Research Paper

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Comparative Evaluation of the *in Vitro* Activity of Three Combinations of Beta-Lactams with Beta-Lactamase Inhibitors: Amoxicillin/Clavulanic Acid, Piperacillin/Tazobactam and Ticarcillin/ Clavulanic Acid.

Medical Science

KEYWORDS : GNB, β-lactam antibiotics, BL-BLI(β-lactam -β-lactamase inhibitors),ESBL

Dr. Payal J. Mankodi	M.D(MICROBIOLOGY), Microbiologist Class-I, P.K General hospital, Rajkot.
Dr. Binita J. Aring	M.D(MICROBIOLOGY), Associate Professor, Department of Microbiology, M.P Shah Medical College, Jamnagar.
Dr. HimanshuKhatri	M.D(MICROBIOLOGY), Associate Professor, Department of Microbiology, , P.D.U Medical College, Rajkot.

ABSTRACT

Background: In the modern era of increased use of β-lactam antibiotics, resistances to bacteria become a major problem. To overcome this specific resistance mechanism, β-lactam antibiotics are often given with β-lactamase inhibitors like clavulanicacid, salbactam or tazobactam. Aims and Objectives: To comparein vitro activity of beta-lactam/beta-lactamase inhibitor combinations (Amoxycillin / Clavulanic acid, Ticarcillin / Clavulanic acid and piperacillin/Tazobactam) among gram negative isolates. Material and method: Gram negative bacilli found resistant to penicillin drugs or one or more cephalosporin drugs, were tested for three β-lactam / β-lactamase inhibitor combinations. Antibiotic susceptibility testing was carried out by disc diffusion method as per CLSI guidelines. Result: Total 7800 samples were received, from these 3816 were positive and 3984 were negative for isolates. From positive culture, 1000 were GPC and 2819 were GNB. Susceptibility of the enterobacteriaceae to Augmentin, Piperacillin-Tazobactam and Ticarcillin-Clavulanicacid were 34.82%, 71.64% & 39.8%. Conclusion: Overall piperacillin/ tazobactam was observed to be the best combination agent.

Introduction:

Antimicrobial resistance among these bacilli is increasing on a world wide basis,especially resistance against β lactam antibiotics[1]. The production of b-lactamase remains the major mechanism of resistance in Gram-negative bacilli to b-lactam antibiotics. In recent years, extended-spectrum b-lactamases (ESBLs) have become progressively widespread due to extensive use of third generation cephalosporins in hospital settings. ESBLs have the ability to hydrolyse b-lactam antibiotics containing an oxyimino group, namely cefotaxime, ceftazidime, ceftriaxone, cefpodoxime and aztreonam, but they are usually inactivated by b-lactamase inhibitors[2]. Beta-lactamase mediated resistance may be overcome by combining beta-lactam antibiotics with beta-lactamase inhibitors which bind irreversibly to the beta-lactamases and render them inactive thus sparing the beta-lactam antibiotic. Currently, three beta-lactamase inhibitors (tazobactam, sulbactam and clavulanic acid) are in clinical use, and in combination with beta-lactam antibiotics, represent a successful strategy to combat a specific resistance mechanism[3]. Experts in Indian subcontinent have advocated use of BL-BLI combinations in moderately severe infections due to ESBL producers[4]. Knowledge about the susceptibility profile of bacteria to different combination agents available is essential to guide appropriate treatment of severe infections in hospitalized patients.The present study compare the in vitro activity of three commercially available beta-lactam/beta-lactamase inhibitor combinations (Amoxycillin/Clavulanic acid, Ticarcillin/ Clavulanic acid and piperacillin/Tazobactam) in comparision to Cephalosporins among gram negative isolates in a tertiary care hospital of Jamnagar, Gujarat.

MATERIAL AND METHOD:

The retrospective study was conducted in the Microbiology Laboratory of the G. G. Hospital, Over a one year period from January 2010 to November 2010. Gram negative isolates from various specimens like urine, blood, respiratory secretion, wound swabs and body fluids were analyzed. The culture media used in our study were blood agar), chocolate agar, MacConkey agar. By standard protocol, all isolates were evaluated for their identification and antibiotic susceptibility. Antibiotic susceptibility testing was carried out by Kirby bauer disc diffusion method on mullerhinton agar plates as per NCCLS guidelines. Those found resistant to penicillin drugs or one or more cephalosporin drugs, were tested for three β-lactam/β-lactamase inhibitor combinations (Amoxycillin + clavulanic acid, Piperacillin + tazobactum and Ticarcillin + clavulanic acid). Interpretation is done as sensitive, intermediate and resistance as per zone of diameter of inhibition measured.

Result:

A total of 7800 samples were received in bacteriology laboratory from medical ward, surgical ward, gynec ward, ICCU, TB and chest and newborn ward. From these, 1579 were urine, 3265 pus, 2139 blood and 817 were other includes sputum, ET secretion, BAL and other body fluids. From these 3816 samples were positive and 3984 samples were negative for isolates.

From these 3816 positive culture, 1000 were GPC and 2819 were GNB. 672(50.52%) *E.Coli*, 532(40%), *Klebsiella* and 126(9.47%) *proteus* species 722 were *pseudomonas* and 21 *acinetobacter*identified. From these, 92 *E.coli*, 91 *Klebsiella*, 18 *proteus* species were resistant to all cephalosporins. They were tested for three BL-BLI combination. All 722 pseudomonas and 21 acinetobacter were tested for AU, PT and TR.

As shown in table-I, percentage of susceptibility of the *enterobacteriaceae*to Augmentin (AU), Piperacillin-Tazobactam (PT) and Ticarcillin-Clavulanicacid (TR) were 34.82%, 71.64% & 39.8% respectively. *Pseudomonas* isolates show susceptibility of 6.98% to AU, 84.90% to PT and 43.62% to TR while *Acinetobacter* were 14.28%, 88.71% and 47.61% susceptible to AU, PT and TR respectively.

Discussion:

The production of β lactamase remains the major mechanism of resistance in Gram negative bacilli to β lactam antibiotics. In recent years, extended spectrum β lactamases (ESBLs) have become progressively widespread due to extensive use of third generation cephalosporin in optimal settings. Thus, β lactamase inhibitors should be investigated as a therapeutic option by combining them with the respective cephalosporins/ monobactam[5]. Clavulanate, sulbactam, and tazobactam are beta-lactamase inhibitors that have little intrinsic antibacterial activity but inhibit the activity of a number of plasmid-mediated beta-lactamases [6]. They generally do not inhibit chromosomally mediated beta-lactamases [7]. Combination of these agents with ampicillin, amoxicillin, ticarcillin, or piperacillin results in antibiotics with an enhanced spectrum of activity against many, but not all, organisms containing plasmid-mediated beta-lactamases.[6,7]

In our study, P/T was showing best activity against all group of organisms followed by T/R. susceptibility to Amoxycillin/clavulanic acid was least for all group of organisms. Amoxicillin-clavulanic acid and piperacillin/tazo-bactam are suitable alternatives to carbapenems for treating patients with bloodstream infections due to ESBL producing *E. coli*, if sensitive in vitro.[8]

Ticarcillin-clavulanate and piperacillin-tazobactam expand the spectrum of the respective penicillins to include beta-lactamase producing *S. aureus, H. influenzae, Neisseria gonorrhoeae*, some *Enterobacteriaceae*, and anaerobes (including *B. fragilis*) [9]. In a controlled clinical trial, P/T and T/C were found to be almost equally effective for the treatment of infections caused by beta-lactamase producing strains. The overall efficacy rates were 90.5 per cent for the P/T group and 88.5 per cent for the T/C group, respectively[10]. Another study from central India on *E. coli, Klebsiella* and nonlactose fermenters reported a lower resistance to P/T (14.7-20.5%) as compared to C/S (27-34.2%) [11].

CONCLUSION :

In conclusion, the results of our in vitro study indicated that of the currently available β-lactam/β- lactamase inhibitor combinations, piperacillin/ tazobactam has the best activity against nosocomial Gram-negative pathogens followed by by T/R.

Table: I

Organisms	BL-BLI combination					
	AU		PT		TR	
Enterobacteriacae (201)	70	34.82%	144	71.64%	80	39.8%
Pseudomonas (722)	50	6.92%	613	84.90%	315	43.62%
Acinetobacter (21)	3	14.28%	18	88.71%	10	47.61%

REFERENCE

[1] Hawser SP, Bouchilllon SK, Hoban DJ, Badal RE, Hsueh Po Ren,Paterson DL. Emergence of High Levels of extended spectrum spectrumβ lactamase producing gram negative bacilli in the Asia pacific regions:Data from the study for Monitoring Antimicrobial Resistance Trends(SMART) Program. Antimicrob Agents and Chemother 2009, 53, 3280-3284. | [2] Bradford PA. Extended-spectrum b-lactamases in the 21st century: characterization, epidemiology and detection of this resistance threat. ClinMicrobiol Rev 2001; 14: 933–51. | [3] Miller LA, Ratnam K, Payne DJ. ß-lactamase-inhibitor combinations in the 21st century: current agents and new developments. CurrOpinPharmacol2001; 1 : 451-8. | [4] Deshpande P, Rodrigues C, Shetty A, Kapadia F, Hegde A, Soman R. New Delhi Metallo-ß-lactamase (NDM-1) in Enterobacteriaceae: Treatment options with Carbapenems Compromised. J Assoc Physicians India 2010; 58:147-9. | [5] Bhattacharjee A, Sen MR, Prakash P, Anupurba S. Role of β lactamase inhibitors in enterobacterial isolates producing extended spectrum β lactamases. J AntimicrobChemother 2008, 61, 309-314. | [6]Bush LM, Johnson CC. Ureidopenicillins and beta-lactam/beta-lactamase inhibitor combinations. Infect Dis Clin North Am 2000; 14:409. | [7] Sensakovic JW, Smith LG. Beta-lactamase inhibitor combinations. Med Clin North Am 1995; 79:695. | [8]Rodríguez-Baño J, Navarro MD, Retamar P, et al. β-Lactam/β- Lactam inhibitor combinations for the treatment of bactere- mia due to extended-spectrum β-lactamase-producing Esch- erichia coli: A post hoc analysis of prospective cohorts. Clin Infect Dis 2012: 54:167-174. | [9] Sanders WE Jr, Sanders CC. Piperacillin/tazobactam: a critical review of the evolving clinical literature. Clin Infect Dis 1996; 22:107. | [10] Hou F, Li J, Gao L, Chen Y. A randomized controlled clinical trial on piperacillin/tazobactam versus ticarcillin/ clavulanic acid for the treatment of bacterial infections. Chin Med J (Engl) 1998; 111 : 1039-43. | [11] Chitnis SV, Chitnis V, Sharma N, Chitnis DS. Current status of drug resistance among Gram-negative bacilli isolated from admitted cases in a tertiary care centre. J Assoc Physicians India 2003; 51 : 28-32. |