LINEZOLID DOSING IN PATIENTS WITH LIVER CIRRHOSIS: STANDARD DOSING RISKS' TOXICITY

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Background

Linezolid is used at a standard dose of 600 mg/12 h regardless of renal or hepatic function but very little data concerning its pharmacokinetics (PK), efficacy and safety in patients with liver cirrhosis is available.

Purpose

The objectives were to describe the PK, efficacy and safety of linezolid in cirrhotic patients.

Material and methods

A prospective case-control 1:1 study performed in a 400-bed tertiary hospital conducted between January 2015-June 2017.

- Cases were all **cirrhotic patients** treated with linezolid at the standard dose (600mg every 12 h; administered as a 1 h infusion) and undergoing therapeutic drug monitoring (TDM).
- Controls were matched by **age** (± 10 years), **actual body weight** (± 10 kilograms), **comorbidities** (matched Charlson Score), **renal function** (± 20% of baseline serum creatinine value) and **severity** (ICU/Not ICU patient).

Therapeutic drug monitoring of linezolid

- Linezolid concentrations were determined using a validated, linear, sensitive and specific high-performance liquid chromatography (HPLC) method.
- Subtherapeutic linezolid concentrations were defined as a through (Cmin) concentration <2 mg/L.
- Supratherapeutic concentrations were defined as a Cmin >10 mg/L.

Assessment of toxicity: Thrombocytopenia was defined as a decrease in platelet count to <75% and anemia as an ≥2 g/dL decrease in hemoglobin, both from baseline.

Statistical analysis: Data are described as the mean ± (standard deviation SD). The Student's t-test or Mann–Whitney U-test for continuous variables and the Chi-square or Fisher's exact test for dichotomous variables were used.

Results

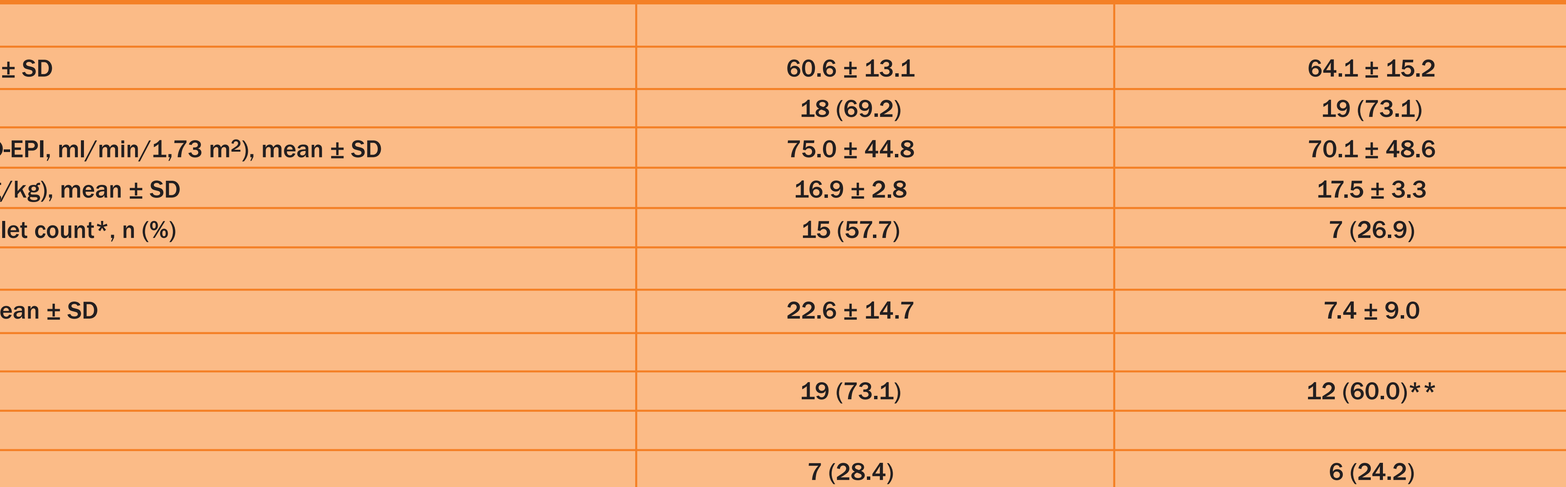
Fifty-two patients were included. Mean age: 62 (± 11.9) years, men 66.1%, without differences in baseline demographic and clinical characteristics excepting for low baseline platelet count (57.7% vs. 26.9%, p=0.025) in cirrhotic patients.

Table 1. Demographic, clinical and PK characteristics.

	Cirrhotic patients Cases (n=26)	Non-Cirrhotic patients Controls (n=26)	p value
Characteristics			
Age (years), mean ± SD	60.6 ± 13.1	64.1 ± 15.2	0.383
Male, n (%)	18 (69.2)	19 (73.1)	0.760
Baseline GFR (CKD-EPI, ml/min/1,73 m^2), mean ± SD	75.0 ± 44.8	70.1 ± 48.6	0.709
Linezolid dose (mg/kg), mean ± SD	16.9 ± 2.8	17.5 ± 3.3	0.479
Low baseline platelet count*, n (%)	15 (57.7)	7 (26.9)	**0.025**
PK data			
Cmin,ss (mg/L), mean ± SD	22.6 ± 14.7	7.4 ± 9.0	**<0.001**
Clinical outcomes			
Clinical cure, n (%)	19 (73.1)	12 (60.0)**	0.348
Toxicity data			
Anemia, n (%)	7 (28.4)	6 (24.2)	0.747
Thrombocytopenia, n (%)	13 (52.0)	8 (33.3)	0.187
Final platelet count < 100.000/mm^3, n (%)	18 (69.2)	4 (16.7)	**<0.001**
Discontinuation of linezolid due to hematological toxicity, n (%)	5 (19.2)	1 (3.8)	0.083

*Baseline value < lower limit of normality (platelet count < 150.000/mm^3)
**Data only evaluated in 20 patients

Graphic 1. Trough concentrations of linezolid in non-cirrhotic and cirrhotic patients.



Conclusions

- This is the first study evaluating the efficacy, safety and PK of linezolid concentrations in cirrhotic patients.
- Cirrhotic patients were more likely to have supratherapeutic concentrations of linezolid, probably due to the reduced non-renal clearance, and presented a lower final platelet count.
- Linezolid showed a good clinical response rate with no differences between patients with and without cirrhosis.
- These results question the use of standard doses of linezolid to this population and highlight the need to perform TDM to reduce toxicity.

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