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Population pharmacokinetics of linezolid among post-operative patients: Implications for dosing strategies

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Abstract: Linezolid is a synthetic antibiotic and produces its antibacterial effect by inhibiting protein synthesis. It is used to treat life-threatening infections caused by MRSA and VRE. Linezolid clearance occurs through both the renal and hepatic routes. The identification of factors associated with linezolid clearance is required in Pakistani patients. A total of 215 samples from 59 post-operative patients were collected from a tertiary care hospital after a first dose of linezolid. The data was used to develop a population pharmacokinetic (popPK) model by using NONMEM® software. Analysis of the available covariates on pharmacokinetic parameters of linezolid was performed by using stepwise covariate modeling approach, A one-compartment model described the popPK and the value for linezolid clearance (CL) was 3.72 L/h while that of volume of distribution (Vd) was 36.9 L. The interindividual variability on linezolid CL was 36.5%. During stepwise covariate analysis, creatinine clearance (CRCL) was proved to be a significant covariate on CL. This is concluded that the clearance of linezolid is influenced by the renal status of patients and there is a dire need for dose optimization of linezolid in Pakistani patients based on renal status in order to avoid toxicity and adverse drug effects.

Keywords: Linezolid, population pharmacokinetics, NONMEM®

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INTRODUCTION

Linezolid belongs to a class of antibiotics called oxazolidinone. These are synthetic in nature and were granted approval from US-FDA in April 2000 for use against pathogenic bacteria. It is used to treat life-threatening infections caused by Gram +ve bacteria like MDR *Streptococcus pneumonia*, vancomycin-resistant *Enterococcus faecium* (VRE), methicillin resistance *Staphylococcus aureus* (MRSA) (Clemett and Markham 2000) and some species of *nocardia* (Rao *et al.* 2020). Linezolid is also used against some anaerobes like *Clostridium Difficile, Bacteroides fragilis* (Vinh and Rubinstein 2009), *C. perfringens, Fusobacterium nucleatum, F. meningosepticum and Peptostreptococcus species*. (Caroline and Linezolid 2003). Linezolid is effective against complex skin and soft tissue infections (SSTIs) and pneumonia cases in which hospitalization is required (Vinh and Rubinstein 2009). Linezolid produces its antibacterial effect by inhibiting the protein synthesis process in bacteria and acts on the 50S ribosomal subunit of prokaryotes (Ippolito *et al.* 2008) which is responsible for minimal cross resistance of linezolid with other drugs like anti-TB or antibiotics. Linezolid is classified as Reserve Group antibiotic in the WHO model Essential medicines list due to its valuable status in treating multi drug resistance infections (Abdelsalam Elshenawy *et al.* 2023). Rational use is advised meaning the judicious choice as well as correct handling, dosing and quality assurance of reserve group antibiotic is advised to ensure their longer efficacious use in combating MDR infections.

Linezolid is normally well tolerated. The most common ADRs for linezolid are vomiting, headache, nausea and diarrhea. Some other adverse reactions have also been documented, like neuropathy, reversible myelosuppression and thrombocytopenia. These ADRs are more prevalent with a long duration of treatment and with high exposure to the drug (Clemett and Markham 2000). Its exposure varies between patients as administration of a normal dose of 600 q12h can lead to toxic effects or failure of treatment (Boak *et al.* 2014).

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Linezolid shows 100% bioavailability after oral administration, as it is completely absorbed due to its lipophilic nature. On intravenous administration, it shows 40L to 50L volume of distribution and 31% is bound to plasma proteins. Pharmacokinetics of linezolid show similar patterns in both adult and children. In children, the equivalent dose on the basis of mg/kg shows a shorter half-life and elevated clearance compared to adult patients (Caroline and Linezolid 2003).

Linezolid is bio-transformed by a non-enzymatic oxidation reaction into two inactive metabolites. It is a nonselective and reversible inhibitor of an enzyme called monoamine oxidase (MAO) (Abe *et al.* 2009) and therefore it may interact with drugs acting on serotonin and adrenergic receptors (Caroline and Linezolid 2003; Reddy *et al.* 2002). The elimination of linezolid occurs through the renal as well as hepatic route. About 30% of the administered drug is eliminated in urine unchanged, while 65% is cleared via routes other than the kidney (Dryden 2011).

As linezolid is a narrow therapeutic index drug and variability in plasma concentration may lead to either toxicity or therapeutic failure. Therefore, population pharmacokinetic (popPK) study is having significant impact on rationale use of linezolid through identification of significant covariates responsible for variation in pharmacokinetics. Recent studies on popPK of linezolid have highlighted the importance of identifying factors which need to be considered for optimizing the dosage regimen and minimizing the risk of toxicity as well as therapeutic failure (Bai *et al.* 2022; Xu *et al.* 2023).

Sophisticated modeling techniques have been used in recent studies to explicate the pharmacokinetics of linezolid among different populations. For example, a popPK study demonstrated that the dosing strategies can be designed on the basis of area under the plasma concentration curve (AUC) in order to achieve the therapeutic target for patients with multidrug resistant tuberculosis (MDR-TB) (Zhang *et al.* 2023). Similarly, a model-informed precision dosing (MIPD) technique was used to tailor linezolid therapy by considering the individual patient characteristics and thereby reducing the risk of adverse drug reactions and treatment failure (Keutzer *et al.* 2023; Mockeliunas *et al.* 2022). Moreover, the influence of different factors such as age, body weight, renal status, and comorbidities on the pharmacokinetics of linezolid has been identified in recent studies. For instance, body weight and estimated glomerular filtration rate (eGFR) have been identified as significant covariates for linezolid clearance in preterm infants, which emphasizes the need for dose optimization (Minotti *et al.* 2022). In adult patients, renal impairment has been identified as most common covariate responsible for variation in linezolid clearance which necessitates the vigilant monitoring and careful dose optimization in order to warrant the safe therapy (Bai *et al.* 2022; Qin *et al.* 2022; Xu *et al.* 2023). In short, the studies on linezolid pharmacokinetics can provide the framework for precision medicine not only to enhance the therapeutic outcome but also to minimize the adverse drug events (Wu *et al.* 2022).

The purpose of this pharmacokinetic study was to develop a popPK model of linezolid in Pakistani patients after general surgical procedures and also to identify the covariates causing the interindividual variability of linezolid CL in Pakistani patients.

MATERIALS AND METHODS

Study design

This was a single-center and non-interventional study conducted in surgical patients of the District Headquarter Hospital (DHQ), Gujranwala, Pakistan. All those patients were included who received linezolid as their routine treatment after surgery. The selection of dose was on discretion of attending surgeons. Ethical approval was obtained from the ethical review committee of the University of Veterinary and Animal Sciences (UVAS), Lahore, Pakistan (Letter No. 023/IRC/BMR, dated 09-10-2018). The sample collection complied with the Declaration of Helsinki for clinical studies (Goodyear *et al.* 2007). Written consent got signed by the patients or their attendants after explaining the purpose of sampling and the objectives of the study.

Patients' selection and sample collection

A total number of 215 samples from 59 post-operative patients were collected after the administration of first dose of linezolid. The centrifugation of collected blood samples was performed at 5000 RPM in order to obtain the plasma and stored at -20°C until the analysis of the samples. The patients' demographics including age, weight, sex, serum creatinine (SeCR) and creatinine clearance (CRCL) were recorded. The CRCL was calculated by using patients' age, body weight, gender and serum creatinine (Cockcroft and Gault 1976).

Sample analysis

The collected samples were quantified for the plasma concentrations of linezolid using an already validated high performance liquid chromatography (HPLC) method for the quantification of linezolid and moxifloxacin in plasma. Briefly, the sample analysis was performed on HPLC Agilent 1100 series with an auto-injector. The separation was done on a C18 (250 x 4.6 mm, 5 µm) column. A mixture of 0.1% formic acid and acetonitrile with ratio of 25:75, v/v was used as mobile phase with 1 mL/min isocratic flow rate (Paal *et al.* 2018). The calibration curve range for standard curve was 0.5 mg/L to 30 mg/L which was linear with coefficient of determination $r^2 \geq 0.999$. The sensitivity of the method was 0.5 mg/L with a RSD% of 14.5% for precision.

Base model development

The data of plasma concentration of linezolid was used to develop a base model using NONMEM® software version 7.4.1 along with the PsN (Pearl-speaks-NONMEM) toolkit (Lindbom *et al.* 2004). The execution of model, management of model and report generations were performed by using Pirana (Keizer *et al.* 2011). The pharmacokinetic parameters of linezolid were estimated by applying first order conditional estimation method (FOCE), while the variability in pharmacokinetic parameters among the individuals described as interindividual variability (IIV) was observed by exponential random effect modeling. The residual error between the observed concentrations and predicted concentrations of linezolid was described by additive, proportional as well as combined residual error modeling (Dosne *et al.* 2016).

Analysis of covariates

Once the base model was developed, the influence of available covariates was observed for variation in linezolid CL by using the stepwise covariate modeling (SCM) technique. The patients' demographics included in covariate analysis were age, weight, sex, SeCR and CRCL. Forward inclusion of covariates with a significance level α=0.05 and backward elimination of covariates with stricter criteria for the significance level (α=0.01) were employed for the covariate analysis. A covariate was included in the model if the drop in Objective Function Value (OFV) of the nested models was more than 3.84 points with that covariate during forward inclusion process. The included covariate was removed if the rise in OFV was more than 6.65 points between two nested models during the backward elimination process. The model obtained after the covariate analysis was chosen as the final model (Eekhout *et al.* 2017).

Model evaluation

The evaluation of final model was performed for predictive performance, stability as well as robustness of final model. The predictive performance was judged by the visual examination of goodness-of-fit (GOF) plots. The stability and robustness were evaluated using bootstrap analysis by running the final model 1000 times with a shuffled number of patients, making 1000 new datasets. The pharmacokinetic parameters of linezolid in the final model were compared with the median pharmacokinetic and model parameters of the bootstraps along with 95% (2.5^{th} and 97.5^{th}) confidence intervals.

RESULTS

Patients' demographics

A number of 215 blood samples obtained from 59 patients post operative patients were included in this particular study meaning an average of 3-4 samples per patient. table 1 shows the summary of the demographics of patients and sampling record.

Table 1: Patients' demographics and sampling data

Patients and sampling data	Median (range)
Number of patients	59
Male/Female	24/35
Age (Years)	54 (25-86)
Body Weight (kg)	74 (50-129)
Serum creatinine (mg/dL)	1.2(0.7-2.9)
Creatinine clearance (mL/min)	101.5 (15.9-177.2)
Samples data	
Total number of samples	215
Samples/patient (Average)	3 to 4
Single dose (mg)	400 to 750
Concentration (mg/L)	7.42 (0.44 to 23.98)

Table 2: Comparison of final model estimates with Bootstrap estimates

Parameter	Final estimates	RSE%	Bootstrap estimates	95% CI[a]	Bias%
OFV	670.1		656.9	582.6 to 732.9	1.97
CL (L/h)[b]	3.72	6	3.69	3.31 to 4.23	0.81
V (L)	36.9	8	37	31.4 to 43.1	-0.27
Proportional error (%)	0.115	39	0.112	0.059 to 0.213	2.61
CL-CRCL[c]	0.0051	17	0.0052	0.003 to 0.007	-1.96
IIV CL (%)[d]	36.7	43	34.4	12.08 to 50.8	6.48
IIV V (%)d	52.7	38	50.8	33.45 to 72.8	3.58

[a]95% confidence interval based on 2.5^{th} to 97.5^{th} percentiles. [b]Clearance of linezolid at median CRCL of 101.5 mL/min. [c]Impact for proportional change in clearance with CRCL. [d]Interindividual variability of CL expressed in percentage

Base model development

The data of plasma concentration of linezolid was well described by the one-compartment model according to evaluations by GOF plots and minimal OFV. Moreover, the value for volume of distribution of peripheral compartment (V_2) and intercompartmental clearance were not stable with a two-compartment model. The interindividual variability was better quantified by the exponential model while the error between observed concentrations and predicted concentrations of linezolid was defined the proportional error.

Analysis of covariates

Use of SCM revealed that the CRCL significantly affected the clearance of linezolid in Pakistani patients and the OFV of the model was reduced by 15.8 points after inclusion of CRCL in the final model. The median value for linezolid clearance (CL) was 3.72 L/h while median value for volume of distribution (Vd) was 36.9 L. The interindividual variability (IIV) on linezolid CL was 36.7% while that on Vd was 52.7%. The influence of CRCL on linezolid CL for the estimation of linezolid CL in individual patients for subsequent dose optimization can be calculated by using equation 1.

$$CL_j = CL_{med} \text{ X } (1 + 0.0051 \text{ X } (CRCLj - 101.53) \quad \text{Eq. 1}$$

Where CL_j and $CRCL_j$ are the values of clearance of linezolid and CRCL of the j^{th} individual and 101.53 mL/min is the median CRCL of the patients included.

The dose of linezolid can be calculated for an individual patient by using Equation 2 (Leon Shargel 2015):

$$\text{Dose}_j = \text{Dose}_{\text{Normal}} \times \frac{CL_j}{CL_{\text{Normal}}} \quad \text{Eq. 2}$$

Where Dose_j is the dose administered on the patients with $CRCL_j$, Dose Normal is the dose administered on patients with a median CRCL (that is 101.53 mL/min), CL_j is the linezolid CL of the patient with the given CRCL and CL_{Normal} is the linezolid CL in the patient with a median CRCL (101.53 mL/min). The interrelationship of the CRCL of the patient and the determined CL of linezolid is displayed in fig. 1 where the CL of linezolid increased with the increase in the CRCL of patients.

Model evaluation

The graphical presentation of goodness of fit plots is shown in fig. 2. The scatterplots of dependent variable (DV) and population predictions (PRED) show closeness of values (fig. 2a) which is further increased in scatterplots of DV and individual predictions (IPRED) (fig. 2b), indicating that the final model is good for the prediction of linezolid concentrations in individual patients. The values for conditional weighted residuals (CWRES), when plotted against PRED and time after dose, are distributed randomly around the zero line, and more than 95% of values are distributed within the acceptable range (fig. 2c & 2d). The results for bootstrap analysis and comparison with final model are shown in table 2. The pharmacokinetic parameters of the final model were compared with bootstrap estimates along with the 95% confidence interval. All the values of final model estimates were close to the bootstrap estimates with small values of bias as shown in table 2.

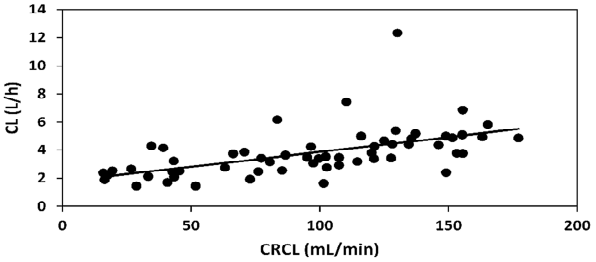

Fig. 1: Scatter plots showing systematic relationships of CRCL versus CL of linezolid

DISCUSSION

Dose tailoring can be achieved through the identification of specific patient characteristics within a population, as well as a comprehensive understanding of the various factors contributing to the pharmacokinetic variability of a given drug. This particular study was carried out using Non-Linear Mixed Effect Modeling (NONMEM®) software to study the pop PK of linezolid in 59 patients by using a pop PK modelling approach. The main goal of the research was to investigate the impact of different covariates, especially age, weight and CRCL, on the pharmacokinetics of linezolid in Pakistani patients.

Linezolid is an antibiotic used in life-threatening infections with MDR cases (Alghamdi *et al.* 2020). So, this study has significance as the pharmacokinetics of patients with life-threatening conditions could be changed and the alteration in volume of distribution can cause interindividual variability of plasma concentration. Drug clearance is altered because of the function of the compromised vital organ (Sazdanovic *et al.* 2016). Linezolid is normally well tolerated but when administered for a longer duration (more than 12 days) it can increase the chance of myelosuppression (Clemett and Markham 2000; Rabon *et al.* 2018). Its exposure varies between patients: Administration of a normal dose of 600 mg in BD can lead to toxic effects or even treatment failure (Boak *et al.* 2014). The risk of myelosuppression, associated with exposure of linezolid in the body, was clearly identified (Cattaneo *et al.* 2013; Dong *et al.* 2014; Tsuji *et al.* 2011).

In our study, the data was most accurately evaluated by a one-compartment modeling approach, as the values for the volume of the peripheral compartment along with the goodness-of-fit plots were not stable for the two-compartment model. The characterization of data using a one-compartment model aligns with the PopPK models of

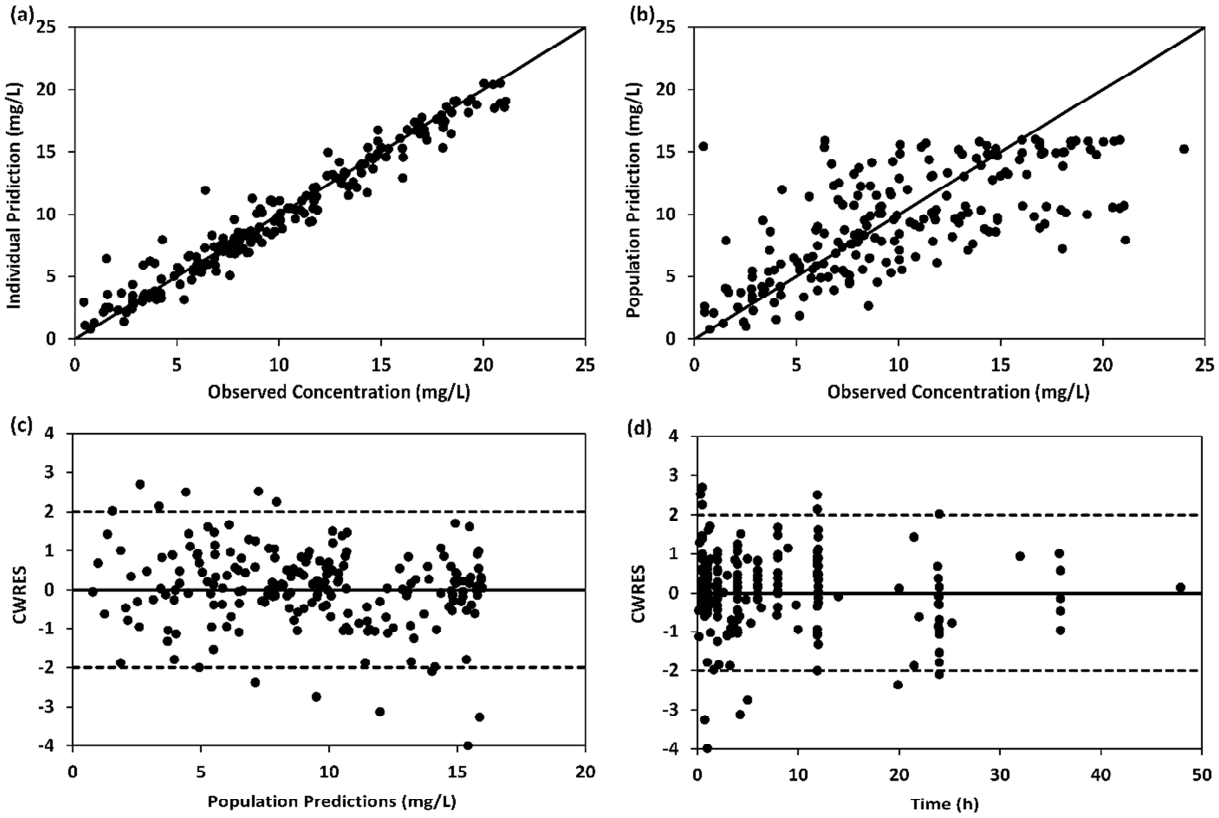

Fig. 2: Combined GOF plots of the final model. (a) observed concentrations versus population predictions, (b) observed concentrations versus individual predictions, (c) CWRES versus population predictions, and (d) CWRES versus time after initial dose of linezolid.

linezolid reported in prior studies conducted on patients with infectious disease (Abe *et al.* 2009), tuberculosis (Alghamdi *et al.* 2020), renal dysfunction (Brier *et al.* 2003), pediatric patients (Li *et al.* 2019), patients with liver dysfunction (Zhang *et al.* 2020), and critically ill patients receiving renal replacement therapy (Roger *et al.* 2016). Although the two-compartment model was reported in a few studies (Soraluce *et al.* 2020; Swoboda *et al.* 2010; Xie *et al.* 2018), the one-compartment model was used here as it would have been difficult to fix parameters for the two-compartment model.

The value for linezolid clearance was 3.72 L/h which is within the range as reported in most of the previously reported popPK studies of linezolid where the value of CL was found as 3.8 L/h in critically ill patients (Roger *et al.* 2016), 2.85 L/h in Japanese patients (Sasaki *et al.* 2011) and 3.57 L/h in African patients (Abdelwahab *et al.* 2021). However, lower value of linezolid CL was reported in elderly patients as 1.28 L/h (Abe *et al.* 2009), patients with renal dysfunction as 2.21 L/h (Tsuji *et al.* 2013) and patients with liver dysfunction as 2.68 L/h (Zhang *et al.* 2020) which can be justified by compromised renal and hepatic status of the patients as linezolid is eliminated through both routs. The CL of linezolid was significantly influenced by renal status of the patients described by creatinine clearance. This finding is in line with the other studies as the most common covariate reported in previous studies conducted in different clinical conditions is also renal status of the patients (Alghamdi *et al.* 2020; Li *et al.* 2019; Sasaki *et al.* 2011; Soraluce *et al.* 2020; Tsuji *et al.* 2011; Zhang *et al.* 2020). The findings of this study can be used in clinical setting to optimize the dose of linezolid in individual patients based on the renal status as described in equation 1 and equation 2. The ultimate advantage of this practice will be implementation of safe therapeutic strategy for treatment with linezolid in surgical patients.

The other significant covariates reported are age and body weight (Abe *et al.* 2009; Xie *et al.* 2018). As a comparison of significant covariates on linezolid CL in other populations, the CL was significantly influenced by CRCL and liver cirrhosis in Japanese patients (Sasaki *et al.* 2011) while in African patients no significant association was observed among tested covariates on linezolid CL and bioavailability (Abdelwahab *et al.* 2021).

The value for volume of distribution in our population was observed as 36.7 L which is in close agreement to Vd reported in different patients such as 47 L in elderly patients (Abe *et al.* 2009), 40.6 L in tuberculosis patients (Alghamdi *et al.* 2020), 26.5 L in critically ill patients

(Roger *et al.* 2016) and 40.2 L in South African patients (Abdelwahab *et al.* 2021). The most common covariate responsible for IIV of Vd reported in other studies was body weight of the patient however, no significant covariate for Vd was observed in our study which is might be due to the fact that most of the samples were collected during the elimination phase after drug administration.

With the combined residual error model, the difference between observed concentrations and predicted concentrations were investigated and the proportional error was found to be 0.115%, while in other studies both proportional and additive errors were determined (Sasaki *et al.* 2011), or only proportional errors found in three studies was 19.8%, 9.53% and 16.48%, respectively (Abdelwahab *et al.* 2021; Li *et al.* 2019; Sasaki *et al.* 2011).

CONCLUSION

In this study, creatinine clearance was shown to have a significant effect on the clearance of linezolid, i.e., clearance decreases with decrease in CRCL, which decreases with age. So, in individuals with an impaired renal function, the linezolid dose must be optimized to avoid toxicity. In terms of clinical impact, our findings underscore the critical necessity for personalized dosing strategies when administering linezolid to Pakistani patients.

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REFERENCES

Abdelsalam Elshenawy R, Umaru N and Aslanpour Z (2023). WHO AWaRe classification for antibiotic stewardship: Tackling antimicrobial resistance - a descriptive study from an English NHS Foundation Trust prior to and during the COVID-19 pandemic. *Front Microbiol*., **14**: 1298858.

Abdelwahab MT, Wasserman S, Brust JCM, Dheda K, Wiesner L, Gandhi NR, Warren RM, Sirgel FA, Meintjes G, Maartens G and Denti P (2021). Linezolid population pharmacokinetics in South African adults with drug-resistant tuberculosis. *Antimicrob. Agents Chemother.*, **65**(12): e0138121.

Abe S, Chiba K, Cirincione B, Grasela TH, Ito K and Suwa T (2009). Population pharmacokinetic analysis of linezolid in patients with infectious disease: Application to lower body weight and elderly patients. *J. Clin. Pharmacol.,* **49**(9): 1071-1078.

Alghamdi WA, Al-Shaer MH, An G, Alsultan A, Kipiani M, Barbakadze K, Mikiashvili L, Ashkin D, Griffith DE, Cegielski JP, Kempker RR and Peloquin CA (2020). Population pharmacokinetics of linezolid in tuberculosis patients: Dosing regimen simulation and target attainment analysis. *Antimicrob. Agents Chemother.,* **64**(10): e01174-01120.

Bai AD, McKenna S, Wise H, Loeb M and Gill SS (2022). Safety profile of linezolid in older adults with renal impairment: A population-based retrospective cohort study. *Open Forum Infect. Dis.,* **9**(12): ofac669.

Boak LM, Rayner CR, Grayson ML, Paterson DL, Spelman D, Khumra S, Capitano B, Forrest A, Li J and Nation RL (2014). Clinical population pharmacokinetics and toxicodynamics of linezolid. *Antimicrob. Agents Chemother.,* **58**(4): 2334-2343.

Brier ME, Stalker DJ, Aronoff GR, Batts DH, Ryan KK, O'Grady M, Hopkins NK and Jungbluth GL (2003). Pharmacokinetics of linezolid in subjects with renal dysfunction. *Antimicrob. Agents Chemother.,* **47**(9): 2775-2780.

Caroline P and Linezolid J (2003). A review of its use in the management of serious gram-positive infections (vol 61, pg 525, 2001). *Drugs,* **63**(19): 2126-2126.

Cattaneo D, Orlando G, Cozzi V, Cordier L, Baldelli S, Merli S, Fucile S, Gulisano C, Rizzardini G and Clementi EJIjoaa (2013). Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. *Int. J. Antimicrob. Agents,* **41**(6): 586-589.

Clemett D and Markham A (2000). Linezolid. *Drugs,* **59**(4): 815-827.

Cockcroft DW and Gault MH (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**(1): 31-41.

Dong H-Y, Xie J, Chen L-H, Wang T-T, Zhao Y-R and Dong Y-L (2014). Therapeutic drug monitoring and receiver operating characteristic curve prediction may reduce the development of linezolid-associated thrombocytopenia in critically ill patients. *Eur. J. Clin. Microbiol. Infect. Dis.,* 33(6): 1029-1035.

Dosne AG, Bergstrand M and Karlsson MO (2016). A strategy for residual error modeling incorporating scedasticity of variance and distribution shape. *J. Pharmacokinet. Pharmacodyn.,* **43**(2): 137-151.

Dryden MS (2011). Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. *J. Antimicrob. Chemother.,* **66**(suppl. 4): 7-15.

Eekhout I, van de Wiel MA and Heymans MW (2017). Methods for significance testing of categorical covariates in logistic regression models after multiple imputation: Power and applicability analysis. *BMC Med. Res. Methodol.*, **17**(1): 129.

Goodyear MD, Krleza-Jeric K and Lemmens T (2007). The declaration of Helsinki. *BMJ,* **335**(7621): 624-625.

Ippolito JA, Kanyo ZF, Wang D, Franceschi FJ, Moore PB, Steitz TA and Duffy EM (2008). Crystal structure of the oxazolidinone antibiotic linezolid bound to the 50S ribosomal subunit. *J. Med. Chem.,* **51**(12): 3353-3356.

Keizer RJ, Van Benten M, Beijnen JH, Schellens JH and Huitema AD (2011). Pirana and PCluster: A modeling environment and cluster infrastructure for NONMEM. *Comput. Methods Programs Biomed.,* **101**(1): 72-79.

Keutzer L, Mockeliunas L, Sturkenboom MGG, Bolhuis MS, Akkerman OW and Simonsson USH (2023). Derivation and clinical utility of safety targets for linezolid-related adverse events in drug-resistant tuberculosis treatment. *Pharmaceuticals* (Basel). **16**(11): 1-18.

Leon Shargel ABY (2015). Applied biopharmaceutics and Pharmacokinetics (7th ed.), McGraw Hill Education.

Li SC, Ye Q, Xu H, Zhang L and Wang Y (2019). Population pharmacokinetics and dosing optimization of linezolid in pediatric patients. *Antimicrob. Agents Chemother.,* **63**(4): e02387-02318.

Lindbom L, Ribbing J and Jonsson EN (2004). Perl-speaks-NONMEM (PsN) — a Perl module for NONMEM related programming. *Comput. Methods Programs Biomed.,* **75**(2): 85-94.

Minotti C, Bonadies L, Liberati C, De Pieri M, Giaquinto C, Baraldi E and Donà D (2022). Enteral linezolid as an effective option to treat an extremely preterm infant with bacillus cereus sepsis. *Children* (Basel), **9**(3): 415.

Mockeliunas L, Keutzer L, Sturkenboom MGG, Bolhuis MS, Hulskotte LMG, Akkerman OW and Simonsson USH (2022). Model-informed precision dosing of linezolid in patients with drug-resistant tuberculosis. *Pharmaceutics,* **14**(4): 753.

Paal M, Zoller M, Schuster C, Vogeser M, Schütze G. 2018. Simultaneous quantification of cefepime, meropenem, ciprofloxacin, moxifloxacin, linezolid and piperacillin in human serum using an isotope-dilution HPLC–MS/MS method. *J. Pharm. Biomed. Anal.,* **152**: 102-110.

Qin Y, Zhang LL, Ye YR, Chen YT, Jiao Z. 2022. Parametric population pharmacokinetics of linezolid: A systematic review. *Br. J. Clin. Pharmacol.,* **88**(9): 4043-4066.

Rabon AD, Fisher JP and MacVane SHJAoP (2018). Incidence and risk factors for development of thrombocytopenia in patients treated with linezolid for 7 days or greater. *Ann. Pharmacother.,* **52**(11): 1162-1164.

Rao GG, Konicki R, Cattaneo D, Alffenaar J-W, Marriott DJ and Neely M (2020). Therapeutic drug monitoring can improve linezolid dosing regimens in current clinical practice: A review of linezolid pharmacokinetics and pharmacodynamics. *Ther. Drug Monit.,* **42**(1): 83-92.

Reddy KK, Rao SM, Reddy GO, Suresh T, Babu JM, Dubey P and Vyas K (2002). Isolation and characterization of process-related impurities in linezolid. *J. Pharm. Biomed. Anal.,* **30**(3): 635-642.

Roger C, Muller L, Wallis S, Louart B, Saissi G, Lipman J, Lefrant J and Roberts JA (2016). Population pharmacokinetics of linezolid in critically ill patients on renal replacement therapy: Comparison of equal doses in continuous venovenous haemofiltration and continuous venovenous haemodiafiltration. *J. Antimicrob. Chemother.,* **71**(2): 464-470.

Sasaki T, Takane H, Ogawa K, Isagawa S, Hirota T, Higuchi S, Horii T, Otsubo K and Ieiri I (2011). Population Pharmacokinetic and pharmacodynamic analysis of linezolid and a hematologic side effect, thrombocytopenia in Japanese patients. *Antimicrob. Agents Chemother.,* **55**(5): 1867-1873.

Sazdanovic P, Jankovic SM, Kostic M, Dimitrijevic A and Stefanovic S (2016). Pharmacokinetics of linezolid in critically ill patients. *Expert Opin. Drug Metab. Toxicol.,* **12**(6): 595-600.

Soraluce A, Barrasa H, Asín-Prieto E, Sánchez-Izquierdo JÁ, Maynar J, Isla A and Rodríguez-Gascón A (2020). Novel population pharmacokinetic model for linezolid in critically ill patients and evaluation of the adequacy of the current dosing recommendation. *Pharmaceutics,* **12**(1): 54.

Swoboda S, Ober MC, Lichtenstern C, Saleh S, Schwenger V, Sonntag H-G, Haefeli WE, Hempel G, Hoppe-Tichy T and Weigand MA (2010). Pharmacokinetics of linezolid in septic patients with and without extended dialysis. *Clinical Trial,* **66**(3): 291-298.

Tsuji Y, Mizoguchi A, Sadoh S, Hiraki Y, Matsumoto K, Morita K, Kobayashi T, Kamimura H, Karube Y (2011). Thrombocytopenia and anemia caused by a persistent high linezolid concentration in patients with renal dysfunction. *J. Infect. Chemother.,* **17**(1): 70-75.

Tsuji Y, Yukawa E, Hiraki Y, Matsumoto K, Mizoguchi A, Morita K, Kamimura H, Karube Y and To H (2013). Population pharmacokinetic analysis of linezolid in low body weight patients with renal dysfunction. *J. Clin. Pharmacol.,* **53**(9): 967-973.

Vinh DC and Rubinstein E (2009). Linezolid: A review of safety and tolerability. *J. Infect. Chemother.,* **59**: S59-S74.

Wu F, Zhang XS, Dai Y, Zhou ZY, Zhang CH, Han L, Xu FM, Wang YX, Shi DW, Lin GY, Yu XB and Chen F (2022). Dosage strategy of linezolid according to the trough concentration target and renal function in Chinese critically ill patients. *Front. Pharmacol.,* **13**: 844567.

Xie F, Mantzarlis K, Malliotakis P, Koulouras V, Degroote S, Koulenti D, Blot S, Boussery K, Van Bocxlaer J and Colin P (2018). Pharmacokinetic evaluation of linezolid administered intravenously in

obese patients with pneumonia. *J. Antimicrob. Chemother.,* **74**(3): 667-674.

Xu Y, Yang X, Liang P and Qu C (2023). Linezolid dose adjustment according to therapeutic drug monitoring helps reach the goal concentration in severe patients, and the oldest seniors benefit more. *BMC Infect. Dis.,* **23**(1): 840.

Zhang H, He Y, Davies Forsman L, Paues J, Werngren J, Niward K, Schön T, Bruchfeld J, Alffenaar JW and Hu Y (2023). Population pharmacokinetics and dose evaluations of linezolid in the treatment of multidrug-resistant tuberculosis. *Front. Pharmacol.,* **13**: 1032674.

Zhang S-h, Zhu Z-y, Chen Z, Li Y, Zou Y, Yan M, Xu Y, Wang F, Liu M-z, Zhang M and Zhang B-K (2020). Population pharmacokinetics and dosage optimization of linezolid in patients with liver dysfunction. *Antimicrob. Agents Chemother.,* **64**(6): e00133-00120.