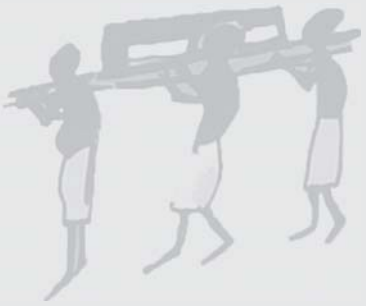

Chapter 3A

Clarithromycin significantly increases linezolid serum concentrations

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Antimicrob Agents Chemother. **2010** Dec; 54(12)5418–9

TO THE EDITOR

A 42-year-old male patient was admitted at our hospital for treatment of smear-positive pulmonary tuberculosis (TB). Drug Susceptibility Testing (DST) revealed extensively drug resistant tuberculosis (XDR-TB) and the isolate appeared only susceptible to cycloserin, linezolid, clarithromycin and clofazimine. According to the WHO treatment guidelines for TB the treatment regimen was composed of these four drugs as no other options were available (11). Linezolid was the cornerstone of this regimen because of the high *in vitro* activity against *M. tuberculosis* (MIC of 0.125 – 0.5 mg/L) (1, 8). Linezolid is a toxic drug and its labelled duration of administration is therefore limited to 28 days to prevent peripheral neuropathy and anaemia. Dose reduction has been evaluated in TB patients as an attempt to reduce toxicity to allow for prolonged treatment for 18 – 24 months (6, 7, 10). The target of linezolid serum concentrations in our hospital is to maintain an AUC (the area under the concentration-time curve over 24 h) / MIC ratio over 100 and time in excess of the MIC of 100%. These conditions are generally reached with a dosage of 300 mg twice daily (2). Serum concentrations are analysed using a validated liquid chromatography tandem mass-spectrophotometer method (5). In this patient, we measured a considerable increase in the AUC of linezolid from 29 mg*h/L to 108 mg*h/L (Figure 1).

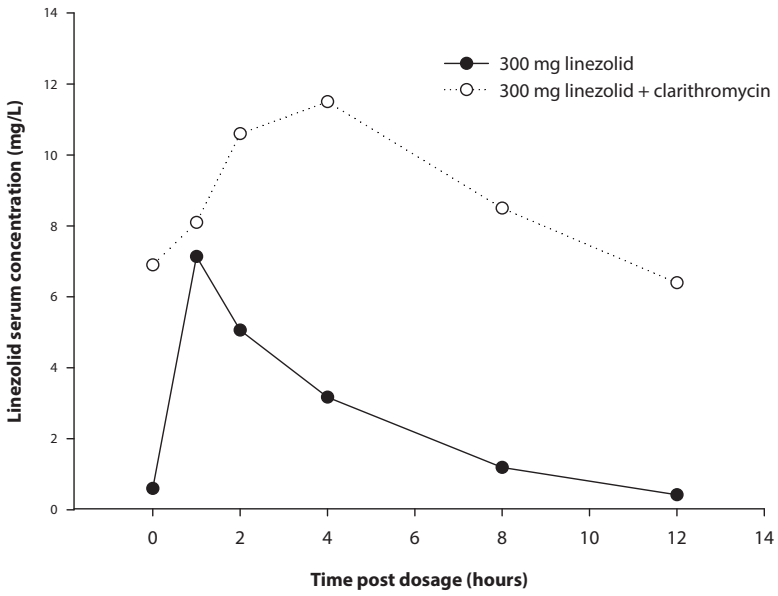

Figure 1 Linezolid serum concentrations over time before (solid circles) and after (open circles) addition of clarithromycin.

This increase appeared to coincide with the start of clarithromycin (1000 mg once daily), a potent inhibitor of P-glycoproteins (3). We also found that the t_{max} of the absorption phase was delayed. Possible other drug-drug interactions were not expected as the patient received only clofazimine, domperidone, insulin, omeprazole, and vitamins. We did not observe any significant changes in his liver- or renal function to account for the sudden raise of linezolid serum concentrations. Based on the serum concentrations, the linezolid dose was decreased to 150 mg twice a day. After 6 months the sputum cultures and smear microscopy became negative. The patient was discharged from our Center in a good clinical condition. At follow-up his sputum cultures have remained negative for the last 12 months of his 18 months treatment, and his clinical condition has remained excellent. The timely reduction of linezolid dosage might have prevented toxicity such as time- and dose dependant myelosuppression (9). This case further strengthens the suggestion that linezolid is a P-glycoprotein substrate. From an earlier case it is known that the addition of a potent P-glycoprotein inducer rifampicin, resulted in a reduction of linezolid concentration (4). In our case the administration of the P-glycoprotein inhibitor clarithromycin resulted in a clear increase of linezolid serum concentrations. Based on our observations, a dose reduction of linezolid and therapeutic drug monitoring should be considered if linezolid is co-administered with clarithromycin in order to prevent potential toxicity. A prospective pharmacokinetic study may help to quantify the interaction that we describe.

Financial support

JWCA; this publication was prepared as part of the training in Clinical Pharmacology and was financially supported by the Dutch Society for Clinical Pharmacology and Biopharmacy.

Conflict of interest

None to declare.

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