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Decreased Linezolid Serum Levels in Critically ill Patients:
Clinical Case Studies of a Drug-Drug-Interaction between Linezolid and Rifampicin (PKP-002)

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Background

Infections caused by multiresistant gram-positive pathogens present a particular challenge to the physician, that result in increased clinical complications. For implant-associated infection (*e.g.* infections of total endoprothesis (TEP) or endocarditis with a flap) the combination therapy of rifampicin and vancomycin is particularly recommended. Linezolid is only used if resistance or a contraindication to vancomycin is known or if oral therapy is indicated. Lack of therapeutic effective linezolid levels due to co-administration of rifampicin has previously been described in healthy subjects [1,2]. However, the clinical significance of this drug-drug-interaction (DDI) for critically ill patients remains unclear.

Purpose

To report about a DDI between linezolid and rifampicin resulting in linezolid levels below the minimal inhibitory concentration (MIC) of methicillin-resistant Staphylococcus aureus (MRSA) in three patients.

Methods

Three patients with linezolid and rifampicin were identified through routine therapeutic drug monitoring. Linezolid serum concentration was measured by a validated high performance liquid chromatography assay. The cases' history is described below.

Patient history:

Case 1: 65-year-old woman (weight 65 kg, height 165 cm) with extraventricular drainage (EVD) infection state after subarachnoid haemorrhage, pretreatment with meropenem + vancomycin + rifampicin for 7 days, switch to meropenem + linezolid (rifampicin is discontinued on day of switch)

Case 2: 75-year-old man (weight 90 kg, height 168 cm) with resection of the humeral head due to a MRSA shoulder empyema, pretreatment with ampicillin/sulbactam, postoperative switch to rifampicin + linezolid

Case 3: 80-year-old man (weight 107 kg, height 178 cm) with knee-TEP infection, pretreatment with rifampicin + vancomycin, switch to rifampicin + linezolid

Results

The majority of observed linezolid trough levels were below 4 mg/l in all three patients, even 13 days after rifampicin discontinuation (Case 1) or dose escalation (Cases 2,3) (Table 1).

	Day of therapy	Dosage linezolid	Infusion time [h]	Trough level [mg/l]	Peak level [mg/l]
Case 1	3	2 x 600 mg	4	0,5	0,5
	5		4	0,5	0,5
	7		4	2,1	3,3
	12		4	2	3,9
	13		4	<0,5	5,2
Case 2	2	2 x 600 mg	0,5	0,6	8,0
	4	3 x 600 mg	0,5	4,1 (1,5 h too early)	11,7
	8		0,5	0,9	ND
	21		p.o.	0,9	ND
	25		p.o.	0,8	ND
Case 3	2	2 x 600 mg	0,5	0,5	ND
	3	3 x 600 mg	0,5	0,5	ND
	7		p.o.	1,9	6,5

Table 1: Linezolid dosage and serum levels (ND = not determined)

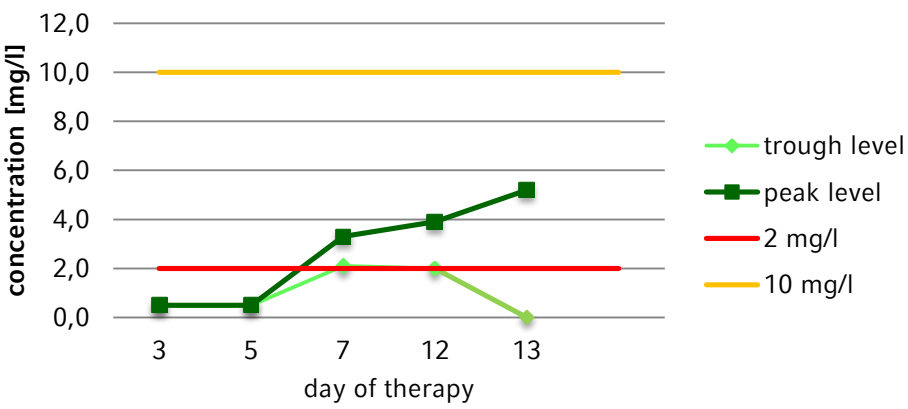

Figure 1: Linezolid serum levels of case 1

Discussion

We observed an accelerated linezolid clearance in critically ill patients. Therapeutic linezolid serum levels are expected between 4 mg/l (2x600 mg i.v.) and 6 mg/l (2x600 mg p.o.). Due to MIC-values serum trough levels between (2)4 – 7(10) mg/l should be achieved for the treatment of MRSA infections [3]. Pea F *et al.* detected a lower incidence of typical blood alterations and at the same time, more treatment failure with rifampicin co-administration in comparison to linezolid monotherapy [4]. This retrospective observational study indicates the clinical relevance of this DDI.

Monitoring of linezolid levels and corresponding dose adjustments could ensure a safe and effective antibiotic therapy in patients with rifampicin co-administration as well as rifampicin premedication. Further investigation should be conducted to assess the clinical significance of combination therapy.

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4. Pea F. et al. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother, 2012. 67(8): p. 2034-4

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