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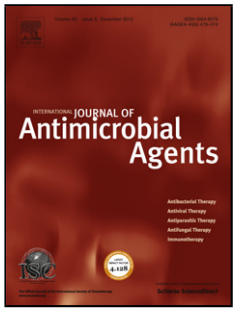

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Plasma and cerebrospinal fluid concentrations of linezolid in neurosurgical critically ill patients with proven or suspected central nervous system infections

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ABSTRACT

Linezolid is a valuable treatment option for central nervous system (CNS) infections caused by multidrug-resistant Gram-positive micro-organisms. Data regarding its penetration into the CNS have shown wide variability. The aim of this study was to describe the population pharmacokinetics of linezolid in plasma and cerebrospinal fluid (CSF) in critically ill patients with external CSF drainage and proven or suspected CNS infections. This was an observational pharmacokinetic (PK) study in 11 critically ill patients with proven or suspected CNS infection receiving linezolid. Serial blood and CSF samples were taken and were subject to population PK analysis. The median (interquartile range) of $AUC_{0–12h}$ was 47.6 (17.9–58.6) mg·h/L in plasma and 21.1 (18.8–30.4) mg·h/L in CSF, with a median CSF/plasma ratio of 0.77. At pre-dose at steady state, a strong positive correlation was observed between linezolid concentrations in CSF and plasma (Spearman's rho = 0.758; *P* = 0.011). For a minimum inhibitory concentration (MIC) of 2 mg/L, the median $AUC_{0–24h}$/MIC values in plasma and CSF were <80 in all patients. A three-compartment linear model was found to be most appropriate. The mean value for linezolid clearance was 16.6 L/h and mean volume of distribution was 101.3 L. No covariate relationships could be supported on any of the parameters. Linezolid demonstrated good penetration into the CNS but high interindividual PK variability. Administration of higher than standard doses of linezolid and therapeutic drug monitoring should therefore be considered as options to optimise linezolid dosing in critically ill patients with CNS infections.

1. Introduction

Neurosurgical critically ill patients frequently require placement of an external central nervous system (CNS) catheter for drainage of cerebrospinal fluid (CSF) to better control intracranial pressure. It is estimated that 1–2% of patients admitted to an intensive care unit (ICU) have an intraventricular catheter in situ [1]. These devices are frequently manipulated to ensure optimal function and, whilst strict aseptic methods are targeted for use [2], CNS infections are common in these patients. The frequency of CNS infections resulting from neurosurgical procedures is estimated to be ca. 4% [3], and Gram-positive cocci, mainly *Staphylococcus* spp., are the most common causative pathogens [4].

Linezolid is considered to be a useful treatment option for CNS infections, particularly where mediated by resistant Gram-positive bacteria [5–7]. Linezolid has good antibacterial activity against these micro-organisms, including meticillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis)* and vancomycin-resistant enterococci [8]. Over the last few years, several studies have become available that support the efficacy and safety of linezolid in the treatment of CNS infections [3,9,10]. Linezolid has been reported to have a favourable pharmacokinetic (PK) profile, achieving high concentrations in CSF and showing a penetration ratio for the area under the drug concentration–time curve (AUC) for CSF to the AUC for serum close to 1 [11]. Some PK studies have been performed in animal models, healthy volunteers or non-critically ill patients [12–14]. Studies evaluating penetration of linezolid into the CNS in critically ill patients have shown widely variable results

[4,12–16]. This population can develop severe pathophysiological changes (e.g. hyperdynamic state, need for vasopressor drugs, augmented or impaired renal function) that can alter the pharmacokinetics of many antimicrobials leading to decreased effectiveness [17]. Such PK changes may affect antibiotic penetration into the CSF and cause wide interindividual variability in CSF concentrations.

In human studies, the time the plasma linezolid concentration exceeds the minimum inhibitory concentration ($T_{>MIC}$) and the ratio of AUC from time 0 to 24 h to MIC ($AUC_{0–24h}$/MIC) have been related to bacteriological and clinical outcomes. In seriously ill patients, higher efficacy rates were observed when the $T_{>MIC}$ was ≥85% and the $AUC_{0–24h}$/MIC was in the range of 80–120 [18,19]. When considering an MIC of 2 mg/L, optimal pharmacokinetic/pharmacodynamic (PK/PD) targets in plasma and CSF were achieved in the majority of the previously described experiences [12–15]. However, using an MIC of 4 mg/L, a value for less susceptible strains [20], these PK/PD ratios were only achieved in two studies [12,15].

To the best of our knowledge, a population PK study of linezolid concentrations in plasma and CSF in critically ill patients with ventricular drains in situ is yet to be performed. Such an analysis could help better describe this interindividual variability and its implications for linezolid dosing in these patients. Given the lack of PK certainty of linezolid penetration into the CSF and the achievement of pharmacodynamic targets, the objective of this study was to describe the population pharmacokinetics of linezolid in plasma and CSF in critically ill patients with external CNS drainage and proven or suspected CNS infections.

2. Materials and methods

2.1. Study design and population

This was a prospective PK study undertaken in the 18-bed ICU of Hospital del Mar, a 400-bed tertiary university hospital in Barcelona, Spain. All consecutive adult patients admitted to the ICU between January 2010 and January 2013 who received intravenous (i.v.) linezolid for >3 days for the treatment of a proven or suspected CNS infection caused by a resistant Gram-positive organism were eligible for inclusion. Only those patients in whom a Gram-positive micro-organism was isolated in a CSF culture were considered as having a proven CNS infection. All enrolled patients had an external CNS drainage (either intraventricular or external lumbar) present. All included patients received linezolid (Zyvoxid; Pfizer, Madrid, Spain) 600 mg every 12 h as a 1-h infusion via a central venous catheter. Informed consent was obtained from all participating patients or their legal representatives.

Various demographic, clinical and treatment data were collected, including age, sex, weight, height, body mass index (BMI), presence of underlying CNS disease, sickness severity score on admission to the ICU [described using the Acute Physiology and Chronic Health Evaluation (APACHE) II score], type of treatment with linezolid (empirical or directed), treatment duration, concomitant therapies [21], presence of oedema, type of external CNS drainage (ventricular or lumbar), glomerular filtration rate (GFR) [calculated by the Modification of Diet in Renal Disease (MDRD-6) equation], haematological parameters (haemoglobin and platelet count) at the start and end of treatment with linezolid), clinical and microbiological data, and crude mortality.

Anaemia and thrombocytopenia related to linezolid administration were defined according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. For patients with normal baseline values, anaemia was defined as a reduction in haemoglobin in the range of 8–10 g/dL or less, and thrombocytopenia was defined as a platelet count <75 000 cells/mm^3 unexplained by any other causes.

The presence of oedema was evaluated on the basis of physical examination by the responsible clinician.

2.2. Plasma and cerebrospinal fluid sample collection

Plasma and CSF sampling occurred after 3 days of treatment. Blood samples (4 mL) were collected just before initiation of the linezolid infusion (trough in plasma; $C_{min,ss}$) and at 1 h (peak in plasma; $C_{max,ss}$) in four patients and also at 3, 5, 8 and 12 h thereafter in seven patients. CSF samples (1 mL) were collected simultaneously with each blood sample. Blood and CSF samples were collected in heparinised tubes, immediately centrifuged (3000 × *g* for 10 min at 4 °C) and the plasma was stored at –80 °C until analysis.

2.3. Bioanalysis

Linezolid concentrations were determined using a validated high-performance liquid chromatography (HPLC) method. For each sample of plasma and CSF, 100 μL was mixed with 100 μL of methanol and was vortexed for 10 s. The mixture was then centrifuged for 5 min at 15 000 × *g* in a refrigerated laboratory centrifuge (MPW-

260R; MPW Med. Instruments, Warsaw, Poland) and 50 μL of the supernatant was injected into the system for assay.

The HPLC equipment was modular, including a binary pump (Waters 1525; Waters Corp., Milford, MA) with column heater oven, a degasser (Waters In-line degasser), an automatic injector (Waters 717plus Autosampler) and a UV-VIS spectrophotometric detector (Waters 2487). The stationary phase was a Waters SunFire® column (C18, 4.6 × 15.0 mm, 5 μm) protected by a Waters SunFire® GuardColumn (C18, 4.6 mm × 20 mm, 5 μm). The mobile phase consisted of a mixture of sodium acetate buffer (pH 3.4) and acetonitrile (80:20 v/v) delivered at an isocratic flux of 1.3 mL/min. The chromatogram run time was 10 min and the detector wavelength was set at 250 nm.

The method was proven to be sensitive and specific to measure linezolid in plasma and CSF. The assay response was linear (coefficient of linearity >0.99) over the full range of concentrations assayed (0.5–30 mg/L in plasma and 0.1–20 mg/L in CSF). The limit of quantification was 0.5 mg/L in plasma and 0.1 mg/L in CSF. Imprecision values were <15% over the entire range of calibration standards, and accuracy was within the range of 85–115% for all concentrations.

2.4. Population pharmacokinetic analysis

The concentration–time data for linezolid in plasma and CSF were fitted using non-linear mixed-effects modelling (NONMEM v.7.2; Globo Max LLC, Hanover, MD) [22]. A Digital Fortran compiler was used and the runs were executed using Wings for NONMEM (http://wfn.sourceforge.net). Data were analysed using the first-order

conditional estimation method with interaction (ADVAN6). Between-subject variability (BSV) was calculated using an exponential variability model and was assumed to follow a log-normal distribution. Residual unexplained variability was modelled using a combined exponential and additive random error model. Visual inspection of diagnostic scatter plots and the NONMEM objective function value (OFV) were used to evaluate goodness of fit. Statistical comparison of nested models was undertaken in the NONMEM program on the basis of a χ^2 test of the difference in OFV. A decrease in the OFV of 3.84 units ($P < 0.05$) was considered statistically significant. Decreases in BSV of one of the parameters of at least 10% were also accepted for inclusion of a more complicated model. Specifically, volume of distribution of the central compartment (V_c), volume of distribution of the peripheral compartment (V_p), volume of distribution of the CSF compartment (V_{CSF}), intercompartmental clearance between plasma and tissue (Q), intercompartmental clearance between plasma and CSF (Q_{CSF}) and linezolid clearance (CL) were calculated using NONMEM.

2.4.1. Population pharmacokinetic model diagnostics

Visual inspection of diagnostic scatter plots and the NONMEM OFV were used to evaluate goodness of fit. Statistical comparison of nested models was undertaken in the NONMEM program using log-likelihood ratios, which are assumed to be χ^2 distributed. On the basis of a χ^2 test of the difference in OFV, a decrease in the OFV of 3.84 units ($P < 0.05$) for one degree of freedom was considered statistically significant. Decreases in BSV of one of the parameters of at least 10% were also accepted for inclusion of a more complicated model.

2.4.2. Population pharmacokinetic covariate screening

Covariate model building was performed in a stepwise fashion with forward inclusion and backward deletion based upon the aforementioned model selection criteria. Age, sex, weight, serum creatinine concentration, APACHE II score and use of vasopressors were evaluated as covariates.

2.4.3. Population pharmacokinetic bootstrap

A non-parametric bootstrap method (n = 1000) was used to study the uncertainty of the PK parameter estimates in the final model. From the bootstrap empirical posterior distribution, we have been able to obtain the 95% confidence interval (CI) for the parameters, as described previously [23].

2.5. Other pharmacokinetic calculations

The maximum (C_{max}) and minimum (C_{min}) concentration in plasma and CSF for the dosing interval were the observed values. The AUC from 0 to 12 h ($AUC_{0–12h}$) was calculated using the trapezoidal rule. $AUC_{0–24h}$ was calculated as $AUC_{0–12h} \times 2$. Penetration of linezolid into the CSF was described using the CSF/plasma ratio, which was calculated by dividing the CSF $AUC_{0–12h}$ by the plasma $AUC_{0\text{-}12h}$.

2.6. Assessment of pharmacodynamics and efficacy thresholds

An $AUC_{0–24h}$/MIC ratio of 80–120 was considered the optimal target for efficacy because this threshold has been related to higher clinical success and bacteriological rates [19,24].

2.7. Statistical analysis

Continuous variables were compared with the Student's *t*-test or Mann–Whitney *U*-test as appropriate, and dichotomous variables were compared using the χ^2 test or Fisher's exact test. Bivariate linear correlations were studied using the Spearman's rho (ρ) test or the Pearson test, when appropriate. For all analyses, a two-sided *P*-value <0.05 was considered statistically significant. SPSS v.13.0 (SPSS Inc., Chicago, IL) was used throughout. GraphPad Prism v.6.0 (GraphPad Software Inc., La Jolla, CA) was used for linear regression calculations. Data are described as the mean ± standard deviation or median [interquartile range (IQR)] as appropriate.

3. Results

Eleven patients were included in the study and 46 blood samples and 45 CSF samples were collected. The demographic and clinical characteristics of the patients are detailed in Table 1. The mean patient age was 51.9 ± 10.3 years and 7 (63.6%) were male. The most frequent neurological disease was subarachnoid haemorrhage, observed in 7 (63.6%) of the patients. Ten patients (90.9%) were CSF-culture negative and one patient (9.1%) cultured *S. epidermidis* that was susceptible to linezolid. The mean treatment duration with linezolid was 9.5 ± 6.2 days. No patient had a GFR < 80 mL/min on the day of sampling.

Plasma peak concentrations of linezolid ranged from 6.3 mg/L to 17.3 mg/L and plasma trough concentrations ranged from <0.2 mg/L to 2 mg/L. In CSF, the peak concentration ranged from 1.3 mg/L to 7.1 mg/L and the trough concentration from

<0.2 mg/L to 3.1 mg/L. The median (IQR) of $AUC_{0–12h}$ was 47.6 (17.9–58.6) mg·h/L in plasma and 21.1 (18.8–30.4) mg·h/L in CSF. This corresponded to a median CSF/plasma ratio between patients of 0.77. The steady-state plasma and CSF concentration–time profiles are shown in Fig. 1. Linezolid concentration profiles in plasma and CSF were not superimposable. The C_{max} in plasma was the observed value at the end of the i.v. infusion, whilst in CSF it was achieved ca. 3–5 h after the beginning of linezolid administration. At the time of C_{min}, a strong positive correlation was observed between linezolid concentrations in CSF and plasma (Spearman's ρ = 0.758; P = 0.011) (Fig. 2). This correlation was not observed at C_{max} (Pearson's ρ = –0.266; P > 0.05).

The $AUC_{0–12h}$ values in plasma and CSF for individual patients as well as the corresponding PK/PD indices related to linezolid efficacy ($AUC_{0–24h}$/MIC) in plasma and CSF relative to different MIC values (1, 2 and 4 mg/L) are described in Table 2. Linezolid was well tolerated by all patients, with no adverse effects observed in any of the patients.

3.1. Pharmacokinetic model building

Eight patients were used to build the model as three patients did not have sufficient data points (more than two plasma and CSF samples) to meet the a priori model-building criteria. The time course of linezolid in plasma and CSF was best described by a three-compartment linear model with combined residual error (additive error for the plasma and CSF predictions was fixed at 0.03 mg/L) and BSV on V_c, V_p, Q and CL. BSV could not be supported on V_{CSF} or Q_{CSF}. This model included zero-order

input of drug into the central compartment. The mean parameter estimates from the final covariate model as well as the 95% CIs from all bootstrap runs are shown in Table 3. The goodness of fit plots are shown in Fig. 3. After screening all relevant biologically plausible covariates, none were found to statistically significantly improve the model so could not be included in the final model.

4. Discussion

To the best of our knowledge, this is the first population PK study of linezolid in plasma and CSF in critically ill neurological patients with proven or suspected CNS infection caused by Gram-positive micro-organisms. It is also the largest study of its type with linezolid. The results showed a moderate-to-good overall penetration of linezolid into the CSF, with a median AUC_{0-12h} CSF/plasma ratio of 0.77. Despite this, a wide variability between patients was observed in the plasma and CSF concentrations and CSF/plasma ratios. This variability is most likely due to the range of sickness severity of the included patients and the consequent effect that the associated altered physiology has on linezolid disposition. These findings, which agree with those from previous studies that have also described large interindividual variability in the concentrations of linezolid in plasma [21] and CSF [12], support the need for therapeutic drug monitoring (TDM) of linezolid in plasma and also potentially in CSF to avoid treatment failures due to underexposure [21]. The strong positive correlation observed between the $C_{min,ss}$ of linezolid in plasma and the concentration in CSF suggests that plasma concentrations could be used as predictors of CSF concentrations if only trough concentration (as opposed to AUC_{0-24h}) monitoring was available.

Variable results have been published on whether plasma linezolid concentrations can be used as a surrogate of CSF concentrations. In one case study of linezolid in meningitis, the authors reported similar drug concentrations in plasma and CSF and suggested that plasma concentrations are a suitable indicator of CSF penetration [15]. This is unsurprising as drug penetration in meningitis should be greater than in patients with non-inflamed meninges. Similar to this case study, other authors also described positive correlations between the $C_{max,ss}$ of linezolid in plasma and in CSF [12]. However, other investigators have not found such correlations between in plasma and CSF concentrations of linezolid [16]. In our patients, although significant correlation between plasma and CSF concentrations was seen for trough concentrations, significant other correlations were not observed. The variable CSF/plasma AUC ratios seen in this study suggest that consistent correlations are generally unlikely with this drug.

In this study, the linezolid concentrations in plasma and CSF were much lower than those reported in most other PK studies performed in critically ill patients [12–15,25]. The population PK model that best described the data was a three-compartment linear model. The mean volume of distribution of linezolid (101.3 L) estimated in this study was much higher than that reported in previous studies in the same patient group (42.8 L or 40.1 L) [13,14]. Our volume of distribution estimates are more in line with those from another critically ill patient PK study [26]. In contrast, the estimated linezolid clearance (16.6 L/h) was found to be much higher (7.3 L/h or 7.9 L/h) [12,13], a fact probably explained by the better apparent renal function of our patients compared with those included in the previous studies. The estimated

clearance values described in this study more closely align with the estimates from a sepsis cohort reported by Plock et al. [27].

From a pharmacodynamic viewpoint, the plasma and CSF trough concentrations of linezolid did not exceed the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for susceptible pathogens (4 mg/L) [20] in any of the patients. Assuming an MIC of 1 mg/L, only four patients achieved a target AUC_{0-24h}/MIC of ≥80 in plasma and only one patient achieved this target in CSF. At higher MIC values (2 mg/L or 4 mg/L), none of the patients achieved the desired pharmacodynamic target. Consequently, in critically ill patients with CNS infections caused by a Gram-positive bacterium with a linezolid MIC ≥ 1mg/L, the standard dosing regimen of linezolid 600 mg twice daily is considered unlikely to achieve optimal plasma and CSF concentrations.

The increased volume of distribution and clearance observed in our patients results from the generally lower linezolid PK exposures observed. The study by Myrianthefs et al. [12] in 14 critical neurosurgical patients receiving linezolid for a mixture of treatment and prophylaxis of CNS infections showed higher mean plasma $C_{max,ss}$ and $C_{min,ss}$ values of 18.6 mg/L (78% higher than our patients) and 5.6 mg/L (1120% higher), respectively. The mean CSF $C_{max,ss}$ and $C_{min,ss}$ values were also higher in the Myrianthefs et al. study at 10.8 mg/L (337% higher) and 6.1 mg/L (1220% higher), respectively [12]. The report from Beer et al. in five critically ill patients with ventriculitis caused by *Staphylococcus* spp. reported less discordant results, with a mean plasma $C_{max,ss}$ and $C_{min,ss}$ of 19.5 mg/L (88% higher) and 1.9 mg/L (380%

higher) [13]; the mean CSF $C_{max,ss}$ and $C_{min,ss}$ were 7.1 mg/L (222% higher) and 3.1 mg/L (620% higher) [13].

One likely explanation for the lower exposures of linezolid observed in our patients is the conserved renal function of our patients. In particular, the mean calculated creatinine clearance (CL_{Cr}) estimates of our patients were much higher than those reported in the Myrianthefs et al. study (151 mL/min compared with 81 mL/min) [12]. A correlation between a low $C_{min,ss}$ of linezolid in plasma and increasing calculated CL_{Cr} has been shown previously [28]. In a recent study of 78 patients with acute infections, a value of calculated CL_{Cr} > 80 mL/min was identified as a risk factor for achieving a linezolid C_{min} < 2 mg/L in plasma (odds ratio = 10; 95% CI 2.732–37.037; P = 0.001) [28]. However, this association was not observed in the current study, where linezolid levels in plasma and CSF were not correlated with patients' renal function, probably due to the comparatively smaller sample size. This phenomenon of augmented renal clearance (ARC) and its association with increased antibiotic clearance and decreased concentrations has been previously shown for β-lactams [29]. In our patients, ARC is likely and would be caused by the pathophysiological response to the CNS pathology, including increased renal blood flow [30]. The effects of ARC on linezolid pharmacokinetics has not been previously described, although direct causality cannot be shown here as measured CL_{Cr} data were not available and neither were urine concentration data. One limitation of this study is the fact that CL_{Cr} of patients was estimated because the measurement is not routinely performed in Hospital del Mar.

Regarding toxicity, administration of linezolid at standard dosages was not associated with any haematological toxicity, although prolonged durations of therapy were not required in this study.

In conclusion, this is the largest PK study of critically ill patients with proven or suspected CNS infection caused by Gram-positive micro-organisms. We found that linezolid showed a generally good distribution into the CSF, although wide interindividual variability in the plasma and CSF concentrations was observed. This variability is associated with suboptimal pharmacodynamic target attainment for pathogens with an MIC ≥ 1mg/L.

To address this challenge, other different dosing strategies, such as administration of higher than standard dosages or administration by continuous infusion, should be considered to avoid treatment failures due to antibiotic underexposure. The alternative approach to optimise drug exposures is to apply individualised dosing in the form of TDM to overcome this PK variability. The feasibility of TDM of linezolid has previously been demonstrated by Pea et al. [21]. The strong linear correlation observed in this study between the trough linezolid concentrations in plasma and in CSF suggests that plasma concentrations can be used as a surrogate of CSF concentrations for TDM in similar critically ill neurosurgical patients.

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References

[1] Estudio Nacional de Vigilancia de Infección Nosocomial en Servicios de Medicina Intensiva (ENVIN-HELICS) 2012. Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC), Grupo de Trabajo de Enfermedades Infecciosas. http://hws.vhebron.net/envin-helics/Help/Informe%20ENVIN-UCI%202012.pdf [accessed 16 January 2014].

[2] Hospital del Mar, Parc de Salut Mar. Protocols i procedimients d'infermeria. Malalt neurocritic. 2010.

[3] Viale P, Pagani L, Cristini F, Stefini R, Bergomi R, Colombini P, et al. Linezolid for the treatment of central nervous system infections in neurosurgical patients. Scand J Infect Dis 2002;34:456–9.

[4] Villani P, Regazzi MB, Marubbi F, Viale P, Pagani L, Cristini F, et al. Cerebrospinal fluid linezolid concentrations in postneurosurgical central nervous system infections. Antimicrob Agents Chemother 2002;46:936–7.

[5] Beer R, Pfausler B, Schmutzhard E. Management of nosocomial external ventricular drain-related ventriculomeningitis. Neurocrit Care 2009;10:363–7.

[6] Hoefnagel D, Dammers R, Ter Laak-Poort MP, Avezaat CJ. Risk factors for infections related to external ventricular drainage. Acta Neurochir (Wien) 2008;150:209–14.

[7] Jiménez-Mejías ME, García-Cabrera E. Infection of cerebrospinal fluid shunt systems [in Spanish]. Enferm Infecc Microbiol Clin 2008;26:240–51.

[8] Xiong YQ, Yeaman MR, Bayer AS. Linezolid: a new antibiotic. Drugs Today (Barc) 2000;36:631–9.

[9] Sabbatani S, Manfredi R, Frank G, Chiodo F. Linezolid in the treatment of severe central nervous system infections resistant to recommended antimicrobial compounds. Infez Med 2005;13:112–9.

[10] Rupprecht TA, Pfister HW. Clinical experience with linezolid for the treatment of central nervous system infections. Eur J Neurol 2005;12:536–42.

[11] Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood–cerebrospinal fluid/blood–brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 2010;23:858–83.

[12] Myrianthefs P, Markantonis SL, Vlachos K, Anagnostaki M, Boutzouka E, Panidis D, et al. Serum and cerebrospinal fluid concentrations of linezolid in neurosurgical patients. Antimicrob Agents Chemother 2006;50:3971–6.

[13] Beer R, Engelhardt KW, Pfausler B, Broessner G, Helbok R, Lackner P, et al. Pharmacokinetics of intravenous linezolid in cerebrospinal fluid and plasma in neurointensive care patients with staphylococcal ventriculitis associated with external ventricular drains. Antimicrob Agents Chemother 2007;51:379–82.

[14] Viaggi B, Paolo AD, Danesi R, Polillo M, Ciofi L, Del Tacca M, et al. Linezolid in the central nervous system: comparison between cerebrospinal fluid and plasma pharmacokinetics. Scand J Infect Dis 2011;43:721–7.

[15] Tsuji Y, Hiraki Y, Matsumoto K, Mizoguchi A, Sadoh S, Kobayashi T, et al. Pharmacokinetics and protein binding of linezolid in cerebrospinal fluid and serum in a case of post-neurosurgical bacterial meningitis. Scand J Infect Dis 2011;43:982–5.

[16] Malacarne P, Viaggi B, Di Paolo A, Danesi R, Del Tacca M. Linezolid cerebrospinal fluid concentration in central nervous system infection. J Chemother 2007;19:90–3.

[17] Roberts JA. Using PK/PD to optimize antibiotic dosing for critically ill patients. Curr Pharm Biotechnol 2011;12:2070–9.

[18] Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. Clin Pharmacokinetic 2003;42:1129–40.

[19] Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 2003;42:1411–23.

[20] European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, 2014. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_4.0.pdf [accessed 16 January 2014].

[21] Pea F, Furlanut M, Cojutti P, Cristini F, Zamparini E, Franceschi L, et al. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother 2010;54:4605–10.

[22] Beal SL, Sheiner LB, Boeckmann AJ, Bauer RJ, editors. *NONMEM 7.2.0 users guides. (1989–2011)*. Ellicott City, MD: Icon Development Solutions. ftp://nonmem.iconplc.com/Public/nonmem720/guides.

[23] Parke J, Holford NH, Charles BG. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. Comput Methods Programs Biomed 1999;59:19–29.

[24] MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J Antimicrob Chemother 2003;51(Suppl 2):ii17–25.

[25] Boak LM, Li J, Spelman D, du Cros P, Nation RL, Rayner CR. Successful treatment and cerebrospinal fluid penetration of oral linezolid in a patient with coagulase-negative *Staphylococcus* ventriculitis. Ann Pharmacother 2006;40:1451–5.

[26] Buerger C, Plock N, Dehghanyar P, Joukhadar C, Kloft C. Pharmacokinetics of unbound linezolid in plasma and tissue interstitium of critically ill patients after multiple dosing using microdialysis. Antimicrob Agents Chemother 2006;50:2455–63.

[27] Plock N, Buerger C, Joukhadar C, Kljucar S, Kloft C. Does linezolid inhibit its own metabolism? Population pharmacokinetics as a tool to explain the observed nonlinearity in both healthy volunteers and septic patients. Drug Metab Dispos 2007;35:1816–23.

[28] Morata L, Cuesta M, Rojas JF, Rodriguez S, Brunet M, Casals G, et al. Risk factors for a low linezolid trough plasma concentration in acute infections. Antimicrob Agents Chemother 2013;57:1913–7.

[29] Roberts JA, Lipman J. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. Crit Care Med 2013;41:489–95.

[30] Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med 2013;39:2070–82.

Fig. 1. Plasma (top panel) and cerebrospinal fluid (lower panel) concentrations of linezolid over one dosing interval. Each individual data point is represented by a black circle, and the unbroken line is the median concentration value.

Fig. 2. Correlation between plasma and cerebrospinal fluid (CSF) concentration of linezolid (LZD) at the trough time (before next dose administration) (n = 10; the 11th patient did not have a true trough value for both plasma and CSF and so could not be included).

Fig. 3. Diagnostic plots for the final population pharmacokinetic model. Individual predicted linezolid concentrations in plasma versus observed plasma concentrations (R^2 = 0.91) (top panel) and individual predicted linezolid concentrations in cerebrospinal fluid (CSF) versus observed CSF concentrations (R^2 = 0.82) (lower panel). The linear regression line of fit is shown by the solid black line.

Table 1

Patient demographics and clinical characteristics

Patient	Sex	Age (years)	Body weight (kg)	Serum creatinine (μmol/L)	GFR on the day of inclusion (mL/min) [a]	APACHE II score	CNS disease	CNS external drainage	LZD dose/kg body weight (mg/kg)	Vasopressor therapy	Crude mortality
1	F	45	90	38	148.3	9	Brain tumour	ELD	13.3	No	N
2	M	42	90	50	164.8	24	SAH	EVD	13.3	Yes	N
3	M	44	55	41	211.4 [b]	16	Hydrocephalus	ELD	21.8	No	Y
4	M	39	65	47	158.5	12	SAH	EVD	18.5	No	N
5	F	51	80	42	113.7	22	Brain tumour	ELD	15.0	Yes	Y
6	M	64	80	51	124.1	19	SAH	EVD	15.0	No	N
7	F	74	60	32	148.7	24	SAH	EVD	20.0	No	N
8	M	48	85	41	89.5	19	SAH	EVD	14.1	Yes	Y
9	F	54	70	20	255.3	24	SAH	ELD and EVD	17.1	Yes	N

10	M	58	75	40	158.7	22	SAH	EVD	16.0	Yes	N
11	M	52	95	36	205.0	26	Cerebellar haemorrhage	ELD and EVD	12.6	No	N
Median	–	51	80	41	158.5	22	–	–	15.0	–	–
IQR	–	46-57	71-89	37-46	136.2-184.9	19-24	–	–	13.7–17.8	–	–

GFR, glomerular filtration rate; APACHE, Acute Physiology and Chronic Health Evaluation; CNS, central nervous system; LZD, linezolid; SAH, subarachnoid haemorrhage; ELD, external lumbar drain; EVD, external ventricular drain; IQR, interquartile range.

[a] GFR calculated by the Modification of Diet in Renal Disease MDRD-6.

[b] GFR was calculated by the Modification of Diet in Renal Disease MDRD-4 due to a lack of serum albumin concentrations.

Table 2

Individual pharmacokinetic results in plasma and cerebrospinal fluid (CSF) and values of the AUC_{0-24h}/MIC of linezolid in plasma and CSF calculated for different MICs

Patient	Plasma AUC_{0-12h} (mg·h/L)	CSF AUC_{0-12h} (mg·h/L)	Ratio CSF AUC_{0-12h} to plasma AUC_{0-12h}	Plasma AUC_{0-24h}/MIC ratio			CSF AUC_{0-24h}/MIC ratio		
				MIC (mg/L):			MIC (mg/L):		
				1	2	4	1	2	4
1	57.6	21.1	0.37	115.2	57.6	28.8	42.2	21.1	10.6
2	61.5	47.4	0.77	123.0	61.5	30.8	94.8	47.4	23.7
4	18.7	17.0	0.91	37.40	18.7	9.4	34.0	17.0	8.5
5	59.5	28.7	0.48	119.0	59.5	29.8	57.4	28.7	14.4
6	17.1	14.2	0.83	34.2	17.1	8.6	28.4	14.2	7.1
7	47.6	32.0	0.67	85.2	47.6	23.8	64.0	32.0	16.0
8	16.3	20.6	1.26	32.6	16.3	8.2	41.2	20.6	10.3
Median	47.6	21.1	0.77	85.2	47.6	23.8	42.2	21.1	10.6
IQR	17.9–58.6	18.8–30.4	0.58–0.87	35.8–117.1	17.9–58.6	9.0–29.3	31.2–60.7	18.8–30.4	9.4–15.2

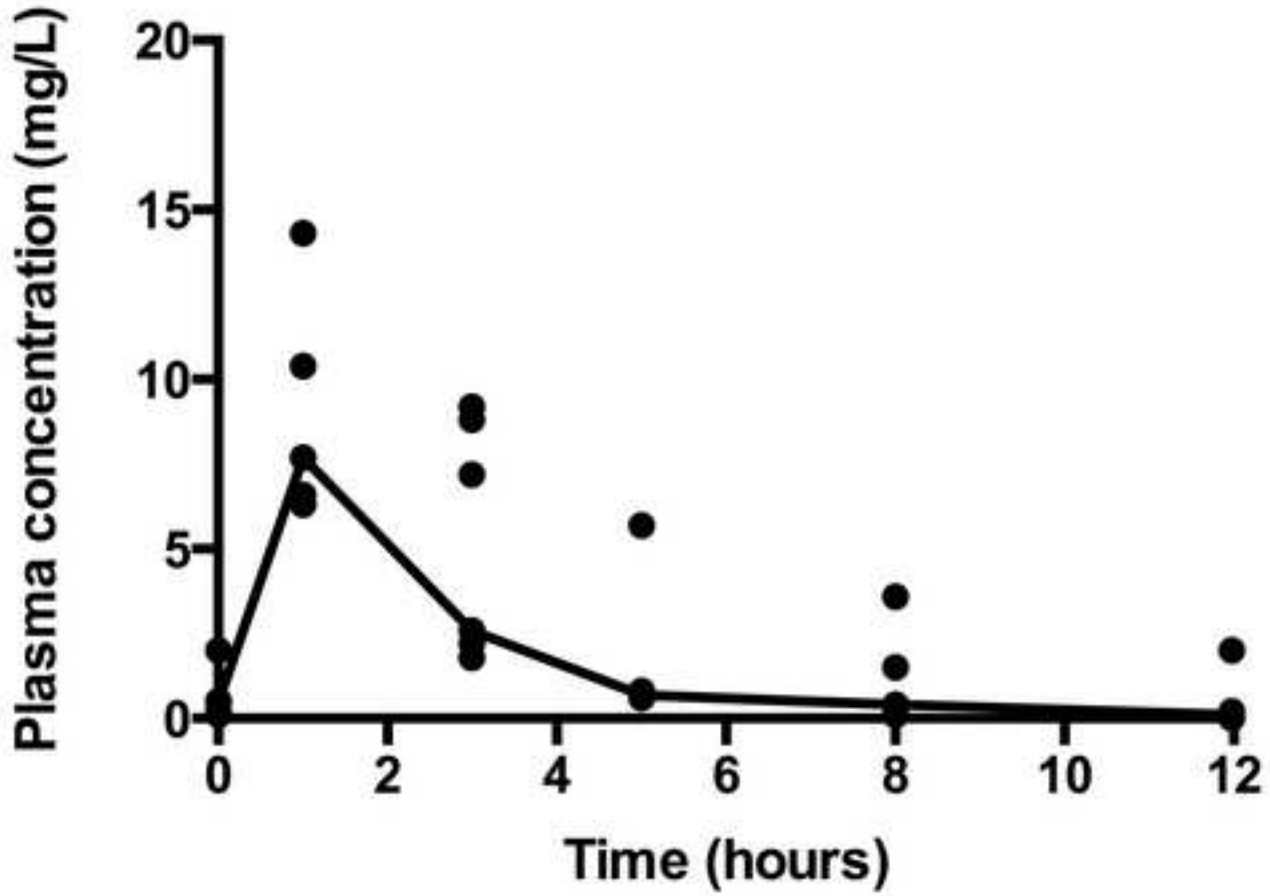
AUC_{0-12h}, area under the drug concentration–time curve from time 0 to 12 h; AUC_{0-24h}, area under the drug concentration–time curve from time 0 to 24 h (calculated as $AUC_{0-12h} \times 2$); MIC, minimum inhibitory concentration; IQR, interquartile range.

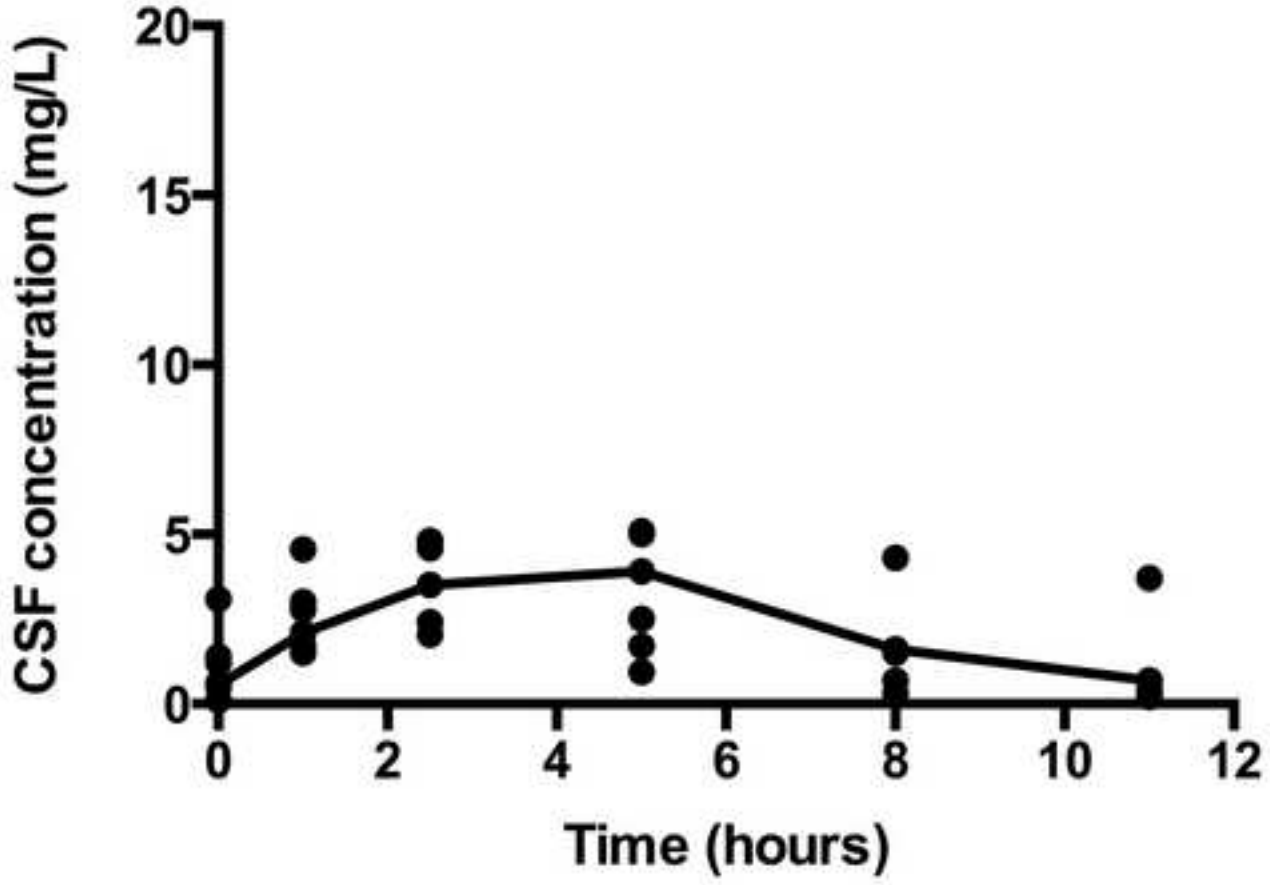
Table 3

Mean parameter estimates and bootstrap mean (95% CI) estimates for the final covariate model

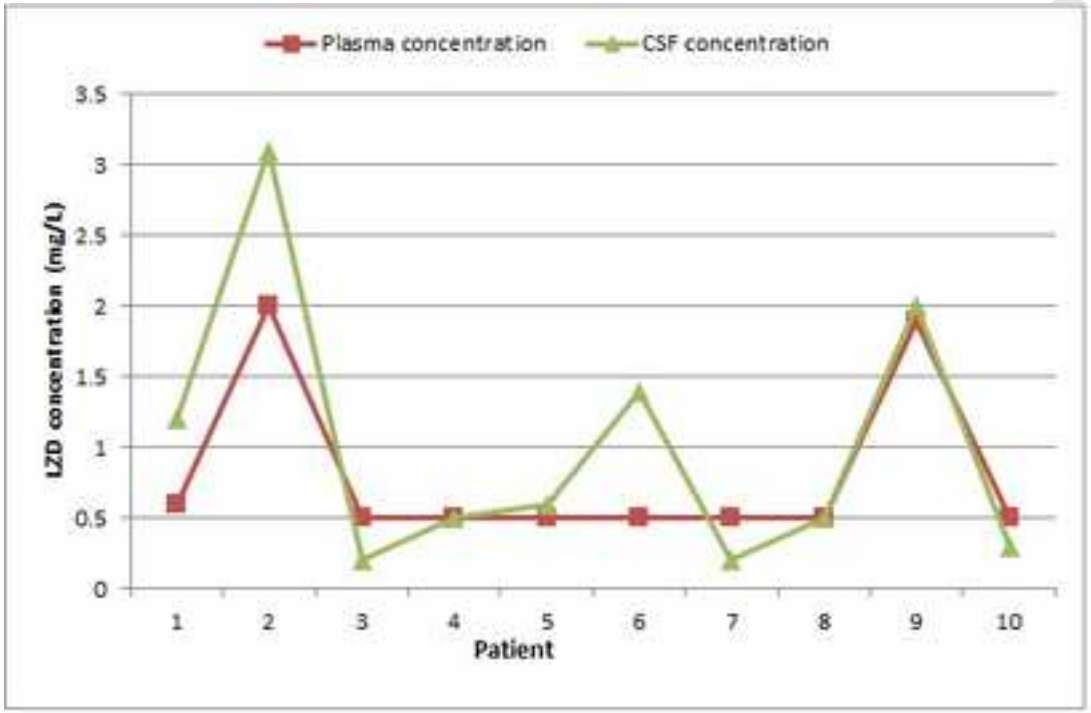
Parameter	Model mean	Bootstrap	
		Mean	95% CI
Fixed effects			
CL (L/h)	16.6	16.7	11.5–23.6
V_c (L)	43.2	42.7	33.6–52.2
V_p (L)	58.0	57.7	50.7–65.9
V_{CSF} (L)	0.11	0.11	0.11–0.11
Q (L/h)	3.1	2.5	0.9–5.5
Q_{CSF} (L/h)	0.05	0.04	0.03–0.05
Random effects BSV (% CV)			
CL (L/h)	50.2	46.7	32.6–60.0
V_c (L)	15.3	10.8	0.1–29.1
V_p (L)	8.2	5.1	0.2–29.1
Q (L/h)	88.9	77.1	0.8–142.4
Random error			
Plasma RUV (% CV)	0.03	0.03	–
CSF RUV (% CV)	29.8	27.7	14.0–38.6
Plasma RUV (S.D., mg/L)	0.03	0.03	–
CSF RUV (S.D., mg/L)	36.6	34.8	27.0–42.5

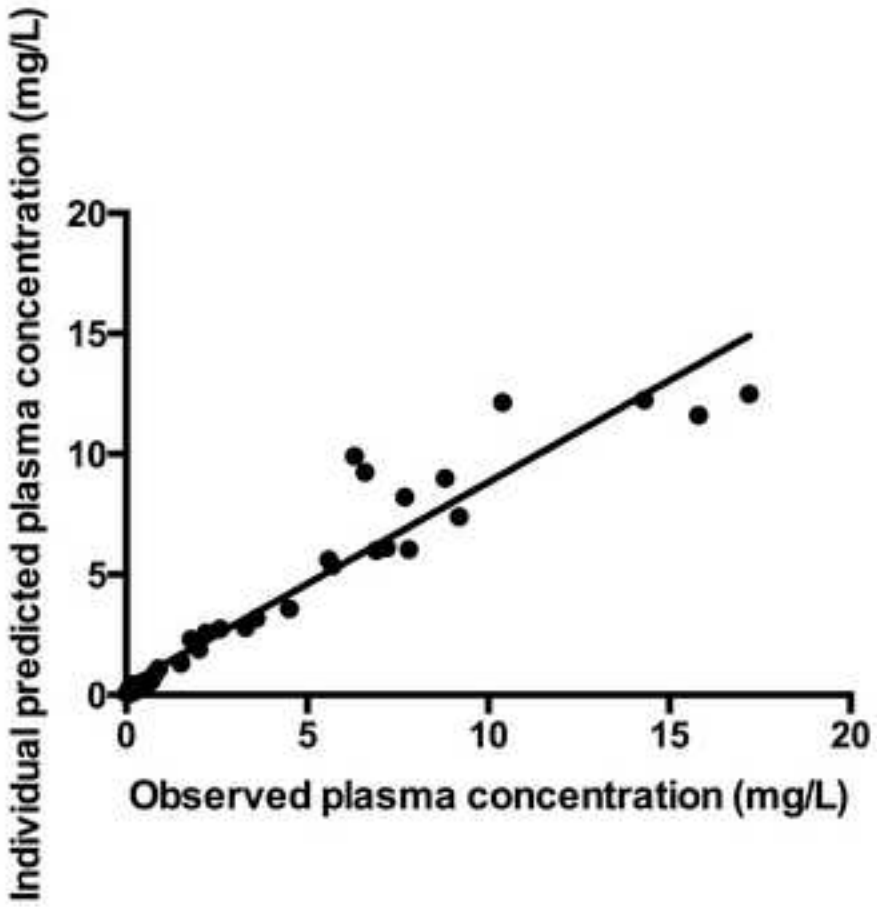
CI, confidence interval; CL, linezolid clearance; V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment; V_{CSF}, volume of distribution of the CSF compartment; Q, intercompartmental clearance between plasma and tissue; Q_{CSF}, intercompartmental clearance of the CSF compartment; BSV, between-subject variability; CV, coefficient of variation; RUV, residual unexplained variability; S.D., standard deviation.

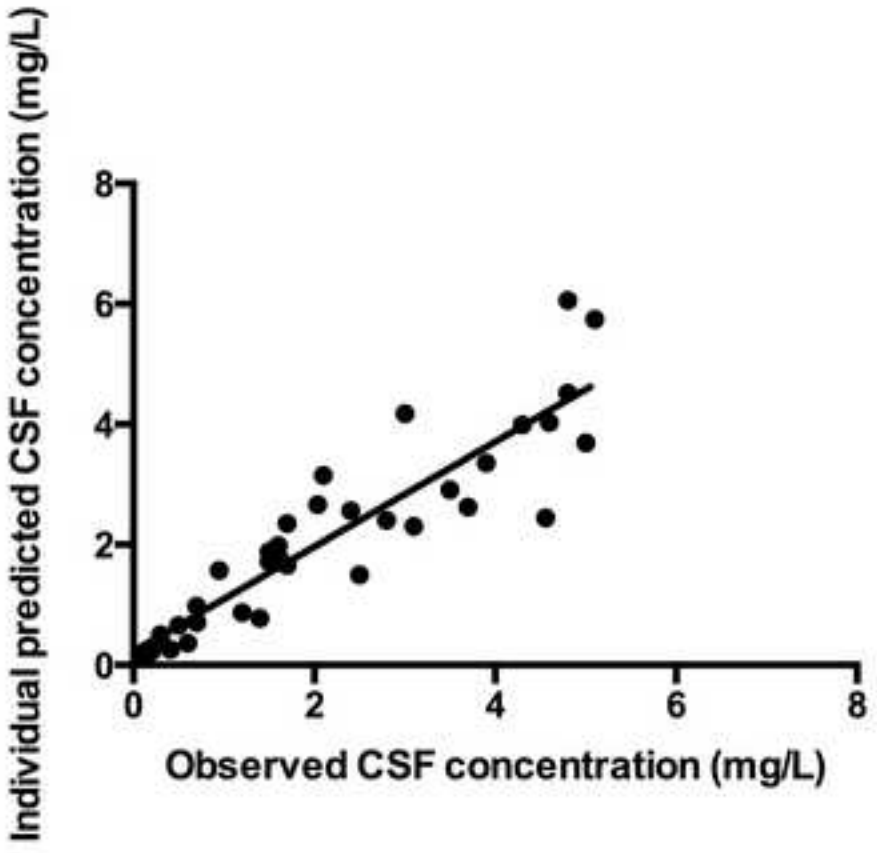




Edited Figure 2







The Highlights section should be as follows:

1. In these patients, Linezolid demonstrated good but variable penetration into the CNS.
2. A 3-compartment model was used; the mean value for linezolid clearance was 16.6 L/h and volume of distribution 101.3L

3. to ensure all patients achieve adequate CNS concentrations the use of higher than standard doses and TDM is necessary.

I hope this meets with your satisfaction