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RESEARCH ARTICLE

IN VITRO ACTIVITY OF CEFTAZIDIME-AVIBACTAM AGAINST CARBAPENEM RESISTANT GRAM NEGATIVE ISOLATES

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Abstract

Introduction: Ceftazidime-Avibactam (CZA) is a β-lactam-β-lactamase inhibitor combination (BL/BLI) that has been given approval by the Food and Drug administration (FDA) for the treatment of different illnesses. However, resistance to Ceftazidime-Avibactam is developing in Carbapenem-resistant Enterobacteriaceae (CRE), Carbapenem-resistant Pseudomonas aeruginosa, and other Gram-negative bacteria, necessitating study of CZA's in vitro activity against these pathogens.

Objective: To assess CZA's in vitro activity against CRE, carbapenem-resistant Pseudomonas aeruginosa, and other Gram-negative bacteria.

Results: Of the 62 Carbapenem-resistant isolates obtained from various samples, Klebsiella pneumoniae accounted for 22 (35.48%), followed by Escherichia coli 21(33.87%), Pseudomonas aeruginosa 10(16.13%), Acinetobacter baumanii 7(11.30%), Citrobacter freundii 1(1.61%), and Proteus mirabilis 1 (1.61%) and the susceptibility rates against CZA showed Klebsiella pneumoniae-45.45% followed by E.coli-27.27%, Pseudomonas aeruginosa-18.18%, Citrobacter freundii-9.09% and the strains of A.baumanii and P.mirabilis were totally resistant to CZA.

Conclusion: Even though CZA is regarded as an alternative form of treatment for infections caused by Carbapenem-resistant organisms (CRO), the higher resistance pattern at our center necessitates additional research involving numerous isolates and at different centers, where the results can be compared in order to ascertain the true prevalence of CZA resistance.

Introduction:-

The discovery of cephalosporin class of antibiotics was reported in 1945 where professor Brotzu from Italy has been credited for the discovery of broad spectrum inhibitory effects of these antibiotic class who subsequently isolated the

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mold called Cephalosporin acremonium (Acremonium crysogenum) and demonstrated the antimicrobial activity of culture filtrates against both Gram positive and Gram negative bacteria.

After the initial discovery investigators such as Florey and Abraham systematically studied the physical, chemical and structural characteristics of cephalosporins where 3 substances were subsequently identified as Cephalosporin P, N, C in which only Cephalosporin-C demonstrated the activity against Gram positive and Gram negative organisms and also were stable in the presence of acid and penicillinases.[1,2,3]

After the usage of Cephalothin which was a 1st generation Cephalosporin in 1964, at present more than 20 Cephalosporin antibiotics are available for clinical use which includes 5 generations of Cephalosporin and also MRSA active Cephalosporin like Ceftaroline and Ceftobiprole.

Although Cephalosporins are active against a variety of aerobic and anaerobic bacteria it has been described that the 3rd and 4th generation Cephalosporins are active 10-100 times more against Gram negative organisms including Enterobacteriaceae & also Pseudomonas aeruginosa.

However, there is emergence of resistance in these organisms by any of the following mechanisms.
1. Production of hydrolyzing β-lactamase enzyme
2. Reduced penetration of drug
3. Enhanced drug efflux
4. Alteration of Penicillin binding proteins (PBP)

Where in this production of β-lactamase enzyme which destroys the β-lactam ring in the antibiotic is the predominant resistant mechanism exhibited by most of the Gram negative isolates.[4]

Ceftazidime (CAZ) which is a 3rd generation Cephalosporin was used for a variety of Gram negative infections including Pseudomonas aeruginosa, but due to emergence of resistance due to production of β-lactamase enzyme, now it is used in combination with Avibactam which is a non β-lactam-β-lactamase inhibitor which targets the active site of serine β-lactamases which is superior to Tazobactam as it binds reversibly to β-lactamases which is an unique feature of this which will enable it for cyclization in order to inactivate another β-lactamases due to which it can inhibit ESBL, AmpC β-lactamases (expressed in Enterobacteriaceae and Pseudomonas aeruginosa) and class A carbapenemases of Klebsiella pneumoniae carbapenemases(KPC).[5]

Ceftazidime-Avibactam (CZA) is a β-lactam-β-lactamase inhibitor combination (BL/BLI) approved by Food and Drug Administration (FDA) for the treatment of various infections including intra-abdominal infections, complicated urinary tract infections (including pyelonephritis), hospital acquired infections (including ventilator associated pneumonia).[6]

However, there is emergence of resistance to Ceftazidime-Avibactam reported especially among Carbapenem resistant Enterobacteriaceae (CRE) and Carbapenem resistant Pseudomonas aeruginosa (CRPA) and other Gram negative isolates also.[7]

We undertook this study to evaluate the in-vitro activity of Ceftazidime-Avibactam combination against Carbapenem resistant Enterobacteriaceae (CPE), Carbapenem resistant Pseudomonas aeruginosa and other Gram negative isolates.

Materials & Methods:-

This is a Cross sectional observational study carried out for a period of 9 months in which the Gram negative isolates from various samples like urine, pus/wound swabs, sputum and endotracheal tube secretions were collected and processed in microbiology laboratory after Institutional Ethics Committee approval and identified up to species level by using conventional and biochemical tests. All the isolates were subjected to antibiotic susceptibility testing by using Kirby-Bauer disc diffusion method on Mueller Hinton agar plates and interpreted as Susceptible (S), Intermediate (I), and Resistant (R) as per CLSI guidelines (2020).[8]

In these, a total of 62 isolates which showed resistance to Imepenem (10µg) & Meropenem (10µg) (Hi-Media labs, Mumbai), were further tested against Ceftazidime (30µg), Ceftazidime-Tazobactam (CAT) (30µg+10µg), Ceftazidime-Avibactam (30µg+20µg) (Hi-Media labs, Mumbai) by Kirby-Bauer disc diffusion method and E-test using E-strips (Hi-Media labs, Mumbai) with MICs ranging from 0.16µg to 256µg and interpretation was done based on manufacturer recommendations.

Results:-

A total of 62 (100%) Carbapenem resistant isolates were collected from various samples **(Table:1)**

Samples	Isolates (%)
Urine	38 (61.29)
Pus/wound swab	17 (27.42)
Sputum	4 (6.45)
ET secretions	3 (4.84)
Total	62 (100)

Of the 62 isolates 45 (72.58%) were Enterobacteriaceae members and 17 (27.42%) were non-fermenters **(Table:2)**

Organism	Number of isolates (%)
Klebsiella pneumoniae	22 (35.48)
Escherichia coli	21 (33.87)
Pseudomonas aeruginosa	10 (16.13)
Acinetobacter baumannii	7 (11.30)
Citrobacter freundii	1 (1.61)
Proteus mirabilis	1 (1.61)
Total	62 (100)

The susceptibility pattern of these isolates against CAZ, CAT, CZA **(Table:3)**

Organism	**No. of isolates**	**CAZ**		**CAT**		**CZA**	
		S(%)	**R(%)**	**S(%)**	**R(%)**	**S(%)**	**R(%)**
Klebsiella pneumoniae	22	0 (0)	22 (36.06)	0 (0)	22 (36.06)	5 (45.45)	17 (33.33)
Escherichia coli	21	0 (0)	21 (34.42)	0 (0)	21 (34.42)	3 (27.27)	18 (35.29)
Pseudomonas aeruginosa	10	1 (100)	9 (14.75)	1 (100)	9 (14.75)	2 (18.18)	8 (15.68)
Acinetobacter baumannii	7	0 (0)	7 (11.47)	0 (0)	7 (11.47)	0 (0)	7 (13.72)
Proteus mirabilis	1	0 (0)	1 (1.63)	0 (0)	1 (1.63)	0 (0)	1 (2)
Citrobacter freundii	1	0 (0)	1 (1.63)	0 (0)	1 (1.63)	1 (9.09)	0 (0)
Total	62	1 (1.61)	61 (98.39)	1 (1.61)	61 (98.39)	11 (17.74)	51 (82.36)

Discussion:-

Emergence of resistance to Carbapenems in various Gram negative isolates of Enterobacteriaceae and non-fermenters has been documented across the globe where in India Carbapenem resistance mediated by $^{bla}_{NDM}$ and $^{bla}_{OXA}$-48-like is of major concern.[9]

Ceftazidime-Avibactam (CZA) is a β-lactam/β-lactamase inhibitor(BL/BLI) combination approved by FDA in 2015 for treatment of various infections with Carbapenem resistant organisms (CRO).

However, there are reports of emergence of resistance to Ceftazidime as well as Ceftazidime-Avibactam globally among Carbapenem resistant Enterobacteriaceae and Carbapenem resistant Pseudomonas aeruginosa and other Gram negatives.[10]

In the present study a total of 62 Carbapenem resistant Gram negative isolates were tested for in vitro susceptibility against CAZ, CAT & CZA.

The sensitivity to CZA was observed to be higher in Klebsiella pneumoniae (45.45%) followed by Escherichia coli (27.27%) and Pseudomonas aeruginosa (18.18%). Resistance to Ceftazidime-Avibactam was predominantly observed in Escherichia coli (35.29%) followed by Klebsiella pneumoniae (33.33%), Pseudomonas aeruginosa (15.68%), Acinetobacter baumannii (13.72%) which correlates with observations of Carmeli et al.,[11] Vasquez et al.,[12] Zeleke Ayenew et al. [13] 17.74% of Gram negative isolates tested were sensitive to CZA compared to 1.61% susceptibility to CAZ and CAT. Though the sensitivity of CZA is low, the in vitro activity is much higher compared to CAZ and CAT against the carbapenem resistant Enterobacteriaceae and Gram negative non-fermenters.

Conclusion:-

Although CZA is considered as alternative for treatment of infections with CRO, the higher resistance pattern at our center needs further studies with larger number of isolates and at various centers to compare the results which can be used to determine the true incidence of resistance to CZA and its clinical application.

Limitations:-

Compared to various studies and review of literature, the lower sensitivity to CZA in Carbapenem resistant Gram negative isolates at our center, was may be due to the less number of isolates considered & non availability of molecular characterization of Carbapenem resistance.

Conflict of interest:-

The authors declare no conflict of intrest regarding the publication of this paper.

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