CLINICAL PHARMACOLOGICAL ADVICE (CPA) FOR OPTIMIZATION OF LINEZOLID THERAPY IN HOSPITALIZED PATIENTS WITH MULTIDRUG RESISTANT GRAM-POSITIVE INFECTIONS

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Introduction

Thrombocytopenia frequently complicates pharmacological therapies with linezolid, often leading to drug withdrawal and the prescription of other less effective antimicrobial agents. This is a reversible, exposure-related adverse effect, which could be limited by targeting linezolid trough concentration (Cmin) within therapeutic range, namely between 2 and 7 mg/L.

Therapeutic drug monitoring (TDM) was shown to be a valuable tool for drug dosage individualization, provided a clinical pharmacological interpretation of the results on the basis of the patient's pathophysiological characteristics and co-medications is produced.

The aim of this study was to assess the role of drug exposure optimization by means of a real-time TDM approach of dose adjustments on containing the risk of developing drug-related thrombocytopenia in a cohort of hospitalized adult patients with infections due to multi-drug resistant Gram-positive organisms.

Methods

This is a prospective evaluation of all those patients who were admitted to the Infectious Diseases Clinic of our Hospital and who received a treatment course with linezolid from February 2015 to March 2016. TDM of linezolid was performed at least twice weekly in each patient and pharmacological advice for dose adjustments was made available via intranet within the same day of analysis. Hematological and clinical parameter as well as any information on concomitant medications were recorded at baseline and at each TDM session. Thrombocytopenia was defined as ≥ 30% decrease of platelet count from baseline at end of therapy. Optimized TDM exposure was defined when TDM-based dose adjustments targeted Cmin within therapeutic range. Clinical outcome was defined at the end of therapy and at 3 month follow-up.

Results

Thirty patients were included in the study. Mean (±SD) age, weight and baseline creatinine clearance (CrCL) were 63.0±16.5 years, 76.2±13.4 kg and 89.1±40.8 mL/min, respectively. Main reasons for linezolid therapy were hospital acquired pneumonia and skin and soft tissue infections along with bone and joint infections/osteomyelitis/spondylodiscitis, which overall accounted for 73.4% of prescriptions. Median (IQR) duration of treatment and linezolid Cmin were 16.5 (14.0 – 31.0) days and 6.96 (4.86 – 8.96) mg/L, respectively. Favorable clinical outcome was observed in 25/30 (83.4 %) patients.

Initial linezolid overexposure was observed in 21/30 (70%) patients. Of them, 15/21 (71.4%) had plasma exposure reduction after TDM-based dose adjustments. Overall, thrombocytopenia occurred in 7/30 (23.3%) patients. Among them, 4/7 (57%) had persistently inadequate exposure. Optimized TDM exposure was obtained in 25/30 (83.3%) cases.

Among the biologically plausible clinical covariates tested at multivariate logistic regression analysis for possible association with thrombocytopenia (age, sex, weight, CrCL, initial daily dose, length of therapy, and optimized TDM exposure), initial daily dose resulted significantly associated with the risk of developing thrombocytopenia (OR 1.732 [1.019-2.944], p = 0.042), whereas optimized TDM exposure was a protective factor (OR 0.009 [0.0 – 0.293], p = 0.008).

No significant differences between lengths of linezolid therapy (0-14, 15-28, >28, >90 days) and time to thrombocytopenia (p=0.366) or anemia (p=0.792) were found.

Conclusion

Optimizing linezolid exposure by means of real-time TDM coupled with clinical pharmacological advice may concur on reducing the risk of developing thrombocytopenia.