

In vitro activity of cefoperazone-sulbactam combination against gram negative bacilli

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ABSTRACT

Cefoperazone is a β -lactam antimicrobial and Sulbactam is an irreversible β -lactamase inhibitor. The objective of this study was to know the susceptibility pattern of gram negative bacilli (GNB) towards cefoperazone-sulbactam. All GNB isolated from different clinical samples during the period of May, 2010 to Aug, 2010 were tested for susceptibility to cefoperazone-sulbactam, meropenem, ceftazidime, cefotaxime, ceftriaxone, chloramphenicol, cotrimoxazole, ampicillin, amikacin, nalidixic acid, ciprofloxacin, carbenicillin and piperacillin using standard Kirby-Bauer disc diffusion antimicrobial susceptibility testing method. The susceptibilities were recorded according to CLSI guidelines. A total of 406 GNB were isolated (urine: 66.7%, pus: 19.2%, and blood: 7.9%). *Escherichia coli* (54.4%) was most frequently isolated organisms followed by *Acinetobacter* species (17.7%), *Klebsiella pneumoniae* (9.1%) and *Pseudomonas* species (6.1%). Overall, 11.8% of isolates showed resistance to cefoperazone-sulbactam. Frequencies of isolates showing resistance to meropenem and amikacin were 14.7% and 26.25% respectively. Only 3.9% of *Escherichia coli* isolates showed resistance to cefoperazone-sulbactam. For other organisms, their lowest frequency ranging from 0-20%, exhibited resistance to meropenem. In *Pseudomonas* spp, *in-vitro* activity of amikacin was also better as only 11.1% isolates showed resistance to it. This study demonstrated the *in-vitro* synergistic effect of cefoperazone-sulbactam and meropenem having good activity against GNB compared to the activity of other commonly tested antimicrobials. Cefoperazone-sulbactam can be recommended for the clinical practice against GNB exhibiting resistant to other antimicrobials as it is cheaper alternative to meropenem. Our results also focused on the continuous surveillance of the trends and features of resistance of common antimicrobials.

Keywords: Cefoperazone-sulbactam, drug resistant, gram negative bacilli.

INTRODUCTION

Cefoperazone-sulbactam is an antimicrobial agent which is the combination form of cefoperazone and sulbactam. Cefoperazone is a β -lactam antimicrobial and sulbactam is an irreversible β -lactamase inhibitor.¹ Generally cefoperazone is relatively stable to staphylococcal β -lactamases and to most chromosomally mediated β -lactamases from gram-negative bacilli, although it can be hydrolysed by some plasmid mediated β -lactamases that may be produced by members of the family *Enterobacteriaceae*.^{2,3} The addition of sulbactam can expand the antibacterial spectrum of cefoperazone by binding irreversibly to the β -lactamases produced by the resistant organisms. Bacterial resistant to antimicrobial agents have become an important public health problem worldwide. Antimicrobial in common use like β -lactams, cephalosporins, aminoglycosides and quinolones are developing resistance against both gram positive and gram negative bacilli (GNB).² β -lactam and β -lactamase inhibitor combination may be considered as

potential alternative. With this background, we aimed to assess the *in-vitro* activity of cefoperazone-sulbactam against GNB isolates and compare it to other commonly used antimicrobials.

MATERIALS AND METHODS

During the period of four months (May, 2010 to Aug 2010), all GNB isolated from different clinical samples received and processed in Department of Microbiology, B. P. Koirala Institute of Health Sciences, Dharan, Nepal were tested against following antimicrobials of concentration in micro g: cefoperazone-sulbactam, meropenem (10), ceftazidime (30), cefotaxime (30), ceftriaxone (30), chloramphenicol (30), cotrimoxazole (1.25/23.75), ampicillin (30), amikacin (30), gentamycin (10), nalidixic acid (30), ciprofloxacin (5), carbenicillin (100) and piperacillin (100) using standard Kirby-Bauer disc diffusion antimicrobial susceptibility testing method. The test was done in Mueller Hinton Agar (Hi-media, USA), inoculated with bacterial suspension

Table-1: Percentage of isolates exhibiting resistance

Isolates	Ampicillin	Amikacin	Ceftazidime	Cefotaxime	Ciprofloxacin	Nalidixic acid	Cotrimoxazole	Cefoperazone-sulbactam	Meropenem	Carbenicillin	Piperacillin
<i>Escherichia coli</i>	88.0	23.0	100	60.0	62.3	67.2	63.1	3.9	7.3	-	-
<i>Acinetobacter</i> species	97.7	41.9	96.3	84.8	53.6	83.3	85.3	28.1	19.2	58.2	48.9
<i>Klebsiella pneumoniae</i>	100	28.5	94.1	84.2	57.1	50.0	73.3	28.1	20.0	-	-
<i>Pseudomonas aeruginosa</i>	100	11.1	93.1	87.5	46.2	100	77.7	25	33.7	42.3	52.0
<i>Proteus</i> species	93.4	33.3	50.0	66.6	40.0	80.0	75.0	0	0	-	-
<i>Citrobacter</i> species	100	0	100	96.2	25.0	100	50.0	11	0	-	-
Others	92.0	23.4	82.2	66.6	18.9	76.2	61.6	9.0	14.0	-	-

equivalent to 0.5 McFarland turbidity standard. The interpretation was done according to CLSI guidelines.⁴ The data obtained were recorded in Microsoft excel sheet and analyzed in terms of percentage.

RESULTS

A total of 406 GNB were isolated from different clinical samples. More than two third (66.7%) of isolates were from urine samples followed by pus (19.2%) and blood (7.9%) samples. Fig-1 shows the frequency distribution of isolated organisms. *Escherichia coli* (54.4%) was isolated in highest frequency followed by *Acinetobacter* species (17.7%), *Klebsiella pneumoniae* (9.1%) and *Pseudomonas* species (6.1%). The percentage resistances of antimicrobials in total isolates are shown in fig-2. Overall, 11.8% of isolates showed resistance to cefoperazone-sulbactam. Frequencies of isolates

showing resistance to meropenem, amikacin and chloramphenicol were 14.7%, 26.25% and 38.46% respectively. Isolates exhibited high degree of resistance to cephalosporins ranging from 73% to 96%.

Distribution of drug resistance percentage amongst the isolated GNB is shown in table-1. Cefoperazone-sulbactam was resistant against only 3.9% of *Escherichia coli* isolates, while other organisms, their frequency ranging from 0-20%, exhibited resistance to meropenem except *Pseudomonas* spp, whose 11.1% isolates showed resistance to amikacin.

DISCUSSIONS

The present study demonstrated that cefoperazone-sulbactam displayed better *in vitro* activity towards gram negative isolates in terms of susceptibility number. Out

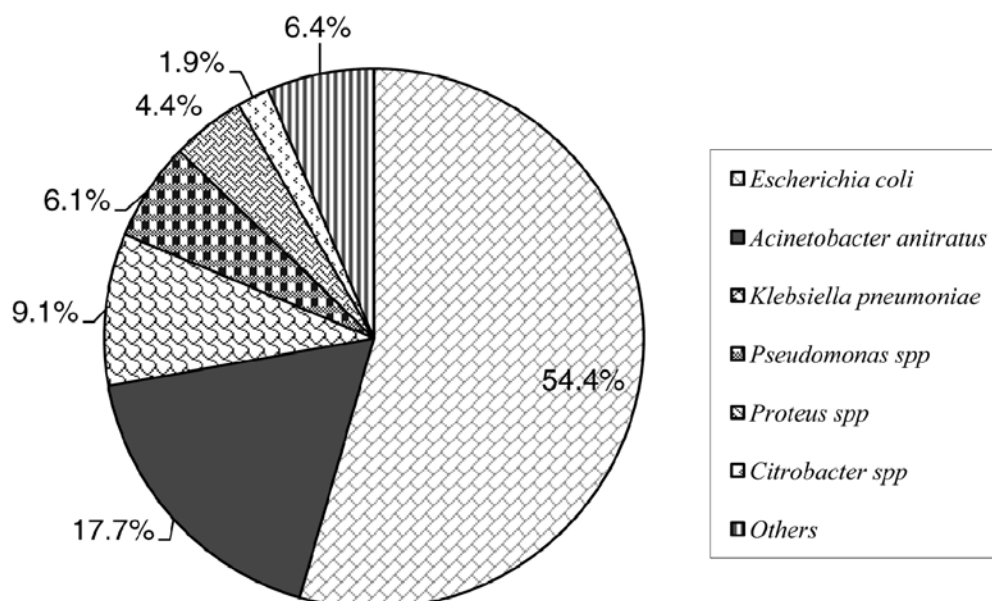


Fig. 1. Distribution of isolated organisms

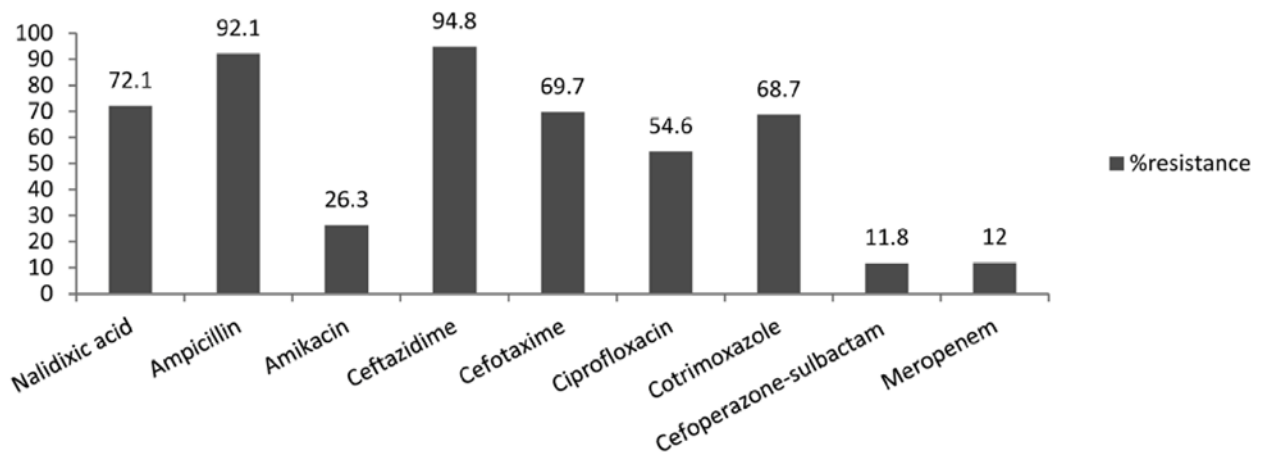


Fig.2. Resistance pattern of antimicrobials in total isolates

of total isolates, 11.8% showed resistance to this combination. Similar results of cefoperazone-sulbactam against GNBs has been shown by Gupta V and Kucutkates *et al.* in India.^{5,6} This must be due to the reason that sulbactam increases the activity of cefoperazone against GNB as stated by various studies.^{6,7}

In our study, next to cefoperazone-sulbactam, more number of isolates were sensitive to meropenem. The data for susceptibility of meropenem obtained from this study were similar to the data previously published for studies conducted in western countries.^{8,9} However, the current study reveals low susceptibility reports when compared with those studies. Meropenem, the drug of carbapenem group was the most effective antimicrobial as reported in many research.^{10,11}

Besides cefoperazone-sulbactam and meropenem, amikacin was the other antimicrobial for which one fourth of the total isolates showed resistance. Various studies have reported ranges of figures for the activity of amikacin in gram negative isolates.^{12,13} In present study, more number of isolates (>60%) were resistant to antimicrobials of cephalosporins and quinolones groups. This reflects the emerging antimicrobial resistance.

The susceptibility of *Escherichia coli* isolates to cefoperazone-sulbactam was 96.1% and 92.7% to meropenem. Except amikacin, other antimicrobials were found to be sensitive towards less than 50% of isolates. The result is different from a study of Legakis *et al.*, conducted a decade ago.¹⁴ However, it is concordant with the newer studies where there are reports of emerging drug resistant problems of many cephalosporins, aminoglycosides and quinolones group of antimicrobials. More isolates of *Klebsiella pneumoniae* were sensitive to meropenem than to cefoperazone-sulbactam. But, the susceptibility patterns to other antimicrobials were not satisfactory as two-third of

Klebsiella pneumoniae isolates were resistant to the used beta lactams and quinolones. In our study, most of the *Acinetobacter species* isolates were sensitive to meropenem as compared to cefoperazone-sulbactam. According to a report of a research by Turner *et al*, susceptibility to meropenem were very high (97.0-100%) in many countries except Italy (70.0%), Turkey (66.0%) and UK (77.0%).¹⁵ However 81.0% of isolated of *Acinetobacter* showed sensitivity to Meropenem, which is near to the report from the UK.¹⁴ These species are now known to be responsible for a wide range of nosocomial infections. Surveys have demonstrated high rates of resistance to aminoglycosides, cephalosporins, quinolones, penicillins, monobactams, and imipenem, often in excess of 50.0% among clinical isolates of *Acinetobacter*, which is consistent with our results.^{16,17}

The results were different for *Pseudomonas species*. The most effective antimicrobial for them was amikacin in terms of *in-vitro* activity. The poor activity of cefoperazone-sulbactam against the Pseudomonads may be because the beta-lactamases produced by these stains were not susceptible to sulbactam. Further studies are needed to explore exact mechanism of resistance. Similar type of result were shown in a Malaysian study.²

The present study showed that 100% isolates of *Proteus species* were sensitive to both cefoperazone-sulbactam and meropenem. Similarly, *Citrobacter species* also showed susceptibility towards cefoperazone-sulbactam and meropenem in terms of 90.0% and 100% respectively.

Comparing with the activity of other antimicrobials, cefoperazone-sulbactam was found to be better in terms of its *in vitro* activity as more than 65.0% of isolates exhibited resistance towards other groups of antimicrobials like ampicillin, amikacin, cephotaxime, ceftazidime, cotrimoxazole, and nalidixic acid. The finding of this study clearly showed that more than two

third of common isolates (*Escherichia coli*, *Acinetobacter species*, *Klebsiella pneumonia*) has expressed resistance to cephalosporins (ceftazidime and cefotaxime). But, majority of same isolates were sensitive to cefoperazone-sulbactam, a combination of cephalosporin and beta-lactamase. With this outcome, this antimicrobial can be recommended for the clinical practice against GNB whenever other antimicrobials are reported to be resistant. Our result clearly shows the necessity for continuous and detailed surveillance of the trends and features of resistance and its dissemination. The more the knowledge of the resistance pattern, the better would be the formulation of effective antibiotic policies.

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