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RESEARCH ARTICLE

COMPARATIVE IN VITRO ACTIVITY OF TOBRACEF AGAINST GRAM NEGATIVE CLINICAL ISOLATES

Manu Chaudhary and Anurag Payasi*

Venus Medicine Research Centre, Hill Top Industrial Estate, Bhatoli Kalan, Baddi, H.P. - 173205 India

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ABSTRACT

The present study was undertaken to evaluate the prevalence of predominant bacterial mpathogens among clinical samples and their drug sensitivity and resistance profiles. The study was done from January 2014 to December, 2014 in the Department of Microbiology, Venus Medicine Research Centre, Baddi, Himachal Pradesh. A total of 1385 clinical samples were collected and subjected for identification of pathogens. The antibiotic sensitivity testing was performed by cup plate method.

Out of 1385 samples, 679 samples showed the growth of bacteria. Further identification revealed the presence of five different Gram-negative organisms with high prevalence of *Pseudomonas aeruginosa* (45.2%), followed by *Aceinetobacter baumannii* (33.6%), *E. coli* (15.0%), *Klebsiella species* (5.9%) and *Proteus species* (0.3%). The susceptibility of Tobracef against *P. aeruginosa*, *A. baumannii*, *E. coli*, *Klebsiella spp.* and *Proteus spp.* was 88.9, 89.0, 89.2, 77.5 and 100 %, respectively which was high compared to ceftazidime, tobramycin, amikacin, gentamicin and ceftazidime plus amikacin. A high resistance to ceftazidime (49.8 to 57.8%), tobramycin (25.5 to 75%), amikacin (27.5 to 100%), gentamicin (50 to 100%) and ceftazidime plus amikacin (15.7 to 50 5) was observed against all the isolates. The results of the present study advocates the superiority of Tobracef over other tested antibiotics for the treatement of infections caused by Gram negative bacteria.

INTRODUCTION

Aminoglycosides are broad-spectrum antibiotics of high potency that have been traditionally used for the treatment of infections caused by Gram-negative organisms particularly, *Pseudomonas aeruginosa*, *Enterobater species*, *Escherichia coli*, *Klebsiella species*, *Acinetobacter species* (Hermann, 2007; Rahim *et al*., 2011;Yao and Moellering, 2007). They exhibit their action by binding to the bacterial 30S ribosomal subunit (some work by binding to the 50S subunit), inhibiting the translocation of the peptidyl-tRNA from the A-site to the P-site and also causing misreading of mRNA, leaving the bacterium unable to synthesize proteins required to its growth (Shakil *et al*., 2008). In India, high level aminoglycoside resistance has been reported from different parts in *Pseudomonas* species, *E. coli*, *Klebsiella* species, *Acinetobacter* species (Padmasini *et al*., 2014; Gade and Quazi, 2014 ; Randhawa *et al*., 2004; Sahid and Malik, 2005). In Gram-negative organisms, resistance to aminoglycosides such as amikacin, tobramycin and gentamycin was reported to vary from 32.6% to 83.6% which is mediated through AAC(6) and APH(2) (Sahid and Malik, 2005; Ubukata *et al*., 1984; Lee, 1985). An earlier study from India noted that 42.8 % and 20.4 % resistance caused by AAC(6')-I and AAC(3)-II (Sahid and Malik, 2005). In the USA, up to 30% of cystic fibrosis (CF) *P. aeruginosa* isolates are resistant to tobramycin (Emerson *et al*., 2010). There are numerous mechanisms of aminoglycoside resistance that includes reduced uptake or decreased cell permeability, alterations at the ribosomal binding sites, production of aminoglycoside modifying enzymes and activation of efflux pump (Shakil *et al*., 2008; Shaw *et al*., 1999; Llano-Sotelo *et al*., 2002; Sobel *et al*., 2003;Vogne *et al*., 2004; Hocquet *et al*, 2003). Among these, modification of aminoglycoside by enzymes is a major mechanism by which clinical isolates of Gram-negative and Gram-positive bacteria cause an enzymatic modification of the amino or hydroxyl groups of aminoglycosides, causing them to bind poorly to ribosomes and thus allows bacteria to survive (Llano-Sotelo *et al*., 2002). The efflux system has been specifically shown to be involved in aminoglycoside resistance in *Pseudomonas aeruginosa* infections in several countries (Llano -Sotelo *et al*., 2002; Sobel *et al*., 2003). In view of increasing incidence of aminoglycoside resistance and failure of monotherapy, a combination therapy may be one of the options to treat infections caused by aminoglycoside resistant organisms (Hughes *et al*., 1997). The combination of aminoglycosides with β-lactams particulary cephalosporins have been demonstrated to be synergistic (Miguel *et al*., 2002). Venus Medicine Research Centre, India has developed a new combination product which was named as Tobracef. It is a novel antibiotic adjuvant entity comprised of a β-lactam moiety (ceftazidime) plus a aminoglycoside (tobramycin). Clinically,

*Corresponding author: **Anurag Payasi**
Venus Medicine Research Centre, Hill Top Industrial Estate, Bhatoli Kalan, Baddi, H.P. - 173205 India

this antibiotic combination has been designed for the treatment of infections caused by multi drug-resistant organisms. In this study, we evaluated the in-vitro effects of ceftazidime/tobramycin (Tobracef) combination in comparison to amikacin, gentamicin, tobramycin, ceftazidime, ceftazidime plus amikacin against multi-drug resistant *P. aeruginosa* and other Gram negative strains.

MATERIALS AND METHODS

Sample collection

A total of 1385 clinical samples (wound, blood, urine, sputum, pus and swab) from various hospitals of India between January 2014 to December, 2014 were collected. Clinical samples were investigated to find the distribution of nosocomial pathogens in causing different opportunistic infections and their antibiotic resistance profile.

Identification of pathogens

Clinical isolates of *A. baumannii*, *P. aeruginosa*, *E. coli*, *Klebsiella species* and *Proteus species* were identified on basis of morphological and biochemical characteristics (Cheesbrough, 2000).

Antibacterial agents

The antibacterial agents included for susceptibility testing were ceftazidime, gentamicin, amikacin, tobramycin, ceftazidime plus amikacin and Tobracef All dry powder injections were reconstituted according to manufacturer instructions

Antibiotic susceptibility testing

Antimicrobial susceptibility testing of the selected drugs were done by cup plate method as described by Bennet *et al*., (1966). Inoculum of 0.5 McFarland standards turbidity was prepared in a Mueller-Hinton broth (MHB, Hi-Media, Mumbai, India) from isolated colony of pathogens selected from 18–24 hrs agar plates. Within 15 minutes, a sterile cotton swab was dipped into the inoculum suspension. The swab was rotated several times and pressed firmly against the inside wall of the tube above the fluid level and inoculated on the dried surface of a Mueller-Hinton agar (MHA) plate by streaking the swab over it. For even distribution of inoculum, the swab was streaked two more times at 60° over the agar surface. After 3–5 minutes, the cups were made in the agar plate using a sterile cork borer (6.5mm). Then, 30 µl of the antibiotic preparation was placed in the wells using a micro-pipette and allowed to diffuse at room temperature. The plates were incubated in the upright position at 37^0C for 18 hrs. After incubation the zone of inhibition around the wells was measured in mm (millimeter), averaged and the mean values were recorded. Sensitivity of isolated organisms against antibiotics were reported as sensitive (S) or resistant (R) based on the breakpoints.

RESULTS AND DISCUSSION

A total of 1385 clinical samples of wound, blood, urine, sputum, pus and swab were collected and subjected for isolation of pathogens by standard methods. Out of the samples analyzed, 679 samples showed the presence of pathogens while 706 samples showed no growth of organisms. Details of the samples showing growth of pathoges is shown in Table 1**.** Among the samples showing growth of pathogens, around 36.1% samples were of wound, followed by blood (23.7%), urine (17.5%), sputum (13.5%), pus (5.6%) and swab (3.5%)**.**

Morphological and biochemical characterization of the samples revealed 5 different Gram negative organisms such as *P. aeruginosa*, *A. baumannii*, *E. coli*, *Klebsiella spp.* and *Proteus spp.* The detailed profile of various organisms collected from various clinical samples is shown in Table 2 and Figure 1. Among the isolates, *P. aeruginosa* (45.2 %) was found to be the most dominant pathogen which is comparable to earlier study of Mahmoud *et al*. (2013) in which they reported 52 % prevalence of MDR *P. aeruginosa*. Another study performed by Ahmed *et al*. (2012) showed that *P. aeruginosa* strains were commonly isolated from medicine department (33.7%) followed by surgical (21.6%) and intensive care units (20.9%). *A. baumannii* (33.6 %), and *E. coli*, (15.0 %), also contributed significantly to the isolated pool of pathogens followed by *Klebsiella spp.* (5.9 %), and *Proteus spp*. (0.3 %). A similar prevalance of *A. baumannii* was reported by Jayanthi and Jeya (2012) from Chennai where they reported 26.9% of *A. baumannii* among the clinical isolates. In a study carried out in Saudi Arabia, *A. baumannii* was the most common isolated organisms among Gram-negative bacteria, with a prevalence of 31.7% (Nageeb *et al.,* 2014). The results of present study showed the prevalence of *E.coli* was (15.0 %), whereas other studies reported prevalence of *E.coli* as low as (7.0%) Chander and Shrestha (2013) and as high as 28 to 67% (Mehrgan and Rahbar, 2008).

Table 1 Details of clinical samples used in the study

Clinical samples	Total	Number of samples showing growth of pathogens (%)	Number of samples not showing growth of pathogens
Wound	389	245 (36.1)	144
Blood	295	161 (23.7)	134
Urine	290	119 (17.5)	171
Sputum	235	92 (13.5)	143
Pus	98	38 (5.6)	60
Swab	78	24 (3.5)	54
Total	**1385**	**679**	**706**

Table 2 Isolation of clinical isolates from various clinical specimens.

Samples showing pathogen growth	Clinical isolates				
	P. aeruginosa	***A. baumannii***	***E.coli***	***Klebsiella spp.***	***Proteus spp.***
Wound (245)	110	89	30	15	1
Blood (161)	75	48	26	12	0
Urine (119)	55	37	17	9	1
Sputum (92)	42	32	14	4	0
Pus (38)	15	14	9	0	0
Swab (24)	10	8	6	0	0
Total	**307**	**228**	**102**	**40**	**2**

Frequency of pathogens among various specimens is depicted in Table 2. *P. aeruginosa* was the most prevalent pathogen among most of the samples accounting for 35.8% in wound, 24.4% in blood, 18.0 % in urine, 13.7 % in sputum,, 4.8% in pus, 3.3% in swab. Previous studies reported the incidence of

P. aeruginosa in wound to be 22.4 to 39.3% (Smith *et al*., 2012; Al-Marzoqi and Al-Taee, 2013). Compared to our study in which 18% *P. aeruginosa* isolated from urine, Velvizi *et al.* (2013) obtained 23% of *P. aeruginosa* isolates from urine samples. Similarly, Khan *et al*. (2008) documented 24.2% *P. aeruginosa* from urine samples. *A. baumannii* contributed 39.0 % in wound, 21.1 % in blood, 16.2% in urine, 14.0% in sputum, 6.1% in pus samples and 3.5% in swab. Jabur *et al.* (2014) reported 30% prevalence of *A. baumannii* in wound and 10% in sputum samples. Jaggi *et al*. (2012) noted high prevalence of *A. baumannii* in blood (23.8%). *E.coli* contributed 29.4% in wound, 25.5% in blood, 16.6% in urine, 13.7% in sputum, and 8.8% in pus samples. Similar results were observed by Kibret and Abera (2011) where prevalence of *E.coli* in wound samples was 18.7%. In an another study by Chaudhary and Payasi *et al*. (2014) where they showed 22.4% prevalence of *E. coli* in blood samples.

Our susceptibility results showed that Tobracef (88.9%) was the most effective antipseudomonal agent, followed by ceftazidime/amikacin (64.8%), amikacin (44.9%), ceftazidime (50.1%), tobramycin (32.9%), and gentamicin (28.9%). Our results showed that Tobracef appears to be more efficacious when compared with other drugs, offering a new therapeutic options for treatment of multidrug resistant bacteria. Figures 2 and 3 depict the sensitivity and resistance patterns of the isolates to different antibiotics. Compared to this study, previous studies reported 74.2 to 83% resistance to ceftazidime among *P. aeruginosa* (Saderi *et al*., 2007; Salimi *et al*., 2009; Mirsalehian *et al*., 2008). In present study *Pseudomonas* isolates showed (71%) resistance to gentamicin, which is comparable to the study done by Mohanasoundaram *et al. (*2011), where resistance rate of *Pseudomonas* to gentamicin was 64%.

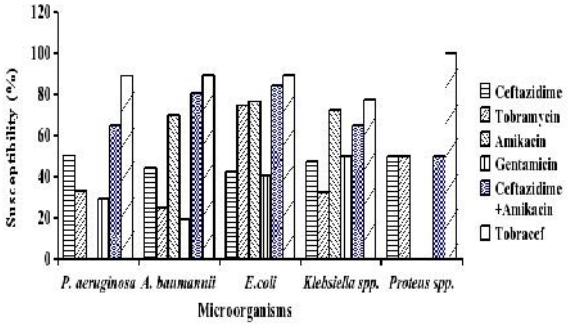

Figure 2 Susceptibility pattern of Gram negative pathogens against antibacterial agents.

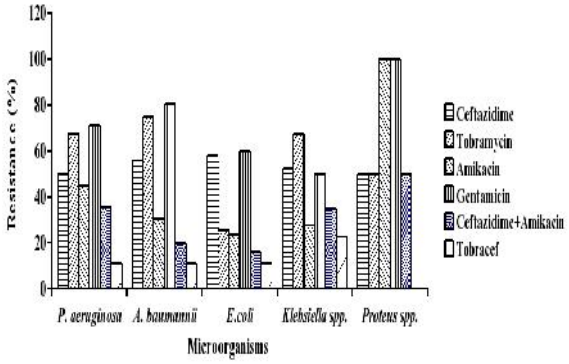

Figure 3 Resistance pattern of Gram negative pathogens against antibacterial agents.

In a study done by Alikhani *et al*. (2013) resistance to amikacin among *P. aeruginosa* was 48.3% which is in accordance with the present study where it showed 44.9% resistance to amikacin. Golshani *et al*. (2013) also found that, resistance to amikacin was 65% in *P. aeruginosa*. In this study, *Pseudomonas* isolates showed high resistance (67.1%) to tobramycin. Recently, 58.2% to 100% resistance of tobramycin to Pseudomonas was noted (Nasrabadi and Hajia 2012; Upadhya *et al*., 2014; Iraj *et al*., 2013). Ceftazidime plus amikacin showed 50% resistance to *Proteus spp.*, followed by *P. aeruginosa* (35.2%), *Klebsiella spp.* (35%), *A. baumannii* (19.7%) and *E.coli* (15.7%).

In current investigation, *A. baumannii* showed high resistance to gentamicin (80.7%) and tobramycin (75%). Vatopolus *et al.* (1999) reported that 75.6% of *A. baumannii* isolated from ICU isolates were resistant to gentamicin and 87.6% of *A. baumannii* isolates were resistant to gentamicin Meniatis *et al.* (2003). Khodadadi *et al.* (2014) reported 52% *A. baumannii* were resistance rate to tobramycin. *A.baumannii* showed 84.1% resistance to ceftazidime (Ruiz *et al*., 1999). Mostofi *et al.* (2011) showed frequency of antibiotic resistance in *A. baumannii* isolates to ceftazidime was 96%. In current study, we observed 30.2% resistant to amikacin in *A. baumannii*, while other studies reported 52% to 58% resistant for the same (Dent *et al*., 2010; Jazani *et al*., 2010).

A high prevalence of resistance to gentamicin (59.8%) and ceftazidime (57.8%) among *E. coli* isolates was observed which is comparable to earlier studies (Vij *et al*., 2014; Mandal *et al*., 2010; Dash *et al*., 2013; Prakash and Saxena, 2013; Akram *et al*., 2007; Mandal *et al*., 2012). Khadri *et al*. (2007) reported that *K. pneumoniae* was highly resistant (55%) to gentamcin which is almost similar to our study where resistant rate to gentamcin was 50%.

CONCLUSION

Our findings suggest that the resistance rates of aminoglycosides, 3th generation antibiotics are increasing progressively in India. Any vary from hospital to hospital The bacterial susceptibility and resistance profile of all isolates in this study have shown that Tobracef remain the most effective drugs against multi-drug resistant gram negative pathogens, suggesting that use of Tobracef over other antibiotics should be prefered. To reduce the emergence and spread of antimicrobial-resistant pathogens, monitoring and optimisation of antimicrobial use should be considered carefully.

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