Original Article

Use of Cefoperazone/sulbactam in neonates

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Abstract Background: Neonates are at high risk for nosocomial infections due to multidrug-resistant pathogens. The use of β-lactamase inhibitors in combination with β-lactam antibiotics broadens the antimicrobial spectrum. Cefoperazone/sulbactam is used in children but there are limited data on its usage in neonates. The purpose of the present study was therefore to evaluate the use of cefoperazone/sulbactam in the treatment of neonatal infections caused by multidrug-resistant pathogens.

Methods: The records of neonates who were hospitalized and who received cefoperazone/sulbactam were reviewed.

Results: There were 90 infants who received cefoperazone/sulbactam. A pathogen could be isolated in 41 (45.6%) of the infants. In total, 17.1% of isolated pathogens were resistant to cefoperazone/sulbactam. Side-effects were seen in four of the infants. Two infants had cholestasis, one infant had neutropenia and one had superinfection with candida.

Conclusion: Cefoperazone/sulbactam can be used in the treatment of nosocomial infections caused by multidrug-resistant pathogens in neonates.

Key words cefoperazone/sulbactam, infection, multidrug-resistant microorganism, neonate, nosocomial infection.

In spite of the advances in the diagnosis and treatment of sepsis in recent years, sepsis is still an important cause of morbidity and mortality in neonatal intensive care units (NICUs). Furthermore, these are units that are at utmost risk for nosocomial infections caused by multidrug-resistant pathogens in hospitals.1–3 Cefoperazone has a broad spectrum activity against both Gram-positive and Gram-negative bacteria,4 which may make it a suitable choice for the treatment of sepsis acquired in NICU. The use of β-lactamase inhibitors in combination with β-lactam antibiotics is currently one of the most successful strategies to combat a specific resistance mechanism. Sulbactam, a β-lactamase inhibitor, has been shown to enhance the in vitro spectrum of cefoperazone.5 Cefoperazone/sulbactam is widely used in older children and adults, but there are limited data on its use in neonates. The aim of the present study was therefore to evaluate the use and the side-effects of cefoperazone/sulbactam in the treatment of nosocomial infections caused by multidrug-resistant pathogens.

Methods

The records of 90 neonates hospitalized at the NICU of Zeynep Kamil Maternity and Children’s Hospital between May 2007 and December 2007 and who received cefoperazone/sulbactam with the diagnosis of sepsis, pneumonia, urinary tract infection and osteomyelitis were reviewed. Thermal instability (fever, hypothermia), not doing well, not sucking well, irritability, hypotonia, lethargy, tachypnea, grunting, retractions, cyanosis, apnea, jaundice, hepatomegaly, vomiting, abdominal distension and seizures were accepted as signs of sepsis.1,3,6 Peripheral blood smear, complete blood count, C-reactive protein and blood culture were obtained from these babies. If a microorganism was isolated from the blood culture, culture-proven sepsis was diagnosed. The diagnosis of clinical sepsis was made in neonates having the aforementioned signs of sepsis supported by laboratory findings, but who had no bacterial growth in their cultures. Nosocomial sepsis was diagnosed in neonates who had the aforementioned clinical and laboratory findings after the third postnatal day or after an invasive procedure. Upon isolation of carbapenem-resistant microorganisms in the blood culture of neonates with nosocomial sepsis, which was meropenem plus vancomycin, was changed to cefoperazone/sulbactam and vancomycin (10 mg/kg per dose, dosing interval dependent on the gestational age of the patient). Before changing the protocol, the resistance pattern of the isolated pathogens against cefoperazone/sulbactam was evaluated, and they were found to be susceptible to this agent.

Cefoperazone/sulbactam was given to babies if (i) the baby’s clinical signs deteriorated under first-line therapy, which was ampicillin and gentamicin (n = 44); (ii) the baby had no sign of infection in the first postnatal day, but had an invasive procedure such as umbilical catheterization and deteriorated afterwards (n = 2); or (iii) the baby developed nosocomial infection during follow up in NICU (n = 44). Those patients who had clinical and laboratory findings of sepsis received 150 mg/kg cefoperazone/sulbactam per day in two divided doses together.

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Received 3 February 2011; revised 11 August 2011; accepted 17 August 2011.

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with vancomycin in order to obtain full coverage of both Gram-positive and Gram-negative microorganisms. If cultures indicated Gram-positive microorganisms, cefoperazone/sulbactam treatment was discontinued. Response to treatment was evaluated according to the changes observed in clinical and laboratory findings. The course of each baby was monitored for side-effects of cefoperazone/sulbactam such as nausea, vomiting, diarrhea, urticaria, drug-induced fever, hypersensitivity syndrome, reversible neutropenia, positive direct Coombs test, anemia, eosinophilia, thrombocytopenia, hypoprothrombinemia, elevated liver enzymes, jaundice and superinfection. Blood cultures were drawn into Bactec bottles and resistance to microorganisms was evaluated using the disk diffusion method (Becton, Dickinson & Company, Sparks, MD, USA; meropenem disks contained 10 μg meropenem; cefoperazone/sulbactam disks contained 30 μg sulbactam and 75 μg cefoperazone). Resistance was detected according to Clinical and Laboratory Standards Institute standards. Parental consent was obtained for all therapies.

**Statistical analysis**

Data are given as percentages for categorical variables, as mean ±SD for approximately normally distributed continuous variables, and as medians (min–max) for skewed continuous variables. The McNemar test was used to compare the resistance pattern of the antibiotics. When accompanied by a clinically significant difference, \( P < 0.1 \) was interpreted as reflecting changes that were not due to chance.

**Results**

There were 90 newborns (41 female, 49 male) with a mean gestational age of 30.3 ± 4.1 weeks (23–40 weeks) and a mean birthweight of 1392 ± 557 g (510–3250 g) who received cefoperazone/sulbactam started at a median of 6.5 postnatal days (range, 3–87 days) for a duration of 12.2 ± 6.6 days (1–30 days). The diagnoses were as follows: sepsis confirmed with clinical findings and/or sepsis work-up, \( n = 80 \); pneumonia, \( n = 8 \); urinary tract infection, \( n = 1 \); or osteomyelitis, \( n = 1 \). Forty-four (48.9%) of the babies received antibiotics prior to cefoperazone/sulbactam for a mean duration of 7.6 ± 7.9 days. A pathogen could be isolated in 41 (45.6%) of the infants. One of the pathogens was isolated from the urine culture and 40 of them were isolated from blood cultures. The isolated pathogens were staphylococcal species (\( n = 20 \); three of them were \( S. epidermidis \), 17 of them were \( S. aureus \), \( Klebsiella (n = 11) \); streptococcal species (\( n = 3 \); one of them was \( S. agalactiae \) whereas species were not defined in the remaining two); \( Escherichia coli (n = 3) \), enterobacteria (\( n = 3 \)) and \( Pseudomonas (n = 1) \). In total, 17.5% of isolated pathogens (7/40) were resistant to cefoperazone/sulbactam (four of the staphylococcal species, one of the streptococcal species, one \( K. pneumonia \), one enterobacteria; Table 1). All the other pathogens (82.5%) were sensitive to this antibiotic. Side-effects were seen in four (4.4%) of the infants. Two infants had cholestasis, one infant had neutropenia and one had superinfection with candida. The baby with candida superinfection died because of candida sepsis. The baby with \( Klebsiella \) sepsis that was resistant to cefoperazone/sulbactam died in the first day of therapy before we could obtain the results of the antibiogram. The baby with enterobacteria sepsis that was resistant to cefoperazone/sulbactam, however, was clinically better when the result of the antibiogram was obtained. The control blood culture was sterile and she was discharged after 14 days of therapy.

A total of 24 patients (26.6%) died. Seven (29.2%) of the patients died due to sepsis with Gram-positive microorganisms. Four (16.7%) of the patients died in the first 72 h of therapy so efficacy of treatment could not be evaluated in these patients. One patient (4.2%) died because of candida superinfection. The remaining 12 patients (50%) who were all premature died after clinical and laboratory improvement, due to reasons other than sepsis such as bronchopulmonary dysplasia, grade 3–4 intraventricular hemorrhage and metabolic disease.

Fifteen (36.6%) of 41 isolated pathogens (six \( Klebsiella \), eight staphylococcal species, one enterobacteria) were resistant to carbapenems, 38.9% of them (14/36 because only 36 of the isolated pathogens had aminoglycoside disk used in the antibiogram) were resistant to aminoglycosides (three \( K. pneumonia \), nine of the staphylococcal species, two of the streptococcal species) and 35.1% (13/37) of them were resistant to third-generation cephalosporins (three \( K. pneumonia \), six of the staphylococcal species, two of \( E. coli \), two of enterobacteria; Table 1). When we compared the resistance pattern of cefoperazone/sulbactam with carbapenems and aminoglycosides, more pathogens were resistant to carbapenems and aminoglycosides and the difference was statistically significant (\( P = 0.09 \) and 0.06 respectively). But although more organisms were resistant to third-generation cephalosporins when compared with cefoperazone/sulbactam, the difference was not statistically significant (\( P = 0.18 \)).

No resistance to vancomycin was observed in staphylococcal or streptococcal species.

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<tr>
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<th>Carbenemens</th>
<th>Aminoglycosides</th>
<th>Third-generation cephalosporins</th>
<th>Cefoperazone/ sulbactam</th>
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<td>52.9</td>
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<tr>
<td><strong>Streptococcus spp</strong></td>
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Discussion

Infections cause significant mortality and long-term morbidity in neonates, especially for very low-birthweight premature infants. The total number of neonates who develop nosocomial infection per admission varies from 6.24% to 33%, or, when reported as total infections per 1000 patient days, from 4.8 to 22.6. The variability in infection rates depends on the gestational age, environmental features and care practices. In the Stoll et al. study done at the academic centers of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, the vast majority (70%) of late-onset infections were caused by Gram-positive organisms (coagulase-negative Staphylococcus, S. aureus, Enterococcus spp., and group B Streptococcus). Gram-negative pathogens (E. coli, Klebsiella, Pseudomonas, Enterobacter, and Serratia) were responsible for 22% of the infections, finding similar to the present one.

Because cefoperazone can be used efficiently for the treatment of infections caused by both Gram-negative and positive microorganisms, it seems logical to use it for nosocomial infections observed in NICUs. Cefoperazone possesses acceptable β-lactamase stability, especially against Gram-positive and chromosome-mediated Gram-negative enzymes. Some more frequently isolated β-lactamases found in members of the Enterobacteriaceae family, however, can efficiently destroy cefoperazone. Also, the cephalosporinasises produced by the Bacteroides fragilis group hydrolyze this newer cephalosporin. Sulbactam combined with cefoperazone prevents its destruction by some clinically prevalent β-lactamases, especially those produced by E. coli and the anaerobes. The addition of sulbactam to cefoperazone inhibits hydrolytic activity of β-lactamases irreversibly and increases its in vitro spectrum of antimicrobial activity, principally among members of the Enterobacteriaceae and Bacteroides species. In one study it was shown that the presence of sulbactam converted 22 of 63 cefoperazone-resistant enteric bacilli to cefoperazone susceptible.

There has been no study done in neonates on cefoperazone/sulbactam so far. In a study in adults comparing the effects of cefoperazone/sulbactam plus vancomycin therapy with imipenem plus vancomycin therapy, the frequency of side-effects was significantly higher for imipenem plus vancomycin, due to therapy-associated nausea and vomiting. The overall frequency of superinfections was similar with both regimens, but Clostridium difficile colitis occurred significantly more often in patients receiving imipenem plus vancomycin, due to therapy-associated nausea and vomiting. In that study it was concluded that cefoperazone-sulbactam plus vancomycin was an effective alternative to imipenem plus vancomycin for initial therapy of fever in neutropenic patients.

In the present study we have shown that the resistance observed against cefoperazone/sulbactam was lower than the resistance observed against other antibiotics (carbapenems, aminoglycosides and third-generation cefalosporins) used in the NICU at Zeynep Kamil Maternity and Children’s Training and Research Hospital. Therefore cefoperazone/sulbactam can be proposed as an alternative agent to carbapenems in the treatment of nosocomial sepsis in NICUs.

The reported side-effects of cefoperazone/sulbactam were nausea, vomiting, diarrhea, urticaria, drug-induced fever, hypersensitivity syndrome-reversible neutropenia, positive direct Coombs test, anemia, eosinophilia, thrombocytopenia, hypoprothrombinemia, elevated liver enzymes, jaundice and superinfection. We could not, however, find any study done or case reported on the neonatal period concerning the side-effects of cefoperazone/sulbactam. In the present study, neutropenia, thrombocytopenia, hypoprothrombinemia, elevated liver enzymes and jaundice were thought to be side-effects of cefoperazone/sulbactam, if they were absent at the beginning of the therapy when the diagnosis of sepsis was made and developed after starting the therapy. These were observed only in four patients (4.4%). In one study the incidence of treatment-related adverse events was reported to be 6.5%, and 3.2% had to discontinue the therapy due to treatment-related adverse events. In another study adverse reactions were noted in two out of 39 patients (5%), and in one of them urticaria requiring discontinuation of the drug was seen. Both of these studies were done in adults. The number of side-effects observed in the present study was lower than that reported in these studies. Therefore, cefoperazone/sulbactam can be used in NICUs for the treatment of nosocomial infections caused by multidrug-resistant pathogens without any apparent adverse effects. The major limitation of the present study, however, is that it was retrospective, but because the drug is not approved for use in neonates, a randomized controlled study could not be performed. Also, blood concentrations of the drug were not obtained and this is not a pharmacokinetic study but a clinical one.

In the study by Pfaffer et al. the sensitivity of 823 bacteria isolated in 11 Colombian hospital laboratories to six broad spectrum β-lactam antimicrobial agents were determined in 1998, and these data were compared with results of a similar study conducted in 1997. It was shown that the sensitivity of isolated pathogens to imipenem decreased from 96.6% to 93.2%, to cefoperazone/sulbactam from 90.5% to 84.1%, to cefepime from 93.6% to 80.9% and to cefotaxime from 74.9% to 65.6%. In short, gradual increase in antibiotic resistance was observed.

In the study by Iregbue et al. Acinetobacter species that cause nosocomial infections showed multiple resistance to the range of antibiotics tested and all the isolates produced β-lactamase. One hundred percent of the isolates were susceptible to cefoperazone-sulbactam, 77.6% were susceptible to cefotaxime, 84.5% to ampicillin-sulbactam, 58.6% to cefazidime, 65.6% to ticarcillin-clavulanic acid and 70.7% to ciprofloxacin.

In the present study 82.5% of the isolated pathogens were sensitive to cefoperazone/sulbactam, 64.9% were sensitive to third-generation cephalosporins, 63.4% were sensitive to carbapenems and 61.1% were sensitive to aminoglycosides. Isolated pathogens showed more resistance to carbapenems and aminoglycosides when compared with cefoperazone/sulbactam and the difference was statistically significant. There was no statistically significant difference, however, between the resistance patterns of cefoperazone/sulbactam and third-generation cephalosporins and this might be due to the low number of cases.
Broad spectrum antibiotics are well shown to cause candida superinfection. In a NICU where meropenem was used, candida superinfection was seen in 20% of patients and Candida albicans colonization was reported in 10% of patients.15 Whereas, in the present study candida superinfection was detected in only one of the babies (1.1%). Furthermore, carbapenems were suggested to contribute to increased detection of metallo-β-lactamase (MBL)-producing Pseudomonas aeruginosa isolates, which are resistant to almost all broad spectrum β-lactams and carbapenems.16 We had only one P. aeruginosa among the isolated pathogens, however, and it was sensitive to all the antibiotics tested.

In order to study the pharmacokinetics and efficacy of a drug, it should be used alone on the subject. Starting two antibiotics for greater coverage of microorganisms (both for Gram-negative and Gram-positive), however, is a common practice in neonatal units and we had to start vancomycin and cefaperazone/sulbactam in the relevant patients. Vancomycin was discontinued usually on the third day of the regimen, once a Gram-negative organism was identified. Starting two antibiotics together may complicate the effect of the other, but otherwise, starting only one drug empirically is not ethically justified. In contrast, we believe that giving vancomycin for 3 days in a patient with Gram-negative sepsis will not have any significant effect on the efficacy of cefoperazone/sulbactam, which is used for much longer periods because, as it is well known, Gram-negative organisms are resistant to vancomycin. We conclude that cefoperazone/sulbactam can be an alternative in the treatment of nosocomial infections caused by multidrug-resistant pathogens in NICUs and, when compared with carbapenems reported in literature, they cause less candida superinfection. Before making any further recommendation, however, prospective randomized controlled studies need to be done to compare its safety and efficacy with other antibiotics. We also emphasize the need to update the antibiotic regimes used in NICUs according to the resistance patterns of the isolated pathogens.

References