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Clinical pharmacokinetic/pharmacodynamic profile of linezolid in severely ill Intensive Care Unit patients

Haiyan Dong[a,1], Xue Wang[b,1], Yalin Dong[a,*], Jin'e Lei[c], Hao Li[b], Haisheng You[a], Maoyi Wang[a], Jianfeng Xing[d], Jinyao Sun[a], Huifang Zhu[a]

[a] Department of Pharmacy, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
[b] Central Intensive Care Unit, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
[c] Department of Laboratory, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China
[d] Department of Pharmacy, Medical School of Xi'an Jiaotong University, Xi'an 710061, China

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ABSTRACT

Severely ill Intensive Care Unit (ICU) patients have an increased risk of developing multiresistant Gram-positive infections, largely due to the inappropriate use of antimicrobials. In this study, the pharmacokinetic/pharmacodynamic (PK/PD) profile of linezolid, an antibiotic against Gram-positive infections, was characterised in eight critically ill patients admitted to the ICU. Remarkable variation amongst patients in the PK parameters of linezolid was observed, including a 5–7-fold difference in peak serum concentration (C_{max}) (mean ± standard deviation 15.70 ± 6.58 mg/L) and 12-h area under the serum concentration–time curve (AUC_{0-12}) (96.73 ± 56.45 mg h/L), although the minimum inhibitory concentration (MIC) was similar amongst patients. In particular, variation amongst patients was found in the ratio of AUC_{0-24}/MIC (range 31.66–216.82, mean 96.73) and the percentage of time that the serum concentration exceeded the MIC (T > MIC) (range 53.4–100%), two parameters used to predict linezolid efficacy. These variations highlight the importance of individual monitoring of linezolid PK/PD properties in critically ill patients. Furthermore, it was observed that regardless of AUC_{0-24}/MIC and T > MIC values, the clinical and microbiological responses of patients were primarily affected by the individual's pathophysiological condition. In summary, these findings point to highly variable PK/PD properties of linezolid in severely ill patients, providing the rationale for targeting linezolid dosage to each individual patient's specific properties. An optimal dosage regimen based on individual PK/PD properties and pathophysiological conditions will help reduce the occurrence of resistance in Gram-positive bacteria.

1. Introduction

Severely ill patients in the Intensive Care Unit (ICU) are often at risk of developing multiresistant Gram-positive bacterial infections. In fact, the growing incidence of the appearance and spread of multiresistant Gram-positive infections in the ICU constitutes a significant health problem in many countries [1,2]. In developed countries, up to 52% of ICU patients with bacteraemia have attributable mortality, more than two-fold that of the general population (23%) [1]. Incorrect use of antimicrobials is a major risk factor contributing to the generation of multidrug-resistant microorganisms, thereby resulting in increased morbidity, mortality and costs [3].

Linezolid is a synthetic antimicrobial agent of the oxazolidinone class of antibiotics used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics. As the first US Food and Drug Administration (FDA)-approved oxazolidinone, linezolid has a broad spectrum of activity against Gram-positive bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant pneumococci and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* [4–7]. Recent studies have indicated that linezolid treatment for high-incidence ICU infections, including pneumonia and catheter-related bacteraemia, resulted in favourable clinical and microbiological responses [8–10]. However, organisms resistant to linezolid have emerged [11,12], which could result in an increase in attributable mortality and morbidity in ICU patients.

Increased knowledge of the pharmacokinetic/pharmacodynamic (PK/PD) properties of antibiotics is useful for optimising dosage. In particular, the ratio of the area under the serum concentration–time curve over 24 h divided by the minimum inhibitory concentration (AUC_{0-24}/MIC) as well as the percentage

* Corresponding author. Tel.: +86 29 8532 3243; fax: +86 29 8532 3241.
E-mail addresses: dongyalin@medmail.com.cn, dongyalin@mail.xjtu.edu.cn (Y. Dong).
[1] These two authors contributed equally to this work.

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of time that the drug concentration exceeds the MIC (T > MIC) are considered predictive parameters for the antimicrobial effect of linezolid. Previous studies in animal models suggest that linezolid has an increased antimicrobial effect against *Streptococcus pneumoniae* when linezolid free-fraction PD parameters (fT > MIC and fAUC$_{0-24}$/MIC) reach >40% and range from 48 to 147, respectively [13]. However, in the case of severely ill patients, multiple pathophysiological factors could interfere with the PK/PD properties of drugs.

For instance, patients with major thermal injuries had increased non-renal clearance, which may result in PK alteration [14]. In addition, previous work has shown that clearance of linezolid was increased and that there was larger individual variability in dialysis patients [15]. Indeed, studies performed in severely ill patients indicate that the probability of eradication and clinical cure at specific infection sites was correlated with AUC$_{0-24}$/MIC and T > MIC values [16,17]. Specifically, higher success rates for linezolid treatment may occur at AUC$_{0-24}$/MIC values of 80–120 and T > MIC values >85% [16]. Therefore, the aim of this study was to evaluate the PK/PD profile of linezolid in severely ill Chinese ICU patients.

2. Materials and methods

2.1. Patients and experimental design

Patients in the ICU of The First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) were included in this study and were selected according to the following criteria: (i) males or non-pregnant females aged ≥18 years with suspected or documented Gram-positive infections, including meticillin-sensitive *S. aureus*, MRSA, enterococci and coagulase-negative staphylococci; (ii) no allergies to linezolid; (iii) not currently exposed to other drugs that may interfere with the analysis of linezolid; and (iv) simultaneous use of antimicrobials against Gram-negative strains and/or fungi was not considered as an exclusion criterion. Prior to the study, and after all patients were informed of the study details, written informed consent was obtained from all patients. When the subject was unable to provide legally effective consent, written informed consent was obtained from a close relative. The study protocol was approved by the Hospital Ethics Committee.

All patients enrolled in the study were given an intermittent intravenous (i.v.) 600 mg dose of linezolid twice daily. Clinical diagnosis and laboratory analysis were performed daily to monitor hepatic and renal function and haemograms. The severity of the patient's condition was determined using the Acute Physiology and Chronic Health Evaluation (APACHE) II score. To assess renal function, serum creatinine concentrations were determined and the creatinine clearance (CL_{Cr}) rate was estimated by the Cockcroft–Gault equation [18]. Although the Cockcroft–Gault equation has some limitations, such as the requirement of a stable body state and lack of a body surface area correction, it is still widely used for calculating CL_{Cr}. Patients were considered to have normal renal function when the CL_{Cr} was >50 mL/min, moderately impaired renal function when the CL_{Cr} was 20–50 mL/min and total renal failure when the CL_{Cr} was <20 mL/min.

2.2. Evaluation of therapeutic efficacy

Before the start of treatment, patient specimens were collected from suspected or documented infection sites and were examined to identify the causative organisms and to perform sensitivity testing. For patients with pathogens sensitive to linezolid, the MIC was measured. A VITEK 2 automated system (bioMérieux, Lyon, France) was used for rapid microbial identification, followed by determination of MIC values by Etest (AB BIODISK, Solna, Sweden). Testing was performed according to the manufacturer's guidelines, and all required quality control tests were included. Bacterial eradication was evaluated by comparing the microbiological culture of samples from the same patient prior to and after treatment. Relief from symptoms was considered to be clinical cure, whilst patients with sustained or reoccurring infections were considered as failing to respond.

2.3. Measurement of serum linezolid concentrations

Venous blood samples were collected prior to the first administration (0 h) and at 0.5, 1, 2, 3, 6, 10 and 12 h after the first administration of linezolid. In addition, 1 mL of venous blood was collected at each peak/trough for the remaining times for 72 h. Samples were centrifuged at 4000 rpm for 10 min and the supernatant was collected and stored at −80 °C for further analysis. The total concentration of linezolid was detected using a high-performance liquid chromatography (HPLC) assay as previously described [19]. Briefly, samples were prepared by mixing the specimen with methanol (1:1) and allowing this mixture to rest at room temperature for 20 min, followed by centrifugation at 10 000 rpm for 10 min. Then, 50 μL of supernatant was injected. The stationary phase was a Hypersil C18 column (150 mm × 4.6 mm, 5 μm; Waters Corp., Milford, MA). The mobile phase consisted of a mixture of acetonitrile:water (23:77, v/v) adjusted to pH 5.0 by addition of phosphoric acid. The pump flow rate was 1.0 mL/min. Ultraviolet absorbance detection was used (λ_{max} = 254 nm). Validation of the method yielded satisfactory results (r = 0.9996). The linear range of linezolid concentration was between 0.31 mg/L and 20 mg/L. The limit of linezolid quantification in serum was 0.31 mg/L. The intra-day and interday coefficients of variation were less than 4% and 3.5%, respectively. Linezolid was stable after storage at room temperature for 24 h, freezing for 20 days or 40 days, or after three freeze–thaw cycles.

2.4. Statistical analysis

Unless otherwise specified, data represent the mean ± standard deviation (S.D.). The concentration of linezolid in this study represents serum concentrations measured by HPLC. PK parameters were determined using DAS 2.0 software v2 (Mathematical Drug and Pharmacology Professional Committee of China, Shanghai, China), and a statistical moments analysis PK model was fitted. Numerical integration of the fitted functions was used to generate the area under the concentration–time curve over 12 h (AUC$_{0-12}$), the AUC$_{0-24}$/MIC ratio and T > MIC. AUC$_{0-24}$ was calculated as AUC$_{0-24}$ = 2 × AUC$_{0-12}$ [20].

3. Results

3.1. Study population

Characteristics of the eight critically ill patients with Gram-positive bacterial infections included in the study are shown in Table 1.

3.2. Pharmacokinetics

First, the dynamic serum concentration of linezolid was monitored at baseline and at 0.5, 1, 2, 3, 6, 10 and 12 h after the first administration (Fig. 1). As shown in Fig. 1, the linezolid concentration reached a peak serum concentration (C_{max}) at 1.4 h following administration. The average C_{max} of all the patients tested was 15.70 ± 6.58 mg/L. Thereafter, the concentration gradually declined until the trough serum concentration (C_{min}) (4.10 ± 4.99 mg/L) was