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Population Pharmacokinetics of Linezolid in Adults with Pulmonary Tuberculosis▽

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Nineteen adults with pulmonary tuberculosis received linezolid (600 mg) once or twice daily in an early bactericidal activity trial. A one-compartment population model produced median values for the absorption rate constant, volume of distribution, and elimination rate constant of 1.5 h^{-1}, 29.6 liters, and 0.25 h^{-1} (once daily) and 2.7 h^{-1}, 32.1 liters, and 0.15 h^{-1} (twice daily). Linezolid administered twice daily produced higher values for free drug area under the concentration-time curve (AUC)/MIC and time above MIC. Both regimens achieved free AUC/MIC ratios > 100. Median times above the MIC for free drug were 100% (twice daily) and 63% (once daily).

Linezolid is used as a second-line agent for treatment of tuberculosis (TB) (4, 8, 12, 19, 20). It exhibits no cross-resistance with other anti-TB drugs (1, 2, 5, 11, 15, 17). Given the long doubling time of *Mycobacterium tuberculosis* populations and the high cost, myelosuppression, and neurotoxicity of linezolid, some clinicians have tried administering one-half of the usual dose (600 mg once daily) (12). Linezolid population pharmacokinetics (PopPK) have been characterized in studies of patients with infections caused by resistant gram-positive bacteria (10). We extend this approach with a study of patients with TB.

As previously described, members of a group of 18-to-65-year-old human immunodeficiency virus-negative Brazilian adults with smear-positive pulmonary TB, >75% ideal body weight, and reasonably normal hematologic (hemoglobin ≥ 8 g/dl), renal (creatinine < 2 mg/dl), and hepatic (aspartate transaminase < 1.5× upper limit of normal [total bilirubin < 1.3 mg/dl]) function were randomized into two subgroups receiving 600 mg of oral linezolid once or twice daily for 7 days (6). The institutional review boards of Universidade Federal do Espírito Santo and Case Western Reserve University approved the study. Patients gave informed consent.

Subjects fasted overnight before the fifth morning dose. Plasma was collected immediately before and 1, 2, 4, 8, 12, 18, and 24 h after the dose was administered (steady state). Samples were stored at −80°C until assayed using a validated high-performance liquid chromatography method. Standards ranged from 0.5 to 30 μg/ml. The within-sample precision coefficient of variation was 0.69%, and precision across all validation standards was 1.04 to 4.39%.

We planned to remove apparent outliers that could not be successfully comodeled with the remaining data (9). Literature values (absorption rate constant [k_a]) (10) and noncompartmental analysis parameter estimates (volume of distribution [V/F] and elimination rate constant [k_{el}]) were used for the initial estimates. Covariates were screened by regression analysis, and those with correlation P values ≤ 0.10 were modeled. Visual inspection of semilog concentration-time plots suggested a one-compartment model, as confirmed by a modification of the Saunders and Natunen method (14). With WinNonlin software, the Akaike information criteria and parameter percent coefficient of variation favored the one-compartment model for nearly all patients. The assay error pattern describing the reproducibility of quality control samples was used during modeling (7). PopPK models that included all 19 patients were created using Non-Parametric Adaptive Grid (NPAG) and USC*PACK software (3). Values for k_a (h^{-1}), k_{el} (h^{-1}), and the apparent V/F (liters) were

TABLE 1. Population demographics of the study subjects[a]

Parameter	Median (range) value for treatment group	
	Linzelolid daily (n = 10)	Linezolid twice daily (n = 9)
No. of males	8	7
No. of females	2	2
Age (yr)	33.5 (18–62)	45 (23–58)
Wt (kg)	56.1 (41–66)	53.6 (44.1–66)
SCR (mg/dl)	0.8 (0.5–1.0)	0.9 (0.6–1.0)
CLcr (ml/min)	106.7 (60.5–158.4)	80.1 (63.9–119.2)
Dose (mg)	600	600
Dose (mg/kg)	10.7 (10.1–13.1)	11.2 (9.1–13.6)

[a] SCR, serum creatinine; CLcr, creatinine clearance; n, number of patients.

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TABLE 2. NPAG PopPK estimates, NCA median values for unbound drug exposure, and simulated unbound exposure values calculated using median population parameter estimates

PK parameter[a]	Median (range) value for treatment group[b]	
	Linezolid daily (n = 10)	Linezolid twice daily (n = 9)
Dose (mg)	600	600
k_a (h^{-1})	1.5 (0.4–1.8)	2.7 (1.1–5.9)
k_{el} (h^{-1})	0.2 (0.1–0.3)	0.2 (0.1–0.2)
k_a $t_{1/2}$ (h)	0.5 (0.4–0.6)	0.3 (0.1–0.6)
k_{el} $t_{1/2}$ (h)	2.9 (2.4–3.9)	4.6 (3.0–5.8)
V/F (liters)	29.6 (26.7–31.9)	32.1 (29.0–32.7)
V/F (liters/kg)	0.52 (0.45–0.56)	0.62 (0.52–0.67)
CL/F (liters/h)	7.1 (4.8–9.2)	4.8 (3.5–7.5)
CL/F (liters/h/kg)[c]	0.1 (0.08–0.2)	0.09 (0.06–0.2)
AUC_{0-24} (μg*h/ml)	84.6 (64.7–125.0)	124.5 (79.7–172.4)
Bias	−0.14	−0.10
Precision	0.89	0.89
WNL NCA parameters		
C_{max} (μg/ml)	14.9 (11.9–21.3)	19.4 (11.7–24.9)
T_{max} (h)	1.5 (1.0–4.0)	1.0 (1.0–4.0)
$AUC_{0-24,ss}$	96.8 (47.8–143.7)	136.4 (51.5–259.2)
$simAUC_{0-24,ss}$[d]		232.8 (100.8–394.4)
WNL simulation parameters (NPAG estimates)		
C_{max} (μg/ml)	15.6 (7.7–30.7)	16.6 (11.4–17.9)
T_{max} (h)	1.7 (0.6–3.6)	1.3 (0.6–5.6)
$AUC_{0-\infty}$	95.4 (69.6–137.8)	122.7 (51.1–199.5)

[a] k_a, k_{el}, and V values were estimated directly with NPAG; half-life ($t_{1/2}$), clearance (CL), and AUC values were calculated from k_a, k_{el}, and V values by the use of standard equations. $AUC_{0-24,ss}$ (AUC_{0-24}, steady state) approximates $AUC_{0-\infty}$. WNL, WinNonlin software; NCA, noncompartmental analysis.

[b] n, number of patients.

[c] Values are based on the median of individual Bayesian parameters estimates rather than on the original population estimate.

[d] Values simulated (sim) to represent the effect of the second daily dose on $AUC_{0-24,ss}$ values.

estimated. Subsequent models examined patients in the daily and the twice-daily administration groups separately. Goodness of fit was assessed by regression with an observed-predicted plot, coefficients of determination, and log-likelihood values. Predictive performance was assessed using the weighted-mean error for bias and the bias-adjusted weighted-mean square error for precision. The Bayesian posterior parameter joint densities from individual subjects were estimated starting from the population parameter joint density. The remaining PK parameters were calculated using standard equations. The values for the population model-based area under the concentration-time curve (AUC [in micrograms per hour per milliliter]) were calculated as dose/CL/F.

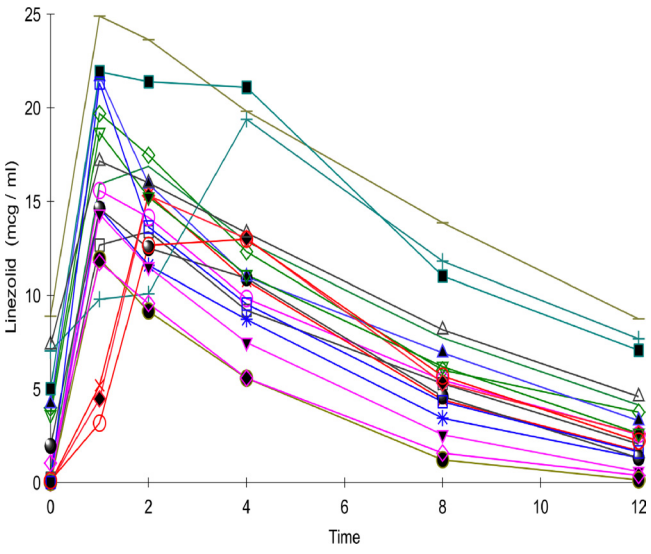

FIG. 1. Linezolid plasma concentrations versus time data for 19 patients.

NPAG parameters were checked using WinNonLin simulations (retrodiction of the original data) for all individuals and for the population as a whole. Free drug AUC values were calculated as 31% of individual AUC values (18). MICs for linezolid were measured using Bactec 460 and Middlebook 7H-10 agar plates. MIC results using both methods were identical. Statistical analyses were performed using JMP statistical software (Version 6.0.3; SAS Institute, Cary, NC). Creatinine clearance was calculated by the method of Cockcroft and Gault. The dependence of PK variables on subject demographics was determined using the bivariate fitting and one-way analysis-of-variance functions of JMP Y by X analysis platform. A P value ≤ 0.05 was considered statistically significant. Given the small sample sizes, P values ≤ 0.10 represented associated covariates that also were further evaluated in the modeling process.

Nineteen subjects completed the study (15 males; median age, 39 years); 84% had cavitary disease (Table 1). The PK parameter estimates are provided in Table 2. Because linezolid was rapidly absorbed in many patients, and due to the lack of samples prior to 1 h, many initial estimates for k_a were unrealistically large. Therefore, k_a was capped at 6 for all subsequent models, a value equivalent to an absorption half-life of 7 min. Inclusion of patient covariates produced only minor improvements in log-likelihood or precision while producing minor degradations in bias. Therefore, the parameter estimates for the simplest model are presented here.

A one-compartment model adequately described the observed results (Table 2). Figure 1 displays the data for plasma concentrations versus time. Data for maximum concentration of drug in serum (C_{max}) ranged from 12 to 25 μg/ml, values similar to those seen with other populations (10, 16). Three patients demonstrated slow drug absorption and lower 1-h plasma concentrations (<5 μg/ml) compared to the other subjects. A secondary analysis was performed with the removal of outlying data points. Although this improved the profiles for patients with slowed absorption, it produced comparatively poorer predictions for the remaining subjects.

Thirteen of 19 linezolid patients had an apparent time to maximum concentration of drug in serum (T_{max}) of 1 h. The remaining six subjects, including two patients with a T_{max} of 4 h, had a T_{max} of more than 1 h. Weight and age accounted for 19% (P = 0.057) and 17% (P < 0.08) of the variability in CL/F. Neither contributed significantly to the development of the PopPK model. The model displayed limited bias and good precision (Fig. 2). Free linezolid AUC/MIC ratios are shown in Table 3. The median C_{max} value for the twice-daily linezolid treatment group was higher than for the once-daily treatment group; this relationship inverts in comparisons of C_{max}/MIC for the two treatment arms. The differences in MICs for the individual subjects are responsible for this inversion and are reflected in the median MIC for each treatment group.

FIG. 2. NPAG model-predicted (*x* axis) versus observed (*y* axis) linezolid concentrations.

The target AUC/MIC ratio for linezolid use against *M. tuberculosis* has not been prospectively established. Compared to established target ratios for gram-positive organisms (AUC/MIC of 100), the calculated ratios in this study were in excess of the target for all patients (10, 13; linezolid rationale document, European Committee on Antimicrobial Susceptibility Testing [http://www.eucast.org]). Compared to established time-above-MIC goal values of >85%, the median values for our population were 100% for the twice-daily treatment regimen and 63% for the once-daily regimen.

This patient population showed rapid absorption of linezolid. Blood sampling earlier than 1 h after administration of the drug should be used for future studies of linezolid looking to better define k_a for TB patients. A one-compartment model adequately described the data for these TB patients. *V*/*F* and Cl/*F* estimates were on the low end of the range of those seen for non-TB patients, which in turn were on the low end of the range of those seen for healthy volunteers (10, 16). Despite higher doses (milligrams/kilogram of body weight), our patients had median values for the AUC from 0 to 24 h ($AUC_{0\text{-}24}$) lower than those described for critically ill patients. However, the range of our $AUC_{0\text{-}24}$ values was contained entirely within the previously described range. The model provides the basis for simulations of doses for patients with TB who require linezolid treatment. Twice-daily dosing of linezolid demonstrated favorable bacteriologic PK and pharmacodynamic (PD) indices, whereas once-daily dosing achieved comparative values for time above MIC of only ~63%. How these bacteriologic PK and PD indices extend to the treatment of mycobacterial infections is still to be determined, but limited associations between these indices and early bactericidal activity have previously been reported (6).

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TABLE 3. PD parameters adjusted for free drug concentration after 5 days of daily administration of study drugs[a]

Drug and treatment regimen	No. of patients	C_{max} (μg/ml)	$AUC_{0\text{–}12}$ (μg · h/ml)	$AUC_{0\text{–}24}$ (μg · h/ml)	MIC (μg/ml)	C_{max}/MIC (IQR[b])	$AUC_{0\text{–}12}$/MIC (IQR)	$AUC_{0\text{–}24}$/MIC (IQR)	% Dosing interval above MIC[c] (IQR)
Linezolid (600 mg twice daily)	9	13.4 (8.1–17.2)	80.3 (34.8–136.1)	160.7 (134.4–225.8)	1.0 (0.5–1.0)	16.2 (14.3–23.0)	121.6 (79.8–141.6)	243.2 (159.7–283.2)	100.0 (100–100)
Linezolid (600 mg once daily)	10	10.3 (8.2–14.7)	60.1 (32.8–82.3)	66.8 (33.0–99.2)	0.5 (0.5–1.0)	20.0 (10.2–21.9)	107.8 (63.4–126.3)	116.2 (71.0–138.4)	62.8 (54.6–77.0)

[a] C_{max} and AUC data represent median (range) values for unbound (free) drug in plasma. Linezolid was assumed to be 31% protein bound. Median (range) values for C_{max}/MIC, $AUC_{0\text{–}12}$/MIC, $AUC_{0\text{–}24}$/MIC, and percent dosing interval above MIC were calculated using the measured linezolid MIC for a pretreatment sputum *M. tuberculosis* isolate from each patient. Data for $AUC_{0\text{–}24}$ and $AUC_{0\text{–}24}$/MIC represent simulated median (range) values to reflect the impact of a second daily dose of linezolid.

[b] IQR, interquartile range.

[c] Determined by linear extrapolation of AUC data to intersection with MIC. Data for twice-daily treatment group represent a 12-h interval; data for once-daily treatment group represent a 24-h interval.

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