Ortho McNeil Pharmaceutical Corporation) or an identically appearing intravenous placebo solution (M.V.C. 9+3; Lypho Med, Inc., Melrose Park, Ill.) administered as a constant-rate intravenous infusion by an infusion pump over 60 min. In both studies, a single dose of study drug was administered orally or intravenously to each subject on day 1, with a washout period on days 2 and 3, followed by once-daily dosing from days 4 to 10. The third study (study C) had an open-label, randomized, three-way crossover design. Subjects were randomly divided equally into six treatment sequence groups and received a 500-mg levofloxacin clinical tablet (R. W. Johnson Pharmaceutical Research Institute), a 500-mg levofloxacin market-image tablet, or 500 mg of levofloxacin administered over 60 min as a constant-rate intravenous

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TABLE 1. Study populations

Treatment group[a]	Age (yr)[b]	Race (no. C/B/O)[c]	Weight (kg)[b]
Study A			
Levofloxacin	27.5 ± 9.3 (18–48)	7/2/1	75.5 ± 10.8
Placebo	29.2 ± 10.7 (20–50)	9/1/0	74.3 ± 6.9
Study B			
Levofloxacin	31.2 ± 9.0 (20–44)	8/1/1	94.4 ± 10.5
Placebo	28.6 ± 6.5 (21–40)	9/1/0	97.9 ± 8.7
Study C, all subjects	25.0 ± 6.1 (19–40)	16/1/6	77.1 ± 8.2

[a] In studies A and B, there were 10 subjects in each group; in study C, all subjects refers to the 23 subjects whose data were evaluable for pharmacokinetic analysis.
[b] Values are reported as means ± SDs (ranges).
[c] C/B/O, Caucasian/black/other.

infusion. A single dose of the assigned study drug was administered to each subject on day 1, with a 1-week washout period, followed by treatments with the alternative single dose on days 8 and 15. (The primary changes from the clinical tablet to the market-image tablet were adjustment of the excipient levels to optimize the processing performance of the marketed formulations; other changes were minor.)

Oral doses were administered with 8 oz. of water (studies A and C). On days 1 and 10 (studies A and B) and days 1, 8, and 15 (study C), doses were administered while the subjects were in a fasting state (i.e., ≥8 h before dosing through 2 to 4 h after dosing). Ingestion of alcohol, caffeine, methylxanthine-containing substances, and antacids was not permitted during the study period for all three trials. Subjects in all studies were confined from 12 h prior to administration of the first single dose until all final plasma and urine samples had been collected for each dosing period.

Sample collection. In study A, samples (5 ml) of venous blood for determination of plasma levofloxacin concentrations were collected from an indwelling catheter on day 1 immediately prior to administration of the first dose and then at the following times postdosing: 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0, 24.0, 36.0, 48.0, and 60.0 h. On days 4 to 9 of therapy, a single blood sample was obtained just prior to administration of the morning dose. Following administration of the last dose on day 10, blood samples were obtained immediately prior to dosing and at the following times postdosing: 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0, 24.0, 36.0, 48.0, 60.0, and 72 h.

For subjects in study B, blood samples were obtained on day 1 immediately prior to administration of the first dose and then at 0.5 h (halfway through the infusion), at 1.0 h (at the end of the infusion) and at 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0, and 60.0 h postdosing. On days 4 to 9 of drug administration, a single blood sample was obtained just prior to administration of the morning dose. Following administration of the last dose (day 10), blood samples were obtained immediately prior to dosing and at 0.5 h (halfway through the infusion), at 1.0 h (at the end of the infusion), and at 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0, 60.0, and 72 h postdosing. Blood samples were collected from the arm not used for the infusion of the study drug.

In study C, samples (5 ml) of venous blood were collected on days 1, 8, and 15 immediately prior to administration of the dose and then at the following times postdosing: 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 30.0, and 36.0 h.

Blood samples in all studies were collected in heparinized tubes and the tubes were centrifuged; the plasma was separated and stored at −20°C until assayed.

In studies A and B, urine samples for assessment of levofloxacin concentrations were collected beginning 8 h prior to administration of the first dose on day 1 and at the following intervals postdosing: 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 h. Specimens were also collected following administration of the last dose on day 10 (studies A and B) at 0 to 2, 2 to 4, 4 to 8, 8 to 24, and 24 to 48 h postdosing. In study C, urine was collected during the following intervals: −8 to 0 h (predosing) and 0 to 12, 12 to 24, and 24 to 36 h postdosing. The volume and pH of each urine sample were recorded, and an 8- to 10-ml aliquot from each collection was frozen at −20°C until assayed.

Safety analysis. All subjects receiving at least one dose of study drug were evaluable for the safety analysis. Adverse events were monitored on a daily basis for the duration of each study. The intensity (mild, moderate, or severe) of each treatment-emergent adverse event and its relationship to the study drug (definite, probable, possible, remote, or unlikely) was assessed. Additionally, clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed while the subject was in the fasting state on the morning of study day 1 prior to the administration of the initial dose and at the end of the study. A complete physical examination was also conducted 1 day after the levofloxacin therapy. In study B, ophthalmology examinations including fundoscopy, slit lamp, visual acuity, and color perception (Farnesworth-Hue color) tests were conducted

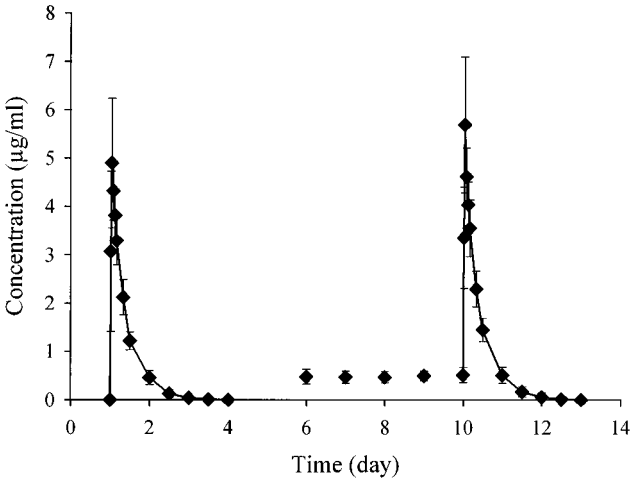

FIG. 1. Mean ± SD plasma levofloxacin concentration-time profiles following the administration of levofloxacin hemihydrate (study A) as a single 500-mg oral dose on day 1 and 500-mg oral doses once daily on days 4 to 10.

again on day 7 and day 11 or 13 of the study; electroencephalograms were also repeated on day 8 or 9 of treatment. Clinical safety data (adverse events, clinical laboratory tests, vital signs) were analyzed with the SAS statistical software package (10). The overall incidence of adverse events by treatment was summarized by body system and in primary and secondary terms. Postbaseline abnormalities in the physical examination, including vital sign abnormalities, were summarized and reviewed for possible clinical relevance. In studies A and B, the mean changes in the hematology, blood chemistry, and urinalysis values from the baseline values were calculated. Two-sided *t* tests for paired data were used to compare the mean change from prestudy values to the values on day 11 for each treatment group. *t* tests for independent samples were used to compare the mean changes in laboratory values between the treatment groups. In study C, analysis of variance for the crossover design was used to test for postbaseline changes in the values of the hematology, serum chemistry, and urinalysis parameters. All statistical inferences regarding safety analyses were based on a type I error rate of 0.05.

Analytical procedures. The total concentrations of levofloxacin in plasma and urine were determined by high-pressure liquid chromatography (HPLC) methods. In study A, samples were analyzed by a sensitive and specific reversed-phase HPLC assay with fluorescence detection (8). The procedure used a single-step liquid-liquid extraction and derivatization with diphenylphosphinyl chloride and L-leucinamide. A reversed-phase C_{18} column was used to separate levofloxacin and the internal standard (the 4-ethylpiperazinyl analog of levofloxacin). Elution was accomplished with a mobile phase consisting of 0.02 M tetraethylammonium

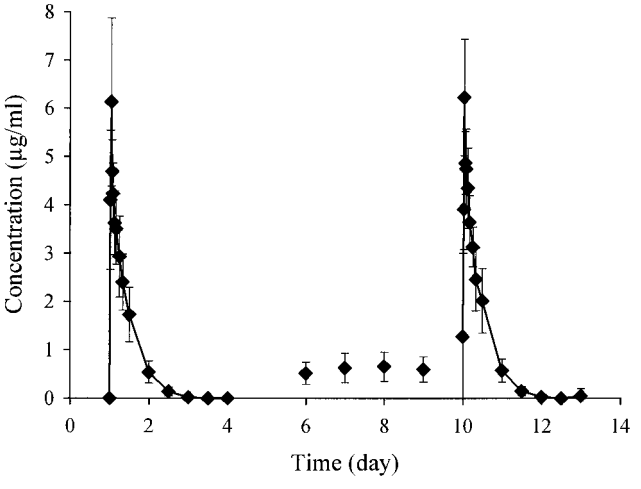

FIG. 2. Mean ± SD plasma levofloxacin concentration-time profiles following the administration of single (day 1) and multiple once-daily (days 4 to 10) 500-mg intravenous doses given as 1-h infusions (study B).

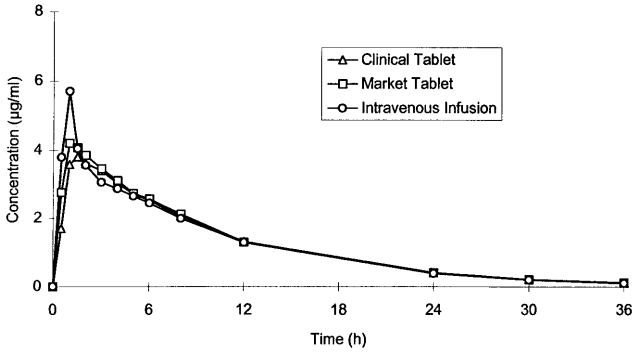

FIG. 3. Mean plasma levofloxacin concentration-time profiles for 23 healthy male subjects following the administration of single 500-mg doses of the clinical tablet, the market-image tablet, and the intravenous infusion (study C).

phosphate (pH 1.85)-acetonitrile (80:20; vol/vol) at a flow rate of 1.0 ml/min. Fluorescence detection (excitation wavelength at 298 nm and emission wavelength at 458 nm) was used to measure the peak area. For plasma the range of detection was linear from 0.082 to 10.5 μg/ml; the inter- and intra-assay precision values (as percent coefficient of variation) for levofloxacin were 7 and 6%, respectively. For urine, the range of detection was linear from 2 to 1,132 μg/ml; the inter- and intra-assay precision values for levofloxacin were consistently below 8%, and accuracy values were consistently within ±10% of the target. The raw data were acquired and processed on an LAS system (Hewlett-Packard 3350 Laboratory Data System via a model 18652 A/D converter). In studies B and C, samples were analyzed by a sensitive and specific reversed-phase HPLC assay with UV detection at 330 nm. This method has been described previously (15).

Pharmacokinetic analysis. Plasma and urine concentration-time data for levofloxacin were analyzed by standard noncompartmental methods (5). The levofloxacin absorption rate following oral administration was assumed to be zero order and complete at the time (T_{max}) that the peak concentration of drug in plasma (C_{max}) was achieved. Elimination was assumed to be linear and first order. This model has successfully been applied to characterization of the pharmacokinetics of levofloxacin following oral administration to healthy and human immunodeficiency virus-seropositive subjects (1, 6). Estimated pharmacokinetic parameters for levofloxacin included the area under the plasma concentration-time curve from time zero to time t (AUC_{0-t}), as measured by the trapezoidal summation method; AUC from time zero to infinity ($AUC_{0-\infty}$), calculated as $AUC_{0-last} + C_{plast}/k_{el}$ (where AUC_{0-last} is the AUC from time zero to the last measurable concentration in plasma, C_{plast} is the last measurable concentration in plasma, and k_{el} is the terminal elimination rate as the slope of the terminal log-linear phase of the plasma concentration-time profile constant determined by ordinary least-squares regression); apparent total body clearance (CL/F), calculated as dose/$AUC_{0-\infty}$ for the single-dose study and as dose/AUC_{0-24} (where AUC_{0-24} is the AUC from 0 to 24 h) at steady state; and the apparent volume of distribution (V/F), calculated as $CL \cdot (MRT - T_{max}/2)$ (where MRT refers to the mean residence time following drug administration, determined by the method of Smith and Schentag [12]). C_{max} and T_{max} were estimated by visual inspection of the plasma drug concentration-versus-time data. Renal clearance (CL_R) of the drug was estimated as Ae_t/AUC_{0-t}, where Ae_t is the cumulative amount of levofloxacin recovered in the urine at time t.

In studies A and B, the test of Page (9) was used to test for the attainment of steady state. Page's test is a nonparametric test for increasing (or decreasing) trends. The null hypothesis in testing for the attainment of steady state is that the mean trough concentrations on the different days under consideration are equal, and the alternative hypothesis is that there is an increasing trend in the means over the days under consideration. Steady state is concluded if the null hypothesis is not rejected at a 5% level of significance. Repeated-measures analysis of variance modeling was used to compare the pharmacokinetic parameters observed on day 1 (single dose) and day 10 (multiple dose at steady state). In study C, the absolute bioavailability was determined by the ratio of the $AUC_{0-\infty}$ between the oral and the intravenous administrations, and bioequivalence comparisons between formulations were performed with log-transformed data by the two one-sided test procedure (11). The statistical analysis was carried out with the SAS statistical software package (10).

RESULTS

Patient demographics. The characteristics of the groups receiving levofloxacin hemihydrate or placebo are presented in Table 1. Sixty-four healthy male subjects ranging in age from 18 to 53 years were enrolled in all three studies. In studies A and B, between-group comparisons of the levofloxacin and placebo treatments did not reveal any statistically significant differences in demographic parameters. Sixty-three subjects completed the study, and data for these subjects were included in the pharmacokinetic and safety analyses; one subject in study C was prematurely discontinued from the study due to a protocol violation (donation of blood). No subject required a dose reduction or concomitant therapy for the duration of the study.

Pharmacokinetics. The mean plasma levofloxacin concentration-time curves for studies A, B, and C are illustrated in Fig. 1 (single and multiple oral daily doses at steady state), Fig. 2 (single and multiple intravenous daily doses at steady state), and Fig. 3 (oral and intravenous formulations), respectively. During the administration of continuous once-daily oral doses of levofloxacin (study A), the mean ± standard deviation (SD) trough plasma levofloxacin concentrations at 48, 72, 96, 120, 144, and 168 h following the start of multiple dosing were 0.48 ± 0.15, 0.47 ± 0.13, 0.47 ± 0.12, 0.50 ± 0.10, 0.52 ± 0.15, and 0.51 ± 0.17 μg/ml, respectively. The corresponding values for the intravenous doses (study B) were 0.52 ± 0.23, 0.63 ± 0.30, 0.66 ± 0.30, 0.60 ± 0.26, 1.28 ± 1.72, and 0.58 ± 0.24 μg/ml. The test of Page (9) suggested that steady state was attained within 48 h following the start of the multiple dosing for both the oral and the intravenous doses. Also, in both studies A and B the lack of statistically significant differences between the mean ± SD predose concentration and the concentration at 24 h postdosing on day 10 confirmed that steady state had been attained on day 10.

The mean ± SD levofloxacin pharmacokinetic parameters observed on day 1 (single dose) and day 10 (multiple doses at steady state) are listed in Tables 2 and 3 for studies A and B, respectively. A summary of the levofloxacin pharmacokinetic parameters obtained from study C is presented in Table 4.

Following oral levofloxacin administration (study A), there was no statistically significant ($P > 0.05$) difference between $AUC_{0-\infty}$ (day 1, single dose) and AUC_{0-24} (day 10, multiple doses at steady state). There were also no statistically significant ($P > 0.05$) differences in V/F, CL/F, and CL_R between the single dose and the multiple dose at steady state. The mean ± SD ratios of the values of C_{max}, C_{p24}, and AUC on day 10 to the values on day 1 were 1.14 ± 0.33, 1.13 ± 0.17, and 1.12 ± 0.08,

TABLE 2. Pharmacokinetic parameters of levofloxacin in 10 healthy male volunteers following administration of levofloxacin hemihydrate as a single 500-mg oral dose on day 1 and 500 mg oral doses once daily on days 4 to 10 (study A)[a]

Day	C_{max} (μg/ml)	T_{max} (h)	C_{min} (μg/ml)[b]	AUC (μg · h/ml)[c]	$t_{1/2}$ (h)	CL/F (ml/min)	A_e (% of dose)[d]	CL_R (ml/min)	V/F (liters)
1	5.19 (1.21)	1.3 (0.5)	0.46 (0.14)	47.7 (7.6)	7.4 (0.9)	175.0 (29.2)	64 (8)	125.5 (30.0)	96.7 (11.9)
10	5.72 (1.40)	1.1 (0.4)	0.51 (0.17)	47.5 (6.7)	7.6 (1.6)	175.0 (24.5)	67 (14)	116.2 (30.8)	102 (21.8)

[a] Data are means (SDs).
[b] C_{min}, concentration in plasma at 24 h postdosing.
[c] $AUC_{0-\infty}$ on day 1 versus AUC_{0-24} on day 10.
[d] A_e from 0 to 24 h on days 1 and 10.

TABLE 3. Pharmacokinetic parameters of levofloxacin in 10 healthy male volunteers following intravenous administration of levofloxacin as a single 500-mg dose on day 1 and 500-mg doses once daily on days 4 to 10 (study B)[a]

Day	C_{max} (μg/ml)	$C_{p_{24}}$ (μg/ml)[b]	AUC (μg · h/ml)[c]	$t_{1/2}$ (h)	CL/F (ml/min)	A_e (% of dose)[d]	CL_R (ml/min)	V/F (liters)
1	6.34 (1.42)	0.542 (0.225)	55.3 (11.9)	7.1 (1.0)	156.8 (32.2)	60 (9)	95.5 (23.0)	88.8 (18.5)
10	6.40 (0.82)	0.583 (0.242)	54.6 (11.1)	7.0 (0.8)	157.7 (28.8)	63 (15)	99.0 (27.7)	90.6 (11.9)

[a] Data are means (SDs).
[b] $C_{p_{24}}$, concentration in plasma at 24 h postdosing.
[c] $AUC_{0-\infty}$ on day 1 versus AUC_{0-24} on day 10.
[d] A_e from 0 to 48 h on day 1 versus A_e from 0 to 24 h on day 10.

respectively. The theoretical accumulation ratio, based on a half-life ($t_{1/2}$) of 7.4 h, is 1.12. Excellent agreement was observed between observed and predicted accumulation ratios for the oral administration of levofloxacin.

Following intravenous levofloxacin administration (study B), there was no statistically significant ($P > 0.05$) difference between $AUC_{0-\infty}$ (day 1, single dose) and AUC_{0-24} (day 10, multiple doses at steady state). There were also no statistically significant ($P > 0.05$) differences in $t_{1/2}$, V, CL, CL_R, or A_e (as a percentage of the dose) between days 1 and 10. The mean ± SD ratios of the values of C_{max}, $C_{p_{24}}$, and AUC on day 10 to the values on day 1 were 1.03 ± 0.13, 1.09 ± 0.21, and 1.11 ± 0.11, respectively. The theoretical accumulation ratio, based on a $t_{1/2}$ of 7.1 h, is 1.11. Therefore, the observed and theoretical accumulation ratios were comparable.

The results from studies A and B indicate that the pharmacokinetics of levofloxacin do not change with multiple once-daily oral or intravenous dosing at a dose of 500 mg. The results also confirm the linearity of levofloxacin pharmacokinetics with this dosing regimen.

Study C indicated that levofloxacin is rapidly and completely absorbed from the orally administered tablets, with mean T_{max} values of approximately 1.5 h and mean absolute bioavailability of ≥99% (Table 4). The systemic availabilities of levofloxacin were equivalent for the oral and intravenous routes of administration (Table 5). As expected, due to the slightly shorter delivery period when levofloxacin was given via a 1-h intravenous infusion versus oral administration (T_{max}, ~1 to 2 h), a higher mean peak concentration in plasma was achieved after intravenous administration compared to that achieved after oral administration (Tables 4 and 5). Other than this transient difference in concentrations in plasma, the remaining plasma concentration-time profiles following administration of the oral formulations (clinical versus market image) and the intravenous formulation were nearly superimposable (Fig. 3).

Safety. No serious adverse events were reported in any of the three studies following the administration of levofloxacin or placebo, and no subject was discontinued from any study due to adverse events. In study A, two levofloxacin-treated subjects experienced a mild, possibly drug-related adverse event during the study (one subject had abdominal pain and one subject had dizziness). In study C, possibly drug-related events were reported in two subjects following administration of the clinical tablet (one subject had diarrhea and one subject had chills) and in nine subjects after delivery of the intravenous infusion (injection site reaction in seven subjects, injection site inflammation in two subjects, headache in two subjects, and nausea in one subject). All of these drug-related events were assessed as being mild and resolved quickly (usually within minutes) without medical treatment. No clinically significant alterations in laboratory parameters or vital signs from baseline measurements or findings on repeat physical examination different for those for the initial physical examination were noted for any treatment group in all three studies over the course of the study.

DISCUSSION

These are the first studies to report the pharmacokinetics of levofloxacin following the administration of single and multiple oral and intravenous doses of 500 mg once daily to healthy male subjects. The study results indicated that levofloxacin given orally or intravenously was well tolerated by the subjects. The pharmacokinetics of levofloxacin give both orally and intravenously were linear and predictable for the single and multiple, 500-mg, once-daily dosing regimens. The degrees of accumulation following administration of drug by the once-daily dosing regimen were in agreement with the theoretical values predicted from the data obtained after the administration of a single dose. Average steady-state peak concentrations in plasma of 5.72 and 6.40 μg/ml were attained following the once-daily oral and intravenous administrations, respectively. Levofloxacin disposition parameter values following the administration of a single intravenous dose (V/F, ~89 liters; CL/F, ~157 ml/min; CL_R, ~96 ml/min; $t_{1/2}$, ~7.1 h) remained unchanged after multiple once-daily i.v. dosing (V/F, ~91 liters; CL/F, ~158 ml/min; CL_R, ~99 ml/min; $t_{1/2}$, ~7.0 h). Similar findings were observed after oral administration; levofloxacin disposition parameter values (V/F, CL/F, CL_R, $t_{1/2}$) remained unchanged following multiple once-daily oral dosing

TABLE 4. Pharmacokinetics of levofloxacin in 23 healthy male volunteers following administration of a single 500-mg dose of clinical tablet, market tablet, and intravenous infusion (study C)[a]

Formulation	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-t} (μg · h/ml)	$AUC_{0-\infty}$ (μg · h/ml)	F[b]	$t_{1/2}$ (h)	CL/F (ml/min)	A_e (% of dose)[c]	V/F (liters)
Clinical tablet	4.51 (0.9)	1.57 (0.8)	41.9 (7.0)	43.2 (7.1)	0.99 (0.1)	6.8 (0.6)	199 (37)	99 (20)	ND[d]
Market-image tablet	4.80 (1.0)	1.37 (0.8)	43.4 (6.5)	44.7 (6.7)	1.03 (0.1)	6.9 (0.6)	191 (28)	102 (17)	ND
Intravenous infusion	5.70 (0.8)	1.00 (0.0)	42.8 (7.2)	44.0 (7.3)	ND	6.7 (0.7)	195 (35)	107 (16)	105 (16)

[a] Data are means (SDs) for 23 subjects completing the study.
[b] F, absolute bioavailability.
[c] $n = 20$.
[d] ND, not determined.

TABLE 5. Summary of two one-sided test results on log-transformed data for market-image tablet versus clinical tablet versus intravenous infusion (study C)

Parameter	Treatment[a]			% Difference in means[b]			Intersubject variability (%)	Intra-subject variability (%)	Two, one-sided test result[c]
	Clinical tablet (A)	Market-image tablet (B)	Intravenous infusion (C)	B:A	A:C	B:C			
C_{max} (μg/ml)	4.51 (0.9)	4.80 (1.0)	5.70 (0.8)	+6.4	−20.9	−15.8	13	15	EQ[d]
$AUC_{0-\infty}$ (μg · h/ml)	43.2 (7.1)	44.7 (6.7)	44.0 (7.3)	+3.5	−1.8	−1.6	18	8	EQ

[a] Values are means (SDs).
[b] With respect to treatment A, (B − A) · 100/A; and treatment C, (A − C) · 100/C or (B − C) · 100/C.
[c] Two, one-sided test results on log-transformed parameters; EQ, 90% confidence interval within 80 to 125% limits with respect to the reference mean.
[d] Comparison of C_{max} includes the C_{max} of clinical tablet versus that of market-image tablet only.
[e] Comparison of $AUC_{0-\infty}$ includes the $AUC_{0-\infty}$ of clinical tablet versus that of market-image tablet, $AUC_{0-\infty}$ of clinical tablet versus that of intravenous infusion, and $AUC_{0-\infty}$ of market-image tablet versus that of intravenous infusion.

and were similar to those obtained following intravenous administration.

Of clinical significance, levofloxacin is rapidly and completely absorbed from the tablet formulations. When equal doses (milligram/milligram) are administered, similar plasma concentration-time profiles are expected following the administration of the drug by the intravenous and oral routes. As noted by other investigators (2, 14), the availabilities of the oral and intravenous formulations potentially offer a practitioner the following desirable treatment options: intravenous therapy for seriously ill and debilitated patients, oral therapy for serious infections which traditionally require intravenous antibiotic therapy, and switching from intravenous to oral therapy with the same dosage and regimen. The results described herein support the clinical evaluation of once-daily oral or intravenous dosing of levofloxacin for appropriate infections.

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