Pharmacokinetics and Pharmacodynamics of Linezolid following Intragastric and Intravenous Administrations in ICU Patients

Zhidan Sun
second affiliated hospital of Harbin Medical University

Xing Zhang
Second Affiliated Hospital of Harbin Medical University

Junbo Zheng
Second Affiliated Hospital of Harbin Medical University

Guiying Hou
Second Affiliated Hospital of Harbin Medical University

Qiuyuan Han
Second Affiliated Hospital of Harbin Medical University

Zhidong Qi
Second Affiliated Hospital of Harbin Medical University

Rui Huang
Second Affiliated Hospital of Harbin Medical University

Yang Yu
Second Affiliated Hospital of Harbin Medical University

Gaofeng Liu
Second Affiliated Hospital of Harbin Medical University

Yang Gao
First Affiliated Hospital of Harbin Medical University

Ming Ye
Second Affiliated Hospital of Harbin Medical University

Ming Li
Second Affiliated Hospital of Harbin Medical University

Kaijiang Yu
First Affiliated Hospital of Harbin Medical University

Hong-Liang Wang (✉ icuwanghongliang@163.com)
Second Affiliated Hospital of Harbin Medical University   https://orcid.org/0000-0002-1407-0072

Research

Abstract

Background. Though intravenous infusion linezolid therapy is common for patients in the intensive care unit (ICU), intragastric linezolid therapy is also provided for those whose gastrointestinal function are feasible. If intragastric linezolid acquired similar pharmacokinetics (PK) and pharmacodynamics (PD) parameters, this might be preferred based on cost and ease of liquid volume management.

Methods. Patients in the ICU treated with intragastric and intravenous linezolid were included. Serial blood samples were collected and linezolid concentrations were measured. PK data were analyzed using Pmetrics. Monte Carlo simulations were used to evaluate PD target achievement.

Results. T_{max} was 1.06 ± 0.82 h of the study period in 10 patients receiving intragastric linezolid and 0.65 ± 0.24 h in 10 patients receiving intravenous linezolid (p<0.001). C_{max} was 9.07 ± 4.99 mg/mL of patients with intragastric linezolid and 12.30 ± 4.06 mg/mL of patients with intravenous linezolid (p=0.904). Clearance was 11.99 ± 11.24 L/h in patients with intragastric linezolid and 14.48 ± 3.56 L/h in patients with intravenous linezolid (p=0.342). For infections with a microorganism with a minimum inhibitory concentration (MIC) of 2 mg/L, simulations demonstrated that with 600 mg every 12 hours, 58.22% would have a linezolid concentration greater than the MIC during 100% of the dosing interval (%T > MIC = 100%) in intragastric group, whereas this was 71.36% in intravenous group. Higher SOFA score and body weight were associated with lower probability of target attainment (PTA) of linezolid with standard regimen.

Conclusions. Patients in ICU may be at high risk for underexposure to linezolid by intragastric administration, especially when their SOFA score and body weight is high and when infected with pathogens with an MIC ≥ 2 mg/L.

Introduction

The preference for intravenous antimicrobial therapy is common in the intensive care unit (ICU), as timely and adequate antimicrobial treatment is essential for improving clinical outcome[1]. ICU patients often need multiple medications, careful fluid management and more medical expenses[2]. Most infected patients in ICU should be treated with 7 days of antibiotics at least[3]. Intravenous administration of linezolid requires additional expense[4], equipment, and liquid volume as compared with intragastric therapy. If administration of intragastric linezolid could provide anti-infective effects comparable with intravenous administration, it might be alternative because of lower cost and greater ease of liquid volume management.

As the first synthetic oxazolidinone antibiotic, linezolid is effective against gram-positive bacteria in critically ill patients[5]. The bioavailability of linezolid is about 100% in health population[6] and obese subjects before and after Roux-en-Y gastric bypass surgery[7]. For a patient who has feasible gastrointestinal function, it is expected to use intragastric linezolid therapy instead of intravenous

therapy. However, whether intragastric administration of linezolid once the patient is in gastrointestinal feeding condition would exhibit efficacy similar to those with intravenous therapy is unknown.

Individualised dosing based on population pharmacokinetics (PK) / pharmacodynamics (PD) models has been shown to increase the probability of achieving therapeutic drug exposures and the likelihood of clinical success[8]. The efficacy of linezolid treatment is reached with %T > MIC of 100% and AUC/MIC values ranging from 80 to 120[9]. Inter- and intraindividual PK variability is extreme in ICU patients[10], whether intragastric linezolid can achieve effective PK/PD target requires further exploration.

To determine whether intragastric linezolid achieves the similar anti-infective effect to intravenous linezolid in the critically ill population, we conducted a randomized controlled trial of intragastric linezolid vs intravenous linezolid in ICU patients.

Methods

Study Design and Patients

Patients with evidence of gram-positive bacteria cultured from sites of infection were enrolled in the study during March 2017 to March 2017, and written informed consent was obtained from all subjects. Exclusion criteria included age ≤ 18 years, recent use of linezolid (within 2 weeks), gastrointestinal bleeding and undergoing hemodialysis or continuous renal replacement therapy.

Study Protocol

The patients were randomly assigned to intragastric or intravenous linezolid group. All patients received linezolid (Zyvox, Pfizer, New York, USA) at 600 mg, scheduled every 12 h. The intravenous group received intravenous linezolid for 60 min. The intragastric group received oral or nasogastric administration for 2 min. Two trained research nurses crushed and dissolved linezolid tablets in 10 mL sterile water for the patients who received nasal feeding. Baseline characteristics, APACHE II, serum albumin, aspartate aminotransferase (AST), and creatinine concentrations were captured within the first 24 hours of administration. Glomerular filtration rate (GFR) was estimated using the Cockroft and Gault formula[11].

Blood Sampling and Drug Assays

A blood sample was collected at the same time as the linezolid adiministration (pre-dose sample), and 0.5, 1, 2, 4, 6, 8, and 12 h (just before the subsequent dose) after the start of infusion of the first and the fifth dose in both intragastric and intravenous groups. Blood samples were centrifuged at 3000 rpm for 10 min at 4 °C. Plasma was then collected and stored at − 80 °C until the assay.

Linezolid concentrations in plasma were measured using a sensitive and selective high-performance liquid chromatography (HPLC; column: Diamonsil ODS, 4.6 × 250 mm, 5 μm; mobile-phase: acetonitrile − 0.01% phosphoric acid water solution (27:73, v/v)) based on previously described researches[12, 13]. The precision and accuracy of the method were evaluated by performing replicate analyses of quality control

samples against calibration standards. Analytical methods were linear ($r^2 > 0.9999$) over the calibration range of 0.25–25 mg/L. Intra- and inter-day precision (relative standard deviation, %) were 2.1% and 5.0%, respectively. The accuracy was within the range of 99.45–104.42%.

Antimicrobial Therapy Responses and Safety Assessment

The antimicrobial effect of linezolid was assessed using the body temperature normalized (< 37.3 °C) within 3 days and 28-day mortality. The safety was determined by the assessment of adverse events reported by the participant or medical provider and laboratory tests monitor. The relationship between adverse reactions and linezolid was graded as definitely related, probably related, possibly related, probably not related or not related.

Pharmacokinetic Modeling

The PK modeling for linezolid was conducted using the Nonparametric Adaptive Grid (NPAG) algorithm within the freely available software Pmetrics package for R (Los Angeles, CA, USA) [14]. One-compartment and two-compartment models were fitted to the linezolid concentration data. PK parameters were estimated based on linezolid concentrations and clearance (CL), central volume of distribution (V) and rate constant for drug distribution from the central to peripheral compartment (Kcp), rate constant for drug distribution from the peripheral to central compartment (Kpc). Patient demographics and pathophysiological factors, which included age, sex, bodyweight, height, BMI, APACHE II, SOFA, serum albumin, AST and GFR, were tested for their association with the identified PK parameters. Model performance was evaluated based on visual fit plots and small Akaike information criterion (AIC).

Monte Carlo Simulation

Monte Carlo simulations (n = 10000) were conducted using Pmetrics to determine the probability of target attainment (PTA) of achieving %T > MIC = 100% for studied regimen. For PD analysis, different MICs at 0.5, 1, 2, and 4 mg/L were tested for *methicillin-resistant Staphylococcus aureus* (*MRSA*), *methicillin-sensitive Staphylococcus aureus* (*MSSA*), *Enterococcus faecalis* (*E. faecalis*), *Enterococcus faecium* (E. faecium), *Viridans Streptococci* (V. Streptococci), *Staphylococcus hominis* (S. hominis) and *Streptococcus pyogenes* (S. pyogenes) on the basis of microorganism susceptibility data obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database (www.eucast.org) [15]. To generate insight in the PTA, 4 different dosing regimens were simulated: 600 mg every 12 h, 600 mg every 8 h, 900 mg every 12 h, and 900 mg every 8 h.

Fractional Target Attainment Calculation

The MIC data for *MRSA*, *MSSA*, *E. faecalis*, *E. faecium*, *V. Streptococci*, *S. hominis* and *S. pyogenes* obtained from the EUCAST database were used to determine fractional target attainment (FTA), which identifies the likely success of treatment by comparing the PTA against the MIC distribution. The FTA was calculated using %T > MIC = 100% for various doses: 600 mg every 12 h, 600 mg every 8 h, 900 mg every 12 h, and 900 mg every 8 h. A dosing regimen was considered optimal if the FTA was ≥ 85%.

Statistical Analysis

A statistical analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL). All data are presented as mean ± SD. The continuous variables were analyzed using the Mann-Whitney U test, and the categorical variables were analyzed using the Fisher's exact test. A P value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 21 patients with gram-positive bacteria infection were enrolled. Of these, 1 patient was excluded from analysis because of gastrointestinal ulcer bleeding. Finally, 320 blood samples were included in the drug concentration analysis. The characteristics of two study groups are shown in Table 1. No significant baseline differences were detected in age, body weight, APACHE II, SOFA score, ALB, AST and GFR between intragastric and intravenous group. The culture results of gram-positive microorganisms are shown in Table 1, the specimens included blood, sputum, bronchoalveolar lavage fluid, ascites or urine.

Table 1
Demographic and clinical data

Patients characteristics	Intragastric group (n = 10)	Intravenous group (n = 10)	P value
Age (years)	59.90 ± 12.22	57.10 ± 10.95	0.932
Male, N (%)	8 (80%)	6 (60%)	0.329
Weight (kg)	69.60 ± 9.34	69.7 ± 9.53	0.832
BMI (kg/m^2)	23.52 ± 2.49	24.65 ± 1.33	0.008
APACHE II at admission	19.40 ± 6.31	17.20 ± 9.52	0.071
SOFA at admission	8.80 ± 3.55	6.20 ± 3.05	0.794
Infection diagnosis, N			
Intra-abdominal infection	1	5	
Pneumonia	8	5	
Urinary tract infection	1	0	
ALB (g/L)	38.74 ± 13.30	26.18 ± 6.61	0.126
AST (U/L)	126.89 ± 241.04	37.9 ± 23.78	0.076
GFR (mL/min)	51.42 ± 38.38	68.07 ± 46.57	0.719
Concomitant beta-lactams antibiotics, N	7	4	0.178
Presence of microorganism, N			
MRSA	2	1	
MSSA	4	3	
E. faecalis	2	1	
E. faecium	0	1	
V. Streptococci	0	1	
S. hominis	1	1	

Data are expressed as the mean ± SD, unless otherwise indicated.

Abbreviations: BMI, Body Mass Index; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; ALB, serum albumin; AST, aspartate aminotransferase; GFR, glomerular filtration rate; *MRSA, methicillin-resistant Staphylococcus aureus*; *MSSA, methicillin-sensitive Staphylococcus aureus*; *E. faecalis, Enterococcus faecalis*; *E. faecium, Enterococcus faecium*; *V. Streptococci, Viridans Streptococci*; *S. hominis, Staphylococcus hominis*; *S. pyogenes, Streptococcus pyogenes*; ICU, intensive care unit.

Patients characteristics	Intragastric group (n = 10)	Intravenous group (n = 10)	P value
S. pyogenes	1	2	
3-day temperature normalized, N(%)	5 (50%)	7 (70%)	0.361
28-day mortality, N (%)	0 (0%)	1 (10%)	0.305
ICU stay (days)	12.80 ± 5.51	9.00 ± 5.81	0.978
Data are expressed as the mean ± SD, unless otherwise indicated.			
Abbreviations: BMI, Body Mass Index; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; ALB, serum albumin; AST, aspartate aminotransferase; GFR, glomerular filtration rate; *MRSA, methicillin-resistant Staphylococcus aureus*; *MSSA, methicillin-sensitive Staphylococcus aureus*; *E. faecalis, Enterococcus faecalis*; *E. faecium, Enterococcus faecium*; *V. Streptococci, Viridans Streptococci*; *S. hominis, Staphylococcus hominis*; *S. pyogenes, Streptococcus pyogenes*; ICU, intensive care unit.			

Outcome

The temperature change between first and third day is shown in Fig. 1. The temperature decreased after linezolid treatment in both groups. Intragastric group had longer ICU stay (12.8 days vs. 9.00 days, P = 0.978) and fewer patients of 3-day temperature normalized (5 vs. 7, P = 0.361) compared to intravenous group as shown in Table 1. None ICU death occurred in both groups. One patient dead at 28 days post-discharge ICU and was attributed to septic shock. Multiple logistic regression analysis showed no evidence of a significant difference between intragastric and intravenous group when adjusted for age, BMI, infection diagnosis and bacteria: the odds ratio (OR) was 2.333 (95% CI: 0.373–14.613; P = 0.365). No adverse effects with linezolid therapy were noted in either group.

Linezolid Concentrations and Model Development

The observed linezolid plasma concentrations for both intragastric and intravenous group are shown in Fig. 2. At the first dose, the patients in the intragastric group had lower linezolid concentrations than those in the intravenous group. Model building was performed using observed 160 plasma linezolid concentrations in each group. A two-compartment model was best fitted the data whether intragastric or intravenous linezolid. The final models had the goodness-of-fit evaluations shown in Fig. 3, as determined by an R-squared of 0.813 in intragastric group and 0.854 in intravenous group. The small AIC score of 655 in intragastric group and of 730 in intravenous group also could be estimated for final models. Between-patient variability could be estimated for linezolid clearance, and coefficient of variation (CV%) was 22.72% in intragastric group and 17.82% in intravenous group. Covariate analysis shown that CL of linezolid was significantly associated with body weight and SOFA score, explaining the between-patient variability.

Pharmacokinetics Parameters

Plasma pharmacokinetic parameters for linezolid from the final covariate pharmacokinetic models analysis are summarized in Table 2. Following intragastric administration, a mean T_{max} occurred at 1.06 h whereas at 0.65 h following intravenous administration (p < 0.001). Intragastric linezolid produced lower C_{max} and AUC compared with intravenous administration (C_{max} 9.07 ± 4.99 mg/mL vs. 12.30 ± 4.06 mg/mL, p = 0.904; AUC 252.27 ± 189.51 mg/mL vs. 293.65 ± 147.86 mg/mL, p = 0.519). The mean volume of distribution for intragastric linezolid was lower than intravenous linezolid (45.97 ± 13.12 L vs. 47.12 ± 5.49 L, p = 0.001). The mean Kcp and Kpc following intravenous administration were higher than those following intragastric administration. The plasma concentrations of linezolid declined slowly in the intragastric group with a mean CL of 11.99 L/h compared to 14.48 L/h in the intravenous group, however, the difference was not significant (p = 0.342). The absolute bioavailability of linezolid was 88.49% ± 1.89% following intragastric administration.

Table 2

Parameter estimates for linezolid from the final covariate two-compartment population pharmacokinetic models in intragastric and intravenous groups

Parameter	Intragastric group	Intravenous group	*P* value
T $_{max}$ (h)	1.06 ± 0.82	0.65 ± 0.24	**< 0.001**
C $_{max}$ (mg/ml)	9.07 ± 4.99	12.30 ± 4.06	0.904
AUC (mg/mL)	252.27 ± 189.51	293.65 ± 147.86	0.519
V (L)	45.97 ± 13.12	47.12 ± 5.49	**0.001**
Kcp (h^{-1})	15.78 ± 2.02	17.87 ± 2.04	0.811
Kpc (h^{-1})	17.30 ± 1.54	16.67 ± 4.22	0.149
CL (L/h)	11.99 ± 11.24	14.48 ± 3.56	0.342
F (%)	88.49 ± 1.89	NA	NA
Data are expressed as mean ± SD.			
Abbreviations: T $_{max}$, time taken to achieve maximal concentration; C $_{max}$, maximal concentration; AUC, area under the curve; V, volume of distribution; Kcp, rate constant for drug distribution from the central to peripheral compartment; Kpc, rate constant for drug distribution from the peripheral to central compartment; CL, clearance; F, bioavailability; NA, Not applicable.			

Dosing Simulations

For microorganisms with a range MIC of 0.5 to 4 mg/mL, the PTAs of linezolid for four dosing regimens in both intragastric and intravenous groups are shown in Fig. 4. The plots show that the PTA decreased in patients receiving linezolid by intragastric administration (Fig. 4A) compared to those by intravenous administration (Fig. 4B). Neither intragastric group nor intravenous group had the PTA of > 75% for the standard linezolid regimen of 600 mg q12h at an MIC of 2 mg/L. Decreasing the linezolid dosing interval or augmenting the linezolid dose improved the PTA of the %T > MIC = 100% PD target. At a MIC of 4 mg/L,

less than 70% of the patients achieved a %T > MIC = 100% with all dosing regimens in the intragastric group. However, more than 70% of patients achieved it with a dosage regimen of 600 mg q 8 h or 900 mg q 8 h in the intravenous group. The PTAs of linezolid for the standard linezolid dose with different MICs based on the SOFA score and body weight are shown in Fig. 5A and 5B. It shows that patients with a higher SOFA score or over weight had lower PTA of linezolid for the dosing regimen of 600 mg q 12 h.

Fractional Target Attainment

For 7 different gram-positive pathogens observed in 20 patients, the FTAs achieved a %T > MIC = 100% with four linezolid dosing regimens by intragastric and intravenous administration against the MIC distribution are shown in Table 3. When treating MRSA, only patients with intravenous linezolid of 600 mg or 900 mg q 8 h can achieve FTA > 85% for %T > MIC = 100%. The FTA of PD target of %T > MIC = 100% for the *E. faecalis* and *E. faecium* with dose 600 mg q 12 h were less than 85% in both intragastric and intravenous patients. In the context of empiric therapy for *V. Streptococci*, *S. hominis*, and *S. pyogenes*, FTA > 85% can be achieved for %T > MIC = 100% in intravenous patients with four dose regimens, but in intragastric patients with more than 600 mg q 12 h.

Table 3

Fractional target attainment for the various linezolid doses for a hypothetical patient with a SOFA score of 8 and body weight of 68 kg by intragastric and intravenous administration for a *MSSA, MRSA, E. faecalis, E. faecium, Viridans Streptococci, Staphylococcus hominis*, and *Streptococcus pyogenes* MIC distribution

Administration	Fractional target attainment (%)						
Intragastric	*MRSA*	*MSSA*	*E. faecalis*	*E. faecium*	*V. Streptococci*	*S. hominis*	*S. pyogenes*
600 mg q 12 h	33.31	41.02	61.06	58.56	72.4	76.00	72.35
900 mg q 12 h	50.89	57.11	72.71	70.64	**81.32**	**84.01**	**81.49**
600 mg q 8 h	65.93	72.81	**87.18**	**85.41**	**94.99**	**96.44**	**94.67**
900 mg q 8 h	80.60	**86.32**	**94.07**	**93.15**	**97.91**	**98.27**	**97.74**
Intravenous							
600 mg q 12 h	46.73	59.17	80.28	77.79	**90.72**	**92.83**	**90.19**
900 mg q 12 h	76.77	81.12	**91.34**	**89.58**	**96.02**	**96.81**	**95.77**
600 mg q 8 h	**85.71**	**91.12**	**96.55**	**96.32**	**98.80**	**98.69**	**98.63**
900 mg q 8 h	**94.78**	**96.88**	**98.84**	**98.71**	**99.50**	**99.18**	**99.47**

Abbreviations: *MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; E. faecalis, Enterococcus faecalis; E. faecium, Enterococcus faecium; V. Streptococci, Viridans Streptococci; S. hominis, Staphylococcus hominis; S. pyogenes, Streptococcus pyogenes*; MIC, minimum inhibitory concentration.

Discussion

This study compared the differences of the PK/PD parameters between intragastric and intravenous linezolid in ICU patients. Our results provide evidence that ICU patients with intragastric administration of linezolid are at substantial risk for underexposure to linezolid than those with intravenous administration. This can be explained by low bioavailability in patients with intragastric administration. The risk for underexposure is also associated with high SOFA score, overweight, and when pathogens with MIC ≥ 2 mg/mL.

Our population PK model of linezolid was best described by a two compartment model, similar to previous studies[16, 17]. The high variability of linezolid PK was observed in present study. It has been shown that the PK of linezolid can be extremely altered in critically ill patients, which is associated with body weight, organ function and renal replacement therapy[18]. We found that patinets with SOFA > 8 and body weight > 68 kg had an increase of linezolid clearance, then resulted in a lower PTA.

The results of our study do not allow us to conclude definitively that intragastric linezolid is noninferior to intravenous in critical patients. The bioavailability of intragastric linezolid observed in this study is inconsistent with that reported in previous studies, which was 100% in health populations and unaltered in the presence of enteral feedings[19, 20]. The lower bioavailability in our study is caused by the reduction of linezolid absorption through the gastrointestinal tract and the loss during crushing and transferring. Inhibition of gastrointestinal tract motility and delayed gastric emptying is a serious problem in critically ill patients[21]. We speculated that linezolid absorption was affected by gastrointestinal dysfunction, especially long T_{max} and low C_{max} in intragastric group. In addition, four patients' linezolid tablets were crushed and dissolved with 10 ml water and injected though nasogastric tube, this procedure may cause the loss of linezolid.

We found that volume of distribution was similar between intragastric and intravenous linezolid administration. However, Kcp was different between intragastric and intravenous therapies. It is generally believed that the rate of drug distribution depends on tissue blood flow and membrane permeability. Low serum album is observed in intravenous group in our study, which lead to accelerating the rate of drug distribution between the peripheral and central compartment, as hypoalbuminaemia is likely to increase the unbound fraction of linezolid which is the only fraction available for distribution[22].

Our results suggested that intravenous linezolid could achieve higher PTA in critically ill patients than intragastric administration. For treatment of gram-positive cocci infections, target %T > MIC = 100% or AUC/MIC ≥ 80 have been proposed for linezolid[23]. The PTA of %T > MIC = 100% target was applied because of the short sampling periods determined by the linezolid dosage intervals and the estimating of ICU stay. C_{min} ≤ 8.2 mg/L was a significant predictor for minimising linezolid-induced thrombocytopenia during treatment[24]. The C_{min} of linezolid was all below 8.2 mg/L in 20 patients of our study population. This simulation showed that the pathogens with MIC ≥ 2 mg/mL did reduce the PTA. This range of MIC is meaningful for clinical treatment, as we found 3 of *S. aureus*, 1 of *E. faecium* and 1 of *S. hominis* had an

MIC of 2 mg/L. Another two studies also revealed the risks of linezolid underdosing in empirical antibiotic therapy for pathogens (MIC ≥ 2 mg/L) in critically ill patients and obese patients[25, 26]. Increasing the linezolid dose or reducing the dose interval was associated with adequate probability of target attainment for MIC ≥ 2 mg/L.

There are some limitations in present study. The size of our study population is small. Our results may not be directly translatable into all ICU patients due to the complexity of their critical illness conditions. In addition, nasal feeding is common in ICU patients. Tablets have to be dissolved for administration in this population, which may cause different absorption effects compared with those who take the whole tablet. In the intragastric linezolid group, four patients were administrated linezolid through nasogastric tube after dissolving the pills because they are unable to take oral tablets.

Conclusions

Intravenous linezolid therapy is superior to intragastric linezolid in critical patients, although our end-points were surrogate PK/PD end-points and not clinical end-points. Using 600 mg every 12 h for linezolid at the EUCAST breakpoint at an MIC ≥ 2 mg/L did not achieve optimal results, especially in the patients with high SOFA score and overweight. Higher dose linezolid therapy combined therapeutic drug monitoring should be considered in these patients.

Declarations

Ethics approval and consent to participate

This prospective clinical PK/PD study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University (No. KY2018-361). Written informed consent was obtained from individual or guardian participants.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

All authors declare no competing interests.

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Corresponding author contact information

Hongliang Wang, Department of Intensive Care Medicine, the Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China. Email: icuwanghongliang@163.com

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Figures
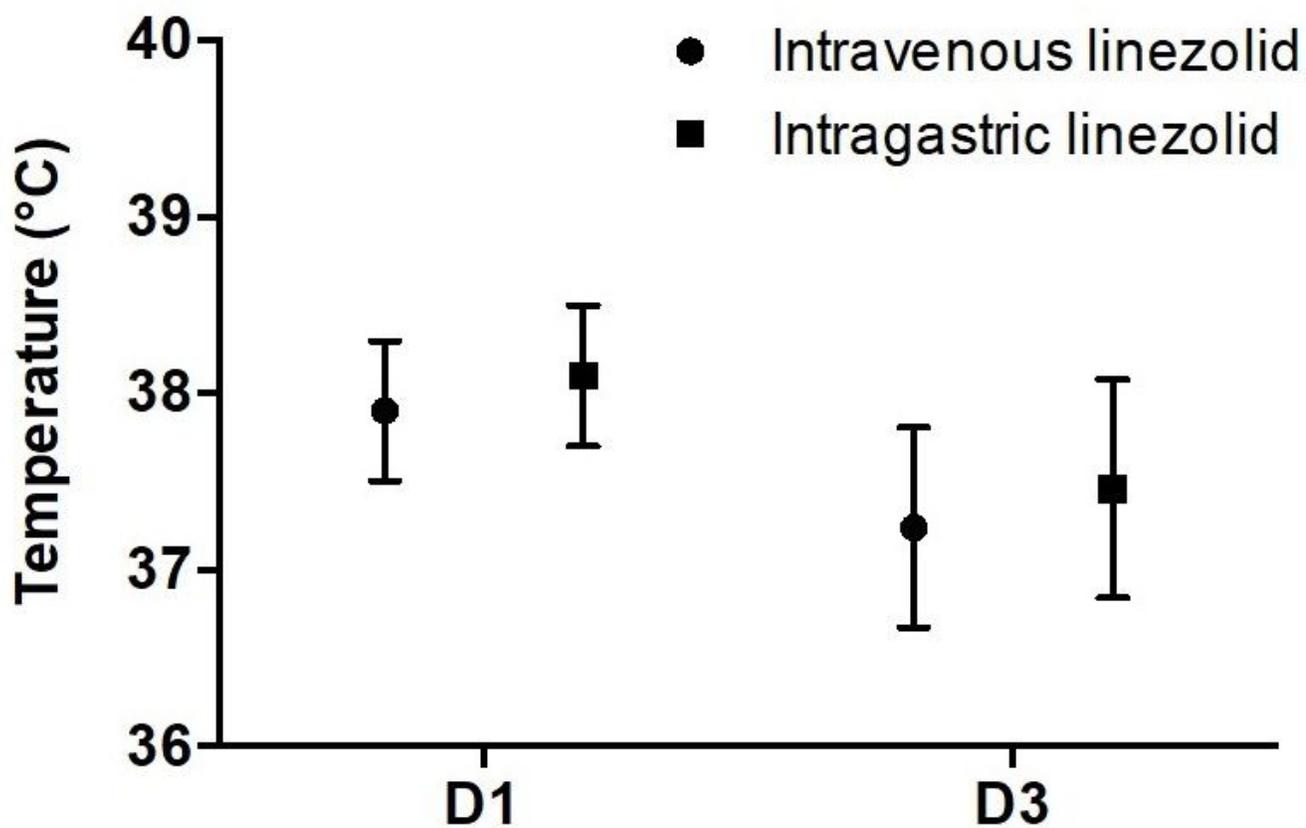
Figure 1

Daily maximum temperature between the first and third day of linezolid administration.
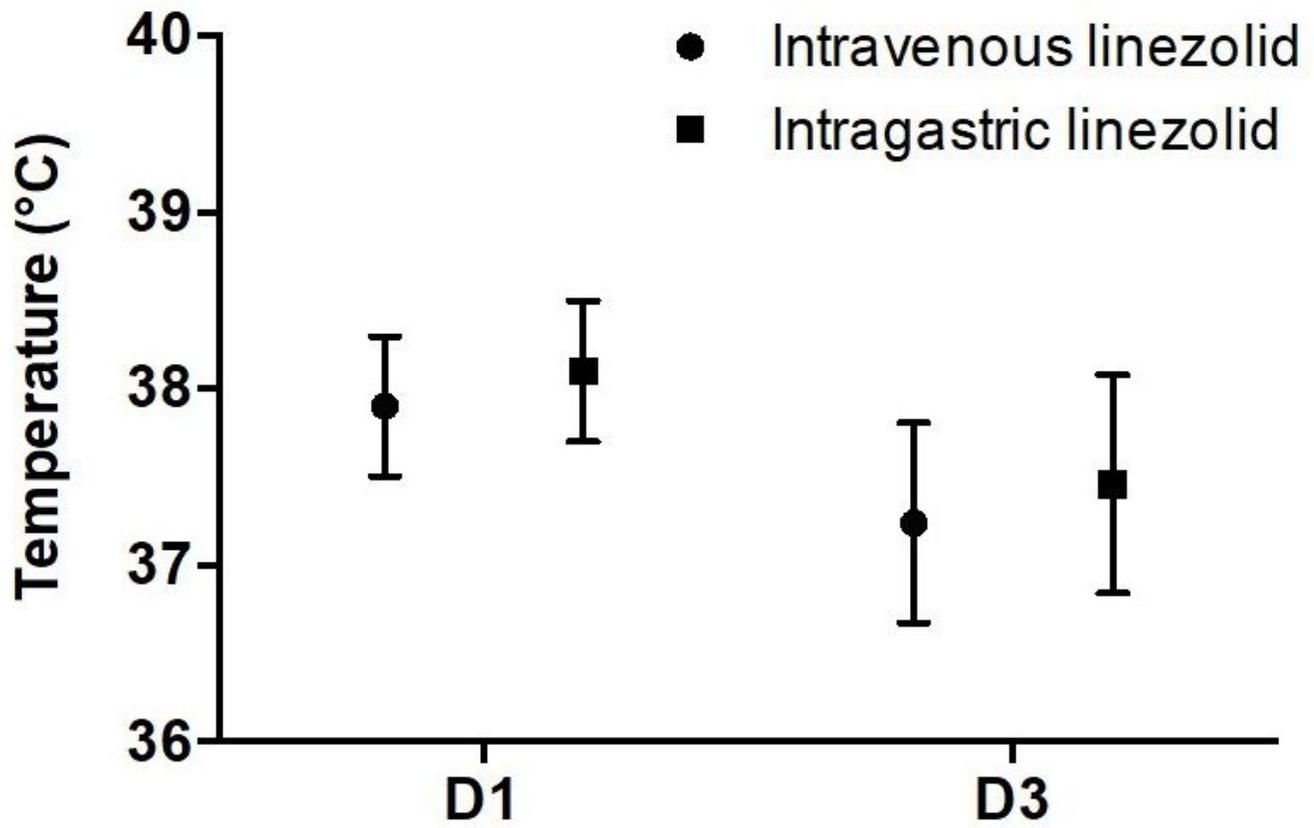
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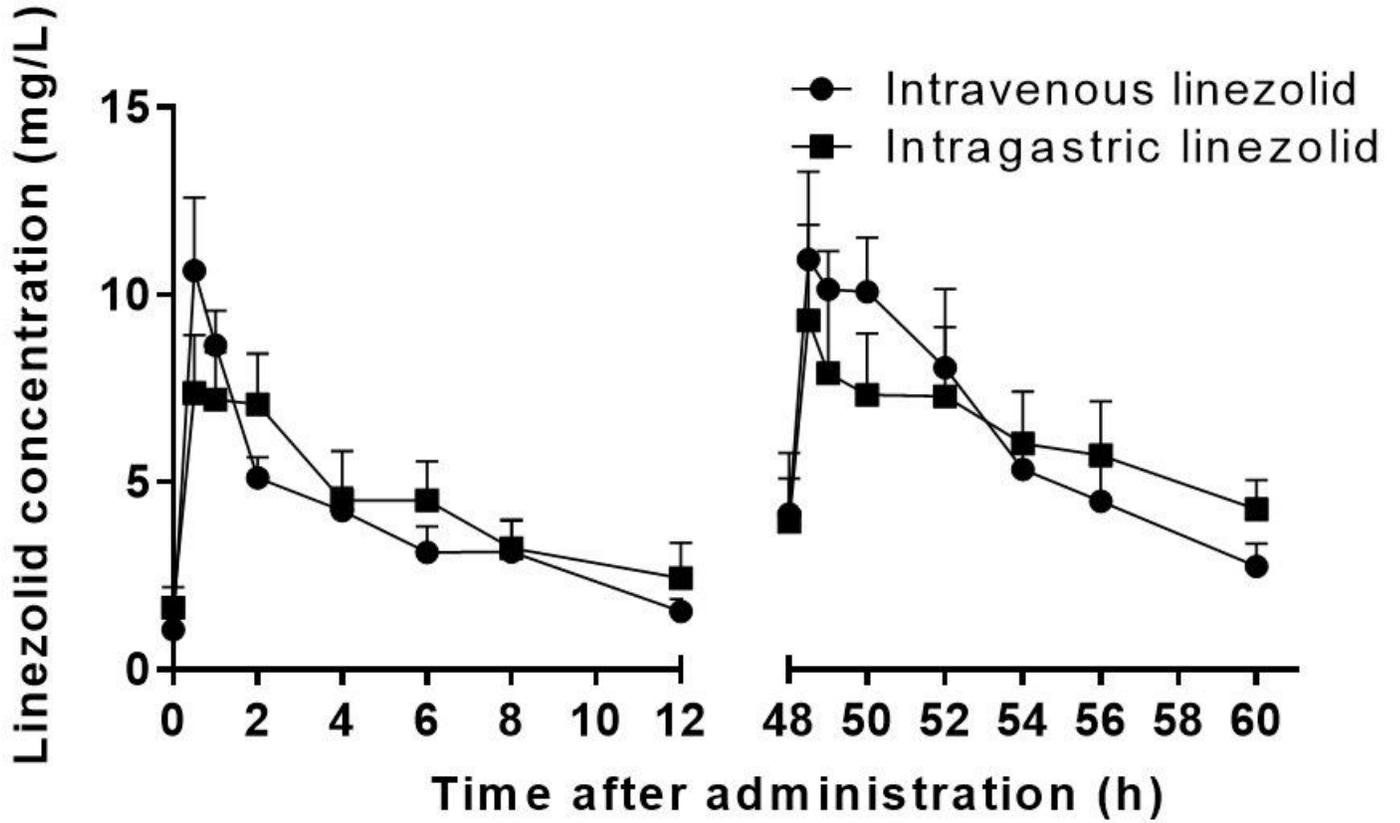
Figure 2

Observed total linezolid concentration-time data after the initial dose (A) and multiple doses (B) in ICU patients with intragastric and intravenous linezolid.
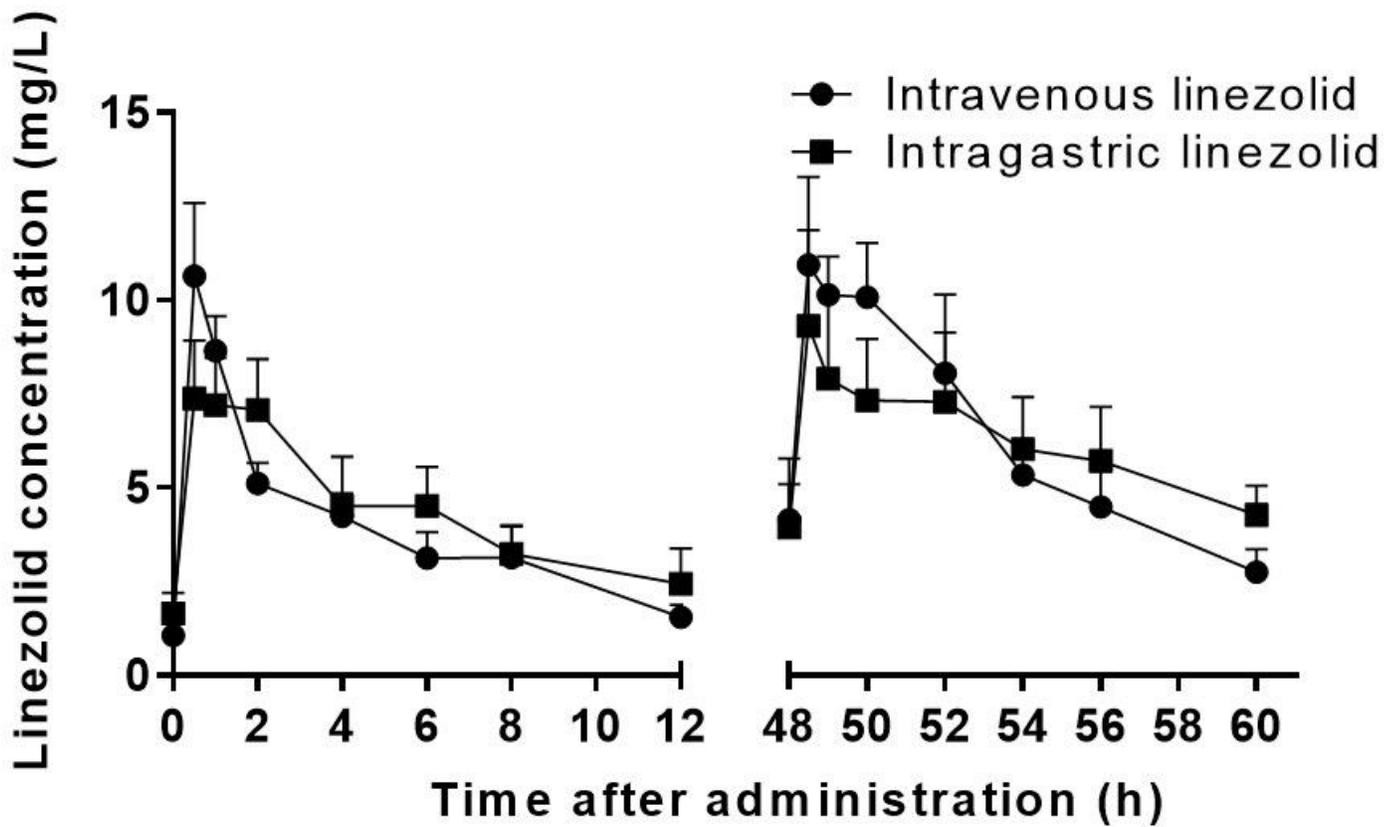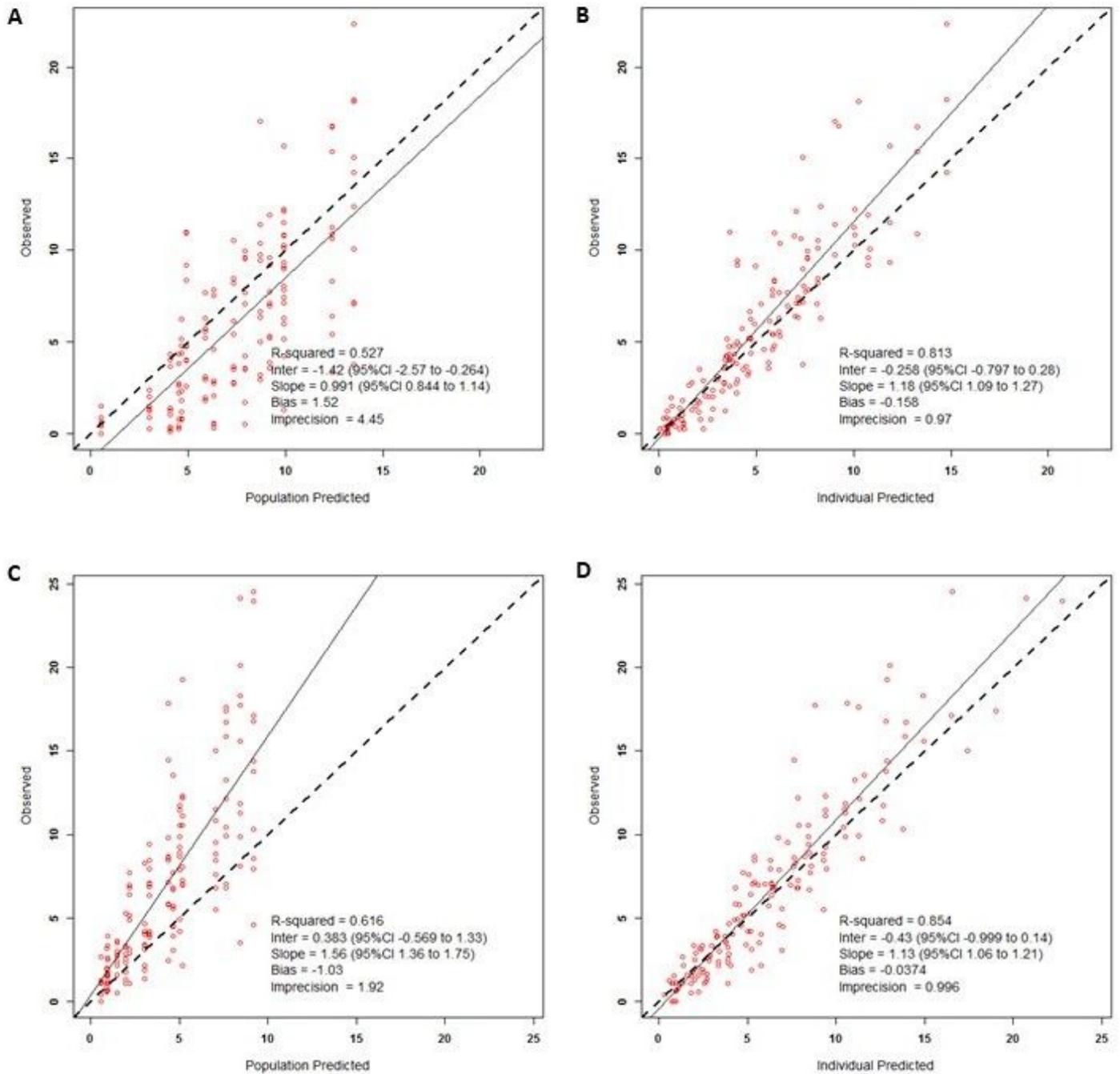
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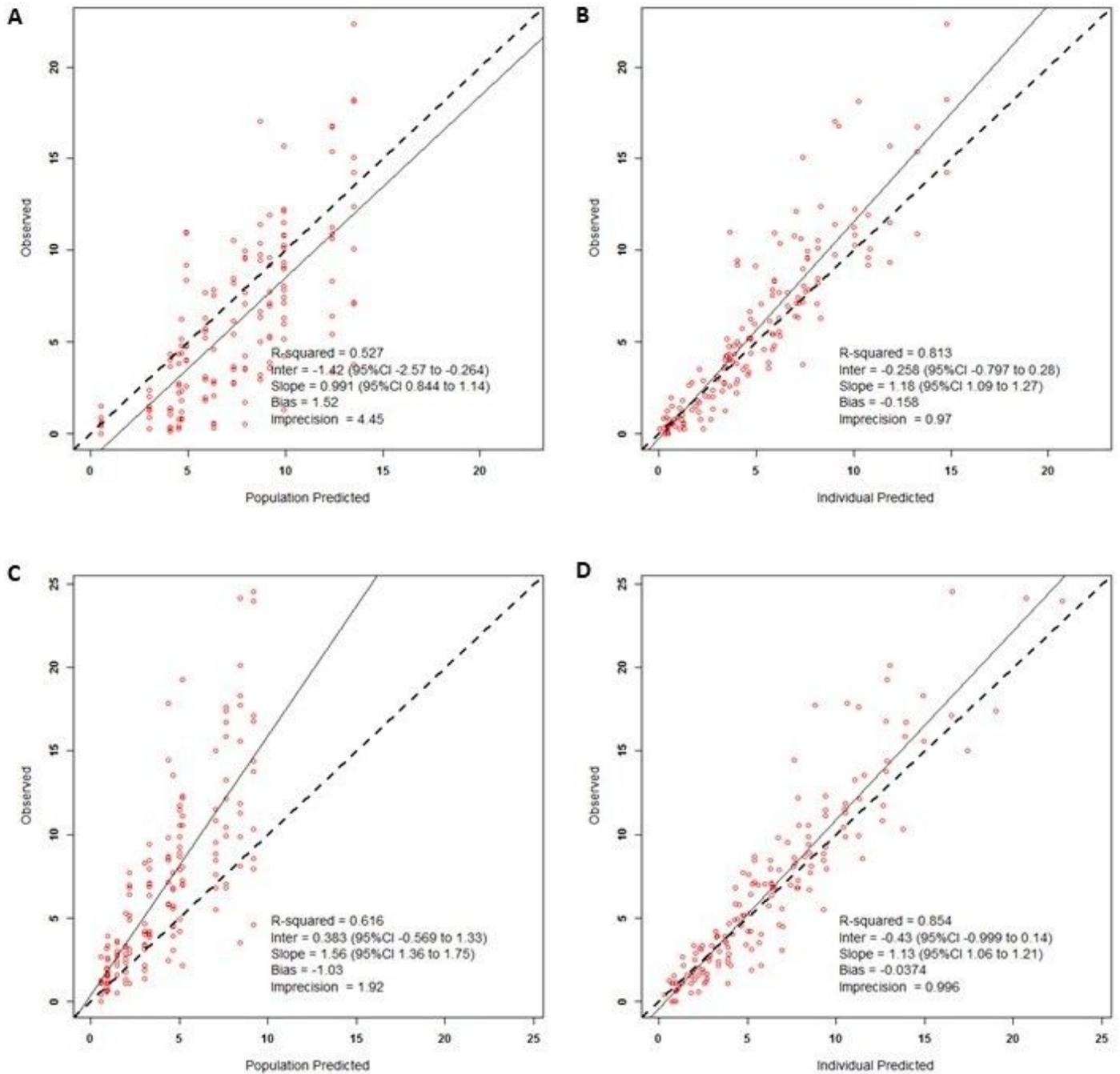
Figure 3

Diagnostic plots for the final covariate models. Observed versus population-predicted concentrations in intragastric group (A), and individual predicted concentrations in intragastric group (B) in plasma; Observed versus population-predicted concentrations in intravenous group (C), and individual predicted concentrations in intravenous group (D). Data are presented in mg/L.
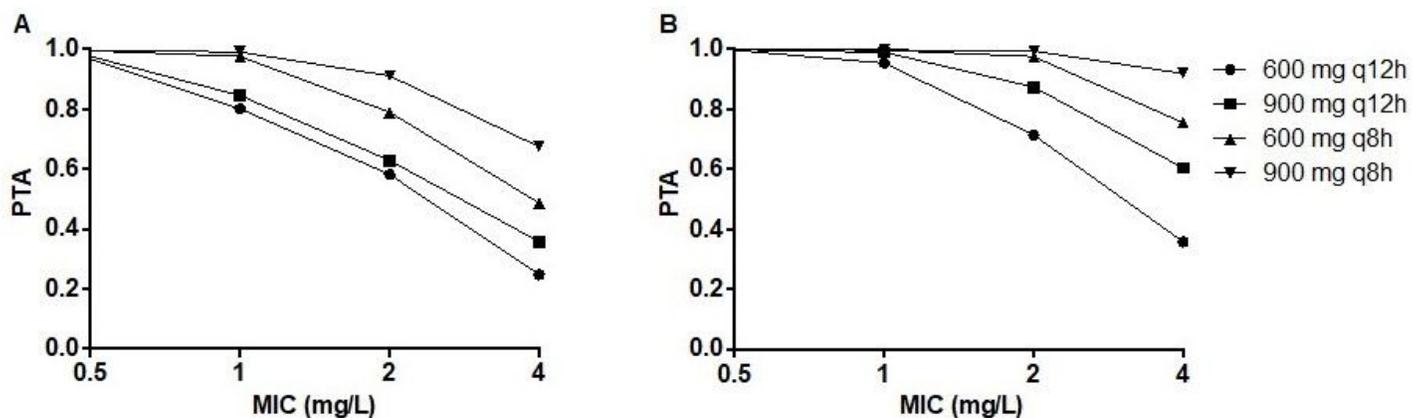
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Figure 4

Probability of target attainment with 4 different linezolid dosing regimens. Percentages of 10000 simulated patients with a median body weight (68 kg) and SOFA score (8) achieving a total linezolid concentration above the MIC during 100% of the dosing interval (%T > MIC = 100%) for four different linezolid dosing regimens and a range of MICs in intragastric (A) and intravenous group (B). Abbreviations: PTA, probability of target attainment; MIC, minimum inhibitory concentration.
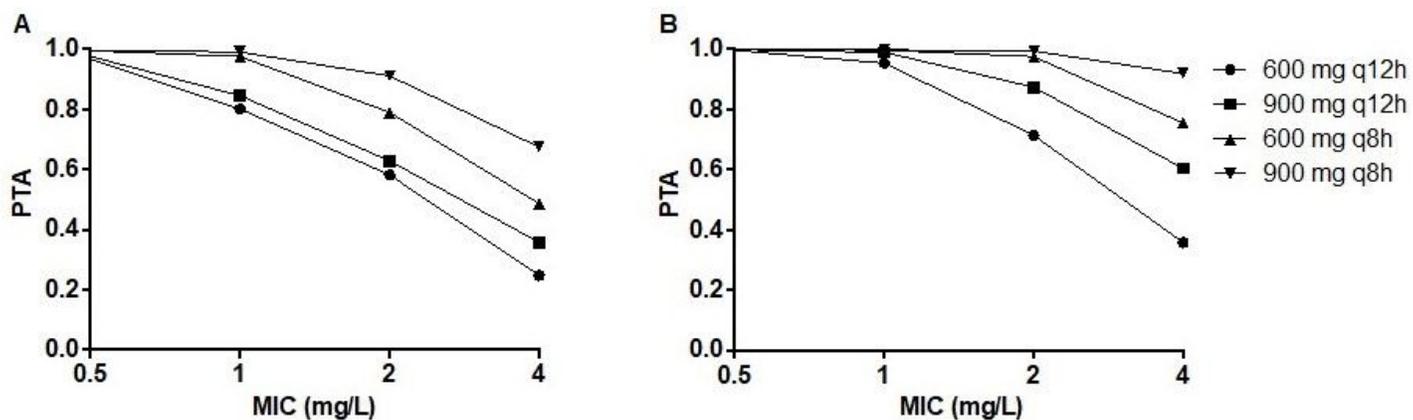

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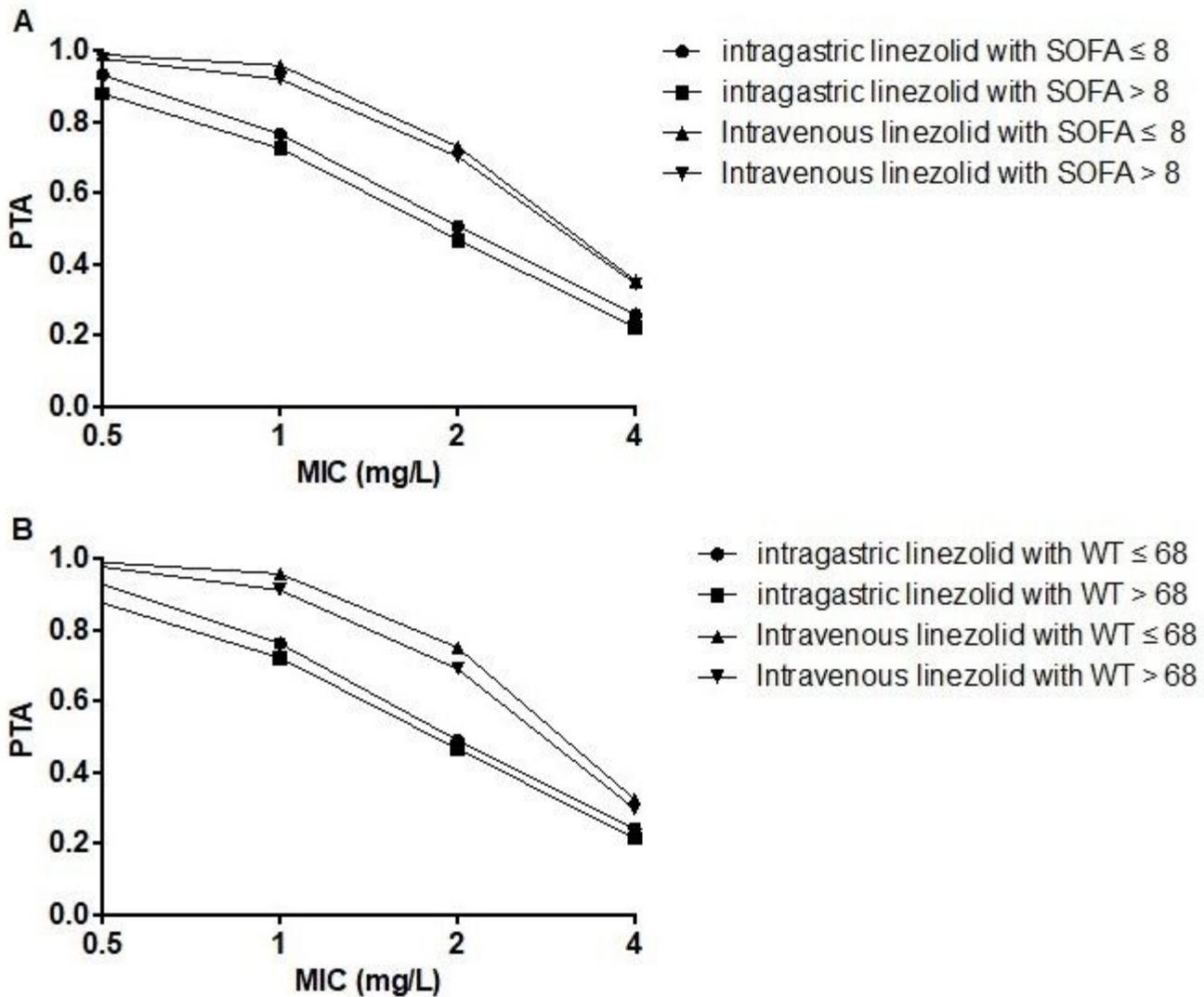
Figure 5

Probability of target attainment with different SOFA and WT in intragastric and intravenous group. Percentages of 10000 simulated patients with different SOFA (A) and WT (B) achieving a total linezolid concentration above the MIC during 100% of the dosing interval (%T > MIC = 100%) for linezolid dosing regimens of 600 mg q 12h and a range of MICs in intragastric and intravenous group. Abbreviations: PTA, probability of target attainment; MIC, minimum inhibitory concentration; WT, body weight.
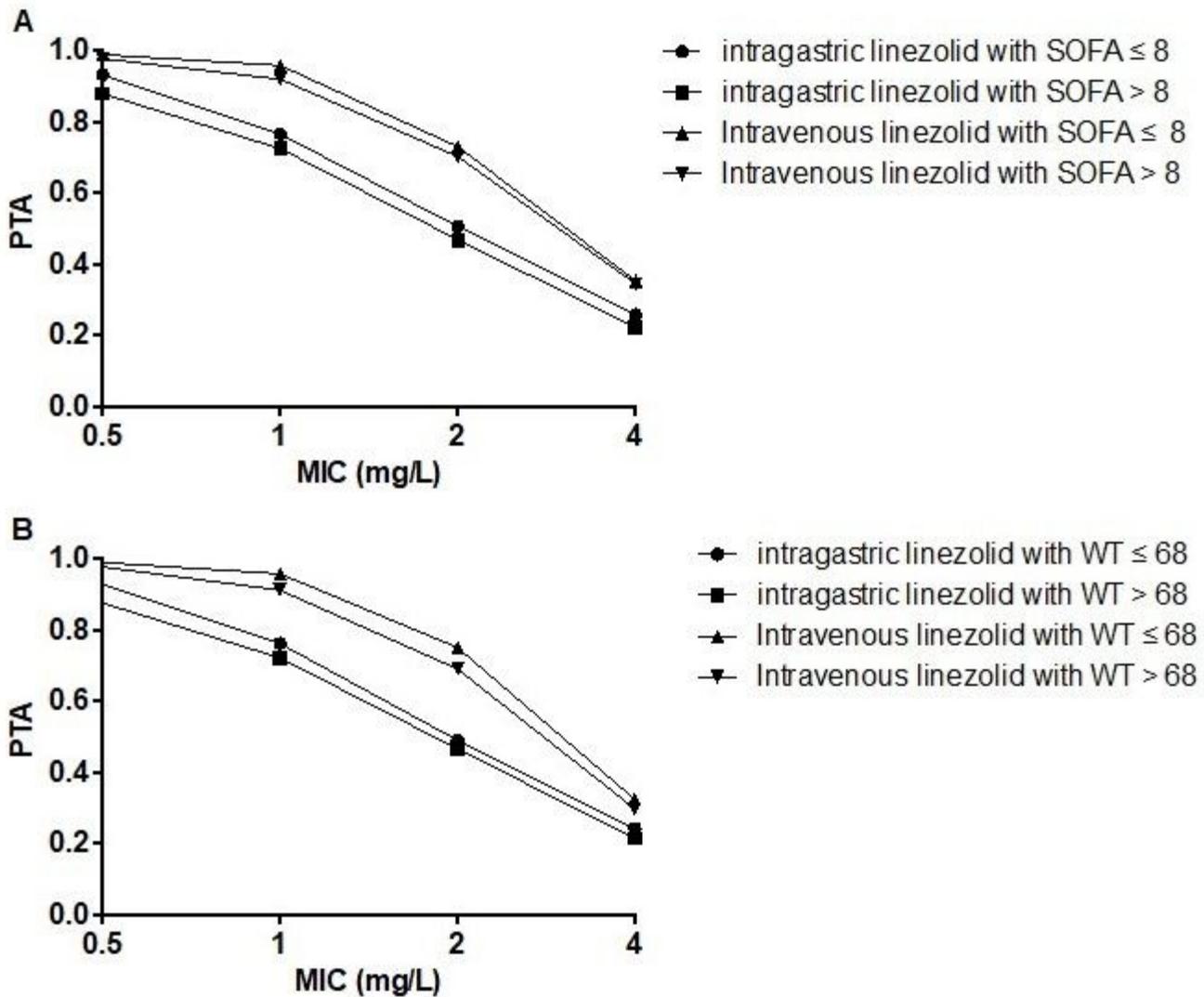
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