

Decreased Linezolid Serum Concentrations in Three Critically Ill Patients: Clinical Case Studies of a Potential Drug Interaction between Linezolid and Rifampicin

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Key Words

Rifampicin · Linezolid · Drug monitoring · Drug interactions · Anti-bacterial agents · Pharmacokinetics

Abstract

Linezolid is a valuable treatment option for treating infections caused by multi-resistant gram-positive pathogens. Lack of effective linezolid levels due to the co-administration of rifampicin has been described in healthy subjects. However, the clinical significance of this potential drug interaction (DI) for critically ill patients is still unclear. This was a retrospective analysis of 3 critically ill patients with the combination therapy of linezolid and rifampicin or rifampicin pre-treatment. Despite increasing the dose of linezolid, the majority of observed linezolid trough concentrations in all 3 patients were below 2 mg/l. Furthermore, linezolid trough concentrations remained below 2 mg/l after discontinuation of rifampicin. This potential DI between linezolid and rifampicin could lead to treatment failure. Therefore, we strongly recommend that linezolid serum concentrations be monitored in patients with rifampicin co-administration or rifampicin pretreatment.

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Introduction

Infections caused by multi-resistant gram-positive pathogens represent a major burden on healthcare. If risk factors for methicillin-resistant staphylococcus aureus (MRSA) are present, vancomycin is indicated [1]. Especially for implant-associated infections (e.g. infections of total endoprosthesis, prosthetic valve endocarditis), the combination therapy with rifampicin and vancomycin is recommended [1]. However, linezolid is often used in case of resistance or contraindication to vancomycin or if sequential therapy is indicated [1]. Due to the long-lasting treatment duration of implant-associated infections, the high oral bioavailability of linezolid (approximately 100%) [2] is an attractive oral alternative to intravenous glycopeptides.

Pharmacodynamic kill characteristics of linezolid are concentration-dependent with time-dependence. Therefore, AUC/MIC >100 (where, AUC = area under the antibiotic concentration-time curve for 24 h, MIC = minimal inhibitory concentration) is proposed as pharmacokinetic index predictive for efficacy [3]. Due to the MIC values of pathogens, trough concentrations ≥ 2 mg/l and/

or $AUC_{24} > 160\text{--}200 \text{ mg}\cdot\text{h/l}$ should be achieved to inhibit the growth of 90% of organisms (MIC90) for staphylococci [3].

Recently, it has been demonstrated that linezolid plasma exposure might significantly vary in some patient populations [4] and in those receiving polypharmacy [5]. Co-administrations of drugs such as clarithromycin, amiodarone, amlodipine, or omeprazole may be responsible for linezolid overexposure, which could favor drug-related adverse events [5]. In contrast, lack of effective linezolid concentrations due to the co-administration of rifampicin is described in healthy subjects, and this could lead to treatment failure [2, 6]. However, the clinical significance of this potential drug interaction (DI) for critically ill patients is still unclear.

The objective of this clinical case study was to report about linezolid serum concentrations in critically ill patients with rifampicin co-administration or rifampicin pretreatment.

Methods

This was a retrospective analysis of critically ill patients who were treated with the combination therapy of linezolid and rifampicin or rifampicin pretreatment due to suspected or proven MRSA infection and therapeutic drug monitoring (TDM) of linezolid. Ethical approval was obtained from the ethics committees (Ludwig-Maximilian-Universität München, München, Germany; Universität Ulm, Ulm, Germany). The ethics committee waived the need for patient consent due to the retrospective nature of the study. Blood samples were collected just before the initiation of the linezolid infusion (trough in serum, steady-state; $C_{\min, ss}$) and within half an hour after linezolid infusion at 3 or 4 h (peak in serum, steady-state; $C_{\max, ss}$). Linezolid trough and peak concentrations in serum were measured by a validated high-performance liquid chromatography with ultraviolet detection, as has been previously described in detail [7].

Results

Three critically ill patients with linezolid and rifampicin co-administration or rifampicin pretreatment were analyzed. In total, 22 blood samples were collected.

Case 1

A 65-year-old patient (weight 65 kg, height 165 cm) with a history of bowel syndrome and pulmonary emphysema was hospitalized because of subarachnoid hemorrhage with concomitant obstructive hydrocephalus. The patient underwent successful clipping of a posterior infe-

rior cerebellar artery aneurysm, and an intraventricular catheter (IVC) was placed for the management of hydrocephalus. Treatment with ceftriaxone and clindamycin was initiated because of aspiration pneumonia and bone infection prophylaxis for 7 days. On day 7, the patient developed an IVC-associated ventriculitis. The IVC was replaced and empirical antibiotic therapy was commenced with vancomycin (2 times daily, targeting serum trough concentration of 15–20 mg/ml) and meropenem (2 g 3 times daily). No pathogens could be isolated from the cerebrospinal fluid (CSF) sample. On day 9, a combination therapy with rifampicin (600 mg once a day) for 7 days was commenced because of a deteriorating condition. On day 15, vancomycin was withdrawn because of an increase in serum creatinine levels (from 0.8 to 1.4 mg/l) and replaced by linezolid (600 mg 2 times daily). Rifampicin was replaced by fosfomycin (5 g 3 times daily) because of persisting inflammatory response and high cell count in the CSF. In addition, aspiration pneumonia was treated with moxifloxacin (400 mg once a day) for 7 days because of progressive pulmonary infiltrates. On day 16, the patient developed acute kidney injury probably due to X-ray contrast medium and was treated with continuous veno-venous hemodialysis for 6 days (dialysate flow 2,000 ml, blood flow 100 ml). TDM of linezolid was started. On days 17 and 19, serum trough concentrations of linezolid were undetectable ($<0.5 \text{ mg/l}$). Linezolid serum concentrations at 7 h were 0.5 mg/l (table 1). On day 19, IVC-associated ventriculitis was cured; however, antibiotic therapy was continued until day 27 as recommended in guidelines. On days 21, 26 and 27, serum trough concentrations of linezolid remained below 2.2 mg/l (table 1). Serum peak concentrations of linezolid increased but remained below 10 mg/l . The IVC was removed on day 35. The patient was discharged from the hospital for further rehabilitation on day 44 (table 1; fig. 1).

Case 2

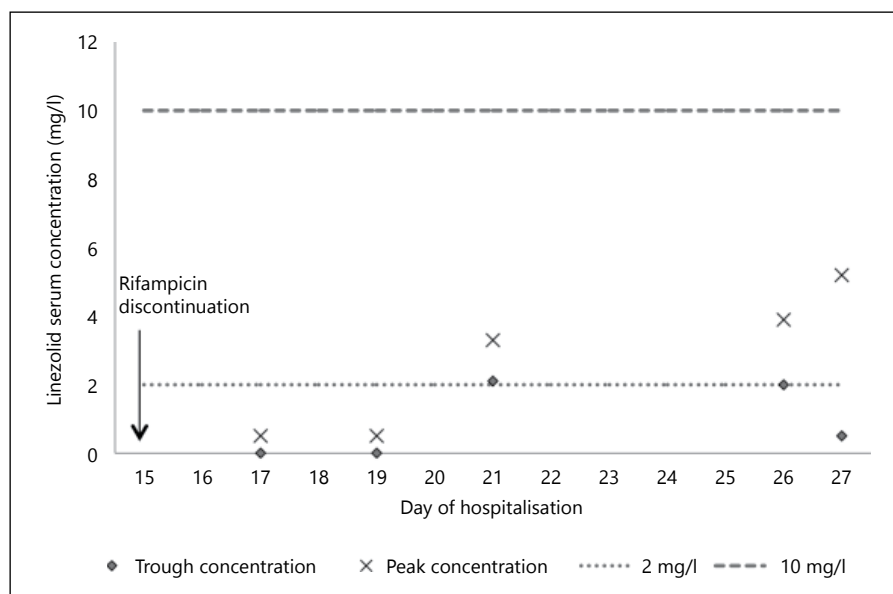
A 72-year-old patient (weight 90 kg, height 168 cm) with a history of coronary heart disease, peripheral arterial disease and kidney disease was hospitalized because of shoulder empyema. The patient underwent humeral head resection. On day 3 of treatment with ciprofloxacin (400 mg 2 times daily), linezolid (600 mg 2 times daily) and rifampicin (600 mg 2 times daily) were initiated due to MRSA growing in the blood cultures after pretreatment with ampicillin/sulbactam. On day 5, ciprofloxacin was stopped due to the results of resistance testing. TDM of linezolid was started. Serum trough concentrations of linezolid were below 1 mg/l at days 4,

Table 1. Linezolid doses and corresponding linezolid serum concentrations in 3 critically ill patients with rifampicin pretreatment (case 1) or rifampicin co-administration (cases 2 and 3)

Day of linezolid therapy	Dosage linezolid, mg	Infusion time linezolid, h	Co-administration with rifampicin, mg	Rifampicin administration	Linezolid Cmin, ss, (mg/l)	Linezolid Cmax, ss, (mg/l)
<i>Case 1</i>						
3	2 × 600	4	Day 3 without rifampicin	–	<0.5	0.5 (7 h after infusion start)
5	2 × 600	4	Day 5 without rifampicin	–	<0.5	0.5 (7 h after infusion start)
7	2 × 600	4	Day 7 without rifampicin	–	2.1	3.3
12	2 × 600	4	Day 12 without rifampicin	–	2.0	3.9
13	2 × 600	4	Day 13 without rifampicin	–	<0.5	5.2
<i>Case 2</i>						
2	2 × 600	0.5	2 × 600	IV	0.6	8.0
4	3 × 600	0.5	2 × 600	IV	4.1–1.5 h too early	11.7
8	3 × 600	0.5	2 × 600	IV	0.9	ND
21	3 × 600	Oral	2 × 600	IV	0.9	ND
25	3 × 600	Oral	2 × 600	IV	0.8	ND
26	3 × 900	Oral	2 × 600	Oral	ND	5
<i>Case 3</i>						
2	2 × 600	0.5	2 × 300	Oral	0.5	ND
3	3 × 600	0.5	2 × 300	Oral	0.5	ND
7	3 × 600	Oral	2 × 450	Oral	1.9	6.5

IV = Intravenous; ND = not determined.

Fig. 1. Linezolid serum concentrations case 1 as example. Therapeutic serum concentrations of linezolid are expected to be between 4 and 10 mg/l using standard dosing (600 mg 2 times daily). Due to the MIC values of pathogens, trough concentrations ≥ 2 mg/l and/or $AUC_{24} > 160$ – 200 mg \cdot h/l should be achieved to inhibit the growth of 90% of organisms (MIC90) for staphylococci [3]. Linezolid trough concentrations were even below 2 mg/l 13 days after rifampicin discontinuation.



6 and 10, despite dose increases to 1,800 mg/24 h (table 1). On days 4 and 6, serum peak concentrations of linezolid were 8.0 and 11.7 mg/l, respectively (table 1). On day 12, intravenous linezolid was switched to oral linezolid (1,800 mg/24 h). Serum trough concentrations

of linezolid remained below 1 mg/l on days 19 and 23 (table 1). On day 24, linezolid was increased to 2,700 mg/24 h. Peak serum concentration of linezolid (1 h after oral administration) was 5 mg/l (table 1). On day 25, linezolid was discontinued due to microbiological cure

after knee puncture. Antibiotic therapy was terminated on day 25. The patient was discharged from the hospital on day 26.

Case 3

A 77-year-old patient (weight 107 kg, height 178 cm) with a history of diabetes and heart disease was hospitalized because of total endoprosthesis infection after knee arthroplasty surgery. The patient underwent endoprosthesis removal and a spacer was placed. *Staphylococcus epidermidis* was isolated from a knee puncture. Treatment with vancomycin (1 g 2 times daily) and rifampicin (600 mg 2 times daily) was initiated. On day 18, vancomycin was switched to linezolid (600 mg 2 times daily). Rifampicin was reduced to 300 mg 2 times daily. Linezolid TDM was started. Serum concentrations of linezolid were measured on days 19 and 20. On day 21, linezolid was switched to oral linezolid and increased to 1,800 mg/24 h because of linezolid serum concentrations below 1.0 mg/l (table 1). On day 25, linezolid serum trough concentration 30 min before administration and 1 h after administration were 1.9 and 6.5 mg/l, respectively (table 1). On day 25, rifampicin was increased to 450 mg 2 times daily. The patient was discharged from the hospital on day 31.

Discussion

In these clinical case studies, we observed an increased linezolid clearance in critically ill patients with rifampicin co-administration as well as rifampicin pretreatment. Although trough serum concentrations of linezolid are supposed to be between 4 and 6 mg/l [3], the majority of observed trough serum concentrations of linezolid in all 3 patients were below the MIC of susceptible MRSA (<2 mg/l) [3], despite increasing the dose of linezolid in 2 patients (see Results). Moreover, linezolid trough concentrations were even below 2 mg/l 13 days after rifampicin discontinuation in case 1 (see Results; table 1).

Rifampicin is able to induce several hepatic enzymes like cytochrome 450 enzymes (CYP) as well as carrier proteins like P-glycoprotein (P-gp). Co-administration of rifampicin and other drugs that are transported by P-gp or metabolized by the hepatic CYP system can lead to clinical relevant DI due to the induction of enzymes in shared metabolic pathways. Therefore, rifampicin has a high potential for pharmacokinetic interactions with other drugs [8].

Linezolid is primarily metabolized by the oxidation of the morpholine ring, which results in 2 inactive major

metabolites. Urinary elimination accounts for 35% of the parent drug [9]. However, the enzyme system or oxidants formation *in vivo* have not been elucidated yet [10]. A discussion on the participation of CYP in the metabolic pathway led to controversial results [5, 9, 10, 11].

Recently, interactions between rifampicin and linezolid have been reported, in which linezolid serum concentrations were reduced [6, 11–13]. Rifampicin was shown to cause about 30% reduction of linezolid exposure in healthy subjects [6, 11]. Yet, in our case study, linezolid trough concentrations are even lower. Zoller et al. [4] described a high variability of linezolid serum concentrations in a heterogeneous group of critically ill patients. One possible reason could be that linezolid serum exposure might significantly vary in some patient populations such as critically ill patients. Indeed, decreased linezolid concentrations by 40–60% were described in a critically ill patient [12] and decreased linezolid concentrations by 87–94% in 2 non-critically ill patients [13].

Moreover, several retrospective observational studies described a lower incidence of hematological adverse events among patients receiving rifampicin and linezolid compared to patients receiving linezolid alone. This might indicate clinical significance of this DI. Soriano et al. [14] investigated the effects of rifampicin on hematological adverse events induced by linezolid in a comparative study. The co-administration of rifampicin was associated with a lower risk of thrombocytopenia. Likewise, Legout et al. [15] described a lower risk of anemia in patients with bone and joint infections if they received rifampicin and linezolid compared to patients receiving linezolid alone or in combination with other drugs. On the contrary, differences in clinical success rates were not observed. Pea et al. [5] investigated the toxicity of long-term treatment with linezolid. Patients receiving rifampicin and linezolid vs. receiving linezolid alone had significantly lower trough concentrations (C_{\min} 1.37 vs. 3.71 mg/l) or AUC_{24} (123.33 vs. 212.77 mg*h/l). Furthermore, there was a lower risk of thrombocytopenia (0 vs. 51.4%). Consequently, rifampicin seemed to display a protective effect against hematological toxicity. More important, treatment failure was observed more often in the rifampicin-linezolid group. Therefore, Pea et al. [5] concluded that there is no benefit of the co-administration that justifies the risk of insufficient dosing and therefore potential antibiotic treatment failure of linezolid. However, the clinical significance of this potential interaction has not yet been established and the mechanism needs further research. The mechanism of the pharmacokinetic DI between rifampicin and linezolid could be due to metabo-

lism induction. Because DI can also be observed after rifampicin pretreatment, induction of protein synthesis would be most plausible, but the mechanism is found to result in controversial outcomes [6, 11].

Conclusions

Our clinical case studies support clinical significance of this potential DI between linezolid and rifampicin for critically ill patients, even if rifampicin is already discontinued. We observed sub-therapeutic linezolid serum concentrations in patients with rifampicin co-administration as well as rifampicin pretreatment. Although decreased linezolid concentrations in healthy subjects are already described in the summary of product characteristics of linezolid [2], recommendations with regard to patient management are not available yet. The decrease in linezolid concentrations could be related to induction

of metabolism by rifampicin but the mechanism of this potential DI is still not understood.

Clinicians should be aware of this potential interaction that could lead to antibiotic treatment failure of linezolid. These clinical case studies emphasize the value and need of monitoring linezolid serum concentrations with rifampicin co-administration and pretreatment. Further investigation is needed to assess the clinical significance of the combination therapy.

Disclosure Statement

The author(s) declare that they have no competing interests.

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