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Objectives

Linezolid (LZD) has a wide spectrum of activity against most Gram positive bacteria but a major concern is its potential haematological toxicity, particularly anaemia and thrombocytopenia, that seem to be associated with LZD plasma concentrations.

The objective was to compare the haematological parameters and toxicity between patients with and without overexposure to LZD.

Methods

Prospective observational study carried out in hospitalized patients treated with intravenous LZD 600mg/12h from 2009 to 2013.

Patients were classified as having overexposure to LZD when they achieved a trough LZD concentration ($C_{min_{ss}}$) \geq 10 mcg/mL or a peak concentration ($C_{max_{ss}}$) \geq 30 mcg/mL, both obtained at steady state.

Data: demographics; clinical and haematological parameters: haemoglobin and platelet count at the beginning of LZD therapy (HbB and PltB, respectively) and at the end of it (HbE and PltE, respectively), Hb ratio (HbE/HbB*100) and platelet ratio (PtE/PtB*100). Anaemia was defined as a \geq 2 g/dL decrease in Hb concentration from baseline and thrombocytopenia as a reduction in platelet count to $<$ 75% from baseline. LZD plasma levels were determined by an HPLC method.

Results

Patients: 50; age: 64.5(14.5) years; male: 32(64%); BMI: 25.4[6] kg/m²; weight: 75 [24] kg; length of LZD therapy: 16.7(14.3) days; serum creatinine baseline: 0.96 [1.6] mg/dL; glomerular filtration rate by MDRD $<$ 60 mL/min: 26 (52%); critically-ill patients: 40(80%).

Table 1: Differences in haematological values between patients with and without overexposure to LZD

	$C_{min_{ss}} < 10$ (mcg/mL)	$C_{min_{ss}} \geq 10$ (mcg/mL)	p		$C_{max_{ss}} < 30$ (mcg/mL)	$C_{max_{ss}} \geq 30$ (mcg/mL)	p
Patients	40	9	-	Patients	35	6	-
HbB (g/dL)	10.6(1.9)	9.6(1.6)	0.225	HbB (g/dL)	10.3(1.8)	9.8(1.8)	0.516
HbE (g/dL)	10.1(1.9)	8.8(1.1)	0.045	HbE (g/dL)	9.9(1.9)	9.0(1.7)	0.283
Hb ratio	99.4[15.9]	99.9 [56.6]	0.327	Hb ratio	96.9[115.5]	98.7[56.6]	0.941
Anaemia,n(%)	5(12.5)	1(11.1)	0.999	Anaemia,n(%)	4(11.4)	1(16.7)	0.567
PtB ($\times 10^3$ cells/mcL)	246[205]	229[128]	0.261	PtB ($\times 10^3$ cells/mcL)	246.0 [205]	229.0[128]	0.811
PtE ($\times 10^3$ cells/mcL)	271.5(\pm 192.8)	103.1(58.3)	<0.001	PtE ($\times 10^3$ cells/mcL)	262.4(205.0)	86.2(46.1)	0.044
Platelet ratio	116.9(\pm 77.4)	54.6(36.5)	0.001	Platelet ratio	117.5(79.7)	42.8(36.7)	0.002
Thrombocytopenia, n(%)	3(7.5)	3(33.3)	0.067	Thrombocytopenia,n(%)	3(8.6)	3(50)	0.031

Continuous variables with normal distribution: mean (standard deviation) and without normal distribution: median [interquartile range].

Conclusion

- The incidence of thrombocytopenia seems to be related to overexposure to LZD, being the peak concentration the most accurate marker of this haematological toxicity.
- Even though no difference in the ratio of anaemia was observed between patients with and without overexposure, lower haemoglobin values at the end of treatment were observed in those who achieved a $C_{min_{ss}} \geq 10$ mcg/mL.
- Therapeutic drug monitoring may be useful for avoiding linezolid-related haematological adverse effects.