Objective: To describe the use of linezolid in vancomycin-resistant Enterococcus infections in a paeditric hospital.

Method: Retrospective, observational study of hospitalised patients at the “Juan P. Garrahan” paediatric hospital receiving linezolid for the treatment of vancomycin-resistant Enterococcus, during the period between January 2002 and July 2004.

Results: During 18 months, linezolid was prescribed 17 times for a total of 15 seriously ill patients. The median age was 7 years old (range: 1 month-15 years) and the median length of the treatment was 15 days, with an average hospital stay of 74 days. Infection with vancomycin-resistant Enterococcus was microbiologically documented in 11 (73.3%) patients; they all responded to treatment with linezolid with the exception of two, who died while receiving treatment. The most frequently reported adverse reactions were of a haematological nature (55.5%).

Conclusions: Linezolid was effective and moderately well tolerated for the treatment of vancomycin-resistant Enterococcus in children with life-threatening infections.

Key words: Linezolid. Vancomycin-resistant Enterococcus. Serious paediatric infections. Risk factors. Reporting of adverse effects to medication.
tis, osteomyelitis, etc. There are several species of Enterococcus, the most frequent of which are E. faecalis (80-90%) and E. faecium (5-10%).

They are characterised by their resistance to a large number of antibiotics (betalactams and to a slight degree to aminoglycosides, clindamycine) and acquired resistance (to betalactam and to a great degree to aminoglycosides and glycopeptides). This latter type of resistance has been a growing problem during recent years, due to the limited therapeutic arsenal available for treatment.

The first reported case of vancomycin-resistant Enterococcus (VRE) in Latin America occurred in a paediatric hospital in Mendoza in 1996, in a patient with haemato-oncological disease. The first documented case of infection in our hospital was in the year 2002. At the time of the study there were a total number of 87 patients colonised with VRE.

Linezolid (LNZ), a synthetic antibiotic belonging to the oxazolidinone family, was approved by the Food and Drug Administration for paediatric use in December 2002, for the treatment of infections produced by gram-positive bacteria including multiresistant types such as meticillin-resistant Staphylococcus aureus (MRSA) vancomycin-resistant Enterococcus. Compared to other available treatments, LNZ has a different action mechanism to the other antibiotic families and presents no cross resistance to other antibiotics. It has 100% oral bioavailability, it does not require dose adjustment in the case of renal failure and has no significant interactions with other drugs. These qualities make it attractive for the treatment of multi-resistant infections. In our hospital, LNZ has been approved solely for the treatment of VRE infections.

The purpose of this work is to describe the use of LNZ in hospitalised paediatric patients at the “Dr. Juan P. Garrahan”, Paediatric Hospital in the city of Buenos Aires, in order to describe the indications, the efficacy of the treatment and the adverse effects for the treatment of VRE infections.

**METHOD**

A retrospective, observational study was carried out on patients hospitalised in “Juan P. Garrahan” Paediatric Hospital receiving LNZ for VRE, for the January 2002 to July 2004 period. Based on the pharmacological records and the respective clinical histories, a pharmacotherapeutic follow-up table was prepared showing the demographics, weight, base diagnosis, length of hospital stay and mortality rate.

The risk factors for acquiring VRE appearing in published literature, such as statistics from the intensive care unit, presence of a central catheter, prior chemotherapy, the number of concomitant antibiotics, immune status of the host (transplant patient and/or immunosuppressive medication and/or leukopenia), earlier surgical procedures, hospitalisations within the previous three months, and exposure to antibiotic inducers (third generation cephalosporin, metronidazole or ornidazole and vancomycin) during the three months prior to the infection were documented.

The information regarding the route of administration, doses, frequency and days of treatment with LNZ were recorded. The correct doses were considered to be those detailed in the CIME and Micromedex® bulletin: In newborns to 11 years of age, 10 mg/kg/dose every 8 hours and in children over the age of 12 years, 600 mg/dose every 12 hours, to a maximum dose of 1,200 mg/day.

The information recorded included the infection site, microbiological material for isolation (blood samples, urine, pleural liquid, etc.).

To study the adverse drug reactions (ADR), the working system of the hospital adverse effect reporting subcommittee was applied. The method of detection corresponds to intensive adverse-effect reporting centred on the medication.

A daily follow up of the laboratory readings was carried out during the LNZ therapy: urea, creatinine, GOT-ASAT, GPT-ALAT, alkaline phosphotase, LDH; white blood cells, neutrophiles, haematocrit, haemoglobin, platelet (reference values: Hospital central laboratory).

The ADR findings were classified according to: a) affected apparatus, according to the adverse effects sub-committee criteria; b) causality: Naranjo algorithm assigned, which has an ascending scale of doubtful, possible, probable and final; c) intensity in accordance with the OMS criteria; and d) preventability, according to whether this was produced by identifiable and controllable causes. The ADR treatment was allocated, as were the patient results.

The efficacy of the treatment was measured in terms of the microbiological results and clinical follow up of the patients.

**RESULTS**

LNZ was prescribed 17 times for a total of 15 patients. The average age was 7 years old (range: 1 month-15 years); 9 patients (60%) were male and 6 (40%) were female. The average weight of the patients was 20 kg (range: 3.65-50). The average hospital stay in days was 74 (range: 25-334).

At the start of the treatment with LNZ, five were transplanted patients (four bone marrow and one liver), three were undergoing oncological treatment and six had undergone surgical procedures (2 abdominal surgery, two traumatological, one urological and one cardiovascular).

The 15 patients had at least 2 associated risk factors for acquiring VRE. The average number of risk factors per patient was 4 (range: 2-6) (Fig. 1).

The average number of concomitant parenteral antibiotics in the LNZ treatments were 2 (range: 0-6) with only a few episodes of multi-resistant infections. A follow up table was prepared showing the demographic, weight, base diagnosis, length of hospital stay and mortality rate.

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The efficacy of the treatment was measured in terms of the microbiological results and clinical follow up of the patients.
one case reported where LNZ was the only antibiotic administered.

The doses prescribed were correct in 14 cases (82.3%) and in 3 (17.7%) incorrect by default. The intervals between the doses were correct in 16 (94.11%) treatments.

47.1% of the patients received LNZ during a 14-28 days period, while 23.5% received it for at least 14 days and 29.4% for a period in excess of 28 days. The average duration of the treatment was 15 days (range: 4-68).

The most commonly used route of administration for the treatment was endovenous (70.6%, 12 treatments), followed by the exclusive oral route (17.6%, 3 treatments) and only 11.7% (2 treatments) used the endovenous and oral route.

With regard to the microbiological results in 10 patients (66.7%), vancomycin-resistant *E. faecium* was isolated, and in one patient the microorganism isolated was vancomycin-resistant *E. faecalis*. Four patients received empiric LNZ and the cultures were always negative for VRE.

VRE infection was documented microbiologically in 11 patients (73.3%). The 4 remaining patients (36.36%), all of whom were diagnosed with bone marrow transplants, received empirical LNZ, following the protocol recommended for the unit for patients colonised with VRE, with signs and symptoms of the infection. In these cases LNZ was withdrawn as soon as the microbiological results became available and/or there was clinical improvement.

All of the microbiological isolations were sensitive to LNZ in the diffusion disc.

In 3 patients (20%), LNZ was administered for bacteremia, while the other sites of infection included intraabdominal collection in 3 cases (20%) and the urinary tract in 2 (13.3%) (Table I).

All of the microbiologically documented infection cultures became negative, with the exception of those belonging to the patients who died during the treatment. None of the patients who continued to be positive were available to carry out a resistance test.

From the analysis of the adverse effects: it can be seen that of the 15 patients, 8 presented with (53.3%) dermatological, haematological and hepatic ADR (Table II).

**DISCUSSION**

There are only a limited number of publications describing the use of LNZ for the treatment of VRE infections in infants and children.

In paediatrics the treatment of choice for serious VRE infections is LNZ, because it is available in an oral pharmaceutical formulation to complete the treatment days, contrasting with quinupristin-dalfopristin, which is only available for parenteral administration, and which is reserved for LNZ-resistant situations in our hospital.

Patients who are seriously ill make up the highest risk group for acquiring multiresistant infections, meaning LNZ therapy is required.

Of the patients receiving LNZ for at least 14 days, one died during the therapy, two received it empirically because they were undergoing bone marrow transplants, and in a final case the reason is unknown. The
extended treatment in five of the patients receiving LNZ for more than 28 days was justified by the location of the infection (endocarditis, pyopneumothorax, osteomyelitis, etc.),

In spite of its excellent oral bioavailability, LNZ was administered parenterally in 82.3% of patients at some stage during the therapy, as might be expected given the likelihood of oral intolerance of the patients in the study. We assume the errors in dosing occurred as a result of the lack of experience with the drug, as it had only

Table I. Infection profile

<table>
<thead>
<tr>
<th>Patient</th>
<th>Site of infection/diagnosis</th>
<th>Culture material</th>
<th>Enterococci</th>
<th>Evolution of treatment/microbiological results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Osteomyelitis</td>
<td>Bone and granulation tissue</td>
<td><em>E. faecium</em></td>
<td>Effective. Clinical follow up with reactants in acute phase until resolution</td>
</tr>
<tr>
<td>2</td>
<td>Peritoneal abscess</td>
<td>Purulent material</td>
<td><em>E. faecium</em></td>
<td>Undetermined: Death during treatment</td>
</tr>
<tr>
<td>3</td>
<td>Urinary infection</td>
<td>Uroculture</td>
<td><em>E. faecium</em></td>
<td>Effective. Uroculture became negative</td>
</tr>
<tr>
<td>4</td>
<td>Abdominal collection</td>
<td>Purulent material</td>
<td><em>E. faecium</em></td>
<td>Effective. Follow up scans until resolution</td>
</tr>
<tr>
<td>5</td>
<td>Endocarditis urinary infection</td>
<td>Haemocultures</td>
<td><em>E. faecium</em></td>
<td>Effective. Ecocardiogram without vegetations</td>
</tr>
<tr>
<td>6</td>
<td>Pyopneumothorax</td>
<td>Pleural liquid</td>
<td><em>E. faecalis</em></td>
<td>Effective. Radiographic/scan follow up</td>
</tr>
<tr>
<td>7</td>
<td>Protocol fever</td>
<td>Haemocultures</td>
<td>None</td>
<td>Undetermined. Patient BMT protocol colonised with VRE when admitted</td>
</tr>
<tr>
<td>8</td>
<td>Protocol fever</td>
<td>Haemocultures</td>
<td>None</td>
<td>Undetermined. Patient BMT protocol colonised with VRE when admitted</td>
</tr>
<tr>
<td>9</td>
<td>Subphrenic abscess</td>
<td>Purulent material</td>
<td><em>E. faecium</em></td>
<td>Effective. Follow up with scan resolution</td>
</tr>
<tr>
<td>10</td>
<td>Bacteriæmia</td>
<td>Haemocultures</td>
<td><em>E. faecium</em></td>
<td>Effective. Cultures became negative</td>
</tr>
<tr>
<td>11</td>
<td>Bacteriæmia associated with catheter</td>
<td>Catheter</td>
<td><em>E. faecium</em></td>
<td>Effective. Catheter removed</td>
</tr>
<tr>
<td>12</td>
<td>Protocol fever</td>
<td>Haemocultures</td>
<td>None</td>
<td>Undetermined. Patient BMT protocol colonised with VRE when admitted</td>
</tr>
<tr>
<td>13</td>
<td>Protocol fever</td>
<td>Haemocultures</td>
<td>None</td>
<td>Undetermined. Patient BMT protocol colonised with VRE when admitted</td>
</tr>
<tr>
<td>14</td>
<td>Burnt patient</td>
<td>Skin and soft parts</td>
<td><em>E. faecium</em></td>
<td>Effective. Clinical follow up with reactants in acute stage until resolution</td>
</tr>
<tr>
<td>15</td>
<td>Protocol fever</td>
<td>Haemocultures</td>
<td><em>E. faecium</em></td>
<td>Undetermined. Death during treatment</td>
</tr>
</tbody>
</table>

References: BMT: bone marrow transplant.

Table II. Adverse reactions to linezolid* (n = 17 treatments)

<table>
<thead>
<tr>
<th>Patient</th>
<th>ADR</th>
<th>Cause</th>
<th>Severity</th>
<th>Treatment</th>
<th>Avoidability</th>
<th>Recovery</th>
<th>Other possible causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Maculopapular rash with adenopathies</td>
<td>Probable</td>
<td>Moderate</td>
<td>Hydroxyzine, diphenhydramine</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Neutropenia (N: 2,450 a 330)</td>
<td>Probable</td>
<td>Major</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Maculopapular eruption on the thorax and lower limbs</td>
<td>Probable</td>
<td>Mild</td>
<td>Diphenhydramine</td>
<td>No</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Leukopenia (WB cells: 6,700 to 2,300), lowering of Hb (10.7 a 7.3)</td>
<td>Doubtful</td>
<td>Moderate</td>
<td>RB transfusion</td>
<td>No</td>
<td>Yes</td>
<td>Concomitant antibiotics, previous surgery</td>
</tr>
<tr>
<td>8</td>
<td>Leukopenia (WB cells: 10,400 a 3,700)</td>
<td>Possible</td>
<td>Mild</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Elevated transaminase (GOT-GPT: 27/16 a 8.53/432)</td>
<td>Possible</td>
<td>Moderate</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Concomitant drugs</td>
</tr>
<tr>
<td>12</td>
<td>Elevated transaminases (GOT-GPT: 22/32 a 1,573/427) that reduced when the LNZ treatment was withdrawn (GOT/GPT: 36/24)</td>
<td>Possible</td>
<td>Moderate</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Concomitant drugs</td>
</tr>
<tr>
<td>15</td>
<td>Thrombocytopenia (P: 339 a 41)</td>
<td>Probable</td>
<td>Major</td>
<td>P transfusion</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Leukopenia (WB: 12,000 a 4,300) and decreased Hb (10.6 a 7.1)</td>
<td>Doubtful</td>
<td>Moderate</td>
<td>RB transfusion</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*Only the initial values are shown and those that varied the most during the follow up.
N: neutrophils; WB: white blood cells; Hb: haemoglobin (mg/dl); GOT/GPT: transaminase glutamic-oxalacetic/transaminase glutamic-piruvic (UI); RB: red blood cells; P: platelets (10³/mm³).
It can be difficult to assess the clinical efficacy of antimicrobial treatment in VRE infections because of the seriousness of these patients’ underlying diseases and other concomitant medications (e.g., removal of catheters, draining abscesses, surgical treatment, etc.). It is important that the doctor determines the pathogenic value of the VRE depending on the type of patient and the infection to be treated. (e.g., hosts with immune deficiency versus normal or monomicrobial infection versus polymicrobial infection).

It is important for healthcare personnel to receive continuous education, and that they maintain isolation from contact at hospital level to avoid clonal dissemination of VRE infection.

Although the limitations of our case are obvious, as we did not have a control group to enable us to compare the clinical and microbiological results with patients in a similar critical condition not treated with LNZ, we can confirm that LNZ was efficacious and moderately well tolerated for the treatment of VRE infections in children with life-threatening infections.

References