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EDITORIAL

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Continuous administration of linezolid in pneumonia: what is the level of proof?

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Linezolid, the first available oxazolidinone derivative, has been shown to be an interesting alternative to glycopeptides against resistant gram-positive strains [1]. It distributes well into the lung, with mean percentage penetration in epithelial lining fluid of approximately 100 %, indicating that serum concentrations adequately predict antibiotic concentrations at the target site for extracellular respiratory tract pathogens [1]. Linezolid is a time-dependent antimicrobial agent with a reduced post-antibiotic effect. The best pharmacokinetic/pharmacodynamic (PK/PD) parameters to define its activity are time with serum concentrations higher than the minimum inhibitory concentration ($T > MIC$) and area under the serum concentration-time curve/minimum inhibitory concentration (AUC/MIC) ratio [1]. Linezolid is mainly a bacteriostatic antimicrobial agent with $T > MIC$ of at least 40 % being predictive of its efficacy. This objective can be easily achieved for pathogens with MICs of 2–4 mg/l by administration of standard dosing (600 mg intravenously twice a day) in healthy volunteers, suggesting that continuous infusion, the best antimicrobial administration modality for most time-dependent antibiotics as it prolongs effective serum concentrations, may not be essential [1].

During the initial phase of septic shock, however, alterations in pharmacokinetic parameters, mostly due to an increase in the volume of drug distribution and/or drug clearance, are frequently observed [2]. These modifications vary from one patient to another and in a single patient from one day to another [2]. They may lead to suboptimal serum and tissue concentrations when drugs are given at the dosage studied in healthy volunteers or in less seriously ill patients. Moreover, critically ill septic patients should be considered as immunosuppressed, and antimicrobials with bactericidal activity may be more effective than those exhibiting only bacteriostatic activity [3]. In an in vivo model of endocarditis, linezolid demonstrated bactericidal activity when $T > MIC$ was maintained for >75 % of the dosing interval [4]. On the basis of these considerations, achieving $T > MIC$ close to 100 % is probably the key to obtaining the highest success rate with linezolid in ICU patients.

Recently, Zoller et al. [5] showed that there was a high variability of linezolid serum concentrations after standard dosing in 30 critically ill infected patients with a median body mass index of 26 kg/m^2 (range 16–35 kg/m^2), mostly with lung infections. Optimal pharmacodynamic exposure over 24 h, with AUC_{0-24h} values between 200 and 400 mg h/l and with C_{min} values between 2 and 10 mg/l, could be observed for only 30 and 43 % of the patients, respectively. Regarding these AUC_{0-24h} and C_{min} values, 63 and 50 % of the patients, respectively, had linezolid concentrations below the lower limit of the corresponding target concentration range and only 7 %

were above the target concentration range. Moreover, only 17 % of the patients continuously attained optimal C_{min} values over the 4 days of the study period. Therefore, there was a high variability of linezolid $AUC_{0–24h}$ and C_{min} values, with C_{min} values differing more than 100-fold between the different patients and more than 30-fold within single patients. These data are in line with other studies observing very low, usually insufficient $AUC_{0–24h}$ or C_{min} linezolid values [6–8] and also in line with papers showing C_{min} values differing more than 50-fold between different patients [8, 9].

This PK/PD conundrum is particularly difficult in obese patients. Despite the worldwide debate related to the increase in the incidence of obesity, few data are available on ventilator-associated pneumonia in morbidly obese patients. In a meta-analysis comprising a total of 62,045 critically ill subjects, obesity was significantly associated with prolonged duration of mechanical ventilation and ICU length of stay, suggesting an increased risk in this population [10]. In a recent analysis gathering more than 4 million morbidly obese hospitalized patients, Kumar et al. [11] reported 119,000 (2.9 %) requiring mechanical ventilation. Interestingly, pneumonia as a cause of mechanical ventilation was reported in proportions similar to those in nonobese patients in this study. In the Nationwide Inpatient Sample database, Masoomi et al. [12] analyzed more than 300,000 patients who underwent bariatric surgery during a 3-year period and reported an incidence of 1.35 % postoperative acute respiratory failure. Similarly, Gupta et al. [13] reported incidences of postoperative pneumonia and respiratory failure after bariatric surgery as low as 0.6 % for both diagnoses. Overall, these reports suggest that the pulmonary risk of morbidly obese patients is close, if not similar, to that of nonobese patients.

Only limited pharmacological data are available in morbidly obese patients in the ICU setting, especially concerning the use of antiinfective agents. The appropriate antibiotic doses in these specific cases have not been clearly defined and are largely based on extrapolations from nonobese patients or plasma assays when available. The majority of the publications focused on plasma concentrations of β-lactams. However, prescribing physicians should always remember that diffusion of antibiotics in anatomical spaces cannot be easily predicted and is impossible to monitor. These patients are at risk of both under- and over-dosing, as recently reported in a study of serum β-lactam concentrations, where insufficient serum concentrations were observed in 32 % of cases and excessive concentrations in 25 % of cases [14]. In addition, some recent data suggest that in patients undergoing scheduled surgery, tissue distribution is altered, with a 30 % decreased penetration ratio compared to nonobese patients [15].

Table 1 Reasons to use linezolid by continuous infusion

Difficult-to-treat infection plus at least one of these conditions
Septic shock
Large volume resuscitation
High cardiac output
Measured creatinine clearance >160 ml/min
Immunosuppressed patients
Body mass index >25 kg/m^2
Staphylococcus aureus with MIC to linezolid >2 μg/ml

In an article recently published in *Intensive Care Medicine*, De Pascale et al. [16] add evidence in favor of using linezolid by continuous infusion, especially in critically ill obese patients. This study shows that intermittent administration in obese critically ill patients with ventilator-associated pneumonia is associated with suboptimal plasma concentrations and that continuous infusion administration is able to safely improve the linezolid pharmacokinetic profile. In this study, critically ill status and obesity did not strongly affect pulmonary distribution but continuous infusion provided a higher alveolar penetration ratio. Nevertheless, even using continuous infusion, the usual dose may still be inadequate for the management of bacteria with high MIC for linezolid.

The dose and dose interval are paramount decisions to achieve antibiotic adequacy, especially in critically ill obese patients. Underexposure at the infection site may lead to reduced efficacy, higher mortality and development of antimicrobial resistance. On the other hand, overexposure may lead to drug-related toxicity. The high variability of linezolid serum levels between patients and within single patients over the course of time leads to the conclusion that therapeutic drug monitoring would be beneficial for its correct use in critically ill patients. Individual antimicrobial dosing by aid of therapeutic drug monitoring would clearly be the best solution, but until linezolid quantification methods are easily available perhaps linezolid should be prescribed by continuous infusion in difficult-to-treat infections and in patients such as those described in Table 1.

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Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator-associated pneumonia: intermittent vs continuous administration

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Take-home message: The possibility of underdosing linezolid in obese critically ill patients is high, and continuous infusion may be a useful tool to reduce this risk.

Electronic supplementary material
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Abstract *Purpose:* Clinical application of an antibiotic's pharmacokinetic/pharmacodynamic (PK/PD) properties may improve the outcome of severe infections. No data are available on the use of linezolid (LNZ) continuous infusion in critically ill obese patients affected by ventilator-associated pneumonia (VAP). *Methods:* We conducted a prospective randomized controlled trial to compare LNZ concentrations in plasma and epithelial lining fluid (ELF), when administered by intermittent and continuous infusion (II, CI), in obese critically ill patients affected by VAP. *Results:* Twenty-two critically ill obese patients were enrolled. At the steady state, in the II group, mean ± SD total and unbound maximum–minimum concentrations ($C_{max}/C_{max,u} - C_{min}/C_{min,u}$) were 10 ± 3.7/6.8 ± 2.6 mg/L and 1.7 ± 1.1/1.2 ± 0.8 mg/L, respectively. In the CI group, the mean ± SD total and unbound plasma concentrations (C_{ss} and $C_{ss,u}$) were 6.2 ± 2.3 and 4.3 ± 1.6 mg/L, respectively. Within a minimum inhibitory concentration (MIC) range of 1–4 mg/L, the median (IQR) time LNZ plasma concentration persisted above MIC (% $T >$ MIC) was significantly higher in the CI than the II group [100 (100–100) vs 100 (89–100), $p = 0.05$; 100 (100–100) vs 82 (54.8–98.8), $p = 0.009$; 100 (74.2–100) vs 33 (30.2–78.5), $p = 0.005$; respectively]. Pulmonary penetration (%) was higher in the CI group, as confirmed by a Monte Carlo simulation [98.8 (IQR 93.8–104.3) vs 87.1 (IQR 78.7–95.4); $p < 0.001$]. *Conclusions:* In critically ill obese patients affected by VAP, LNZ CI may overcome the limits of standard administration but these advantages are less evident with difficult to treat pathogens (MIC = 4 mg/L). These data support the usefulness of LNZ continuous infusion, combined with therapeutic drug monitoring (TDM), in selected critically ill populations.

Keywords Linezolid · VAP · Continuous infusion · Pharmacokinetics

Introduction

Ventilator-associated pneumonia (VAP) due to methicillin-resistant *Staphylococcus aureus* (MRSA) still remains a leading cause of morbidity and mortality. Inadequate antimicrobial treatment against these strains is widely described as a risk factor for worse outcome [1–5].

Linezolid (LNZ) is now considered the first choice for the treatment of MRSA VAP, especially in the presence of strains with vancomycin minimum inhibitory concentration (MIC) values of 1 mg/L or more [6–9]. LNZ acts by a time-dependent antimicrobial killing mechanism: time with plasma concentrations higher than MIC ($T > MIC$) exceeding 85 % and area under the serum–time concentration curve/MIC (AUC/MIC) more than 80 h are the pharmacodynamic (PD) parameters that best predict the clinical efficacy [10, 11]. LNZ optimally penetrates different organs; however, in critically ill patients plasma and pulmonary concentrations may significantly differ from healthy volunteers [9, 12, 13]. A wide array of pathophysiological changes occurring in critically ill patients may influence antibiotics' pharmacokinetic (PK) properties according to either their lipophilic or hydrophilic nature [14, 15]. Continuous infusion has been proposed as a strategy to minimize the risk of time-dependent antibiotic underexposure in the presence of difficult to treat infections [16–18].

Obesity is now becoming a worldwide healthcare issue and the incidence of obese patients admitted to the ICU has also been increasing. In these patients, many physiological changes may influence antibiotics' tissue distributions but few data are available to adapt drug dosages and the administration schedule [19, 20]. Data from the literature regarding the LNZ PK in obese critically ill patients are rare and the need to increase LNZ daily dose in accordance with the patients' body mass index (BMI) is now a matter of debate [21–24].

To the best of our knowledge, no information is available on the plasma and pulmonary pharmacokinetics of continuous LNZ infusion use in obese ICU patients with pneumonia. Therefore, we conducted a randomized controlled trial with the aim of comparing the plasma and pulmonary [epithelial lining fluid (ELF)] PK profile of LNZ when administered as intermittent infusion (II) or continuous infusion (CI) in critically ill obese patients with VAP.

Materials and methods

Patients and study design

This study was performed in the 18-bed ICU of a 1,500-bed teaching hospital in Rome, Italy. The protocol was approved by the Catholic University's Ethical Committee (approval number P/951/CE/2010). Written informed consent was obtained from the patients' legally authorized representative. Critically ill obese (BMI $\geq$ 30 kg/m^2) adult patients were considered eligible for the study when the attending physician prescribed LNZ as empirical treatment (within 12 h from microbiological pulmonary sampling) of a possible MRSA VAP, in the absence of any exclusion criteria: known LNZ allergy; creatinine clearance less than 40 mL/min (calculated according to the Cocrockft–Gault formula) apart from those ones who were anuric and on continuous veno-venous hemodiafiltration (CVVHDF); thrombocytopenia (platelet count less than 80,000/mm^3); severe hepatic failure (Child–Pugh C); little chance of survival as defined by SAPS II; concomitant treatment with other drugs that can potentially interfere with LNZ (i.e., macrolides, serotonin modulators, omeprazole) [25] [see electronic supplementary material (ESM)]. Patients were randomized (using the opaque sealed envelope method) to receive linezolid (Zyvoxid®; Pfizer, Italia) by intermittent infusion (II) or continuous infusion (CI). The II group received LNZ as a 60-min intermittent intravenous (i.v.) administration (600 mg every 12 h); the CI group received LNZ as 600 mg i.v. loading dose (given in 60 min) followed by 1,200 mg continuous infusion/24 h (50 mg/h). After 2 days of therapy, at steady state, PK analyses of the study group were performed. Thereafter, therapy was continued by standard intermittent dosing. Clinical and demographic data were recorded upon enrollment (see ESM). Safety and adverse events were determined through the observed biochemical abnormalities, documented according to the Department of Health and Human Services–Common Terminology Criteria for Adverse Events (DHHS-CTCAE v.3.0) classification [26].

Sample collection

In the II group blood samples were collected after the fifth dose (on day 3 of treatment) at *T*0 (immediately before the initiation of the infusion) and 1, 2, 4, 8, 10, and 11 h after the end of the infusion (i.e., 2, 3, 5, 9, 11, and 12 h after the start of infusion). In the CI group blood samples were collected at 48, 53, 57, and 60 h after the first dose (i.e., on day 3 of treatment). According to patients' respiratory status, one microbronchoalveolar lavage (BAL) (40 mL sterile 0.9 % saline solution was blindly instilled through a telescopic catheter and immediately aspirated in a trap) was performed at steady state.

Pharmacokinetic/pharmacodynamic analysis

Pharmacokinetic parameters were determined by a one-compartment model with first-order elimination. The 0–12 h ($AUC_{0–12}$) was determined by the linear trapezoidal rule. $AUC_{0–24}$ was calculated as $AUC_{0–12} \times 2$. LNZ

maximum, minimum, and steady-state concentrations (C_{max}, C_{min}, and C_{ss}) were directly obtained from observed peak, trough, and steady-state concentrations. Epithelial lining fluid (ELF) linezolid (LNZ_{ELF}) concentration was calculated from BAL concentration (LNZ_{BAL}) using urea as dilution marker: $LNZ_{ELF} = LNZ_{BAL} \times$ urea dilution index (plasma urea concentration/BAL urea concentration) [12]. In all patients receiving II, distribution volume (V_d), drug clearance (CL), and elimination half-life ($t_{1/2}$) were calculated after a single 600-mg intravenous dose at steady state. Time above the minimum inhibitory concentration ($T > MIC$) of 85 and 100 % and area under the concentration curve $(AUC)_{0-24}$/MIC ratio more than 80 h were used as PD targets [11]. Graphing of data was undertaken using Prism version 6.0 for Windows (graphPad Software, San Diego, CA).

Statistical analysis

All statistical analyses were performed using the Intercooled Stata program, version 11 (StatCorp LP). The Kolmogorov–Smirnov test was used to test the variables' distribution. The data with a non-Normal distribution were assessed with the Mann–Whitney test and the median and selected centiles (25–75th) are given. The data with a normal distribution were assessed with Student's test. Categorical variables are presented as proportions and were analyzed with the use of the Chi-square test or Fisher's exact test, as appropriate. A p value less than 0.05 was considered significant. A power calculation for independent patients with an alpha of 0.05 and a power of 90 %, using a delta (difference of C_{min} between population means) of 4 and a sigma (SD) of 200 %, required a sample size of 12 patients. For ELF/plasma ratio results, a Monte Carlo simulation involving 1,000 iterations was also performed [27].

Linezolid assays and microbiological analysis

Plasma and pulmonary LNZ concentrations and microbiological isolates were analyzed as previously reported [28, 29] (see ESM).

Results

Patient demographics

During the study period (April 2011–April 2013) 22 obese critically ill obese patients were enrolled (see Fig. A in the ESM). Eleven patients were randomized to receive LNZ by II and 11 by CI. Patients' clinical and demographic characteristics are described in Table 1.

Median BMI (IQR) was 33.2 kg/m^2 (32.6–37.5) without significant intergroup differences ($p = 0.28$). The two groups were similar regarding disease severity (SOFA scores), type of admission (55 % medical), and concomitant organ failures (respiratory, cardiovascular, and renal function), but admission SAPS II score was significantly higher in the CI group ($p = 0.02$). Two patients receiving CI were anuric and underwent CVVHDF during all the infusion period Table 1.

Plasma pharmacokinetic parameters

Total and unbound LNZ plasma concentration versus time curves are shown in Fig. 1 for both groups. At steady

Table 1 Clinical and demographic data of the 22 enrolled patients

Patients' characteristics	II group ($n = 11$)	CI group ($n = 11$)	p value
Age, years	62.5 ± 10.5	64.7 ± 10.4	0.63
Male, *N* (%)	3 (27.3)	5 (45.5)	0.66
BMI, kg/m^2 (IQR)	33.3 (32.7–39.1)	33.1 (32.3–34.9)	0.28
SAPS II	42.7 ± 8.6	54.8 ± 12.5	0.02*
SOFA	6.4 ± 3.2	5.6 ± 2.8	0.68
Medical admission, *N* (%)	7 (63.6)	5 (45.5)	0.7
PaO_2/F_iO_2 ratio, mmHg (IQR)	184.6 (143.4–246)	289.5 (194–350.4)	0.13
Creatinine clearance, mL/min[a]	146.1 ± 60	149.2 ± 61	0.9
Septic shock, *N* (%)	6 (54.5)	6 (54.5)	1
Albumin concentration, g/dL	2.6 ± 0.5	2.5 ± 0.6	0.43
Gram-positive infection	5 (45.5)	2 (18.2)	0.36
Day 4 clinical improvement, *N* (%)	8 (72.7)	9 (81.8)	1
ICU mortality, *N* (%)	4 (36.4)	1 (9)	0.31

Data are expressed as mean ± SD unless otherwise indicated

II intermittent infusion, *CI* continuous infusion, *IQR* interquartile range *BMI* body mass index, *SAPS II* simplified acute physiology score II, *SOFA* sequential organ failure assessment, *ICU* intensive care unit

* $p < 0.05$

[a] Two patients on continuous renal replacement therapy (CRRT) are not included. Creatinine clearance was calculated according to the Cockcrocft–Gault formula

state, in the II group, mean ± SD $C_{max}/C_{max,u}$ and $C_{min}/C_{min,u}$ were 10 ± 3.7/6.8 ± 2.6 mg/L and 1.7 ± 1.1/1.2 ± 0.8 mg/L, respectively. In the CI group, the mean ± SD total and unbound plasma concentrations (C_{ss} and $C_{ss,u}$) were 6.2 ± 2.3 and 4.3 ± 1.6 mg/L, respectively. In the CI group, during all the infusion time, total LNZ plasma concentration was above 4 mg/L and unbound LNZ concentration above 2 mg/L. Otherwise, in the II group, $T >$ MIC (expressed as dosing intervals percentage) was significantly lower than in the CI group except for the 0.5 mg/L MIC value (total and unbound LNZ) and 4 mg/L MIC value (LNZ_u), Table 2.

Patients receiving CI, compared to those in the II group, had a significantly higher probability of target attainment (PTA) ($T > 85$ %) at the 2 mg/L MIC value for both total and unbound drug (100 vs 45.5 %, $p = 0.02$ and 90.9 vs 27.3 %, $p = 0.01$, respectively). Similar results were observed for $T > 100$ % PTA: 100 vs 45.5 %, $p = 0.02$ (total LNZ and 2 mg/L MIC); 72.7 vs 9.1 %, $p = 0.01$ (total LNZ and 4 mg/L MIC); 100 vs 36.4 %, $p = 0.01$ (LNZ_u and 1 mg/L MIC); 90.9 vs 27.3 %, $p = 0.01$ (LNZ_u and 2 mg/L MIC), Fig. 2.

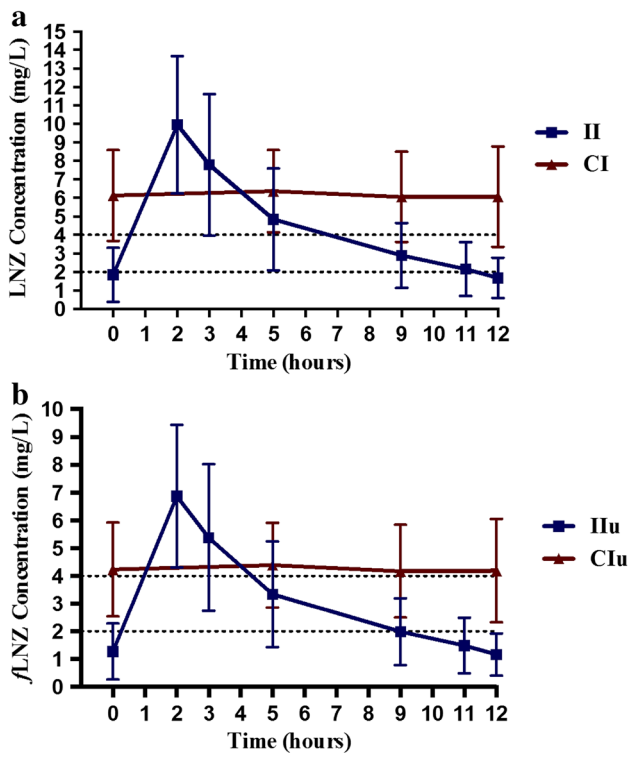

Fig. 1 **a** Total and **b** unbound linezolid plasma concentration (mean ± SD) versus time of administration by II (*blue lines* and *symbols*) and CI (*red lines* and *symbols*). *CI* continuous infusion total drug, CI_u continuous infusion unbound drug, *II* intermittent infusion total drug, II_u intermittent infusion unbound drug, *SD* standard deviation, *LNZ* linezolid. Samples were collected on day 3 of treatment

Comparing the two groups, patients receiving CI showed a trend toward higher mean ± SD $AUC_{0–24}$ and $AUC_{u,0–24}$ (146.3 ± 51.5 vs 110.6 ± 55.3 mg h/L, $p = 0.13$ and 101 ± 35.5 vs 76.34 ± 38.1, $p = 0.13$). Although not statistically significant, the percentage of patients with an $AUC_{0–24}$/MIC (2 mg/L) ratio ≥80 was higher in the CI group (36.3 vs 18.2 %, $p = 0.64$), Table 2. For patients receiving II, V_d, CL, and $t_{1/2}$ were 45.1 ± 18 L, 14.3 ± 7 L/h, and 2.4 ± 1 h, respectively.

In the two patients undergoing CRRT during CI, CL_{CVVHDF}, C_{ss}, and $AUC_{0–24}$ were 2.4/0.67 L/h, 4.1/5.6 mg/L, and 101.1/134.9 h, respectively. The exclusion of these subjects from the CI group did not significantly change the PK results (see Table 1 in the ESM). Creatinine clearance in the remaining 20 patients was between 40 and 80 mL/min in two subjects (one for each group) and more than 120 mL/min in 13 subjects (5 in the CI group and 8 in the II group).

ELF penetration

Fourteen out of 22 patients underwent LNZ ELF concentrations determination: 7 in the CI group and 7 in the II group. LNZ did diffuse well into the lungs and the ELF/plasma penetration ratio (%) was slightly higher in the CI group [106 (IQR 71.6–116) vs 80 (IQR 56.6–130.5); $p = 0.46$].

However, using a Monte Carlo simulation, a significant difference was observed in the ELF/plasma penetration ratio (%) between the two groups [CI group, 98.8 (IQR 93.8–104.3) vs II group, 87.1 (IQR 78.7–95.4); $p < 0.001$] (Fig. 3).

Discussion

In critically ill obese patients with VAP, LNZ CI was more effective than II in obtaining PD parameters that predict its in vivo activity, even though for AUC/MIC the difference did not reach statistically significant power. Intrapulmonary drug penetration was optimal in both groups, but CI appeared to have a better distribution in the lung.

Critically illness status may strongly influence the PK profile of many antibiotics. Variations of extracellular fluids and renal clearance are the main determinants of antimicrobial drug distribution and elimination [14].

In our II group, C_{max} and C_{min} were remarkably low, and the $AUC_{0–24}$ and $T >$ MIC values were inadequate to optimally treat MRSA strains with high MICs (2–4 mg/L). Our results are consistent with a randomized controlled trial which compared LNZ CI vs II in 16 septic patients [18], wherein Adembri et al. observed that in all the subjects receiving standard intermittent dosing the

Table 2 Steady-state serum and alveolar LNZ PK/PD parameters in the 22 enrolled patients

Parameter	II group ($n = 11$)	CI group ($n = 11$)	p value
V_d, L	45.1 ± 18.2	–	–
CL, L/h	14.3 ± 6.8	–	–
$t_{1/2}$, h	2.4 ± 0.8	–	–
C_{max}, mg/L	10 ± 3.7	–	–
$C_{max,u}$, mg/L	6.8 ± 2.6	–	–
C_{min}, mg/L	1.7 ± 1.1	–	–
$C_{min,u}$, mg/L	1.2 ± 0.8	–	–
C_{ss}, mg/L	–	6.2 ± 2.3	–
$C_{ss,u}$, mg/L	–	4.3 ± 1.6	–
ELF/plasma ratio (%), median (IQR)	80 (56.6–130.5)	106 (71.6–116)	0.46
C_{maxELF}, median (IQR)[a]	8.3 (6.7–9.8)	–	–
$C_{ss>ELF}$, median (IQR)[b]	–	5.3 (3.8–7.6)	–
$AUC_{0–24}$, mg h/L	110.6 ± 55.3	146.3 ± 51.5	0.13
$AUC_{u,0–24}$, mg h/L	76.3 ± 38.1	101 ± 35.5	0.13
$AUC_{0–24}$/2 mg/L MIC, h	55.3 ± 27.6	73.2 ± 25.7	0.13
$AUC_{u,0–24}$/2 mg/L MIC, h	38.2 ± 19.1	50.5 ± 17.8	0.13
$AUC_{0–24}$/2 mg/L MIC ≥ 80, %	18.2	36.3	0.64
$AUC_{u,0–24}$/2 mg/L MIC ≥ 80, %	0	0	–
% $T > 0.5$ mg/L MIC, median (IQR)	100 (97.1–100)	100 (100–100)	0.23
% $T_u > 0.5$ mg/L MIC, median (IQR)	100 (96.8–100)	100 (100–100)	0.22
% $T > 1$ mg/L MIC, median (IQR)	100 (89–100)	100 (100–100)	0.05*
% $T_u > 1$ mg/L MIC, median (IQR)	96.7 (68–100)	100 (100–100)	0.003*
% $T > 2$ mg/L MIC, median (IQR)	82 (54.8–98.8)	100 (100–100)	0.009*
% $T_u > 2$ mg/L MIC, median (IQR)	66.3 (39.3–95.8)	100 (100–100)	0.006*
% $T > 4$ mg/L MIC, median (IQR)	33 (30.2–78.5)	100 (74.2–100)	0.005*
% $T_u > 4$ mg/L MIC, median (IQR)	21.2 (16.3–55.3)	0 (0–100)	0.72

Data are expressed as mean ± SD unless otherwise indicated
LNZ linezolid, *PK/PD* pharmacokinetic/pharmacodynamic, *II* intermittent infusion, *CI* continuous infusion, V_d volume of drug distribution, *IQR* interquartile range, *CL* drug clearance, $t_{1/2}$ elimination half-life, C_{max} peak plasma concentration, C_{min} trough plasma concentration, $C_{max,u}$ unbound peak plasma concentration, $C_{min,u}$ unbound trough plasma concentration, C_{ss} steady-state plasma concentration, $C_{ss,u}$ unbound steady-state plasma concentration, *ELF* epithelial lining fluid, *MIC* minimum inhibitory concentration, AUC/AUC_u total drug/unbound area under the time–concentration curve, $T > MIC$ time above the minimum inhibitory concentration, $T_u > MIC$ time above the minimum inhibitory concentration (unbound fraction), – not applicable, *BAL* brochoalveolar lavage
* $p \leq 0.05$
[a] BALs were collected in 7 patients 2 h after of the fifth infusion (peak concentration on day 3 of treatment)
[b] BALs were collected in 7 patients on day 3 of treatment at the mid-interval (53 or 57 h)

mean trough levels (both total and free) were below 4 mg/mL and in half of them less than 1 mg/L. On the other hand all the patients in the CI group showed unbound and total LNZ C_{ss} above the susceptibility threshold. In our patients undergoing CI, although not significantly, mean $AUC_{0–24}$ values for both total and unbound LNZ were higher than in the II group, showing values about 100 mg h/L. In the same way, CI provided significantly higher $T >$ MIC and PTA than II, but these advantages were not so evident for the extreme values of the MIC susceptibility range (0.5 mg/L and 4 mg/L).

In our study LNZ $t_{1/2}$ was lower than previously reported in healthy subjects (2.4 ± 0.8 h). However many pathophysiological changes (i.e., increased cardiac output, leaky capillaries, augmented renal clearance, low protein concentration and altered bounding) occurring in severe critically ill patients may modify antibiotics' PKs, increasing their body clearance. Indeed, septic patients studied by Adembri et al. showed similar $t_{1/2}$ values (3.5 ± 2.2 h).

Continuous infusion is a simple strategy to optimize the duration of exposure above the MIC for time-dependent antibiotics. Concentrations up to 4–5 times the MIC, increasing the AUC value, may maximize killing activity, but higher values do not add any benefits [30]. Few data are available on LNZ CI use. In addition to the study by Adembri et al. the only other report addressing this issue was recently published by Boselli et al. [13]. These authors, in a cohort of 12 ICU patients undergoing LNZ CI, described C_{ss}, $AUC_{0–24}$ and alveolar penetration values similar to those we observed in our cohort [7.1 mg/L (6.1–9.8), 169 mg h/L (146–235), 97 % (80–108), respectively] [13]. However in this study neither obese nor hyperfiltrating patients were included and no detail about their severity degree was provided (i.e., SOFA score, presence of septic shock).

Our critically ill patients were moderately obese [median BMI (IQR) 33.2 kg/m^2 (32.6–37.5)]. Obesity may significantly influence antibiotics' PK, but few clinical data are available in this field. V_d is modified by

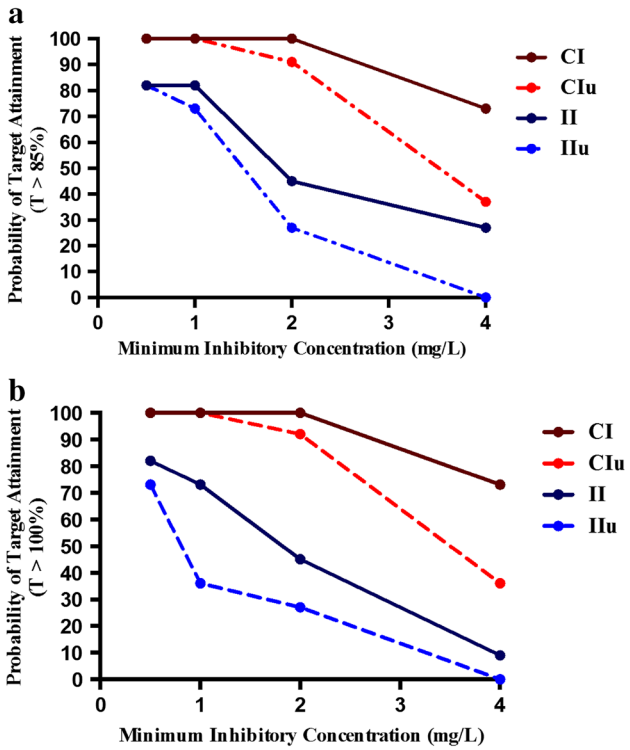

Fig. 2 Probability of target attainment of pharmacodynamic indices (**a** 85 % $T > \text{MIC}$, **b** 100 % $T > \text{MIC}$) in plasma for intermittent infusion and continuous infusion (unbound and total drug). *CI* continuous infusion total drug, CI_u continuous infusion unbound drug, *II* intermittent infusion total drug, II_u intermittent infusion unbound drug, *MIC* minimum inhibitory concentration. Samples were collected on day 3 of treatment

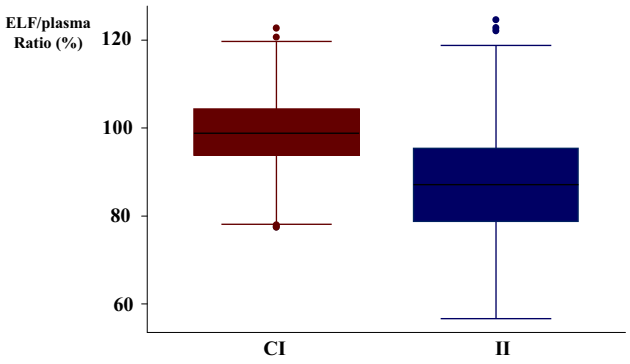

Fig. 3 *Box plot* showing percentage differences between II and CI LNZ ELF/plasma ratio. The results are based on a Monte Carlo simulation with 1,000 iterations. *Boxes* represent interquartile ranges (*lower border* 25th percentile; *upper border* 75th percentile), and the *horizontal lines* within the boxes indicate the medians (50th percentile). Whiskers indicate minimum and maximum values. *CI* continuous infusion total drug, *II* intermittent infusion total drug, *ELF* epithelial lining fluid. Samples were collected on day 3 of treatment

the increase in both lean body weight and adipose tissue. Furthermore kidney mass and the correspondent global filtration may influence drugs' CL. Linezolid is a moderately lipophilic drug and, in our patients, both critically ill status and obesity could have impaired the PK profile during II administration. This detrimental effect was blunted by the adoption of continuous infusion.

Subtherapeutic LNZ concentrations have been reported after bolus administration in obese patients. Both increased CL and V_d have been previously observed [23, 31]. Different results were recently shown after orally intermittent LNZ administration to 20 healthy obese (moderately and morbidly) volunteers [22]. In that paper mean ± SD $AUC_{0–12}$ and C_{max} values (119.8 ± 46.24 mg h/L and 19.8 ± 4 mg/L, respectively) were adequate to ensure optimal bacterial killing and mean ± SD V_d value (44.1 ± 9.9 L) was comparable to normal weight subjects. In any case, a significant positive relationship between the body weight and AUC values was found ($r^2 > 0.5$). Our data are partially in accordance with what was stated previously. After II, we observed lower C_{max}, C_{min}, and $AUC_{0–24}$ than previously reported but the V_d was not so increased (45.1 ± 18.2 L). This finding may be explained by the low obesity degree of our patients whose total body weight was less than 150 kg [32]. On the other hand our patients showed high creatinine clearance values which certainly have contributed to the low observed LNZ concentrations in the II group. However calculated creatinine clearance may be not appropriate to identify augmented renal clearance in septic patients. Additionally our results may not be applied to morbidly obese patients where a larger V_d is supposed to further modify LNZ PK.

Our report is the first to investigate LNZ pulmonary distribution in obese critically ill patients according to infusion modality. It is well known that LNZ optimally penetrates the lung and this PK property has been recently confirmed in 12 critically ill patients receiving CI [13]. Our study confirms this PK property, in a population of moderately obese critically ill patients receiving either II or CI infusion. However, after performing a Monte Carlo simulation, CI was associated with a higher median ELF/plasma ratio percentage [CI group, 98.8 (IQR 93.8–104.3) vs II group, 87.1 (IQR 78.7–95.4); $p < 0.001$], resulting in ELF C_{ss} above 4 mg/L in all studied patients. However, the limited number of analyzed samples (7 for each group) and the absence of $AUC_{0–24}$ data (every patient underwent a single BAL sampling) certainly reduce the significance of the difference showed by our simulation.

Mean SAPS II values were not similar between the two groups. The presence of few outliers in a small sample sized PK study is the main reason for this heterogeneity. However, the most relevant clinical variables that correlated with our endpoint (BMI, septic shock, albumin concentration, renal function) were homogeneously distributed.

Finally we did not identify any LNZ-related AE. This is not surprising, since the observed concentrations were far from the safety thresholds (C_{min} 10 mg/L and AUC_{0-24} 400 mg h/L) [10, 11]. In addition we excluded patients who were receiving drugs which could interfere with LNZ metabolism.

This study has some limitations. First, our population was represented by moderately obese patients and the results may not be generalized to subjects with BMI higher than 40 kg/m^2. Secondly, we could perform only 14 out of the 22 planned BALs. Thirdly, the number of Gram-positive VAP, the duration of CI administration, and some baseline differences (i.e., SAPS II, PaO_2/F_iO_2 ratio) do not allow us to address any conclusive clinical consideration.

However, to the best of our knowledge, this is the first randomized trial investigating the plasma and pulmonary PK profile of LNZ CI administration, compared to II, in critically ill obese patients with VAP.

Conclusions

In summary, II LNZ administration in obese critically ill patients with VAP is associated with suboptimal plasma concentrations. CI administration is able to safely improve the LNZ PK profile but it may still be inadequate for the management of difficult to treat germs (i.e., MRSA with a MIC of 4 mg/L). Critically ill status and obesity do not strongly affect pulmonary distribution but CI provides a higher alveolar penetration ratio. Clinical trials are needed to verify the potential clinical advantages of LNZ CI in ICU patients at risk of antibiotic underexposure.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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