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Pharmacokinetics of linezolid during extracorporeal membrane oxygenation

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Pharmacokinetics Of Linezolid

During Extracorporeal Membrane Oxygenation

Sir,

The extracorporeal membrane oxygenation (ECMO) is increasingly used in the critical setting for patients with respiratory failure and there is a growing body of knowledge describing the associated variations in plasma concentrations of drugs, including antibiotics, due to drug adsorption on the different components of the ECMO circuit. Currently, a multicentre study is ongoing to confirm if the standard antibiotic dosing in adult patients may still be considered appropriate [1]. Linezolid (LNZ) is extensively used in patients with pneumonia in critical care because of its strong activity against *Staphylococcus aureus* and its high pulmonary penetration, but there are no data on LNZ pharmacokinetics during ECMO [2]. Here we report the main pharmacokinetic parameters in three critically ill patients on ECMO treated with LNZ.

Patient 1 was a 61-year-old man, with a body mass index (BMI) of 24, who underwent lung transplantation because of chronic obstructive pulmonary disease and was treated with LNZ for pneumonia caused by methicillin-resistant *S. aureus* (MRSA) with a LNZ minimum inhibitory concentration (MIC) of 1 mg/L. Patient 2 was a 40-year-old woman (BMI = 18) with cystic fibrosis (CF) who was on the transplant list, empirically treated with LNZ and previously colonised by MRSA. Patient 3 was a 32-year-old woman (BMI = 31) with severe pneumonia caused by influenza H1N1 and pulmonary bacterial superinfection by methicillin-susceptible *S. aureus* (LNZ MIC

= 4 mg/L) isolated from bronchoalveolar lavage, previously treated with oxacillin that was stopped because of jaundice.

Plasmatic concentrations of LNZ were studied during ECMO, after informed consent was signed, at steady-state with the standard dosage of 600 mg every 12 h intravenously by 1-h infusion. The area under the curve (AUC) of daily (AUC_{0-24}) plasma concentrations of LNZ was calculated with blood samples collected before (time 0) and 1, 2.5, 4, 6 and 8 h after the intravenous administration. Minimum plasma concentration (C_{min}) is defined as the concentration before the administration and the maximum plasma concentration (C_{max}) is defined as the concentration at the end of the infusion. LNZ was determined in plasma by ultra performance liquid chromatography-photodiode array (UPLC-PDA) method. Pharmacokinetic data were studied using Kinetica software (Thermo Scientific, Waltham, MA) and AUC_{0-24} was calculated as $AUC_{0-24} = 2 \times AUC_{0-12}$ [3]. In Table 1 the main LNZ pharmacokinetic parameters are reported, such as C_{max} , C_{min} , AUC_{0-24} , half-life ($t_{1/2}$), clearance (CL), time above the MIC ($t > MIC$) and volume of distribution (V_d); we also reported in Table 1 the LNZ pharmacokinetic parameters calculated with *S. aureus* MICs corresponding to 1, 2 and 4 mg/L for Patients 1, 2 and 3, respectively.

These results show that the calculated pharmacokinetic parameters of LNZ during ECMO are satisfactory when the MRSA MIC is ≤ 1 mg/L, with AUC_{0-24}/MIC ratio ≥ 80 in all patients [3, 4]. Only patient 3 did not display a full 24-hour plasma concentration above the MIC = 1 mg/L, with $t > MIC$ corresponding to 66% of the

dosing interval. The rate of achievement of pharmacological parameters decreases for all patients with MIC values > 1 mg/L, as detailed in Table 1, for both AUC_{0-24}/MIC ratios and $t > MIC$.

This is the first report of LNZ plasma concentrations in patients treated with ECMO, where we also included calculated data for different MICs to provide a reference for future patients. According to our data, even if limited, pharmacokinetic targets are not achieved with standard dosage of LNZ when the MRSA MIC is >1 mg/L.

Notwithstanding the limited sample size and heterogeneity of patients, including lung transplant, CF and high BMI, we conclude that plasma pharmacodynamic targets are easily achieved only when the *S. aureus* MIC is ≤ 1 mg/L. According to our results, patients infected by *S. aureus* with MICs > 1 mg/L on ECMO should be considered, pending future confirmation, at considerable risk of inadequate pharmacokinetic coverage. Prolonged or continuous infusion of LNZ might be needed in critically ill patients to increase AUC_{0-24}/MIC ratios or $t > MIC$, as well as increased dosage or combination therapy.

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Ethical approval: Ethical approval was given by the Ethical Committee of the S.Giovanni Battista - Molinette Hospital in Turin, Italy.

References

- [1] Shekar K, Roberts JA, Welch S, Buscher H, Rudham S, Burrows F, et al. ASAP ECMO: Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation: a multi-centre study to optimise drug therapy during ECMO. *BMC Anesthesiol* 2012;12:29.
- [2] Boselli E, Breilh D, Rimmelé T, Djabarouti S, Toutain J, Chassard D, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med* 2005;33:1529–33.
- [3] Dong H, Wang X, Dong Y, Lei J, Li H, You H, et al. Clinical pharmacokinetic/pharmacodynamic profile of linezolid in severely ill intensive care unit patients. *Int J Antimicrob Agents* 2011;38:296–300.
- [4] Pea F, Furlanut M, Cojutti P, Cristini F, Zamparini E, Franceschi L, et al. Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. *Antimicrob Agents Chemother* 2010;54:4605–10.

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Table 1.

Pharmacokinetic parameters of linezolid for patients 1, 2 and 3, and calculated data for *Staphylococcus aureus* minimum inhibitory concentrations (MICs) of 1, 2 and 4 mg/L.

	Patient 1	Patient 2	Patient 3
Pharmacokinetic parameters			
C_{\max} (mg/L)	15.67	18.51	15.61
C_{\min} (mg/L)	4.25	0.47	0.43
AUC_{0-24} (mg h/L)	212.58	165.65	100.59
CL (L/h)	5.65	7.24	13.35
V_d (L)	49.7	17.6	46.77
$t_{1/2}$ (h)	6.10	1.68	2.20
Calculated data			
AUC_{0-24} / MIC (MIC = 1)	212.58	165.65	100.58
AUC_{0-24} / MIC (MIC = 2)	106.29	82.83	50.30
AUC_{0-24} / MIC (MIC = 4)	53.14	41.41	25.15
$t > MIC$ (MIC = 1) (% over 12 h)	100	100	66
$t > MIC$ (MIC = 2) (% over 12 h)	100	75	41
$t > MIC$ (MIC = 4) (% over 12 h)	100	58.3	30

C_{\max} , maximum plasma concentration; C_{\min} , minimum plasma concentration; AUC_{0-24} : area under the curve of plasma daily concentrations; CL, clearance; V_d , volume of distribution; $t_{1/2}$, half-life; $t > MIC$, time of plasma concentrations above the MIC.