IN VITRO ACTIVITY OF CEFOPERAZONE-SULBACTAM: SINGAPORE EXPERIENCE

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Abstract. *In vitro* activity of commonly used antimicrobial agents against consecutively isolated 521 strains of Gram negative bacilli causing serious infections in the National University Hospital, Singapore were tested in parallel with cefoperazone-sulbactam combination. With the combination complete resistance of 2% and intermediate resistance of 5% were noted among the 521 strains tested. Resistance to imipenem was low (5%) but resistance against other antimicrobial agents varied from 12% (amikacin) to 80% (ampicillin). *In vitro* data demonstrated a possible future role for cefoperazone-sulbactam in the treatment of sepsis caused by Gram negative bacilli in our hospital.

INTRODUCTION

The third generation cephalosporin Cefoperazone has been combined with sulbactam which is a penicillinic acid silfone to counteract the effects of beta lactamases and to expand the spectrum of antibacterial activity of the compound (Barry *et al,* 1988).

A series of *in vitro* studies have been conducted to study the susceptibility patterns of clinically important bacterial pathogens including Enterobacteriaceae, *Pseudomonas* spp and *Staphylococcus aureus* (MacLaughlin *et al,* 1994; Payne *et al,* 1994; Barry *et al,* 1990).

The increasing resistance of bacterial pathogens to many types of antimicrobial agents (Kumarasinghe *et al,* 1992) and the prevalence of extended spectrum beta lactamase producing strains (Inglis *et al,* 1995) in Singapore have been reported before. Hence there is a need to look for new antimicrobial agents that are likely to encompass the common pathogens causing serious infections locally.

The purpose of this project was to examine the activity of cefoperazone combined with sulbactam (C-S) against Gram negative bacteria causing serious infections in the National University Hospital, Singapore and to find out whether C-S provides any additional coverage of above organisms compared to 17 other antimicrobial agents.

MATERIALS AND METHODS

521 consecutive isolates of Gram negative bacilli; *Escherichia coli* (116), *Klebsiella* spp (172), *Acinetobacter* spp (88), *Enterobacter* spp (37), *Pseudomonas aeruginosa* (81) and *Pseudomonas* spp (27) isolated from blood cultures and from the specimens collected from patients in the Intensive Care Unit during the period October 1994 through to April 1995 were included in the study. The proportion of isolates from each species was representative of the prevalence of that species in clinical specimens.

The susceptibility testing and interpretation of results were based on the NCCL M2-A4 standards. *Escherichia coli* ATCC 25922, *Acinetobacter baumanii* ATCC 43498 and *Pseudomonas aeruginosa* ATCC 27853 were used as control strains.

In vitro susceptibility tests of C-S were performed in parallel with cephalosporins (cephalexin, cefuroxime, ceftriaxone, ceftazidime and cefoperazone), aminoglycosides (gentamicin, amikacin and netilmicin), betalactams (ampicillin, ampicillin/clavulanic acid, ampicillin/sulbactam, piperacillin, aztreonam and imipenem), quinolones (perfloxacin and ciprofloxacin) and cotrimoxazole.

RESULTS

The commonest Gram negative bacilli isolated from blood cultures and from patients in the Intensive Care Unit in the hospital were *Klebsiella* spp, *Acinetobacter* spp and *Pseudomonas* spp.

Complete resistance (R) to C-S was detected in 11 of 521 (2%) organisms and intermediate resist-

Table 1

Percentages of overall susceptibility pattern of 521 Gram negative bacilli.

Susceptibility	C-S	Cephalosporins					Beta-lactams						Aminoglycosides			Quinolones		Co-tri
		Cfp	*Cep*	*Cef*	*Cro*	*Cz*	*Am*	*Aug*	*Una*	*Pip*	*Atm*	*Imi*	*Gm*	*Ak*	*Net*	*Pf*	*Cip*	
R	2	13	56	41	30	27	80	19	22	33	32	5	25	12	16	29	14	30
I	5	22	3	8	23	1	4	19	8	4	10	0	4	16	4	0	3	1
S	93	65	41	51	47	72	16	62	70	63	58	95	71	82	80	71	83	69

R = resistant, I = intermediate resistant, S = sensitive, C-S = cefoperazone/sulbactam, Cfp = cefoperazone, Cep = cephalexin, Cef = cefuroxime, Cro = ceftriaxone, Cz = ceftazidime, Am = ampicillin, Aug = augmentin, Una = unasyn, Pip = piperacillin, Atm = aztreonam, Imi = imipenem, Gm = gentamicin, Ak = amikacin, Net = netilmicin, Pf = perfloxacin, cip = ciprofloxacin, Co-tri = co-trimoxazole

Table 2

Percentages of complete and intermediate resistance ( ) of common Gram negative bacilli to commonly used drugs.

Organism		C-S	Cephalosporins			Beta-lactams		Aminoglycosides		Quinolones	Co-tri
Number tested [ ]			*Cfp*	*Cro*	*Cz*	*Pip*	*Imi*	*Gm*	*Ak*	*Cip*	
Esch coli	[116]	0 (2)	2 (1)	2 (2)	2 (1)	19 (9)	0 (0)	3 (1)	0 (1)	4 (0)	31 (0)
Klebsiella spp	[172]	2 (3)	11 (30)	32 (24)	55 (1)	57 (0)	1 (0)	38 (7)	20 (8)	13 (5)	38 (4)
Enterobacter spp	[37]	0 (8)	22 (16)	27 (5)	30 (0)	35 (3)	0 (0)	3 (5)	8 (0)	11 (3)	24 (0)
Acinetobacter spp	[88]	0 (10)	32 (51)	31 (57)	23 (3)	26 (9)	7 (0)	27 (4)	8 (9)	26 (0)	15 (0)
P. aeruginosa	[81]	5 (12)	10 (11)	58 (32)	8 (1)	4 (0)	14 (0)	25 (1)	4 (5)	14 (1)	NT
Pseudomonas spp	[27]	15 (4)	15 (11)	41 (4)	15 (0)	15 (7)	26 (0)	67 (0)	63 (4)	18 (15)	26 (0)

Legend : Refer to Table 1

ance (I) in 5% of the 521 organisms tested, compared to the other antimicrobial agents are shown in Table 1.

The susceptibility pattern of common Gram negative bacilli causing serious infections in the hospital to antimicrobial agents commonly used against them is given in Table 2. *Escherichia coli* remained susceptible to all the drugs tested, except to ampicillin where 46% resistance was noted. The organisms that demonstrated less than 15% resistance to the antimicrobial agents tested are as follows: *Klebsiella* spp to C-S, cefoperazone, imipenem and ciprofloxacin, *Enterobacter* spp to gentamicin, amikacin, ciprofloxacin and imipenem, *Acinetobacter* spp to amikacin and imipenem. Against *Pseudomonas aeruginosa* only ceftriaxone (58%) and gentamicin (25%) showed a high incidence of resistance. *Pseudomonas* spp exhibited more than 15% resistance to all the drugs tested.

DISCUSSION

Gram negative bacilli causing serious infections in the hospital were selected for the study to find out what additional coverage is provided by C-S over the other antimicrobial agents. Gram positive bacteria were not included as no further benefit of the combination was noted in previous studies (Eliopoulos *et al,* 1989). However, Fasola *et al* reported that there may be a role of C-S in the therapy for MRSA infections due to the increased affinity of the combination to the PBP2a of the resistant *S. aureus* (Fasola *et al,* 1995). The study also did not cover the anaerobes but efficacy of C-S against anaerobes has already been demonstrated (Wexler *et al,* 1988).

Klebsiella spp was the commonest cause of Gram negative septicaemia in 1994 (Inglis *et al,* 1995). In the intensive care unit *Acinetobacter* spp, *Klebsiella* spp and *Pseudomonas* spp are the commonest pathogens (personal communication, Dr Ng). The highest incidences of antibiotic resistance in the hospital are seen among *Klebsiella* spp and *Acinetobacter* spp and not with *Pseudomonas aeruginosa* (Wexler *et al,* 1988).

The results of this study shows that the *in vitro* resistance of cefoperazone against the 521 organisms tested was 13%, compared to ceftriaxone 30% and ceftazidime 27% and that the antimicrobial properties of cefoperazone are significantly improved by combining with sulbactam (Table 1). As described in other institutions activity against less susceptible organisms also improved with the combination (McLaughlin *et al,* 1994).

Pseudomonas aeruginosa showed the lowest incidence of resistance to piperacillin (4%) and to amikacin (4%) compared to other anti-*Pseudomonas* drugs. Although there was an improvement in the anti-*Pseudomonas aeruginosa* activity from 8% with cefoperazone to 4% with the combination C-S, similar to the observation made in some centers the incidence of resistant *Pseudomonas* spp did not get better with C-S (Knapp *et al,* 1990).

C-S remains the most active agent overall against 521 strains of Gram negative bacilli tested; a factor that suggests the potential future role in empirical therapy.

In summary, the results of the study demonstrates the broad spectrum *in vitro* antibacterial properties of C-S against organisms causing serious Gram negative sepsis in the hospital. The findings also highlight the need for clinical trials to determine the place of C-S in the management of severe sepsis.

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