percentages of patients colonized upon ICU admission were 12.8% in Greece and 7% in Israel; 27% acquired colonization during ICU stay occurred in the hospital in Israel.

A low prevalence of CPE enteric carriage upon ICU admission was observed in this study, but individual hospital variations in the incidence of ICU-acquired CPE were observed. Four hospitals (36%) had an incidence rate higher than 3%; in three of them nosocomial dissemination of CPE had been reported. 9–11

In a recent study including 379 CPE from 45 Spanish hospitals, OXA-48 (71.5%) and VIM-1 (25.3%) were the most frequent carbapenemases and K. pneumoniae (74.4%), E. cloacae (10.3%) and E. coli (8.4%) were the species most affected. In that study, a wide inter-regional spread of CPE in Spain was observed, mainly due to a few successful clones of K. pneumoniae of ST11 and ST405, which mainly carried OXA-48, and ST15, which more often carried VIM.1

All of the 11 patients colonized by CPE were assigned to contact precautions, and the standard cross-transmission control measures were reinforced. In this regard, it is strongly advisable to implement the guidelines for the management of the infection control measures to reduce transmission of MDR Gram-negative bacteria recommended by ESCMID. 12 Active targeted surveillance in combination with early implementation of infection control measures is needed in hospitals to prevent dissemination of CPE.

Acknowledgements

We thank José Ignacio Ayestaran (Hospital Universitario Son Espases), Maria Nieves Larrosa (Hospital Universitario Vall d’Hebrón), Borja Suberviola (Hospital Universitario Marqués de Valdecilla), Mª José Barba (Complejo Hospitalario Universitario A Coruña), Silvia Capilla (Corporación Sanitaria Parc Taulí), Isabel Morales (Hospital Universitario Virgen Macarena), Gema Fresco (Hospital Universitario Ramón y Cajal) and Verónica Bautista, Adriana Ortega and José Campos (Centro Nacional de Microbiología) for technical and scientific support.

Funding

This work was supported by: (i) a grant from the Fondo de Investigación Sanitaria (grant number PI12/01242); (ii) the Antibiotic Resistance Surveillance Programme of the Spanish Centro Nacional de Microbiología, Instituto de Salud Carlos III, Ministerio de Economía y Competitividad; (iii) the Plan Nacional de I-D+i 2008-2011; and (iv) the Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD12/0015)—co-financed by the European Regional Development Fund ‘A Way to Achieve Europe’.

Transparency declarations

None to declare.

References


Advance Access publication 3 July 2015

Is it time to revise linezolid doses in peritoneal dialysis patients? A case series

Cristina Gervasoni1*, Roberto Bergia2, Valeria Cozzi3, Emilio Cemcit1,4,5 and Dario Cattaneo3

1 Department of Infectious Diseases, L. Sacco University Hospital, Milan, Italy; 2 Unit of Nephrology and Dialysis, Degli Infermi Hospital, Biella, Italy; 3 Unit of Clinical Pharmacology, L. Sacco University

Advance Access publication 3 July 2015

Research letters
Sir,

No specific indications on dose adjustments for linezolid in patients with renal insufficiency or on haemodialysis are actually given on the drug’s label sheet. Nevertheless, consistent evidence is now available showing that, due to a systemic increased accumulation of linezolid, such patients treated with the conventional dose of linezolid of 600 mg twice daily are at higher risk of experiencing haematological toxicity than patients with normal renal function.1–4 However, only anecdotal reports are available for patients receiving peritoneal dialysis (PD).5,6 Here, we describe four patients on PD who experienced an increased exposure to linezolid and eventually life-threatening drug toxicity while being treated with linezolid at 600 mg twice daily for vancomycin-resistant infections.

The first case was a 66-year-old man who had been on PD since 2012 and was given linezolid to treat lumbor spondylodiscitis. This resulted in a progressive reduction in his platelet count, reaching a nadir of 53 × 10⁹ cells/µL on Day 30 after starting therapy with linezolid. A blood sample for therapeutic drug monitoring (TDM) of linezolid revealed a plasma trough concentration of 25.5 mg/L. According to the available literature, a concentration window of 2–8 mg/L is considered to be the therapeutic range.7,8 After the dose had been reduced to 300 mg twice daily, the patient showed a progressive recovery of both platelet count and haemoglobin level and was able to complete the 2-month linezolid therapy (more-detailed information on this case has been published previously, see Gervasoni et al.9).

The second patient was a 74-year-old woman who had been on PD since 2010 and started linezolid 600 mg twice daily for leg ulcers. Blood and peritoneal fluid samples collected 1 week after starting therapy revealed plasma trough and peritoneal fluid concentrations of linezolid of 22.5 and 5.8 mg/L, respectively. Given both the high linezolid concentrations and the observed reduction in platelet count (from 400 to 233 × 10⁹ cells/µL), we decided to reduce the dose to 300 mg twice daily. At the second monitoring of linezolid, performed 3 days after the dose adjustment, the plasma and peritoneal fluid concentrations of linezolid were 18.4 and 2.3 mg/L, respectively. Since the patient had optimal tolerability of the therapy (platelet count 254 × 10⁹ cells/µL), we decided to maintain the dose of linezolid at 300 mg twice daily. Plasma and peritoneal fluid concentrations of linezolid measured 10 days after the dose reduction were 6.9 and 1.9 mg/L, respectively. The patient successfully completed the planned 1-month therapy.

The third patient was an 87-year-old woman who had been receiving PD since 2013. In January 2015, the patient started therapy on linezolid 600 mg twice daily for Enterococcus faecalis peritonitis. Eighteen days after starting therapy, the patient experienced a slight reduction in platelet count (from 276 to 206 × 10⁹ cells/µL) and haemoglobin level (from 11.6 to 10.3 g/dL) together with a modest increase in blood lactate values (resulting in a concentration of 2.6 mmol/L). On Day 21 of linezolid therapy, a blood sample collected 6 h after the morning drug intake revealed a concentration of 31.4 mg/L. According to our database, which included detailed daily pharmacokinetic assessments of linezolid from more than 50 patients, we estimated that this concentration corresponded to a linezolid plasma trough level of around 30 mg/L. However, before the planned dose adjustment, the patient decided to stop the drug because of nausea, lack of appetite and asthenia.

The last patient was a 57-year-old woman with a history of chronic renal insufficiency secondary to systemic lupus erythematosus who had been receiving PD since 2009. In January 2015, she started linezolid 600 mg twice daily for MDR Staphylococcus epidermidis peritonitis. Linezolid was withdrawn 20 days later due to pancytopenia (haemoglobin, leucocyte and platelet levels dropped from 11.2 to 9.8 g/dL, from 5.85 × 10⁹ to 3.44 × 10⁹ cells/µL and from 147 × 10⁹ to 75 × 10⁹ cells/µL, respectively). Three days later, the patient experienced severe lactic acidosis (blood pH 7.21, bicarbonates 9.5 mmol/L and lactates 12.4 mmol/L) and was transferred to the ICU, where she died. A plasma sample collected nearly 90 h after stopping linezolid revealed a plasma concentration of 1.0 mg/L. By assuming a terminal half-life for the drug of 8 h, we estimated that, during therapy, the patient was exposed to concentrations of linezolid of at least 20–30 mg/L, largely exceeding the therapeutic window concentration of 2–8 mg/L.

We recently reported the case of a PD patient (Case 1 above) experiencing haematological toxicity while being treated with the conventional dose of linezolid of 600 mg twice daily, who benefitted from TDM-guided drug dose adjustments.5 This experience prompted us to search for other cases, with the goal of verifying whether this concept could be eventually applied to all patients on PD. Three additional patients were identified (Cases 2–4 above) who had consistent documentation that the 600 mg twice-daily dose of linezolid resulted in an increased systemic drug accumulation. This case series reported all PD patients who consecutively underwent TDM for linezolid at our centre. All the patients had plasma trough concentrations that were 3- to 4-fold higher than the upper therapeutic threshold of 8 mg/L.7,8 Most importantly, three out of the four patients experienced severe toxicity, whereas in the remaining case, the development of toxicity was probably avoided due to an early reduction of the dosage of linezolid.

Our findings are apparently at variance with previous reports of an optimal safety outcome in PD patients given linezolid at 600 mg twice daily for the treatment of vancomycin-resistant peritonitis.9 However, this discrepancy may only be apparent, being potentially biased by (i) the duration of therapy (our patients experienced drug-related toxicity after 3 weeks, whereas in the previous reports linezolid was given for a shorter time) and (ii) differences in the patients’ ages. In fact, we have previously documented that patients experiencing haematological toxicity were older than patients with good drug tolerability (69.8 ± 11.7 years versus 50.8 ± 11.7 years, P < 0.05).7 These findings are in line with results from Abe et al.,9 showing that younger patients were less likely to experience linezolid-related toxicity than elderly patients. Moreover, in agreement with our working hypothesis, it has also recently been shown that the duration of linezolid treatment is an additional risk factor for the development of drug-related thrombocytopenia.10

Taken together, these findings call for a careful revision of the most appropriate linezolid dose in PD patients, especially when they are elderly and/or require prolonged treatment. Our case series also confirmed that linezolid-related toxicity can be easily handled in clinical practice by TDM-guided early dose adjustments or, if TDM is not available, by stringent haematological examinations.

*Corresponding author. E-mail: cristina.gervasoni@unimi.it

Hospital, Milan, Italy; *Clinical Pharmacology Unit, CNR Institute of Neuroscience, Department of Biomedical and Clinical Sciences, L. Sacco University Hospital, Università di Milano, 20157 Milan, Italy; 5Scientific Institute IRCCS E. Medea, 23842 Bosisio Parini, Italy

Research letters
**Funding**
This study was carried out as part of our routine work.

**Transparency declarations**
None to declare.

**References**