Pancytopenia due to linezolid treatment

Emine Parlak¹, Hüseyin Tan²

¹Department of Infectious Diseases and Clinical Microbiology, Atatürk University Faculty of Medicine, Erzurum, Turkey

²Department of Pediatrics, Division of Pediatric Neurology, Atatürk University Faculty of Medicine, Erzurum, Turkey

Abstract

Antibiotic-resistant infections constitute a significant portion of severe childhood infections. A gradually increasing resistance and treatment difficulty are observed in infections caused by enterococci, staphylococci and pneumococci. Linezolid is one of the new antibiotics which has recently been introduced for clinical use with gram positive efficiency. In this article, a pediatric patient with vancomycin-resistant enterococcus infection who developed reversible bone marrow suppression related with use of linezolid was presented. A shunt was inserted in a ten-month old female patient who had been operated at the age of one month because of meningomyelocele and who had developed hydrocephalus. Linezolid and meropenem treatment was started when vancomycin-resistant *Enterococcus faecium* and extended-spectrum beta-lactamase positive *Escherichia coli* grew in cerebrospinal fluid culture. In the second week of treatment, cerebrospinal fluid findings improved. However, bone marrow suppression was observed. Linezolid treatment was discontinued. In the follow-up, the blood cell counts returned to normal levels. (Turk Pediatri Ars 2015; 50: 185-8)

Keywords: Enterococcus, linezolid, pancytopenia, shunt infection

Introduction

Linezolid is the first antibiotic introduced from the oxazolidinone group. Linezolid was approved by Food and Drug Administration for use in children. In Great Britain, Linezolid has no approval for use in children. Linezolid stops bacterial growth by inhibiting protein synthesis. It is effective against microorganisms including vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis*, methicillin-resistant staphylococcus and penicillin-resistant pneumococcus (PRP) (1-3). The bioavailability of linezolid is very good. After linezolid is taken orally, it is absorbed rapidly and fully. In the absence of meningeal involvement, the level of linezolid in the cerebrospinal fluid (CSF) is 70% of the plasma level. It is used in children, because it penetrates into the CSF to a great extent and has few side effects (3). It is preferred in treatment of resistant gram positive bacterial infections especially in treatment of vancomycin resistant enterococcal (VRE) infections in the childhood.

Case

Ventriculoperitoneal shunt was placed in the patient who was operated because of meningomyelocele at the

age of one month. The patient presented to the emergency department with complaints of fever, vomiting, abdominal distention and irritability which started two months after the operation. The patient was admitted to our clinic, because her fever did not subside despite antibiotic treatment administered in another center. There was no pathology in the prenatal history. In the history, it was learned that the patient was born by normal vaginal delivery with a birth weight of 3 400 g from the third delivery of a 27 years - old mother. In the familial history, there was no consanguinity between the mother and father and no morbidity. The patient was receiving breast-milk and solid foods. At the time of admission, she was ten months old and her physical examination findings were as follows: weight: 8 400 g, height: 68 cm, head circumference: 46 cm, apical heart beat: 156/min and respiratory rate: 44/min. Her general status was moderate, she was macrocephalic, her anterior fontanelle was open and she had a meningo-myelocele operation scar on the sacral region and an operation scar on the abdomen. The liver was palpable one cm below the costal margin. No abscess or infection was observed in the abdomen. It was observed that she could not hold her head and could not sit with or

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Address for Correspondence: Emine Parlak, Atatürk Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Erzurum. E-mail: eparlak1@yahoo.com

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Table 1. Monitoring of the blood counts of the patient

Days of antibiotic usage	White blood cells/mm ³	Neutrophils /mm ³	Lymphocytes /mm ³	Hemoglobin g/dL	Platelets /mm ³	
Before antibiotic use	11 400	3 500	6 300	10.7	605 000	
5 th day	19 900	14 400	4 100	9	544 000	
9 th day	9 300	4 000	5 000	11	99 000	
10 th day	6 500	2 000	4 400	9.8	43 000	
11 th day	3 400	1 000	2 300	7.8	62 000	Erythrocyte suspension
12 th day	5 500	1 000	4 100	9.1	34 000	Platelet suspension
16 th day	2 500	600	1 600	8.8	183 000	Erythrocyte suspension
First day after antibiotic discontinuance	4 200	800	3 000	8.2	145 000	
2 nd day	5 500	1 400	3 700	11.2	91 000	
7 th day	2 800	300	2 300	9.8	117 000	
11 th day	3 700	800	2 500	11.6	299 000	

without support. She was admitted to the intensive care unit. Transaxial puncture was made, since the shunt was not operating. Erythrocytes and leukocytes were found on examination of the cerebrospinal fluid. External ventricular drainage set (EVDS) was inserted by the neurosurgery department because of hydrocephalus. Examination of the cerebrospinal fluid was repeated. Ceftriaxon and vancomycin treatment was initiated considering shunt infection. Fever persisted and the treatment was switched to vancomycin plus meropenem with a diagnosis of healthcare associated central nervous system infection. In the mean time, VRE and extended spectrum beta lactamase positive *E. coli* were grown in CSF culture and the patient was placed under contact precautions. Vancomycin was discontinued and linezolid was started. The CSF findings improved. The drug was discontinued two weeks later because of bone marrow suppression. In the follow-up, the blood counts returned to normal (Table 1).

Discussion

Healthcare associated central nervous system infections constitute 0.4% of all nosocomial infections. Healthcare associated central nervous system infections have a high morbidity and mortality rate. The risk factors include interventions directed to the brain, prolonged operation time, presence of EVDS and prolonged use of EVDS, intracerebral hemorrhage, CSF leak and presence of another infectious focus in the body (4-6). A history of surgery for two times and insertion of EVDS catheter were risk factors for our patient.

The most common pathogens in healthcare associated central nervous system infections include *Staphylococ-*

cus aureus, *Staphylococcus epidermidis*, *Enterococcus spp.*, *Pseudomonas aeruginosa* and *E.coli* (4-7). Enterococci are members of the normal intestinal flora. Enterococci are among the significant causes of nosocomial infections. Enterococcal infections are observed in cases of prolonged hospitalization, antibiotic usage, catheter usage and in gastrointestinal tract problems. Resistance is gradually increasing among enterococci. Especially the number of vancomycin resistant pediatric cases is gradually increasing (8, 9). In a seven-year study conducted by Çelebi et al. (10), the prevalence of VRE was reported to be 1-15% and vancomycin resistance for *Enterococcus spp.* was reported with a rate of 2%. In this study, the risk factors were specified to be immune suppression, mechanical ventilation, treatment in the intensive care unit, antibiotic usage, surgical intervention and presence of catheter. Vancomycin resistance is observed more commonly in *E.faecum* strains. In comparative studies conducted with vancomycin, it was found that linezolid was as efficient and safe as vancomycin (3). Linezolid is the most appropriate treatment option in treatment of infections caused by vancomycin resistant enterococci (1). Our patient was considered to have healthcare associated central nervous system infection. Strict contact precautions were taken because of vancomycin resistant enterococcus. Internalization in the intensive care unit, antibiotic treatment, surgical intervention, mechanical ventilation support and presence of catheter were found to be risk factors for VRE.

The most important factor in nosocomial central nervous system infections is selection of the right antibiotic. Linezolid has been approved for use in treatment of community acquired and nosocomial pneumonia and skin and soft tissue infections (1). Treatment indications

include skin infections caused by methicillin resistant *S. aureus*, nosocomial pneumonia, VRE bacteriemia and community acquired pneumonia accompanied by PRP bacteriemia (3). Linezolid shows high efficiency against resistant pathogens in serious gram positive infections. Similar efficiency of parenteral and oral preparations provides easy dosing and management, early discharge and low cost. It is thought that resistance may develop in prolonged use (1, 9).

In a study conducted in 180 children in which the pharmacokinetics of the drug was investigated, it was found that clearance of the drug was dependent on the age. In the same study, penetration of the drug into the cerebrospinal fluid was shown to be very well. In newborns and children aged below 12 years, the clearance of the drug was found to be high and different from adults. In this study, a dose of 10 mg/kg three times a day was recommended for children aged below 12 years and a dose of 10 mg/kg twice a day was recommended for children aged above 12 years. Below 34 weeks, a dose of 10 mg/kg/dose twice a day was recommended for the first week and a dose of 10 mg/kg/dose three times a day was recommended after the first week (2). Linezolid treatment was initiated in our patient in accordance with the culture result. A dose of 10 mg/kg three times a day was given. In the follow-up of our patient, no cell was found on examination of the CSF and no microorganism was grown in culture.

In a study conducted with 950 children, the frequently reported side effects included nausea, vomiting, diarrhea, headache, increased liver enzymes and rash (6.5-10.8% of the patients). Reversible bone marrow suppression, serotonin syndrome, lactic acidosis and optic neuropathy were reported with lower frequency (11). The doses of phenylpropanolamine and pseudoephedrine should be reduced when used in combination with linezolid, since linezolid is a monoamine oxidase inhibitor (1, 3, 8). Bone marrow suppression (especially thrombocytopenia) has been reported in the second week of treatment in many studies (1, 12, 13). Thrombocytopenia has been observed with a lower rate in children (3). Bone marrow suppression depends on time and dose (1, 14, 15). The possibility of side effects and especially bone marrow suppression has been reported to increase as the time of usage prolongs (16). Gerson et al. (15) could not find any statistical difference in terms of the side effects of anemia and thrombocytopenia between vancomycin and linezolid. In our patient, pancytopenia developed in the second week. Linezolid was discontinued considering that pancytopenia

might be caused by the drug. The blood counts returned to normal in the follow-up. During the follow-up in the intensive care unit, supportive treatment was administered, because development of anemia and thrombocytopenia was not initially linked to the drug. The blood counts should be monitored during use of linezolid (17).

The recommended duration of treatment is 10-14 days for pneumonia and skin infections and 14-28 days for bacteriemia occurring as a result of VRE. Linezolid is supplied in the forms of tablet (600 mg) for oral administration, vials for intravenous administration (600 mg/100 mL and 600 mg/300 mL) and suspension for oral administration (100 mg/5 mL). It should be administered in 30-120 minutes when the intravenous route is to be used (3).

In conclusion, linezolid is an efficient drug in treatment of resistant gram positive bacterial infections in children. Its penetration into the cerebrospinal fluid is very well. Bone marrow suppression as a side effect of linezolid should be kept in mind. Hematological side effects improve after the drug is discontinued. The blood counts should be monitored during treatment with linezolid.

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