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Impact of augmented renal clearance on the pharmacokinetics of linezolid: Advantages of continuous infusion from a pharmacokinetic/pharmacodynamic perspective

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ABSTRACT

Objectives: The aim of this study was to assess the influence of renal function, in particular the presence of augmented renal clearance (ARC), on the pharmacokinetics of linezolid in critically ill patients. The effect of continuous infusion on the probability of therapeutic success from a pharmacokinetic/pharmacodynamic (PK/PD) perspective was also evaluated.
Methods: Seventeen patients received linezolid (600 mg every 12 h) as a 30-min infusion and 26 as a continuous infusion (50 mg/h). The PK parameters were calculated and the probability of PK/PD target attainment (PTA) was estimated by Monte Carlo simulation (MCS) for different doses administered by intermittent (600 mg every 12 h or 600 mg every 8 h) or continuous infusion (50 mg/h or 75 mg/h).
Results: In patients without ARC, the standard dose was adequate to attain the PK/PD target. However, linezolid clearance was significantly higher in ARC patients, leading to sub-therapeutic concentrations. Continuous infusion (50 mg/h) provided concentrations ≥2 mg/l in 70% of the ARC patients. MCS revealed that concentrations ≥2 mg/l would be reached in >90% of patients receiving 75 mg/h.
Conclusions: ARC increases linezolid clearance and leads to a high risk of underexposure with the standard dose. Continuous infusion increases the PTA, but an infusion rate of 75 mg/h should be considered to ensure concentrations ≥2 mg/ml.
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Introduction

Nowadays, antimicrobial treatment remains challenging, especially in critically ill patients, mainly due to their severe clinical condition, and also because they often undergo pathophysiological changes that may alter the pharmacokinetics of drugs (Blot et al., 2014). Some of the most commonly observed alterations are an increased volume of distribution (Vd), altered protein binding, and changes in drug clearance due to hepatic or renal dysfunction.

Traditionally, renal function in critically ill patients has been assessed to identify renal dysfunction, and dose adjustment is generally accepted in this context. Nevertheless, augmented renal clearance (ARC) is a less well-studied phenomenon that could lead to faster elimination of drugs, resulting in sub-therapeutic concentrations and poorer clinical outcomes when standard dosage guidelines are followed (Bilbao-Meseguer et al., 2018). ARC refers to the enhanced elimination of solutes as compared with an expected baseline, and it is defined as creatinine clearance (CrCL) of ≥130 ml/min/1.73 m^2. This manifestation of enhanced renal function is seen in 20% to 65% of critically ill patients (Bilbao-Meseguer et al., 2018; Udy et al., 2014).

Several conditions have been described as risk factors for ARC, such as younger age, trauma admission, lower severity illness, male sex, mechanical ventilation, high diastolic blood pressure, vasopressor use, high diuretic volumes, and a less positive fluid

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balance, among others (Bilbao-Meseguer et al., 2018). ARC has a clear influence on the pharmacokinetic profile of antimicrobial drugs that are renally cleared, and research on the need to stage ARC and establish specific dosing guidelines is warranted. Several studies have shown a relationship between ARC and sub-therapeutic levels of time-dependent antibiotics with renal elimination, such as vancomycin and beta-lactams (Minkute et al., 2013; 2012; Carlier et al., 2013), although there is less information available for other drugs.

Linezolid, the first commercialized oxazolidinone antibiotic, has activity against a wide variety of gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (Cunha, 2006; Weigelt et al., 2005). The authorized dose of linezolid is 600 mg every 12 h, regardless of the patient's hepatic or renal function.

Linezolid is moderately bound to plasma proteins (31%), and the volume of distribution is about 40–50 l, which is approximately the total body water. Linezolid is metabolized by oxidation to two inactive metabolites, and approximately 65% of its elimination is through non-renal clearance (Bouza and Muñoz, 2001; Dryden, 2011). Renal clearance accounts for 30–35% of the total clearance, and there is controversy regarding the correlation between creatinine clearance and linezolid clearance. Some authors have concluded that there is not a strong relationship, whereas others have suggested that renal function is a relevant factor affecting the pharmacokinetics of linezolid in critically ill patients, and thus the probability of attaining the pharmacokinetic/pharmacodynamic (PK/PD) target (Barrasa et al., 2019). It is important to bear in mind that the pharmacokinetic profile of linezolid shows great variability in critically ill patients (Meagher et al., 2003; Boselli et al., 2005; Buerger et al., 2006; Adembri et al., 2008; Viaggi et al., 2011; Pea et al., 2010) and, therefore, the standard dose may not be the most suitable for all patients.

Thus, based on the reasons mentioned above, the aim of this study was to assess the influence of renal function, especially the presence of ARC, on the pharmacokinetics of linezolid after the administration of the authorized standard dose (600 mg every 12 h) to critically ill patients. The influence of different dosage strategies, such as continuous infusion, on the probability of therapeutic success from a PK/PD point of view was also evaluated.

Materials and methods

Study design

A prospective open-label study was conducted on patients admitted to the intensive care units (ICUs) of two Spanish university hospitals: University Hospital Araba (Vitoria-Gasteiz) and Doce de Octubre Hospital (Madrid). The protocol was approved by the Basque Clinical Research Ethics Committee (LINE_IC_2015) and the Spanish Agency of Medicinal Products and Medical Devices (EudraCT No. 2015-002987-17). All patients or their legal representatives were informed about this study and written informed consent was obtained.

Patients, linezolid administration, and sample collection

Patients were eligible for inclusion if (1) they were admitted to the ICU; (2) they suffered from an infection probably caused by a Gram-positive microorganism and were therefore treated with linezolid; (3) they gave informed consent; and (4) it was possible to obtain plasma samples. The exclusion criteria were (1) age <18

Table 1
Characteristics of patients stratified by level of renal function based on the creatinine clearance rate.

ID	Infection	Sex	AP II	Age (years)	Weight (kg)	BMI (kg/m^2)	Cr (mg/dl)	CrCL (ml/min/ 1.73 m^2)	Glucose (mg/dl)	Hb (g/dl)	Alb (g/dl)	TP (g/dl)	BR (mg/dl)	GOT (U/l)	GPT (U/l)	PR %
Group I																
1	Intra-abdominal	M	30	77	85	27.8	0.9	43	117	7.0	2.8	5.1	0.4	16	6	95
2	Respiratory	M	12	76	65	23.4	1.5	44	150	9.2	2.1	4.9	0.2	16	21	83
3	Respiratory	F	13	70	78	25.4	0.7	53	170	13.2	3.0	7.4	1.3	31	18	83
4	Others	M	12	74	72	25.6	1.4	11	144	12.2	2.1	4.8	0.7	34	36	103
5	Intra-abdominal	M	16	85	75	23.1	1.0	39	165	9.7	1.9	4.6	0.3	34	49	87
6	CNS	F	13	79	80	26.6	1.0	51	144	8.6	3.2	6.6	0.9	19	17	106
7	Respiratory	M	36	77	65	23.9	2.1	28	187	7.7	3.8	6.2	1.0	18	24	113
	Mean		18.9	76.9	74.3	25.1	1.2	38.4	153.9	9.7	2.7	5.8	0.7	24.0	24.4	95.7
	SD		9.9	4.6	7.5	1.7	0.5	14.6	22.5	2.3	0.7	1.1	0.4	8.5	14.1	12.0
Group II																
8	Respiratory	M	24	63	70	24.8	1.0	72.6	100	9.9	2.6	6.5	1.3	230	165	68
9	CNS	F	11	37	60	23.4	0.7	86.0	73	12.7	2.9	6.9	0.2	38	6	105
10	Respiratory	M	18	83	80	24.7	1.1	71.6	161	9.8	2.8	6.1	0.4	54	53	81
11	CNS	F	26	22	60	22.0	0.5	60.2	126	9.4	2.9	6.5	0.4	18	15	105
12	Intra-abdominal	F	21	47	60	20.8	0.8	101.0	156	12.6	2.5	4.2	1.0	330	340	76
13	CNS	M	12	81	85	26.8	0.8	99.2	147	12.5	2.8	6.9	0.9	35	25	87
	Mean		18.7	55.5	69.2	23.8	0.8	81.8	127.2	11.2	2.8	6.2	0.7	117.5	100.7	87.0
	SD		6.2	24.5	11.1	2.2	0.2	16.4	34.8	1.6	0.2	1.0	0.4	130.3	130.9	15.3
Group III																
14	CNS	M	NA	54	65	23.9	0.6	131.0	75	11.8	2.9	5.3	0.6	23	59	NA
15	CNS	M	16	43	70	24.2	0.7	179.5	113	15.5	4.0	6.8	1.0	16	15	110
16	Soft tissue	M	14	49	95	29.3	0.8	167.0	106	8.1	2.5	5.5	0.8	102	112	70
17	Respiratory	M	15	65	90	26.3	0.4	135.4	162	13.0	2.5	4.8	0.6	48	52	99
	Mean		15.0	52.8	80.0	25.9	0.6	153.2	114.0	12.1	3.0	5.6	0.8	47.3	59.5	93.0
	SD		1.0	9.3	14.7	2.5	0.2	23.7	36.0	3.1	0.7	0.9	0.2	39.0	40.0	20.7
	p-Value		NS	NS	NS	NS	0.031*	0.001**	NS	NS	NS	NS	NS	NS	NS	NS

Alb, albumin; AP II, Apache II score; BMI, body mass index; BR, bilirubin; CNS, central nervous system; Cr, creatinine; CrCL, creatinine clearance; F, female; GOT, serum glutamic oxaloacetic transaminase; GPT, serum glutamic pyruvic transaminase; Hb, hemoglobin; M, male; NA, not available; NS, non-significant; TP, total proteins; PR, prothrombin ratio, SD, standard deviation.
* Differences between groups I and III.
** Differences among all three groups.

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years; (2) pregnancy; (3) hypersensitivity to linezolid or any of the excipients; and (4) being on any medicinal product that inhibits monoamine oxidase A or B. Demographic, clinical, and biochemical data at the time of inclusion in the study were obtained for all patients.

The study was divided into two parts. In the first part, 17 patients recruited during a 3-year period (2013–2015) received the standard dose of 600 mg administered every 12 h by intravenous infusion over 30 min. Blood samples were collected pre-dose, at the end of infusion, and at 1, 2, 3, 6, 8–10, and 12 h under steady-state conditions over one dosing interval. Time points were selected to adequately characterize the peaks and troughs and the elimination phase. In most patients, blood sample collection was performed within the first week of therapy. Patients were grouped by renal function: group I included patients with renal dysfunction, defined as CrCL <60 ml/min/1.73 m^2; group II patients had CrCL ≥60 and <130 ml/min/1.73 m^2; group III patients had ARC (CrCL ≥130 ml/min/1.73 m^2).

In the second part, linezolid was administered as a continuous infusion (infusion rate 50 mg/h) to 26 patients recruited from 2015 to 2017. The inclusion and exclusion criteria were the same as those for the first part of the study, but, in addition, the presence of a CrCL value <40 ml/min/1.73 m^2 was added as an exclusion criterion to avoid the potential accumulation of linezolid. These patients were grouped into group IV (no ARC, CrCL >40 and <130 ml/min/1.73 m^2) if they were found not to have ARC on any day of the study and into group V (ARC, CrCL ≥130 ml/min/1.73 m^2) if ARC was detected on at least 1 day of the study. One blood sample per patient per day was obtained for 4 consecutive days.

Collected plasma samples were centrifuged and the plasma was stored at −80 °C until analysis. For all patients, CrCL was measured using urine collected over a period of 10 h the night before each day of the study, because the use of equations based on plasma creatinine would not accurately show the patients' renal function (Barrasa et al., 2019; Baptista et al., 2011).

Linezolid quantification

Linezolid plasma concentrations were quantified using a previously validated high performance liquid chromatography (HPLC) assay with ultraviolet detection (at a wavelength of 254 nm), following the US Food and Drug Administration (FDA) (FDA, 2018) and European Medicines Agency (EMA) (EMA, 2009) guidelines for parameters such as specificity, linearity and range, accuracy, precision, and stability. Separation was performed on a Symmetry C8 column (4.6 mm × 150 mm × 5 μm). The mobile phase contained ammonium phosphate (0.5%) and acetonitrile (66:34, volume:volume) and was delivered at 1 ml/min. In brief, sample preparation consisted of protein precipitation with acetonitrile, where propyl-4-hydroxybenzoate (internal standard) was previously diluted. After centrifugation (10 min at 12 000 rpm), the supernatants were injected into the HPLC system.

The assay was linear over the concentration range from 0.5 μg/ml to 50 μg/ml. Specificity was assessed using six blank standards and lower limit of quantification (LLOQ) level samples. The chromatograms were checked for any interference, and no interfering peaks were detected with the assay. Intra-batch and inter-batch accuracy and precision were evaluated at four different concentration levels (LLOQ and low, middle, and high quality control) in six replicates. The intra-day and inter-day coefficients of variation (CV) and bias were never above 15%. Moreover, stock solution stability, long-term storage stability, short-term temperature stability, freeze–thaw stability of the analyte in the matrix from freezer storage conditions to room temperature, and auto-sampler rack stability were confirmed. Linezolid substance for standards and quality controls was kindly provided by Pfizer Inc.

Pharmacokinetic analysis

For the first part of the study, one- and two-compartment open models with first-order elimination were explored to fit plasma concentration–time data using Phoenix WinNonlin (version 6.4, Pharsight Corporation). Objective function values, parameter estimation precision, and goodness-of-fit plots were used as model selection criteria.

For patients in whom linezolid was administered as a continuous infusion, the total clearance (CL) was calculated for each day as follows: $CL = K_0/C$, where K_0 is the infusion rate constant and C the concentration measured each day. In addition, the area under the plasma concentration–time curve at steady state over 24 h (AUC_{24}) was calculated for each day, using the following equation: $AUC_{24} = D/CL$, where D is the daily dose (1200 mg).

Pharmacokinetic/pharmacodynamic analysis (PK/PD)

The probability of target attainment (PTA), understood as the probability of achieving a specific PK/PD index related to the efficacy of an antibiotic treatment at a certain pathogen susceptibility (minimum inhibitory concentration, MIC) (Mouton et al., 2005), was calculated using Monte Carlo simulations implemented in Oracle Crystal Ball Version 11.1.1.1.00. Linezolid is an antibiotic with concentration- and time-dependent activity; therefore, the time that plasma concentrations are above the MIC ($\%T_{>MIC}$) and the AUC_{24}/MIC ratio are the PK/PD parameters that best predict clinical efficacy (Adembri et al., 2008; Craig, 2003; Rayner et al., 2003). An $AUC_{24}/MIC > 80$ and $\%T_{>MIC}$ >85% (Minichmayr et al., 2017; Barrasa et al., 2019) were selected as the targets to calculate the probability of treatment success or PTA.

By using the PK parameters estimated in patients from groups I, II, and III (mean values and variability, assuming lognormal distribution), 1000 studies of 1000 subjects were simulated, to calculate the PTA over a range of doubling MICs between 0.25 mg/l and 8 mg/l. The 95% confidence intervals were calculated as the range from the 2.5th to the 97.5th percentile of the set of estimated values (Kümmel et al., 2018). Dosing regimens evaluated were 600 mg every 12 h and 600 mg every 8 h, administered as a 30-min infusion.

From the values of the PK parameters calculated in patients with ARC (groups III and V), Monte Carlo simulations were conducted to estimate the PTA for linezolid continuous infusion at rates of 50 mg/h and 75 mg/h. In this case, the PTA was defined as

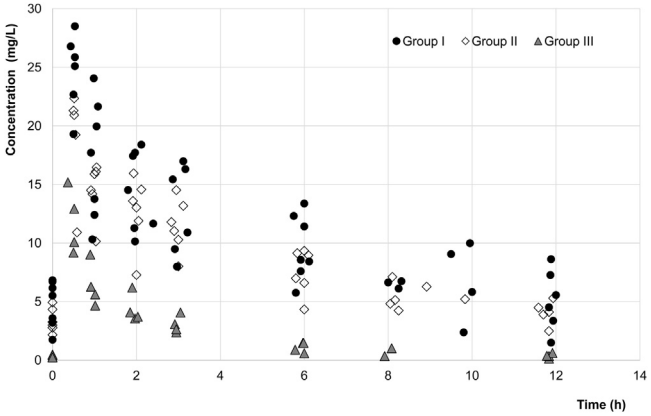

Figure 1. Linezolid plasma concentration versus time in patients grouped by renal function. Filled circles: group I (CrCL <60 ml/min/1.73 m^2); open diamonds: group II (CrCL ≥60 and <130 ml/min/1.73 m^2); grey triangles: group III (CrCL ≥130 ml/min/1.73 m^2).

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Table 2
Pharmacokinetic parameters of linezolid in patients stratified by level of renal function and achievement of PK/PD target.

Pharmacokinetics								Pharmacodynamics	
ID	Vd (l)	Vd/kg (l/kg)	$t_{1/2}$ (h)	CL (l/h)	AUC_{24} (mg h/l)	C_{max} (mg/l)	C_{min} (mg/l)	$\%T_{>MIC}$ >85% (MIC =2 mg/l)	AUC_{24}/MIC > 80 (MIC =2 mg/l)
Group I									
1	35.8	0.4	6.3	3.96	303.4	25.1	6.2	Yes	Yes
2	54.7	0.8	6.2	6.11	196.2	19.3	4.5	Yes	Yes
3	28.8	0.4	3.8	5.32	225.5	26.8	3.6	Yes	Yes
4	28.8	0.4	2.1	9.64	124.5	22.7	1.5	No	No
5	27.6	0.4	4.8	4.01	299.4	28.5	5.6	Yes	Yes
6	33.6	0.4	4.0	5.86	204.7	25.9	3.2	Yes	Yes
7	37.8	0.6	7.2	3.64	329.0	24.1	6.7	Yes	Yes
Mean	35.3	0.5	4.9	5.5	240.4	24.6	4.5		
SD	9.4	0.2	1.8	2.1	73.2	8.7	1.8		
Group II									
8	75.8	1.1	6.0	8.71	137.8	10.9	2.8	Yes	No
9	38.3	0.6	4.1	6.48	185.1	16.1	2.5	Yes	Yes
10	39.3	0.5	5.6	4.87	246.5	22.4	4.9	Yes	Yes
11	37.1	0.6	4.6	5.65	212.4	21.3	2.2	Yes	Yes
12	38.6	0.6	4.0	6.72	178.6	19.2	3.3	Yes	Yes
13	36.8	0.4	4.9	5.21	230.0	20.9	3.9	Yes	Yes
Mean	44.3	0.6	4.9	6.3	198.4	18.5	3.3		
SD	15.5	0.2	0.8	1.4	39.4	4.3	1.0		
Group III									
14	61.2	0.9	1.1	38.8	31.0	9.2	0.1	No	No
15	33.4	0.5	0.7	32.3	37.2	15.2	0.4	No	No
16	54.8	0.6	1.1	33.8	35.5	10.1	0.4	No	No
17	44.5	0.5	1.5	20.5	58.7	12.9	0.2	No	No
Mean	48.5	0.6	1.1	31.3	40.6	11.9	0.3		
SD	12.2	0.2	0.3	7.8	12.3	2.7	0.1		
p-Value	NS	NS	<0.001*	<0.001*	<0.001*	0.006**	<0.001*		

AUC_{24}, area under the plasma concentration–time curve in a period of 24 h; CL, plasma clearance; C_{max}, maximum plasma linezolid concentration; C_{min}, minimum plasma linezolid concentration; MIC, minimum inhibitory concentration; NS, non-significant; PK/PD, pharmacokinetics/pharmacodynamics; SD, standard deviation; $\%T_{>MIC}$, time that plasma concentrations are above the MIC; $t_{1/2}$, half-life; Vd, volume of distribution.
* Differences between groups I and II versus group III.
** Differences among all three groups.

the probability of continuously maintaining drug concentrations at steady state above the MIC value ($C \geq MIC$).

The dosing regimens were considered optimal if the PTA was ≥90%, whereas a PTA between 80% and 90% was considered to indicate a moderate probability of success (Asuphon et al., 2016; Drusano et al., 2004; Bradley et al., 2003).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, version 22. The normality of the data distribution was assessed with the Shapiro–Wilk test and the homogeneity of variance with the Levene test, while the *t*-test, Mann–Whitney *U*-test, analysis of variance (ANOVA), or Kruskal–Wallis test was used to compare the physiological and pharmacokinetic parameters of linezolid between patients in the different groups, as appropriate. Spearman correlation coefficients were calculated to determine the correlation between estimated AUC_{24} and observed trough concentrations (C_{min}) and between linezolid clearance and CrCL. Statistical significance was set at $p < 0.05$.

Results

Seventeen critically ill patients with different levels of renal function were included in the first part of the study: seven in group I (CrCL <60 ml/min/1.73 m^2), six in group II (CrCL ≥60 and <130 ml/min/1.73 m^2), and four in group III (CrCL ≥130 ml/min/1.73 m^2). Table 1 summarizes demographic, anthropometric, and illness

Table 3
Probability of target attainment (PTA) for linezolid in simulated patients receiving 600 mg q12 h or 600 mg q8h. Numbers in parenthesis indicate the 2.5th and 97.5th percentiles.

	AUC_{24}/MIC >80		$\%T_{>MIC}$ >85%	
MIC (mg/l)	600 mg q12h	600 mg q8h	MIC (mg/l)	600 mg q12h
Group I				
0.25	100	100	100	100
0.50	100	100	99 (98–100)	100
1	100	100	95 (94–97)	100
2	85 (82–86)	98 (98–99)	86 (84–88)	98 (97–99)
4	21 (17–23)	60 (57–63)	58 (55–61)	90 (88–92)
8	1 (0–2)	5 (4–7)	22 (19–26)	60 (57–63)
Group II				
0.25	100	100	100	100
0.50	100	100	99 (99–100)	100
1	100	100	98 (84–89)	100
2	85 (83–87)	100 (99–100)	86 (84–89)	99 (99–100)
4	1 (1–2)	34 (31–37)	49 (46–51)	93 (92–95)
8	0	0	4 (3–5)	47 (44–50)
Group III				
0.25	100	100	5 (3–6)	41 (38–44)
0.50	45 (43–48)	95 (93–96)	1 (1–2)	19 (17–21)
1	0	11 (9–13)	0	4 (3–6)
2	0	0	0	0
4	0	0	0	0
8	0	0	0	0

AUC_{24}, area under the plasma concentration–time curve in a period of 24 h; MIC, minimum inhibitory concentration; q12 h, every 12 h; q8h, every 8 h; $\%T_{>MIC}$, time that plasma concentrations are above the MIC.

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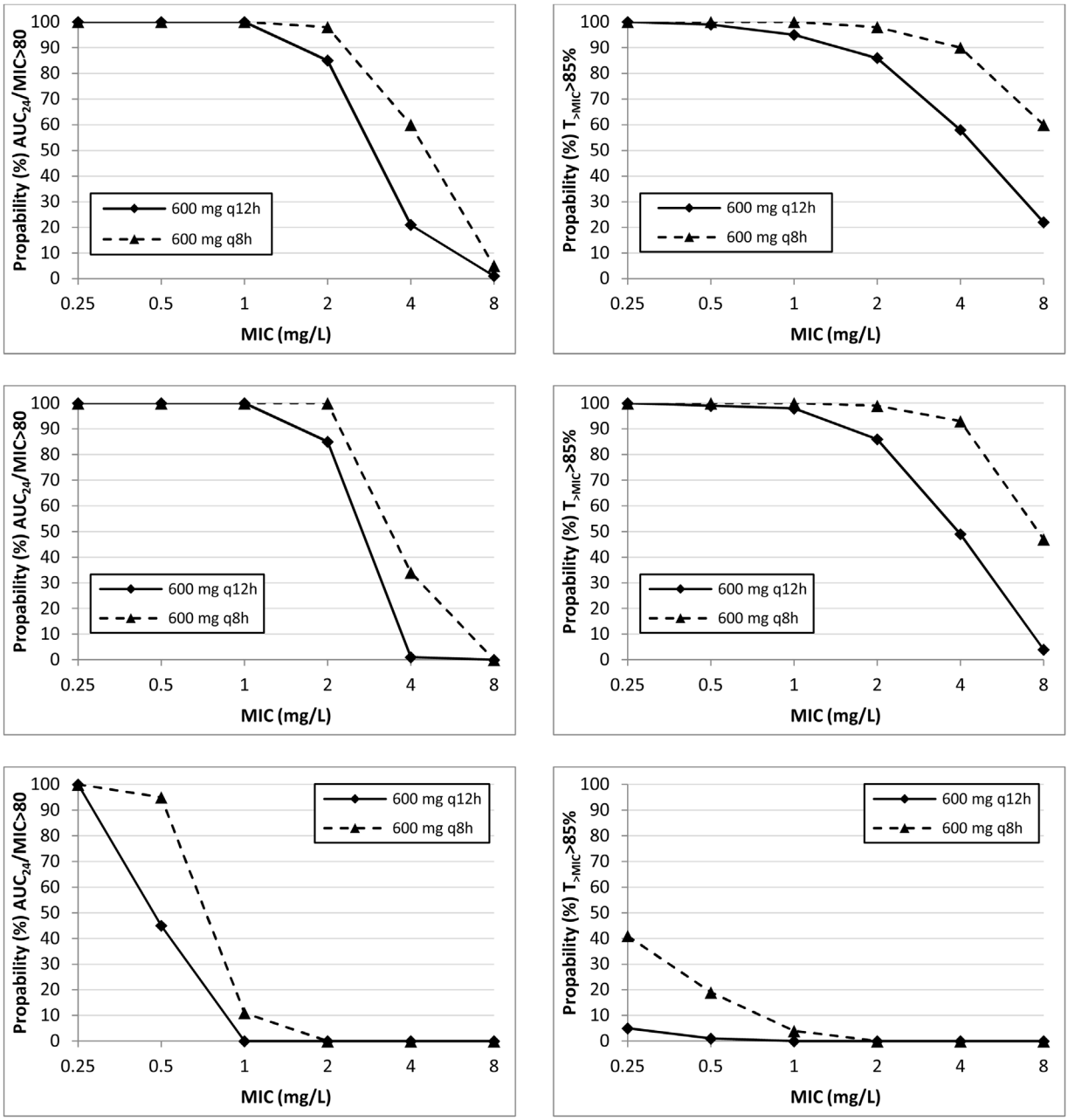

Figure 2. Estimated probability of target attainment (PTA) values with the four dose regimens in each group of simulated patients.

severity data for all patients. The source of infection was respiratory in six cases, neurological in six, abdominal in three, and soft tissues in one, with 'other sources' being cited in one other case. Differences between groups were only significant for serum creatinine and CrCL. No adverse effects attributable to linezolid treatment were reported.

Overall, 136 plasma samples were analyzed. Figure 1 displays the plasma concentrations of linezolid over time in the three groups. In groups I, II, and III, the linezolid concentration ranged from 19.3 mg/l to 28.5 mg/l, from 10.9 mg/l to 22.4 mg/l, and from 9.2 mg/l to 15.2 mg/l, respectively, at the end of the infusion and from 1.5 mg/l to 6.7 mg/l, from 2.2 mg/l to 4.9 mg/l, and from 0.1 mg/l to 0.4 mg/l, respectively, at the end of the dosing interval (12 h after infusion). Plasma concentrations of linezolid were markedly lower in the samples from group III than in those from the other two groups, while differences between groups I and II were less marked.

A one-compartment open model was selected to explain and compare the pharmacokinetic parameters of linezolid. Table 2 lists the calculated values in all of the patients. Significant differences were detected between group III and the other two groups in elimination half-life ($t_{1/2}$), CL, AUC_{24}, and C_{min}. In groups I and II, $t_{1/2}$ was significantly higher than in group III (4.9 h vs 1.1 h) and CL was nearly 5-fold lower; consequently, AUC_{24}, maximum plasma linezolid concentration (C_{max}), and C_{min} were significantly higher ($p < 0.006$). Significant differences were only observed for C_{max} between groups I and II, with higher values in group I (24.6 mg/l vs 18.5 mg/l). For a MIC of 2 mg/l, the AUC_{24}/MIC was >80 and $\%T_{>MIC}$ was >85% in more than 80% of the patients in groups I and II. However, no patient with ARC attained the values related to efficacy for either of the two PK/PD targets (Table 2).

Table 3 and Figure 2 feature the PTA values calculated by Monte Carlo simulation for the targets AUC_{24}/MIC > 80 and $\%T_{>MIC}$ >85%. The standard dose (600 mg every 12 h) provided PTA values higher

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Table 4
Characteristics of patients stratified by whether they had augmented renal clearance (ARC).

ID	Infection	Sex	AP II	Age (y)	Weight (kg)	BMI (kg/m^2)	Glucose (mg/dl)	CrCL[a] (ml/min/ 1.73 m^2)	Hb (g/dl)	Alb (g/dl)	TP (g/dl)	BR (mg/dl)	GOT (U/l)	GPT (U/l)	PR %
Group IV (No ARC)															
1	CNS	F	23	84	70	25.7	217	65–85	11.5	3.0	5.4	0.6	18	20	83
2	CNS	M	11	72	80	29.4	115	77–128	10.1	3.0	5.4	0.8	16	18	69
3	Intra-abdominal	F	19	42	51	NA	165	73–115	8.5	2.2	4.9	3.8	41	27	68
4	CNS	M	9	65	70	25.7	94	69–70	10.9	2.7	NA	0.2	59	57	97
5	CNS	M	18	46	90	27.8	173	85–129	11.4	3.1	NA	0.3	87	76	69
6	CNS	M	12	51	85	27.8	144	106–126	9.7	3.5	7.4	0.6	27	40	80
7	Respiratory	F	9	58	70	27.3	176	41–66	8.7	3.1	5.6	0.5	49	24	72
8	Respiratory	F	10	76	75	27.5	159	74–83	9.4	3.9	6.6	0.4	33	35	101
9	CNS	F	16	59	63	28.0	69	88–122	10.7	2.7	5.1	0.4	22	32	78
10	Respiratory	M	16	22	NA	NA	125	76–123	10.9	3.1	5.6	0.3	43	37	99
11	Respiratory	M	23	71	72	27.8	112	84–87	11.4	2.2	5.2	1.1	41	25	74
12	CNS	M	14	76	70	24.2	184	63–77	10.6	2.5	4.9	0.2	19	12	98
13	Respiratory	M	18	68	70	22.9	122	66–127	7.9	2.7	6.1	1.1	36	49	81
	Mean		15.2	60.8	72.2	26.7	142.7		10.1	2.9	5.7	0.8	37.8	34.8	82.2
	SD		4.9	17.0	10.0	1.9	41.1		1.2	0.5	0.8	1.0	19.7	17.6	12.4
Group V (ARC)															
14	Respiratory	M	17	48	95	30.0	139	115–153	10.6	3.1	6.3	2.1	74	220	75
15	CNS	F	6	68	80	29.4	133	45–155	8.4	2.6	5.5	0.5	16	21	79
16	CNS	M	25	71	75	27.5	157	86–146	11.7	3.6	6.7	1.1	24	34	128
17	Others	F	21	27	70	24.2	117	118–138	8.2	2.5	5.3	0.8	41	42	92
18	Respiratory	M	16	24	115	35.5	114	160–240	11	2.7	5.4	0.5	70	61	86
19	Respiratory	M	9	40	65	21.2	113	125–180	13.7	2.8	6.4	0.3	38	39	112
20	Respiratory	M	35	78	75	24.5	111	125–160	11.6	3.0	5.6	0.3	60	89	82
21	Respiratory	M	10	47	70	24.2	116	94–170	11.6	3.5	6.3	1.3	161	40	83
22	CNS	M	12	62	82	31.2	169	130–245	14.9	3.5	7.5	0.5	28	15	69
23	Respiratory	M	14	45	81	28.7	152	185–220	8.1	3.0	5.6	0.4	31	35	84
24	Respiratory	M	8	48	101	30.5	120	278–345	8	2.5	4.7	0.2	76	77	84
25	Respiratory	F	6	34	122	46.5	78	230–331	10.7	3.9	6.5	0.3	84	63	90
26	Others	M	20	50	89	28.4	113	220–339	8.8	2.5	6.9	0.5	25	23	67
	Mean		15.3	49.4	86.2	29.4	125.5		10.6	3.0	6.1	0.7	56.0	58.4	87.0
	SD		8.4	16.6	17.6	6.4	24.0		2.2	0.5	0.8	0.5	39.0	53.3	16.7
	p-Value		NS	NS	0.023	NS	NS		NS	NS	NS	NS	NS	NS	NS

Alb, albumin; AP II, Apache II score; BMI, body mass index; BR, bilirubin; CNS, central nervous system; CrCL, creatinine clearance; F, female; GOT, serum glutamic oxaloacetic transaminase; GPT, serum glutamic pyruvic transaminase; Hb, hemoglobin; M, male; NA, not available; NS, non-significant; TP, total proteins; PR, prothrombin ratio, SD, standard deviation.

[a] Minimum and maximum CrCL during the study.

than 80% for microorganisms up to a MIC of 2 mg/l in patients without ARC (groups I and II). In contrast, in patients with ARC (CrCL ≥130 ml/min/1.73 m^2, group III), neither 600 mg every 12 h nor 600 mg every 8 h provided PTA values ≥80% for the MIC of 2 mg/l, these being close to zero.

The second part of the study included 26 critically ill patients with CrCL ≥40 ml/min/1.73 m^2 who received linezolid as a continuous infusion at a rate of 50 mg/h. Table 4 summarizes the demographic and clinical data for these patients. Figure 3 shows the plasma concentrations over time in these patients. Overall, 94 plasma samples were analyzed. The linezolid concentration ranged from 1.3 mg/l to 15.5 mg/l in group IV and from 1.0 mg/l to 7.4 mg/l in group V. Table 5 presents the daily CrCL and the pharmacokinetic parameters for each subject. The mean daily CrCL ranged from 81.2 ml/min/1.73 m^2 to 93.5 ml/min/1.73 m^2 in group IV (no ARC) and from 167.9 ml/min/1.73 m^2 to 197.4 ml/min/1.73 m^2 in group V (ARC). Linezolid CL was significantly higher ($p < 0.05$) in the patients with ARC, with this leading to significantly lower values of C ($p < 0.05$) and AUC_{24} ($p < 0.05$). Linezolid concentrations were maintained above 2 mg/l in 94% of samples from patients without ARC (group IV) and in 70% of samples from patients with ARC (group V). No adverse effects attributable to linezolid were observed.

Figure 4 shows the PTA values calculated by Monte Carlo simulation for virtual patients with ARC receiving linezolid as a continuous infusion at two different rates: 50 mg/h and 75 mg/h. It was observed that the probability of attaining the PK/PD target was notably higher than with the intermittent infusions. With continuous infusion, for a MIC of 2 mg/l, the PTA was 68% for 50 mg/h and 93% for 75 mg/h.

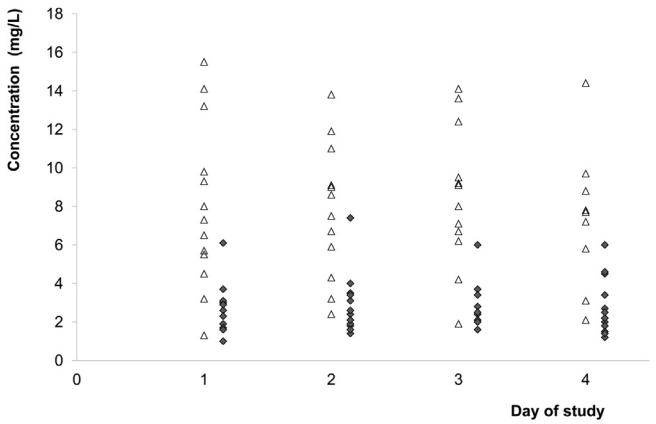

Figure 3. Linezolid plasma concentration versus time in patients grouped by the presence (grey diamonds, group V) or not (white triangles, group IV) of ARC.

Figure 5 shows the correlation between CrCL and linezolid CL, obtained with all values from the five groups of patients; Spearman's correlation coefficient was 0.77 ($p < 0.001$).

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Table 5
Pharmacokinetic parameters of linezolid stratified by whether the patient had augmented renal clearance (ARC).

ID	Day 1 CrCL (ml/min/1.73 m^2)	C (mg/l)	CL (l/h)	AUC_{24} (mg h/l)	Day 2 CrCL (ml/min/1.73 m^2)	C (mg/l)	CL (l/h)	AUC_{24} (mg h/l)	Day 3 CrCL (ml/min/1.73 m^2)	C (mg/l)	CL (l/h)	AUC_{24} (mg h/l)	Day 4 CrCL (ml/min/1.73 m^2)	C (mg/l)	CL (l/h)	AUC_{24} (mg h/l)
Group IV (No ARC)																
1	85	9.3	5.4	222	72	8.6	5.8	207	65	9.1	5.5	218	65	9.1	5.5	218
2	77	5.5	9.0	133	128	3.2	15.8	76	105	4.2	12.1	100	105	4.2	12.1	100
3	73	15.5	3.2	371	78	13.8	3.6	332	91	12.4	4.0	298	91	12.4	4.0	298
4	70	3.2	15.7	76	69	4.3	11.7	103	69	8	6.2	193	69	8	6.2	193
5	123	4.5	11.2	107	129	6.7	7.5	161	85	6.7	7.5	161	85	6.7	7.5	161
6	106	1.3	37.3	32	126	2.4	21.3	56	111	1.9	26.4	45	111	1.9	26.4	45
7	53	13.2	3.8	316	66	11.9	4.2	285	41	14.1	3.5	339	41	14.1	3.5	339
8	83	6.5	7.7	156	74	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	97	14.1	3.5	339	88	9.0	5.6	216	112	9.5	5.3	227	112	9.5	5.3	227
10	123	5.7	8.8	136	115	5.9	8.4	142	76	6.2	8.1	148	76	6.2	8.1	148
11	84	9.8	5.1	236	87	7.5	6.7	179	NA	7.1	7.1	170	NA	7.1	7.1	170
12	70	8.0	6.2	193	77	11	4.5	265	60	13.6	3.7	326	60	13.6	3.7	326
13	127	7.3	6.8	175	86	9.1	5.5	218	78	9.2	5.4	221	78	9.2	5.4	221
Mean	90.1	8.0	9.5	191.7	91.9	7.8	8.4	186.7	81.2	8.5	7.9	203.8	93.5	7.4	9.2	177.5
SD	23.4	4.3	9.0	102.6	23.8	3.5	5.3	84.3	22.4	3.7	6.3	88.1	25.1	3.6	6.7	86.9
Group V (ARC)																
14	153	1.9	26.2	46	115	1.8	27.3	44	127	2.1	24.1	50	141	2.0	25.3	47
15	45	2.6	18.9	63	84	3.1	16.4	73	155	2.8	17.7	68	107	4.5	11.2	107
16	92	3.0	16.5	73	146	4.0	12.7	95	86	6.0	8.4	144	87	6.0	8.4	143
17	120	3.1	15.9	75	138	3.5	14.2	84	118	2.4	21.3	56	128	2.2	22.9	52
18	182	1.6	31.2	38	208	2.1	23.8	50	240	2.5	19.9	60	160	2.7	18.8	64
19	125	3.7	13.5	89	130	1.9	25.7	47	153	2.1	24.3	49	180	2.5	19.9	60
20	147	2.6	19.6	61	153	2.4	20.6	58	125	3.7	13.5	89	160	4.6	10.8	111
21	170	6.1	8.2	146	94	7.4	6.8	177	NA	NA	NA	NA	NA	NA	NA	NA
22	170	1.7	29.2	41	230	2.1	23.5	51	130	2.0	25.6	47	245	1.8	27.2	44
23	185	2.9	17.4	69	210	2.6	19.6	61	220	2.5	20	60	NA	1.2	42.7	28
24	340	1.6	32.1	37	280	1.4	36.7	33	345	1.6	30.6	39	278	1.5	32.7	37
25	234	1.0	48.4	25	264	1.6	30.7	39	331	1.6	30.9	39	230	1.4	36.5	33
26	220	2.3	22.0	55	238	3.4	14.7	82	339	3.4	14.8	81	277	3.4	14.9	81
Mean	167.9	2.6	23.0	62.9	176.2	2.9	21.0	68.8	197.4	2.7	20.9	65.2	181.2	2.8	22.6	67.3
SD	72.4	1.3	10.4	30.9	65.4	1.6	8.1	37.6	95.0	1.2	6.7	29.2	66.9	1.5	10.8	36.0

AUC_{24}, area under the plasma concentration–time curve in a period of 24 h; CL, linezolid clearance; CrCL, creatinine clearance; C, linezolid concentration each day of the study (days 1–4); NA, not available; SD, standard deviation.

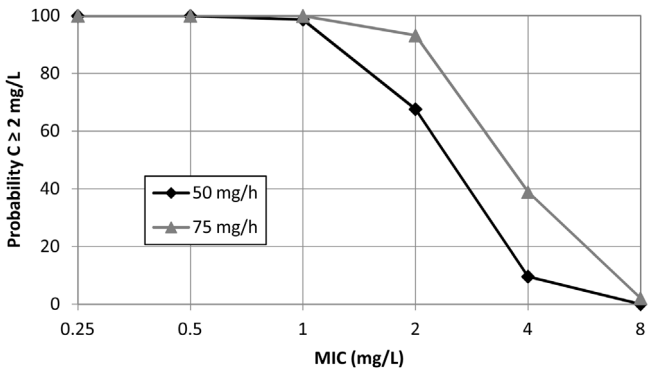

Figure 4. Estimated probability of target attainment (PTA) values with the continuous infusion of linezolid at rates of 50 mg/h and 75 mg/h.

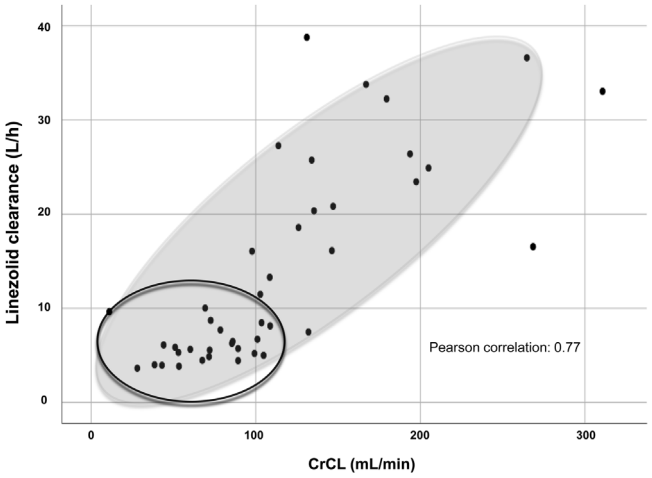

Figure 5. Correlation between CrCL and linezolid clearance.

Discussion

This study is novel in showing that the presence of ARC in critically ill patients significantly affects the pharmacokinetics of linezolid, as well as in evaluating the effect of ARC on the adequacy of the dosing regimen. ARC is a clinical stage that can lead to faster elimination of drugs, resulting in sub-therapeutic concentrations and poorer clinical outcomes when standard dosage guidelines are followed (Bilbao-Meseguer et al., 2018). This is particularly important for antibacterial agents that are eliminated by the kidney and whose activity is time-dependent (Carlier et al., 2013; Udy et al., 2010; Udy et al., 2012).

The total number of patients with ARC included in this study was 17, representing 40% of all recruited patients; this is similar to other series (Udy et al., 2014). We defined ARC as the clinical situation in which CrCL was $\geq$130 ml/min/1.73 m^2 on at least 1 day of the study, as proposed by most authors (Bilbao-Meseguer et al., 2018; Udy et al., 2014). In other studies, patients have been considered to have ARC if more than 50% of the CrCL measurements during admission were $\geq$130 ml/min/1.73 m^2. Other works, however, have shown that between 55.4% and 74% of patients who have CrCL $\geq$130 ml/min/1.73 m^2 in one measurement have values higher than this level in more than 50% of measurements (Baptista et al., 2011; Udy et al., 2014). In another study, it was reported that a high percentage of patients with CrCL $\geq$130 ml/min/1.73 m^2 measured once, had ARC throughout their ICU stay (De Waele et al., 2015).

When comparing patient characteristics among groups, it was observed that, although patients with ARC seemed to be younger and had a lower severity illness score, differences among the groups were not statistically significant. Moreover, no patients received concomitant medication that could modify linezolid pharmacokinetics. Therefore, the observed differences in drug pharmacokinetics and in PK/PD results cannot be attributed to these factors.

The standard dose of linezolid is 600 mg every 12 h administered as an intermittent infusion over the course of 30 min. Bearing in mind that only 30–35% of linezolid is excreted in urine (Stalker and Jungbluth, 2003), no dosage adjustments are recommended in patients with renal dysfunction. However, at the other end of the renal function spectrum, i.e. patients with ARC, dose recommendations have not been established, and whether or not higher doses are required has not been adequately studied.

This study confirmed that if the patient does not have ARC, differences in CrCL do not lead to changes in linezolid CL, and therefore dose adjustment is not necessary; this supports the recommendations of the clinical practice guidelines. Moreover, we also found that the standard dose (600 mg every 12 h as a 30-min infusion) provides a high probability of treatment success in patients with infections due to microorganisms with a MIC $\leq$ 2 mg/l, which is the European Committee on Antimicrobial Susceptibility Testing (EUCAST) PK/PD (non-species related) breakpoint for linezolid and the MIC_{90} of most *Staphylococcus* species in Europe (EUCAST, 2018).

In contrast, in the presence of ARC, there is a significant increase in linezolid clearance and a high risk of underexposure. Actually, the PK/PD targets (AUC_{24}/MIC > 80 and $\%T_{>MIC}$ >85%) for the MIC of 2 mg/l were not reached in any of the patients with ARC. Moreover, the PK/PD analysis and Monte Carlo simulation revealed that 600 mg every 8 h, also given as a 30-min infusion, did not substantially increase the probability of treatment success, being very low for MICs higher than 0.5 mg/l; this makes the intermittent infusion of linezolid at the doses evaluated inappropriate for this group of patients.

We found only one relevant case in the literature, which reported the pharmacokinetics of linezolid in a woman with ARC receiving 600 mg every 12 h (Cojutti et al., 2018). As in our study, linezolid CL was higher than that observed in healthy volunteers; moreover, therapeutic drug monitoring revealed suboptimal exposure, with C_{min} of 0.3 mg/l, similar to that obtained in our patients.

Previous studies have suggested that continuous infusion of linezolid may be an alternative to ensure antibiotic exposure in critically ill patients (Adembri et al., 2008; Dong et al., 2011; Richards and Brink, 2014). Thus, in the second part of the study, we sought to determine whether the administration of linezolid as a continuous instead of an intermittent infusion to patients with high CL could improve their exposure to the antibiotic and therefore increase the probability of treatment success. With this purpose in mind, we administered linezolid to patients at an infusion rate of 50 mg/h (same daily dose as the standard dose) and investigated whether this dosing regimen would be sufficient to provide plasma concentrations (C) $\geq$2 mg/l (PK/PD target). It was observed that this target was reached in 94% of the patients with CrCL <130 ml/min/1.73 m^2, and what is more relevant, in 70% of the patients with ARC.

Monte Carlo simulations confirmed that the administration of linezolid to patients with ARC as a continuous infusion of 50 mg/h notably increases the probability of attaining the PK/PD target, being close to 100% for a MIC of 1 mg/l and almost 70% for a MIC of 2 mg/l, which agrees with the results obtained experimentally. Additionally, we simulated the administration of linezolid as a

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continuous infusion of 75 mg/l and found that with this dosing regimen, the probability of treatment success in patients with ARC and infections due to microorganisms with a MIC of 2 mg/l increases to 93%. These results confirm that linezolid administered as a continuous infusion may be an adequate alternative for patients with ARC, although we have to bear in mind that the unique dose regimen included in the summary of product characteristics is 600 mg twice daily.

As mentioned previously, the relationship between CrCL and linezolid CL is controversial. In fact, dose adjustment is not required in patients with renal failure. From the CrCL and linezolid CL values measured in our patients, a significant ($p < 0.001$) correlation was established, with Pearson coefficient of 0.77 (Figure 4). However, it can be observed that for CrCL <100 ml/min/1.73 m^2, the correlation is very weak, which confirms that dose adjustment is not necessary in patients with renal insufficiency. In contrast, if the patient presents ARC, the subsequent increase in linezolid CL justifies the need to modify the dosing strategy to ensure adequate antibiotic exposure.

Regarding distribution, the mean Vd approximated the total body water (35–49 l), and was similar to values obtained in other studies on critically ill patients (Ide et al., 2018) and on healthy volunteers (Slatter et al., 2001). Although the Vd of many drugs is known to be modified in critically ill patients, this occurs principally with hydrophilic molecules. The moderate lipophilic nature of linezolid may explain the lack of differences in this parameter among critically ill patients and healthy volunteers.

The great variability in linezolid pharmacokinetics, described previously by other authors (Dong et al., 2011; Zoller et al., 2014) and confirmed in the present study, justifies the use of therapeutic drug monitoring as a helpful tool for optimizing linezolid therapy (Richards and Brink, 2014), especially in patients with ARC (Cojutti et al., 2018). In our opinion, C_{min} and C (in the case of administration as a continuous infusion) of 2 mg/l are good targets, considering that this is the EUCAST non-species related breakpoint for linezolid.

This study has some limitations. First of all, linezolid was administered as an empirical treatment. Microbiological analysis found no microorganisms susceptible to linezolid in most of the samples obtained, and therefore direct pharmacodynamic correlation was not possible. Second, the concentration of linezolid in urine was not measured, which may have provided more information on the contribution of renal clearance to total clearance of linezolid.

In conclusion, this study shows that ARC significantly increases linezolid CL and leads to a high risk of suboptimal exposure when the standard dose is used. Continuous infusion may be a useful strategy to increase the probability of treatment success, becoming one of the few options for patients with ARC. To ensure drug concentrations above 2 mg/ml in these patients, a higher infusion rate (75 mg/h) should be considered.

Ethical approval

The protocol of this study was approved by the Basque Clinical Research Ethics Committee (LINE_IC_2015) and the Spanish Agency of Medicinal Products and Medical Devices (EudraCT No.: 2015-002987-17). All patients or their legal representatives were informed about this study and written informed consent was obtained.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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