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Authors

Peloquin, Charles A
Phillips, Patrick PJ
Mitnick, Carole D
et al.

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PHARMACOLOGY

Increased Doses Lead to Higher Drug Exposures of Levofloxacin for Treatment of Tuberculosis

Charles A. Peloquin,[a] Patrick P. J. Phillips,[b,c] Carole D. Mitnick,[d] Kathleen Eisenach,[e] Ramonde F. Patientia,[f] Leonid Lecca,[g] Eduardo Gotuzzo,[h] Neel R. Gandhi,[i,j,p] Donna Butler,[k] Andreas H. Diacon,[f] Bruno Martel,[g] Juan Santillan,[h] Kathleen Robergeau Hunt,[k] Dante Vargas,[g] Florian von Groote-Bidlingmaier,[f] Carlos Seas,[h] Nancy Dianis,[k] Antonio Moreno-Martinez,[l,m] Pawandeep Kaur,[q] C. Robert Horsburgh, Jr.[n,o]

[a]Infectious Disease Pharmacokinetics Lab, University of Florida, Gainesville Florida, USA
[b]Division of Pulmonary and Critical Care Medicine, University of California San Francisco, San Francisco, California, USA
[c]MRC Clinical Trials Unit at UCL, London, United Kingdom
[d]Department of Global Health & Social Medicine, Harvard Medical School, Boston, Massachusetts, USA
[e]University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA
[f]Stellenbosch University and Task Applied Science, Cape Town, South Africa
[g]Socios en Salud Sucursal Peru, Lima, Peru
[h]Universidad Peruana Cayetano Heredia, Lima, Peru
[i]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA
[j]Department of Medicine (Infectious Diseases), Emory School of Medicine, Emory University, Atlanta, Georgia, USA
[k]Westat, Bethesda, Maryland, USA
[l]TB Investigation Unit of Barcelona, Barcelona, Spain
[m]CIBER de Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
[n]Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA
[o]Departments of Epidemiology, Biostatistics and Global Health, Boston University School of Public Health, Boston, Massachusetts, USA
[p]Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA
[q]Department of Global Health, Boston University School of Public Health, Boston, Massachusetts, USA

ABSTRACT Patients with multidrug-resistant tuberculosis in Peru and South Africa were randomized to a weight-banded nominal dose of 11, 14, 17, or 20 mg/kg/day levofloxacin (minimum, 750 mg) in combination with other second-line agents. A total of 101 patients were included in noncompartmental pharmacokinetic analyses. Respective median areas under the concentration-time curve from 0 to 24 h (AUC_{0-24}) were 109.49, 97.86, 145.33, and 207.04 μg · h/ml. Median maximum plasma concentration (C_{max}) were 11.90, 12.02, 14.86, and 19.17 μg/ml, respectively. Higher levofloxacin doses, up to 1,500 mg daily, resulted in higher exposures. (This study has been registered at ClinicalTrials.gov under identifier NCT01918397.)

KEYWORDS tuberculosis, levofloxacin, pharmacokinetics, antitubercular agents

Fluoroquinolones, including levofloxacin, display concentration-dependent killing of *Mycobacterium tuberculosis* (1, 2). Typical daily levofloxacin doses (750 to 1,000 mg) do not reach high AUC/MIC (area under the concentration-time curve over 24 h in the steady state to MIC ratio) targets that have been suggested by studies of the treatment of bacterial pneumonia and murine studies of tuberculosis (TB) (3–7). High levofloxacin exposures could offer less selection of drug-resistant mutants and a shorter time to sputum culture conversion and relapse-free cure (8,

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Address correspondence to Charles A. Peloquin, peloquin@cop.ufl.edu.

TABLE 1 Participant characteristics by treatment arm

Characteristic	Values according to levofloxacin dose (mg/kg) (no. of participants):				*P* value[a] (*n* = 101)
	11 mg/kg (22)	14 mg/kg (26)	17 mg/kg (26)	20 mg/kg (27)	
Age (median [range]) (yrs)	31 (18–69)	25 (18–61)	28 (18–60)	31 (18–67)	0.8910
Male (no. [%])	13 (59)	18 (69)	16 (62)	13 (48)	0.4736
Weight baseline (median [range]) (kg)	56 (41–71)	59 (42–82)	52 (40–75)	53 (44–67)	0.1688
Creatine clearance[b] (median [range]) (ml/min)	102 (56–165)	102 (54–189)	91 (49–180)	103 (51–156)	0.7630
HIV positive (no. [%])	6 (27)	4 (15)	5 (19)	6 (22)	0.7784
Levofloxacin dose received					
750 mg	22	14	0	0	
1000 mg	0	12	24	0	
1250 mg	0	0	2	19	
1500 mg	0	0	0	8	

[a]Kruskal-Wallis or chi-square test.
[b]According to the Cockcroft Gault equation.

9). The Opti-Q study (ClinicalTrials registration no. NCT01918397) was a phase II, double-blinded, randomized, dose-ranging clinical trial in patients with multidrug-resistant tuberculosis (MDR TB). We compared 11, 14, 17, and 20 mg/kg/day of levofloxacin administered orally as a single daily dose 7 days per week for 26 weeks, along with an optimized background regimen of second-line TB medications, in patients in Peru and South Africa. Weight banding gave respective doses of 750, 1,000, 1,250, and 1,500 mg daily for patients who weighed ≥60 kg and, due to a minimum dose floor, 750, 750, 1,000, and 1,250 mg daily for patients who weighed <60 kg. Here, we report the noncompartmental pharmacokinetic (PK) results of this comparison.

This study was reviewed and approved by the institutional review board of each participating institution. The study included consenting adults with newly diagnosed, previously untreated, smear-positive (≥2+) pulmonary MDR TB. We used line probe results (MTBDRplus and MTBDRsl; Hain, Nehren, Germany) to screen patients for eligibility pending phenotypic drug susceptibility testing results. Those showing isoniazid and rifampin resistance and fluoroquinolone susceptibility were eligible. Other inclusion criteria included known HIV status (regardless of result and therapy), a weight of ≥40 kg, and a Karnofsky Performance Status score of >60. Full details of eligibility criteria and trial design are available in the published protocol (10). All study treatment doses were directly observed. The optimized background regimen (OBR), comprised of other second-line drugs without a fluoroquinolone, was selected by local investigators in order to conform with local standards of care and guidelines. Levofloxacin 250-mg capsules and matching placebo 250-mg capsules were provided by Macleods Pharmaceuticals and combined in a dose package by the unblinded pharmacist at each site. Each participant received 6 tablets, but investigators, clinicians, and participants were blinded to the dose of levofloxacin. All treatment was ambulatory and supervised by study staff. Study participants were advised to avoid aluminum- and magnesium-containing antacids within several hours of each levofloxacin dosing. Food intake was recorded but not restricted. After 14 to 28 total and at least 3 consecutive daily doses of levofloxacin, plasma samples were collected at 0, 1, 2, 4, 8, 12, and 24 h postdose. Samples were

TABLE 2 Actual dose and pharmacokinetic parameters sorted by assigned, nominal dose

Parameter	Median value (range) by nominal dose in mg/kg (*n* = no. of subjects)				Differences	*P* value
	11.0 (*n* = 22)	14.0 (*n* = 26)	17.0 (*n* = 26)	20.0 (*n* = 27)		
Dose (mg)	750 (750–750)	750 (750–1,000)	1,000 (1,000–1,250)	1,250 (1,250–1,500)	20 > 17 > 14 > 11	
T_{max} (h)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)	20 = 17 = 14 = 11	0.9747
C_{max} (μg/ml)	11.90 (5.82–18.69)	12.02 (6.90–21.03)	14.86 (9.89–29.17)	19.17 (13.01–35.42)	20 > 17 > 14 = 11	<0.0001
AUC_{0-24} (μg · h/ml)	109 (69–204)	98 (70–248)	145 (103–457)	207 (143–534)	20 > 17 > 14 = 11	<0.0001
$t_{1/2}$ (h)	6.1 (4.2–14.7)	6.2 (4.9–11.9)	6.7 (4.8–19.4)	6.5 (1.8–19.2)	20 = 17 = 14 = 11	0.8062

TABLE 3 Pharmacokinetic parameters sorted by actual dose

Parameter	Median value (range) by actual dose in mg (n = no. of subjects)				Differences	P value
	750 (n = 36)	1,000 (n = 36)	1,250 (n = 21)	1,500 (n = 8)		
T_{max} (h)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)	20 = 17 = 14 = 11	0.5159
C_{max} (μg/ml)	11.93 (5.82–18.69)	14.35 (8.77–24.83)	19.17 (13.01–35.42)	18.29 (14.27–26.30)	20 = 17 > 14 > 11	<0.0001
AUC_{0-24} (μg · h/ml)	101 (69–204)	139 (77–456)	193 (129–534)	211 (146–277)	20 = 17 > 14 > 11	<0.0001
$t_{1/2}$ (h)	6.1 (4.2–14.7)	6.7 (4.9–19.4)	6.7 (1.8–19.2)	6.0 (4.9–11.0)	20 = 17 = 14 = 11	0.4654

shipped frozen and stored at −80°C until assayed at the University of Florida using a validated high-performance liquid chromatography (HPLC) assay with fluorescence detection. The plasma standard curve for levofloxacin ranged from 0.20 to 15 μg/ml; overall precision was 0.58% to 4.09% (coefficient of variation); quality control sample precision was 2.88% to 3.79%. Phoenix v7.0 (Certara LP, Princeton, NJ) was used for noncompartmental analysis and JMP 10 (SAS Institute, Cary, NC) for Y by X nonparametric statistical analysis (Kruskal-Wallis test, chi-square test) or linear regression (adjusted R^2, analysis of variance [ANOVA]). Pairwise comparisons were made using Tukey's honestly significant difference (HSD) test and a comparison of each pair using Student's t test.

Among the 111 participants randomized, 101 participants had evaluable pharmacokinetic data. There were 22, 26, 26, and 27 patients evaluable in the 11-, 14-, 17-, and 20-mg/kg/day levofloxacin dose groups, respectively. Participant characteristics and the levofloxacin doses received are presented in Table 1. Pharmacokinetic results for each of the dosing groups are presented in Tables 2 and 3. The maximum plasma concentration (C_{max}) ranged from a low of 5.82 to a high of 35.42 μg/ml (roughly 6-fold range). For comparison, the normal C_{max} range for 750 to 1,000-mg doses is 8 to 12 μg/ml (11). Within each dosing group, the C_{max} varied approximately 3-fold (Fig. 1). Four of 36 patients (10%) who received a 750-mg dose (using an 11 or 14-mg/kg dose) achieved a C_{max} value below 8 μg/ml, the low end of the normal range (11). No patients who received 1,000 mg levofloxacin or more had a C_{max} value below 8 μg/ml. Due to weight banding and the 750-mg minimum dose, 14 (54%) patients in the 14-mg/kg group received the same dose as patients in the 11-mg/kg group (Table 1).

When the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) was

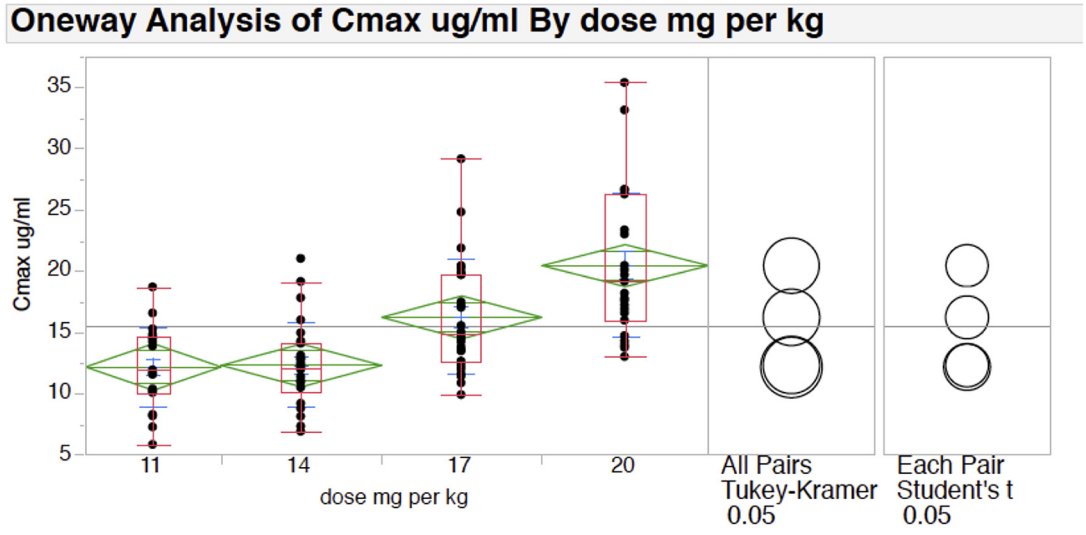

FIG 1 Box-and-whisker plot of levofloxacin C_{max} (in μg/ml) versus randomized dose (in mg/kg). The ends of the boxes correspond to the 25th and 75th percentiles, respectively, and the middle line corresponds to the median. The diamond center line indicates the means, and the top and bottom of the diamonds show the 95% confidence interv al about the means. Separated circles show statistically significantly different pairs.

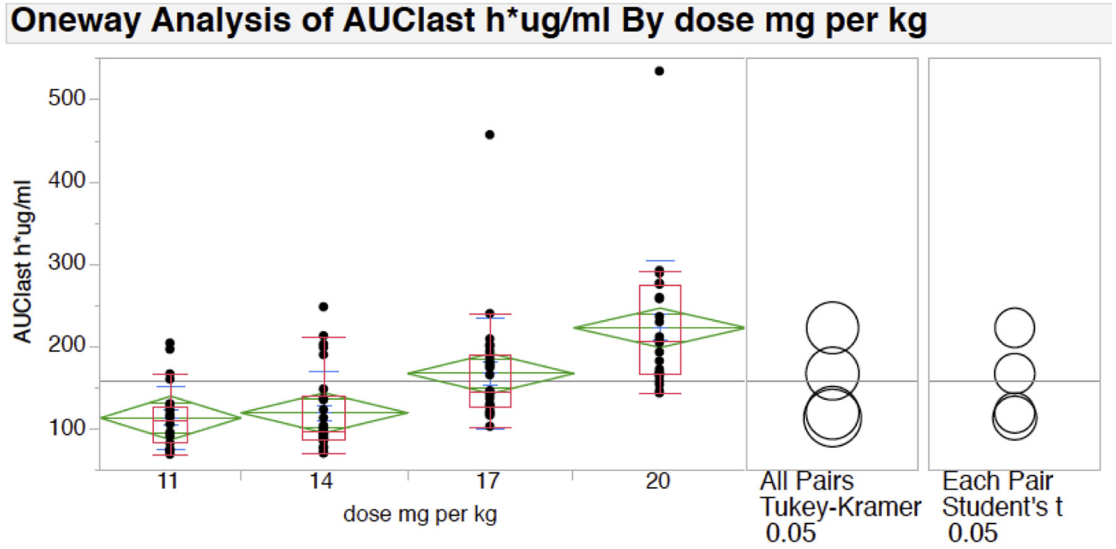

FIG 2 Box-and-whisker plot of levofloxacin AUC_{0-24} (in $\mu g \cdot h/ml$) versus randomized dose (in mg/kg). Symbols are as described for Fig. 1.

evaluated by the milligram dose administered, it increased proportionally. Within each mg/kg dosing group, the AUC_{0-24} varied approximately 3-fold (Fig. 2). The median T_{max} was 2 h across all groups, and median half-lives ($t_{1/2}$) were 6.1 to 6.7 h. Thus, increasing levofloxacin doses did not change the apparent rates of absorption or elimination. In univariate analyses, females had higher C_{max}s and higher AUC_{0-24}s, despite having shorter $t_{1/2}$s, than the males (Table 4), although there were slightly more female patients in the two higher-dose groups combined (24 [45%] of 53) than in the two lower-dose groups combined (17 [35%] of 48). HIV-positive patients had slightly higher C_{max}s, higher AUC_{0-24}s, and longer $t_{1/2}$s than the HIV-negative patients (Table 4). Across all ages, older patients had higher AUC_{0-24}s and longer $t_{1/2}$s than the younger patients (Table 4). In a multivariate analysis of these three key covariates, sex remained significant for C_{max}, while sex, HIV status, and age all remained significant covariates for AUC_{0-24} and $t_{1/2}$. The independent data safety and monitoring board (DSMB) met every 6 months throughout the study, which was not interrupted at any point due to safety concerns; a full analysis of the safety data is under way.

These results demonstrate that increased doses of levofloxacin in the presence of a background MDR-TB regimen lead to increased levofloxacin C_{max}s and AUC_{0-24}s. Thus, patients with low serum levofloxacin concentrations can be expected to respond to increased dosing. Moreover, if increased serum concentrations of levofloxacin are associated with increased clinical efficacy without dose-limiting toxicity, increased dosing may improve the proportion of favorable treatment responses. If proven safe and efficacious, these pharmacokinetic data support further exploration of high-dose levofloxacin in MDR-TB regimens.

TABLE 4 Pharmacokinetic parameters sorted by demographic characteristics

	Sex			HIV status			Increase age	
Parameter	Female	Male	*P* value (chi-square)	Positive	Negative	*P* value	Adjusted R^2	*P* value
T_{max} (h)	2 (1–4)	2 (1–4)	0.9308	2 (1–4)	2 (1–4)	0.8088	−0.008	0.6787
C_{max} (μg/ml)	16.56 (5.82–35.42)	13.64 (6.90–26.66)	0.0022	15.03 (7.25–35.42)	14.22 (5.82–33.17)	0.1960	0.017	0.1023
AUC_{0-24} ($\mu g \cdot h/ml$)	168 (72–534)	130 (69–457)	0.0151	199 (75–534)	130 (69–292)	0.0008	0.088	0.0015
$t_{1/2}$ (h)	6.0 (4.2–19.2)	7.0 (1.8–19.4)	0.0015	7.8 (6.3–19.4)	6.0 (1.8–12.4)	<0.0001	0.097	0.0009

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