Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia*

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Objective: **To determine the steady-state plasma pharmacokinetic variables and epithelial lining fluid concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia.**

Design: **Prospective, open-label study.**

Setting: **An intensive care unit and research ward in a university hospital.**

Patients: **Sixteen critically ill adult patients with ventilator-associated pneumonia.**

Interventions: **All subjects received 1-hr intravenous infusions of linezolid 600 mg twice daily. After 2 days of therapy, the steady-state plasma pharmacokinetic variables and epithelial lining fluid concentrations of linezolid were determined by high-performance liquid chromatography.**

Measurements and Main Results: **The mean ± SD linezolid peak and trough concentrations were 17.7 ± 4.0 mg/L and 2.4 ± 1.2 mg/L in plasma and 14.4 ± 5.6 mg/L and 2.6 ± 1.7 mg/L in epithelial lining fluid, respectively, showing a mean linezolid percentage penetration in epithelial lining fluid of approximately 100%. The mean ± SD area under concentration-time curve during the observational period (AUC_{0-12}) was 77.3 ± 23.7 mg·hr/L, corresponding to a mean AUC_{0-24} of 154.6 mg·hr/L.**

Conclusions: **Our study shows satisfactory results, with linezolid concentrations exceeding the susceptibility breakpoint for Gram-positive bacteria in both plasma and epithelial lining fluid. This suggests that a dosage of 600 mg administered intravenously twice daily to critically ill patients with Gram-positive ventilator-associated pneumonia would achieve success against organisms with minimum inhibitory concentrations as high as 2–4 mg/L in both plasma and epithelial lining fluid. (Crit Care Med 2005; 33:1529–1533)**

KEY WORDS: linezolid; pharmacokinetics; lung diffusion; intensive care; ventilator-associated pneumonia

Linezolid is the first member of a new class of antibacterial agents, the oxazolidinones, which act by inhibiting the initiation of bacterial protein synthesis (1). Linezolid exhibits *in vitro* activity (mostly bacteriostatic) against many important human pathogens, including oxacillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* (1). Linezolid lacks significant effects against most Gram-negative pathogens but shows activity against certain anaerobes, including *Clostridium perfringens*, *C. difficile*, *Peptostreptococcus* spp., and *Bacteroides fragilis* (1).

Due to this particular spectrum, linezolid is indicated for the treatment of Gram-positive ventilator-associated pneumonia (VAP), mainly caused by oxacillin-resistant *S. aureus* (2). Pharmacokinetics, pharmacodynamics, and intrapulmonary diffusion of linezolid have been widely studied in *in vitro* models or in healthy volunteers (1–5). Although clinical studies have evaluated the efficacy of linezolid during the treatment of nosocomial pneumonia in critically ill patients, few pharmacokinetic data concerning this subset of patients are available (6).

Most infections occur in the tissues of the body rather than in the blood, so that it is accepted today that appropriate antibiotic therapy requires achievement of significant concentrations of antibiotics at the sites of infection. Epithelial lining fluid (ELF) has been advocated as a reliable marker of extracellular antibiotic concentration in lung tissue (7, 8). Although the pharmacokinetics of linezolid in plasma and ELF have been studied in healthy volunteers, no data are available in critically ill patients on mechanical ventilation with nosocomial pneumonia, who often present with some pathophysiologic conditions that may alter the pharmacokinetic behavior of this agent (3). Therefore, we conducted a study to determine the steady-state plasma pharmacokinetic variables and ELF concentrations of intravenous linezolid 600 mg administered twice daily to critically ill patients with VAP.

SUBJECTS AND METHODS

This was a prospective, open-label, single-center study approved by the local ethics committee. Before inclusion in the study, all patients or their closest relative provided written informed consent. Critically ill adult patients on mechanical ventilation for ≥5 days who were hospitalized in our intensive care unit

*See also p. 1654.

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Support was provided only by institutional sources. The authors have no financial interests to disclose.

Presented, in part, at the 24th ICAAC, Washington, DC, 2004, abstract A1131.

DOI: 10.1097/01.CCM.0000168206.59873.80

were considered eligible for inclusion when suspected of having late-onset VAP, defined according to the criteria of the Centers for Disease Control and Prevention (9). It is usual to distinguish early-onset VAP, which occurs during the first 4 days of mechanical ventilation, from late-onset VAP, which develops ≥5 days after initiation of mechanical ventilation and usually is caused by high-risk pathogens, such as oxacillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, or *Acinetobacter* spp., mostly when previous antimicrobial therapy was administered (10). At our institution, the incidence of late-onset VAP caused by *S. aureus* with previous antimicrobial therapy is approximately 40% with 25–30% oxacillin-resistant strains.

The patients were excluded from the study if they were allergic to oxazolidinone antibiotics, exhibited renal dysfunction defined by a calculated creatinine clearance (using the urine of 24 hrs) of <40 mL/min or a plasma creatinine concentration of >200 μmol/L, or had impairment of hepatic function (alanine aminotransferase, aspartate aminotransferase, or bilirubin greater than twice the upper limit of normal).

Before initiation of therapy, specimens for microbiological diagnosis were obtained using a plugged telescoping catheter (Combicath, Plastimed, St-Leu-La-Forêt, France) from all patients, as previously described (11). All patients were on sedation and mechanical ventilation during procedure, which is simple, noninvasive, and easily repeatable at the bedside. Due to the high-risk pathogens usually encountered in late-onset VAP, linezolid was then administered as antistaphylococcal empirical therapy in addition to an antipseudomonal β-lactam (ceftazidime or piperacillin/tazobactam) and amikacin, as recommended, until identification of the pathogen and determination of its antibiotic susceptibility (10). No potential interactions (and as a result altered distribution of linezolid) have been reported between this series of antibiotics, either molecule to molecule or by means of intermediate effects of hepatic-renal-serum protein binding (1, 2).

All subjects received 1-hr intravenous infusions of linezolid 600 mg twice daily. All samples for linezolid concentration determinations were obtained at steady state after 2 days of therapy. Blood samples were collected before the initiation of infusion and 10, 20, 30, and 45 mins and 1, 2, 4, 8, and 12 hrs after the end of infusion and were immediately centrifuged at 3000 rpm for 5 mins. The serum was removed and stored at −80°C until analyzed. Each subject underwent blood sampling 1 and 12 hrs after the end of infusion of two standardized bronchoalveolar microlavage (mini-BAL) procedures, as previously described (12–15). A standard bronchial brush tube (Combicath, Plastimed) was inserted in the endotracheal tube and used to perform a mini-BAL with 40 mL of sterile 0.9% normal saline solution. The aspirate was immediately centrifuged at 3000 rpm for 5 mins, and a single aliquot of supernatant was separated and frozen for the urea assay. The remaining volume was frozen at −80°C until the assays were performed. All blood and BAL samples were assayed within 6 months from the time of their collection.

Linezolid concentrations in plasma and BAL were measured simultaneously by a high-performance liquid chromatography method validated in our laboratory (16). The sample extraction was based on a fully automated solid-phase extraction with an OASIS HLB cartridge. The method used ultraviolet detection set at a wavelength of 254 nm and separation with a Zorbax Eclipse XDB C8 column. The assay has been found linear over the concentration range 2.5–30 μg/mL for linezolid in plasma and BAL. It provided good validation data for accuracy and precision (relative standard deviations <3.41% and 5.13%, accuracy in the range 97.42–103.30% and 97.00–104.79%, respectively, for intra- and interday coefficients of variation). The limits of quantification of linezolid were 0.02 μg/mL in serum and 0.04 μg/mL in BAL.

As previously described, the concentration of linezolid in ELF (LIN_{ELF}) was determined as follows, using urea as an endogenous marker (8, 12–15):

$$LIN_{ELF} = LIN_{BAL} \times urea_{SER}/urea_{BAL} \quad [1]$$

where LIN_{BAL} is the measured concentration of linezolid in BAL fluid, $urea_{SER}$ is the concentration of urea in serum, and $urea_{BAL}$ is the concentration of urea in the BAL fluid.

Individual patient steady-state concentration-time data were analyzed by a two-compartment model with first-order elimination from central compartment using the SIPHAR software package (Simed, Créteil, France). The pharmacokinetic variables determined were elimination half-life, volume of distribution, total body clearance, and area under the plasma concentration-time during the observational period (AUC_{0-12}). The peak and trough plasma concentrations, time to reach peak plasma concentration, and peak and trough ELF concentrations were determined directly from observed individual pharmacokinetic profiles. Plasma linezolid AUC_{0-12} was calculated with trapezoidal rule from individual concentrations.

RESULTS

Sixteen adult subjects (ten men and six women) with late-onset VAP completed the study (Table 1). Linezolid administration and mini-BAL procedures were well tolerated, and no adverse effects were observed. Of the 16 patients undergoing linezolid sampling, 12 had one organism recovered using the plugged telescoping catheter technique (three oxacillin-resistant and one oxacillin-susceptible *S. aureus*, four *P. aeruginosa* and four Enterobacteriaceae). All patients infected by oxacillin-resistant *S. aureus* treated with linezolid had favorable outcome after 10 days of therapy.

Patients' demographics and characteristics appear in Table 1. Figure 1 shows the steady-state plasma and ELF linezolid concentrations vs. time. Linezolid plasma and ELF pharmacokinetic variables appear in Table 2. The mean ± SD linezolid peak and trough plasma concentrations were 17.7 ± 4.0 mg/L and 2.4 ± 1.2 mg/L in plasma and 14.4 ± 5.6 mg/L and 2.6 ± 1.7 mg/L in ELF, respectively, showing a mean linezolid percentage penetration in ELF of approximately 100% (Table 2). The mean ± SD area under concentration-time curve during the observational period (AUC_{0-12}) was 77.3 ± 23.7 mg·hr/L (Table 2), corresponding to a mean AUC_{0-24} of 154.6 mg·hr/L, where $AUC_{0-24} = 2 \times AUC_{0-12}$.

DISCUSSION

The pharmacokinetics/pharmacodynamics (PK/PD) and tissue penetration of linezolid have been extensively studied in various *in vitro* and human models, as shown in Table 3 (1–4, 17, 18). However, these studies were generally carried out in healthy volunteers, and few pharmacokinetic data concerning infected patients are available, which may present pathophysiologic conditions influencing the pharmacokinetic profile of linezolid. Moreover, although the clinical efficacy of linezolid has been evaluated during the

Table 1. Patients' characteristics at enrollment (n = 16)

Age, yrs	59 ± 15
Gender, M/F	10/6
Weight, kg	73 ± 15
SAPS II	40 ± 13
Creatinine clearance, mL/min	81 ± 45
Main diagnosis	
Pneumonia	7 (44)
Abdominal surgery	5 (31)
Pancreatitis	2 (12.5)
Encephalitis	2 (12.5)
Pao_2/Fio_2 ratio, mm Hg	231 ± 117

M, male; F, female; SAPS, Simplified Acute Physiology Score (24).

Data are expressed as mean ± SD or n (%).

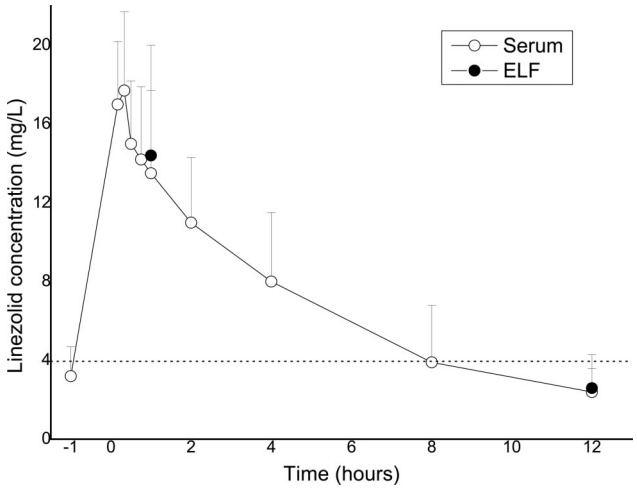

Figure 1. Mean steady-state plasma (*open circles*) and epithelial lining fluid (*ELF, filled circles*) concentrations of intravenous linezolid 600 mg administered twice daily to critically ill patients with nosocomial pneumonia (n = 16). The dotted line represents the susceptibility breakpoint (4 mg/L) of staphylococci for linezolid (1). Error bars represent standard deviations.

treatment of Gram-positive nosocomial pneumonia, no pharmacokinetic and intrapulmonary diffusion data in critically ill patients on mechanical ventilation are available (6).

Some reported pharmacokinetic variables of linezolid in healthy volunteers are similar to ours, such as mean steady-state peak plasma concentration, or elimination half-life values of 12.7–18.3 mg/L and 4.8–6.4 hrs, respectively, although considerable variability is observed when standard deviations are taken into account (4, 17, 18). Besides, a wider mean volume of distribution (57 L) and a greater mean AUC_{0-24} (154.6 mg·hr/L), conditioned by a lower mean total body clearance (9.2 L/hr, which corresponds to 66.1 mL/min), were observed in our critically ill patients than in healthy volunteers (mean volume of distribution,

Table 2. Steady-state plasma and epithelial lining fluid (ELF) linezolid pharmacokinetic variables following intravenous administration of 600 mg twice daily to critically ill patients with ventilator-associated pneumonia (n = 16)

Patient No.	C_{max} mg/L	C_{min} mg/L	T_{max}, hrs	$T_{1/2\beta}$, hrs	CL, L/hr	VD_β, L	AUC_{0-12}, mg·hr/L	Plasma/BAL Urea Concentration Ratio	ELF C_{max} [a] mg/L	ELF C_{min} [b] mg/L	ELF Percentage Penetration, % Peak	ELF Percentage Penetration, % Trough
1	23.6	1.5	0.2	6.5	4.8	43	126.3	6.4	16.1	3.3	81	220
2	18.7	4.1	0.3	5.2	5.4	42	110.3	8.2	14.6	4.6	92	112
3	15.9	0.7	0.2	3.9	18.1	100	33.2	14.6	6.4	0.3	76	43
4	18.4	2.2	0.2	4.2	8.5	50	70.2	8.9	22.3	3.9	53	177
5	13.4	4.2	0.3	6.0	6.0	50	100.4	8.0	12.1	5.8	95	138
6	19.5	4.1	0.5	4.0	6.6	39	90.7	6.2	25.2	2.1	188	51
7	15.6	0.8	0.2	3.3	9.6	45	62.8	8.0	4.5	0.5	139	63
8	16.9	3.2	0.3	3.7	8.6	45	70.0	5.6	9.1	2.4	75	75
9	11.5	1.4	0.2	4.0	16.1	94	37.4	4.7	5.6	0.6	136	43
10	17.4	2.6	0.3	3.8	8.9	48	78.2	4.9	19.3	4.1	61	158
11	23.2	1.6	0.2	4.2	7.5	52	84.8	1.8	25.4	1.8	113	113
12	25.4	3.4	0.3	4.7	8.4	56	78.4	5.4	17.9	4.2	96	124
13	13.2	2.0	0.2	3.9	10.5	66	74.2	4.0	11.3	1.5	113	75
14	15.3	0.9	0.2	5.0	7.8	51	60.4	11.8	13.2	0.6	126	67
15	19.8	2.1	0.2	3.6	11.4	68	80.6	20.7	12.9	2.0	118	95
16	14.6	3.8	0.3	4.7	9.4	62	79.4	11.3	14.3	4.3	110	113
Mean	17.7	2.4	0.3	4.4	9.2	57	77.3	8.2	14.4	2.6	105	104
SD	4.0	1.2	0.1	0.9	3.6	18	23.7	4.6	5.6	1.7	34	28

C_{max}, peak serum concentration; C_{min}, trough serum concentration; T_{max}, time to reach C_{max}; $T_{1/2\beta}$, elimination half-life; CL, total body clearance; VD_β, volume of distribution during the β phase; AUC_{0-12}, area under concentration-time curve during the observational period; BAL, bronchoalveolar lavage; ELF C_{max}, peak ELF concentration; ELF C_{min}, trough ELF concentration.

[a]1 hr after the end of infusion; [b]12 hrs after the end of infusion. Data are mean ± SD.

Table 3. Mean ± SD linezolid pharmacokinetic variables in healthy volunteers

Linezolid	Dose	No.	C_{max}, mg/L	T_{max}, hrs	$T_{1/2\beta}$, hrs	VD_β, L	AUC_{0-12}, mg·hr/L	Ref.
600 mg PO	M	6	18.3 ± 6.0	0.7 ± 0.3	4.9 ± 1.8	—	107.5 ± 40.6	4
600 mg PO	S	6	12.7 ± 2.6	1.3 ± 0.8	6.4 ± 2.2	52 ± 17	110 ± 22	17
625 mg PO	S	6	12.7 ± 3.4	1.33 ± 0.6	4.9 ± 1.4	45.0 ± 13.9	—	18
625 mg IV	S	6	13.4 ± 1.73	0.5 ± 0.1	4.4 ± 2.4	46.0 ± 11.2	79.2 ± 27.8	18
625 mg PO	M	6	18.8 ± 6.2	2.1 ± 1.1	5.4 ± 0.9	36.1 ± 10.5	147 ± 57.9	18
625 mg IV	M	6	15.7 ± 2.6	0.5 ± 0.0	4.8 ± 1.7	45.5 ± 4.9	93.4 ± 32.3	18

PO, oral dose; M, multiple doses; S, single dose; IV, intravenous.

Our study shows satisfactory results, with linezolid concentrations exceeding the susceptibility breakpoint for Gram-positive bacteria in both plasma and epithelial lining fluid.

AUC_{0-24}, and total body clearance values in the ranges of 45–52 L, 93.4–140.3 mg·hr/L, and 95–123 mL/min, respectively), whereas a wider mean AUC_{0-24} of 221.4 mg·hr/L with extreme variability (range = 62.7–869.8 mg·hr/L) was observed in severely debilitated adult patients with numerous comorbid conditions and complicated infections (4, 17–19). Moreover, two previous studies devoted to the pulmonary penetration of orally administered linezolid have been performed in healthy volunteers or in patients undergoing bronchoscopy for diagnosis purposes (3, 5). In these studies, the ratios of linezolid concentration in ELF to those in plasma, ranging from 2:1 to 8:1, were surprisingly much higher than the 1:1 ratio observed in the current study with no clear explanation, since the capillary leak syndrome often seen in pneumonia would theoretically produce higher ELF concentrations than in healthy volunteers.

Tissue concentrations of antibiotics at the target site contribute to therapeutic effects: Using plasma concentrations may frequently overestimate the target site concentrations and therefore clinical efficacy (20). This is the first study to report the steady-state plasma and ELF concentrations and the ELF percentage penetration of linezolid 600 mg administered twice daily to critically ill patients with VAP. Considering PK/PD variables such as the time during which the concentration is above the MIC ($T > MIC$) our study shows satisfactory results, with linezolid concentrations both in plasma and ELF exceeding the susceptibility breakpoint for Gram-positive bacteria (2 mg/L for *Enterococcus* spp. and *Streptococcus* spp. including *S. pneumoniae*, and 4 mg/L for *Staphylococcus* spp. including oxacillin-resistant *S. aureus*) during 70–100% of time (1). Moreover, since an AUC_{0-24}/MIC ratio of 50–100 hrs seems the major PK/PD variable determining the efficacy of linezolid, our results suggest that a dosage of 600 mg administered intravenously twice daily to critically ill patients with nosocomial pneumonia would achieve success against organisms with MICs as high as 2–to 4 mg/L in both serum and ELF (19, 21, 22).

Our study, however, presents some limitations. First, the relatively small number of patients does not permit extrapolation to all critically ill patients with VAP. Moreover, in our study population, patients had relatively similar weight and creatinine clearance with no hepatic failure. Therefore, our results may not be applied to all populations, such as morbidly obese or pediatric patients. Besides, the observed AUC_{0-24} in our study population presents wide variability among patients (AUC_{0-12} ranging from 33.2 to 126.3 mg·hr/L) and is toward the lower range of that found in infected patients and the upper range of that found in healthy volunteers (17–19). Considering the likely high frequency of organisms with MIC values close to 4 mg/mL in intensive care unit settings (giving AUC/MIC ratios of approximately 40), this extreme pharmacokinetic variability suggests that more frequent dosage of linezolid concentrations should be considered in critically ill patients to optimize individual PK/PD variables. Last, although mini-BAL has been validated for the diagnosis of VAP, no data exist to indicate that mini-BAL can be used to determine ELF concentrations. A bronchoscopic microsampling method has been reported to be reliable for measuring antimicrobial concentrations in the respiratory tract, suggesting that mini-BAL should be a reliable method for the dosage of linezolid (23, 24). However, a study comparing bronchoscopic BAL and mini-BAL for the dosage of antimicrobial agents in ELF would be of interest to determine the accuracy of the mini-BAL procedure for this purpose.

CONCLUSIONS

Our study shows that the intravenous administration of linezolid 600 mg twice daily in critically ill patients with Gram-positive VAP provides satisfactory pharmacokinetic results in this particular subset of patients, with a linezolid percentage penetration in ELF of 100% and concentrations exceeding the MIC of the targeted pathogens in both plasma and ELF. This suggests that intravenous linezolid 600 mg administered twice daily to critically ill patients with VAP should be effective against organisms with MICs as high as 2–4 mg/L in both plasma and ELF. However, considering the wide interindividual pharmacokinetic variability encountered in critically ill patients with VAP, dosages of linezolid concentrations should be considered to ensure optimal individual PK/PD variables.

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