Pharmacokinetics of linezolid for methicillin-resistant *Staphylococcus aureus* pneumonia in an adult receiving extracorporeal membrane oxygenation

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Purpose. We present a case of a 55-year-old man post right lung transplantation receiving ECMO for treatment of respiratory failure secondary to methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia.

Summary. Extracorporeal membrane oxygenation (ECMO) is a frequently utilized support therapy for patients with cardiac and/or respiratory failure. Dosing of medications during ECMO can be challenging due to several factors, including sequestration of medications within ECMO circuits, alterations in volume of distribution, and changes in drug clearance. The patient was initiated on empiric antibiotics, then switched to linezolid at a dose of 600 mg every 8 hours. Linezolid plasma concentrations were collected 30 minutes prior to the sixth administered dose and 30 minutes following the 1-hour infusion of the sixth dose, which resulted in values of 0.4 and 1.7 µg/mL, respectively. The ratio of 24-hour area under the curve (AUC_{0-24}) to minimum inhibitory concentration (MIC), assuming a MIC of 2 µg/mL, was calculated using the extrapolated maximum concentration (1.9 µg/mL) and minimum concentration (0.35 µg/mL), resulting in an AUC_{0-24}/MIC value of 10.8. Due to subtherapeutic linezolid plasma concentrations, ceftaroline was initiated and continued for a total of 18 days. To our knowledge, this is the second report to describe inadequate plasma concentrations of linezolid during ECMO.

Conclusion. In the case described here, linezolid at a dose of 600 mg every 8 hours did not achieve target plasma concentrations in a patient receiving concomitant venovenous ECMO support.

Keywords: critical care, infectious diseases, pharmacokinetics

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Extracorporeal membrane oxygenation (ECMO) is an increasingly utilized support therapy for patients with cardiac and/or respiratory failure in the intensive care unit setting. Despite increased usage, the impact of ECMO on medication dosing is poorly understood. During ECMO support, multiple pharmacokinetic changes may occur, including the sequestration of medication within the ECMO circuit, increases in volume of distribution (V_d), and alterations in drug clearance.[1] As a result, understanding the impact of ECMO on drug therapy is essential to ensure appropriate medication dosing. Vital medications such as antimicrobials are frequently used during ECMO; however, little information on dosing during ECMO is available. Linezolid is an oxazolidinone antibiotic that is indicated for the treatment of gram-positive, bacteria-associated infections. Based on linezolid's physicochemical and pharmacokinetic characteristics, dose adjustment and therapeutic drug monitoring (TDM) are not routinely recommended. Linezolid is moderately lipophilic, and its drug clearance is not notably affected by renal and/or hepatic impairment.[2] Although TDM and dose adjustment are not necessary in the majority of patients, variability in plasma concentrations has been reported in patients at extremes of weight or with renal dysfunction and in the

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critically ill.[3] In addition, the effect of ECMO on the pharmacokinetics of linezolid has not been fully elucidated.

In order for linezolid to achieve optimal efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA), a minimum plasma concentration (C_{min}) of >2 μg/mL and a ratio of 24-hour area under the cure (AUC_{0-24}) to minimum inhibitory concentration (MIC) of >80 is recommended. These targets are based on the concept that the MIC_{90} for linezolid against MRSA is 2 μg/mL (with a breakpoint for susceptibility of ≤4 μg/mL).[4] To date, the only published report of linezolid plasma concentrations and pharmacokinetic parameters in patients receiving ECMO includes a case series of 3 critically ill patients treated with standard doses of linezolid (600 mg) every 12 hours. The authors of that report concluded that pharmacodynamic targets were consistently achieved only when the linezolid MIC for *S. aureus* was ≤1 μg/mL.[5] In this report, we present a patient case describing the pharmacokinetics and pharmacodynamics of linezolid in a patient receiving venovenous ECMO support.

KEY POINTS

- During extracorporeal membrane oxygenation (ECMO) support, multiple pharmacokinetic changes may occur, including the sequestration of medication within the ECMO circuit, increases in volume of distribution, and alterations in drug clearance.
- The effect of ECMO on the pharmacokinetics of linezolid has not been fully elucidated.
- Linezolid pharmacokinetic and pharmacodynamic targets may not be achieved in patients receiving concomitant ECMO support.

Case report

A 55-year-old male (weight, 105 kg; body mass index, 33) with an extensive past medical history notable for combined pulmonary fibrosis and emphysema presented to the hospital for right lung transplantation. Following transplantation, the patient remained critically ill and developed multiple complications, including severe hypoxemic respiratory failure secondary to pneumonia, presumed primary graft dysfunction, and anastomotic dehiscence. On hospital day 14 the patient was intubated due to right lower lobe pneumonia and underwent emergent bronchoscopy. Bronchoalveolar lavage samples were obtained, and empiric antimicrobial therapy with vancomycin 1 g i.v. every 8 hours and piperacillin/tazobactam 3.375 g by i.v. extended infusion every 8 hours was initiated. Additional notable concomitant medications included an immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone, as well as opportunistic infection prophylaxis with valganciclovir and voriconazole. At the time of initiation of antimicrobials, vital signs were as follows: temperature, 36.7°C; heart rate, 88 beats per minute; mean arterial pressure, 69 mm Hg; and oxygen saturation, 97%. Initial ventilator settings included the following: assist-control with a respiratory rate of 19 breaths per minute; tidal volume, 500 mL; positive end-expiratory pressure (PEEP), 5 cm H_2O; and fraction of inspired oxygen (FIO_2), 100%. Pertinent laboratory data included a white blood cell (WBC) count of 17,600 cells/mm^3, a platelet count of 377,000 cells/mm^3, and the following concentrations: serum creatinine, 0.58 mg/dL (with an estimated glomerular filtration rate of >120 mL/min/1.73m^3); blood urea nitrogen, 13 mg/dL; total bilirubin, 0.4 mg/dL; direct bilirubin, 0.1 mg/dL; alkaline phosphatase, 87 units/L; alanine aminotransferase, 47 units/L; aspartate aminotransferase, 24 units/L; and albumin, 2.1 g/dL.

On hospital day 15, prior to the fifth vancomycin dose, a steady-state serum vancomycin trough concentration was obtained, with a result of 5.9 μg/mL. Later that same day, due to worsening hypoxemia and physical exam findings consistent with primary graft dysfunction, the patient was initiated on venovenous ECMO support. The ECMO circuit was comprised of P.h.i.s.i.o coated polyvinylchloride (PVC) perfusion tubing (LivaNova USA, Inc., Arvada, CO) and a Rotaflow Centrifugal Pump with Quadrox-iD Adult oxygenator (Maquet Getinge Group, Rastatt, Germany). Initial ECMO settings included the following: pump flow, 4.11 L/min; pump speed, 3,500 rotations/min; blender flow, 4 L/min; and blender FIO_2, 100%. Based on the subtherapeutic vancomycin trough concentration (goal, 15-20 μg/mL) and an estimated vancomycin requirement of >6 g daily, the decision was made to discontinue vancomycin and initiate linezolid. In addition, since a blood sample for the trough determination was drawn prior to ECMO cannulation, it was felt that the subsequent increase in V_d during cannulation would have an additional negative impact on vancomycin therapy. It should be noted that although it is potentially helpful, at the time of this patient's admission AUC-based vancomycin dosing and monitoring were not performed at the admitting institution. Given previous literature illustrating the failure of standard linezolid dosing (600 mg every 12 hours) to achieve optimal pharmacodynamic targets in critically ill patients as well as those receiving ECMO support, a higher-than-standard dose (600 mg every 8 hours) was initiated.[6] On hospital day 17, the bronchoalveolar lavage culture from the bronchoscopy resulted in growth of MRSA and *Enterobacter cloacae* isolates. The MRSA isolate was identified as susceptible to vancomycin (MIC, 1 μg/mL, as determined via BD Phoenix Automated Microbiology System [BD, Franklin Lakes, NJ]), linezolid (MIC, 2 μg/mL, also as determined via BD Phoenix Automated Microbiology System), and ceftaroline (MIC, 0.38 μg/mL, as determined via Etest [bioMérieux, Durham, NC).

Given the complexities associated with dosing during ECMO support, linezolid plasma concentrations were obtained on hospital day 17. Linezolid plasma concentrations were collected 30 minutes prior to the sixth administered dose and 30 minutes following the 1-hour infusion of the sixth dose. Samples were sent to an independent laboratory (Atlantic Diagnostic Laboratories, Bensalem, PA) and analyzed using liquid chromatography–tandem mass spectrometry (LC-MS/MS). Due to the necessity of sending samples to an outside laboratory, a delay in results was expected. On hospital day 19, despite an improving WBC count (8,000 cells/mm^3), the patient's clinical status worsened, requiring the placement of a chest tube, initiation of vasopressor support, and a repeat bronchoscopy. Results of the bronchoscopy showed anastomotic dehiscence as well as copious purulent secretions.

On hospital day 20, linezolid plasma concentrations that were collected 30 minutes prior to and 30 minutes following the 1-hour infusion of the sixth dose resulted as 0.4 and 1.7 µg/mL, respectively. The patient's calculated linezolid pharmacokinetic and pharmacodynamic parameters are reported in Table 1. The extrapolated C_{min} of 0.35 µg/mL and calculated AUC_{0-24}/MIC ratio (at a MIC of 2 µg/mL) of 10.8 were well below the accepted linezolid pharmacodynamic targets associated with efficacy.[4] Due to these results and the patient's deteriorating clinical status, linezolid therapy was discontinued, and ceftaroline was initiated at a dose of 600 mg i.v. every 8 hours infused over 60 minutes for a total of 18 days of therapy. Unfortunately, ceftaroline TDM was not readily available at the admitting institution and was not pursued. In addition, given the patient's improving clinical status during ceftaroline therapy, TDM was felt to be unnecessary during the remainder of pneumonia treatment. Of note, the patient did not develop renal insufficiency or require renal replacement therapy during the hospital stay. Following treatment of MRSA pneumonia, the patient remained critically ill. Despite a complicated course and prolonged hospital stay of 92 days, the patient survived and was discharged home.

Discussion

Patients requiring ECMO support are susceptible to numerous pharmacokinetic changes, namely drug-device interactions along with significant increases in V_d. In the presence of ECMO, medications frequently interact with circuit components, such as membrane oxygenators, perfusion tubing, and blood pumps. The degree of interaction is unclear but may be related to the composition of ECMO components as well as the type of blood pump and age of circuitry.[7] While there is a paucity of available guidance regarding antibiotic dosing in these patients, there are several important factors to consider when developing dosing regimens. Depending on a particular antimicrobial and its pharmacokinetic properties, drug sequestration may significantly impact serum concentrations. Factors that influence the tendency for drugs to sequester within the ECMO circuit include lipophilicity and protein binding.[8] Highly lipophilic drugs have been shown to sequester to a greater extent than hydrophilic drugs, partially due to increased solubility within the organic components of the circuitry. Additionally, high protein binding may lead to enhanced drug sequestration due to the presence of proteins in the priming solution (eg, 5% albumin) and/or the binding of patient blood within the circuitry.[9] Interestingly, the chemical properties of linezolid in healthy adults correspond to moderate lipophilicity (log P 0.9) and relatively low protein binding (31%).[10] In accordance with these properties, the interaction between ECMO components and linezolid would be expected to be minimal except for a significant increase in V_d following ECMO cannulation.

Based on previous literature, recommended target pharmacokinetic and pharmacodynamic parameters during MRSA-targeted linezolid therapy include a plasma C_{min} of >2 µg/mL and an AUC_{0-24}/MIC value of >80 in order to ensure optimal efficacy.[4] Although TDM and dose adjustments are not required for linezolid therapy, multiple studies have illustrated significant variability in linezolid pharmacokinetics and pharmacodynamics in critically ill patients.[11,12] Dong and colleagues[11]

Table 1. Linezolid Pharmacokinetics and Calculated AUC/MIC Ratios

Variable	Patient Data
Pharmacokinetic parameters	
C_{max} (µg/mL)	1.9
C_{min} (µg/mL)	0.35
AUC_{0-24} (µg·h/L)	21.6
CL (L/h)	75.8
V_d (L)	314
$t_{1/2}$	2.9
Calculated AUC_{0-24}/MIC	
Linezolid MIC of 1 µg/mL	21.6
Linezolid MIC of 2 µg/mL	10.8
Linezolid MIC of 4 µg/mL	5.4

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; C_{max}, maximum concentration of drug in serum; C_{min}, minimum concentration of drug in serum; AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; CL, clearance; V_d, volume of distribution; $t_{1/2}$, half-life.

described the pharmacokinetic and pharmacodynamic parameters of 8 critically ill patients and illustrated profound variability in C_{max} (mean [SD], 15.7 [6.58] mg/L) and $AUC_{0\text{-}12}$ (mean [SD], 96.73 [56.45] mg·h/L). In addition, there was significant interpatient variability in the $AUC_{0\text{-}24}$/MIC ratio (range, 31.66-216.82; mean, 96.73), leading to an inability to achieve recommended pharmacokinetic and pharmacodynamic targets in all patients. In a separate study, Yagi and colleagues[12] evaluated the variability of free linezolid plasma concentrations in 20 critically ill patients. Like Dong and colleagues, they found significant alterations in free linezolid plasma concentrations. Patients with the highest variability in free linezolid concentrations included those with renal impairment and/or hypoalbuminemia. These findings suggest that linezolid pharmacokinetics and pharmacodynamics can be highly variable in critically ill patients and that dose optimization with TDM may be necessary. Crass and colleagues[13] developed a population pharmacokinetic model of linezolid based on analysis of 1,309 concentrations obtained from 603 adult patients. This analysis indicated that doses up to 600 mg every 8 hours may be needed to achieve target trough concentrations in patients with an estimated GFR of ≥90 mL/min, a level of dosing that is consistent with that used in our patient but which has been associated with an increased risk of hematological toxicity, specifically in patients with renal dysfunction and obesity.[14]

To our knowledge, this is the second report describing inadequate plasma concentrations of linezolid during ECMO. De Rosa and colleagues[5] published a case series of critically ill patients requiring ECMO support and receiving antimicrobial therapy with linezolid. The investigators obtained linezolid plasma concentrations at steady state in 3 patients receiving standard dosing of 600 mg every 12 hours infused over 1 hour. They then calculated $AUC_{0\text{-}24}$/MIC values for 3 different MIC values (1, 2, and 4 μg/mL). Assuming a MIC of 2 μg/mL, calculated $AUC_{0\text{-}24}$/MIC values for the 3 patients were 106.3, 82.8, and 50.3, respectively. Based on these results, the researchers concluded that recommended pharmacokinetic/pharmacodynamic targets are not consistently achievable during ECMO support unless the linezolid MIC for *S. aureus* is ≤1 μg/mL. These findings are similar to those in our patient, in whom we were unable to achieve target pharmacokinetic and pharmacodynamic parameters given a linezolid MIC for *S. aureus* of 2 μg/mL. One interesting difference between our patient and those included in the study of De Rosa et al is that our inability to achieve optimal targets occurred despite the use of an initial high dose strategy.

For our patient with MRSA pneumonia, who was receiving venovenous ECMO support, an increased dose (600 mg i.v. every 8 hours) failed to achieve pharmacodynamic targets, including a plasma C_{min} of >2 μg/mL and an $AUC_{0\text{-}24}$/MIC ratio of >80.[4] The patient's C_{min} of 0.35 μg/mL and calculated $AUC_{0\text{-}24}$/MIC of 10.8 (given a linezolid MIC of 2 μg/mL) were significantly lower than recommended. Interestingly, when compared to reported V_d and drug clearance values in healthy adults, our calculated V_d was almost 4 times greater, and drug clearance was 5 times faster than expected.[15] During treatment with linezolid, the patient had normal renal and liver function, with the exception of significant hypoalbuminemia. Reduced serum albumin may have resulted in an increase in the free plasma concentration of linezolid, thereby enhancing the V_d and drug clearance. Compared to values in healthy adults, free linezolid concentrations can vary greatly in the setting of critical illness and hypoalbuminemia.[12] While these factors may have contributed to low plasma linezolid concentrations in our patient, it is unlikely to have been the only factor, considering the degree of suboptimal dosing in our case. We postulate that ECMO significantly altered linezolid pharmacokinetic and pharmacodynamic parameters in our patient by significantly increasing the V_d and subsequently calculated clearance.

There are several potential limitations that may have impacted our case conclusions. Firstly, while measuring linezolid concentrations within the epithelial lung fluid would have been preferable in our patient, we were only able to obtain plasma concentrations. In pharmacokinetic studies, linezolid has been found to have significantly higher concentrations within the epithelial lung fluid vs plasma. Based on linezolid's ability to achieve high concentrations within the epithelial lung fluid, it is possible that despite low plasma concentrations, concentrations within the pulmonary system may remain sufficient.[16] Another potential limitation was that we were able to obtain only 2 plasma concentrations. Due to the cost associated with use of an outside laboratory, as well as the expected delay in results, additional sampling was not feasible. Lastly, the second plasma sample was collected 30 minutes after the 1-hour linezolid infusion, which we believe was appropriate based on a previous study of healthy individuals.[17] Based on our results, linezolid pharmacokinetic and pharmacodynamic target attainment is not easily achieved in patients receiving concomitant ECMO support, specifically when the linezolid MIC is 2 μg/mL.

Conclusion

In the case described here, linezolid at a dose of 600 mg every 8 hours did not achieve target plasma concentrations in a patient receiving concomitant venovenous ECMO support.

Disclosures

The authors have declared no potential conflicts of interest.

Additional information

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