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Pharmacokinetics of Temafloxacin in Humans after Single Oral Doses

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Temafloxacin (A-63004) is a new quinolone antibacterial agent with a broad spectrum of activity against gram-positive and gram-negative aerobes and anaerobes. The pharmacokinetics and metabolism of temafloxacin were determined in healthy volunteers after administration of single oral doses of 100, 200, 400, 600, 800, and 1,000 mg. The corresponding peak concentrations in plasma (mean ± standard deviation) were 0.98 ± 0.26, 1.61 ± 0.57, 2.43 ± 0.56, 3.87 ± 0.64, 4.54 ± 1.03, and 6.67 ± 0.74 μg/ml. The times that elapsed to attain peak levels ranged from 1.25 to 3.5 h. Statistical analyses of parameters related to the extent of absorption and the linearity of the dispositional pharmacokinetics detected no dose-related trends. Study-wide, total clearance (223 ml/min) and renal clearance (125 ml/min) showed low intersubject variability, with coefficients of variation near 20%. The terminal-phase rate constant of 0.090 ± 0.008 h^{-1} corresponds to a half-life of 7.7 h. Temafloxacin was excreted mainly in the urine, with 57 ± 11% of the dose appearing in the urine unchanged. Conjugated temafloxacin, oxidative metabolites, and conjugates thereof were minor components in urine, collectively accounting for 5 to 8% of the dose. Since intravenously dosed dogs eliminated 50% of the dose by nonrenal processes, urinary recoveries approaching two-thirds of the dose in humans were consistent with high, if not quantitative, absorption. Reported adverse events were generally mild, were randomly distributed between temafloxacin- and placebo-treated subjects, and were not dose related.

Temafloxacin [A-63004; 1-(2,4-difluorophenyl)-6-fluoro-7-(3-methylpiperazin-1-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid] is a new quinolone antibacterial agent. This drug has shown marked in vitro activity against gram-positive and gram-negative bacteria. It is a member of the 6-fluoro-7-piperazino-4-quinolones, a group of compounds that is highly active in vitro against a broad range of gram-negative bacilli and gram-positive organisms, is able to control systemic infections after oral administration, and is well tolerated when so administered (19). The activity of temafloxacin is similar to those of ciprofloxacin and ofloxacin (2) against gram-negative organisms; its activity is greater than those of ciprofloxacin and ofloxacin against gram-positive, anaerobic, and intracellular organisms (6, 12).

This is the first reported study of the pharmacokinetics of temafloxacin after administration of a range of single oral doses. The results of this randomized, double-blind, placebo-controlled study are reported below.

MATERIALS AND METHODS

Subjects. Thirty healthy adult male volunteers were initially recruited for the study at Guy's Hospital Medical School, London, England. The demographics of the subjects receiving temafloxacin are summarized in Table 1. The subjects' mean age was 23 years (range, 19 to 28 years), body weight (mean ± standard deviation) was 75.2 ± 7.1 kg (range, 60.0 to 89.0 kg), and creatinine clearance (CL_{CR}) was 128 ± 26 ml/min (range, 65 to 180 ml/min). Intergroup differences in mean ages, weights, and renal functions were minimal.

The subjects were prohibited from medication of any sort for at least 48 h prior to dosing. Urinary screens for drugs of abuse were negative, and high-performance liquid chromatographic (HPLC) analyses of predosing plasma and urine samples revealed no interfering peaks. The protocol was reviewed and approved by the ethical committee of Guy's Hospital. All subjects provided informed written consent.

Study design. Subjects were divided into three groups, 10 to a group, with each group assigned to two dose levels during the study. Subjects in group 1 received one dose of 100 mg of temafloxacin or placebo during their first study confinement (5 days) and 400 mg of temafloxacin or placebo during the second confinement (5 days), but the second confinement was separated from the first confinement by at least 1 week. The doses in group 2 were 200 and 800 mg of temafloxacin or placebo, and those in group 3 were 600 and 1,000 mg of temafloxacin or placebo. Replacements were required for two subjects who completed only the first confinement. At each dosing, six subjects were randomized to receive temafloxacin and four were randomized to receive placebo. By the study's end, 27 subjects received a total of 36 doses of temafloxacin, which was supplied by Abbott Laboratories as the hydrochloride salt and formulated as 100- and 200-mg capsules. There were 23 doses of placebo in matching capsules.

Confinement began 36 h prior to administration of drug or placebo. Subjects fasted for 8 h before taking drug or placebo and did not eat until 4 h afterward. Temafloxacin or placebo capsules were given with 380 ml of water, and water was permitted ad libitum throughout the study.

Sampling. Sampling was identical for subjects receiving placebo and temafloxacin. Urine was collected for assay of temafloxacin and its metabolites before dosing and at the following intervals after dosing: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 48, and 48 to 60 h. Samples were stored frozen until analysis.

Blood (5 ml) for assay of the concentration of temafloxacin

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TABLE 1. Subject characteristics

Dose (mg)	Age (yr)	Ht (cm)	Wt (kg)	CL_{CR} (ml/min)	No. of smokers (n = 6)
100	24.2 ± 2.5	176.3 ± 8.0	75.4 ± 8.8	122 ± 10	2
200	22.2 ± 2.3	179.0 ± 7.6	75.5 ± 8.4	127 ± 25	2
400	24.7 ± 2.9	182.9 ± 7.5	78.8 ± 8.1	135 ± 24	3
600	22.7 ± 2.0	173.8 ± 4.6	72.1 ± 6.4	115 ± 24	3
800	21.7 ± 1.0	182.0 ± 7.5	75.4 ± 7.5	133 ± 40	3
1,000	22.8 ± 2.5	178.1 ± 5.7	74.0 ± 3.4	135 ± 31	4

in plasma was collected into lithium-heparinized VACUTAINER tubes at the base line and at the following times post dosing: 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 32, 48, and 60 h. Blood specimens and were centrifuged; and the plasma was frozen at −10°C or colder, packed in solid carbon dioxide, and shipped to Abbott Laboratories for assay.

Safety. Safety was monitored throughout the study. Vital signs were taken at 0, 1, 2, 4, 8, 12, and 24 h. Physical examination, ophthalmologic examination, and neurologic assessment were performed at the base line and at 2 to 5, 24, and 48 h; if any abnormalities were found at 48 h, examinations were repeated at 4 to 6 days. Laboratory tests included the following: prothrombin time and activated partial thromboplastin time at 0, 6, 12, and 32 h; 4-h CL_{CR} at the base line and 24 to 48 h; urinalysis at the base line, 24 h, 48 h, and 4 to 6 days; and examination of freshly collected urine for crystals at 2 and 4 h after dosing. Electrocardiograms were performed at the base line, 1 to 3 h, and 48 h, and electroencephalograms were performed at the base line and 24 to 36 h.

HPLC. The concentrations of temafloxacin and its known metabolites in plasma and urine were determined by reversed-phase HPLC with tandem fluorescence and UV detection (4). Plasma, after treatment with a displacing reagent, was ultrafiltered with an Amicon Centrifree apparatus. The reagent for quantitatively displacing temafloxacin from plasma proteins contained 0.5% sodium dodecyl sulfate and 30% acetonitrile, with a bromophenyl-substituted quinolone serving as the internal standard. Ultrafiltrates were analyzed with an Adsorbosphere HS C_{18} column (particle size, 7 μm; 250 by 4.6 mm; Alltech Associates), with UV and fluorescence detectors operated at 280 nm (fluorescence emission cutoff, 389 nm). The mobile phase consisted of 1:1 water-acetonitrile containing 0.04 M H_3PO_4, 0.01 M NaH_2PO_4, 0.2% sodium dodecyl sulfate, and 0.005 M *N*-acetylhydroxamic acid. The procedure has been shown to have a mean intraassay coefficient of variation (CV) of 0.7% over the concentration range of 0.05 to 10 μg/ml. Repeated analyses of quality control samples containing 0.2 and 2 μg/ml provided interassay CV estimates of 1.88 and 1.98%, respectively, at the end of the study. Calibration curves typically comprised nine standards with concentrations ranging from the limit of quantitation of 0.01 to 5 or 7.5 μg/ml. The mean calibration curve correlation coefficient for 13 assays was 0.9996. Urine standards and unknowns, after dilution (typically 1/50 to 1/100), were supplemented with internal standard and analyzed without further processing. The extent of conjugation of temafloxacin and its metabolites in pooled urine specimens was determined by comparison of results of HPLC analyses before and after hydrolysis by base (0.5 h at 60°C in 1 N NaOH) and also by incubation with β-glucuronidase (18 h at 37°C with 4,500 U/ml).

Both the plasma and urine calibration curves were supplemented with standards of potential metabolites of temafloxacin. The known metabolites of temafloxacin (Fig. 1) originate from sequential oxidation of the piperazinyl moiety to an oxo derivative (5′-OXO), then to ethylenediamine analogs (EDA and MEDA), and finally to an aminoquinolone (AQ). The identities of these compounds in the urine and plasma specimens of subject were verified by cochromatography with authentic references and by comparisons of relative fluorescence efficiencies (i.e., ratios of the UV and fluorometric responses) with those of the standards.

Pharmacokinetic analysis. The pharmacokinetics of temafloxacin were evaluated by use of both noncompartmental and curve-fitting techniques. In the former approach, groups were compared for the time elapsed to peak drug level (T_{max}; hours), dose-normalized maximal concentrations in plasma (C_{max}/D; micrograms per milliliter per 100 mg), trapezoidal areas under the temafloxacin concentration in plasma-time curve from 0 to 60 h (AUC_{0-60}; microgram hours per milliliter), apparent total body clearances (CL_T/F; milliliters per minute [F is the fraction of the dose absorbed]), and renal clearances (CL_R; milliliters per minute). CL_R was calculated as A_e/AUC_{0-60}, where A_e is the amount excreted from 0 to 60 h. CL_{CR} was computed as the urinary excretion rate divided by the concentration in plasma. The terminal-phase rate constant (β) was used to extrapolate from AUC_{0-60} to $AUC_{0-\infty}$ (AUC from 0 h to infinity). Total clearance was computed as dose/$AUC_{0-\infty}$. In the curve-fitting approach (Table 2), initial estimates for NONLIN (9) were obtained with the program CSTRIP (14). Model selection was based on comparisons of data fitted to biexponential (one-compartment open model) and triexponential equations, using the information criterion of Akaike (1, 20). In general, the data from the lower doses were better fitted by the triexponential equations; however, with increasing size

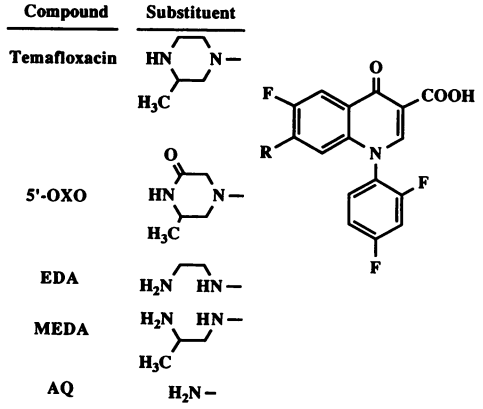

FIG. 1. Chemical structures of temafloxacin and its oxidative metabolites.

TABLE 2. Nonlinear regression analysis results[a]

Dose (mg)	Data	Lag time (h)	A (μg/ml/mg)	B (μg/ml/mg)	K_a (h^{-1})	α (h^{-1})	β (h^{-1})
100	Mean	0.47	0.0053	0.0062	7.16	0.568	0.0971
	GMC	0.26	0.0049	0.0074	3.01	0.907	0.1032
200	Mean	0.67	0.0045	0.0052	8.60	0.395	0.0882
	GMC	0.31	0.0019	0.0062	1.88	0.212	0.0894
400	Mean	0.37		0.0067	2.27		0.0873
	GMC	0.26		0.0067	1.34		0.0869
600	Mean	0.57		0.0074	2.30		0.0891
	GMC	0.32		0.0075	1.21		0.0873
800	Mean	0.33		0.0071	3.22		0.0903
	GMC	0.16		0.0069	1.00		0.0884
1,000	Mean	0.26		0.0077	2.21		0.0894
	GMC	0.18		0.0077	1.20		0.0887

[a] NONLIN regressions are of data from individual subjects (n = 6) or group mean curves (GMC) determined by a biexponential equation [C_p = dose $B(e^{-\beta t} - e^{-K_a t})$, where C_p is the concentration of temafloxacin in plasma, B is the zero time intercept for the β phase, t is time, and K_a is the absorption rate constant] for the 400- through 1,000-mg dose groups and a triexponential equation [C_p = dose $(A_e^{-\alpha t} + B_e^{-\beta t}) - (A + B)\, e^{-K_a t}$, where A is the zero time intercept for the α phase] for the 100- and 200-mg groups.

of dose, absorption and dissolution processes obscured the distributive phase, rendering the biexponential equation more appropriate. The curves were all fitted several times, with various initial estimates. The initial weighting scheme was 1/concentration^2, which reflects the reciprocal analytical variances; however, in some cases, the absorptive-phase kinetics were clearly more complex than specified by the model. Accordingly, it was necessary to down-weight the data in this phase; otherwise, bias of the disposition phase and underestimation of peak levels occurred.

Statistical analyses. Equivalence among the dosage groups in the pharmacokinetic parameters was examined by a one-way analysis of variance. Calculations were performed with PROC GLM of SAS (13). When the P value for the dosage was less than 0.05, indicating differences among groups, pairwise comparisons were made at the 0.05 significance level by use of the t test (the Fisher least significant difference test). The determinants of intersubject variability in CL_T/F and CL_R were assessed by stepwise linear regression analyses, with CL_{CR}, weight, age, urinary output, tobacco use, and alcohol use used as variables.

Protein binding. The binding to plasma proteins was evaluated by supplementing blank human plasma from fasting male and female subjects with [^{14}C]temafloxacin at concentrations of 0.3, 1, 3, 10, and 30 μg/ml. The free fraction in plasma was determined at ambient temperature by ultrafiltration with Amicon Centrifree devices. Adsorption to the device was checked and found to be negligible by ultrafiltration of saline solutions of temafloxacin.

RESULTS

Pharmacokinetics. The mean concentrations of temafloxacin in plasma after the various oral doses are presented in Fig. 2. The observed C_{max}s ranged from 0.98 ± 0.26 to 6.67 ± 0.74 μg/ml for the six dosage groups. Although peak levels increased with increasing dose size (Table 3), the increase was slightly less than proportionate, as was indicated by a decline in dose-normalized levels (C_{max}/D; micrograms per milliliter per 100 mg administered) from 0.98 at 100 mg to 0.67 at 1,000 mg. Intergroup differences in C_{max}/D were statistically significant (P = 0.005). Least significant difference t tests found the C_{max}/D for the 100- and 200-mg groups to be statistically different from those of the higher-dose groups. Attendant with these changes were increases in T_{max}, which averaged 1.25 ± 0.52 h at 100 mg and 2.5 ± 0.6 h at 1,000 mg. In several cases in the higher-dose groups (400 to 1,000 mg), secondary peaks occurred during the absorptive process, perhaps because of delayed absorption of one or more capsules at higher doses.

The results of the nonlinear regression analyses of individual and group mean curves are summarized in Table 2. Most subjects had a lag between the time of dose administration and the appearance of temafloxacin in plasma. The lag times calculated by NONLIN, which were independent of dose, averaged 0.44 h (26 min). The apparent absorption rate constants, which reflect the combined kinetics of ab-

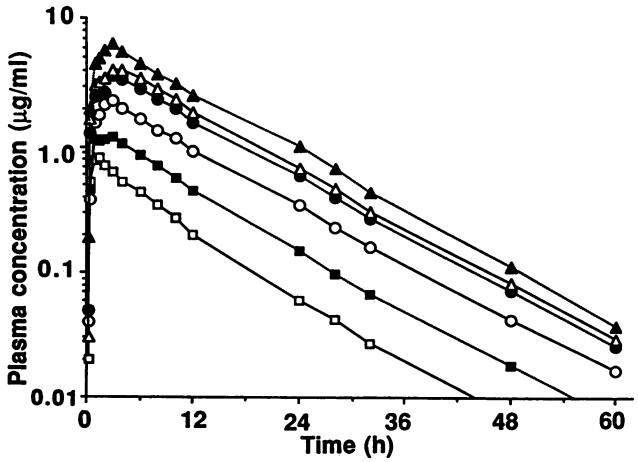

FIG. 2. Mean plasma temafloxacin concentrations in humans after single oral doses of 100 (□), 200 (■), 400 (○), 600 (●), 800 (△), and 1,000 (▲) mg.

TABLE 3. Temafloxacin pharmacokinetic parameters after single oral doses[a]

Dose (mg)	C_{max}		T_{max} (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL_T/F (ml/min)	CL_R (ml/min)	CL_R/CL_{CR}	β (h^{-1})	$t_{1/2}$ (h)	V_β/F (liters)	X_u^{60} (% dose)
	μg/ml	Per 100 mg									
100	0.98 (27)	0.98	1.25 (42)	7.51 (16)	227 (16)	133 (20)	1.09 (21)	0.097 (13)	7.1	143 (25)	59.4 (21)
200	1.61 (35)	0.81	1.92 (63)	15.02 (24)	237 (33)	138 (14)	1.12 (25)	0.088 (9)	7.9	161 (30)	60.9 (22)
400	2.43 (23)	0.61	2.50 (22)	29.69 (19)	232 (19)	138 (29)	1.01 (17)	0.087 (4)	7.9	159 (19)	59.2 (24)
600	3.87 (17)	0.65	2.58 (50)	49.54 (15)	205 (13)	96 (14)	0.86 (26)	0.089 (10)	7.8	138 (8)	46.8 (11)
800	4.54 (23)	0.57	3.50 (59)	58.66 (14)	232 (15)	132 (21)	1.04 (25)	0.090 (6)	7.7	154 (14)	56.5 (15)
1,000	6.67 (11)	0.67	2.50 (22)	82.25 (15)	206 (12)	117 (14)	0.90 (19)	0.089 (7)	7.8	139 (13)	56.5 (10)
Mean[b]	0.71 (31)		2.38 (54)	7.71 (17)	223 (20)	125 (22)	1.00 (23)	0.090 (9)	7.7	149 (20)	56.5 (19)

[a] Values are means from six subjects, with CVs given in parentheses. V_β/F, Volume of distribution in the β phase; X_u^{60}, amount excreted in the urine after 60 h; abbreviations for all other parameters are defined in the text.

[b] Study-wide mean (n = 36) of parameter or dose-normalized parameter (per 100 mg administered).

sorption and dissolution, declined with increasing dose; however, there were subjects in all dosage groups who showed rapid absorption (half-life [$t_{1/2}$], <15 min).

The decline in temafloxacin levels was usually monoexponential, except in the 100- and 200-mg groups, for which a distributive phase lasting 3 to 6 h was usually evident. Temafloxacin levels in plasma 24 h after dosing were typically one-eighth to one-fifth of the peak levels.

The group mean AUCs of temafloxacin were highly correlated with the dose (r = 0.998), and the intercept of the regression was not statistically significant (Fig. 3). The slope of the regression forced through the origin was 7.71 μg · h/ml/100 mg administered. The apparent total clearance of temafloxacin, CL_T/F, showed little change with increasing dose, ranging from 205 to 237 ml/min for the six dosage groups, and was 223 ± 44 ml/min study-wide (Table 3). Normalization of CL_T/F by body surface area (200 ± 39 ml/min/1.73 m^2) had a negligible effect on the intersubject CV. Intergroup differences in CL_T/F were not statistically significant.

Mean CL_R values ranged from 96 to 138 ml/min, averaging 125 ml/min study-wide. Intergroup differences in CL_R, or in the ratio of CL_R to CL_{CR}, were not statistically significant. The temafloxacin CL_R averaged 100.3% of the corresponding CL_{CR} for the individual subjects. The free fraction of temafloxacin in plasma, determined by ultrafiltration, was found to be independent of concentration, averaging 74%; thus, the renal clearance of unbound temafloxacin slightly exceeds the glomerular filtration rate, as estimated by CL_{CR}.

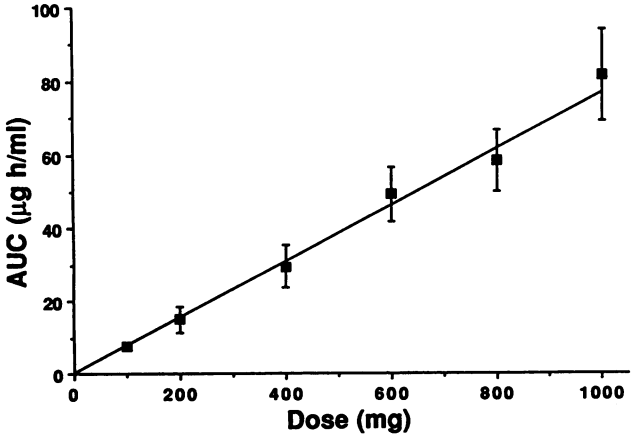

FIG. 3. Dose proportionality of temafloxacin based on AUC comparison (correlation coefficient = 0.998; AUC = 7.71 μg · h/ml/100 mg administered).

A one-way analysis of variance found no intergroup differences among the terminal-phase rate constants (β), which averaged 0.0902 h^{-1} for all subjects, corresponding to a $t_{1/2}$ of 7.7 h. Mean $t_{1/2}$s for the six dosage groups ranged from 7.1 to 7.9 h (Table 3).

The determinants of intersubject variance in the CL_T/F and CL_R of temafloxacin were evaluated by stepwise linear regression. From the variety of variables tested, only CL_{CR} was found to be statistically significant (PR > F = 0.022 for CL_T/F and 0.0001 for CL_R), accounting for 14.5 and 35% of the variances in CL_T/F and CL_R, respectively. The low indices of determination from the regressions reflect the narrow ranges in the temafloxacin clearances, which had study-wide CVs of 20%, and in the CL_{CR} of the panel of young, healthy volunteers (CV, 26%). Tobacco use was associated (PR > F = 0.019) with lower CL_R (113 versus 135 ml/min) and CL_{CR} (120 versus 132 ml/min); however, CL_T/F (225 versus 222 ml/min) and the CL_R/CL_{CR} ratios (0.98 versus 1.04) for smokers and nonsmokers were comparable. A small, but significant (PR > F = 0.010) circadian effect was also observed with CL_R, which averaged 120 and 143 ml/min for the night and day collection intervals, respectively.

Excretion and metabolism. Group 0- to 60-h urinary recoveries of unchanged temafloxacin were 59.4 ± 12.7, 60.9 ± 13.2, 59.2 ± 14.1, 46.8 ± 5.0, 56.5 ± 8.4, and 56.5 ± 5.4% for the respective 100-, 200-, 400-, 600-, 800-, and 1,000-mg doses; the intergroup differences were not statistically significant. The study-wide recovery of unchanged temafloxacin at 0 to 60 h was 56.5 ± 10.5% of the dose. Based on the kinetic parameters discussed earlier, less than 1% of the dose remained to be excreted at the end of the 60-h interval.

Hydrolysis of pooled urine specimens revealed that unconjugated temafloxacin was the preponderant component. Levels of the glucuronide conjugate, determined by the difference between HPLC analyses of untreated and hydrolyzed urine specimens, were typically less than 6% of the levels of free drug and, as such, approached the analytical limit of precision of this approach; however, a study-wide mean concentration difference of 3.5% between paired analyses of nonhydrolyzed and hydrolyzed samples was found to be statistically significant. The levels of the oxidative metabolites and their conjugates were collectively about 2% of the levels of temafloxacin and its conjugate; thus, the urinary recovery of temafloxacin and its metabolites from time zero to infinity represented approximately two-thirds of the administered dose.

Safety. No clinically significant changes were observed in any subject for any of the safety evaluations performed. The adverse events reported were generally mild and randomly distributed between temafloxacin- and placebo-treated subjects. The incidence of adverse events was not dose related. The most frequently reported adverse event was headache for both the temafloxacin (22.2%) and placebo (21.7%) groups. No study drug crystals were observed in the urine.

DISCUSSION

After administration of single oral doses of temafloxacin ranging from 100 to 1,000 mg, the extent of absorption was essentially constant and the dispositional kinetics were linear. Dose-related trends in CL_T/F, CL_R, $t_{1/2\beta}$, and urinary recovery were not statistically demonstrable. Intersubject coefficients of variation were low for an orally administered drug, ranging from 8.6% for β to about 20% for CL_R and CL_T/F.

In experiments in dogs (unpublished data), orally administered temafloxacin was found to be quantitatively absorbed; yet, the urinary recovery accounted for only 50% of the intravenously administered dose. The extent of absolute absorption (F) of temafloxacin after oral administration could not be determined in the present study. However, the finding of constancy of urinary recovery with dose in our human subjects, as well as data from dog experiments, indicated that absorption is extensive, if not quantitative, in humans. The fact that urinary recoveries were higher in humans than they were in dogs may reflect interspecies differences in biliary secretion thresholds. Temafloxacin has a molecular weight of 417; thus, both parent and conjugates are above the biliary secretion threshold of 325 ± 50 in dogs (17). Humans have a generally higher threshold with less efficient secretion, so clearance of unchanged temafloxacin by this route would be expected to be less competitive against renal excretion.

The collective observations of decreases in C_{max}/D and increases in T_{max} with increasing dose indicate that the rate of dissolution of temafloxacin may have been a major factor. The solubility of temafloxacin at pH 1 to 2 or 5.5 to 7 is approximately 0.5 to 1 mg/ml; thus, the gastrointestinal fluid present and the 380 ml of water ingested with each dose should have been sufficient to allow rapid dissolution of the 100- and 200-mg doses. With larger doses, dissolution may have progressively become the rate-limiting process in absorption. Prolongation of the absorptive process also masked the distributive phase of temafloxacin. In the six subjects of the 100- and 200-mg groups who had T_{max} values of less than or equal to 1 h, NONLIN-calculated values for the distributive rate constant averaged 0.74 h^{-1}; however, with increasing dose size, the magnitudes of the rates of the absorptive and distributive processes became similar enough to obscure the former process, resulting in curves that were essentially biexponential.

Since renal excretion is the predominant component of the total clearance of temafloxacin, appreciation of the underlying mechanisms is important: renal function is expected to be an important predictor of interpatient variability. The observation that the CL_R of unbound drug slightly exceeded the CL_{CR} indicates that glomerular filtration is the dominant process and that tubular secretion plays a minor role in the renal elimination of temafloxacin. Close inspection of the mean plasma-concentration-versus-time courses revealed a very slight sinusoidal fluctuation in the postdistributive phases, with shallower slopes during the evening periods. The underlying phenomenon appears to be the reduction in CL_R at night. Similar circadian effects have been noted in the review of chronopharmacokinetics by Reinberg and Smolensky (11). Since cardiac output, renal blood flow, glomerular filtration rate, and the associated renal regulatory hormones are at their daily minimum during the nighttime period of inactivity, a slightly lower CL_R at night would be expected.

Eight quinolone antibacterial agents are sufficiently well-described in the recent literature to allow comparisons with temafloxacin: ciprofloxacin, difloxacin, enoxacin, fleroxacin, lomefloxacin, norfloxacin, ofloxacin, and pefloxacin (3, 5, 7, 8, 10, 15, 16, 18). Because the metabolic clearances of these quinolones are low, compared with hepatic blood flow, the primary determinant of kinetic differences among them is the mechanism of renal elimination. Pefloxacin and difloxacin, which are the least polar, are renally reabsorbed and, as a result, have the longest $t_{1/2}$s. With the more polar quinolones, such as ciprofloxacin, norfloxacin, and enoxacin, CL_Rs exceed the glomerular filtration rate by factors of up to 3:1, which results in $t_{1/2}$s in the 3- to 7-h range. The present data for temafloxacin indicate that it is mechanistically intermediate, with the CL_R approximating the glomerular filtration rate. Accordingly, the dose-invariant and apparently high absorption efficiency, as well as a somewhat longer $t_{1/2}$, results in AUCs that equal or exceed those reported for the renally eliminated quinolones.

From the results of this study of single ascending doses of temafloxacin (100 to 1,000 mg) given to healthy subjects, it was determined that temafloxacin is primarily eliminated renally, ostensibly with linear pharmacokinetics. Oral administration of 400 mg twice daily for several days or more is anticipated to produce steady-state minima of about 2 μg/ml. This is above the MIC for 90% of the strains for the majority of the organisms examined by Hardy et al. (6) and Barry and Jones (2). Thus, it is expected that temafloxacin will prove to be useful in the treatment of infections of the urinary tract, lower respiratory tract, and skin or skin structure.

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