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Rifampicin reduces plasma concentration of linezolid in patients with infective endocarditis

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Background: Linezolid in combination with rifampicin has been used in treatment of infective endocarditis especially for patients infected with staphylococci.

Objectives: Because rifampicin has been reported to reduce the plasma concentration of linezolid, the present study aimed to characterize the population pharmacokinetics of linezolid for the purpose of quantifying an effect of rifampicin cotreatment. In addition, the possibility of compensation by dosage adjustments was evaluated.

Patients and methods: Pharmacokinetic measurements were performed in 62 patients treated with linezolid for left-sided infective endocarditis in the Partial Oral Endocarditis Treatment (POET) trial. Fifteen patients were cotreated with rifampicin. A total of 437 linezolid plasma concentrations were obtained. The pharmacokinetic data were adequately described by a one-compartment model with first-order absorption and first-order elimination.

Results: We demonstrated a substantial increase of linezolid clearance by 150% (95% CI: 78%–251%), when combined with rifampicin. The final model was evaluated by goodness-of-fit plots showing an acceptable fit, and a visual predictive check validated the model. Model-based dosing simulations showed that rifampicin cotreatment decreased the PTA of linezolid from 94.3% to 34.9% and from 52.7% to 3.5% for MICs of 2 mg/L and 4 mg/L, respectively.

Conclusions: A substantial interaction between linezolid and rifampicin was detected in patients with infective endocarditis, and the interaction was stronger than previously reported. Model-based simulations showed that increasing the linezolid dose might compensate without increasing the risk of adverse effects to the same degree.

Introduction

Infective endocarditis (IE) carries high mortality rates even with treatment according to therapeutic guidelines.[1] The randomized Partial Oral Endocarditis Treatment (POET) trial demonstrated that oral antibiotic step-down treatment was non-inferior to traditional full-length IV therapy for the treatment of IE after 6 months.[2] To ensure optimal efficacy and safety of oral treatments of IE, evaluation and development of different antibiotic combinations are needed. Linezolid is regarded as a possible treatment option for IE caused by linezolid-sensitive pathogens.

Linezolid is an oxazolidinone that inhibits protein synthesis by binding to the bacterial 23S rRNA of the 50S subunit.[3] It is useful in the treatment of infections by a wide spectrum of Gram-positive pathogens including MRSA and VRE.[4] Both the ratio of AUC to MIC and time above MIC have been reported as predictors for efficacy and outcome.[5,6] The magnitude of AUC and treatment duration has also been related to linezolid-induced thrombocytopenia, which is a common adverse effect.[7–10] Linezolid is rapidly absorbed from the gastrointestinal tract and has a bioavailability of ~100%.[11] The volume of distribution is 30–50 L and 31% is bound to proteins in plasma.[12] Linezolid is metabolized in the liver through enzymatic and non-enzymatic processes to two major inactive metabolites, and approximately 30% of a dose is excreted unchanged in the urine.[13]

Oral antibiotic treatment regimens were developed as part of the POET trial.[2] All regimens were designed as combinations of two different antibiotics to ensure sufficient antibacterial activity in cases of inadequate individual absorption or increased elimination. In addition, antibiotic combinations were preferred due to the biofilm characteristics of IE such as increased tolerance to host responses and antibiotics.[14] As a safety parameter, patients in the POET trial had plasma concentrations determined for each antibiotic. One recommended oral regimen was linezolid combined with rifampicin.[2] Although previous studies have indicated that coadministration with rifampicin reduces the exposure of linezolid,[7,15–17] which may increase the risk of treatment failure or antibiotic resistance, no study has quantified the effect using population pharmacokinetic (PK) modelling. Thus, the aims of this study were to (i) describe the population PK of linezolid in patients with IE in order to (ii) identify and quantify a drug–drug interaction between rifampicin and linezolid and (iii) explore the possibility of dosing adjustments to compensate for the effect of rifampicin.

Patients and methods

Ethics

The POET trial was approved by the regional scientific ethics committee for the Capital Region of Denmark (H-R-2011-40) and by the Danish Data Protection Agency (30-0598) and was performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Patients and study design

The protocol and results from the POET trial have been published elsewhere.[2,18] The present data were partly included in a previous paper analysing pharmacokinetic/pharmacodynamic (PK/PD) target attainment for the oral antibiotics used in the POET trial.[19] However, no previous analyses of interactions have been performed.

In short, eligible subjects were adult patients with left-sided IE and positive blood cultures for either *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus* spp. or *Enterococcus faecalis*. At the time of randomization, the patients had received at least 10 days of IV antibiotic treatment with a satisfactory response. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteraemia with the primary pathogen.

Orally treated patients received two oral antibiotics. Patients in the IV group received at least one antibiotic IV. Some patients were changed to alternative antibiotic drugs at randomization, and others were maintained on the same antibiotics. Thus, the study population for linezolid at Day 1 comprised both patients who were already receiving linezolid and patients who received the first dose of linezolid. At Day 5, the patients cotreated with rifampicin and linezolid had received at least 4 days of treatment with both antibiotics.

In the present study, all patients from the POET trial who were treated with linezolid orally or IV were screened for inclusion. Demographic data, clinical characteristics and outcome of patients were collected. CL_{CR} was calculated using the CKD-EPI formula (based on age, gender and plasma creatinine concentration),[20] and fat free mass (FFM) was estimated using gender, body weight (BW) and BMI.[21]

Drug administration and PK sampling

All eligible patients received 600 mg linezolid q12h orally or by IV infusion. Patients who were cotreated with rifampicin received 600 mg rifampicin q12h orally or IV. Blood samples were obtained at Day 1 and Day 5 after randomization for the orally treated group, and at Day 1 for the IV treated group. For each patient, up to five blood samples were collected approximately 0.5, 1, 2, 4 and 6 h after administration. Samples were analysed by HPLC using Agilent 1290 Infinity (Agilent Technologies, Santa Clara, CA, USA) providing the total concentration in plasma. The plasma samples were analysed at an accredited hospital laboratory at the Department of Clinical Biochemistry at Aarhus University Hospital, Denmark (DS/EN/ISO/IEC 15189), by existing methods validated according to standard laboratory procedures, essentially as described in a previous publication.[22]

Patients with extreme (more than five SDs from the mean of the remaining concentrations) or unrealistic concentrations (e.g. a concentration rise not possible with the administered dose) presumably related to measurement errors were excluded. Patients with extreme fluctuations presumably related to measurement or sampling errors (e.g. exchange of sampling times) were excluded (criteria and excluded data series are provided in Supplementary Material S1 (available as Supplementary data at *JAC* Online). All exclusions were performed before any further analysis to avoid bias.

Population PK analysis

The population PK analysis was carried out in Monolix (Version 2023R1, Lixoft, Antony, France) using the Stochastic Approximation Expectation-Maximization algorithm. The graphic processing of the Monolix output was partly performed with GraphPad Prism 9 (Version 9.0.0, GraphPad Software Inc., San Diego, CA, USA).

In the structural model building we visually inspected the semilogarithmic concentration–time plots and evaluated PK models with one or two compartments, first-order absorption and first-order elimination. Inter-individual variability (IIV) and inter-occasional variability (IOV) was modelled using a log-normal distribution for each parameter (Supplementary Methods), except for oral bioavailability, which was modelled with a logit-normal distribution to constrain it between 0 and 1.

To describe the absorption phase, we modelled the absorption without lag time, with lag time and with absorption transit compartments.

The residual unexplained variability was modelled with additive, proportional and combined additive and proportional error models (Supplementary Methods).

Due to the previously described heterogeneity in terms of treatment onset and prior treatment duration as well as no blood samples obtained at 0 h (the time of dose administration), we compared models with and without estimation of the initial plasma concentrations (the pre-dose plasma concentrations at Day 1).

The structural models were evaluated in terms of the objective function value (OFV), goodness-of fit (GOF) plots, and the accuracy and reliability of the estimated parameters. OFV was defined as $-2 \times$ log likelihood value.

The model code used for the final structural model is provided in Supplementary Material S2.

Covariate model

Based on correlation analyses and existing literature we selected BW, FFM, CL_{CR} and coadministration of rifampicin as candidates for PK covariates.[8–10,16,23–31] BW, FFM and CL_{CR} were normalized to 70, 60 and 120 mL/min respectively and introduced as power functions. For BW and FFM, the allometric exponents were fixed to 1.0 for V and 0.75 for CL. Rifampicin cotreatment was defined as a dichotomous variable RIF and introduced as a log-transformed factor (Supplementary Methods). BW, FFM, CL_{CR} and RIF were evaluated as covariates for each of the PK parameters in the final model. The covariate model was built using stepwise forward inclusion and backwards elimination. Covariates were added during forward inclusion if they significantly improved the OFV ($P < 0.05$). Covariates were removed during backwards elimination if their removal did not significantly increase the OFV ($P < 0.01$).

Finally, we retested whether changing the number of compartments or changing the absorption model improved the final model with covariates.

Model evaluation

GOF plots were created to evaluate the adequacy of the final model. The observed concentrations were plotted against the population predictions and individual predictions in two separate plots. Individual weighted residuals were plotted against the individual predictions and time after last dose, respectively.

A visual predictive check (VPC) was conducted by simulating the final model 500 times. In the simulations, we did not sample initial concentrations because they are not stochastic parameters but rather model estimates of actual concentrations that were not measured in the study. Thus, we treated the estimated initial concentration obtained from the final model as a fixed covariate for each patient in each simulation. We produced six separate plots stratifying for rifampicin cotreatment, route of administration and examination day. In each plot, the 10th, 50th and 90th percentiles of observed data in each bin were shown with 90% prediction intervals from simulations.

Model-based simulations for dosage adjustments

To investigate the effect of dosage adjustments in patients cotreated with rifampicin, we performed a simulation of the final model in Simulx (Version 2023R1, Lixoft). First, PK parameters were sampled for 1000 patients without coadministration of rifampicin. In addition, PK parameters were sampled for 4000 patients cotreated with rifampicin organized into four groups, each comprising 1000 patients undergoing treatment with distinct dosing regimens: 600 mg q12h, 900 mg q12h, 1200 mg q12h and 1500 mg q12h. For all patients, we assumed a standard BW of 70 kg and initial concentrations of 0. Second, we simulated the model and computed individual estimates of AUC_{12}, C_{max}, and C_{min} at Day 5. Third, we estimated the PTA and risk of haematological adverse effects by defining the target of efficacy as $AUC_{12}/MIC \geq 50$ and the threshold for increased risk of haematological toxicity as $C_{min} \geq 7$.[32] The PTAs were calculated for MIC values of 4 mg/L corresponding to the EUCAST breakpoint of enterococci and staphylococci,[33] and 2 mg/L corresponding to the breakpoint for viridans streptococci.

Results

Patient characteristics

Seventy-one linezolid-treated patients from the POET study were identified. Two patients were excluded due to missing data, two patients were excluded due to extreme and unrealistic concentration measurements, and five patients were excluded due to extreme fluctuations (Supplementary Material S1 and Figure S1). Thus, 62 patients were included in the present study. The demographics and clinical characteristics of the patients are summarized in Table 1. Fifty-three patients received linezolid orally and nine patients IV. Fifteen patients were cotreated with rifampicin. None of the rifampicin-cotreated patients reached an endpoint in the POET trial, whereas an endpoint occurred in six (13%) patients in the group without rifampicin cotreatment.

Population PK model development

A total of 437 plasma concentrations from 62 patients were included for the population PK modelling. Semilogarithmic concentration–time plots showed a monophasic concentration decline, and a one-compartment model with first-order absorption and first-order elimination adequately described the data. Absorption lag time or absorption transit compartments did not improve the fit. The model was parameterized in terms of absorption rate coefficient (K_a), volume of distribution (V) and clearance (CL). All estimates of oral bioavailability were above 97% (except for one) and inclusion did not improve the model. Therefore, it was fixed to 100% as reported by the literature.[11] We included IOV of K_a and omitted IIV for this parameter, because the model could not estimate both. Estimation of the initial plasma concentrations was included in the model, and Figure S2 shows the distribution of the individual model estimates. The residual variability was best described by a combined additive and proportional error model.

In the forward inclusion process, rifampicin cotreatment and BW were selected for CL, and BW was selected for V. CL and V were allometrically scaled using BW ($\Delta OFV = -19.49$) instead of FFM ($\Delta OFV = -18.88$) because the drop in OFV was larger. Adding rifampicin cotreatment to the model as a covariate for CL caused a decrease in the OFV of 19.06 ($P < 0.0001$) and a reduction in the IIV of CL from 77.3% to 55.6%. Including rifampicin cotreatment as a covariate for V did not significantly improve the model ($\Delta OFV = -0.05$, $P = 0.82$). Further, inclusion of CL_{CR} as a covariate for CL did not improve the OFV. In the backwards elimination process, all the included covariates were retained in the final model (Table 2).

The effect of rifampicin cotreatment on CL of linezolid was estimated to 2.50 (95% CI: 1.78–3.51) corresponding to an increase by 150% (95% CI: 78%–251%). The population estimate of CL for a standard BW of 70 kg was 2.81 L/h (95% CI: 2.33–3.29) for patients without rifampicin cotreatment and 7.02 L/h (95% CI: 5.00–9.86) for patients with rifampicin cotreatment.

Model evaluation

The population PK models were evaluated according to standard practices.[34] GOF plots for the final model are provided in Figure 1.

Table 1. Demographic and clinical data of the study population

		Without coadministration of rifampicin	With coadministration of rifampicin	*P* value[a]
Total patients, *N*		47	15	
Male, *n* (%)		37 (78.7)	14 (93.3)	
Female, *n* (%)		10 (21.3)	1 (6.7)	
Pathogen, *n* (%)	*Staphylococcus* spp.	12 (25.5)	6 (40.0)	
	Streptococcus spp.	13 (27.7)	9 (60.0)	
	Enterococcus spp.	22 (46.8)	0 (0)	
Administration route of linezolid, *n* (%)	p.o.	39 (83.0)	14 (93.3)	
	IV	8 (17.0)	1 (6.7)	
Administration route of rifampicin, *n* (%)	p.o.	—	14 (93.3)	
	IV	—	1 (6.7)	
Coadministration of other antibiotic, *n* (%)	Amoxicillin	17 (36.2)	—	
	Moxifloxacin	14 (29.8)	—	
	Fucidic acid	5 (10.6)	—	
	Ampicillin	5 (10.6)	—	
	Penicillin	2 (4.3)	—	
	Cefuroxime	2 (4.3)	—	
	Meropenem	1 (2.1)	—	
	Vancomycin	1 (2.1)	—	
Characteristic: median (IQR)	Age (years)	71.0 (64.5–76.5)	71.0 (50.5–75.5)	0.27
	Body weight (kg)	76.0 (70.5–91.5)	78.0 (73.5–99.0)	0.42
	BMI (kg/m^2)	25.6 (23.9–28.9)	24.9 (24.2–31.7)	0.96
	FFM (kg)	58.9 (52.5–65.7)	60.9 (58.1–69.5)	0.33
	CL_{CR} (mL/min)	65.7 (51.2–87.2)	69.3 (55.3–99.4)	0.34

FFM, fat free mass; p.o., per os (orally).
[a]*P* values were calculated with Mann–Whitney *U* test.

Table 2. Estimated population pharmacokinetic parameters for linezolid

	Parameter	Estimate	%RSE
Population mean	*V* (L)	30.4	5.9
	CL (L/h)	2.81	8.7
	K_a (h^{-1})	2.22	22.8
	F	1 (fixed)	—
	RIF on CL (factor)	2.50	(95% CI: 1.78–3.51)[a]
	BW on *V* (power)	1 (fixed)	—
	BW on CL (power)	0.75 (fixed)	—
Inter-individual variability (%CV)	ω^2_V	32.0	14.8
	ω^2_{CL}	50.2	15.3
Inter-occasional variability (%CV)	κ^2_{Ka}	242.6	14.6
Residual error	Additive error (mg/L)	1.56	13.0
	Proportional error (%)	9.06	14.6

BW, body weight; CL, clearance; F, bioavailability ; K_a, absorption rate coefficient; RIF, rifampicin cotreatment; *V*, volume of distribution; %CV, coefficient of variation in percentage; %RSE, relative standard error in percentage; ω^2, variance of the inter-individual random effects; κ^2, variance of the inter-occasional random effects.
[a]For rifampicin cotreatment the CI is displayed instead of %RSE for interpretability, because the effect was estimated in log-space.

They demonstrated an acceptable fit with no visible systematic trends. The performed VPC is presented in Figure 2. A small underestimation of linezolid plasma concentrations by the PK model in orally treated patients at Day 1 (Figure 2a) was observed. This observation was not present for orally treated patients at Day 5 (Figure 2b).

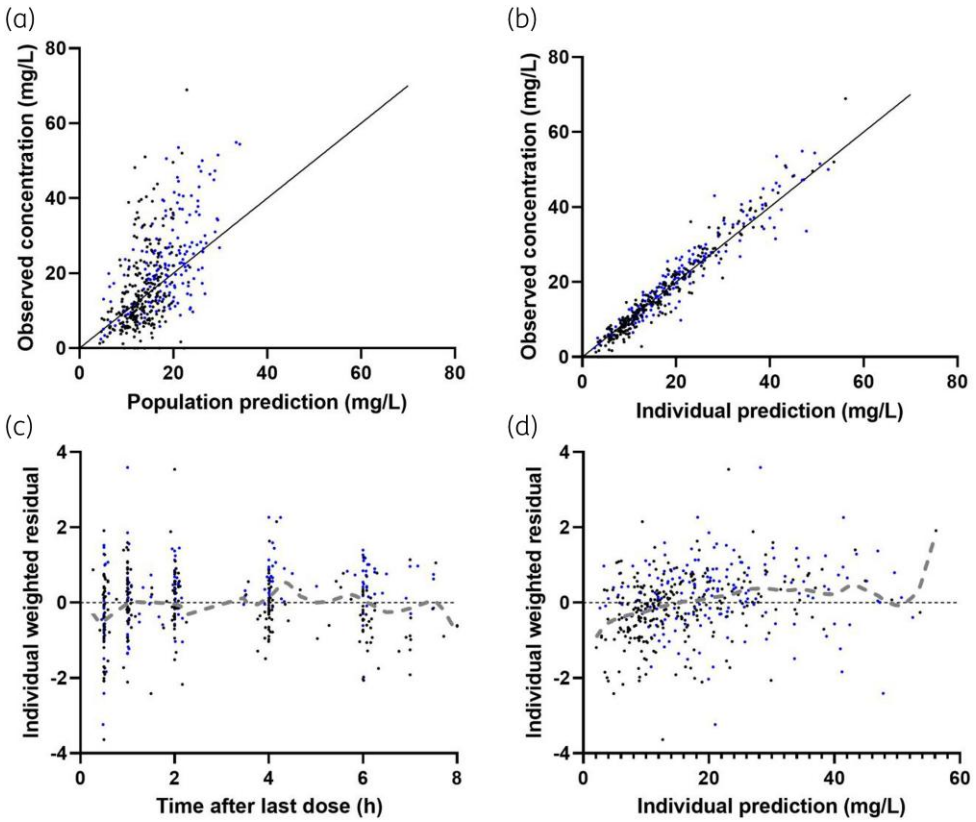

Figure 1. Goodness-of-fit plots of the final model. Observed concentrations are plotted against population predictions (a) and individual predictions (b). Individual weighted residuals are plotted against time after last dose (c) and individual predictions (d). The black dots represent data points from Day 1, while the remaining dots belong to data points from Day 5. The solid lines represent lines of identity. The dashed grey lines are smoothing lines). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Model-based simulations for dosage adjustments

The simulation results are shown in Table 3. The median of the simulated AUC_{12} at Day 5 was 206 mg h/L (IQR: 151–283) with the standard dosing regimen for the patients without cotreatment of rifampicin. Using a target of $AUC_{12}/MIC \geq 50$, the estimated PTAs were 52.7% and 94.3% for MIC values of 4 mg/L and 2 mg/L, respectively. The probability of reaching the reported threshold for increased risk of haematological adverse effects was 67.5%.

For the rifampicin-cotreated patients, the median of the simulated AUC_{12} at Day 5 was 83 mg h/L (IQR: 60–114) with the standard dosing regimen, and the PTAs were 3.5% and 34.9% for MIC values of 4 mg/L and 2 mg/L, respectively. The PTAs were increased to 52.7% and 94.3% when a dose of 1500 mg q12h was simulated. Correspondingly, the probability of reaching the reported threshold for toxicity risk increased from 9.7% to 34.5%.

Discussion

In the present study we evaluated the population PK of linezolid and the effect of rifampicin cotreatment in patients included in the POET trial. To our knowledge, this study is the first to demonstrate the effect of rifampicin cotreatment on the clinical population PK of linezolid, and no other study has reported a similar increase (150%; 95% CI: 78%–251%) of linezolid CL. However, other studies have found evidence of a drug–drug interaction between rifampicin and linezolid. A study of eight healthy individuals showed that rifampicin reduced the serum concentrations of linezolid by 35% 12 h after a single dose.[15] In a crossover study of 16 healthy individuals, coadministration of rifampicin reduced the AUC_{τ} and C_{max} of linezolid by 32% and 21%, respectively.[16] Further, a retrospective study of 45 patients showed that linezolid trough concentrations and AUC_{24} were significantly smaller for patients cotreated with rifampicin,[7] and a prospective clinical study of 10 patients found that rifampicin reduced the trough concentration of linezolid by 65%.[17] The studies used different doses of rifampicin. In our study, the patients received doses of 600 mg rifampicin q12h for multiple days, which is more than previously evaluated.[15–17]

Different mechanisms have been suggested to explain the drug–drug interaction. Rifampicin is known as a strong inducer of several cytochrome P450 enzymes (CYPs) and enhances the metabolism of several drugs.[35] However, an animal study indicated that rifampicin reduced linezolid concentrations independently of hepatic microsomal enzymes,[36] and linezolid is not known as a major substrate of common CYPs.[37] However, CYP3A5 polymorphisms have been shown to alter the exposure of linezolid,[38] and a recent study found CYP2J2 and CYP4F2 to

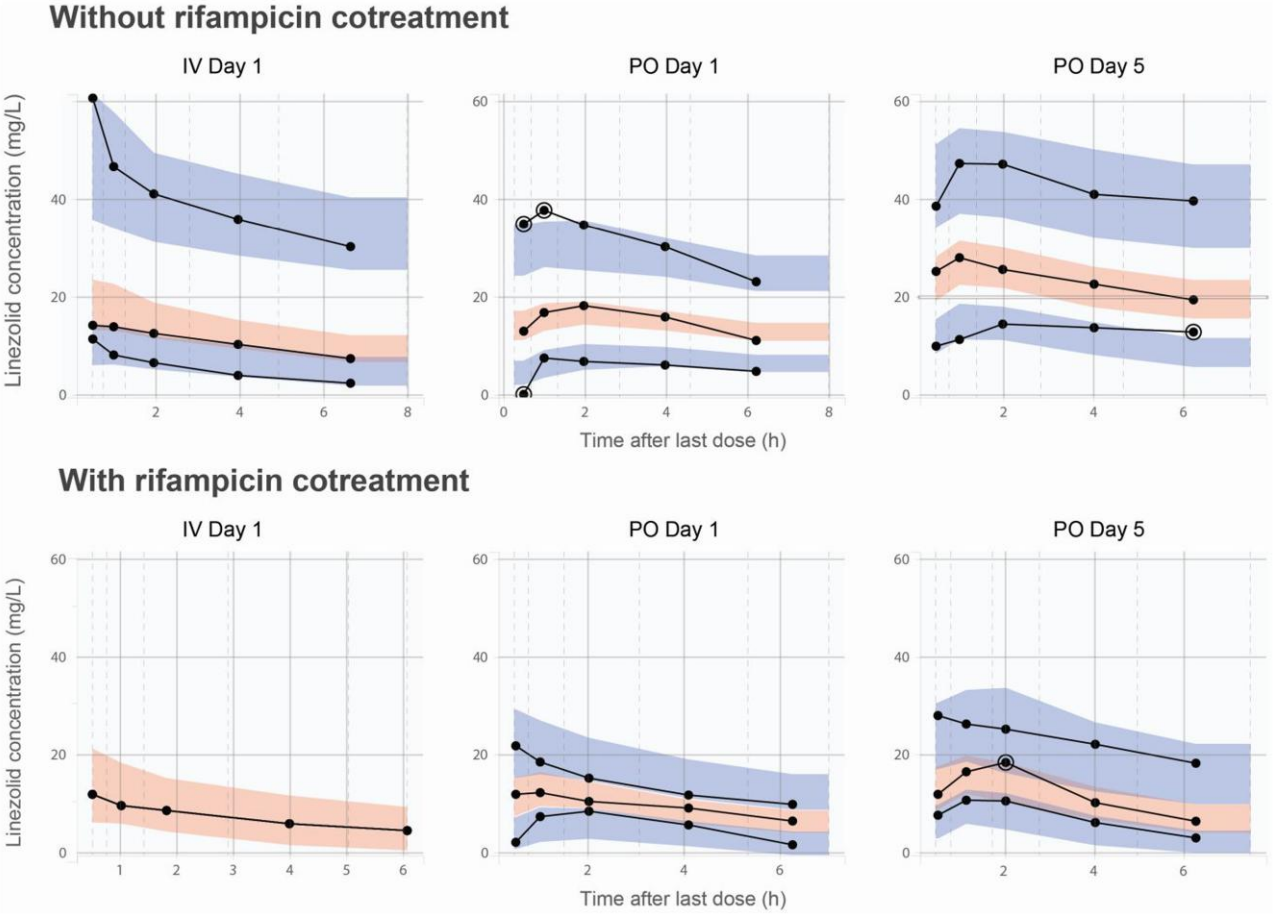

Figure 2. Visual predictive check (VPC) of the final model. The 10th, 50th and 90th percentiles of the observed data are displayed together with the 90% prediction intervals (shaded areas). The dashed lines represent the bin limits. The observed percentiles lying outside the prediction intervals are marked with circles. Note that only one patient cotreated with rifampicin was in the IV group. The observed concentration for this patient is plotted with the prediction interval of the median. PO, per os (oral). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 3. Monte Carlo simulations of alternative dosing regimens

		No cotreatment	With cotreatment of rifampicin			
Dosing regimen		600 mg q12h	600 mg q12h	900 mg q12h	1200 mg q12h	1500 mg q12h
AUC_{12} (mg h/L)		206	83	124	165	207
Median (IQR)		(151–283)	(60–114)	(91–171)	(121–228)	(151–285)
C_{min} (mg/L)		10.3	1.6	2.4	3.2	4.0
Median (IQR)		(5.7–16.6)	(0.5–3.8)	(0.8–5.7)	(1.0–7.6)	(1.3–9.5)
C_{max} (mg/L)		26.0	16.1	24.1	32.2	40.2
Median (IQR)		(20.8–32.1)	(12.8–20.3)	(19.1–30.4)	(25.5–40.5)	(31.9–50.6)
PTA (%)	MIC = 4 mg/L	52.7	3.5	15.2	34.9	52.7
	MIC = 2 mg/L	94.3	34.9	67.6	88.2	94.3
Probability of increased toxicity risk (%)		67.5	9.7	19.4	27.8	34.5

be the main enzymes responsible for linezolid hepatic metabolism.[39] Rifampicin is also able to cause drug–drug interactions by inducing P-glycoprotein (P-gp), a membrane protein that pumps foreign substances out of cells. In the gut, P-gp is highly expressed and may inhibit the absorption of linezolid by increasing drug transport back to the intestinal lumen. However, to our knowledge, linezolid has not been reported as a major substrate for P-gp, and one animal study found no changes in intestinal

permeability of linezolid after rifampicin pretreatment.[17] In the present study, the bioavailability was fixed at 100%, and the observed effect of rifampicin can emerge due to either reduced bioavailability (e.g. increased first-pass effect) and/or increased metabolism/elimination. Hence, the underlying mechanism for a drug–drug interaction between rifampicin and linezolid remains unclear.

The estimated effect size and the model-based simulations indicate that the evaluated drug–drug interaction may be clinically relevant because the PTA is significantly reduced. Two studies have found that a combination of linezolid and rifampicin is associated with a tendency to a higher probability of treatment failure in prosthetic joint infections,[40,41] although the difference in treatment failure rates was not statistically significant in one of the studies.[40] In the POET trial, no patients had treatments changed due to critically low serum concentrations of both provided drugs, and the primary outcome did not occur in any of the 15 patients treated with linezolid and rifampicin, but the trial was not designed to evaluate outcome data in such subgroups of patients. Nevertheless, the combination of rifampicin and linezolid may impose a need for treatment change to alternative combinations or dosage optimization of linezolid for some patients to obtain a satisfactory treatment response. Additionally, our results predict that cotreatment with rifampicin decreases the risk of linezolid-induced haematological adverse effects. This is supported by studies showing diminished risks of thrombocytopenia or anaemia and a less frequent need for dosage adjustments or change of drug due to toxic concentrations.[7,42,43] The model-based simulations predicted that raising the dose of linezolid due to insufficient concentrations can increase the PTA without increasing the risk of adverse effects to the same degree. Nevertheless, the toxicity threshold remains a subject of debate, warranting cautious interpretation. The defined threshold was based on studies showing a 50% probability of thrombocytopenia (defined in the studies as a decrease in platelet count from baseline of at least 30%) if C_{min} exceeds 6.53–8.2 mg/L.[7,8] To our knowledge, no clinical PK/PD thresholds for other adverse effects like anaemia or peripheral neuropathy have been established.[32,44]

In the present study, the PK data were best described by a one-compartment model with first-order absorption and first-order elimination possibly due to the sparse nature of the data set. The estimated CL of 2.81 L/h (95% CI: 2.33–3.29) for patients without rifampicin treatment was low compared with findings by others (2.68 to 9.54 L/h), although direct comparisons are difficult due to major differences in study designs, study populations, structural models and covariate inclusion.[8–11,13,23–31,45–51] IE is a serious illness affecting primarily older people with predisposing cardiac diseases, diabetes, cancer or renal failure.[2,52] These characteristics in combination with the nature of IE in itself could reduce linezolid CL. It should also be noted that age, renal impairment and liver disease have been related to lower linezolid CL in some studies.[8,23,24,26,29,30] The variation in CL_{CR} did not explain the IIV of CL in our study, presumably due to insufficient spread in the data, but it is possible that the median CL_{CR} of 65.7 mL/min (IQR: 51.2–87.2) of the patients without rifampicin-cotreatment could have influenced the population estimate of CL compared with studies of patients with better renal function.

The final model was validated by GOF plots and a VPC showing an adequate fit and no structural misspecification except for a small underestimation of the concentrations for orally treated patients at Day 1. Because this phenomenon was not observed at Day 5, a possible explanation is a remaining effect of the differences in treatment onset leading to high pre-dose linezolid concentrations at Day 1 for some patients. Hence, we do not expect this to substantially influence or bias the estimated effects of rifampicin cotreatment nor the reliability of the simulated AUC_{12} distributions at Day 5.

Our study has limitations. First, the study had a limited sample size of 62 patients, of whom only 15 were cotreated with rifampicin. Studies with larger patient populations are needed to estimate the effect of rifampicin on linezolid PK with more precision and to evaluate the consequences for clinical outcome and adverse effects, not least if higher doses are used. Second, we cannot be sure whether pharmacogenetics and/or other drugs and/or comorbidities had an impact on CL of linezolid, which may have biased the effect size of rifampicin cotreatment. Third, information regarding the duration of linezolid and rifampicin treatment at the time of PK measurement was not extracted at the end of the study and is, unfortunately, not available. Such data could have indicated whether the interaction is substantial from early on or appears significant only after a period of cotreatment. Still, the effect of rifampicin has been shown to emerge already after a single dose.[15]

In conclusion, by developing a population PK model of linezolid in patients with IE we demonstrated that rifampicin cotreatment of patients with IE decreases the plasma concentration of linezolid substantially. Model-based simulations showed an associated decrease in PTA and predicted that increasing the linezolid dose might be a preferable option.

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The present data were partly included in a previous paper analysing PK/PD target attainment for the oral antibiotics used in the POET trial.[19] However, no analyses of interactions were performed, and the results reported in this article have not been published previously.

Author contributions

K..I, N.I., J.H.-L., C.M. and H.B. designed the POET trial and wrote the protocol. K.I. and H.B. led the POET trial. The PK interaction study was planned by C.M., M.B., K.I., N.I., S.G., U.C., H.E., J.A.P., N.E.B., D.E.H., E.L.F., J.H.-L., L.K., M.I.P.-H., C.T.P., N.T., J.J.C., F.S.R., K.F. and H.B. PK analyses were conducted by M.B., J.G.C.V.H., F.S., H.W., N.H., K.F., K.I., H.B. and C.M.. M.B. did the initial manuscript writing. All co-authors contributed to the manuscript and approved the final version. All authors had access to data.

Supplementary data

Supplementary Material S1 and S2, Supplementary Methods and Figures S1 to S2 are available as Supplementary data at *JAC* Online.

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