

CASE REPORT

Variable linezolid exposure and response and the role of therapeutic drug monitoring: Case series

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Abstract

Two patients with normal renal function, yet each showed unexpected, supra- and subtherapeutic linezolid plasma concentrations resulting in toxicity and ineffective therapy, respectively. TDM helps to early identify and correct such excursions.

KEYWORDS

efficacy, linezolid, monitoring, safety, thrombocytopenia

1 | BACKGROUND

Two young adult patients with normal renal function receiving standard linezolid dosing. Despite similarities in age and renal function, the first patient experienced an elevated trough concentration. The second patient had trace amounts of linezolid. These cases illustrate the importance of TDM in early identification and correction of such problems.

Clinical trial data typically produce a recommended usual dose for achieving clinical cure while minimizing toxicity. Following years of preclinical and clinical assessment, an effective dose is approved by the Food and Drug Administration and faithfully integrated into clinical practice. Although this strategy provides evidence for achieving minimal effectiveness; it does not result in 100% cure, nor

does it prevent toxicity. Numerous variables contribute to clinical outcomes, and one commonly overlooked is interpatient variability. The question is, Can we dose better than one size fits all?

Linezolid is an oxazolidinone antimicrobial and is commonly used in the management of acute bacterial skin and skin structure and respiratory infections. The available pharmacokinetic data show wide interpatient variability.¹ Further, with prolonged dosing, linezolid displays a narrow therapeutic window.^{2,3} Trough concentrations in the range of 2–8 mcg/mL appear to define the desired window for acute bacterial infections. Thus, some patients will be at risk for clinical failure, while others may develop concentration-related thrombocytopenia. The following two clinical cases highlight the advantages of linezolid therapeutic drug monitoring (TDM) for dosing linezolid.

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2 | CASE PRESENTATION 1

A 19-year-old woman (weight: 43 kg, body mass index [BMI]: 17.9 kg/m²) with past medical history significant for cystic fibrosis (CF) presented to the emergency department with shortness of breath, productive cough, and tachycardia. Chest X-ray findings were consistent with the patient's history of CF. Basic metabolic panel was within normal limits, and complete blood count showed a white count of 13 000/mm³ and platelet count of 442 000/mm³. Renal function was normal; creatinine clearance (CrCL) based on Cockcroft-Gault Equation⁴ was 125 mL/min at admission (serum creatinine concentrations obtained during hospitalization ranged from 0.44 to 0.73 mg/dL). Sputum, blood, and urine cultures were collected, and piperacillin-tazobactam 3.375 grams intravenously (IV) every 6 hours and linezolid 600 mg IV twice daily were initiated. Sputum culture was positive for *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) (linezolid's minimum inhibitory concentration = 2). On day 3, linezolid was switched to oral treatment (600 mg twice daily) and stopped on day 10. In contrast, piperacillin-tazobactam was continued through day 15. Blood samples were obtained from the patient to measure linezolid concentration using a validated liquid chromatography-tandem mass spectrometry assay with a linear curve over the range 0.3-30 mcg/mL. Serum samples obtained revealed an initial linezolid trough concentration (see Table 1) of 13.6 mcg/mL. The timing of the sample was questioned, and another sample was drawn. The subsequent trough value obtained while using oral therapy remained elevated at 11.7 mcg/mL. Platelet counts were tracked during treatment and dropped approximately 50% from baseline (442 000-210 000 cells/mm³) starting on day 7, with nadir at day 15. Due to plunging platelet counts, linezolid was discontinued on day 10, with counts returning to baseline within three weeks of linezolid discontinuation.

TABLE 1 Linezolid concentrations for both patients

Patient	Day of therapy	Regimen	Peak/trough	Values (mcg/mL) ^a
#1	1	600 mg IV q12 h	Peak	19.66
	2	600 mg IV q12 h	Trough	13.56
	3	600 mg PO q12 h	Trough	11.74
#2	4	600 mg IV q12 h	Peak	3.24
	4	600 mg IV q12 h	Peak	trace
	8	600 mg IV q8 h	Peak	2.34
	8	600 mg IV q8 h	Trough	trace
	13	600 mg IV q6 h	Peak	4.86
	13	600 mg IV q6 h	Trough	1.66

Abbreviations: h, hours; IV, intravenously; PO, orally; q, every.

^aQuantification range for linezolid is 0.3-30 mcg/mL.

3 | CASE PRESENTATION 2

A 26-year-old man (weight: 97.6 kg, body mass index [BMI]: 28.4 kg/m²) with no prior medical history presented with cough, fever, and shortness of breath. A right lower lobe pneumonia with empyema and abscess formation was visualized on routine imaging. Complete blood count showed a white count of 13 300/mm³ and platelet count of 518/mm³. Renal function was normal; CrCL⁴ was 163 mL/min at admission (serum creatinine concentrations ranged from 0.44 to 1.12 mg/dL). Despite initiation of broad-spectrum antibiotics (vancomycin and piperacillin-tazobactam), his respiratory status declined, requiring intubation and bilateral chest tube placement to facilitate drainage of his empyema. Bronchoalveolar cultures revealed MRSA and *influenza B*. Antimicrobial therapy was modified to vancomycin (goal trough 15-20 mcg/mL), extended infusion cefepime 2 g IV q8h, metronidazole 500 mg IV q8hr, and oseltamivir 150 mg orally q12h.

Unfortunately, his respiratory status continued to decline. Chest CT revealed bilateral diffuse opacities consistent with acute respiratory distress syndrome. Despite broad-spectrum antimicrobial therapy, the infection progressed as evidenced by worsening leukocytosis, persistent fever, and increased oxygen demands. Antimicrobial therapy was modified to linezolid 600 mg IV q12h and piperacillin-tazobactam 4.5 g IV q6h administered over 3 hours. Due to the patient's young age and severe infection, augmented renal clearance was suspected and TDM was ordered. Linezolid trough concentrations on q12h dosing were described as trace amounts requiring dosing interval modifications to every 6 hours in order to achieve desirable trough concentrations (Table 1). After optimizing the antimicrobial regimen, he was weaned from the ventilator and showed clinical resolution of his pneumonia.

4 | DISCUSSION

One of the appealing characteristics of linezolid is the comparable bioavailability between oral and intravenous routes (~100%).^{3,5} Since there is no need to make any dose adjustments, this makes switching patients from intravenous to oral tablets a smooth process once they are improving and able to take medications orally. Linezolid is 50% metabolized to inactive metabolites, and 30% is cleared renally as an unchanged drug. It has 100% penetration to the epithelial lining fluid, making the drug very useful for lung infections such as pneumonia.³

These pharmacokinetic features of linezolid might persuade clinicians to ignore the importance of TDM. The mainstream thinking that only specific kinds of patients (ie, elderly, renal or hepatic failure, etc) need TDM, but this is not always true. Previous case reports have shown the difficulty of achieving the desired concentration of linezolid in morbidly obese patients, pediatric patients when switching from IV to oral dosage forms, and in patients who are taking other drugs (eg, rifampin) that can potentially affect linezolid concentrations.^{6,7}

In the cases presented here, both patients were young adults with normal renal function, yet they achieved very different drug exposures. One resulted in thrombocytopenia (trough concentration >11.7 mcg/mL), and one resulted in suboptimal therapy (trough concentration: trace). For the second case, once drug exposure was increased, he rapidly improved and was extubated within 48 hours of the dosing modifications. The absence of these serum drug concentrations might have led to clinical failure. These cases illustrate that significant interindividual variability exists among patients receiving linezolid, and a direct way to optimize drug exposure is with TDM.

Cattaneo et al stated that renal function, age, weight, and concurrent medications can significantly affect the pharmacokinetics of linezolid.² Of these covariates, body weight correlates with linezolid clearance and volume of distribution and might have contributed to the variability we observed.⁸ However, the second patient was classified as overweight (BMI 28.5) and required a doubling of the total daily dose from 1200 mg to 2400 mg per day to achieve the desired peak and trough concentrations (Table 1). Therefore, weight alone did not explain the initial low drug exposure. This further emphasizes the importance of TDM for linezolid, regardless of the patient's age and weight. Indeed, a recent study showed that only 51% of the patients achieve the desired trough target (2–7 mg/L) when the conventional dose was used (600 mg twice daily).⁹

5 | CONCLUSION

TDM for linezolid is important in patients with serious infections due to the high interindividual variability.

These cases describe two young patients with normal kidney function, yet each showed unexpected, supra- or subtherapeutic plasma concentrations. Such excursions from the desired range can only be corrected promptly using TDM.

ETHICS APPROVAL

Ethical approval was obtained from the Institutional Review Board at the University of Florida (IRB201802116).

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

WA, MA, KK, and CP: contributed to conception, acquisition, and interpretation of data, and drafted or revised the article. All authors approved the final version to be published.

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REFERENCES

- Cattaneo D, Orlando G, Cozzi V, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. *Int J Antimicrob Agents*. 2013;41(6):586-589.
- Cattaneo D, Alffenaar JW, Neely M. Drug monitoring and individual dose optimization of antimicrobial drugs: oxazolidinones. *Expert Opin Drug Metab Toxicol*. 2016;12(5):533-544.
- Roger C, Roberts JA, Muller L. Clinical pharmacokinetics and pharmacodynamics of oxazolidinones. *Clin Pharmacokinet*. 2018;57(5):559-575.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
- Welshman IR, Sisson TA, Jungbluth GL, Stalker DJ, Hopkins NK. Linezolid absolute bioavailability and the effect of food on oral bioavailability. *Biopharm Drug Dispos*. 2001;22(3):91-97.
- Corcione S, Pagani N, Baietto L, et al. Pharmacokinetics of high dosage of linezolid in two morbidly obese patients. *J Antimicrob Chemother*. 2015;70(8):2417-2418.
- Ashizawa N, Tsuji Y, Kawago K, et al. Successful treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis with combination therapy using linezolid and rifampicin under therapeutic drug monitoring. *J Infect Chemother*. 2016;22(5):331-334.
- Abe S, Chiba K, Cirincione B, Grasel TH, Ito K, Suwa T. Population pharmacokinetic analysis of linezolid in patients with infectious

- disease: application to lower body weight and elderly patients. *J Clin Pharmacol*. 2009;49(9):1071-1078.
9. Pea F, Cojutti PG, Baraldo M. A 10-Year Experience of Therapeutic Drug Monitoring (TDM) of Linezolid in a Hospital-wide Population of Patients Receiving Conventional Dosing: Is there Enough Evidence for Suggesting TDM in the Majority of Patients? *Basic Clin Pharmacol Toxicol*. 2017;121(4):303-308.

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