Hyperlactacidemia Potentially Due to Linezolid Overexposure in a Liver Transplant Recipient

Sir—A 59-year-old white liver transplant recipient developed bilateral pneumonia on day 4 after the operation. After performing bronchoscopy with bronchoalveolar lavage, empirical therapy with piperacillin-tazobactam (4.5 g every 6 h) and levofloxacin (500 mg every 12 h) was commenced. During the subsequent 24 h, the patient’s clinical condition worsened until he developed severe sepsis. Drotrecogin-α was administered, but because of the persistence of the patient’s critical condition, and because no bacteria were isolated, antibiotic therapy was shifted 48 h later to meropenem (500 mg every 6 h) plus linezolid (600 mg every 12 h).

Over the subsequent days, the patient’s clinical condition slowly improved. However, despite there being no evidence of graft dysfunction or renal failure, a progressive asymptomatic increase in the plasma lactate level was noted (peak level, 8.4 mmol/L) (figure 1). On day 10 of the second-line antibiotic regimen, therapy was de-escalated by withdrawing meropenem. In accordance with our institution’s antibiotic policy, which is oriented at optimizing therapy for critically ill patients [1], multiple blood samples were obtained to assess linezolid exposure during a dosing interval and were subsequently analyzed by high-performance liquid chromatography [2]. Pharmacokinetic analysis revealed significant plasma overexposure to linezolid (12-h area under the curve, 412.55 mg·h/L; maximum concentration, 43.32 mg/L; minimum concentration, 26.99 mg/L) because of impaired clearance (1.51 L/h) with a prolonged elimination half-life (16.57 h) [3].

We hypothesized that the patient potentially had drug-induced hyperlactacidemia. On day 12 of hospitalization, linezolid was withdrawn, and blood samples were obtained to determine whether plasma drug levels were decreasing. During the subsequent 2 days, concomitantly with a decrease in the plasma linezolid level, a progressive decrease of the plasma lactate level (until complete normalization occurred) was documented (figure 1).

Hyperlactacidemia during linezolid therapy has been previously reported to be an adverse event that mainly develops after long treatment periods and that slowly resolves after withdrawal of the drug [4–6]. Conversely, in the case we report, lactate levels started increasing just after the first week of treatment, rapidly achieved the maximum level, and returned to a normal level within 48 h after drug withdrawal.

It has been suggested that, on the basis of its mechanism of action, linezolid may cause hyperlactacidemia by inhibiting mitochondrial protein synthesis [6]. Therefore, hyperlactacidemia should be expected to occur earlier in the course of treatment and to be more severe in patients who

Figure 1. Plasma linezolid concentrations and lactate levels during linezolid therapy and after withdrawal of linezolid. Dotted lines delimit the range of normal lactate values (0.5–1.8 mmol/L).

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Hyperlactacidemia

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presented with drug accumulation. Accordingly, it could be hypothesized that the time at which hyperlactacidemia occurs could be related to drug exposure (e.g., late-onset hyperlactacidemia could occur after very prolonged exposure to normal drug doses, and early-onset hyperlactacidemia could occur during unexpected drug overexposure).

The interindividual pharmacokinetic variability of linezolid has been reported to be mild [3], which is consistent with mainly nonrenal, nonenzymatic clearance pathways. However, to our knowledge, we describe the second patient to have presented with a plasma level of linezolid that was 4–6-fold higher than expected [2].

Actually, it is very difficult even to hypothesize about which mechanism may have caused this drug accumulation. Perhaps the critical status of the patient affected drug clearance. Additionally, a drug-drug interaction might have occurred. In a recent case report, concurrent treatment with rifampin and linezolid was considered to be a possible cause of linezolid underexposure [7]. The authors suggested that linezolid could be a substrate of P-glycoprotein and that its accelerated clearance might have been caused by a rifampin-related induction of P-glycoprotein expression [7].

Conversely, inhibition of P-glycoprotein activity could lead to impaired linezolid clearance. Interestingly, while receiving linezolid therapy, our patient was also being administered sertraline—a very potent inhibitor of P-glycoprotein—for the treatment of major depression [8]. In this particular case, it may be speculated that sertraline could have potentially impaired linezolid clearance by blocking P-glycoprotein activity.

This case suggests that early-onset hyperlactacidemia during linezolid therapy may be related to unexpected drug overexposure. Additional studies are needed to confirm its pathogenesis.

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**References**


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**Linezolid and Continuous Venovenous Hemofiltration**

Str—In their report, Trotman et al. [1] reviewed the literature for studies that gave pharmacokinetic data on antibiotics frequently used to treat critically ill patients receiving continuous renal replacement therapy. Regarding linezolid, they report the data from patients with various degrees of renal failure, as well as from case studies of patients receiving hemodialysis and patients receiving continuous venovenous hemofiltration [1]. They infer that a dosage of 600 mg of linezolid every 12 h “provides a serum trough concentration of >4 mg/L, which is the upper limit of the MIC range for drug-susceptible *Staphylococcus* species” (p. 1161). Trotman et al. [1] conclude that no dosage adjustment is necessary for patients receiving any form of continuous renal replacement therapy.

We recently demonstrated, in a series of 20 critically ill patients undergoing continuous venovenous hemofiltration, that linezolid is significantly eliminated by continuous venovenous hemofiltration [2]. In our study, the total clearance was 125% higher and the trough serum concentration was 50% lower than in normal conditions. Using a standard dosage of 600 mg every 12 h, we calculated that a time linezolid concentration in the blood remained above the minimum inhibitory concentration (\(t > MIC\)) of 93% of the dosing interval for pathogens with an MIC of 2 mg/L. However, the mean \(t > MIC\) (± SD) was only 57% of the dosing interval (± 32%) for pathogens with an MIC of 4 mg/L. With regard to the large interindividual variability, we conclude that the standard dosage of 600 mg every 12 h might be ineffective for some patients receiving continuous venovenous hemofiltration; that is, it might be an ineffective treatment for the least-susceptible pathogens that have an MIC of 4 mg/L. We conclude that dose escalation (600 mg of linezolid every 8 h) might be warranted in selected patients to assure optimal antibacterial activity.

In our study, we recently demonstrated that both of the main metabolites of linezolid—PNU-142300 and PNU-142585—show significant accumulation...