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Use of linezolid in critically ill patients admitted to Intensive Care Units

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All indications of linezolid (LZD) in Intensive Care Units (ICU) were included as cases in an observational, prospective and multicentre study. One hundred thirty-nine indications were analyzed. In most cases (92.7%), treatment for nosocomial infections was indicated. The most frequent infection was pneumonia (42.7%), followed by catheter-related bacteraemias (CRB). A total of 58.7% of the indications were empirical and in 45.7% of the cases the cultures confirmed infection by gram-positive cocci (GPC). In 43 cases (31.2%), the indication was made as a rescue measure (mainly due to clinical failure) in patients previously treated with glycopeptides. Of isolated GPC, 70.2% were methicillin-resistant. The cure rate of the population per intent-to-treat was 73.2%. Only one case of thrombocytopenia was recorded.

Conclusions. LZD is used with a high degree of diagnostic safety. In the ICU, it is primarily indicated to treat pneumonias and CRB with good clinical and microbiological response. This antibiotic has acted as a good therapeutic resource against clinical failure in infections treated with glycopeptides.

Key words:
Linezolid. Critically ill patient. ICU.

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Uso del linezolid en pacientes enfermos admitidos en las Unidades de Cuidados Intensivos

En un estudio observacional, prospectivo y multicéntrico, los casos incluidos fueron todas las indicaciones de linezolid en las Unidades de Cuidados Intensivos (UCI). Se analizaron 139 indicaciones. En la mayoría de los casos (92,7%), había indicación para un tratamiento de infecciones nosocomiales. La infección más frecuente fue la neumonía (42,7%), seguida de bacteriemias relacionadas con catéteres. Un total del 58,7% de las indicaciones fue empírico, mientras que, en el 45,7% de los casos, los cultivos confirmaron una infección por cocos grampositivos. En 43 casos (31,2%), la indicación se estableció como medida de rescate (principalmente por fracaso clínico) en pacientes tratados previamente con glucopéptidos. El 70,2% de los cocos grampositivos aislados fue meticilina resistente. La tasa de curación de la población de intención de tratar fue del 73,2%. Únicamente se registró un caso de trombocitopenia.

Conclusiones. El uso de linezolid demostró un elevado grado de seguridad diagnóstica. Su indicación principal en la UCI es el tratamiento de neumonías y bacteriemias relacionados con catéteres obteniéndose una buena respuesta clínica y microbiológica. Este antibiótico ha actuado como un buen recurso terapéutico frente al fracaso clínico en las infecciones tratadas con glucopéptidos.

Palabras clave:
Linezolid. Pacientes con enfermedades graves. UCI.

INTRODUCTION

Gram-positive bacteria have experienced a noticeable increase among microorganisms responsible for infections coinciding with the appearance and spread of multiresistant gram-positive cocci (MR-GPC).[1-6] The growing incidence of MR-GPC isolations, in samples from patients with nosocomial infections, especially those acquired in Intensive Care Units (ICU),[7] constitutes a significant health problem in many countries. This situation has worsened in recent years due to the increase of community infections caused by these pathogenic agents.[8] In Spain, according to data from the Estudio Nacional de Vigilancia de Infección Nosocomial (ENVIN),[2,3] the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) has gradually increased in patients admitted to the ICU between 1994 and 2006, in the latter year reaching 42.3% of all *S. aureus* isolates in samples from infections related to invasive devices. In parallel, resistance of coagulase-negative *Staphylococcus* (CNS) to methicillin has remained, in recent years, above 80%. On the other hand, resistance to glycopeptides as well as to linezolid for both bacteria was practically nil. Similarly, the pres-

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ence of glycopeptide resistant *Enterococcus* spp. in Spain, for infections acquired in the ICU, continues to be low, less than 1%. This is in contrast to data from the National Nosocomial Infection Surveillance (NNIS) System[4] for the year 2003, in which the percentage of vancomycin-resistant *Enterococcus* spp. in the ICU was 28.5%.

In keeping with this epidemiological situation, the use of specific antibiotics (ATB) against MR-GPC has gradually increased.[9,10] Since the appearance of vancomycin (VAN) and the incorporation of teicoplanin (TPN) in the 1990s, no new active drugs against multiresistant GPC had come on the scene until the development of quinupristine/dalfopristine (Q/D)[13,14] and linezolid (LZD)[15-19] in the early 2000s, although their consumption in Spain has been very uneven. While Q/D prescription is very limited, the use of LZD has increased since it was introduced in 2003, especially for the treatment of infections in critically ill patients. Recently, in 2007, daptomycin and tigecyclin, ATBs for which no information is available with regard to their consumption and method for use in Spain, have been incorporated

In this article, usage data for Linezolid in critically ill patient areas is exclusively analyzed based on information from a study designed to discover the reasons for and ways of using specific ATBs for the treatment of MR-GPC-MR before the last ATBs mentioned above were introduced.

PATIENTS AND METHODS

An observational, prospective and multicentre study has been carried out, in which 28 ICUs participated, predominantly hospitals from three Spanish regions: Catalonia, Andalusia and the Valencian Community (together comprising 50% of the participating centres). Data was gathered between January, 2003 and April, 2004. All patients admitted to the ICU who were prescribed LZD, in monotherapy or combined with other antimicrobials, for the treatment of proven or suspected infections with any localisation produced by MR-GPC, as well as in prophylaxis, were included as cases. MR-GPC has been defined as the strains of *S. aureus* and CNS that are resistant to methicillin and/or VAN, as well as VAN-resistant enterococci. Patients were monitored until treatment ended by evaluating clinical and microbiological responses and tolerability.

Demographic variables, pathological histories, diagnosis upon admittance to the ICU and the risk factors of acquiring an infection were recorded in a case report form. The localisation and type of infection, its form of presentation, the bacteria involved and their sensitivity to LZD as well as clinical and microbiological evolution, treatment characteristics including doses used, tolerance and appearance of resistance were also recorded. Included among infection risk factors were insertion of intravascular catheters, mechanical ventilation, placement of a urinary probe, use of extrarenal purification techniques and the use of corticoids. Cases in which the patient received more than 40 mg/day of prednisone or its equivalent for at least 15 days were classified as corticotherapy. Severity upon admission was calculated using the APACHE II scale and the form of presentation of the infections was classified according to the Bone[38] criteria as sepsis, severe sepsis and septic shock.

Infections were classified as community or hospital-acquired, the latter differentiated as to those acquired in and outside of the ICU. Infections diagnosed 48 hours or more after admission were considered hospital infections, while those diagnosed after 48 hours of stay in the ICU were considered ICU-acquired. LZD indications were classified as prophylaxis and treatment, the latter being distinguished as to empirical or specific treatment based on prior knowledge of the causative agents as well as their sensitivity. Whether the treatment was administered in monotherapy or in combined therapy and concomitant antibiotherapy was also included. Moreover, whether LZD was administered as a first choice or as a rescue treatment in patients previously treated with glycopeptides or other active ATBs against MR-GPC was noted. Treatment modifications and their causes were recorded, as well as rescue treatment after LZD administration and the clinical and microbiological efficacy of the new ATBs. LZD rescue treatment was classified as that performed with ATBs indicated as the second choice prescribed for any reason at least 48 hours after receiving LZD. Those that were indicated in order to adjust, deescalate or perform sequential therapy were excluded from this definition. Baseline diseases were classified as medical, surgical, coronary and traumatic. Diagnoses of pneumonia were made in accordance with the standards defined by the Centers for Disease Control and Prevention.[37] Evaluation of clinical efficacy was performed in the intention-to-treat (ITT) population, which includes all patients who received at least one dose of LZD to treat an infection, and in the evaluable population (EP), which is understood to be the group of patients who received at least three days of treatment and in which GPC was identified as the cause of the infection. Microbiological efficacy was performed in the microbiologically-evaluable (ME) population, which included only those cases for which the microorganism causing the infection had been isolated. Assessment of cure and microbiological eradication were performed by each one of the participating investigators in compliance with the previously agreed-upon definitions.

Statistical analysis

A descriptive analysis was performed showing qualitative variables as a percentage and quantitative variables as averages if showing a normal distribution or as median and range if not. All analyses were performed using the SPSS®13 program.

RESULTS

One hundred thirty-nine cases in which LZD was used for the treatment or prevention of infections where the presence of MR-GPC was known or suspected were included. An aver-

Table 1 Demographic variables and characteristics of patients treated with LZD against multiresistant gram-positive cocci (MR-GPC) según serodiagnóstico

	n = 139
Age (years), median (min-max)	66 (19-79)
Male (%)	95 (68.3)
APACHE II, median (min-max)	18 (3-39)
Length of stay in ICU (days), median	25
Exitus (%)	69 (49.6)
Patient type n (%)	
Medical patients	78 (56.1)
Surgical patients	51 (36.7)
Trauma patients	9 (6.5)
Coronary patients	1 (0.7)

LZD: linezolid.

Table 2 Pathological histories and risk factors

	Total n = 139
Pathological histories n (%)	
Diabetes mellitus	50 (36.0)
Chronic renal insufficiency	22 (15.8)
COPD	26 (18.7)
Severe cardiac insufficiency	12 (8.6)
Chronic hepatopathy	10 (7.2)
Alcoholism	8 (5.8)
Solid neoplasia	11 (7.9)
Hematologic neoplasia	4 (2.9)
Immunodeficiency	10 (7.2)
Organ transplant	8 (5.8)
Corticotherapy	19 (13.7)
Immunosuppressive treatment	13 (9.4)
Risk factors n (%)	
Mechanical ventilation	109 (78.4)
Urinary probe	135 (97.1)
Central venous catheter	130 (93.5)
Arterial catheter	95 (68.3)
Pulmonary artery catheter	19 (13.7)
Extrarenal purification techniques	26 (18.7)

COPD: Chronic Obstructive Pulmonary Disease, n (%); LZD: linezolid.

age of five cases per centre was included. The characteristics of the patients included and their demographic variables are shown in table 1. These patients had an average age greater than 65, with significant severity upon admission (median APACHE II of 18) with a prolonged stay in the ICU. LZD was indicated in a greater proportion in medical patients and intra-ICU global mortality was high (49.6%).

Table 3 Reason for the indication, type and form of presentation of the infection (n = 138)

Indication, n (%)	
. Treatment	138 (99.3)
. Prophylaxis	1 (0.7)
Infection type, n (%)	
. Community	10 (7.2)
. Hospital, extra-ICU	39 (28.2)
. Hospital, intra-ICU	89 (64.5)
Manner of presentation, n (%)	
. Without sepsis	12 (8.7)
. Mild sepsis	38 (27.5)
. Severe sepsis	38 (27.5)
. Septic shock	50 (36.2)
. Severe sepsis/septic shock	88 (63.7)
Severe renal insufficiency	37 (26.8)

LZD: linezolid.

Pathological histories and infection risk factors are included in table 2. Patients treated with LZD showed significant comorbidities: notably, *diabetes mellitus*, chronic obstructive pulmonary disease, chronic renal insufficiency and use of corticoids. In addition, 78.4% needed mechanical ventilation, the frequency of application of extrarenal purification techniques and monitoring with pulmonary artery catheters (18.7% and 13.7%, respectively) being the most notable.

The reason for the therapeutic indications, as well as the type of infection and its form of presentation, are broken down in table 3. One hundred thirty-eight (99.3%) patients with infections were treated and in only one case was it administered as a prophylaxis for a patient with a liver transplant. In the majority of the cases, LZD was used to treat nosocomial infections [128 (92.7%)], of which 89 (69.5%) were acquired in the ICU and 39 (30.5%) were acquired outside of the ICU. The infections presented as severe sepsis or septic shock in 88 (63.7%) cases and 37 (26.8%) cases had severe renal insufficiency. The localisation of the infections is shown in table 4, broken down according to infection type. The most frequent infection was pneumonia of which 59 were treated (42.7% of infections), the majority (41) being related to mechanical ventilation (VAP), followed by bacteraemias [42 (30.4% of infections)], which were mainly catheter-related (CRB). The manner of LZD admistration is included in table 5. In more than half of the cases, the indication was made empirically (58.7%) and in 45.7% of cases the cultures confirmed GPC infection. The mean treatment time was 10.5 days (SD 7.18) and in 125 (89.9%) patients was administered for three or more

Table 4 Localisation of the infections based on infection type (n = 138)

INFECTIONS n (%)	CI	EICUI	IICUI
VAP			41 (46.1)
Pneumonias	3 (30.0)	15 (38.5)	
Bacteraemias related to catheter use	0 (0.0)	5 (12.8)	25 (28.1)
Secondary bacteraemias	2 (20.0)	6 (15.4)	4 (4.5)
Urinary infections related to probe use			2 (2.2)
Soft tissue infections	1 (10.0)	4 (10.3)	4 (4.5)
Surgical infection of an organ or a space		5 (12.8)	1 (1.1)
CNS infections	1 (10.0)		1 (1.1)
Febrile syndrome treated with ATB		1 (2.6)	5 (5.6)
Others	3 (30.0)	3 (7.7)	6 (6.7)
Total infections	10 (100)	39 (100)	89 (100)

CI: Community infection; EICUI: Extra-ICU nosocomial infection; IICUI: Intra-ICU nosocomial infection; CNS: Central nervous system; ATB: antibiotics; VAP: Ventilator-associated pneumonia; ICU: Intensive Care Unit.

days. It should be noted that in 43 (31.2%) treatment cases, the indication was made as a rescue therapy in patients previously treated with other active ATBs for MR-GPC. In 27 of the cases, the reason for change was clinical failure and in nine cases it was due to renal insufficiency in patients treated with VAN. In two cases, the rescue treatment was justified by lack of adequate VAN plasma levels and in one in order to be able to continue ward oral treatment against MRSA. In 27 cases (19.6%) the drug was administered in monotherapy and in the rest in association with one or more active ABTs against gram-negative bacilli (GNB). The most frequent associations were with carbapenems (44 cases), piperacillin/tazobactam (19 cases), ciprofloxacin (19 cases), amikacin (17 cases), tobramycin (14 cases) and cefepime (13 cases). In all cases, the recommended doses (1200 mg/day) were administered and in only one case was it given orally in the ICU prior to discharge. LZD treatment was modified in 13 cases (9.4%), in 12 due to therapeutic adjustment or de-escalation and in one case due to thrombocytopenia. In this case, VAN was indicated as a rescue treatment with good clinical results after 14 days of treatment with LZD. In the 12 cases in which treatment was adjusted based on the culture results, methicillin-sensitive cocci were isolated in five and in seven cases the diagnosis of infection by GPC was not confirmed. Four cases were treated with active ATBs against methicillin-sensitive GPC and in the rest the administration of LZD which had been indicated in combination with broad spectrum ATBs was suspended.

Table 5 Manner of LZD usage against MR-GPC n = 139

Treatment n (%)	**138 (99.3)**
Empirical	**81/138 (58.7)**
Negative cultures	36/81 (44.4)
Non-GPC microorganisms	8/81 (9.9)
GPC infection	37/81 (45.7)
Specific	**57/138 (41.3)**
Prophylactic	**1/139 (0.7)**
FCT n (%)	95 (68.8)
RT n (%)	43 (31.2); VAN 25 (18.1); TPN 18 (13.1)
Treatment length in days (SD)	10.46 (7.18)
Reasons for which LZD was indicated as a rescue treatment n = 43	
Clinical failure	27/43 (67.4)
Renal insufficiency	9/43 (20.9)
Insufficient VAN plasma levels	2/43 (4.6)
Oral treatment against MRSA	1/43 (2.3)
Monotherapy	27/138 (19.6)
Combined therapy	11/138 (80.4)
Modification of initial treatment	13/138 (9.4)
Reason for change from initial treatment	
Therapeutic de-escalation	12/13 (92.3)
Thrombocytopenia	1/13 (7.7)

LZD: linezolid; VAN: vancomycin; TPN: teicoplanin; FCT: First choice treatment; RT: Rescue treatment on infections previously treated with glycopeptides.

In 94 (68.1%) patients, 94 GPC were identified as responsible for the infections treated with LZD. In 66 (70.2%) cases, the GPC were methicillin-resistant as shown in table 6. MRSA, *S. epidermidis* and CNS predominated.

The clinical and microbiological efficacy of the infections treated with LZD is shown in table 7. The ITT population's cure rate was 73.2%. The cure percentage in the EP (85 cases) was 85.9%. The cure rates of the EP with pneumonia (69.7%) or with CRB (91.7%) are also compiled in that table. No significant differences were found in the clinical efficacy of the total infections (ITT) (75.8 vs. 67.4 p.50) or microbiological efficacy (ME) (78.2 vs. 61.5 p.15) between the patient group given LZD as a first choice therapy and those who received the drug as a rescue treatment.

With regard to adverse events, only one case of thrombocytopenia, probably or possibly related to the drug, was recorded. This was resolved without consequences after its withdrawal.

Table 6 Microbiological isolations n = 102

Total positive cultures	102/138 (73.9)
Enterococcus spp.	1 (0.7)
Enterococcus faecalis	6 (4.3)
Enterococcus faecium	3 (2.2)
MS *Staphylococcus aureus*	11 (8.0)
MR *Staphylococcus aureus*	34 (24.6)
Staphylococcus epidermidis	17 (12.3)
CNS	14 (10.1)
Staphylococcus Others	4 (2.9)
Streptococcus pneumoniae	2 (1.4)
Streptococcus pyogenes	2 (1.4)
Total GPC isolated	94/138 (68.1)
Total MR-GPC	66/94 (70.2)
GNB	4/138 (2.9)
Anaerobes	4/138 (2.9)

GPC: gram-positive cocci; MR-GPC: multiresistant gram-positive cocci; GNB: gram-negative bacilli; CNS: coagulase-negative staphylococci.

Table 7 Clinical and microbiological efficacy of LZD, comparing whether it was indicated as a first choice or as a rescue treatment in those treated with glycopeptide

Cure n (%)	**Total**	**FCT**	**RT**	**p**
Total infections				
ITT n = 138	101 (73.2)	72 (75.8)	29 (67.4)	0.50
EP n = 85	73 (85.9)	46 (86.8)	27 (84.0)	0.75
Pneumonias and CRB				
Pneumonia (EP) n = 33	23 (69.7)	12 (66.7)	11 (73.3)	0.67
CRB (EP) n = 24	22 (91.7)	11 (91.7)	11 (91.7)	>0.99
Eradication (ME) n (%)	**Total**	**FCT**	**RT**	
Total infections n = 94	67 (71.3)	43 (78.2)	24 (61.5)	0.15
Pneumonias n = 36	20 (55.6)	10 (52.6)	10 (58.8)	0.77
CRB n = 27	22 (81.5)	12 (100)	10 (66.7)	0.08

ITT: Intention to treat; EP: Evaluable population (documented infection by GPC and at least 3 days of treatment); ME: Microbiologically evaluable (documented infection by GPC); FCT: First choice treatment; RT: Rescue treatment in infections previously treated with glycopeptides; CRB: Bacteraemias related to catheter use.

DISCUSSION

The primary contribution of this study has been the analysis of the reasons for which LZD is used in the critically ill patient area, the profile of patients and infections for which it is indicated as well as its efficacy and tolerability in clinical practice. In the population studied, this drug is mainly used to treat nosocomial infections acquired in the ICU, especially VAP and CRB, in which a high clinical success rate is obtained with low morbidity.

LZD has been predominantly used as an empirical treatment (58.7% of cases), which confirms its inclusion in therapeutic protocols in situations in which glycopeptides are risky or not indicated. The use of vancomycin in the empirical treatment of severe infections may be suboptimal[11]. Different studies have shown a greater clinical failure rate and greater mortality when vancomycin MIC against MRSA are 1 µg/ml[28] and the presence of these strains is a progressive phenomenon.[27,29] In parallel, increasing the dosage of vancomycin has been proposed to achieve plasma levels in the trough of >15 µg/ml, which has been associated with greater renal toxicity.[26,27,30] Furthermore, when vancomycin has been used for treatment of beta-lactamase sensitive strains (allergic to penicillin) it has shown less clinical response than the beta-lactams.[25] Both clinical situations suggest the need to reconsider the future inclusion of vancomycin in the guidelines for empirical treatment of severe infections in critically ill patients.

In 31.2% of indications, it was used as a rescue treatment in patients previously treated with glycopeptides in whom clinical failure or the onset of adverse effects, primarily renal insufficiency, were seen. Both facts are widely documented in the literature. The choice of LZD as a rescue treatment, where it was not possible to reach adequate VAN plasma levels, deserves special attention in our data. Although there were only two cases, it indicates the need to include pharmacokinetic tests when VAN is chosen for use in severe infections in view of the interindividual variability of the plasma concentrations and its limited tissue penetration, above all in the lung and the central nervous system, which would justify the need to maintain plasma levels in the trough greater than 15 µg/ml.[20-24]

The global intra-ICU mortality of the patients included in this study was high (49.6%) although neither its relationship to the infections treated nor to the treatment response has been analyzed. The mortality rate is consistent with the severity upon admission (median APACHE II of 18) and with the form of presentation of the infection (63.7% of severe sepsis/septic shock), the presence of severe renal insufficiency (26.8%), as well as the significant comorbidity of the patients in this sample.

S. aureus was the most frequently identified pathogen, especially those resistant to methicillin. This is due to the fact that a significant group of the LZD treatments was performed in a targeted manner, in patients with pulmonary infections caused by MRSA, most of which were acquired in the ICU. In this indication LZD has proven superior to VAN in a meta-analysis including two randomized clinical trials.[31-33] Even though methodological problems exist which call into question the results of the meta-analysis, most intensive care physicians administer LZD for the treatment of pneumonia caused by MRSA.

In the near future, it is probable that targeted treatments for pneumonia will increase, given the fact that rapid identification of MRSA is possible with the application of PCR techniques.[34,35]

The indication of LZD was modified in few cases (13/138), mainly for therapeutic adjustment and only in one case due to the onset of adverse effects. The substitution of LZD for another narrower-spectrum antibiotic based on the microbiological results indicates a rational use of antibiotherapy in ICU participants.

Clinical and microbiological efficacy of LZD therapy was high, considering that these are severe infections, with significant systemic repercussions and high supplementary treatment needs for organ or system failures (78.4% of patients on mechanical ventilation) and that, in a significant percentage of cases, LZD treatment was established as a rescue treatment after treatment with glycopeptides. The rates of clinical and microbiological response observed in this study coincide with the results from other comparative studies in which the effectiveness of LZD in the treatment of GPC infections in critically ill patients admitted to the ICU has been analyzed. Cepeda[18] and Alvarez Lerma[12] have evaluated the effectiveness and tolerability of LZD in a comparative manner with teicoplanin[18] or with glycopeptides[12] in a specific population of critically ill patients admitted to the ICU, in which the criterion for inclusion was that a patient have clinical signs of a known or suspected infection in which potentially multiresistant GPC might exist. In both studies, no significant differences were observed in clinical and microbiological response, in the evolution (mortality) and in the tolerability of the ATB compared. Clinical success was achieved in more than 80% of microbiologically evaluable patients treated with LZD, values similar to those identified in this observational study.

One of the limitations of this endeavor is that it is an observational and multicentre study designed to describe the use of specific ATBs against MR-GPC in Spain. This circumstance prevents the automatic extrapolation of these results to other countries and especially to those having a distinct health care and social structure. Moreover, since the research has had the technical support of the pharmaceutical industry, a recruitment bias may have been incorporated. However, the proportion of LZD use with respect to other possible active ATBs against MR-GPC[36] does not vary from the data obtained in the ENVIN-UCI registry for the years in which this observation was performed.

As a conclusion for this study, it can be affirmed that in the critically ill patient area LZD is used on those severe GPC infections having a high percentage of methicillin-resistant strains with a high degree of diagnostic safety. In this context, it is primarily indicated for the treatment of VAP and CRB with good clinical and microbiological response. Lastly, this ATB has acted as a good therapeutic resource against clinical failure in infections treated with glycopeptides. All of the information indicates a rational use of LZD in the ICU.

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DECLARATION OF CONFLICT OF INTERESTS

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