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Pharmacokinetics and Tolerance of Lomefloxacin after Sequentially Increasing Oral Doses

P. J. MORRISON,[1] T. G. K. MANT,[1] G. T. NORMAN,[1] J. ROBINSON,[1] AND R. L. KUNKA[2]*

Guy's Drug Research Unit, Guy's Hospital Medical School, London, England,[1] and G. D. Searle & Co., Skokie, Illinois 60077[2]

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The pharmacokinetics of five dose levels of lomefloxacin (100, 200, 400, 600, and 800 mg) were examined in a single-dose, double-blind, placebo-controlled study involving 40 subjects. There were eight subjects in each group: five received active drug and three received placebo; each subject was given only one dose. All subjects completed the study, and lomefloxacin was well tolerated at all doses. No drug crystals were noted in the urine at 3 and 6 h after the dose. The mean maximum concentration in serum (C_{max}) ranged from 1.11 to 7.46 μg/ml for the 100- to 800-mg doses, respectively, and the AUC increased proportionally with the dose. The mean time to C_{max} (T_{max}) values averaged 64.8 ± 28.8 min. The elimination half-life and plasma clearance averaged 7.7 ± 0.52 h and 259 ± 37 ml/min, respectively. Mean concentrations in urine were highest during the first 4 h after the dose and ranged from 104 to 713 μg/ml following the 100- and 800-mg doses, respectively. Concentrations above 20 μg/ml in urine were observed in most subjects over 24 h at the three lower doses and averaged over 120 μg/ml during the 12- to 24-h interval at the 400-mg dose, thus supporting once-per-day dosing. Excretion rates from urine and the cumulative amount excreted increased in a dose-related fashion. Renal clearance decreased moderately at the higher doses. Thus, lomefloxacin was well tolerated, and dose proportionality was demonstrated by most pharmacokinetic parameters. The 400-mg dose produced concentrations in plasma and urine above the MIC for susceptible pathogens.

Since the introduction of nalidixic acid, many other drugs with similar chemical structures have been synthesized in an effort to increase the concentration in serum and the half-life, as well as to broaden the antibacterial spectrum.

Lomefloxacin (NY-198; SC-47111) [1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid monohydrochloride] is a new difluorinated quinolone antimicrobial agent which has been demonstrated to have a broad antibacterial spectrum in vitro and in vivo, with activity similar to that of norfloxacin (1; N.-X. Chin, A. Novelli, and H. C. Neu, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 254, 1987) and enoxacin (Chin et al., 27th ICAAC). Lomefloxacin inhibited 90% of ampicillin- and/or cephalexin-resistant *Escherichia coli* strains and *Klebsiella, Salmonella, Shigella, Yersinia, Proteus,* and *Citrobacter* species at ≤1 μg/ml.

In addition, lomefloxacin has been identified as having a promising efficacy and safety profile, as well as advantageous pharmacokinetic properties, in the initial clinical trials conducted in Japan (K. Shiba, A. Saito, J. Shimada, and T. Miyahara, Proc. 15th Int. Congr. Chemother., abstr. no. 106, 1987; A. Saito, O. Nagata, T. Yamada, E. Okezaki, Y. Takahara, and H. Kato, Proc. 15th Int. Congr. Chemother., abstr. no. 260, 1987; S. Kamidono, A. Fujii, H. Nagata, and J. Ishigami, Proc. 15th Int. Congr. Chemother., abstr. no. 1340, 1987; F. Matsumoto, T. Imai, and I. Sakurai, Proc. 15th Int. Congr. Chemother., abstr. no. 1129, 1987; M. Tanaka, N. Ogata, A. Nagayama, and J. Kumazawa, Proc. 15th Int. Congr. Chemother., abstr. no. 1407, 1987). In addition to the pharmacokinetic advantages of lomefloxacin, it appears that, unlike enoxacin, ciprofloxacin, and pefloxacin, this drug will not affect theophylline levels. These quinolones decrease the metabolic clearance of theophylline and elevate theophylline levels in plasma (6). Some patients experience theophylline toxicity. In contrast, lomefloxacin had little effect on theophylline levels in serum when measured after concomitant administration during a 5-day period (R. Soejima, Y. Niki, Y. Tasaka, and M. Sumi, Proc. 15th Int. Congr. Chemother., abstr. no. 1267, 1987).

The purpose of this study was to determine the pharmacokinetics, safety, and tolerance of single oral doses of lomefloxacin administered to healthy male subjects.

MATERIALS AND METHODS

Subjects. Forty healthy, drug-free males, aged from 21 to 24 years (mean age, 22.1 years), weighing from 60.6 to 101.4 kg (mean weight, 74.7 kg), and within 10% of standard height and weight norms, who had given written informed consent, were enrolled in the study. All subjects underwent physical examination, including electrocardiography, electroencephalography, visual acuity and color vision testing, complete blood count, platelet count, a panel of serum chemistry tests, urinalysis with microscopy, and blood and urine drug screening to confirm their healthy status. Creatinine levels in serum at screening averaged 95 μmol/liter and ranged between 69 and 116 μmol/liter (normal range, 45 to 120 μmol/liter). Serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, blood urea nitrogen and gamma glutamyl transpeptidase (GGPT) screening values were all within normal limits, except for two alkaline phosphatase values and one SGPT value, none of which were clinically significant. These laboratory tests were repeated and the vital signs were taken at various times after dosing.

Drug administration. This trial was a double-blind, placebo-controlled study. Eight subjects were assigned to each of the five dose groups (100, 200, 400, 600, and 800 mg); in each group, five subjects received active drug and three received placebo. Dose administration proceeded sequentially, with

* Corresponding author.

increasing doses given only after the safety and tolerance of the previous dose was assured.

Lomefloxacin and placebo were supplied as identical-appearing capsules by G. D. Searle & Co. Each active capsule contained 100 mg of lomefloxacin; placebo capsules contained excipients only. Subjects were assigned to a dose level in the order of their enrollment into the study and to treatment according to a blinded randomization schedule prior to the start of the study.

The subjects were confined to the Drug Research Unit at Guy's Hospital, London, England, for 12 h before and 32 h after drug administration. In addition, they fasted for at least 8 h prior to dosing and for 4 h after dosing.

Sample collection. Blood samples (10 ml) were collected before dosing and at 20, 40, 60, and 90 min and 2, 2.5, 3, 4, 6, 8, 12, 14, 24, 30, and 48 h after dosing. Plasma, separated by centrifugation, was frozen at −20°C until analyzed. Urine was collected for 2 h prior to dosing (−2 to 0) and over the following intervals after dosing: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 48, 48 to 72, and 72 to 96 h. All urine samples were frozen at −20°C until analyzed. Microscopic urinalysis to detect the presence of drug crystals was performed on fresh urine within 5 min of collection at 3 and 6 h after dosing.

Lomefloxacin assay. Concentrations of lomefloxacin in plasma and urine were determined by a sensitive and specific high-performance liquid-chromatographic assay (E. Okezaki, E. Makino, K. Ohmochi, O. Nagata, T. Yamada, and K. Takahashi, Chemother. Jpn., in press). Following extraction into chloroform-isoamyl alcohol (19:1, vol/vol) at pH 7.0 and evaporation, the residue was dissolved in a mobile phase (acetonitrile, 0.05 M citric acid, 1.0 M ammonium acetate [22:77:1]) and analyzed on a reverse-phase Macherey-Nagel Nucleosil C-18 column (4.6 mm by 25 cm) supplied by Alltech with fluorescence detection (excitation, 280 nm; emission, 455 nm). The assay precision ranged between 2.91 and 11.7% at the concentrations tested. The plasma assay sensitivity was 0.010 μg/ml, and the urine assay sensitivity was 0.100 μg/ml. Values below the assay sensitivity were listed as zero.

Pharmacokinetic analysis. The following model-independent plasma parameters were calculated: maximum concentration in plasma (C_{max}); time to C_{max} (T_{max}); area under the drug concentration curve over the 48-hour plasma sampling period, (AUC_{0-48}); plasma clearance (CL), defined as dose/AUC_{0-48}; elimination rate constant, (β); and elimination half-life ($t_{1/2}$), defined as 0.693/β. AUC_{0-48} was calculated by using the trapezoidal rule. Absorption was assumed to be complete for calculation of CL.

The onset of the terminal (β) phase was approximated from the individual semilog plots of lomefloxacin concentration is plasma. β was estimated by linear regression of the natural logarithms of the concentrations in plasma on time (h 6 to 48) as follows: β = − slope of the regression line.

The following urine parameters were calculated: cumulative amount excreted at the end of each time interval; cumulative amount excreted in 24 h (X_u^{24}) and 96 h (X_u^{96}); the X_u^{24} and X_u^{96} as a percentage of dose; urinary excretion rate during each collection interval; maximum excretion rate (R_{max}); time to R_{max} (T_{max}); and renal clearance (CL_R), defined as (X_u^{96}/AUC_{0-48}).

Times for excretion rates were taken as the midpoints of the collection time intervals.

Statistical analyses. Changes from base-line values were calculated for the laboratory and vital-sign variables. The data from all groups were subjected to one-way analysis of

TABLE 1. Comparative plasma and renal pharmacokinetic parameters for lomefloxacin after oral doses[a]

Dose (mg)	C_{max} (μg/ml)	T_{max} (min)	AUC (μg · min/ml)	β (h^{-1})	$t_{1/2}$ (h)	CL (ml/min)	CL_R (ml/min)
100	1.11 ± 0.29 (25.90%)	48.0 ± 11.0 (22.8%)	381.0 ± 38.5 (10.1%)	0.096 ± 0.006 (6.632%)	7.13 ± 0.50 (7.0%)	264.7 ± 27.1 (10.3%)	210.0 ± 24.3 (12.0%)
200	2.46 ± 0.51 (20.77%)	44.0 ± 8.9 (20.3%)	790.8 ± 103.7 (13.1%)	0.096 ± 0.012 (12.542%)	7.34 ± 0.87 (11.9%)	256.4 ± 33.3 (13.0%)	186.8 ± 20.2 (11.0%)
400	3.02 ± 0.44 (14.70%)	76.0 ± 41.0 (53.9%)	1,641.0 ± 201.1 (12.3%)	0.090 ± 0.006 (5.691%)	7.78 ± 0.47 (6.0%)	246.7 ± 30.2 (12.2%)	189.3 ± 35.8 (18.9%)
600	4.79 ± 1.99 (41.60%)	98.0 ± 62.6 (63.9%)	2,127.8 ± 393.6 (18.5%)	0.090 ± 0.006 (5.912%)	7.98 ± 0.46 (5.8%)	289.9 ± 54.5 (18.8%)	162.0 ± 66.9 (41.3%)
800	7.46 ± 1.14 (15.33%)	58.0 ± 20.5 (35.3%)	3,421.3 ± 523.2 (15.3%)	0.084 ± 0.006 (3.959%)	8.03 ± 0.32 (3.9%)	238.4 ± 37.3 (15.7%)	160.6 ± 51.1 (31.8%)
All doses		64.8 ± 28.8 (44.4%)		0.090 ± 0.006 (6.7%)	7.65 ± 0.52 (6.8%)	259.2 ± 36.5 (14.1%)	181.7 ± 39.7 (21.8%)

[a] There were five subjects per dose. Each parameter is expressed as mean ± standard deviation (coefficient of variation).

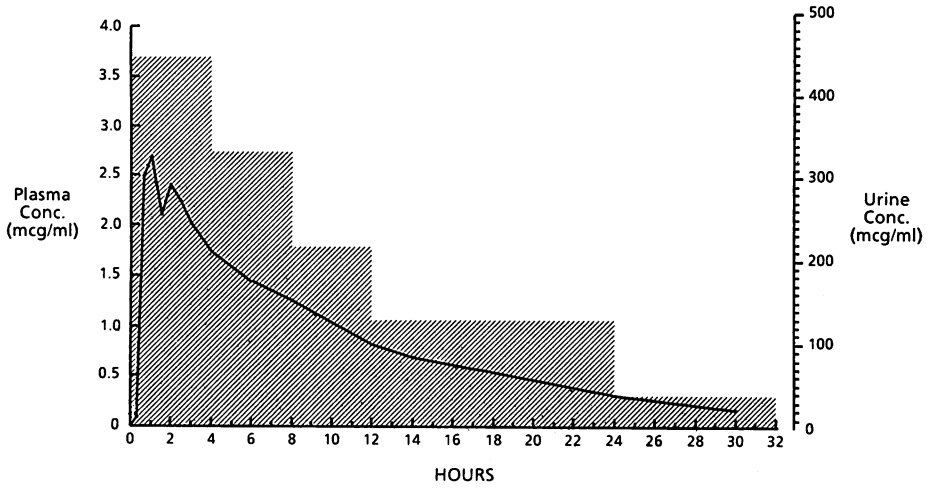

FIG. 1. Mean concentrations of lomefloxacin in plasma and urine following single oral 400-mg doses. Blood samples were taken after dosing at the indicated times, and the lomefloxacin concentrations in plasma were determined. Urine samples were collected at 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 32 h after administration, and the lomefloxacin concentrations were determined.

variance by the Shapiro-Francia or Mann-Whitney U test, as appropriate.

All the data have been summarized by means, standard deviations, and the percent coefficient of variation.

RESULTS

Pharmacokinetics. Concentrations of lomefloxacin in plasma increased rapidly, with maximum levels occurring in approximately 1 h (Table 1). The 400-mg concentration curve is shown in Fig. 1. When the plasma data were plotted on a semilog scale (data not shown), a distribution phase occurring over 2 to 4 h after administration was observed. A monoexponential decline in drug levels in plasma (β phase) was seen in all subjects after 6 h.

The mean C_{max} ranged between 1.11 μg/ml for the 100-mg dose and 7.46 μg/ml for the 800-mg dose (Table 1) and increased linearly with the dose. Except for the 600-mg data, C_{max} variability was approximately 20%. Mean T_{max} values ranged between 44 and 98 min and averaged 64.8 ± 28.8 min (Table 1).

Mean concentrations in plasma at 24 h after administration ranged between 0.06 μg/ml following the 100-mg dose and 0.62 μg/ml at the 800-mg dose. Following the 400-mg dose, mean levels in plasma were 0.82 and 0.31 μg/ml at 12 and 24 h, respectively. A good correlation was found between AUC_{0-48} and dose, indicating dose proportionality (Fig. 2).

The elimination half-life increased slightly from 7.1 h following the 100-mg dose to 8.0 h following the 800-mg dose and averaged 7.7 ± 0.52 h (Table 1). Decreases in β were correspondingly small (Table 1). Except for the 600-mg dose, CL decreased slightly over the dose range from 265 ml/min

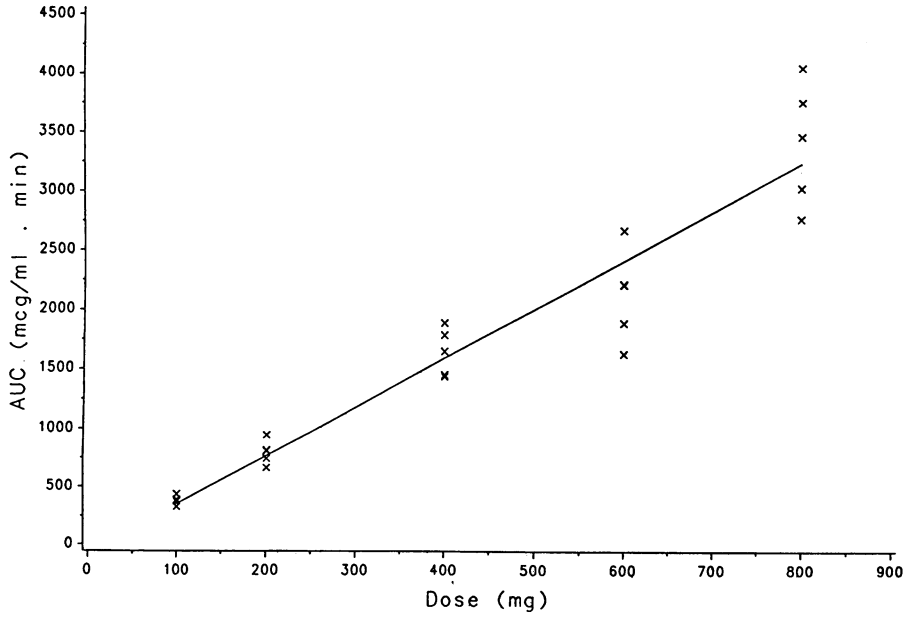

FIG. 2. Plasma AUC for lomefloxacin concentration versus dose. The AUC for each subject who received lomefloxacin is plotted. R^2 = 0.92.

TABLE 2. Comparative urine pharmacokinetic parameters for lomefloxacin after oral doses[a]

Dose (mg)	Comparative excretion over 24 h		Comparative excretion over 96 h		R_{max} (mg/h)	T_{max} (h)
	Amt (mg)	% per dose	Amt (mg)	% per dose		
100	69.3 ± 4.6 (7%)	69.3 ± 4.6 (6.6%)	79.3 ± 4.7 (6%)	79.3 ± 4.7 (6.0%)	7.55 ± 0.97 (13%)	2.0 ± 0.0 (0.0%)
200	128.4 ± 11.6 (9%)	64.2 ± 5.8 (9.0%)	146.3 ± 9.8 (7%)	73.2 ± 4.9 (6.7%)	13.02 ± 3.34 (26%)	2.8 ± 1.8 (63.9%)
400	264.6 ± 25.6 (10%)	66.2 ± 6.4 (9.7%)	305.1 ± 24.4 (8%)	76.3 ± 6.1 (8.0%)	21.61 ± 1.30 (6%)	3.6 ± 2.2 (60.9%)
600	276.3 ± 68.3 (25%)	46.0 ± 11.4 (24.7%)	326.2 ± 89.3 (27%)	54.4 ± 14.9 (27.4%)	24.44 ± 3.97 (16%)	2.0 ± 0.0 (0.0%)
800	455.8 ± 90.5 (20%)	57.0 ± 11.3 (19.9%)	530.4 ± 104.1 (20%)	66.3 ± 13.0 (19.6%)	41.11 ± 11.62 (28%)	2.8 ± 1.8 (63.9%)
All doses	238.9 ± 40.1 (17%)	60.5 ± 7.9 (13.1%)	277.5 ± 46.5 (17%)	69.9 ± 8.7 (12.5%)		2.6 ± 1.2 (45.0%)

[a] There were five subjects per dose. Each parameter is expressed as mean ± standard deviation (coefficient of variation).

for the 100-mg dose to 238 ml/min for the 800-mg dose and averaged 259 ± 37 ml/min (Table 1).

At even the lowest doses, mean lomefloxacin concentrations in urine were above 20 μg/ml for the first 24 h. The mean concentration for subjects who received the 400-mg dose was 127 μg/ml during the 12- to 24-h collection period (Fig. 1).

Excretion rates in urine generally followed a patternsimilar to that of the concentration in urine. That is, in most subjects, maximum excretion rates (R_{max}) were observed during the first sampling period (Table 2). Dose proportionality was also observed with R_{max}.

Table 2 lists the amounts of drug excreted within 24 and 96 h (X_u^{24} and X_u^{96}) and the amount expressed as a percentage of the dose. Although between 73% and 79% of the dose was excreted following the 100-, and 200-, and 400-mg doses after 96 h, mean values for the 600- and 800-mg doses were 54 and 66%, respectively. A comparison of the amounts excreted within 24 and 96 h revealed approximately 85% of the amount excreted over 96 h can be accounted for by sampling over 24 h and that excretion is essentially complete within 48 h.

Excretion generally was dose proportional. Intersubject variability was less than 10% for the three lowest doses and higher at the 600- and 800-mg doses.

CL_R averaged between 210 ml/min for the 100-mg dose and 161 ml/min for the 800-mg dose (Table 1). However, the decrease did not correlate with the dose in a linear fashion. Rather, CL_R values were similar for the 200- and 400-mg doses and for the 600- and 800-mg doses.

Safety. All subjects completed study participation, and lomefloxacin was well tolerated at all doses. No clinically significant adverse change in any laboratory or vital-sign variable was noted, nor was any adverse change noted in any electrocardiography or electroencephalography test, neurologic assessment, vision test, or physical examination. No clinically significant abnormalities were observed in the urinalyses or microscopic analyses, and no drug crystals were found in any subject at any time tested. Trial emergent signs and symptoms were spontaneously reported to the investigational staff and/or recorded in subject diaries. Most of these were mild, and none required medication. Headaches were the most commonly reported trial emergent signs and symptoms in both the placebo (3 of 15) and active (11 of 25) groups, and no dose-related pattern was observed.

DISCUSSION

In studies reported previously, single doses of 200 mg (Kamidono, 15th ICC; Matsumoto et al., 15th ICC) and 600 mg (Tanaka et al., 15th ICC) of lomefloxacin were well tolerated. In this study, single doses up to 800 mg doses were administered without significant side effects. No clinically significant adverse changes were detected in any variable examined, and no drug crystals were noted in the urine. The absence of crystals is especially significant in view of the low water solubility of many of the quinolones, which can lead to crystalluria, as has been seen following the administration of ciprofloxacin (5) or high doses of norfloxacin (3).

The model-independent pharmacokinetic parameters determined in this study were quite similar to those obtained in previous studies performed in Japan (Shiba et al., 15th ICC; Saito et al., 15th ICC; Kamidono, 15th ICC). Lomefloxacin was absorbed rapidly, with peak concentrations occurring after approximately 1 h. C_{max} values obtained in this study were also comparable to those obtained previously.

The presence of a distribution phase prior to the monoexponential decay in drug levels in plasma observed in most subjects indicates that lomefloxacin probably would be best described by two-compartment kinetics. Changes in elimination parameters with dose were slight. Both C_{max} and AUC increased proportionally with dose.

At the 400-mg dose, the mean concentration in plasma at 12 h after dosing remained higher than the MIC for 90% of strains for such common members of the family *Enterobacteriaceae* as *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Salmonella* species, *Shigella* species, *Enterobacter aerogenes*, *E. cloacae*, *Morganella morganii*, *Proteus vulgaris*, *Yersinia enterocolitica*, and *Citrobacter diversus*, as well as *Haemophilus influenzae* and *Neisseria gonorrhoeae* (Chin et al., 27th ICAAC). Even at 24 h, the mean concentration in plasma was 10-fold higher than the MIC for 50% of strains of *L. pneumophila* (Chin et al., 27th ICAAC).

Urine results generally supported the plasma results, which suggested linear elimination kinetics. However, there was some indication of nonlinearity. The percent cumulative amount excreted was lower at the higher doses, and β, CL, and CL_R decreased slightly with increasing doses. The variability in CL_R observed in this study has also been observed with ciprofloxacin (4).

At all dose levels, the concentrations in urine were generally ≥20 μg/ml through 24 h. The 400-mg dose produced a concentration in urine of 127 μg/ml during the 12- to 24-h collection, thus providing a concentration in urine exceeding the MIC for 90% of clinical isolates tested including *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, and methicillin-resistant *S. aureus*, which are difficult to treat (1; Chin et al., 27th ICAAC). Thus, single daily doses of 400 mg of lomefloxacin should deliver sufficient and continuous levels of drug to the urine to permit effective treatment of urinary tract infections.

Single oral 400-mg doses of lomefloxacin produce a C_{max} in plasma significantly above that produced by an equivalent dose of norfloxacin (7) and 500 mg of ciprofloxacin (3). Furthermore, the $t_{1/2}$ of lomefloxacin is significantly longer

than the $t_{1/2}$ of enoxacin (8), norfloxacin (7), ciprofloxacin (4), and ofloxacin (2). The $t_{1/2}$ of lomefloxacin may be sufficiently long to permit once-daily dosing in many clinical situations.

In conclusion, lomefloxacin was well tolerated in doses up to 800 mg and was rapidly absorbed from capsules with an elimination half-life of 7 to 8 h, providing appreciable concentrations in plasma and urine over the dosing interval of 24 h. Thus, on the basis of this pharmacokinetic profile and an excellent antibacterial spectrum, lomefloxacin is a promising new quinolone in the anti-infective arena.

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