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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 ($T > \text{MIC}$) and area under the serum concentration-time curve/minimum inhibitory concentration (AUC/MIC) ratio [1]. Linezolid is mainly a bacteriostatic antimicrobial agent with $T > \text{MIC}$ 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 $T > \text{MIC}$ was maintained for >75 % of the dosing interval [4]. On the basis of these considerations, achieving $T > \text{MIC}$ 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/m² (range 16–35 kg/m²), 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 anti-infective 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

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
<i>Staphylococcus aureus</i> with MIC to linezolid >2 μ g/ml

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].

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 sub-optimal 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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