The Clinical Efficacy of Cephoperazone-Sulbactam and Amikacin Sulfate Combination in Pediatric Febrile Neutropenic Patients

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ABSTRACT

The efficacy of cephoperazone-sulbactam and amikacin sulfate combination in febrile neutropenic patients followed in pediatric hematology department was retrospectively evaluated in this study.

We retrospectively investigated 20 patients whom were treated with the cephoperazone-sulbactam and amikacin sulfate combination due to febrile neutropenia between June 2007 and February 2008 which were followed in pediatric hematology department of our hospital. Their diagnoses were acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Fanconi aplastic anemia (FAA) and acquired aplastic anemia (AA). All cultures of patients were taken and then 3 doses of 150 mg/kg/day cephoperazone-sulbactam intravenously and one dose of 15 mg/kg/day amikacine sulphate intravenously were administered. Patients were divided into 3 groups according to the clinical findings and C-reactive protein (CRP) levels in the 5th day of treatment.

The response to cephoperazone-sulbactam-amikacin treatment was good in 14 patients, moderate in 2 patients and poor in 4 patients. The average time for fever to decrease were 2.5 days in good response group and 5 days in moderate response group, while average time for fever to decrease was more than 5 days in poor response group. Statistically the 5th day absolute neutrophile value was not significantly higher between the groups. The efficacy ratio of the drug was 70%.

Although cephoperazone-sulbactam plus amikacin regimen was shown to be effective in febrile neutropenia treatment of pediatric hematology patients, large prospective clinical trials are necessary to determine the clinical affectivity and safety of that particular regimen in patients with ANC values of 500 /µl and lower.

Keywords: Febrile neutropenia, Cephoperazone-sulbactam
INTRODUCTION

Infections are the most frequent and important morbidity and mortality etiology of neutropenic fever in hematology patients.1,2 After the clear understanding of the importance of empirical broad spectrum antibiotic treatment in the prevention of infection related early mortality, the combination of an aminoglycoside agent with a ß-lactam antibiotic has become a standard approach.3

The most important mechanism of resistance against ß-lactam antibiotics is the inactivation of antibiotics by ß-lactamase producing bacteria. The primary (essential) solution against the ß-lactamase resistance is to add ß-lactamase inhibitors to the ß-lactam antibiotics.4 Cephoperazone-sulbactam is the ß-lactam and ß-lactamase inhibitor combination which is prepared in one-to-one ratios and can be used in febrile neutropenic attacks. Cephoperazone is one of the third generation cepham antibiotics. Sulbactam is a ß-lactamase inhibitor and widened cephoperazone’s effectiveness spectrum involving plasmid mediated ß-lactamase producing bacteria.5 Cephoperazone-sulbactam are effective against various gram (+) and gram (-) microorganisms like Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus epidermidis, Escherichia coli, Klebsiella, Proteus mirabilis, Neisseria meningitis, H. influenza, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Bacteroides fragilis, Acine-}

ÖZET

Pediatrik Febril Nötropeni Hastalarında Sefoperazon-sulbaktam ve Amikasin Sülfat Birlikteliginin Klinik Etkinliği

Bu çalışmada pediatrik hematoji bölümünde takip edilen febril nötropenik oğullarda sefoperazon-sulbaktam ve aminoglykosid kombinasyonunun etkinliği retrospektif olarak değerlendirilmiştir.

Haziran 2007- Şubat 2008 tarihleri arasında hastanemizin pediatrik hematoji bölümünde akut lenfoblastik lösemi (ALL), akut myeloid lösemi (AML), Fanconi aplastik anemi (FAA), aköz aplastik anemi (AA) tanıları ile febril nötropeniden neden olan sefoperazon-sulbaktam ve amikasin sülfat tedavisi alan 20 hastanın kayıtları retrospektif olarak incelemiştir. Hastaların kültürleri alınmadıktan sonra sefoperazon-sulbaktam 150 mg/kg/gün 3 dozda intravenöz ve amikasin sülfat 15 mg/kg/gün tek dozda intravenöz olarak başlanmıştır. Tedavinin 5. gününe de klinik bulgular ve C-reaktifi protein (CRP) degerlerine göre hastalar 3 grupta incelendi.


Sefoperazon-sulbaktam ve amikasin rejiminin pediatrik hematoji hastalarındaki febril nötropenide etkin gibi görünse de, ANS değeri 500/µl ve altında olan hastalarda klinik etkinliğinin değerlendirilebilmesi için prospektif olarak yapılacak daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Febril nötropeni, Sefoperazon-sulbaktam

MATERIAL AND METHODS

We retrospectively investigated 20 patients whom were treated with the cephoperazone-sulbactam (Sulperazon®, Pfizer, England) and amikacine sulfate (Amikozit®, Eczacıbaşı) combination due to febrile neutropenia between June 2007 and February 2008 which were followed up in pediatric hematology department of our hospital. Their diagnoses were acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), fanconi aplastic anemia (FAA), acquired aplastic anemia (AA). Patients, whose absolute neutrophile count were (ANC) below 1000/µl and axillary body temperatures were above 38°C, were physically examined and their hemogram, C-reaktifi protein (CRP, N:6-8 mg/L), liver and kidney function tests (urea, creatinine, aspartate aminotransf erase, alanin aminotransferase), urine culture and three consecutive blood cultures were withdrawn and then 3 doses of 150 mg/kg/day cephoperazone-sulbactam intravenously and one
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<th>ANC (/ml) 5th day</th>
<th>CRP (mg/L) Initial</th>
<th>CRP (mg/L) 5th day</th>
<th>Culture</th>
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dose of 15 mg/kg/day amikacin sulfate intravenously were administered. None of the cases had been administered antibiotics for the last one month. Patients were divided into 3 groups according to their clinical findings and CRP levels on the 5th day of treatment. The patients whose fever and CRP levels decreased within first 5 day were defined as good response group, while the patients whose clinical state were good but fever persisted, CRP levels increased and a glicopeptide and/or an antifungal agent had to be added to the treatment, was classified as the moderate response group. The patients whose treatment regimens have to be changed due to no response both clinically and laboratory results, was described as the poor response group.

Statistics: All data were analysed by using SPSS 16.0 packet program. To compare the initial and 5th day of CRP and ANC values, Wilcoxon test was used. To compare the initial and 5th day of CRP and ANC value among the groups, Bonferoni correction Kruskal-Wallis test was used. The initial and 5th day percentage changes of CRP and ANC were analysed with Kruskal-Wallis test. ANC and CRP levels were presented as Median levels (Min-Max). p< 0.05 was accepted as statistically significant.

RESULTS

In this study, 14 ALL, 1 AML, 4 FAA and 1 AA; totally 20 patients between the ages of 3-18 years were analysed. In Table 1, patients' demographic findings and laboratory results were shown. The absolute neutrophil count were between 500-1000/µl, below 500/µl, and below 100/µl in 8, 12 and 3 patients respectively. The average cephoperazone-sulbactam administration duration was 4-19 days (7±3.8 days). The median initial and 5th day ANC levels were found as 395/µl (min: 80-max: 980) and 450/µl (min: 50 - max: 3900) respectively (p= 0.34). The median levels of initial and 5th day of CRP were 40.5 mg/L (min: 4-max: 231) and 8 mg/L (min: 1 - max: 204) respectively (p= 0.02). No statistically significant difference was found among groups of initial and 5th day ANC and CRP values, by using Bonferoni correction Kruskal-Wallis test. The fifth day ANC median values were 750/µl ( min: 100 - max: 3900) and 95/µl (min: 50-

max: 400) in good response group and poor response group respectively. The higher median ANC level in good response group was not statistically significant. When compared the percentage changes of CRP and ANC count in groups, the CRP levels were different in good response group and moderate response group. While the CRP levels in good response group were decreasing 85% , the CRP levels in moderate group were increasing 19% (p= 0.032).

The response to cephoperazone-sulbactam-amikacin treatments were good, moderate, and poor in 14, 2, and 4 patients respectively. The average time for fever to decrease were 2.5 days in good response group and 5 days in moderate response group, whereas average time for fever to decrease was more than 5 days in poor response group. The Staphylococcus aureus colonised in 2 blood and 1 urine cultures. Cephoperazone-sulbactam was sensitive to one patient's S. aureus colonised blood culture and urine culture. In the other patient's S. aureus colonised blood culture cephoperazone-sulbactam was found to be resistant. In the remaining 3 poor response patients cephoperazone-sulbactam was stopped and carbapenem was started. There was no blood culture colonisation in these 3 patients. In one moderate response patient, since the pulmonary aspergillosis related findings were observed in lung computerized tomography, the antifungal therapy was combined to treatment. In the remaining 14 patient, the treatment responses were good and all were discharged after clinical and laboratory improvement. The efficacy ratio of drug was found to be 70%. As the untoward effect, allergic skin rash was observed only in 1 patient and the drug was accepted to be well tolerated by the patients.

DISCUSSION

It is difficult to detect the etiologic agent in pediatric febrile neutropenic patients. Beginning from the year of 1985, while the gram positive bacteria have been mostly isolated agent, the gram negative bacteria have also been expressing difficulties to antibiotic treatment processes by many different resistance mechanisms. Thus, the antibiotic choice for treatment should primarily control wide spectrum β-lactam producing enterobacteria and nonfermentated gr(+) bacteria. Since the cephalosporines do have wide spectrum effectivity, good pharmacoki-
netics and high tolerability, they are frequently used antibiotics in febrile neutropenia.\textsuperscript{7}

Cephoperazone is a third generation cephalosporin and expresses dramatic activity loss against high level \beta-lactamase producing gr(-) microorganisms. The combination of cephoperazone with a \beta-lactamase inhibitor sulbactam interrupts this resistance.\textsuperscript{7} The combination of cephoperazone-sulbactam with aminoglycosides has been reported to express similar efficacy as tienam group in \textit{P. aeruginosa} infections.\textsuperscript{7} The antianaerobic efficacy of cephoperazone-sulbactam has been found to be similar to carbapenem group in many studies and its treatment cost is highly low when compared to carbapenem group.\textsuperscript{11} In a study evaluating the effectiveness of cephoperazone-sulbactam in 264 children without febrile neutropenia, cephoperazone-sulbactam expressed effectiveness in 148 of 156 children with bacterial etiology. The efficacy ratio was found to be 94.9%. In the remaining 108 children with obscure etiologic agent, the efficacy ratio was found to be 91.7%. This ratio did not carry statistically significant difference when compared to first group. As a result, the sulperazone treatment was found to be effective in 247 out of 264 patients. The efficacy ratio was found to be 93.6%. In 166 out of 174 cases, whose etiologic agent was isolated, these bacterial series were eliminated and the elimination ratio was found to be 95.4%. The 25 out of 27 high \beta-lactamase activity carrying bacterial series were eliminated (92.6%). In 40 out of 44 patients, whose former antibiotic treatment was ineffective, the sulperazone treatment was observed to be effective (90.9%).\textsuperscript{12}

Studies related to effectiveness of cephoperazone-sulbactam in febrile neutropenic patients have been totally targeted to adult age group, so far. In Fukudo's hematologic patients with severe infectious complications, the effectiveness of empirical administration of cephoperazone-sulbactam and amikacin combination was studied. Totally 82 patients were evaluated and efficacy ratio was found to be 70.7%.\textsuperscript{13} Matsushima et al administered cephoperazone-sulbactam and amikacin combination to 57 hematologic patients with febrile neutropenia and reported the clinical efficacy as 67.6%.\textsuperscript{14}

In another study of Fukudo et al, it has been reported that the clinical efficacy ratio was 65.6% for cepha-

perazone-sulbactam and amikacin sulfate combination in hematologic patients with febrile neutropenia.\textsuperscript{15} Ozyilk\.an et al compared the cephoperazone-sulbactam and amikacin sulfate treatment effectiveness with imipenem-cilastatin treatment effectiveness in solid tumor patients and hematologically malignant patients with febrile neutropenia. They showed that these two combinations had the same degree of clinical effectiveness.\textsuperscript{16} We found that, in this study for the treatment of febrile neutropenia in children, the efficacy ratio of cephoperazone-sulbactam and amikacin sulfate combination was 70%. This result is in correlation with the literature. In our 2 patients with S.aureus colonisation in blood culture, the response to cephoperazone-sulbactam was poor. Similarly in literature the effect of cephoperazone-sulbactam on S.aureus was found to be 42.6%.\textsuperscript{17} Cephoperazone-sulbactam is a well tolerated agent and has infrequent and temporary untoward effects, like urticaria and diarrhea. In adult patient studies its effectiveness and safety has been proved.\textsuperscript{18} In our study only one case of urticaria was observed.

The drawbacks of our study were having less number of patients and only 2 blood culture colonizations. Since the infectious focus determination is somehow difficult in febrile neutropenia, CRP level decrement and clinical improvement were taken in to account for healing criteria. As a result, we found that, cephoperazone-sulbactam and amikacin combination regimen was clinically effective in the treatment of pediatric hematologic patient with febrile neutropenia. Even the Bonferoni correction Kruskal-Wallis test did not reveal statistically significant difference, the 5th day ANC level in good response group (median: 750, min: 100 - max: 3900) was higher when compared to bad response group (median: 95, min: 50 - max: 400). Thus we suggested to administer cephoperazone-sulbactam and amikacin sulfate combination in patients with ANC level 500/\mu l and higher. Since there have been no report about the administration of cephoperazone-sulbactam in pediatric febrile neutropenic patients in the literature so far, this retrospective study could be accepted as the first study, reporting the cephoperazone-sulbactam and amikacin administration effectiveness in pediatric age group febrile neutropenia cases.

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In order to evaluate the clinical effectivity and safety of cephoperazone-sulbactam administration in pediatric febrile neutropenic cases, prospective, larger studies, comparing antibiotic combinations, are needed.

REFERENCES

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