Linezolid Pharmacokinetics in Adult Patients with Cystic Fibrosis

John A. Bosso,^{1*} Patrick A. Flume,² and Susan L. Gray²

Department of Pharmaceutical Sciences, College of Pharmacy,¹ and Department of Medicine,²
Medical University of South Carolina, Charleston, South Carolina

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The pharmacokinetics of many drugs are altered in patients with cystic fibrosis (CF), often necessitating different dosage requirements than those used in non-CF patients. The objective of this study was to determine the pharmacokinetics of linezolid, an antibiotic with good activity against gram-positive organisms such as methicillin-resistant *Staphylococcus aureus*, in patients with CF so that dosage requirements could be established. Twelve adult patients (6 male) ranging in age from 22 to 39 years were studied. A single 600-mg dose was administered intravenously over 0.5 h, and plasma samples were collected at 0 (predose), 0.5, 0.75, 1, 2, 4, 8, and 24 h. Linezolid concentrations were determined with a validated high-performance liquid chromatography assay. Pharmacokinetic parameters were estimated using standard noncompartmental methods. Blood chemistry and hematologic indices were determined before and after the study for safety purposes. All patients completed the study without encountering any adverse reactions. The pharmacokinetic parameters, while variable, with half-lives varying from 1.76 to 8.36 h, were similar to those previously described in other populations. Mean ($\pm$ standard deviation) values for pharmacokinetic parameters of interest were as follows: elimination rate constant, 0.21 (0.11) h⁻¹; half-life, 4.41 (2.43); volume of distribution at steady state, 0.87 (0.19) liters/kg of body weight; and total body clearance, 0.12 (0.06) liters/h/kg. No patient would have achieved the pharmacodynamic target of an area under the concentration-time curve/MIC ratio of 83 h for pathogens for which the MIC was 4 μ g/ml. Patients with inadequate clinical responses to linezolid may require more frequent dosing.

Most morbidity and mortality associated with cystic fibrosis (CF) is due to the pulmonary component, which is characterized by infection with such pathogens as *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus* and subsequent inflammation (5). Treatment with antibiotics is considered standard care for exacerbations of pulmonary infections. Methicillin-resistant *S. aureus* (MRSA), which has become common in hospitals since the 1980s, is now more commonly seen in patients with CF (18). MRSA is typically treated with vancomycin, but with the advent of strains with decreased susceptibility (7) and, more recently, outright resistance (2), alternatives to this agent are needed. Because of its marked in vitro activity against the common gram-positive pathogens (9, 20), including MRSA (19), and penetration into pulmonary fluid (3), the oxazolidinone antibiotic linezolid represents a potential therapeutic option for this disease.

The pharmacokinetics of a wide variety of drugs have been demonstrated to be altered in patients with CF (12). Drugs eliminated either unchanged by the kidneys (e.g., aminoglycosides) or through metabolism by the liver (e.g., sulfamethoxazole) may have altered disposition. To date, no unified explanation of altered pharmacokinetics with CF has emerged. Altered renal clearance, enhanced metabolism, and varying distribution volumes are all possibilities, depending on the drug in question. Because the pharmacokinetic differences can be dramatic enough in some cases to justify altered dosing and because such changes are unpredictable, it is necessary to de-

termine the pharmacokinetics of any drug that might be used in this population so that the optimal dosage regimen can be designed. The objective of this study was to characterize the pharmacokinetics of linezolid in patients with CF so that appropriate dosing recommendations could be derived.

MATERIALS AND METHODS

Subjects. Adult patients of either sex who were admitted to the hospital for treatment of an acute pulmonary exacerbation of CF were invited to participate in the study, which had been approved by the local Institutional Review Board. A diagnosis of CF was documented in these patients either with two positive sweat tests or through genetic testing. Written informed consent was obtained from each subject. Patients with clinical or laboratory evidence of significant renal (estimated creatinine clearance of ≤ 30 ml/min) or hepatic (Child-Pugh class A or greater) impairment or a history of allergy to linezolid or who were receiving monoamine oxidase inhibitors were excluded. Further, a pregnancy test was performed on all female subjects of childbearing potential, and negative pregnancy status was confirmed. Pregnant females were excluded. Demographic information and results of admission pulmonary function testing (forced expiratory volume in one second [FEV₁]) were recorded. All medications being taken by the subjects immediately prior to or during the study were also noted in the study record.

Study design. Information collected regarding all subjects included age, gender, weight, concurrent medications, and fluid intake and output during the period of study. All subjects received a single, 600-mg intravenous dose of linezolid (supplied as premixed intravenous bags) administered as a one-half-hour infusion delivered by a programmable infusion pump. Blood samples were collected immediately before the drug infusion (time zero) and at 0.5 (immediately at the end of the drug infusion), 0.75, 1, 2, 4, 8, and 24 h. The exact time each specimen was collected was noted. Plasma was immediately harvested and then frozen at -70°C until the time of assay (stability at -70°C is ≥ 1 year). The exact times of the dosage infusions were recorded, and a sample from the dosage container was obtained for later determination of the linezolid concentration so that the exact dose administered could be determined. Serum chemistries and hematology (complete blood count and white cell differential) were assessed within 24 h prior to the study and within 48 h poststudy to assess potential side effects of the drug.

* Corresponding author. Mailing address: Medical University of South Carolina College of Pharmacy, 280 Calhoun Street, Charleston, SC 29425. Phone: (843) 792-8501. Fax: (843) 792-1712. E-mail: bossoja@musc.edu.

Drug assay. The concentrations of linezolid in plasma and in the administered drug solution were determined by the Pharmacokinetics Laboratory at the National Jewish Medical & Research Center (Denver, Colo.) with a validated, reverse-phase high-performance liquid chromatographic (HPLC) method. Briefly, the samples were assessed with a system consisting of a model 515 HPLC pump, model 680 gradient controller and solvent select valve (Waters Inc., Milford, Mass.), model 8875 fixed volume autosampler (Spectra Physics, San Jose, Calif.), model 486 UV light detectors (Waters), Macintosh 7100 computer (Apple Computers, Inc., Cupertino, Calif.), and Dynamax HPLC data management system (Ranin, Woburn, Mass.). The five-point standard curve (weighted as $1/y^2$) ranged from 0.5 to 30 $\mu\text{g/ml}$, and the assay precision across all concentrations was $\leq 4.4\%$.

Pharmacokinetic analysis. Pharmacokinetic parameters were determined using standard noncompartmental methods (6). The terminal elimination rate constant (k_{el}) was determined by linear regression of the final linear portion of the natural log of the concentration-time curve for concentrations in plasma. This analysis included at least five data points. The area under the concentration-time curve ($\text{AUC}_{0-\infty}$) was determined with the linear trapezoidal rule, with the area from the last measurable concentration in plasma to infinity determined as that concentration divided by k_{el} . Peak concentrations in plasma were determined by visual inspection of the concentration-time profiles. The parameters of interest from all patients were used to generate mean, median, and standard deviation (SD) values. Correlations between pharmacokinetic parameters and patient age and FEV_1 were examined using Spearman rank correlation.

RESULTS

All 12 subjects completed the study successfully. The studied population consisted of six males and six females ranging in age from 22 to 39 years. Patient characteristics, including pulmonary function status as reflected by FEV_1 , are displayed in Table 1. Concomitant medications that the patients were receiving at the time of or just prior to the study included inhaled and systemic antibiotics (tobramycin, vancomycin, piperacillin-tazobactam, azithromycin, ceftazidime, amoxicillin-clavulanate, cefepime, and ciprofloxacin); systemic, inhaled, and nasal corticosteroids (prednisone and fluticasone); pancreatic enzymes; inhaled and systemic bronchodilators (albuterol and ipratropium); rofecoxib; vitamins; iron; narcotic analgesics; megestrol; dronabinol; proton pump inhibitors (lansoprazole and omeprazole); insulin; inhaled rhDNase; cetirizine; ursodiol; ranitidine; and antidepressants (paroxetine, fluoxetine, and sertraline).

Pharmacokinetics. The pharmacokinetic parameter estimates varied widely between patients, although mean values were similar to those reported for adults elsewhere in the literature. For example, elimination half-lives varied from <2 to >8 h. Individual and mean values for all pharmacokinetic parameters of interest are listed in Table 2. No correlation between pharmacokinetic characteristics and either patient age or disease status (FEV_1) was found. Mean ($\pm$ SD) concentrations in plasma for all patients are shown in Fig. 1. Seven of the 12 patients had undetectable concentrations of linezolid at the 24-h sampling point.

Safety. No clinically evident adverse effects were noted during the infusion or over the period of sample collection. Further, no adverse effects as noted by laboratory tests were detected.

DISCUSSION

The pharmacokinetics of a number of drugs, mostly antibiotics, have been shown to vary in patients with CF. Aminoglycosides, which are chiefly eliminated by the kidneys, vary markedly in their elimination pharmacokinetics in CF patients.

TABLE 1. Demographic characteristics of CF patients in this study

Patient	Sex ^b	Age (yr)	Weight (kg)	Creatinine concn in serum (mg/dl)	FEV_1^a (liter)	FEV_1^a (% predicted)
1	M	37	54.5	1.7	0.89	25
2	M	25	57.4	0.8	1.08	25
3	M	29	63.6	0.9	1.46	36
4	F	23	46.6	0.6	2.35	81
5	F	22	57.3	0.7	2.16	69
6	F	22	48.2	0.7	2.16	71
7	F	22	38.2	0.7	1.67	60
8	M	39	89.1	1.1	2.17	50
9	F	28	58.2	0.6	1.55	50
10	M	34	55.5	0.7	0.85	23
11	M	39	66.8	1.0	3.09	78
12	F	24	40.9	0.4	0.55	19

^a FEV_1 , forced expiratory volume in one second.

^b M, male; F, female.

Clearance is commonly increased, and the apparent volume of distribution may be greater as well (12), resulting in the need for higher-than-normal doses. The variability observed requires careful monitoring of concentrations in individual patients with CF to optimize efficacy and avoid toxicity. Drugs eliminated by metabolism may also exhibit altered disposition in this population. For example, both sulfamethoxazole and theophylline have been demonstrated to exhibit increased clearance in patients with CF (8, 11). No one explanation has emerged for these changes, although it has recently been suggested that for at least some drugs for which enhanced clearance is associated with increased renal clearance the changes may be explained by increased expression of P-glycoprotein and a resultant increase in tubular secretion (17). Thus, pharmacokinetic studies are often performed on drugs with potential therapeutic utility in CF to establish appropriate dosing guidelines. Because *S. aureus* plays an important role in the pathophysiology of CF airways disease, drugs such as linezolid, with good gram-positive activity in general and additional activity against MRSA in particular, will be considered for use. At least one report of successful therapeutic use has already appeared in the literature (4). In that report, MRSA was cultured from the sputum of the 24-year-old patient and was no longer detected after a 30-day course of linezolid given intravenously for 6 days and then orally for another 24 days. The 600-mg intravenous and oral doses produced similar peak and trough concentrations, suggesting good gastrointestinal absorption.

The results of the present study should be viewed in the light of previously published studies of linezolid disposition, which are numerous. The drug is chiefly cleared by nonrenal mechanisms, with only 30% of a dose appearing in the urine as unchanged drug (16). Fifty percent is accounted for as two major metabolites, also found in the urine. Total and renal clearances have been reported as 120 and 50 ml/min, respectively (D. J. Stalker, C. P. Wasjczczuk, and D. H. Batts, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-115 and A-116, 1997). In healthy adult subjects, the reported mean half-life has ranged from 4.4 to 6.9 h with both single-dose and steady-state conditions (3, 14, 16; Stalker et al., 37th ICAAC, abstr. A-115 and A-116). Although linear elimination

TABLE 2. Pharmacokinetic parameters^a

Patient	k_{el} (h ⁻¹)	$t_{1/2}$ (h)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg · h/ml)	$AUC_{0-\infty}/MIC$ ratio ^b	V_{ss} (liters/kg)	Cl_T (liters/ h/kg)
1	0.08	8.36	17.36	208.94	52.24	0.95	0.06
2	0.26	2.68	17.31	65.20	16.30	0.81	0.16
3	0.09	7.98	21.57	167.53	41.88	0.87	0.05
4	0.19	3.63	20.41	108.78	27.20	1.32	0.12
5	0.32	2.20	22.00	66.21	16.55	0.68	0.16
6	0.19	3.60	25.49	135.71	33.93	0.95	0.09
7	0.39	1.76	25.30	68.71	17.18	0.94	0.25
8	0.17	4.11	13.02	69.89	17.47	0.70	0.10
9	0.17	4.01	27.03	113.42	28.36	0.65	0.10
10	0.17	3.99	21.63	99.91	24.98	0.79	0.12
11	0.08	8.36	16.94	155.14	38.79	1.06	0.06
12	0.31	2.25	28.36	86.76	22.19	0.77	0.18
Mean	0.20	4.41	21.37	112.18	28.09	0.87	0.12
SD	0.10	2.43	4.64	46.35	11.57	0.19	0.06
Median	0.18	3.81	21.60	104.34	26.09	0.84	0.11

^a $t_{1/2}$, half-life; $AUC_{0-\infty}$, area under the concentration in plasma versus the time curve from time 0 to infinity; V_{ss} , steady-state volume of distribution; Cl_T , total body clearance; C_{max} , maximum observed concentration in plasma.

^b Theoretical value based on a MIC of 4 μg/ml.

had been reported initially (Stalker et al., 37th ICAAC, abstr. A-115 and A-116), subsequent studies by two different investigative groups provided evidence of nonlinear elimination, which probably reflects the saturability of one of the two major metabolic pathways for the drug (13; B. Cirincione, L. Phillips, T. Grasela, D. Stalker, and G. Jungbluth, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1205, 1999). This finding may explain the wide range of reported half-lives and clearance values in healthy adults. Neither age nor sex is associated with sufficient variation of linezolid disposition in adults to warrant dosage adjustment (15). However, higher estimates of both total clearance and apparent volume of distribution were observed in a single-dose pharmacokinetic study in children 3 months to 16 years of age (10). Based on those findings, a dose of 10 mg/kg administered two to three times daily was recommended. Lastly, studies in patients with mild hepatic impairment and renal dysfunction (creatinine clear-

ance as low as 10 ml/min) revealed insufficient alterations in pharmacokinetics to justify dosage adjustments (P. E. Hendershot, G. L. Jungbluth, S. K. Cammarata, and N. K. Hopkins, Abstr. 21st Int. Congr. Chemother., 1999; M. E. Brier, D. J. Stalker, G. R. Aronoff, D. H. Batts, K. K. Ryan, M. A. O'Grady, and N. K. Hopkins, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-54, 1998). In the present study of adults with CF, we noted marked variation in pharmacokinetic parameters. It might be that potential drug interactions influenced the variability we observed (e.g., with serotonin reuptake inhibitors), but this possibility could not be assessed in a single-dose study. Regardless, the extremes of the observed pharmacokinetic values were within the ranges already reported for healthy adults in the publications cited above. Nonetheless, this variability may have implications for proper dosing in the CF population.

There are reasons to question the universal adequacy of a

FIG. 1. Mean (±SD) concentrations of linezolid in plasma versus time.

600-mg dose administered twice daily in the CF population. Pharmacodynamic studies in both humans and animals suggest that the $AUC_{0-24\text{ h}}/\text{MIC}$ ratio may be the parameter best correlated with antimicrobial effect (1; B. Cirincione, T. Grasele, S. Ardella, E. Ludwig, D. Stalker, B. Harkin, J. Bruss, and E. Antal., Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1389, 2000; C. R. Rayner, A. Forrest, A. K. Meagher, and M. C. Birmingham, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1390, 2001). These same studies suggest a target $AUC_{0-24\text{ h}}/\text{MIC}$ ratio of 83 to 100 h. Based upon our data, the standard 600-mg dose would not appear to achieve an $AUC_{0-24\text{ h}}/\text{MIC}$ ratio in this range for the least susceptible staphylococcal isolates considered susceptible to linezolid (4 $\mu\text{g}/\text{ml}$). While this is a worst-case scenario, even patients with isolates for which MICs are 1 or 2 might fail to achieve this pharmacodynamic target (see Table 2). The second reason that a 600-mg twice-daily dose may not be appropriate for all patients relates to the typical body habitus of CF patients. As is usual for CF patients, most of our patients weighed less than their ideal body weight based on height. Further, as all patients received the same dose, it is not surprising that the maximum observed concentrations in plasma were higher in patients with low body weight (range, 13 to 28.4 mg/liter), which may be explained by the fact that a standard 600-mg dose represents weight-normalized doses varying from 7 to 17 mg/kg. Higher observed concentrations and longer half-lives could have implications for the clinical safety of this agent. Thus, in patients with an inadequate clinical response with a standard dosage, a 600-mg three-times-per-day dosage regimen might be appropriate, but again, the possibility for nonlinear pharmacokinetics of the drug must be kept in mind. One would predict disproportional changes in the concentrations in plasma as doses were increased, at least in some patients. Unless monitoring of the concentrations of linezolid in plasma becomes commonplace or until the population models for nonlinear pharmacokinetics are proven appropriate for CF patients, one should use doses above the usual 600-mg twice-daily dose with caution because of the risk of hematologic and other side effects.

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