Therapeutic Drug Monitoring of Linezolid: a Retrospective Monocentric Analysis[▽]

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The objective of the present retrospective observational study carried out in patients receiving a standard dosage of linezolid and undergoing routine therapeutic drug monitoring (TDM) was to assess the interindividual variability in plasma exposure, to identify the prevalence of attainment of optimal pharmacodynamics, and to define if an intensive program of TDM may be warranted in some categories of patients. Linezolid plasma concentrations (trough [$C_{\min}$] and peak [$C_{\max}$] levels) were analyzed by means of a high-performance liquid chromatography (HPLC) method, and daily drug exposure was estimated (daily area under the plasma concentration-time curve [AUC_{24}]). The final database included 280 $C_{\min}$ and 223 $C_{\max}$ measurements performed in 92 patients who were treated with the fixed 600-mg dose every 12 h (q12h) intravenously ($n = 58$) or orally ($n = 34$). A wide variability was observed (median values [interquartile range]: 3.80 mg/liter [1.75 to 7.53 mg/liter] for $C_{\min}$, 14.70 mg/liter [10.57 to 19.64] for $C_{\max}$, and 196.08 mg · h/liter [144.02 to 312.10 mg · h/liter] for estimated AUC_{24}). Linezolid $C_{\min}$ was linearly correlated with estimated AUC_{24} ($r^2 = 0.85$). Optimal pharmacodynamic target attainment (defined as $C_{\min}$ of ≥ 2 mg/liter and/or AUC_{24}/MIC_{90} ratio of >80) was obtained in about 60 to 70% of cases, but potential overexposure (defined as $C_{\min}$ of ≥ 10 mg/liter and/or AUC_{24} of ≥ 400 mg · h/liter) was documented in about 12% of cases. A significantly higher proportion of cases with potential overexposure received cotreatment with omeprazole, amiodarone, or amlodipine. Our study suggests that the application of TDM might be especially worthwhile in about 30% of cases with the intent of avoiding either the risk of dose-dependent toxicity or that of treatment failure.

Linezolid is the first commercially available oxazolidinone, whose use in the treatment of infection caused by multidrug-resistant (MDR) Gram-positive bacteria is continuously increasing (37).

Among the several reasons for this, two appear to be the most clinically relevant. First, linezolid retains its efficacy even against bacterial strains which become tolerant of glycopeptides. This fact may justify even its empirical use in settings with high incidences of bacterial strains with borderline susceptibility to vancomycin (23) or its use for salvage therapy (13). Second, it presents very favorable rates of penetration into tissues (33), even in the presence of intact anatomical barriers (18). This suggests a potential pharmacokinetic advantage over glycopeptides in the treatment of deep-seated infections, such as pneumonia (1, 33) and/or central nervous system infections (27).

Based on the drug's intrinsic chemico-physical and pharmacokinetic characteristics, it is expected that dosing adjustment and intensive therapeutic drug monitoring (TDM) may be unnecessary in most cases. Linezolid is a moderately lipophilic drug whose pharmacokinetic behavior is not expected to vary

significantly according to renal and/or hepatic failure and/or to polytherapy (32). The oxidative metabolism of linezolid is non-enzymatic and does not involve the hepatic microsomal oxidative system CYP450. Nonrenal clearance accounts for 65% of an administered linezolid dose, with roughly 30% of the dose appearing unchanged in the urine (31). Additionally, in contrast to those of more hydrophilic antimicrobial agents such as the beta-lactams, linezolid pharmacokinetics did not appear to be substantially affected by the pathophysiological changes occurring during sepsis and/or septic shock (36).

However, some recent studies suggest that TDM of linezolid could be especially helpful for dosage adjustment in some settings. Significant underexposure with increased risk of therapeutic failure was documented in patients with major thermal injuries (10, 17) and with cystic fibrosis (4), whereas, conversely, significant overexposure with increased toxicity risk was observed in some critically ill patients (21, 25).

To the best of our knowledge, no observational data in daily clinical practice on linezolid plasma exposure during routine use at standard fixed doses are available to date.

On the basis of an institutional program devoted to improving knowledge of the pharmacokinetic behavior of newly commercially available antimicrobial agents in the clinical setting, in 2003 we started to measure plasma levels of linezolid in patients treated because of documented and/or suspected MDR Gram-positive bacterium-related infections.

The present retrospective observational study aimed to as-

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sess the interindividual pharmacokinetic variability in plasma exposure to linezolid, to identify the prevalence of optimal pharmacodynamic exposure enabled by the standard dosing regimen according to the pharmacokinetic/pharmacodynamic principles and to the pattern of susceptibility to this antibiotic, and to define if an intensive program of TDM may be warranted in some categories of patients.

MATERIALS AND METHODS

Study design. Plasma TDM of linezolid carried out in the period between December 2003 and May 2009 at the Institute of Clinical Pharmacology and Toxicology, Azienda Ospedaliero-Universitaria, University of Udine, represented the starting database. Patients included in this retrospective observational study were those admitted in intensive care units (ICUs) or medical or surgical wards who were treated intravenously or orally with linezolid at the standard daily dosage of 600 mg every 12 h (q12h) because of documented or suspected MDR Gram-positive bacterial infections and who underwent TDM. At our institution linezolid TDM is performed three times a week (on Monday, Wednesday, and Friday) and the feedback to the clinician is given in real time (within the same day). However, since the aim of this study was to assess the degree of interindividual variability in plasma exposure to linezolid observed during the standard fixed-dosing regimen, only the TDM carried out before the eventual application of TDM-guided dosage adjustments was considered in this analysis.

The study was approved by the Ethical Committee.

Measurement of linezolid plasma concentrations. Venous blood samples were drawn just before the next administration to assess trough plasma concentration ($C_{\min}$) and 30 min after a 1-h intravenous infusion or 2 h after oral administration to assess peak plasma concentration ($C_{\max}$). Times for blood collections were carefully checked and recorded in each single case, and whenever doubts on appropriate sampling arose, samples were excluded from this analysis. Linezolid concentrations in plasma were analyzed by means of a validated high-performance liquid chromatography (HPLC) analysis method, as previously described (25, 26). Precision and accuracy were assessed by performing replicate analyses of quality control samples against calibration standards, intra- and interassay coefficients of variation always being less than 10%. The low limit of detection was 0.2 mg/liter.

Estimation of CL_{CR} . Creatinine clearance (CL_{CR}) was estimated by means of the Cockcroft and Gault formula (5).

Pharmacokinetic analysis. Pharmacokinetic analysis of linezolid was performed using the Abbottbase Pharmacokinetic System (PKS) program using Bayesian forecasting (16). Intravenous administration data were fitted to a standard one-compartment model with zero-order input (1-h drug infusion) and first-order elimination. For oral administration, the concentration data were fitted to a standard one-compartment model with first-order absorption and first-order elimination. The calculated pharmacokinetic parameters were clearance and volume of distribution. Daily area under the plasma concentration-time curve (AUC_{24}) was estimated using the pharmacokinetic parameters. Only patients having at least one complete set of $C_{\min}$ and $C_{\max}$ measurement samples drawn at steady state were included for AUC_{24} estimation.

Assessment of pharmacodynamics. (i) **Efficacy thresholds.** Optimal theoretical pharmacodynamic determinants of efficacy for the time-dependent antibacterial activity of linezolid against methicillin-resistant (MR) staphylococci and against vancomycin-resistant (VR) enterococci were defined as plasma $C_{\min}$ s of ≥ 2 mg/liter and/or AUC/MIC ratios of >80 . The rationale behind these choices derives from the notion that the MIC_{90} for linezolid against both MR staphylococci and VR enterococci is 2 mg/liter (14) and from the finding that, in one study conducted in seriously ill adult patients, higher success rates were achieved when the cumulative percentage of a 24-h period that the drug concentration exceeded the MIC under steady-state pharmacokinetic conditions ($\%T_{MIC}$) exceeded 85% of the dosing interval and AUC/MIC ratios were between 80 and 120 (28). Indeed, the achievement of these targets may become especially relevant for critically ill septic patients, who may often be immunocompromised (24, 28).

(ii) **Toxicity thresholds.** Conversely, the thresholds of potential overexposure to linezolid were arbitrarily defined as $C_{\min}$ s of ≥ 10 mg/liter and/or AUC_{24} of ≥ 400 mg $\cdot$ h/liter. The reason for this choice is that exposures higher than these, being more than 2-fold higher than those normally observed with similar dosages in healthy volunteers (12, 32), might significantly increase the risk of dose-

TABLE 1. Patient characteristics^a

Characteristic	Value
No. of patients	92
Age (yr)	57.2 $\pm$ 14.3
Gender (no. M/no. F)	67/25
Body wt (kg)	75.2 $\pm$ 18.2
CL_{CR} (ml/min) ^b	84.8 (6.1–349.5)
Normalized dose of linezolid (mg/kg/12 h)	8.37 $\pm$ 1.74
Hospital admission (no. [%] of patients)	
Surgical ward	40 (43.5)
ICU	28 (30.4)
Medical ward	24 (26.1)
Main reason for linezolid treatment (no. [%] of patients)	
Bloodstream infections	18 (19.6)
CNS infections	18 (19.6)
Empirical use for severe sepsis	16 (17.4)
Intra-abdominal infections	11 (12.0)
Hospital-acquired pneumonia	10 (10.9)
Bone/joint infections	10 (10.9)
Cardiosurgical infections/endocarditis	8 (8.7)
SST infections	1 (0.9)

^a Values are expressed as means $\pm$ standard deviations, median (range), or numbers (percentages). Abbreviations: CL_{CR} , estimated creatinine clearance by means of the Cockcroft and Gault formula; CNS, central nervous system; ICU, intensive care unit; SST, skin and soft tissue; TDM, therapeutic drug monitoring; M, male; F, female.

^b At time of first TDM.

dependent toxicity with linezolid (37). Concomitant drug treatments were reviewed in order to identify the frequency of recurrence.

Statistical analysis. The Kolmogorov-Smirnov test was performed to assess whether data were normally or nonnormally distributed. Accordingly, descriptive data were expressed as means $\pm$ standard deviations (SD) or as medians and interquartile (IQ) ranges. Categorical variables were compared by the χ^2 test with Yates' correction or Fisher's exact test when necessary, and continuous variables were compared using Student's *t* test. A *P* value of <0.05 was required to achieve statistical significance. The statistical analysis was carried out with SigmaStat version 3.1.

RESULTS

Patient characteristics are shown in Table 1. The most frequent hospital admission was surgical (43.5%), and the main reasons for linezolid therapy were bloodstream infections (19.6%) and central nervous system infections (19.6%).

The database included 280 $C_{\min}$ (median per patient = 3; IQ range, 1 to 4) and 223 $C_{\max}$ measurements performed in 92 patients, who were treated with the fixed 600-mg q12h dosing regimen of linezolid intravenously in 58 cases and orally in the other 34.

Median pharmacokinetic values (IQ ranges) were 3.80 mg/liter (1.75 to 7.53 mg/liter) for $C_{\min}$, 14.70 mg/liter (10.57 to 19.64 mg/liter) for $C_{\max}$, and 196.08 mg/liter $\cdot$ h (144.02 to 312.10 mg $\cdot$ h/liter) for estimated AUC_{24} .

No significant linear relationships between linezolid $C_{\min}$ and either estimated CL_{CR} ($r^2 = 0.01$) (Fig. 1) or body weight ($r^2 = 0.06$) (Fig. 2) were found. Conversely, linezolid $C_{\min}$ was linearly correlated with estimated AUC_{24} ($r^2 = 0.85$) (Fig. 3).

For linezolid trough levels sorted according to patients' hospital admissions (Fig. 4), medians (IQ ranges) of $C_{\min}$ were 4.78 mg/liter (2.12 to 7.68 mg/liter) in surgical patients, 2.94 mg/liter (1.10 to 6.93 mg/liter) in intensive care unit (ICU)

FIG. 1. Relationship between linezolid trough levels ($C_{\min}$) and patients' estimated creatinine clearance (CL_{CR}).

patients, and 2.94 mg/liter (1.66 to 7.25 mg/liter) in medical patients. Although a trend toward higher exposure was observed among surgical patients, these differences were not statistically significant.

As far as pharmacokinetic/pharmacodynamic relationships are concerned, optimal pharmacodynamic exposure in terms of $C_{\min}$ being higher than MIC_{90} was documented in 71.4% of cases and AUC/MIC_{90} ratios were estimated to be >80 in as many as 61.9% of the 223 evaluable cases.

The trend over time of linezolid $C_{\min}$ showed that median values persisted above the pharmacodynamic threshold of efficacy from day 2 onward (Fig. 5). Potential overexposure in terms of $C_{\min}$ s of ≥ 10 mg/liter was found in 11.8% of instances (33 instances of TDM in 23 patients; median, 12.40 mg/liter; range, 11.0 to 19.2 mg/liter), and AUC_{24} was estimated to be >400 mg $\cdot$ h/liter in 8.1% of cases.

When patients with potential overexposure were compared with those having trough levels within the lower range (<10 mg/liter), normalized daily doses per kg of body weight and

FIG. 2. Relationship between linezolid trough levels ($C_{\min}$) and patients' weight.

FIG. 3. Relationship between linezolid trough levels ($C_{\min}$) and estimated daily area under the plasma concentration-versus-time curve (AUC_{24}) ($n = 223$).

route of administration of linezolid were similar (Table 2). However, a significantly higher proportion of the patients with linezolid $C_{\min}$ s of ≥ 10 mg/liter received cotreatment with omeprazole (78.8 versus 27.5%, $P < 0.001$), amiodarone (21.2 versus 2.4%, $P < 0.001$), or amlodipine (21.2 versus 5.2, $P < 0.003$).

DISCUSSION

Our findings suggest that during routine clinical use linezolid exposure after standard fixed daily dosages may vary among patients, irrespective of the type of ward of admission.

Indeed, although median values for $C_{\min}$, $C_{\max}$, and AUC_{24} were similar to those observed in healthy volunteers (17, 32), their ranges were significantly wider.

From this perspective, it would be of interest to clarify if

FIG. 4. Box (median and 25th to 75th percentile) and whisker (5th and 95th percentile) plots of trough plasma concentrations ($C_{\min}$) of linezolid observed according to the type of ward of admission (surgical wards [Surg], intensive care units [ICU], and medical wards [Med]). Filled circles are outliers.

FIG. 5. Box (median and 25th to 75th percentile) and whisker (5th and 95th percentile) plots of trough plasma concentrations ($C_{\min}$) of linezolid observed over time. Filled circles are outliers; n is the number of observations on each day of treatment. The dashed line refers to 2 mg/liter, namely, the MIC_{90} of linezolid for staphylococci and enterococci. Median $C_{\min}$ was almost always above the MIC_{90} of linezolid for staphylococci and enterococci, regardless of the day of treatment.

some patient characteristics, pathophysiological conditions, and/or drug cotreatments might account for this variability.

Indeed, in our study neither estimated CL_{CR} nor body weight was found to be a useful predictor of linezolid exposure. The absence of a significant relationship between linezolid $C_{\min}$ and estimated CL_{CR} is attributable to the mainly nonrenal clearance of linezolid (32). This finding allows us to confirm that no major dosage adjustments need to be recommended in patients with impaired renal function. Likewise, linezolid $C_{\min}$ did not show a clear relationship with patients' body weight. In our study very low drug exposures in terms of $C_{\min}$, $C_{\max}$, and AUC_{24} among obese patients were observed only in some cases, even if the limited number of instances of TDM carried out in this subpopulation did not enable any definite conclusion. Indeed, we recognize that linezolid pharmacokinetics may be influenced by the degree of obesity, but considering that existing data for this patient demographic are quite sparse and variable (11, 19), no empirical alterations of linezolid dosage in obese patients can be suggested to date (19).

Overall, these observations and the wide interpatient variability seen in this study suggest that it would be difficult to accurately predict the pharmacokinetic disposition of linezolid in all patients, so that the application of TDM, at least in some cases, seems logical.

The good linear relationship between $C_{\min}$ and estimated AUC_{24} ($r^2 = 0.85$) suggests that $C_{\min}$ may represent a useful predictor of linezolid total body exposure in daily clinical practice. Interestingly, our hypothesis is in agreement with a recent population pharmacokinetic study carried out in patients with MDR tuberculosis treated with linezolid which showed that the estimation of AUC based on a trough concentration did not differ significantly from that based on multiple samples (3). Accordingly, it may be speculated that TDM of $C_{\min}$ could be used to guide dosage adjustment with linezolid in individual patients with the intent of avoiding either the risk of toxicity or that of therapeutic failure.

In a pharmacodynamic study with linezolid, it was shown that the two parameters most strongly associated with linezolid efficacy were AUC/MIC ratios of >80 to 100 and $\%T_{MIC}$ of 85 (28). Additionally, it has been postulated that a $C_{\min}$ higher than the MIC may be especially useful for linezolid efficacy in immunocompromised patients (24, 28). Considering that 2 mg/liter is the MIC_{90} of linezolid against staphylococci and enterococci (14) and that from our estimates the achievable AUC_{24} in the presence of $C_{\min}$ of >2 mg/liter is >160 mg $\cdot$ h/liter, this means that for a $C_{\min}$ of linezolid greater than 2 mg/liter both the pharmacodynamic targets of efficacy ($C_{\min}$ higher than MIC_{90} and AUC/MIC_{90} ratio of >80) may be attained. Accordingly, this plasma trough value could be proposed as the lower threshold for efficacy with the standard dosage of linezolid.

In our study standard dosages of linezolid ensured the attainment of these pharmacodynamic targets in the majority of cases (almost 70 to 75%). Interestingly, median $C_{\min}$ was >2 mg/liter just on day 2 and then it was maintained over this threshold throughout the entire treatment period, even if the range of variability was consistent. This fact seems to suggest that perhaps the role of TDM in order to avoid potential underexposure with linezolid could be limited if the susceptibility breakpoint for staphylococci was lower than that currently recommended (i.e., 2 mg/liter rather than 4 mg/liter).

The role of TDM might be especially valuable in lowering the risk of exposure-dependent toxicity with linezolid, which in our study could have related to the 12% of cases with potential overexposure. It was shown that some adverse events with linezolid, namely, hematological alterations and hyperlactacidemia, are dose dependent (37) and may be related to a reversible inhibition of the mitochondrial protein synthesis (8). In our study potential overexposure was not correlated with the use of higher dosage per kg of body weight or with different administration routes and, of note, its onset seemed to be unrelated to the length of treatment. Some years ago we reported the case of a liver transplant patient who experienced

TABLE 2. Comparison of linezolid dosages, administration routes, and most frequent drug cotreatments in cases with trough levels ($C_{\min}$) of ≥ 10 mg/liter versus those with trough levels of <10 mg/liter

Parameter	No. (%) of cases by linezolid $C_{\min}$:		<i>P</i> value
	≥ 10 mg/liter (<i>n</i> = 33)	<10 mg/liter (<i>n</i> = 247)	
Linezolid administration route			
Intravenous	21 (63.6)	157 (63.6)	0.847
Oral	12 (36.4)	90 (36.4)	0.845
Linezolid dosage, median (IQ range) (mg/kg/q12h)			
Overall	9.3 (7.5–10.2)	8.0 (7.1–10.0)	0.067
Intravenous	10.0 (7.9–10.0)	8.0 (7.1–10.0)	0.071
Oral	7.9 (7.9–10.3)	8.5 (7.1–10.0)	0.876
Cotreatments			
Omeprazole	26 (78.8)	68 (27.5)	<0.001
Amiodarone	7 (21.2)	6 (2.4)	<0.001
Amlodipine	7 (21.1)	13 (5.2)	0.003

an unexpected early onset of hyperlactacidemia due to a consistent linezolid overexposure ($C_{\min}$, 26.99 mg/liter; AUC_{12} , 412.55 mg · h/liter) (21). Among the various hypotheses, we postulated that this overexposure could have been due to drug-drug interaction.

Of note, in the present study patients experiencing linezolid overexposure were found to be more frequently cotreated with omeprazole, amiodarone, and/or amlodipine than were those with $C_{\min}$ s of <10 mg/liter, and all of these drugs are potent inhibitors of P-glycoprotein (P-gp) (7, 15, 20). These findings seem to suggest that linezolid overexposure might occur especially in patients cotreated with some drugs which may act as P-gp inhibitors, who might especially benefit from TDM in the prevention of linezolid-related toxicity. Unfortunately, this study was not set up to verify this hypothesis and its retrospective nature did not allow us to assess the incidence of toxicity in these cases.

Likewise, TDM could be relevant for avoiding potential underexposure, which may have occurred in 28% of cases. Conflicting opinions exist about the role that severe sepsis and septic shock may have in affecting linezolid pharmacokinetics. Some authors found no major influence (36), whereas others found a very wide interindividual variability (2, 35) and recommended the use of TDM (35). In our study, the lack of relevant differences in linezolid exposure among patients according to the type of ward of admission suggests that the pharmacokinetic variability in ICU patients does not seem to be significantly higher than that in surgical and/or medical patients. Additionally, considering the intrinsic characteristics of linezolid (a moderately lipophilic drug with mainly nonrenal, nonenzymatic clearance), it is expected that the pathophysiological changes occurring during sepsis should be less relevant than they would be for hydrophilic compounds, like the beta-lactams (29). Indeed, we recognize that measurement of the free moiety rather than of total concentration would have enabled more exhaustive consideration. However, the relatively small extent of protein binding of linezolid (around 30%), which could be even lower in hypoalbuminemic patients, is expected to affect to a limited extent its pharmacokinetics. Besides, in this population of patients, according to pharmacokinetic/pharmacodynamic principles, continuous infusion may be considered a useful tool to improve linezolid activity since it has theoretical advantages over intermittent infusion (2).

In any case, the wide variability observed and the complex management of critically ill patients should induce clinicians to consider TDM an invaluable tool for the management of antibiotic therapy in this setting (22). This could be especially true for patients with severe burn injuries and/or with cystic fibrosis, in whom linezolid clearance was recently shown to be significantly increased (4, 10, 17, 30). Interestingly, in patients with cystic fibrosis, among the various mechanisms that could be responsible for the well-known enhanced clearance of antimicrobial drugs, it has been suggested that the overexpression of P-gp may play a major role (30, 34). Additionally, the overexpression of P-gp was recently cited to explain the significant drop of linezolid concentration during coadministration of rifampin, a potent inducer of P-gp (6, 9). Indeed, although in our database only four patients with rifampin cotreatment underwent TDM, it is noteworthy that very low $C_{\min}$ s of linezolid

(median, 1.21 mg/liter; IQ range, 0.68 to 1.73 mg/liter) were observed in these cases.

Obviously, further prospective studies are warranted before any definitive conclusion about the major factors which may affect linezolid pharmacokinetics can be drawn.

We are well aware of the methodological limitations of our study, particularly its retrospective nature; the limited sample size, which is too small to allow us to draw definite conclusions; and the fact that the observational nature of the study obliged us to limit sampling to only two time points. However, the good correlation between $C_{\min}$ and estimated AUC_{24} supports the idea that TDM of trough levels might represent a useful predictor of linezolid efficacy and/or toxicity in routine clinical practice. Indeed, the thresholds for $C_{\min}$ here proposed have not yet been validated and might change with future data that may emerge on this topic.

In conclusion, our study suggests that the standard fixed 600-mg q12h dosage may ensure adequate pharmacodynamic exposure to linezolid in about 60 to 70% of cases but also that, conversely, in the remaining 30 to 40% of cases the application of TDM might be especially worthwhile with the intent of avoiding the risk of treatment failure or of dose-dependent toxicity.

A prospective study focused on assessing the clinical relevance of the correlation between linezolid TDM and efficacy or toxicity is ongoing.

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