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Usefulness of monitoring linezolid trough serum concentration in prolonged treatments

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ABSTRACT

Linezolid has proven valuable in musculoskeletal infections, however, failure and resistance have been described and toxicity is worrisome when more than 28 days are necessary. We describe the first 5 cases in whom linezolid trough serum concentrations were weekly measured and its relationship with clinical outcome and toxicity.

Keywords: linezolid, therapeutic drug monitoring, musculoskeletal infections.

Utilidad de monitorizar la concentración sérica en el valle de linezolid en pacientes que reciben tratamientos prolongados

RESUMEN

Linezolid ha demostrado ser eficaz en el tratamiento de infecciones musculo-esqueléticas, sin embargo, se han descrito casos de fracaso, desarrollo de resistencia y toxicidad en tratamientos de más de 28 días. Describimos nuestra experiencia en 5 casos consecutivos en los que la concentración de linezolid se determinó semanalmente y su relación con la respuesta clínica y la toxicidad.

Palabras clave: linezolid, monitorización, infecciones musculo-esqueléticas.

INTRODUCTION

Linezolid belongs to a new family of antibiotics (oxazolidinones) that has shown excellent activity against gram-positive cocci, including *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and streptococci[1]. The fact that it has 100% oral bioavailability and reaches high concentrations at different sites (including bone and synovial fluid) makes it a good alternative for the long-term treatment of orthopedic implant infections[2]. Several studies have proven its value in these type of infections but some cases end up failing either as persisting/relapsing infections or as forced discontinuation of linezolid due to drug toxicity[3,4]. Indeed, a major concern with this antibiotic is its safety profile, especially when it is administered for a prolonged period of time. Adverse events associated with linezolid are due to mitochondrial toxicity[5] and include hematological disturbances (thrombocytopenia and anemia), peripheral neuropathy, hyperlactacidemia and metabolic acidosis[6-9].

Linezolid is administered at 600 mg/12h and no dose adjustments have been recommended in renal or liver failure. We have evaluated the usefulness of monitoring trough serum linezolid concentrations in 5 consecutive patients with an orthopedic implant infection that received standard linezolid dose.

PATIENTS AND METHODS

Five patients presenting orthopedic implant related infections due to Gram-positive cocci were treated with 600 mg linezolid every 12h orally and were prospectively followed-up. Four had an acute post-surgical infection managed with debridement and implant retention and 1 a chronic infection treated with 2-stage revision. Infected implants were a thoraco-lumbar spinal instrumentation for traumatic first lumbar vertebrae fracture, 3 total knee and 1 total hip arthroplasties. Demographic information, co-morbidities and treatment information were gathered. Rifampin is systematically used in our institution in staphylococcal orthopedic implant infections unless resistance or liver impairment are present. Clinical and laboratory monitoring of potential adverse events (including complete blood counts, lactate and renal function) as well as trough serum concentrations of linezolid were performed once a week during treatment. Serum linezolid concentration was measured using a reverse-phase high-performance liquid chromatography with ultraviolet detection.

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RESULTS

Patient characteristics and linezolid trough serum concentrations are shown in table 1 and figure 1. Patient 1, a young woman treated with linezolid plus rifampin (600 mg/24h) had persistent low trough linezolid concentration, averaging 1.5 mg/L. The tolerance was good and no adverse events were registered, however, wound discharge persisted and C-reactive protein (CRP) levels were above normal values after more than 6 weeks of therapy. No evidence of super-infection due to a different pathogen was documented. Patients 2 and 3 had trough linezolid levels from the second week between 5 and 10 mg/L, no adverse event was registered, CRP levels decreased below 1 mg/dL and a favorable outcome at the end of treatment was observed. Both patients were treated with open debridement without removing the implant. Patient 4 had a chronic infection and the implant was removed, for this reason he received linezolid for 3 weeks with good clinical and serological evolution and without adverse reactions. Linezolid levels were between 2-3 mg/L during the first 2 weeks and 6 mg/L in the last week. Patient 5 had a chronic liver disease (Child-Pugh B) and linezolid was stopped after 2 weeks of treatment due to severe hematologic toxicity, including anemia and thrombocytopenia (table 1). This patient had high trough linezolid levels (over 25 mg/L) and lactate concentration (over 50 mg/dL). Treatment was switched to alternative antibiotics and the outcome was good at the end of therapy.

Table 1 | **Characteristics of patients treated with linezolid.**

Nº	Age/sex	Comorbidity	Implant	Etiology	Other antibiotic	BMT	Lactate (mg/dL)	Creatinine (mg/dL)	Outcome*
1	28/F	-	SI	MR-CNS	Rifampin	No	14,7	0,72	wound discharge
2	64/M	RA	TKA	MR-CNS	-	No	14,5	1,07	Resolution
3	75/M	-	TKA	MR-CNS	-	No	18	0,83	Resolution
4	67/M	Cardiopathy	TKA	MR-CNS	-	No	17	1,07	Resolution
5	62/M	LC	THA	MR-CNS	Ciprofloxacin	Yes	51	0,85	Resolution

F, female. M, male. RA, rheumatoid arthritis. LC, liver cirrhosis. SI, spinal instrumentation. TKA, total knee arthroplasty. THA, total hip arthroplasty. MR-CNS, methicillin-resistant coagulase-negative staphylococci. BMT, bone marrow transplantation.

* Outcome at the end of therapy.

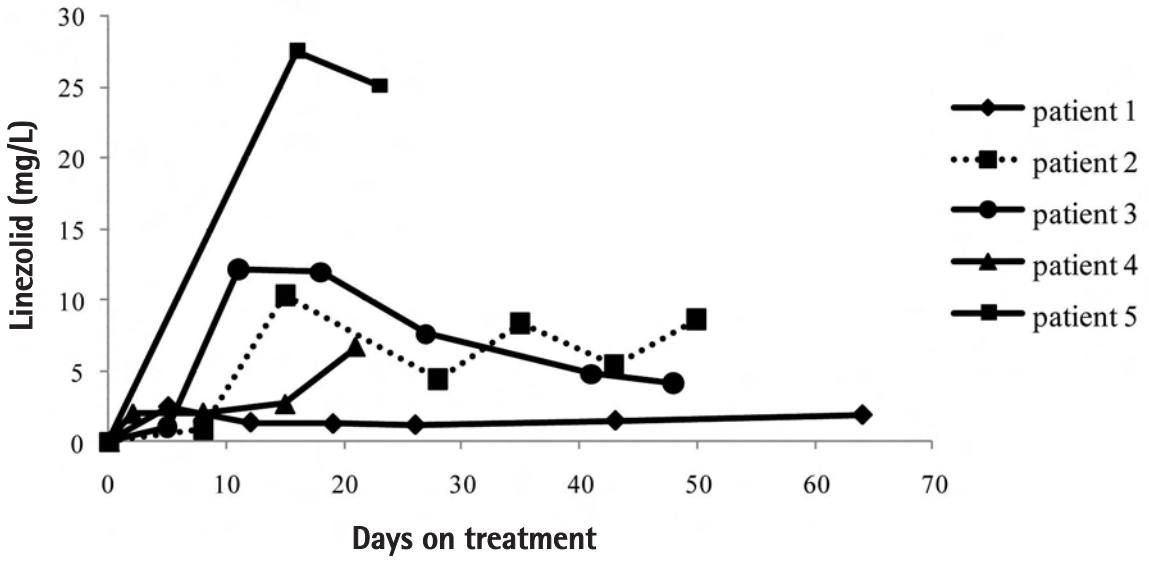

Figure 1 | **Weekly linezolid trough serum concentration during treatment in each patient.**

DISCUSSION

Linezolid has proven effectiveness in orthopedic implant related infections caused by Gram-positive bacteria. However, failure has also been reported and the major concern is its safety profile most especially in prolonged treatments. These circumstances, at least in part, may be due to inadequate serum linezolid concentrations.

An area under the concentration-time curve (AUC) by MIC ratio ≥100 is the pharmacodynamic value that predicts the efficacy of linezolid against staphylococci. Therefore, the low trough concentration observed in the patient 1 could have been the reason for failure. This patient received rifampin plus linezolid and previous data from our group showed that co-administration of rifampicin was associated with a lower risk of thrombocytopenia[10]. Although linezolid is not a substrate of P-450 citochrome, these data suggest an increased clearance of linezolid induced by rifampin through an unknown mechanism. Indeed, a recent communication in 16 healthy volunteers showed a 30% reduction in the AUC when linezolid was co-administered with rifampin[11]. In patient 5, trough serum concentrations after 2 weeks of linezolid therapy were high and the patient developed hematological toxicity (figure 1). Interestingly, the patient had liver cirrhosis and although linezolid needs no adjustment in patients with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B), there is no data about pharmacokinetics of linezolid in these patients, except some data in liver transplant recipients showing high linezolid levels[8,12]. Our results suggest that clearance of linezolid is reduced in moderate hepatic insufficiency, but further studies are needed to support this finding.

In conclusion, our results showed great variability among patients that received linezolid at standard dosage (600 mg/12h) and suggest that monitoring trough linezolid serum concentration could be helpful to optimize the efficacy of linezolid and to avoid resistance and toxicity.

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