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Clinical experience with linezolid for the treatment of neurosurgical infections

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ABSTRACT

Objectives: We sought to evaluate the clinical use of linezolid for the treatment of neurosurgical infections.

Methods: Retrospective observational study of a cohort of hospitalized patients who received linezolid for a culture-positive neurosurgical infection from July 2004 to February 2009 in a tertiary hospital in Spain.

Results: Seventeen patients were included in the study. Main comorbidities among these patients included one or more of the following: subarachnoidal or intraventricular hemorrhage (n=8), solid neurological cancer (n=7), corticosteroids (n=9) and hydrocephalus (n=6). Eight patients underwent a craniotomy and fourteen patients had an external ventricular drainage (EVD) as predisposing factors for infection.

Meningitis was the most common infection (11; 64.7%), followed by ventriculitis (4; 23.5%) and brain abscesses (2; 11.8%). The main causative organisms were coagulase-negative *Staphylococcus* spp. (13; 76.5%). Linezolid was used as the initial therapy in 8 episodes, after therapy failure in 6 and for other reasons in 3. The oral route was used in 9 (52.9%) episodes; linezolid was initiated orally in 2 cases. The mean duration of treatment was 26.5 days (range 15-58). No adverse events were reported. Sixteen (94.1%) patients were considered cured. There was one recurrence. The mean length of hospital stay was 45.6 (range 15-112) days and the mean duration of follow-up was 7.2 (range 0.4-32) months. No related deaths occurred during active episodes.

Conclusions: Linezolid was mainly indicated in post-neurosurgical EVD-associated infections due to coagulase-negative *Staphylococcus* spp. It was used as initial therapy in most cases. A high rate of clinical cure was observed and no related adverse events were reported. More than half of the patients were benefited by the advantages of the oral route of administration.

Key words: oxazolidone, grampositive, neurosurgical, meningitis, ventriculitis

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Experiencia clínica del uso de linezolid en el tratamiento de las infecciones neuroquirúrgicas

RESUMEN

Objetivos: Evaluar el uso clínico de linezolid en el tratamiento de las infecciones neuroquirúrgicas.

Métodos: Estudio retrospectivo observacional de una cohorte de pacientes hospitalizados que recibieron linezolid para tratamiento de infecciones neuroquirúrgicas con cultivo positivo, desde Julio de 2004 a febrero de 2009 en un hospital terciario español.

Resultados: En el estudio se incluyeron 17 pacientes. Las principales comorbilidades fueron una o más de las siguientes: hemorragia subaracnoidea o intraventricular (n= 8), tumor sólido neurológico (n= 7), corticoides (n= 9) e hidrocefalia (n= 6). Ocho pacientes fueron sometidos a craneotomía y 14 tenían un drenaje ventricular externo (EVD) como factor predisponente de infección. La meningitis fue la infección más común (11; 64,7%), seguida de ventriculitis (4; 23,5%) y absceso cerebral (2; 11,8%). El principal agente causal fue *Staphylococcus* spp coagulasa negativa (13; 76,5%). Linezolid fue usado como tratamiento incicial en 8 episodios, tras fracaso en 6 y por otras razones en 3. La vía oral fue usada en 9 (52,9%) episodios, de forma inicial en 2 casos. La duración media del tratamiento fue de 26,5 días (rango 15-58). No se observaron efectos adversos. Dieciseís pacientes (94,1%) fueron considerados curados. Hubo una recurrencia. La estancia media en el hospital fue de 45,6 (rango 15-112) días y la duración media del seguimiento fue de 7,2 (rango 0,4-32) meses. No hubo muertes relacionadas con los episodios activos.

Conclusiones: Linezolid fue principalmente indicado en las infecciones postquirúrgicas asociadas a EVD por *Staphylococcus* spp coagulasa negativa. Fue inicialmente usado en la ma-

yoría de los casos. Una alta tasa de curación clínica fue observada y no se detectaron efectos adversos. Más de la mitad de los pacientes se beneficiaron de las ventajas de la vía oral.

Palabras clave: oxazolidona, grampositivos, neuroquirúrgico, meningitis, ventriculitis

BACKGROUND

Neurosurgical infections, despite adequate drainage and antimicrobial treatment, continue to be life-threatening diseases. The frequency[1] of post-neurosurgical infections is estimated to be ~4% Gram-positive cocci, more often meticillin-resistant *Stapylococcus* spp., are the microorganisms most frequently involved and vancomycin, despite its poor central nervous system (CNS) penetration and toxicity, is still considered the drug of choice for the treatment of meningitis, ventriculitis, brain abscess and other infections subsequent to neurological procedures.

Linezolid is an oxazolidone with an excellent CNS penetration[2-4]. Although considered bacteriostatic against *Staphylococcus* and *Enterococcus* species, this drug meet several characteristics that turn it into an attractive choice for the treatment of CNS infections; as its capability of achieving good penetration through the blood-brain barrier regardless of the use of steroids, its good activity against susceptible and drug resistant gram-positive cocci and its excellent bioavailability when taken orally.

According to the existing CSF pharmacokinetic evidence, linezolid has been increasingly used for the treatment of CNS infections[5]. Unfortunately, no randomized, controlled trials and no large studies have been conducted to guarantee its effectiveness and safety in this setting. Current clinical evidence is limited to anecdotal cases and, since treatment failures are unlikely to be published, the possibility of a reporting bias cannot be excluded. The objective of this study is to describe the clinical experience with linezolid in neurosurgical infections at a tertiary hospital and to analyze its therapeutic effectiveness and safety in this patient population.

METHODS

Study design and Setting. This is a retrospective study of a cohort of patients hospitalized from July 2004 to February 2009 who received linezolid for a culture-proven neurosurgical infection.

Our institution is a tertiary-care teaching hospital with 1,434 beds serving a ~545,000 area inhabitants. We have medical and surgical specialities and very active bone marrow and solid organ transplantation programs and also serve as a referral institution. The neurosurgery speciality comprises a 36-bed division that accomplishes more than 700 interventions per year.

Data collected. Data on linezolid dispensation and isolated microorganisms were obtained from the Pharmacy and Microbiology databases, respectively. Clinical records were reviewed to collect the clinical characteristic of the patients and to assess the antimicrobial use and the outcomes. Those episodes without a microbiological diagnosis (no culture-positive infection) were excluded from the study. Microorganisms were identified using standard procedures and the antimicrobial susceptibility tests were carried out with broth microdilution, using the criteria of the CLSI (Clinical Laboratory Standards Institute) as breakpoints for antimicrobial susceptibility.

The following clinical data were recorded: age, sex, underlying diseases, predisposing factors for infection, type of CNS infection, antimicrobials, outcomes and adverse events. The following predisposing factors were taken into account: external ventricular drainages, CSF-derivation shunts, neurosurgery, neutropenia, corticosteroid therapy (equivalent to ≥10 mg of prednisone daily for two weeks), and the antimicrobial therapy prescribed in the previous week to the episode.

Definitions. Meningitis and ventriculitis were defined by a positive CSF culture accompanied by altered CSF laboratory findings (leukocyte count $>5x10^6$ cells/L, protein >0.45 g/L, CSF-glucose ratio <0.5) or appropriate clinical signs and symptoms (T° ≥38°C, headache, neck stiffness, nausea, vomiting, and/or reduced level of consciousness). A nosocomially-acquired infection was considered if it presented no sooner than 48 hours after admission to the hospital. In the case of persistent positive CSF cultures or no clinical improvement, antibiotic-failure was determined. Death was attributed to the infection, if it occurred during the active episode or while the patient was undergoing antimicrobial treatment and no alternative cause of death was detected.

Statistical analysis. The analysis was conducted using SPSS Statistics 17.0 for Windows. The quantitative variables were expressed as mean and range and qualitative variables as the absolute value and percentage.

RESULTS

Linezolid was used to treat 17 culture-positive CNS infections during the 55-months period of the study. Demograghic and microbiologic characteristics of the episodes, indications for linezolid, treatments and outcomes, are given in table 1.

The mean age of the patients was 56.5 (range 17-78) years and 9 (52.9%) were male. Meningitis was the most common infection (11, 64.7%), followed by ventriculitis (4, 23.5%) and brain abscesses (2, 11.8%). Main commorbidities among these patients included one or more of the following: intraventricular or subarachnoidal hemorrhage (n=8), neurological cancer (n=7), corticosteroids (n=9) and hydrocephalus (n=6). Eight patients underwent a previous craniotomy and 14 patients had an external ventricular device as predisposing conditions for infection. All episodes, but one (number 16), had a nosocomial onset. Linezolid was initiated a mean of 32.9 days (10-98) after admission.

The causative microorganisms were coagulase-negative *Staphylococcus* (n=13), penicillin-susceptible *Enterococcus* spp. (n=3), penicillin-susceptible *Streptococcus pneumoniae*

Table 1 **Clinical and microbiological characteristic of the episodes (Period of study: 55-months)**

Case	Sex / Age(yrs)	Commorbidities	Prosthetic Devices	Infection	Microorganism	Previous Antimicrobials (days)	Reason Linezolid Initiated	Days of Linezolid Therapy (iv/or)
1	F/76	Hemorrhagic ictus with increased intracranial pressure	EVD	Meningitis	*Staphylococcus epidermidis*	None	Initial therapy	15 (15/0)
2	M/23	Neoplasia (glial tumor), craniotomy, corticosteroids	EVD	Meningitis	*Staphylococcus epidermidis*	Vancomycin iv (2)	Not available	22 (22/0)
3	F/46	SAH, hydrocephalus	EVD	Meningitis	*Staphylococcus epidermidis*	Vancomycin (11) + cefepime (11)	Failure of treatment	49 (49/0)
4	M/75	SAH	EVD	Meningitis	*Staphylococcus epidermidis*	Vancomycin (10) + trimetroprim-sulphametoxazole (2)	Failure of treatment	29 (29/0)
5	M/62	Neoplasia+craniotomy, hydrocephalus (meningeal carcinomatosis-lung cancer), corticosteroids	EVD	Meningitis	Penicillin-susceptible *Enterococcus faecalis*	None	Initial therapy	31 (31/0)
6	M/41	Neoplasia+craniotomy, corticosteroids	EVD	Meningitis	*Staphylococcus haemolyticus*	Vancomycin iv (6) + ceftazidime (6)	Failure of treatment	30 (8/22)
7	F/69	Ehler- Danlos disease, SAH, hydrocephalus, corticosteroids	EVD	Meningitis	*Staphylococcus hominis*	Vancomycin iv (4)	Initial therapy	21 (13/0)
8	F/56	Meningioma, hydrocephalus, craniotomy 6 months before	VP shunt	Meningitis and subdural empiema	*Stapylococcus hominis*	None	Initial therapy	31 (0/31)
9	F/78	SAH, hydrocephalus	EVD	Meningitis	*Enterococcus faecalis* *Proteus mirabilis*	Vancomycin (4) + meropenem (4)	Failure of treatment	19 (12/7)
10	M/52	SAH, craniotomy	EVD	Meningitis	*Staphylococcus haemolyticus*	Vancomycin (6)	Not available	17 (10/7)
11	M/17	Craneo-encephalic traumatism, SAH	EVD	Meningitis	*Staphylococcus hominis*	Cloxacilin (14)	Initial therapy	14 (4/14)
12	M/57	Craneo-encephalic traumatism, SAH, corticosteroids, craniotomy	EVD	Ventriculitis	*Enterococcus sp.* *Staphylococcus hominis,* *Stenotrophomonas maltophilia*	None	Initial therapy	21 (16/5)
13	F/67	Meningioma, craniotomy, corticosteroids	EVD	Ventriculitis	*Staphylococcus haemolyticus*	None	Initial therapy	33 (33/0)
14	F/76	Intraventricular haemorrhage, hydrocephalus	EVD	Ventriculitis	*Staphylococcus epidermidis*	Vancomycin iv (8)	Failure of treatment	18 (13/5)
15	F/26	Neoplasia+craniotomy, corticosteroids	EVD	Ventriculitis	*Staphylococcus haemolyticus*	Vancomycin iv (7)	Failure of treatment	16 (16/0)
16	M/75	Cardiopathy, neurosurgical evacuation of a temporal abscess, corticosteroids	No	Cerebral abscess	Penicillin-susceptible *Streptococccus pneumoniae*	Ceftriaxone (6) Previously: broad spectrum antimicrobials (44)	Adverse event (fever, skin rash and eosinophylia). Consolidation therapy	23 (0/23)
17	M/64	Diabetes Mellitus, hemangiopericitoma, craniotomy, corticosteroids	No	Cerebral abscess	*Propionibacterium acnes*	None	Initial therapy	58 (15/43)

EVD: external ventricular drainage. VP-shunt: ventriculoperitoneal shunt. SAH: subarachnoidal hemorrhage

(n=1) and *Propionibacterium acnes* (n=1). There were 2 polimicrobial infections, where gram-negative rods were identified together with gram-positive microorganisms (numbers 9 and 12). The coagulase-negative *Staphylococcus* isolates were identified as: *S. epidermidis* (n=5), *S. hominis* (n=4) and *S. haemolyticus* (n=4); all were resistant to oxacillin and sensible to vancomycin; the MIC to linezolid was ≤2 in all of them. Overall, eleven cases of ventriculo-meningitis associated to an external ventricular drain due to coagulase-negative *Staphylococcus* spp. were identified in the study.

Linezolid was used as first-line therapy in 8 (47.1%) episodes, after failure of previous antimicrobial treatment in 6 (35.3%), allergy in 1 (5.9%) and data was not available in 2 (11.7%) cases. The mean length of previous treatment regimens with other standard drugs was 10.2 (range: 2-44) days. The mean duration of linezolid therapy was 26.5 (range 15-58) days. The oral route of administration was used in 9 (52.9%) episodes. In 2 cases linezolid was initiated orally. All patients were given linezolid at the standard dose (600mg / 12 hr). Concomitant antimicrobials with coverage to gram-positive bacteria were prescribed in 4 cases: intrathecal vancomycin in 2 episodes, trimetroprim-sulfametoxazole in 1 and intravenous vancomycin (just for 2 days) in 1. In 5 cases, linezolid was used without previous and concomitant antimicrobials with coverage for the isolated microorganism. Removal of infected external ventricular catheters was carried out in all cases with a mean of 3.1 (0-7) days.

Sixteen patients (94.1%) were considered cured at the end of the episodes. One patient experienced relapse by the same microorganism one week after treatment discontinuation (number 13); the MIC to linezolid was as previous; a predisposing factor for relapse in this patient was a VP shunt placed in the 23rd day of therapy. Microbiological eradication was documented in 11 (64.7%) cases, there was 1 microbiological recurrence (number 13) and no control cultures were obtained in 5 cases.

The mean length of hospital stay was 45.6 days (range 15-112). Transition from inpatient to outpatient oral linezolid was possible in 2 cases. The mean duration of follow up was 7.2 (range 0.4-32) months. Five patients died (numbers 2, 4, 6, 7, and 13) during the follow up period after a mean of 106.6 (23-330) days. The deaths were due to complications of the underlying disease in 3 cases and due to newly developed neurosurgical infections by a different microorganism in 2 cases (numbers 4 and 13). No deaths occurred during active episodes. Neither side-effects of linezolid therapy, nor hematological disturbances as anemia or thrombocytopenia, were reported during the treatment of the episodes.

DISCUSSION

The results of the present study revealed that linezolid was mainly used for the treatment of EVD-related meningitis and ventriculitis caused by Gram-positive microorganisms, particularly methicillin-resistant coagulase-negative *Staphylococcus* spp. Linezolid was prescribed as first-line therapy in most cases or after previous antimicrobial failure. In this setting linezolid showed good efficacy without relevant adverse effects.

Coagulase-negative staphylococci are the organisms involved more frequently in CNS infections subsequent to neurosurgical procedures. Intravenous administration of vancomycin is considered the treatment of choice of these infections, but it has several limitations. The CSF penetration of intravenous vancomycin is very poor even through inflamed meninges[6]. The recommended through level of 5-10 mg/L can be achieved only by higher and potentially nephrotoxic doses. Direct instillation of vancomycin into the ventricles has been used, but intrathecal administration may be associated with neurotoxicity[7] and with an increased risk of nosocomial ventriculitis.

Linezolid is an oxazolidone with a good CNS penetration. Beer et al. (2007)[3] found in a study of five neurointensive care patients with staphylococcal ventriculitis, that the CSF linezolid concentration largely exceeded the MIC of the bacterial isolates. Linezolid levels were monitored in serum and cerebrospinal fluid. The mean CSF to plasma ratio was 0.8 ± 0.3. For isolates with a linezolid MIC of 2 mg/L the time above MIC in CSF was 99.8%, but for an isolate with MIC of 4 mg/L the time above MIC in CSF was 57.2%[3]. Myrianthefs *et al.*[4] studied the CSF penetration of LNZ in 14 neurosurgical patients; mean C_{max} and C_{min} linezolid levels in serum were 18.6 ± 9.6 and 5.6 ± 5.0 mg/L, and in CSF were 10.8 ± 5.7 and 6.1 ± 4.2 mg/L. In patients with shunts, but no inflamed meninges, the CSF levels of linezolid also reach ~70% of serum concentration.

Clinical experience on the efficacy and safety of linezolid for[8-18] the treatment of CNS infections is limited to anecdotal cases and small series of 6-10 patients[1,19,21]. Post-neurosurgical and post-traumatic *S. epidermidis* meningitis; as well as, *S. epidermidis* or vancomycin-resistant *Enterococcus* spp. shunt infections has been successfully treated with linezolid. Successful outcome of pneumococcal meningitis[22,23] and brain abscess[24] have also been reported.

Unfortunately, published studies have included groups of patients with very heterogeneous diagnoses and type of microorganisms. More over, linezolid have been used after failure of standard therapy (vancomycin) and combined with additional antimicrobials, where the possibility of a successful outcome due to these regimens cannot totally be ruled out. To the best of our knowledge, the present study includes the largest series of post-neurosurgical infections treated with linezolid from a single institution. Most patients suffered an infection associated to a temporary external ventricular drainage, caused by a meticillin-resistant coagulase-negative *Staphylococcus* (n=11). First-line therapy with linezolid was used in half of the episodes and in five patients, neither previous nor concomitant antimicrobial treatment, was prescribed.

In the literature, we located 5 other reports of EVD related ventriculo-meningitis caused by coagulase-negative staphylococci, treated with linezolid[1,15,17,25,26]. The main features of these

5 cases are summarized as follows: all patients underwent CSF drainage because of hydrocephalus or increased intracranial pressure due to hemorrhage or intracranial tumor. Linezolid was used after failure of previous vancomycin during a mean of 24.9 days (range: 5-55) in 4 cases and after severe adverse effects (skin rash) after 2 days of vancomycin in 1 case. The mean duration of linezolid therapy was 30.2 (range 14-84) days. Rifampin was added to linezolid in 1 case. All patients were cured at the end of treatment without presenting adverse effects. No relapses were documented in the 3 cases that were followed during 3, 9 and 12 months respectively. The characteristics of these episodes did not greatly differ from the characteristics of the episodes presented in our study, although linezolid was not used as initial therapy in any of the previous reported cases.

The oral bioavailability of linezolid is approximately 100% [27,28] and there is an equivalence of oral and intravenous doses; accordingly many patients in this study (52.9%) were benefited by the oral route of administration. Reversible, time-dependant, myelosupression is the most important adverse effect of prolonged linezolid therapy[20] and weekly blood counts are recommended after 10 days of treatment; but 7 patients in this series received linezolid for more than 28 days and no adverse events or hematological disorders were documented during the episodes. Overall, a high rate of successful outcome was observed (94.1%) and there were no deaths related to the infection. A good clinical outcome was also reported in the vast majority (90.5%) of previous studies[5], although reporting bias cannot be excluded when interpreting these findings.

This study has some limitations inherent to its retrospective design: there was not a comparator, CSF/plasma linezolid levels were not monitored, and the small number of patients recruited does not allow drawing any recommendations. Still, this is a valuable descriptive analysis that provides further evidence for coagulase-negative staphylococcal EVD-associated infections and with inclusion of cases whose outcomes cannot be attributed to other antimicrobial regimens.

In summary, emergent clinical experience seems to encourage the use of linezolid for the treatment of CNS infections. Despite the absence of data from randomized controlled trials, linezolid could be a reasonable alternative for neurosurgical infections; not only reserved for multidrug-resistant bacteria or conventional therapy failure.

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