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Analysis of thrombocytopenic effects and population pharmacokinetics of linezolid: a dosage strategy according to the trough concentration target and renal function in adult patients

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ABSTRACT

The pharmacokinetic/pharmacodynamic (PK/PD) index for the efficacy of linezolid is a 24-h area under the plasma drug concentration–time curve (AUC_{24})/minimum inhibitory concentration (MIC) ratio of ≥100. The main adverse event associated with administration of linezolid is thrombocytopenia. Therefore, the aims of the present study were to define PD thresholds that would minimise linezolid-induced thrombocytopenia and to perform a population PK analysis to identify factors influencing the pharmacokinetics of linezolid. Population PK analysis revealed that creatinine clearance (CL_{Cr}) significantly affected linezolid pharmacokinetics: the mean parameter estimate of drug clearance (CL; in L/h) = 0.0258 × CL_{Cr} + 2.03. A strong correlation (r = 0.970) was found between AUC_{24} and trough plasma concentrations (C_{min}) [AUC_{24} = 18.2 × C_{min} + 134.4]. The C_{min} value for AUC_{24} = 200 (in the case of MIC = 2 μg/mL) was estimated to be 3.6 μg/mL. Regarding safety, C_{min} was a significant predictor of thrombocytopenia during treatment, and its threshold to minimise linezolid-induced thrombocytopenia was 8.2 μg/mL. A Kaplan–Meier plot revealed that the median time from initiation of therapy to the development of thrombocytopenia was 15 days. Therefore, the target C_{min} range was 3.6–8.2 μg/mL. The following formula to achieve a target C_{min} in patients with different degrees of renal function was proposed based on these results: initial daily dose (mg/day) = CL × AUC_{24} = (0.0258 × CL_{Cr} + 2.03) × (18.2 × C_{min} + 134.4). This recommended initial dosage and subsequent dosage adjustment for the target concentration range should avoid adverse events, thereby enabling effective linezolid-based therapies to be continued.

1. Introduction

Linezolid is a member of the oxazolidinone class of synthetic antibacterial agents. It exhibits a broad spectrum of activity against Gram-positive bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. The pharmacokinetic/pharmacodynamic (PK/PD) index for the efficacy of linezolid was previously shown to be a 24-h area under the plasma drug concentration–time curve (AUC_{24})/minimum inhibitory concentration (MIC) ratio of ≥100 [1–3].

The main adverse event associated with administration of linezolid is reversible myelosuppression, mostly thrombocytopenia [4–6]. Several studies reported that the incidence of linezolid-induced thrombocytopenia was high (7.5–64.7%) [4,7–15]. Risk factors for the development of thrombocytopenia during linezolid therapy include impaired renal function [7,8,10,11,16–20], chronic liver disease [20,21], the duration of linezolid therapy (≥14 days) [6,7] and respiratory tract infection [7]. Furthermore, recent studies reported that the incidence of linezolid-induced thrombocytopenia was significantly higher in patients with impaired renal function than in patients with normal renal function [7,8,16,17]. The incidence of severe thrombocytopenia (<100 000/mm^3) in 62 patients treated with linezolid for >2 weeks was 64.7% in patients with renal insufficiency compared with 35.6% in the control group (P = 0.039) [8]. Wu et al. conducted a retrospective case–control study and observed a higher incidence of severe thrombocytopenia in patients with end-stage renal disease (ESRD) than in subjects with non-ESRD (78.6% vs. 42.9%; P = 0.03) [16]. We also previously demonstrated that pre-treatment values for both creatinine clearance (CL_{Cr})

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and blood urea nitrogen (BUN) were associated with a linezolid-induced low platelet count, which suggested that renal function is a predictor of linezolid-induced thrombocytopenia [22]. Meagher et al. reported that linezolid clearance could be described by a model involving two elimination pathways (parallel linear renal clearance and Michaelis–Menten non-renal clearance) and showed that higher linezolid concentrations in patients with reduced renal clearance saturated the non-renal pathway [23]. Accumulation of linezolid in patients with insufficient renal function causes the saturation of non-renal clearance; therefore, the contribution of the renal pathway is relatively high. Plock et al. investigated the mechanism underlying the non-linearity of linezolid clearance using a population PK modelling approach and suggested that this non-linearity may be attributed to the inhibition of metabolism by linezolid itself [24]. Furthermore, we provided a PK explanation for the mechanism of the adverse event in which impaired renal function increased the trough plasma concentration (C_{min}) and AUC_{24} of linezolid, with the result that exposure to higher drug concentrations induced thrombocytopenia; however, the number of patients (nine) examined was too small for statistical analysis [18]. The threshold C_{min} and AUC_{24} to minimise linezolid-induced thrombocytopenia as well as the dosage to achieve AUC_{24}/MIC of $\geq$100 for a therapeutic response in patients with impaired renal function have yet to be determined. Cossu et al. suggested that further studies should be encouraged to determine whether the incidence of linezolid-related thrombocytopenia could be reduced by dosage adjustments according to renal function, for which there is currently no specific recommendation [25].

The present study aimed to define PD thresholds that could minimise linezolid-induced thrombocytopenia by assessing the relationship between exposure to linezolid and decreases in the platelet count in adult patients. This study also aimed to conduct population PK analysis to identify factors influencing linezolid pharmacokinetics and to confirm the need for dosage adjustment based on linezolid plasma levels.

2. Patients and methods

2.1. Patients

This study was approved by the Ethics Review Board of Kagoshima University Hospital (Kagoshima, Japan). Written informed consent was obtained from 44 adult patients who were administered linezolid between October 2008 and March 2013 at Kagoshima University Hospital.

2.2. Drug administration and sample collection

All patients were administered 300 mg or 600 mg of linezolid twice daily intravenously or orally. On Days 3–14 [mean ± standard deviation (S.D.) 5.8 ± 2.2 days] after the initial administration (under steady-state conditions), venous blood samples were drawn just before the next administration (C_{min}) and just after the end of the 1-, 1.5- or 2-h infusion or 2 h after the oral administration (approximately the peak concentration).

2.3. Measurement of linezolid plasma concentrations

Linezolid plasma concentrations were measured by high-performance liquid chromatography (HPLC) with minor modifications to the methods described by Borner et al. [26]. The analytical column was a Mightysil RP-18 (5 μm, 250 mm × 4.6 mm) (Kanto Chemical Co., Tokyo, Japan), the ultraviolet wavelength for linezolid was 251 nm, and the mobile phase consisted of 0.1 M acetate buffer (pH 3.5):acetonitrile:water = 2.5:1:6.5. The lowest detectable concentration of linezolid was 0.2 mg/L. The intraday and interday accuracy (as absolute values of the relative errors of the means) and precision [as coefficient of variation (CV) values] were within 10%.

2.4. Population pharmacokinetic modelling

All PK data were modelled with a one-compartment PK model with a first-order absorption process, using the first-order conditional estimation method in the NONMEM program v.7.2.0 (ICON Development Solutions, Ellicott City, MD). The structural parameters used were the volume of distribution (V; in L) and drug clearance (CL; in L/h). Interindividual variability was modelled exponentially: $\theta_i = \theta \times \exp(\eta_i)$, where θ_i is the fixed-effects parameter for the i-th subject, θ is the mean value of the fixed-effects parameter in the population, and η is a random interindividual variable that is normally distributed with mean 0 and variance ω^2. Residual (intra-individual) variability was modelled proportionally: $C_{obs,ij} = C_{pred,ij} \times (1 + \varepsilon_{ij})$, where $C_{obs,ij}$ and $C_{pred,ij}$ denote the j-th observed and predicted concentrations for the i-th subject, and ε is a random intra-individual error that is normally distributed with mean 0 and variance σ^2. The first-order absorption rate constant (ka) for oral administration was fixed at 0.583 h^{-1} [27] because of a lack of sampling during the drug absorption phase. The fraction of the absorbed drug (bioavailability) was assumed to be 100% [28].

Age, body weight, serum creatinine, CL_{Cr} estimated using the Cockcroft–Gault formula, and BUN were chosen as candidates for the PK covariate. The effect of each covariate on the individual PK parameters was screened graphically. Covariates showing a correlation with the PK parameters were then further assessed based on the difference in the minimum value of the objective function value estimated by NONMEM. Forward inclusion and backward elimination were used to develop the covariate model. The significance levels for forward inclusion and backward elimination were set at $P < 0.05$ and $P < 0.01$, respectively. The adequacy of the final model was assessed by goodness-of-fit plots. A non-parametric bootstrap analysis was performed using Perl-speaks-NONMEM software to assess the reliability and stability of the estimated parameter [29]. The 95% confidence intervals (CIs) of the parameters from 1000 bootstrap replicates were compared with the estimates of the final model.

2.5. Assessment of thrombocytopenia

Thrombocytopenia was defined as a decrease to ≤70% in the ratio of platelet counts during treatment with linezolid to the baseline levels (pre-treatment with linezolid) [7,9,22]. Furthermore, the ratio of minimum platelet counts during treatment to the baseline levels was also calculated. The effects of drug exposure on thrombocytopenia were investigated in 44 patients. Platelet counts were measured once a day ($n = 17$), once every 2 days ($n = 7$), once every 3 days ($n = 8$) and once a week ($n = 12$).

2.6. Determination of minimum inhibitory concentration

The MICs of linezolid for a total of 444 MRSA strains from hospitalised patients were determined by the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) [30].

2.7. Statistical analysis

A linear regression analysis was performed to examine the PK relationship between the linezolid C_{min} and AUC_{24}. Logistic regression modelling for the pharmacodynamics of linezolid was conducted to determine whether the concentration of or exposure to linezolid was a significant predictor of thrombocytopenia