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Use and toxicities of linezolid in severely-ill patients in two teaching hospitals: a retrospective pilot study revealing a large incidence of side effects

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Introduction

Linezolid, active against Gram-positive organisms resistant to other antibiotics, has a restricted use in Belgium (hospital delivery only) because of concerns about resistance emergence, toxicities upon prolonged treatments, and cost. The current Summary of Product Characteristics (SmPC) states that linezolid is only indicated for (i) nosocomial and community acquired pneumonia and (ii) complicated skin and skin structure structures infections, with a maximal duration of treatment of 28 days.

Aims and objectives

To assess the linezolid attributable toxicities (primary objective) and its uses as per actual indications (second. object.) in two teaching hospitals in Belgium.

Methods

Hospital pharmacy records were screened for patients having received linezolid through the hospital pharmacy*. The table shows the number of patients selected for analysis

* by law, linezolid is only available through hospital pharmacies in Belgium for both hospitalized and discharged patients (continuing therapy as outpatients)

Hospital	Total no. of patients	Patients selected for analysis *	Patients with treatment > 14 days
St-Luc	66 (in 2014)	20	17
Erasme	143 (in 2013-2014)	19	15
Total	209	**39**	**32**

* selection based on treatement > 7 days and availability of data

Medical files were retrieved and analysed by clinical pharmacists for indication (type of infection and supporting microbiology), reason for choosing linezolid over another, not-restricted antibiotic, duration of treatment, routes of administration, side effects and contra-indicated drugs administered to the patient (the two latter based on the corresponding listings of the SmPC).

Description of the analyzed population

- Files analyzed: 40 treatments from 39 patients with > 7 days treatment an with sufficient data for analysis
- Nature of treatment: all curative
- Prescription according to label: 37/40 off-label (endocarditis, deep infected trauma, septicemia, catheter-related infection, tuberculosis, …)
- Microbiology: all treatments based on isolation of a susceptible organism to linezolid (often resistant to conventional β-lactams)
- Reason to choose linezolid: replacing vancomycin in 24/40 cases (non-susceptibility [n=5], renal toxicity [n=7]; difficulties in maintaining an IV line [n=7] or, generally, to facilitate patient's discharge).
- Treatment duration: up to 92 days (median: 24; mean 33.1)
- Administration: IV but often sequential (IV followed by oral) or oral

Untoward effects

- attributable or likely to be attributable to linezolid: 9/40 and 22/40, respectively
- reported by the attending physician: only 10 cases
- most frequent and severe:
  - ➢ anemia (>20% decreased of red blood cell counts) 10/39 patients (26%);
  - ➢ thrombocytopenia (>50 % and >20% decrease of platelets) in 13/39 (33%) and 26/39 (67%) patients, respectively (5 patients required transfusion[s]), without correlation with treatment duration;
  - ➢ lactic acidosis: 3/39 (8%) but of uncertain origin.
- Administration of drugs considered as contraindicated (monoamine oxidase inhibition): 29/39 (74%) patients with 15 being susceptible to cause a serotoninergic syndrome (not observed).

Conclusions and Points for Discussion

- Although limited by the low proportion of files analysed over the total number of treatments, the study shows linezolid is often used off-label (but for good microbiological reasons) and for longer periods than recommended.
- In patients treated for > 7 days, the incidence of side effects (often not reported) markedly exceeds what was reported in registration clinical trials and is currently noted in the European Summary of Product Characteristics (SmPC). While this may concern only the patient population examined, it underscores that "well known" side effects are often under-reported by attending physicians.
- Direct analysis of medical files could help in better assessing the true benefit/risk ratio of restricted drugs especially when used largely off-label or for longer periods than recommended in the SmPC.

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