ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2006, p. 1937–1945 Vol. 50, No. 6
0066-4804/06/$08.00+0 doi:10.1128/AAC.01466-05


# Levofloxacin Pharmacokinetics and Pharmacodynamics in Patients with Severe Burn Injury

Tyree H. Kiser,[1] Dorie W. Hoody,[2] Marilee D. Obritsch,[3] Colleen O. Wegzyn,[2] Paulus C. Bauling,[4] and Douglas N. Fish[1]*

*Department of Clinical Pharmacy, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado[1]; Department of Pharmacy Services, University of Colorado Hospital, Denver, Colorado[2]; Department of Pharmacy: Clinical and Administration Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center, Tulsa, Oklahoma[3]; and Burn Surgery, University of Colorado Health Sciences Center, Denver, Colorado[4]*

Received 11 November 2005/Returned for modification 12 February 2006/Accepted 21 March 2006

**Levofloxacin pharmacokinetics were studied in 11 patients with severe burn injuries. Patients (values are means ± standard deviations; age, 41 ± 17 years; weight, 81 ± 12 kg; creatinine clearance, 114 ± 40 ml/min) received intravenous levofloxacin at 750 mg ($n$ = 10 patients) or 500 mg ($n$ = one patient) once daily. Blood samples were collected on day 1 of levofloxacin therapy; eight patients were studied again on days 4 to 6. The pharmacodynamic probability of target attainment (PTA) was evaluated by Monte Carlo simulation. Mean systemic clearance, half-life, and area under the concentration-time curve over 24 h after levofloxacin at 750 mg were 9.0 ± 3.2 liters/h, 7.8 ± 1.6 h, and 93 ± 31 mg · h/liter, respectively. There were no differences in pharmacokinetic parameters between day 1 and day 4; however, large intrapatient and interpatient variability was observed. Levofloxacin pharmacokinetics in burned patients were similar to those reported in other critically ill populations. Levofloxacin at 750 mg achieved >90% PTA for gram-negative and gram-positive pathogens with MICs of ≤0.5 μg/ml and MICs of ≤1 μg/ml, respectively. However, satisfactory PTA was not obtained with less-susceptible gram-negative organisms with MICs of 1 μg/ml or any organism with a MIC of ≥2 μg/ml. The results of this study indicate that levofloxacin should be administered at 750 mg/day for treatment of systemic infections in severely burned patients. However, even 750 mg/day may be inadequate for gram-negative organisms with MICs of 1 to 2 μg/ml even though they are defined as susceptible. Alternative antibiotics or treatment strategies should be considered for infections due to these pathogens.**

Patients with severe thermal injuries have multiple defects in both humoral and cellular immunity and are at high risk for serious infections including pneumonia, cellulitis and wound infections, urinary tract infections, and bloodstream infections (1, 9, 15, 21, 23, 30). Optimizing antimicrobial therapy in these patients can be difficult due to numerous physiologic alterations affecting organ function and drug metabolism (2, 9, 23, 31).

Several antimicrobials, including fluoroquinolones, have demonstrated significant pharmacokinetic alterations in severely burned patients. These changes often require increased doses to maintain adequate concentrations for successful treatment of severe infections (3, 4, 12, 13, 29, 34, 35). The potential for suboptimal dosing of antibiotics is particularly of concern in this population because of the frequency of infection with difficult, less-susceptible pathogens along with highly variable pharmacokinetics. Inability to attain pharmacodynamic targets may lead to clinical failure in the treatment of severe infections and contribute to increased resistance among bacterial pathogens.

Levofloxacin (Levaquin; Ortho-McNeil Pharmaceutical, Raritan, NJ) is frequently used in the empirical and definitive treatment of infections in burn patients; however, levofloxacin pharmacokinetics in this population have not been previously described. It may be hypothesized that the higher 750-mg/day dose of levofloxacin would be more desirable in patients with severe burn injury due to the high incidence of severe infections caused by less-susceptible organisms and possibly poor perfusion of infected tissue, which may limit drug penetration (5, 6, 14).

The primary objective of this study was to characterize the pharmacokinetics of intravenous levofloxacin in patients with severe burn injuries. A second objective was to evaluate the pharmacodynamic adequacy of prescribed dosing regimens by comparing levofloxacin concentrations with MICs of pathogens commonly found in this population.

(A portion of this work was presented at the 35th Congress of the Society of Critical Care Medicine, San Francisco, Calif., on 10 January 2006.)

## MATERIALS AND METHODS

**Study conduct.** This was a prospective, open-label, nonrandomized study of levofloxacin (Ortho-McNeil Pharmaceutical, Raritan, NJ). The study was approved by the institutional review board of the hospital where the study was performed, and written informed consent was obtained from all patients or their legally designated representatives prior to study entry.

**Patient eligibility.** All adult patients admitted to the University of Colorado Hospital Burn Unit who were >18 years of age, had thermal injuries involving ≥30% total body surface area (TBSA) and creatinine clearance ($CL_{CR}$) rates of ≥50 ml/minute (determined by 24-hour urine collection and also estimated according to the Cockcroft-Gault method [7] using calculated ideal body weight), and who were prescribed intravenous levofloxacin as part of their required medical care were eligible for inclusion in this study. Exclusion criteria included age less than 18 years, presence of significant renal impairment (creatinine clearance of <50 ml/min), or requirement for hemodialysis (either conventional hemodialysis or continuous renal replacement therapy). Patients initially en-

* Corresponding author. Mailing address: Department of Clinical Pharmacy, School of Pharmacy, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, Campus Box C-238, Denver, CO 80262. Phone: (303) 315-5136. Fax: (303) 315-4630. E-mail: doug.fish@uchsc.edu.

rolled into the study were excluded from subsequent pharmacokinetic evaluations if the creatinine clearance decreased to <50 ml/min at any time during the study or if levofloxacin therapy was discontinued for any reason. Patients receiving therapy with any drugs capable of causing pharmacokinetic drug interactions with levofloxacin (e.g., cyclosporine, cimetidine, and probenecid) were also excluded.

**Study protocol.** Pharmacokinetic studies were conducted after the initial resuscitative phase of the management of the burn injury (i.e., >3 days following the injury). All decisions regarding initial use of levofloxacin and subsequent changes from levofloxacin to other antibiotics were made by the surgical team caring for the patients. Patients enrolled into the study received levofloxacin at 500 mg or 750 mg once daily administered as a 60-minute or 90-minute intravenous infusion, respectively, through either an indwelling peripheral or a central venous catheter as part of each patient's regular and required medical care. The decision to use the 500-mg or 750-mg dose was based on the perceived clinical indication and judgment of the physicians caring for the patient. Patients with more severe documented or presumed infections (e.g., nosocomial pneumonia, bacteremia/sepsis, or severe skin/skin structure infection) received the 750-mg dose while those patients with less severe infections (mild to moderate skin/skin structure infection or urinary tract infection) often received the 500-mg dose. Patients were not randomized per study protocol to receive low-dose versus higher-dose levofloxacin due to the hypothesized alteration in levofloxacin pharmacokinetics and the clinical concern that patients with more-severe infections could be randomized to a potentially subtherapeutic lower dose. Complete medical histories were obtained for each enrolled patient, and complete physical examinations and laboratory review of serum chemistry and hematology profiles were obtained and reviewed prior to collection of samples for pharmacokinetic analysis. All subjects were monitored for adverse effects of levofloxacin throughout the duration of the study.

**Sample collection and storage.** Serum samples for pharmacokinetic analysis were obtained through a separate indwelling catheter during two separate time periods: with the first levofloxacin dose (hereafter referred to as day 1) and again after the drug had presumably achieved steady-state concentrations with the fourth through sixth doses (hereafter referred to as day 4). Sampling during each of these two dosing periods was performed in order to examine potential pharmacokinetic variability over time, i.e., to determine whether pharmacokinetic changes in burn patients, if any, are more pronounced in the immediate postinjury period and whether such alterations may persist throughout the course of antibiotic therapy. Blood samples (3 ml) for levofloxacin assay were obtained just before the start of drug infusion (predose, time zero), at the end of drug infusion (1 or 1.5 h), and at 2, 3, 4, 6, 9, 12, and 24 h after the start of drug infusion. Blood samples were centrifuged immediately after collection and placed in labeled polyethylene vials. Serum samples were frozen at −80°C immediately after processing and kept frozen until assayed.

**Sample assay.** Levofloxacin plasma concentrations were determined using high-performance liquid chromatography (HPLC) with UV detection according to a previously published method with minor modifications (26, 32). The HPLC system utilized a Kingsorb $C_{18}$ 5-μm 4.6-mm × 150-mm column (Phenomenex, Torrance, CA) with a guard column containing μBondapak $C_{18}$ 10-μm inserts (Waters, Milford, MA), and the detector was set at a wavelength of 330 nm. The mobile phase consisted of 20 mM potassium phosphate buffer, acetonitrile, and methanol (81:12:7 [vol/vol]), with 3 ml tetrabutylammonium hydroxide added to each liter and adjusted to a pH of 3.0 with hydrochloric acid. Analytical-grade levofloxacin powder for validation and quality control of the HPLC assay was supplied by Ortho-McNeil Pharmaceutical (Raritan, New Jersey). Ciprofloxacin (Bayer Pharmaceuticals, West Haven, Connecticut) was used as an internal standard. Coefficients of determination ($r^2$) for plasma levofloxacin over the standard curve concentrations of 0.10 to 25.00 μg/ml were 0.998 to 0.999 for the entire study. Intraday and interday coefficients of variation for plasma levofloxacin samples ranged from <7% at 0.10 μg/ml to <1% at 25.00 μg/ml. The lower limit of levofloxacin detection in plasma was 0.05 μg/ml. The accuracy and precision of this assay met standards set for bioanalytical method validation (27).

**Pharmacokinetic analysis.** Plasma concentration-time data for levofloxacin were analyzed by standard noncompartmental pharmacokinetic methods with elimination of levofloxacin assumed to be first order. Peak drug concentrations in plasma ($C_{max}$) and the times at which these concentrations were achieved ($T_{max}$) were estimated by visual inspection of the plasma concentration-versus-time data. Minimum plasma concentration ($C_{min}$) was also determined by direct measurement. The apparent terminal elimination rate constant ($k_{el}$) was determined by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. Elimination half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$. The area under the concentration-time curve from time zero to the end of the 24-hour dosing interval ($AUC_{0-24}$) was calculated by the linear trapezoidal summation method. Total systemic clearance ($CL_s$) was calculated as dose/$AUC_{0-24}$. Since levofloxacin concentrations were not at steady state during the first sampling period, the volume of distribution ($V$) was calculated by nonsteady-state methods (28); for the second sampling period the steady-state volume of distribution ($V$) was calculated as dose/($k_{el} \times AUC_{0-24}$). All calculations were made by programming pharmacokinetic equations into Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) spreadsheets and were validated using WinNonlin version 5.0.1 (Pharsight Corporation, Mountain View, CA). Also using Microsoft Excel, measures of central tendency and variability were evaluated for all patient characteristics and pharmacokinetic parameters.

**Analysis of pharmacodynamic targets.** Pharmacodynamic parameters were also evaluated in order to determine whether 500-mg and/or 750-mg once-daily doses of levofloxacin result in initial and steady-state plasma concentrations that are adequate for treatment of infections due to common pathogens. The targeted pharmacodynamic goals for levofloxacin, using total drug concentrations, were a ratio of $C_{max}$ to MIC ($C_{max}$/MIC) of ≥8 and/or a ratio of $AUC_{0-24}$ to MIC ($AUC_{0-24}$/MIC) of ≥50 for gram-positive pathogens and ≥87 for gram-negative pathogens (8, 10, 11, 19, 25, 33, 36). For evaluation of free (unbound) drug levels, $C_{max}$/MIC and $AUC_{0-24}$/MIC can be multiplied by 0.70, the approximate free fraction of levofloxacin in human plasma (24), to obtain corresponding pharmacodynamic parameters for free drug ($fC_{max}$/MIC and $fAUC_{0-24}$/MIC, respectively).

Monte Carlo simulation (Crystal Ball version 7; Decisioneering, Inc., Denver, CO) was used in this study to calculate probability of target attainment (PTA) for pharmacodynamic goals. The PTAs for desired $C_{max}$/MIC and $AUC_{0-24}$/MIC goals were evaluated at MICs of 0.25 μg/ml, 0.5 μg/ml, 1 μg/ml, and 2 μg/ml; these MICs represent those of organisms which would be considered susceptible to levofloxacin, up to and including the approved susceptibility breakpoint. The model randomly applied values for $C_{max}$ and $AUC_{0-24}$ derived from data obtained in this study in severely burned patients. Monte Carlo simulation was also used to evaluate PTA for $C_{max}$/MIC and $AUC_{0-24}$/MIC goals using recent (2004) MIC data specific to the University of Colorado Hospital for *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. MICs at which 50% and 90% of isolated strains are inhibited and which were used in model development were as follows: *E. coli*, 1 and 4 μg/ml; *K. pneumoniae*, 0.5 and 0.5 μg/ml; and *P. aeruginosa*, 2 and 16 μg/ml, respectively. Custom MIC frequency distributions were constructed and used in the Monte Carlo simulations. Five thousand simulations were performed at each MIC and for each of the selected pathogens. The PTAs for $C_{max}$/MIC of ≥8 or ≥10 and $AUC_{0-24}$/MIC of ≥50, ≥87, ≥125, or ≥250 were calculated. Achieving a PTA of ≥90% for specified $C_{max}$/MIC and $AUC_{0-24}$/MIC goals was considered adequate for the use of levofloxacin as empirical therapy in this population.

**Statistical analysis.** Differences between demographic variables among patients were assessed for statistical significance using the Fisher exact test, the chi-square test for independence, or the one-way analysis of variance mixed-effects model where appropriate. Mean values of pharmacokinetic parameters on day 1 and day 4 were compared using a two-tailed Wilcoxon matched pairs test for paired nonparametric data. Differences among calculated pharmacokinetic parameters obtained in this study versus those from previously published literature in other populations (6, 26) were assessed by a two-tailed Mann-Whitney test for nonparametric data or one-way analysis of variance. Correlation between patient weight or $CL_{CR}$ and various pharmacokinetic variables was determined using the Spearman rank correlation coefficient for nonparametric data. All statistical tests were performed using GraphPad InStat version 3.06 for Windows (GraphPad Software, San Diego, CA). $P$ values of <0.05 were considered significant. Assuming that a 20% difference in plasma $C_{max}$ or $AUC_{0-24}$ between study patients and published literature values could be clinically significant and estimating standard deviations (SDs) based on previously published pharmacokinetic values, it was calculated that a sample size of 10 subjects would result in greater than 80% power to detect a 20% difference at an α level of 0.05.

## RESULTS

A total of 11 patients with serious burn injury were enrolled in this study. Although all 11 of these patients completed pharmacokinetic sampling during the first study period, only eight patients completed the entire protocol and were fully evaluable. Three patients were unable to complete the second sampling period: two patients died prior to day 4 of levofloxacin therapy and one patient developed acute renal failure and was disqualified from further participation per protocol exclu-

TABLE 1. Patient demographics and clinical characteristics

| Characteristic | Value |
|---|---|
| Age (yr), mean ± SD (range) | 41 ± 17 (21–75) |
| Gender (no. [%] of patients) | |
| Male | 10 (91) |
| Female | 1 (9) |
| Race (no. [%] of patients) | |
| African American | 1 (9) |
| Caucasian | 8 (73) |
| Hispanic | 1 (9) |
| Native American | 1 (9) |
| Wt (kg), mean ± SD | |
| Admission | 81 ± 12 |
| Day 1 | 93 ± 11 |
| Day 4 | 90 ± 13 |
| Albumin (g/dl), mean ± SD | 1.8 ± 0.5 |
| Creatinine clearance (ml/min), mean ± SD (range) | 114 ± 40 (64–177) |
| Extent of burn injury (% total body surface area), mean ± SD (range) | 47 ± 14 (30–68) |
| No. [%] of patients with positive bacterial cultures | 9 (82) |
| Infection site (no. [%] of patients) | |
| Respiratory tract | 2 (18) |
| Blood | 3 (27) |
| Respiratory tract and blood | 4 (36) |
| Urine | 2 (18) |
| Infecting pathogen (no. [%] of patients) | |
| *Staphylococcus aureus* | 6 (55) |
| *Pseudomonas aeruginosa* | 4 (36) |
| *Escherichia coli* | 3 (27) |
| *Enterobacter cloacae* | 2 (18) |
| Beta-hemolytic streptococcus | 2 (18) |
| Other | 5 (45) |

sion criteria. These adverse outcomes were attributed to complications of the underlying burn injury rather than the study drug. Although the original study protocol specified that a total of 10 patients completing the protocol were required for adequate pharmacokinetic evaluations, additional patients were not enrolled and the study was terminated early due to the physician investigator (P. Bauling) leaving the institution and changes in institutional review board requirements. Levofloxacin pharmacokinetic analyses thus included 11 patients in the first sampling period and 8 patients in the second sampling period. However, the study was still sufficiently powered to evaluate levofloxacin pharmacokinetics on day 1 of therapy.

Demographic information for all patients is presented in Table 1. Ten patients received levofloxacin at 750 mg once daily, and one patient received 500 mg once daily. Patients had a mean weight of 81 ± 12 kg upon hospital admission, which significantly increased to 93 ± 11 kg during the resuscitative phase of management of the burn injuries ($P = 0.001$). Weight on day 4 was significantly less than on day 1 (90 ± 13 kg versus 93 ± 11 kg; $P = 0.02$). Renal function was generally good with a mean creatinine clearance of 114 ± 40 ml/minute (range, 64 to 177 ml/minute) as measured by 24-hour urine collection (7 of 11 patients) or calculated by the Cockcroft-Gault method (4 of 11 patients) when 24-hour urine collection samples were not available.

Levofloxacin therapy was initiated subsequent to positive bacterial cultures in nine patients and for presumed infection and sepsis in two patients. A total of 17 organisms were isolated from the 11 patients (Table 1). Pathogens were isolated from respiratory tract cultures in two patients, from blood cultures in three patients, and from both blood and respiratory tract cultures in four patients. Two patients had positive urine cultures in addition to positive blood cultures. *Staphylococcus aureus* was the most common pathogen identified (6 of 11 patients), followed by *Pseudomonas aeruginosa* (four patients), *Escherichia coli* (three patients), *Enterobacter cloacae* and beta-hemolytic *Streptococcus* (two patients each), and finally *Serratia marcescens*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Haemophilus influenzae*, and *Peptostreptococcus* (one patient each).

Initial pharmacokinetic evaluations were performed a mean of 6 ± 4 days (range, 3 to 15 days) after hospital admission. Six patients had initial pharmacokinetic evaluations on day 3 or 4 after the burn injury and directly following the resuscitation phase. Levofloxacin day 1 pharmacokinetics were evaluated in all 11 patients (Table 2). Three patients were excluded from the day 4 to 6 analysis as previously noted. Mean values ± SDs for levofloxacin $C_{max}$, $C_{min}$, $t_{1/2}$, $CL_s$, $AUC_{0-24}$, and $V$ in all patients receiving levofloxacin at 750 mg and including both study periods were 11.3 ± 3.1 mg/liter, 1.2 ± 0.6 mg/liter, 7.8 ± 1.6 h, 9.0 ± 3.2 liter/h, 92.9 ± 30.6 mg · h/liter, and 1.1 ± 0.3 liter/kg of body weight, respectively. As expected, the mean $C_{max}$ in patients receiving levofloxacin at 750 mg was substantially higher than that after the 500-mg dose (11.3 ± 3.1 and 7.3 mg/liter, respectively), but no statistical inferences could be made since only a single patient received the lower dose. A moderate association was found between measured or calculated $CL_{CR}$ and levofloxacin $CL_s$ ($r^2 = 0.42$; $P = 0.02$) but not between percent TBSA of the burn injury and $CL_s$ ($r^2 = 0.03$; $P = 0.96$) or $V$ ($r^2 = 0.23$; $P = 0.14$). Seven patients with $CL_{CR}$ of ≥99 ml/min ($CL_{CR}$ mean ± SD, 133 ± 33 ml/min) had significantly higher mean levofloxacin clearance (10.0 ± 3.2 liter/h versus 6.3 ± 1.4 liter/h; $P = 0.01$) than did the four patients with $CL_{CR}$ of <99 ml/min ($CL_{CR}$ mean ± SD, 72 ± 7 ml/min). In the patients receiving levofloxacin at 750 mg, seven patients with $CL_{CR}$ of ≥99 ml/min ($CL_{CR}$ mean ± SD, 133 ± 33 ml/min) had lower $AUC_{0-24}$ (81.7 ± 24.1 mg · h/liter versus 112.6 ± 29.7 mg · h/liter; $P = 0.04$) than did the three patients with $CL_{CR}$ of <99 ml/min ($CL_{CR}$ mean ± SD, 74 ± 6 ml/min).

There were no statistically significant differences in pharmacokinetic parameters between day 1 and day 4; however, considerable intrapatient and interpatient variability was observed. Decreases in $V$ were observed in five of eight patients, with a mean reduction of 25% in all patients (104 ± 23 liters on day 1 versus 92 ± 31 liters on day 4; $P = 0.055$). This difference may perhaps be associated with the significantly greater body weight after the intensive fluid resuscitation which occurred in most patients just prior to initiation of levofloxacin therapy, followed typically by a pronounced diuresis and weight loss before the day 4 study period. There were also substantial changes observed in several other parameters be-

TABLE 2. Pharmacokinetics of levofloxacin on days 1 and 4 of treatment in patients with severe burn injuries

| Patient (dose in mg) and day | $CL_{CR}$ (ml/min) | $t_{1/2}$ (h) | $CL_s$ (liters/h) | $V$ (liters/kg) | $C_{max}$ (mg/liter) | $C_{min}$ (mg/liter) | $AUC_{0-24}$ (mg · h/liter) |
|---|---|---|---|---|---|---|---|
| Patient 1 (750) | | | | | | | |
| Day 1 | 162 | 5.7 | 6.3 | 0.6 | 18.2 | 1.0 | 118.2 |
| Day 4[a] | | | | | | | |
| Patient 2 (750) | | | | | | | |
| Day 1 | 142 | 7.4 | 8.6 | 1.1 | 12.3 | 1.1 | 87.4 |
| Day 4 | 142 | 6.9 | 8.9 | 1.2 | 9.5 | 0.9 | 84.6 |
| Patient 3 (750) | | | | | | | |
| Day 1 | 162 | 7.4 | 10.4 | 1.1 | 10.5 | 0.8 | 72.1 |
| Day 4 | 162 | 5.9 | 9.8 | 0.8 | 11.3 | 0.6 | 76.2 |
| Patient 4 (750) | | | | | | | |
| Day 1 | 100 | 6.7 | 10.6 | 1.2 | 9.9 | 0.7 | 70.9 |
| Day 4 | 100 | 7.7 | 7.0 | 0.9 | 17.4 | 1.1 | 107.2 |
| Patient 5 (750) | | | | | | | |
| Day 1 | 66 | 8.1 | 8.8 | 0.9 | 8.3 | 1.7 | 85.0 |
| Day 4 | 73 | 9.9 | 5.7 | 0.8 | 12.1 | 2.3 | 131.5 |
| Patient 6 (750) | | | | | | | |
| Day 1 | 80 | 9.9 | 6.5 | 1.0 | 10.1 | 2.0 | 116.2 |
| Day 4 | 80 | 9.8 | 4.6 | 0.7 | 11.9 | 2.5 | 161.4 |
| Patient 7 (750) | | | | | | | |
| Day 1 | 177 | 7.4 | 11.4 | 1.1 | 14.2 | 0.7 | 65.8 |
| Day 4 | 177 | 4.8 | 17.6 | 1.2 | 8.5 | 0.2 | 42.6 |
| Patient 8 (750) | | | | | | | |
| Day 1 | 103 | 9.2 | 7.9 | 1.5 | 12.5 | 1.4 | 94.8 |
| Day 4 | 103 | 6.8 | 6.1 | 0.8 | 12.6 | 1.5 | 123.2 |
| Patient 9 (750) | | | | | | | |
| Day 1 | 72 | 10.5 | 6.5 | 1.0 | 11 | 1.9 | 115.8 |
| Day 4[a] | | | | | | | |
| Patient 10 (750) | | | | | | | |
| Day 1 | 99 | 7.7 | 12.6 | 1.5 | 7.7 | 0.8 | 59.7 |
| Day 4 | 99 | 8.3 | 12.8 | 1.7 | 6.4 | 0.8 | 58.8 |
| Patient 11 (500) | | | | | | | |
| Day 1 | 64 | 15.6 | 5.8 | 1.5 | 7.3 | 2.4 | 85.5 |
| Day 4[a] | | | | | | | |
| Mean ± SD | | | | | | | |
| Day 1 | 112 ± 42 | 8.7 ± 2.7 | 8.7 ± 2.3 | 1.1 ± 0.3 | 11.4 ± 3.1[b] | 1.2 ± 0.5[b] | 88.6 ± 22.1[b] |
| Day 4 | 117 ± 39 | 7.5 ± 1.8 | 9.1 ± 4.3 | 1.0 ± 0.3 | 11.2 ± 3.3[b] | 1.2 ± 0.8[b] | 98.2 ± 39.9[b] |
| $P$[c] | 0.99 | 0.55 | 0.38 | 0.25 | 0.74 | 0.58 | 0.15 |
| Days 1 + 4 | 114 ± 40 | 8.2 ± 2.4 | 8.8 ± 3.2 | 1.1 ± 0.3 | 11.3 ± 3.1[b] | 1.2 ± 0.6[b] | 92.9 ± 30.6[b] |

[a] Day 4 pharmacokinetic sampling not performed.
[b] Includes data only from patients receiving 750-mg doses; data from patient 11 (500-mg dose) not included.
[c] Values on day 1 versus those on day 4.

tween the two study periods. Renal function was stable between day 1 and day 4 in all patients; however, mean $CL_s$ was decreased by nearly 20% and four of the eight evaluable patients had reductions in $CL_s$ of between 30% and 55%. Although these reductions in $CL_s$ and $V$ were apparently offsetting and the mean change in $AUC_{0-24}$ between days 1 and 4 was only +8%, an increased $AUC_{0-24}$ of from 23% to 35% was observed in four of eight patients during the two study periods.

Levofloxacin pharmacokinetics observed in this study were generally similar to those previously reported for both healthy subjects and severely ill patients in a medical intensive care unit (ICU) (Table 3) (6, 26). The mean weight at time of levofloxacin administration was significantly higher for the severely burned patients than for either medical ICU patients or healthy subjects, but in the present study no association was found between weight and $CL_s$, $t_{1/2}$, or $V$ ($r^2 = 0.19$, $P = 0.18$; $r^2 = 0.05$, $P = 0.49$; and $r^2 = 0.14$, $P = 0.27$, respectively). Mean levofloxacin $CL_s$ was somewhat higher and $AUC_{0-24}$ was slightly lower in severely burned patients than in healthy subjects given similar 750-mg intravenous doses, but these differ-

TABLE 3. Comparison of levofloxacin pharmacokinetics in patients with severe burn injuries and other populations

| Parameter | Severely burned ICU patients ($n$ = 10) | Medical ICU patients (reference 26) ($n$ = 26) | Healthy subjects (reference 6) ($n$ = 10) |
|---|---|---|---|
| Dose (mg; intravenous) | 750 | 500 | 750 |
| Age (yr) | 42 ± 18 | 51 ± 12 | 41 |
| Wt (kg) | 92 ± 11 | 77 ± 7 | 72 |
| $t_{1/2}$ (h) | 7.8 ± 1.6 | 8.0 ± 1.7 | 7.5 ± 1.5 |
| $CL_s$ (liters/h) | 9.0 ± 3.2 | 8.0 ± 2.1 | 8.0 ± 2.5 |
| $V$ (liters/kg) | 1.1 ± 0.3 | 1.2 ± 0.3 | 1.1 ± 0.2 |
| $C_{max}$ (mg/liter) | 11.3 ± 3.1 | 7.5 ± 0.8 | 11.3 ± 3.6 |
| $C_{min}$ (mg/liter) | 1.2 ± 0.6 | 1.0 ± 0.5 | 1.1 ± 0.5 |
| $AUC_{0-24}$ (mg · h/liter) | 93 ± 31 | 66 ± 16 | 103 ± 35 |

ences in $CL_s$ and $AUC_{0-24}$ could not be compared statistically. The observed changes in $CL_s$ and $AUC_{0-24}$ are nevertheless consistent with changes previously observed with ciprofloxacin in severely burned patients (12). Both $C_{max}$ and $AUC_{0-24}$ in burn patients receiving 750 mg were significantly higher than those following the 500-mg dose previously studied in medical ICU patients ($P = 0.03$ and $P = 0.004$, respectively). However, as previously mentioned, there were no significant differences between the two patient populations among non-dose-dependent parameters.

Table 4 illustrates the $C_{max}$/MIC and $AUC_{0-24}$/MIC ratios at each of three MICs evaluated, these being representative of susceptible pathogens isolated from patients in the burn ICU. The majority of patients achieved the desired $C_{max}$/MIC goals for MICs of ≤1 μg/ml with the levofloxacin 750-mg dose, although only 70% of patients achieved the higher threshold of $C_{max}$/MIC of ≥10 at the highest MIC (Table 5). All patients achieved the desired $AUC_{0-24}$/MIC of ≥50 for treatment of infections caused by gram-positive pathogens with MICs of ≤1 μg/ml. All patients also successfully achieved the desired $AUC_{0-24}$/MIC of ≥87 for gram-negative organisms with MICs of ≤0.5 μg/ml; however, at a MIC of 1 μg/ml, only 50% of patients achieved an $AUC_{0-24}$/MIC ratio of ≥87.

Table 5 displays the PTA for pharmacodynamic goals with levofloxacin at 750 mg intravenously daily as evaluated using Monte Carlo simulation. $C_{max}$/MIC ratios of ≥8 were reliably obtained with a 97% probability of target attainment for pathogens with MICs of ≤1 μg/ml. For gram-positive pathogens, the probabilities of attaining targeted $AUC_{0-24}$/MIC ratios of ≥50 were virtually 100% for organisms with MICs of ≤1 μg/ml. For gram-negative pathogens, the PTA for $AUC_{0-24}$/MIC ratios of ≥87 was also 100% for organisms with MICs of ≤0.5 μg/ml, but the PTA fell to 55% for organisms with MICs of 1 μg/ml. For both gram-positive and gram-negative pathogens, the PTA at the approved susceptibility breakpoint of a MIC of 2 μg/ml was very low (28% and 0%, respectively). The ability to reliably achieve desired $AUC_{0-24}$/MIC goals for gram-negative pathogens during treatment with levofloxacin was therefore poor for all but the most susceptible organisms used in the simulations. For *P. aeruginosa* the Monte Carlo simulation-derived PTAs for $C_{max}$/MIC of ≥8 and ≥10 were only 43% and 40%, respectively, and the probabilities of attaining $AUC_{0-24}$/MIC of ≥87 and ≥125 were only 39% and 33%, respectively. For *E. coli*, the probabilities of achieving $C_{max}$/MIC of ≥8 and ≥10 were 87% and 83%, respectively, and the PTAs for $AUC_{0-24}$/MICs of ≥87 and ≥125 were 84% and 81%, respectively. For *K. pneumoniae*, the probabilities of attaining $C_{max}$/MIC of ≥8 and ≥10 were 95% and 93%, respectively, while the PTAs for $AUC_{0-24}$/MIC of ≥87 and ≥125 were 94% and 92%, respectively. Thus, of the three organisms modeled, *K. pneumoniae* was the only one for which probabilities of achieving optimal pharmacodynamic targets were consistently high.

## DISCUSSION

The results of this study demonstrate that the mean pharmacokinetics of levofloxacin in patients with severe burn injury are not significantly different from those reported in other critically ill populations. However, this study also demonstrates very clearly that great intrapatient and interpatient variabilities of levofloxacin pharmacokinetic parameters are present in severely burned patients. In the 11 patients evaluated, the half-life of levofloxacin ranged from 4.8 to 15.6 h and the $AUC_{0-24}$ from 43 to 161 mg · h/liter; other parameters were similarly associated with high variability (Table 2). It is notable that this high degree of variability was observed in patients without renal impairment and with apparently stable creatinine clearance. This high degree of variability is consistent with that reported for other antimicrobials in seriously burned patients (4, 12, 13). Since infections requiring systemic antibiotics do not typically occur during the first several days following acute burn injury, our evaluation of levofloxacin occurred after the resuscitative phase of treatment had been completed (range, 3 to 15 days postadmission). Prior to performing this study we had hypothesized that the pronounced hypermetabolic and catabolic state commonly present in patients with severe burn injuries (2, 9, 23, 31) would lead to significant alterations in the pharmacokinetics of levofloxacin but that these alterations would resolve as the time since the acute injury grew longer. Although this study demonstrated no statistically significant changes in pharmacokinetic parameters when patients were studied on two different occasions several days apart, intrapatient variability in drug pharmacokinetics during this time was quite apparent. As previously noted, five of the eight fully evaluable patients had decreases in both $CL_s$ and $V$ of >25% between days 1 and 4.

Garrelts and colleagues previously reported an association between ciprofloxacin clearance and both $CL_{CR}$ ($r = 0.85$) and percent TBSA of the burn injury ($r = -0.55$) (12). We were unable to find similar strong correlations with levofloxacin in this study. A moderate association was found between measured 24-hour $CL_{CR}$ and $CL_s$ ($r^2 = 0.42$; $P = 0.02$). Although still statistically significant, the strength of the association between renal function and levofloxacin clearance was reduced somewhat when using the Cockcroft-Gault method for estimating $CL_{CR}$ ($r^2 = 0.25$, $P = 0.03$). As expected, $CL_{CR}$ was a useful tool for predicting which patients would have the highest levofloxacin $CL_s$. In this study patients with a $CL_{CR}$ of ≥99 ml/min had significantly higher $CL_s$ ($P = 0.01$) and lower $AUC_{0-24}$ ($P = 0.04$) than did patients with a $CL_{CR}$ of <99 ml/min. No association between percent TBSA of the burn injury and levofloxacin $CL_s$ was found overall ($r^2 = 0.02$), and $CL_s$ was likewise not significantly different between patients

TABLE 4. Calculated $C_{max}$/MIC and $AUC_{0-24}$/MIC ratios achieved with levofloxacin in patients with severe burn injuries[c]

| Patient and day | Value for MIC: | | | | | |
|---|---|---|---|---|---|---|
| | 0.25 μg/ml | | 0.5 μg/ml | | 1 μg/ml | |
| | $C_{max}$/MIC | $AUC_{0-24}$/MIC | $C_{max}$/MIC | $AUC_{0-24}$/MIC | $C_{max}$/MIC | $AUC_{0-24}$/MIC |
| Patient 1 | | | | | | |
| Day 1 | 73 | 473 | 36 | 236 | 18 | 118 |
| Day 4 | | | | | | |
| Patient 2 | | | | | | |
| Day 1 | 49 | 350 | 25 | 175 | 12 | 87 |
| Day 4 | 38 | 339 | 19 | 169 | 10 | 85 |
| Patient 3 | | | | | | |
| Day 1 | 42 | 288 | 21 | 144 | 10 | 72 |
| Day 4 | 45 | 305 | 23 | 152 | 11 | 76 |
| Patient 4 | | | | | | |
| Day 1 | 40 | 284 | 20 | 142 | 10 | 71 |
| Day 4 | 70 | 429 | 35 | 214 | 17 | 107 |
| Patient 5 | | | | | | |
| Day 1 | 33 | 340 | 17 | 170 | 8 | 85 |
| Day 4 | 48 | 526 | 24 | 263 | 12 | 132 |
| Patient 6 | | | | | | |
| Day 1 | 40 | 465 | 20 | 232 | 10 | 116 |
| Day 4 | 48 | 646 | 24 | 323 | 12 | 161 |
| Patient 7 | | | | | | |
| Day 1 | 57 | 263 | 28 | 132 | 14 | 66 |
| Day 4 | 34 | 171 | 17 | 85 | 8 | 43 |
| Patient 8 | | | | | | |
| Day 1 | 50 | 379 | 25 | 190 | 12 | 95 |
| Day 4 | 50 | 493 | 25 | 246 | 13 | 123 |
| Patient 9 | | | | | | |
| Day 1 | 44 | 463 | 22 | 232 | 11 | 116 |
| Day 4 | | | | | | |
| Patient 10 | | | | | | |
| Day 1 | 31 | 239 | 15 | 119 | 8 | 60 |
| Day 4 | 26 | 235 | 13 | 118 | 6 | 59 |
| Patient 11[a] | | | | | | |
| Day 1 | 29 | 342 | 15 | 171 | 7 | 86 |
| Day 4 | | | | | | |
| Mean ± SD | | | | | | |
| Day 1 | 46 ± 12[b] | 354 ± 88[b] | 23 ± 6[b] | 177 ± 44[b] | 11 ± 3[b] | 89 ± 22[b] |
| Day 4 | 45 ± 13[b] | 393 ± 159[b] | 22 ± 7[b] | 196 ± 80[b] | 11 ± 3[b] | 98 ± 40[b] |

[a] Patient 11 received levofloxacin at 500 mg intravenously. All other patients received levofloxacin at 750 mg intravenously.
[b] Includes data only from patients receiving 750-mg doses; data from patient 11 (500-mg dose) not included.
[c] Pharmacodynamic ratios for free drug ($^fC_{max}$/MIC and $^fAUC_{0-24}$/MIC) can be estimated by multiplying values in Table 4 by 0.7, the approximate unbound fraction of levofloxacin in plasma.

with relatively less severe burns (<45% TBSA) and those with more severe burns (>45% TBSA) (8.8 ± 4.2 versus 8.9 ± 2.5 liters/h, respectively; $P = 0.95$). Demographic and clinical variables evaluated in this study were not able to clearly account for the pharmacokinetic characteristics present in these patients.

Studies have shown that both the $C_{max}$/MIC and $AUC_{0-24}$/MIC ratios are good predictors of fluoroquinolone efficacy (8, 10, 11, 16–20, 25, 36). $C_{max}$/MIC ratios of ≥8 have been suggested as being favorable targets, although $C_{max}$/MIC ratios of ≥10 have also been suggested as being more appropriate (8, 10, 11, 19, 25, 36). An $AUC_{0-24}$/MIC ratio of ≥87 to 125 is desired to effectively manage gram-negative bacterial infections while a lower ratio of ≥35 to 50 may be more appropriate for gram-positive pathogens (8, 10, 11, 16–18, 20, 25, 33). The results of the present study indicated that most streptococci and staphylococci (other than methicillin-resistant *S. aureus*) occurring in burn patients would be adequately treated with

TABLE 5. Percentage of severely burned patients achieving desired pharmacodynamic targets with administration of levofloxacin 750 mg intravenously once daily

| Pharmacodynamic target | % of patients achieving target at pathogen MIC: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.25 μg/ml | | 0.5 μg/ml | | 1 μg/ml | | 2 μg/ml[a] | |
| | Obs[b] | MCS[c] | Obs[b] | MCS[c] | Obs[b] | MCS[c] | Obs[b] | MCS[c] |
| $C_{max}$/MIC | | | | | | | | |
| 8 | 100 | 100 | 100 | 100 | 90 | 97 | 10 | 6 |
| 10 | 100 | 100 | 100 | 100 | 70 | 73 | 0 | 0 |
| $AUC_{0-24}$/MIC | | | | | | | | |
| 50 | 100 | 100 | 100 | 100 | 100 | 100 | 30 | 28 |
| 87 | 100 | 100 | 100 | 100 | 50 | 55 | 0 | 0 |
| 125 | 100 | 100 | 90 | 98 | 0 | 0 | 0 | 0 |
| 250 | 90 | 98 | 0 | 0 | 0 | 0 | 0 | 0 |

[a] Approved susceptibility breakpoint for levofloxacin.
[b] Obs, percentage of severely burned patients achieving specified pharmacodynamic targets on day 1 of treatment, calculated from observed pharmacokinetic parameters in individual patients, after administration of levofloxacin at 750 mg intravenously once daily.
[c] MCS, Monte Carlo simulations—probability of pharmacodynamic target attainment for specified pharmacodynamic targets on day 1 of treatment after administration of levofloxacin at 750 mg intravenously once daily.

500-mg to 750-mg doses of levofloxacin due to the lower pharmacodynamic targets required. However, because of the high incidence of infections caused by *Enterobacteriaceae* and *P. aeruginosa* in patients with burn injuries, higher targeted $AUC_{0-24}$/MIC ratios (≥87) are necessary for effective empirical therapy. In this study, levofloxacin administered intravenously in doses of 750 mg reliably achieved favorable $AUC_{0-24}$/MIC ratios only for those gram-negative organisms with MICs of ≤0.5 μg/ml and gram-positive organisms with MICs of ≤1 μg/ml; only 50% of patients achieved suitable $AUC_{0-24}$/MIC ratios for gram-negative organisms with MICs of ≥1 μg/ml (Table 5). Levofloxacin at 750 mg did, however, achieve targeted $C_{max}$/MIC ratios (≥8) in all but one patient for MICs up to and including 1 μg/ml. Since $C_{max}$ and $AUC_{0-24}$ are closely related pharmacokinetic parameters, it is difficult to say which of these variables is more important in optimizing the pharmacodynamics of the fluoroquinolones. It has been suggested that the $C_{max}$/MIC ratio may actually be the most suitable pharmacodynamic target for these concentration-dependent drugs and that achieving favorable $AUC_{0-24}$/MIC ratios becomes more important when appropriate $C_{max}$/MIC targets cannot be reached (8, 10, 25, 36). Levofloxacin at 750 mg intravenously achieves targeted ratios for both $C_{max}$/MIC and $AUC_{0-24}$/MIC for gram-negative pathogens with MICs of ≤0.5 μg/ml; at our institution this would include most strains of *E. coli*, *Klebsiella*, *Enterobacter*, and other *Enterobacteriaceae*. Gram-negative organisms with MICs of 1 μg/ml, which include some strains of *Enterobacteriaceae* as well as *P. aeruginosa*, are more problematic because one of these pharmacodynamic goals ($C_{max}$/MIC) is reached while the other is not. It is arguable whether levofloxacin should be considered reliable as monotherapy in this clinical situation, and the selection of an alternative agent should be considered. Lower doses (i.e., 500 mg/day) of levofloxacin would clearly be inadequate for the treatment of most systemic gram-negative bacterial infections and should not be routinely used in this population.

It is also clear, based on the results of this study, that even the 750-mg dose of levofloxacin would not achieve optimal pharmacodynamic targets against either gram-positive or gram-negative organisms with higher MICs (≥2 μg/ml). Higher doses of levofloxacin (i.e., greater than 750 mg/day) would be necessary to reliably achieve higher levofloxacin $C_{max}$ and/or $AUC_{0-24}$ values for treatment of infection caused by such organisms. These conclusions are supported not only by the pharmacokinetic analyses but also by the Monte Carlo simulations, which indicate virtually 0% probability of achieving either $C_{max}$/MIC of ≥8 or $AUC_{0-24}$/MIC of ≥87 for gram-negative organisms with MICs of ≥2 μg/ml and only a 28% probability of achieving $AUC_{0-24}$/MIC of ≥50 for gram-positive organisms with this MIC (Table 5). This finding is particularly alarming since the levofloxacin susceptibility breakpoint for most organisms is a MIC of 2 μg/ml (24). Although pathogens with MICs of 2 μg/ml would be reported by clinical microbiology laboratories as being susceptible to levofloxacin, the probability of achieving clinical success against these organisms appears to be very low. At our institution, this means that many "susceptible" strains of organisms such as *E. coli* and *P. aeruginosa*, which often have MICs at the susceptibility breakpoint, would possibly not be adequately treated with levofloxacin monotherapy and would result in clinical failures. This is probably also the case at many other institutions since the susceptibility of *E. coli*, *P. aeruginosa*, and certain other gram-negative organisms to the fluoroquinolones is decreasing across the United States (22). Although levofloxacin has been, and will continue to be, an effective antibiotic for the treatment of infections in burn patients, the results of this study clearly suggest that levofloxacin monotherapy is inadequate for empirical treatment of severe systemic infections in this population. Use of levofloxacin as part of combination regimens would be the most appropriate clinical approach to empirical treatment of infections; levofloxacin as a single agent should be appropriately considered only once the pathogens are identified and antibiotic susceptibility determined. Although levofloxacin at 500 mg was shown in an earlier study at this institution to be adequate for treatment of most infections in medical ICU patients (26), changes in institutional susceptibilities of gram-negative organisms since the time of that study now make even the higher 750-mg dose less reliable.

Several limitations need to be considered when evaluating the results of this study. A multitude of factors may potentially influence the pharmacokinetics of medications in severely burned patients including, but not limited to, age, weight, fluid status, underlying disease states, size and depth of the burn, time since burn injury, organ blood flow and clearance, serum protein binding, and the presence of sepsis. While the influence of each of these specific variables on levofloxacin pharmacokinetics could not be individually controlled for or studied in detail, we believe that this group of patients does represents a broad cross section of the population commonly encountered in burn units and for whom antimicrobials are commonly prescribed. Only one patient received levofloxacin at 500 mg, largely because of concerns on the part of the treating physicians regarding the potential for subtherapeutic concentrations in severely injured patients. Therefore, few conclusions can be made regarding the pharmacokinetics of the 500-mg dose in severely burned patients. However, based on pharmacodynamic evaluations of the 750-mg dose, it is safe

to conclude that lower 500-mg doses would clearly not be optimal for the treatment of serious systemic infections in this population. Comparisons between the patients in this study and either medical ICU patients or healthy subjects are made only to illustrate possible differences between patient populations but do not adequately account for any covariates that may be present and affect drug disposition. Three patients in the present study did not have a second levofloxacin pharmacokinetic evaluation due to death or renal failure, which further reduced the already relatively small number of patients studied. Use of Monte Carlo simulations for pharmacodynamic modeling requires that a number of assumptions be made. For instance, this study utilized MIC data which are specific for our own institution; the prevalence and susceptibility of various pathogens may be quite different at other institutions. Thus, the specific conclusions of this study, particularly in regards to the pharmacodynamic assessments, may not necessarily be representative or generalized to other institutions. Finally, as in most studies, determinations of drug pharmacokinetics in plasma were utilized for the pharmacodynamic evaluations and may not adequately take into account drug concentrations within specific tissues, changes in protein binding, or other factors that may influence patient response to antibiotic therapy. Despite these several limitations, this study nevertheless provides the only data currently available regarding the pharmacokinetic disposition of levofloxacin in patients with severe burn injury and provides useful information for making clinical decisions regarding levofloxacin use and dosing in this population.

**Summary.** Levofloxacin pharmacokinetics are apparently not significantly different in severely burned patients compared to patients in medical ICUs or healthy volunteers. However, the pharmacokinetics of levofloxacin do exhibit significant interpatient and intrapatient variability in the burn population. Levofloxacin should be administered at doses not lower than 750 mg/day for empirical treatment of systemic infections in severely burned patients. Higher 750-mg doses more reliably achieve targeted $C_{max}$/MIC and $AUC_{0-24}$/MIC goals and are associated with >90% probabilities of pharmacodynamic target attainment for gram-negative pathogens with MICs of ≤0.5 μg/ml and gram-positive pathogens with MICs of ≤1 μg/ml. However, levofloxacin does not reliably achieve high probabilities of pharmacodynamic target attainment for treatment of gram-negative organisms with MICs of ≥1 μg/ml. Levofloxacin at 750 mg also did not achieve concentrations necessary to provide high probabilities of target attainment for pathogens with MICs at the drug's approved susceptibility breakpoint (MICs of 2 μg/ml). Alternative antibiotics or use of combination regimens appears to be necessary for successful treatment of these organisms even though they are considered "susceptible" to levofloxacin.

## ACKNOWLEDGMENTS

We express our appreciation to the staff of the University of Colorado Hospital Burn Intensive Care Unit for their assistance with data collection.

No outside source of funding was provided for this research.

## REFERENCES

1. **Bjerknes, R., H. Vindenes, and O. D. Laerum.** 1990. Altered neutrophil functions in patients with large burns. Blood Cells **16:**127–141.
2. **Bonate, P. L.** 1990. Pathophysiology and pharmacokinetics following burn injury. Clin. Pharmacokinet. **18:**118–130.
3. **Boucher, B. A., S. R. King, H. L. Wandschneider, W. L. Hickerson, S. D. Hanes, V. L. Herring, T. W. Canada, and M. M. Hess.** 1998. Fluconazole pharmacokinetics in burn patients. Antimicrob. Agents Chemother. **42:**930–933.
4. **Bourget, P., A. Lesne-Hulin, R. Le Reveille, H. Le Bever, and H. Carsin.** 1996. Clinical pharmacokinetics of piperacillin-tazobactam combination in patients with major burns and signs of infection. Antimicrob. Agents Chemother. **40:**139–145.
5. **Chow, A. T., A. Chen, H. Lattime, N. Morgan, F. Wong, C. Fowler, and R. R. Williams.** 2002. Penetration of levofloxacin into skin tissue after oral administration of multiple 750 mg once-daily doses. J. Clin. Pharm. Ther. **27:**143–150.
6. **Chow, A. T., C. Fowler, R. R. Williams, N. Morgan, S. Kaminski, and J. Natarajan.** 2001. Safety and pharmacokinetics of multiple 750-milligram doses of intravenous levofloxacin in healthy volunteers. Antimicrob. Agents Chemother. **45:**2122–2125.
7. **Cockcroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16:**31–41.
8. **Craig, W. A.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. **26:**1–10.
9. **Demling, R. H.** 1985. Burns. N. Engl. J. Med. **313:**1389–1398.
10. **Drusano, G. L., S. L. Preston, C. Fowler, M. Corrado, B. Weisinger, and J. Kahn.** 2004. Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J. Infect. Dis. **189:**1590–1597.
11. **Forrest, A., D. E. Nix, C. H. Ballow, T. F. Goss, M. C. Birmingham, and J. J. Schentag.** 1993. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob. Agents Chemother. **37:**1073–1081.
12. **Garrelts, J. C., G. Jost, S. F. Kowalsky, G. J. Krol, and J. T. Lettieri.** 1996. Ciprofloxacin pharmacokinetics in burn patients. Antimicrob. Agents Chemother. **40:**1153–1156.
13. **Garrelts, J. C., and J. D. Peterie.** 1988. Altered vancomycin dose vs. serum concentration relationship in burn patients. Clin. Pharmacol. Ther. **44:**9–13.
14. **Graham, D. R., D. A. Talan, R. L. Nichols, C. Lucasti, M. Corrado, N. Morgan, and C. L. Fowler.** 2002. Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. Clin. Infect. Dis. **35:**381–389.
15. **Hasslen, S. R., R. D. Nelson, T. K. Kishimoto, W. E. Warren, D. H. Ahrenholz, and L. D. Solem.** 1991. Down-regulation of homing receptors: a mechanism for impaired recruitment of human phagocytes in sepsis. J. Trauma **31:**645–651.
16. **Lacy, M. K., W. Lu, X. Xu, P. R. Tessier, D. P. Nicolau, R. Quintiliani, and C. H. Nightingale.** 1999. Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin against *Streptococcus pneumoniae* in an in vitro model of infection. Antimicrob. Agents Chemother. **43:**672–677.
17. **Lister, P. D.** 2003. Impact of AUC/MIC ratios on the pharmacodynamics of the des-F(6) quinolone garenoxacin (BMS-284756) is similar to other fluoroquinolones. J. Antimicrob. Chemother. **51:**199–202.
18. **Lister, P. D., and C. C. Sanders.** 1999. Pharmacodynamics of levofloxacin and ciprofloxacin against *Streptococcus pneumoniae*. J. Antimicrob. Chemother. **43:**79–86.
19. **Madaras-Kelly, K. J., B. E. Ostergaard, L. B. Hovde, and J. C. Rotschafer.** 1996. Twenty-four-hour area under the concentration-time curve/MIC ratio as a generic predictor of fluoroquinolone antimicrobial effect by using three strains of *Pseudomonas aeruginosa* and an in vitro pharmacodynamic model. Antimicrob. Agents Chemother. **40:**627–632.
20. **Mattoes, H. M., M. Banevicius, D. Li, C. Turley, D. Xuan, C. H. Nightingale, and D. P. Nicolau.** 2001. Pharmacodynamic assessment of gatifloxacin against *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **45:**2092–2097.
21. **Mileski, W., D. Borgstrom, E. Lightfoot, R. Rothlein, R. Faanes, P. Lipsky, and C. Baxter.** 1992. Inhibition of leukocyte-endothelial adherence following thermal injury. J. Surg. Res. **52:**334–339.
22. **Neuhauser, M. M., R. A. Weinstein, R. Rydman, L. H. Danziger, G. Karam, and J. P. Quinn.** 2003. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA **289:**885–888.
23. **Nguyen, T. T., D. A. Gilpin, N. A. Meyer, and D. N. Herndon.** 1996. Current treatment of severely burned patients. Ann. Surg. **223:**14–25.
24. **Ortho-McNeil Pharmaceutical.** 2005. Levaquin (levofloxacin) prescribing information. Ortho-McNeil Pharmaceutical, Raritan, N.J.
25. **Preston, S. L., G. L. Drusano, A. L. Berman, C. L. Fowler, A. T. Chow, B. Dornseif, V. Reichl, J. Natarajan, and M. Corrado.** 1998. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA **279:**125–129.
26. **Rebuck, J. A., D. N. Fish, and E. Abraham.** 2002. Pharmacokinetics of intravenous and oral levofloxacin in critically ill adults in a medical intensive care unit. Pharmacotherapy **22:**1216–1225.
27. **Shah, V. P., K. K. Midha, J. W. Findlay, H. M. Hill, J. D. Hulse, I. J. McGilveray, G. McKay, K. J. Miller, R. N. Patnaik, M. L. Powell, A. Tonelli,**

**C. T. Viswanathan, and A. Yacobi.** 2000. Bioanalytical method validation—a revisit with a decade of progress. Pharm. Res. **17:**1551–1557.
28. **Shargel, L., and A. B. C. Yu.** 1999. Applied biopharmaceutics and pharmacokinetics, 4th ed. Appleton & Lange, Stamford, Conn.
29. **Walstad, R. A., L. Aanderud, and E. Thurmann-Nielsen.** 1988. Pharmacokinetics and tissue concentrations of ceftazidime in burn patients. Eur. J. Clin. Pharmacol. **35:**543–549.
30. **Warden, G. D., A. D. Mason, Jr., and B. A. Pruitt, Jr.** 1974. Evaluation of leukocyte chemotaxis in vitro in thermally injured patients. J. Clin. Investig. **54:**1001–1004.
31. **Weinbren, M. J.** 1999. Pharmacokinetics of antibiotics in burn patients. J. Antimicrob. Chemother. **44:**319–327.
32. **Wong, F. A., S. J. Juzwin, and S. C. Flor.** 1997. Rapid stereospecific high-performance liquid chromatographic determination of levofloxacin in human plasma and urine. J. Pharm. Biomed. Anal. **15:**765–771.
33. **Wright, D. H., G. H. Brown, M. L. Peterson, and J. C. Rotschafer.** 2000. Application of fluoroquinolone pharmacodynamics. J. Antimicrob. Chemother. **46:**669–683.
34. **Zaske, D. E., R. J. Sawchuk, D. N. Gerding, and R. G. Strate.** 1976. Increased dosage requirements of gentamicin in burn patients. J. Trauma **16:**824–828.
35. **Zaske, D. E., R. J. Sawchuk, and R. G. Strate.** 1978. The necessity of increased doses of amikacin in burn patients. Surgery **84:**603–608.
36. **Zelenitsky, S. A., G. K. Harding, S. Sun, K. Ubhi, and R. E. Ariano.** 2003. Treatment and outcome of *Pseudomonas aeruginosa* bacteraemia: an antibiotic pharmacodynamic analysis. J. Antimicrob. Chemother. **52:**668–674.