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Short communication

Improving linezolid use decreases the incidence of resistance among Gram-positive microorganisms

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ABSTRACT

Surveillance studies have shown the emergence of infections with linezolid-resistant bacteria. The relationship between appropriate linezolid use and the spread of linezolid resistance among Gram-positive microorganisms in a single tertiary referral centre was evaluated. In an initial observational study, a prospective prescription-indication study was conducted on intensive care areas and haematology, neurosurgery, vascular surgery and nephrology wards during 2009. An intervention through follow-up feedback on audit results from May–June 2010 was then conducted. From July–December 2010, a second drug-use study of linezolid was conducted, with the same objectives and methodology. To assess the antimicrobial pressure of linezolid, an ecological study was conducted from 2006–2010 in the same hospital wards. Indications for linezolid in the initial study were considered suitable in 38.5% of cases, whilst in the second study the rate was 51.2% (33% increase). Linezolid consumption fell by 57% in the second half of 2010. A significant correlation was found between its inadequate use (DDD/1000 patient-days) and the incidence of linezolid-resistant strains/1000 patient-days ($r = 0.93$; $P = 6.9e\text{-}024$); 85% of the variability in the incidence of linezolid resistance was predicted by its inadequate use. Its partial correlations were significant for *Enterococcus faecium* ($r = 0.407$; $P = 0.049$), *Staphylococcus epidermidis* ($r = 0.874$; $P = 2.3e\text{-}008$) and *Staphylococcus haemolyticus* ($r = 0.406$; $P = 0.049$) but not *Staphylococcus aureus* ($r = 0.051$; $P = 0.704$). A relationship was found between appropriate linezolid use and the incidence of linezolid-resistant strains of *E. faecium*, *S. epidermidis* and *S. haemolyticus*.

1. Introduction

Linezolid is a member of the oxazolidinone class of antibiotics, which were licensed by Spain's health authority in July 2001. Linezolid exerts antibacterial activity by inhibiting formation of the 70S initiation complex, ultimately preventing the translation and replication of bacterial proteins.

The LEADER surveillance programme monitors linezolid resistance in US hospitals and has reported an increase in linezolid resistance from 1% in 2004 to 2.11% in 2009 [1], whilst rates as low as 0.1% have been described among Gram-positive isolates at non-US medical sites [2]. Resistance to linezolid has been observed, particularly among enterococci (*Enterococcus faecium* and *Enterococcus faecalis*) and coagulase-negative staphylococci (CoNS) species [3]. These resistance events have usually been associated with recognised risk factors such as prolonged therapeutic exposure and/or indwelling infective devices [4]. A number of resistant strains have appeared in patients with no prior drug exposure. Each occurrence is probably attributable to endemic spread from other patients in the same healthcare environment. Furthermore, Scheetz et al. found a link between genetically proven linezolid resistance among vancomycin-resistant *E. faecium* strains and linezolid consumption [5]. Mulanovich et al. found that increased linezolid use preceded the appearance of a linezolid-resistant CoNS [6].

In this study, the relationship between appropriate use of linezolid and the spread of linezolid resistance among Gram-positive microorganisms in a single tertiary referral centre in Spain was evaluated.

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2. Design, patients and methods

2.1. Design

To evaluate the characteristics of use and the appropriateness of prescriptions, the initial observational study consisted of a prospective prescription-indication audit study of antibiotics for Gram-positive microorganisms (linezolid, vancomycin, teicoplanin, tigecycline, cloxacillin and daptomycin) conducted in intensive care areas and haematology, neurosurgery, vascular surgery and nephrology wards during 2009. An intervention was conducted by formally presenting the results of this study to the Pharmacy Commission, the Infectious Commission and the Infectious Unit of La Paz University Hospital (Madrid, Spain) from May–June 2010. No educational training was conducted during the intervention. Subsequently, a prospective prescription-indication drug-use study of linezolid was conducted from July–December 2010 with the same objectives and methodology as the initial study. In the second drug-use study, the antimicrobial pressure of linezolid was assessed in an ecological study conducted from 2006–2010 in the same hospital wards. Approvals were obtained from the Institutional Preview Board at La Paz University Hospital.

La Paz University Hospital is a 1365-bed tertiary-care teaching facility. This was the sample size needed for a specified margin of error of ± 5% in the precision of prescriptions, assuming a variability of 20% in both studies. The appropriateness of linezolid use was evaluated separately by two expert groups, each composed of at least one pharmacist, microbiologist and clinical pharmacologist, according to the indications established by the Spanish Summary of Product Characteristics and recommendations of international and national guidelines. Appropriate use was established in accordance with clinical information available at the time of prescription and was subsequently re-established with the knowledge acquired from the microbiological results of all infections.

2.2. Isolate identification

The laboratory information system provided the total number of linezolid-resistant strains obtained from clinical cultures from 2006–2010, month by month, in the target wards.

2.3. Susceptibility testing

Identification and susceptibility testing were performed with microdilution plates using the Wider automated system (Francisco Soria Melguizo, S.A., Madrid, Spain) or the VITEK® 2 system (bioMérieux, Marcy-l'Étoile, France) according to the manufacturers' recommendations. Minimum inhibitory concentrations (MICs) of linezolid were confirmed by Etest as described by the manufacturer (bioMérieux). MICs were interpreted using the criteria of the Clinical and Laboratory Standards Institute (CLSI). Isolates with a linezolid MIC > 4 μg/mL were considered resistant.

2.4. Antibiotic consumption

Antibiotic consumption was characterised as defined daily doses (DDDs) per 1000 patient-days. Linezolid doses of 1200 mg/day were considered 1 DDD. Linezolid consumption was obtained from antibiotic prescription data from the hospital pharmacy department. Consumption was tallied for each month from 2006–2010.

2.5. Incidence of linezolid resistance

One isolate per patient per month was considered for inclusion. Events were standardised to obtain rates from the data for patient-days.

2.6. Statistics

Data analysis was performed using SPSS v.15.0 statistical analysis software (SPSS Inc., Chicago, IL). A descriptive statistical analysis of the variables was conducted. Cohen's κ index was used to calculate the degree of agreement between the groups. Pearson or Spearman's correlation coefficient was used, when appropriate, to assess the possible link between antibiotic consumption and antibiotic resistance, with the data standardised for patient-days. The coefficient was also used to assess a possible correlation between the number of strains per 1000 patient-days (linezolid resistance) and linezolid DDD/1000 patient-days (linezolid consumption or the appropriateness of linezolid use). Simple linear regression was employed, with the number of strains per 1000 patient-days as the dependent variable and linezolid DDD/1000 patient-days as the independent variable. Time lags were fitted by examining the association between antibiotic consumption and linezolid resistance.

3. Results

3.1. Drug-use studies

Among the 245 patients who received oral or intravenous (i.v.) antibiotics for Gram-positive microorganisms in the first observational study, linezolid ($n = 65$ cases) was the second most prescribed antibiotic after vancomycin. Forty-one patients who received oral or i.v. linezolid were included in the second study. The Cohen's κ index showed substantial agreement ($\kappa > 0.7$) in both studies; any disagreement was resolved by consensus. Linezolid indications were considered suitable in 25/65 cases (38.5%) in the first study and in 21/41 cases (51.2%) in the second study, resulting in a 33% increase over the first study.

3.2. Institutional linezolid use

Linezolid consumption in the target wards ranged from a mean ± standard deviation of 5 ± 0.8 to 7 ± 2.5 DDDs/1000 patient-days from 2006 to 2009, and consumption increased linearly by 36% from 2006 to June 2010, except for July 2009 owing to stock shortages. Linezolid consumption fell by 57% to 3 ± 0.52 DDDs/1000 patient-days in the second half of 2010.

3.3. Linezolid resistance and use of linezolid

The number of linezolid-resistant strains increased from 21 (one isolate per patient) to 59 strains per 1000 patient-days from 2006 to 2009. Linezolid-resistant strains decreased to 9 isolated per 1000 patient-days in the second half of 2010. No decrease was observed in the number of hospital-acquired infections during the study period. The data were obtained by Pearson's correlation coefficient ($r = 0.68$; $P = 2.9e\text{-}009$) (Fig. 1). The partial correlations were significant for *E. faecium* ($r = 0.397$; $P = 0.049$), *Staphylococcus epidermidis* ($r = 0.532$; $P = 1.5e\text{-}005$) and *Staphylococcus haemolyticus* ($r = 0.445$; $P = 0.0004$), but not for *E. faecalis* ($r = 0.001$; $P = 0.991$), *Staphylococcus aureus* ($r = 0.051$; $P = 0.704$) or *Staphylococcus hominis* ($r = 0.22$; $P = 0.866$). A correlation was observed between linezolid consumption (measured as DDD/1000 patient-days) and the incidence of linezolid-resistant isolates per 1000 patient-days ($r = 0.90$; $P = 1.18e\text{-}023$), and 82% of the variability in the incidence of linezolid-resistant strains per 1000 patient-days was predicted by linezolid consumption. Comparison of the periods before and after June 2010 showed a significant difference in terms of linezolid consumption ($P = 3.6e\text{-}10$) and the incidence of linezolid-resistant strains ($P = 0.001$), *E. faecalis* ($P = 2.9e\text{-}005$), *E. faecium* ($P = 0.044$), *S. epidermidis* ($P = 0.022$) and *S. haemolyticus* ($P = 0.032$). However, there were no significant differences for *S. aureus* ($P = 0.322$) and