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Pharmacokinetics of linezolid in septic patients with and without extended dialysis

Stefanie Swoboda · Michael C. Ober · Christoph Lichtenstern · Soundos Saleh · Vedat Schwenger · Hans-Günther Sonntag · Walter Emil Haefeli · Georg Hempel · Torsten Hoppe-Tichy · Markus A. Weigand

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Abstract

Purpose Linezolid is an option for the treatment of infections caused by multiresistant Gram-positive bacteria. The survival of critically ill patients with acute renal failure (ARF) can be improved by increasing the dose of renal replacement therapy. Extended (daily) dialysis (ED) is a new and important

approach to renal replacement therapy in intensive care units. The aim of the study was to evaluate the pharmacokinetics of linezolid in septic patients without ED and on ED, respectively. **Methods** We studied the pharmacokinetics of linezolid in adult intensive care patients with sepsis ($n=5$) and anuric septic patients with ARF being treated with ED ($n=10$). Linezolid 600 mg was administered intravenously twice daily. The pharmacokinetic parameters, their variability, and possible covariates were analyzed using NONMEM.

Results The pharmacokinetics of linezolid followed a two-compartment model with clearance (Cl)= $0.159 \text{ L h}^{-1} \text{ kg}^{-1} \pm 51\%$ (population mean \pm interindividual variability), central volume of distribution (V_1)= $0.273 \text{ L/kg} \pm 21\%$, intercompartmental clearance (Q)= $0.369 \text{ L h}^{-1} \text{ kg}^{-1}$, and peripheral volume of distribution (V_2)= 0.271 L/kg . The clearance in ED patients while on dialysis was increased by 3.5 L/h, and patients with liver transplantation/resection had their clearance reduced by 60%. Intra-individual variability was much smaller than inter-individual variability.

Conclusions Our results suggest that linezolid pharmacokinetics in critically ill patients with ARF undergoing ED is not comparable to that in healthy subjects and patients without ARF. The best method of managing linezolid dosage in such a complex group of patients, whose physiology can vary daily, would be to use therapeutic drug monitoring.

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Keywords Intensive care unit · Linezolid · Methicillin-resistant *Staphylococcus aureus* · Renal replacement therapy · Septic shock · Vancomycin-resistant enterococci

Introduction

Adequate antimicrobial therapy is of crucial importance for the survival of critically ill patients with severe nosocomial

infections. In intensive care patients suffering from sepsis and multiple organ failure, extended dialysis is an important supportive extracorporeal renal replacement therapy. Despite the increasing use of extended dialysis in the intensive care unit (ICU) throughout Europe and the USA [1–7], little data are available on the effect of this highly efficient renal replacement therapy on the elimination of frequently used drugs in critically ill patients.

Antimicrobial agents are among the most commonly prescribed drugs in this population. The aim of antimicrobial chemotherapy is to eliminate an infection as rapidly as possible. To accomplish this, sufficiently high concentrations of antimicrobial agents must reach the site of infection. Linezolid has a low molecular weight (337 Da), only 31% protein binding, and a distribution volume ranging from 0.5 to 0.8 L/kg, which approximates that of total body water. It is therefore likely that an important fraction of linezolid is removed during renal replacement therapy, potentially resulting in plasma concentrations below therapeutic concentrations, thereby promoting resistance and limiting linezolid effectiveness in severe infections caused by multi-resistant Gram-positive bacteria [8–11].

Recently published scientific data have improved our understanding of the pharmacokinetic/pharmacodynamic factors governing optimal bactericidal activity of different classes of antibiotics and has resulted in a re-evaluation of dosing and monitoring strategies. Animal models suggest that linezolid has a time-dependent activity and that a time above minimum inhibitory concentration ($T > MIC$) of 39% of the dosing interval and an area under the plasma concentration time curve (AUC) to MIC ratio ($AUC/MIC > 147$) are associated with increased survival [12]. In humans, optimal pharmacokinetic/pharmacodynamic indices have been described for the antimicrobial efficacy of linezolid as a $T > MIC$ of $>85\%$ and $AUC/MIC > 100$ [13].

To date, no data are available on linezolid kinetics and dynamics in critically ill septic patients on extended dialysis (e.g., for GENIUS batch dialysis system; Fresenius Medical Care, Bad Homburg, Germany), and drug administration is thus extrapolated from data obtained in healthy volunteers or patients differing substantially from ICU patients. However, large interindividual variability in linezolid interstitial concentrations in patients with sepsis or septic shock suggest that a scheme of more frequent daily dosing would be more appropriate for at least some of the critically ill patients [14].

Patients with sepsis or septic shock are usually highly catabolic and often need a larger dose of renal replacement therapy. Indeed, two recent controlled studies have revealed that increasing the dose of renal replacement therapy increases the survival of critically ill patients with renal failure [1, 2]. Thus, the progress to renal replacement therapies with higher clearances as well as their wider

application requires a reassessment of dosing regimes and pharmacokinetic data, particularly of drugs easily removed by dialysis [15]. We have therefore assessed the pharmacokinetics of an important antimicrobial agent against infections due to multiresistant strains in septic ICU patients. The aim of our study was to investigate the pharmacokinetics of linezolid in septic patients and anuric critically ill patients undergoing extended dialysis (ED).

Patients and methods

Patients and study protocol

This was a 24-h pharmacokinetic study carried out in the interdisciplinary surgical intensive care unit (SICU) of the University Hospital of Heidelberg, Germany, which is a large tertiary care center. The SICU cares for abdominal, urological, vascular, and trauma surgery patients. The study protocol was approved by the independent Ethics Committee of the University of Heidelberg, Germany and the responsible German authority BfArM (EudraCT-number: 2006-002338-39). It was conducted in accordance with the Declaration of Helsinki and German federal guidelines.

We enrolled 15 adult intensive care patients with sepsis treated with linezolid. Of these, ten sepsis patients had acute anuric renal failure that was being treated with ED ($n=10$), and five septic patients had no acute anuric renal failure and did not receive ED. Sepsis was defined as the systemic inflammatory response to infection, as stated by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee [16]. Women had to be at least 2 years postmenopausal to be included in the study. The choice of the antibiotic for each patient was made at the attending physician's discretion, according to the recommendations of the German Paul-Ehrlich-Society and the guidelines of the Infectious Disease Society of America. Patients were entered into the study after written informed consent had been obtained from the patient or the patient's legal representative. Clinical patient data as well as diagnoses at SICU admission were recorded. Predicted mortality rates were calculated according to the Acute Physiology And Chronic Health Evaluation II (APACHE II) score. To assess and compare organ dysfunction in the two groups of patients, we calculated the Sequential Organ Failure Assessment (SOFA) score for each patient at study entry.

Linezolid (600 mg) was infused twice daily over a period of 60 min. Extended dialysis was performed in ten septic patients using the GENIUS batch dialysis system with a polysulphone high-flux dialyzer (F60S, surface area 1.3 m²; Fresenius Medical Care) as described previously [17, 18]. The average dialysis time of these ten patients was

19.5 h (range 12–24 h) with blood flow rates set to 110–150 mL/min during the study. The technical aspects of the system, in brief, are: sterile bicarbonate dialysate is filled into the air-free 90-L tank and then circulated in a closed loop circuit; during dialysis, fresh dialysate is withdrawn from the top of the tank while the spent dialysate flows back to the bottom.

Blood samples (EDTA plasma) were drawn from the arterial line in all patients at time points $t=0, 1, 1.5, 2, 3, 4, 6, 8, 11.9, 13, 13.5, 14, 15, 16, 18, 20,$ and 23.9 h (on administration days 2–4). Linezolid infusions were administered at time points $t=0$ and 12 h. Using this design, we obtained three trough concentrations (C_{\min}) immediately before linezolid administration ($t=0, 11.9,$ and 23.9 h) and two peak concentrations (C_{\max}) right at the end of the 1-h linezolid infusion ($t=1$ and 13 h) in each patient. Additional blood samples were drawn from the afferent and efferent blood lines of the dialyser membrane in order to calculate dialyser clearance from the arterio-venous concentration difference and blood flow.

Linezolid quantification

Linezolid concentrations were determined in plasma samples using a previously described high-performance liquid chromatography method with UV absorbance detection [19]. This method has a lower limit of quantification of 0.1 mg/L and a linear calibration range of 0.5 – 40 mg/L. The method showed excellent reproducibility, with an inter- and intraday assay precision of $<5\%$ [percentage relative standard deviation (SD)], as well as excellent accuracy, with an inter- and intraday assay accuracy ranging from 100.6 to 103.2% . The stability of standard solutions kept for up to 6 months in water and plasma under -70°C freezer conditions was proven. Quantitative recovery was possible after up to three freeze–thaw cycles.

Data analysis

All pharmacokinetic calculations were performed with NONMEM ver. VI (University of California, San Francisco, USA) using the first-order conditional estimation method with the interaction option. Pharmacokinetic parameters of linezolid with or without ED were estimated using a two-compartment model. For the main question addressed, the effect of ED on the clearance of linezolid, the population pharmacokinetic method is the best method, as only this method can distinguish between the different sources of variability (interindividual, intra-individual, and residual variability) as well as the effects of liver transplantation/resection, weight, or other parameters. Non-compartmental analysis with descriptive statistics cannot precisely distinguish between these different confounders.

Observed linezolid plasma concentrations versus fitted plasma concentrations (Goodness-of-fit plot) were analyzed by linear regression analysis.

Several models were tested using NONMEM, including the influence of dialysis therapy and liver transplantation/resection on linezolid clearance. The best fitting model for these patients was a two-compartment-model. Individual clearance (Cl) values were calculated according to Eq. 1:

$$Cl = (Cl_{\text{pop}} * BW * \exp(\text{ETA}(1)) + (F_{\text{Dia}} * \text{Dialysis})) * (1 - F_{\text{LS}} * \text{LS}) \quad (1)$$

where Cl_{pop} = Population average of the clearance, BW = body weight, $\text{ETA}(1)$ = interindividual variable, F_{Dia} = factor of dialysis therapy, $\text{Dialysis} = 1$ with Dialysis, 0 without Dialysis, F_{LS} = factor for liver transplantation/resection, and $\text{LS} = 1$ for liver transplantation/resection, 0 without liver transplantation/resection.

The volume of distribution in the central compartment (V_1) and the peripheral compartment (V_2) and the inter-compartmental Cl (Q) were also calculated, using Eqs. 2, 3, and 4.

$$V_1 = (V_1 \text{ pop} * BW * \exp(\text{ETA}(2))) \quad (2)$$

where $V_1 \text{ pop}$ = population average of the volume of distribution in the central compartment and $\text{ETA}(2)$ = interindividual variable.

$$V_2 = (V_2 \text{ pop} * BW) \quad (3)$$

where $V_2 \text{ pop}$ = population average of the volume of distribution in peripheral compartment.

$$Q = (Q \text{ pop} * BW) \quad (4)$$

where $Q \text{ pop}$ = population average of the intercompartmental clearance. Extracorporeal clearance across the dialysis membrane was calculated from concentrations in the afferent (C_{in}) and efferent (C_{out}) blood lines according to Eq. 5:

$$Cl_{\text{dial}} = (F_{\text{in}} \cdot C_{\text{in}} - F_{\text{out}} \cdot C_{\text{out}}) / C_{\text{in}} \quad (5)$$

where F_{in} is the afferent and F_{out} the efferent blood flow.

Statistical analysis was carried out using Origin Pro 8 SRO (OriginLab Corp, Northhampton, MA) and SPSS ver. 16.0 (SPSS, Chicago, USA). Demographic and clinical data were analyzed with the Mann–Whitney test for continuous variables. Data are reported as mean \pm standard deviation (SD) unless otherwise stated. P values <0.05 were considered to be significant.

Results

Data from 15 patients with severe sepsis or septic shock treated with linezolid were analyzed in this 24-h pharmacokinetic

Table 1 Demographics and co-morbidity scores of critically ill patients treated with intravenous linezolid

Patient demographics and disease severity scores	Septic patients on extended dialysis	Septic patients without dialysis
Number of patients	10	5
Gender (female/male)	4 / 6	1 / 4
Age (years)	57.2±11.9*	68.6±4.2*
Body weight (kg)	97.4±19.4	88.8±9.1
BMI (kg/m ²)	33.5±6.8	30.3±5.3
APACHE II-Score	30.2±5.6	26.3±5.6
SOFA-Score	13.9±3.4	12.0±2.6
liver transplantation/resection (<i>n</i>)	5	1
Serum creatinine (mg/dL)	1.03±1.04 **	0.78±0.35

* $p=0.03$, indicating significant difference

All values are given as the mean ± standard deviation (SD)

BMI, Body mass index; APACHE-II, Acute Physiology And Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment

**Serum creatinine value under extended dialysis (renal replacement therapy) because of acute renal failure

study after written informed consent had been obtained from the patient.

Patient characteristics

Patient demographics and disease severity scores within the 24-h observation period are reported in Table 1. Dialysis patients were younger, but otherwise the two patient groups were similar in terms of disease, organ dysfunction severity, and predictable death risk. Patient diagnoses and surgical interventions are shown in Table 2. No adverse events attributable to linezolid were observed during the

24-h pharmacokinetic study. Causative pathogens of infection in all patients were either methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE), and all had been tested to be susceptible to linezolid.

Pharmacokinetic parameters

Model-predicted and observed concentrations (Goodness-of-fit plot) randomly spread around the line of identity, with values close to the line of identity. The overall R^2 was 0.75, indicating a good precision of the predictions.

Peak and trough concentrations in the two groups were similar. In the dialysis group, C_{\min} values showed a range of <0.1–8.8 mg/L (median 1.0; SD 2.7 mg/L), and the C_{\max} ranged from 7.9 to 22.0 mg/L (median 14.1; SD 4.9 mg/L). In the non-dialysis group, C_{\min} values showed a range of 0.1–9.5 mg/L (median 0.5; SD 3.6 mg/L), and the C_{\max} ranged from 7.5–24.9 mg/L (median 11.8; SD 5.9 mg/L). Patients with liver transplantation ($n=3$) or liver resection ($n=3$) had significantly higher trough concentrations ($p=0.008$) (range 0.5–9.5; median 2.7; SD 3.7 mg/L) and higher peak concentrations ($p=0.016$) (range 12.0–24.9; median 18.8; SD 3.9 mg/L,) than patients without liver transplantation/resection. Figure 1 shows the linezolid concentration–time profiles of the septic patients divided into the four experimental groups: with dialysis, without previous liver transplantation/resection (a); with dialysis, with previous liver transplantation/resection (b); without dialysis, without previous liver transplantation/resection (c); without dialysis, with previous liver transplantation/resection (d).

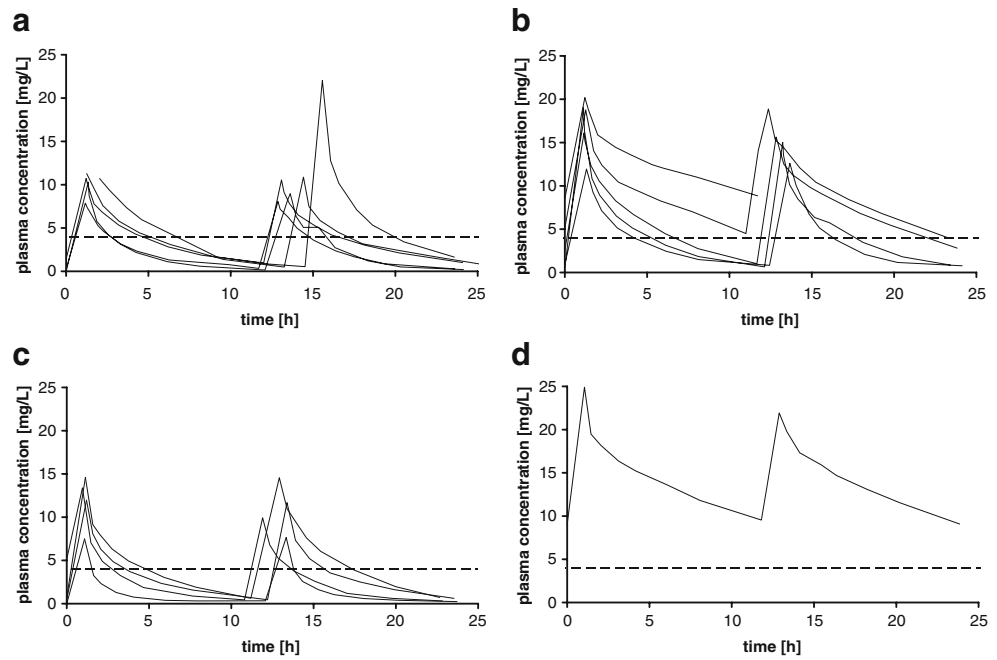
The population pharmacokinetics is shown in Table 3. Interindividual variability in CI was large (51%), even after the covariates weight, dialysis, and liver transplantation/

Table 2 Diagnosis and surgical intervention of the critically ill patients treated with intravenous linezolid

Patient no.	Diagnosis	Surgical intervention
1	Uterus myomatosus	Hysterectomy
2	Cryptogenic liver cirrhosis	Liver transplantation
3	Aortic aneurysm	Aorta prosthesis
4	Ethyltoxic liver cirrhosis	Liver transplantation
5	Rectum carcinoma with liver metastasis	Hemihepatectomy
6	Perforation of colon	Colectomy
7	Ethyltoxic liver cirrhosis	Liver transplantation
8	chronic hepatitis C, cholangiocarcinoma	Hemihepatectomy
9	Abscess-forming inflammation of kidney transplant	Nephrectomy
10	Adenocarcinoma of cardia	Esophagus resection
11	Aortic aneurysm	Aorta prosthesis
12	Hepatic necrosis with tumour infiltration	Hemihepatectomy
13	Cystic carcinoma of head of pancreas	Pancreas resection
14	ischemic necrosis of stub	Upper limb amputation
15	Peritonitis with acute pancreatitis, colonic fistula	Colectomy

Patients 1–10 were on extended dialysis (ED); patients 11–15 were without renal replacement therapy

Fig. 1 Plasma concentration–time profiles of the 15 septic patients, divided into different groups: **a** With dialysis, without previous liver transplantation/resection, **b** with dialysis, with previous liver transplantation/resection, **c** without dialysis, without previous liver transplantation/resection, **d** without dialysis, with previous liver transplantation/resection. Broken line = minimum inhibitory concentration=4 mg/L



resection were taken into account. Dialysis increased the CI of linezolid by 3.5 L/h, corresponding to a mean increase of 23%. In patients after liver transplantation/resection, linezolid CI was reduced by 60% relative to patients without prior liver transplantation/resection. The mean initial half-

life $t_{1/2\alpha}$ was 0.23 h and the terminal half-life $t_{1/2\beta}$ was 4.10 h for all septic patients.

Table 3 Linezolid population pharmacokinetics in 15 septic patients with and without extended dialysis

Pharmacokinetic parameter	Population mean	Interindividual variability	Intra-individual variability
CI (L h ⁻¹ kg ⁻¹)	0.159 (14%)	51% (31%)	10% (27%)
Effect of dialysis on CI	+ 3.5 L/h (30%)		
Effect of liver transplantation/resection on CI	-60% (22%)		
V ₁ (L/ kg)	0.273 (8.4%)	21% (31%)	20% (33%)
Q (L h ⁻¹ kg ⁻¹)	0.369 (11%)		
V ₂ (L/ kg)	0.271 (5.5%)		
Terminal half-life (t _{1/2β})	4.10 h		
Residual error			
Proportional	4.13% (23%)		
Additive (mg/L)	0.285 (23%)		

Standard error (SE) is given in parenthesis

V₁, Volume of distribution in the central compartment; V₂, volume of distribution in the peripheral compartment; Q, intercompartmental clearance; CI, total clearance

Across the dialysis membrane linezolid plasma concentrations decreased on average by 50% (range 30–58%). The part of the CI created by the dialysis membrane calculated according to Eq. 5 was 3.7±0.8 L/h, i.e., 38±22.4% of total linezolid CI. The population model revealed a prognostic value for CI at the dialysis filter of 3.5 L/h (Table 2). Clearance data are summarized and compared with the results reported for renal replacement therapy in the literature in Table 4.

Pharmacokinetic / pharmacodynamic indices

Table 5 shows time above MIC (T > MIC), AUC₂₄, and the ratio AUC₂₄ to MIC (AUC₂₄/MIC) of both groups (patients with or without ED) and for patients with or without previous liver transplantation/resection. The calculation was made with a MIC based on the susceptibility breakpoint for linezolid being 4 mg/L [20]. There was no statistically significant difference between patients with or without ED at a T > MIC (p=0.42) and AUC₂₄/MIC (p=0.5) but, in accordance with the smaller CI, values were higher in patients with previous liver transplantation/resection: T > MIC (p=0.01) and AUC₂₄/MIC (p=0.01).

Discussion

Our pharmacokinetic analysis of septic patients with acute renal failure and with or without ED revealed that: (1) linezolid concentration–time profiles are highly variable;

Table 4 Clearance data of linezolid in intensive care patients with acute renal failure undergoing renal replacement therapy. Data of present study were compared with data reported in the literature

Data sources	Number of patients	Dialysis ^a	Cl _{tot} (L/h)	Cl _{dial} (L/h)	APACHE II score	Removed drug fraction (mg)
Present data	10	ED	12.8±6.5	3.7±0.8	15–36	211–266
Meyer [28]	20	CVVH	9.3±3.5	1.9±0.8	7–40	n.d.a.
Fiaccadori [31]	5	IHD	6.0	n. d. a.	23–29	n.d.a.
Mauro [29]	1	CVVHDF	11.3	0.9–1.3	n.d.a.	50
Kraft [30]	1	CVVH	5.1 L/h	n.d.a.	n.d.a.	n.d.a.
Pea [21]	2	CVVH	n.d.a.	1.2 / 1.6	n.d.a.	n.d.a.
Fiaccadori [32]	8	IHD	n.d.a.	4.9 L/h	18–31	194±38
	5	ED	n.d.a.	2.0 L/h	21–36	205±77
	2	CVVH	n.d.a.	1.2 L/h	27	75–105

Cl_{dial}, Dialysis clearance due to the dialysis system; n.d.a., no data available

^a IHD, Intermittent hemodialysis; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; ED extended dialysis

(2) linezolid trough concentrations are often below the susceptibility breakpoint and only transiently above the MIC, suggesting that (3) the best method would be a therapeutic drug monitoring (TDM) approach to achieve effective antimicrobial therapy. In light of the emerging resistance to antimicrobials such as the oxazolidinone linezolid, the optimization of antimicrobial use through the integration of pharmacokinetic and pharmacodynamic data appears to be important. The results of a large compassionate-use study revealed that both an AUC/MIC >100 and a T > MIC of >85% are optimal biomarkers for linezolid clinical effectiveness [13].

Sepsis is known to influence drug pharmacokinetics owing to changes in the hemodynamics, capillary permeability, third spacing, acid–base status, serum proteins, and organ function of the patient. For example, underexposure may occur because of an increased volume of distribution (e.g., as a result of edema in sepsis) and/or enhanced renal clearance (e.g., as a result of hyperdynamic conditions during sepsis). On the other hand, overexposure may occur because of a drop in renal clearance caused by renal impairment [21, 22]. Due to these factors, plasma and tissue concentrations of antibiotics are often suboptimal when

drugs are administered at dosages suggested for healthy volunteers [23]. In our patient cohort, large interindividual variations in plasma concentrations and low C_{min} values were associated with an increase in the CI and volume of distribution relative to those found in healthy volunteers [24]. The increased CI may be a result of renal replacement therapy, and the increased volume of distribution may be due to septic conditions, such as edema. The half-life was also shortened in our study population with sepsis or septic shock. Our data therefore confirm recent findings in patients with sepsis or septic shock [14]. In this earlier study, the large fluctuations in linezolid plasma concentrations were also reflected in the considerable fluctuation of linezolid interstitial concentrations, suggesting that a regimen with more frequent dosing may be more appropriate and ultimately more effective [14]. Our data confirm this suggestion for septic patients with or without ED, but not for patients with liver transplantation/resection. Severe liver failure may occur in some cases after liver transplantation or resection. However, severe liver failure in the ICU would be characterized by significantly elevated bilirubin levels and/or a decreased production of coagulation factors. Both did not correlate in our study with elevated linezolid

Table 5 Time above MIC, AUC₂₄, and AUC₂₄/MIC of linezolid therapy of septic patients with or without extended dialysis

Patient groups	T > MIC (%)	AUC ₂₄ [h mg L ⁻¹]	AUC ₂₄ /MIC (h)
With dialysis	50.6±29.7	115.2±70.6	28.8±17.7
Without dialysis	40.4±35.9	123.5±124.4	30.9±31.1
With previous liver transplantation/resection	74.5±30.4	196.6±109.9	49.1±27.5
Without previous liver transplantation/resection	28.9±13.0	75.2±30.4	18.8±7.6

Values are given as the mean ± SD

T > MIC, Time above the minimum inhibitory concentration; area under the plasma concentration time curve at 24 h (AUC₂₄) to MIC ratio. The MIC based on the susceptibility breakpoint for linezolid being 4 mg/L [20]

plasma levels. The cause of the decreased linezolid metabolism in patients following liver transplantation/liver resection is as yet undetermined. However, alterations in the activity of liver enzymes after ischemia/reperfusion due to liver transplantation or resection is likely, although common clinical markers (bilirubin, coagulation system) may not have been sensitive enough to detect this in our investigation.

Because changes in the volume of distribution and CI can occur quite rapidly, it may be possible to avoid subtherapeutic concentrations by the continuous administration of antimicrobials with a time-dependent profile [23, 25]. One problem associated with continuous infusion without TDM, however, is its potential to promote resistance development when concentrations of linezolid are maintained constantly around the MIC [26].

We would like to point out that the population pharmacokinetic approach applied in our study is preferable to the non-compartmental method with descriptive statistics. The former method can also be applied in rich data situations, not only with sparse data. We had only 15 subjects; however, the availability of a lot of data for each individual resulted in precise estimates for the pharmacokinetic parameters. The reliability of the parameter estimates can be seen from the low SE of the estimates. In contrast, non-compartmental analysis with descriptive statistics can only provide rough estimates of interindividual variability. It has been shown that the latter method overestimates interindividual variability [27], while the population pharmacokinetic approach can distinguish between interindividual, intra-individual, and residual (i.e., analytical measurement error) variability, resulting in reliable estimates. For the main question addressed, the effect of ED on the CI of linezolid, the population pharmacokinetic method is the best method, as only this method can distinguish between the different sources of variability (as described above) as well as the effects of liver transplantation/resection, weight, or other parameters. Non-compartmental analysis with descriptive statistics cannot precisely distinguish between these different confounders.

Published data on linezolid plasma concentrations under continuous venovenous hemofiltration (CVVH) shows that no dose adjustment is necessary for patients undergoing continuous venovenous hemofiltration or hemodiafiltration [21, 28–30]. In contrast, two studies revealed either significantly reduced serum linezolid concentrations in critically ill patients on intermittent hemodialysis (IHD) [31] or serum concentrations of linezolid reduced to subtherapeutic values following renal replacement therapy [32]. Fiaccadori studied two patients on ED in which the ED session lasted 8–9 h, whereas the average time of ED in our study was 19.5 h. They also found an important fraction of the administered dose of linezolid was removed, especially in the case of IHD with ED.

Unless other causes for CI reductions are present, we expect that higher doses for septic patients are necessary during ED dialysis with the GENIUS system because of the higher efficacy of ED compared to CVVH. Extended dialysis is very important for the survival of critically ill patients with acute renal failure, but the consequences, such as on drug clearance, of this highly efficient renal replacement therapy must be considered, and adequate dose optimization must be carried out.

Limitations of the study

One major limitation of our study is that it was not prospectively designed in terms of liver patients and defined liver failure. The aim of our study was to determine the pharmacokinetics of linezolid in septic patients with ED and not on ED. The statistical significance in the pharmacokinetic parameters of septic patients with previous liver transplantation/resection was determined retrospectively. We have therefore initiated a new study for septic patients with defined liver failure.

Conclusion

In conclusion, our results provide the first pharmacokinetic data of intravenous linezolid administered during extended dialysis with the GENIUS dialysis system. They indicate that in the course of ED, linezolid plasma concentrations can be reduced to subtherapeutic values. Septic patients with and without ED—but not septic patients with liver transplantation/resection or patients with severe liver failure—may require higher doses. More data are necessary for the latter two groups of patients. The best method for achieving effective antimicrobial therapy in critically ill patients would be a TDM approach to dosing.

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