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Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion☆

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Abstract

Pharmacokinetics and pharmacodynamics are significantly altered in critically ill septic patients and the risk of prolonged periods with concentrations below the minimum inhibitory concentration (MIC) and of low area under the serum concentration–time curve/MIC (AUC/MIC) ratios is of concern. We compared the pharmacokinetic/pharmacodynamic (PK/PD) profile of linezolid administered by intermittent or continuous infusion in critically ill septic patients. Patients were divided into two groups: intermittent infusion (Group I) (600 mg/12 h); or continuous infusion (Group C) (300 mg intravenous loading dose +900 mg continuous infusion on Day 1, followed by 1200 mg/daily from Day 2). Linezolid serum levels were monitored for 72 h and microbiological data were collected. The clinical outcome was monitored. Sixteen patients completed the study. MICs of susceptible pathogens were 2 mg/L for 80% of the isolates. In Group I, linezolid trough serum levels (C_{min}) varied widely and were below the susceptibility breakpoint (4 mg/L) during the study period; in 50% of patients C_{min} was <1 mg/L. In Group C, mean linezolid serum levels were more stable and, starting from 6 h, were significantly higher than C_{min} levels observed in Group I and were always above the susceptibility breakpoint. Time that the free drug concentration was above the MIC ($T_{free} > MIC$) of > 85% was more frequent in Group C than in Group I ($P < 0.05$). Finally, with continuous infusion it was possible to achieve AUC/MIC values of 80–120 more frequently than with intermittent infusion ($P < 0.05$). According to PK/PD parameters, continuous infusion has theoretical advantages over intermittent infusion in this population of patients.

Keywords: Linezolid; Pharmacokinetics; Pharmacodynamics; Sepsis; Critically ill patients; Continuous infusion

1. Introduction

Linezolid, an oxazolidinone derivative, has been shown to be a valid therapeutic alternative to glycopeptides against multiresistant Gram-positive strains, which are particularly frequent in Intensive Care Units (ICUs) [1–3]. Consistent with in vitro findings, linezolid is a time-dependent antimicrobial agent with persistent post-antibiotic effect [4]. The pharmacokinetic/pharmacodynamic (PK/PD) parameters best suitable 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 [5]. In vitro time–kill experiments have demonstrated linezolid to be a bacteriostatic antimicrobial agent with $T > MIC$ of at least 40% being predictive of efficacy. However, in an in vivo model of endocarditis, when serum levels higher than the MIC were maintained for >75% of the dosing interval, linezolid also demonstrated bactericidal activity [6]. Linezolid serum levels with $T > MIC$ of >50% for pathogens with MICs of 2–4 mg/L can be obtained by administration of 600 mg every 12 h (q12h)

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in healthy volunteers [7], suggesting that continuous infusion (the best antimicrobial administration modality for most time-dependent antibiotics as it prolongs effective serum levels [8]) may not be essential. However, in critically ill septic patients alterations in PK parameters, mostly due to an increase in the volume of drug distribution (V) and/or drug clearance (CL), are frequently observed, and suboptimal serum and tissue concentrations are achieved when drugs are administered at the same dosage studied in healthy volunteers or in less seriously ill patients (for review see [9,10]). Moreover, since critically ill septic patients are often immunosuppressed [11–13], antimicrobials with bactericidal activity may be more effective than those exhibiting only bacteriostatic activity. On the basis of these considerations, it is important to optimise PK/PD parameters. Accordingly, in one study conducted in seriously ill adult patients, higher success rates were achieved when $T > \text{MIC}$ exceeded 85% and AUC/MIC values were between 80 and 120 [5].

To date, few data are available regarding the PK/PD of linezolid in critically ill septic patients and the drug is thus administered according to data obtained in healthy subjects or other types of patients. However, there is high interindividual variability in linezolid interstitial concentrations in patients with sepsis or septic shock, suggesting that a scheme of more frequent daily dosing would be more appropriate in these patients [14]. Therefore, in this study we compared two different modalities of linezolid administration (intermittent versus continuous infusion) in critically ill septic patients to establish which is better according to the PK/PD profile.

2. Patients and methods

This was a prospective, open-label, randomised study performed in a university hospital ICU. Written informed consent was obtained from all study participants.

2.1. Patients

Septic ICU patients with a microbiologically documented infection caused by either glycopeptide-resistant or glycopeptide-sensitive Gram-positive strains but with no clinical improvement after 5 days of glycopeptide therapy were considered eligible for enrolment in the study. Sepsis was defined as systemic inflammatory response to infection as stated by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee [15,16].

Exclusion criteria were the following: age <18 years; pregnancy; previous known allergic reaction to linezolid; creatinine clearance (Cl_{CR}) <40 mL/min, calculated according to the Cockcroft–Gault formula [17]; platelet count <80 000; and the simultaneous administration of other drugs (such as erythromycin) capable of interfering with the linezolid assay. Simultaneous use of antimicrobials against Gram-negative strains and/or fungi was not considered an exclusion criterion.

2.2. Study design

Enrolled patients ($n = 18$) were randomly (by the closed envelope method) divided into two groups according to linezolid administration modality (total daily dose 1200 mg): Group I ($n = 9$) received linezolid as a 30-min intermittent intravenous (i.v.) administration (600 mg q12h); and Group C ($n = 9$) received linezolid as 300 mg i.v. loading dose (given in 30 min) + 900 mg continuous infusion on Day 1, followed by continuous infusion of 1200 mg/daily. In both groups of patients, linezolid administration started as soon as entry criteria were satisfied.

Clinical patient data as well as diagnosis at ICU admission were recorded. Predicted mortality rates were calculated according to the Simplified Acute Physiology II Score (SAPS II) [18]. To assess and compare organ dysfunction in the two groups of patients, the Sequential Organ Failure Assessment (SOFA) score [19] was calculated for each patient at study entry. Platelets and white cells were assessed daily.

The global response to therapy was graded as 'clinical success' if there was improvement or resolution of signs and symptoms of diseases noted at enrolment and 'clinical failure' if there was persistence of presenting signs and symptoms and/or new unfavourable findings related to efficacy measures subsequent to study entry. In addition to linezolid, patients in both groups received standard therapy for the treatment of sepsis according to published guidelines [20]. Fluid replacement was performed with crystalloids and colloids according to clinical need. Microbiological cultures were obtained from blood or any other suspected site of infection prior to the first dose of linezolid. The presence of vancomycin-resistant Gram-positive strains or the presence of vancomycin-sensitive strains with no response to therapy was an entry criterion to the study. The MICs of the most common antimicrobials and linezolid for the isolates were obtained using the automated VITEK® system (bioMérieux Inc., Roma, Italy) and vancoscreen agar was used to confirm enterococcal resistance to vancomycin. Microbiological efficacy was determined at the end of treatment by repeating microbiological culture of the previously sampled site. Results were described as 'eradication' if the original isolate was no longer present, 'failure' if there was persistence or re-appearance of the previous phenotypic isolate and 'not evaluable' when there were no available follow-up data.

2.3. Sampling times

To assess linezolid serum levels, 4 mL of blood was drawn from an arterial line placed contralaterally to the i.v. infusion site, centrifuged at 4000 rpm at 4 °C for 10 min and then stored at −80 °C until assayed. Samples were collected at the following times:

- Group I: T_0 (baseline) and 0.5, 1, 2, 3, 6, 12, 12.5, 18 and 24 h after the first dose and then at each peak/trough for the remaining times for 72 h; and