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Abstract (oral session)

Penetration of linezolid over time into the central nervous system in critically ill patients with proven or suspected central nervous system infections

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Objectives: Recent studies have suggested the role of linezolid (LZD) as an agent for central nervous system (CNS) infections caused by Gram-positive microorganisms due to its favourable pharmacokinetics. However, limited data are available on its penetration in patients with CNS infections and meningeal inflammation. The objective was to assess the penetration of LZD over time in patients with proven or suspected CNS infections. Methods: Prospective pharmacokinetic study in 8 critically ill patients treated with intravenous LZD 600mg twice daily for proven or suspected CNS infections. LZD levels were measured at steady state at different times (Cminss or trough (pre-dose), and Cmaxss (at the end of the 1-h infusion of LZD) in plasma and cerebrospinal fluid (CFS) by a validated high-performance liquid chromatography method. All patients underwent an external ventricular drainage (EVD) or an external lumbar drainage (ELV). Measures: demographics; illness severity (APACHE score), type of CNS drainage, LZD data; Cmaxss and Cminss in plasma and CSF and the ratio CFS: plasma concentration and concomitant inotropic drugs to LZD administration. Results: Data of patients and pharmacokinetics of LZD in plasma and CNS are shown in table 1. Conclusions: Different degree of penetration of LZD was observed over time, being the ratio CSF: plasma concentrations of the trough at least 5 times higher than the ratio of the Cmaxss. what evidences a delay in the penetration of LZD into CNS after its intravenous administration. Despite LZD showed a good pharmacokinetic behaviour into CNS at the end of the dosing interval, Cminss of LZD in plasma and CSF were below the optimal pharmacodynamic index of efficacy (2 mg/L) in almost all cases, what suggests the need to assess the possible benefits of administering higher doses or a continuous-infusion regimen to critically ill patients.

Table 1. Patient's characteristics and pharmacokinetic parameters

Pt nº	Age (years) Gender	BMI[1] (kg/m^2)	Illness severity APACHE	Inotropic drugs	CNS external drainage	Plasma $Cmax^{ss}$ [4] (mcg/ml)	CSF[3] $Cmax^{ss}$ (mcg/ml)	CSF: plasma ratio of $Cmax^{ss}$	Plasma $Cmin^{ss}$ [5] (mcg/ml)	CSF $Cmin^{ss}$ (mcg/ml)	CSF: plasma ratio of $Cmin^{ss}$
1	45 Female	29.4	9	No	ELD[6]	10.3	2.8	0.3	0.6	1.2	2.0
2	54 Female	22.9	24	Yes	ELD and EVD[7]	14.3	-	-	0.5	0.5	1.0
3	58 Male	25.9	22	Yes	EVD	11.0	2.4	0.2	1.9	2.0	1.1
4	42 Male	24.7	24	Yes	EVD	10.4	3.0	0.3	2.0	3.1	1.6
5	52 Male	28.1	26	No	ELD and EVD	-	-	-	0.5	0.3	0.6
6	39 Male	21.2	12	No	EVD	7.7	<0.5	<0.1	<0.5	<0.5	-
7	51 Male	29.4	22	No	EVD	17.2	2.1	0.1	0.5	0.5	1.0
8	64 Female	24.2	19	No	EVD	6.3	1.5	0.2	0.5	0.6	1.2

[1]BMI: body mass index; [2]CNS: Central nervous system; [3]CSF: cerebrospinal fluid; [4]$Cmax^{ss}$: peak plasma concentration at steady state; [5]$Cmin^{ss}$: pre-dose concentration at steady state; [6]ELD: external lumbar drainage; [7]EVD: external ventricular drainage