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

Pamir ISIK[1], Nese YARALI[1], Ali BAY[2], Rukiye SAC[1], Abdurrahman KARA[1], Bahattin TUNC[1]

[1] Dr. Sami Ulus Children's Hospital, Department of Pediatric Hematology, Ankara
[2] Gaziantep University Department of Pediatric Hematology, Gaziantep, TURKEY

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

ÖZET

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

Bu çalışmada pediatrik hematoloji bölümünde takip edilen febril nötropenik olgularda sefoperazon-sulbaktam ve aminoglikozid kombinasyonunun etkinliği retrospektif olarak değerlendirilmiştir.

Haziran 2007- Şubat 2008 tarihleri arasında hastanemizin pediatrik hematoloji bölümünde akut lenfoblastik lösemi (ALL), akut myeloid lösemi (AML), Fanconi aplastik anemi (FAA), akkiz aplastik anemi (AA) tanıları ile izlenen ve febril nötropeni nedeni ile sefoperazon-sulbaktam ve amikasin sülfat tedavisi alan 20 hastanın kayıtları retrospektif olarak incelendi. Hastaların kültürleri alındıktan sonra sefoperazon-sulbaktam 150 mg/kg/gün 3 dozda intravenöz ve amikasin sülfat 15 mg/kg/gün tek dozda intravenöz olarak başlanmıştı. Tedavinin 5. günündeki klinik bulguları ve C-reaktif protein (CRP) değerlerine göre hastalar 3 grupta incelendi.

Sefoperazon-sulbaktam ve amikasin tedavisine yanıt 14 hastada iyi, 2 hastada orta, 4 hastada ise kötü idi. Ortalama ateş düşme süresi iyi olan grupta 2.5 gün, orta olan grupta 5 gün olarak bulundu. Kötü olan grupta ise ortalama ateş düşme süresi 5 günden uzundu. Beşinci gün Absolü nötrofil sayısı (ANS) değeri gruplar arasında farklı bulunmadı. İlacın etkinlik oranı %70 bulundu.

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

Anahtar Kelimeler: Febril nötropeni, Sefoperazon-sulbaktam

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 standart approach.[3]

The most important mechanism of resistance against beta-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 cephem antibiotics. Sulbactam is a ß-lactamase inhibitor and widened cephoperazone's effectivity spectrum involving plasmid mediated ß-lactamase producing bacteria[5,6]. 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 auroginosa, Stenotrophomonas maltophilia, Bacteroides fragilis, Acinetobacter calcoacetucis, Enterobacter auregenes*.[7,8] Its antipseudomonal effectivity is high and it is the highest concentrated cephalosporin in the bile.[5]

In this study, the clinical efficacy of cephoperazone-sulbactam and amikacin sulfate combination in pediatric febrile neutropenic patients were analysed retrospectively.

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 departmant 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^{0}C, were physically examined and their hemogram, C-reaktif protein (CRP, N:6-8 mg/L), liver and kidney function tests (urea, creatinine, aspartate aminotransferase, 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

Table 1. Clinical data and laboratory findings of patients

Case number	Age (year)	Diagnosis	Infectious focus	ANC (/ml)		CRP (mg/L)		Culture	Duration of treatment (day)	Duration of fever (decrement [day])	Clinical efficacy
				Initial	5th day	Initial	5th day				
1	3	ALL	-	260	190	4	15	B.C: S.aureus	15	2	Moderate
2	7	ALL	pneumonia	100	260	26	31	NC	7	4	Good
3	12	FAA	-	80	100	41	204	B.C: S.aureus	4		Poor
4	5	ALL	URTI	230	3900	18	2.6	NC	7	3	Good
5	6	ALL	pneumonia, otitis media	650	750	77.4	1	NC	5	2	Good
6	7	ALL	-	200	940	40	10.7	NC	8	4	Good
7	7	ALL	pneumonia	960	500	43.7	7.3	NC	8	2	Good
8	4	ALL	mucositis	470	1000	7	3.8	NC	7	2	Good
9	6	ALL	mucositis, tonsillitis	800	100	102	69	NC	12	4	Good
10	7	ALL	pneumonia, herpes labialis	80	1100	32	1.5	NC	10	2	Good
11	18	AA	pneumonia	460	530	129	5	NC	11	3	Good
12	9	ALL	pneumonia, dental abcess	800	50	45.9	147	NC	19	8	Moderate
13	10	FAA	pneumonia, pleural effusion	570	400	231	68	NC	4	3	Poor
14	4	ALL	-	330	90	33	1	NC	5		Poor
15	8	ALL	-	150	3500	20	8	NC	6	2	Good
16	12	FAA	-	100	180	34	11.8	NC	10	2	Good
17	14	AML	-	80	50	20	8	NC	7		Poor
18	3	ALL	Diarrhea	920	3300	61	4.9	NC	6	2	Good
19	8	FAA	-	570	720	98.5	20	NC	5	1	Good
20	17	ALL	UTI	980	100	85.5	6	UC: S.aureus	7	2	Good

NF: No infectious focus, NC: No colonisation, FAA: Fanconi Aplastic Anemia, AA: Acquired Aplastic Anemia, URSI: Upper respiratory tract infection, UTI: Urinary tract infection, BC: Blood culture, UC: Urine culture

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 in to 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 leves (Min-Max). $p< 0.05$ was accepted as statistically significiant.

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 dischanged 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.[9] Thus, the antibiotic choice for treatment should primarily control wide spectrum ß-lactam producing enterobacteria and nonfermentated gr(-) bacteria.[10] Since the cephalosporines do have wide spectrum effectivity, good pharmacoki-

netics and high tolerability, they are frequently used antibiotics in febrile neutropenia.[5]

Cephoperazone is a third generation cephalosporin and expresses dramatic activity loss against high level ß-lactamase producing gr(-) microorganisms. The combination of cephoperazone with a ß-lactamase inhibitor sulbactam interrupts this resistance.[5] The combination of cephoperazone-sulbactam with aminoglycosides has been reported to express similar effectivity as tienam group in *P. aeruginosa* infections.[6] The antianaerobic effectivity 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.[11] In a study evaluating the effectivity of cephoperazone-sulbactam in 264 children without febrile neutropenia, cephoperazone-sulbactam expressed effectivity 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 ß-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%).[12]

Studies related to effectivity 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 effectivity of empirical administration of cephoperazone-sulbactame and amikacine combination was studied. Totally 82 patients were evaluated and efficacy ratio was found to be 70.7 %.[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%.[14]

In another study of Fkudo et al, it has been reported that the clinical efficacy ratio was 65.6% for cephoperazone-sulbactam and amikacin sulfate combination in hematologic patients with febrile neutropenia.[15] Ozyılkan et al. compared the cephoperazone-sulbactam and amikacine sulfate treatment effectivity with imipenem-cilastatin treatment effectivity in solid tumor patients and hematologically malignant patients with febrile neutropenia. They showed that these two combinations had the same degree of clinical effectivity.[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%.[17] Cephoperazone-sulbactam is a well tolerated agent and has infrequent and temporary untoward effects, like urticaria and diarrhea. In adult patient studies its effectivity and safety has been proved.[7,14] 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 colonisations. 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 hematology 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/µl 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 amikacine administration effectivity in pediatric age group febrile neutropenia cases.

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

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Correspondence

Dr. Ali BAY

Gaziantep Universitesi Tıp Fakültesi

Çocuk Hematoloji Kliniği

Gaziantep / TURKEY

Tel: (+90.342) 360 60 60

Fax: (+90.342) 360 39 28

e-mail: abay1968@yahoo.com