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Antimicrobial activity of tigecycline against nosocomial pathogens in Pakistan: a multicenter study

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Original Article

Antimicrobial activity of Tigecycline against nosocomial pathogens in Pakistan: A multicenter study

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Abstract

Objective: To measure the in-vitro activity of various antibiotics including tigecycline against Gram negative and positive nosocomial aerobic isolates.

Methods: A total of 430 clinical isolates of both Gram positive (143) and negative (287) aerobic bacteria were used from 3 centres during the year 2006 and 2007. Minimum inhibitory concentration (MIC) was determined using broth micro dilution panels. Antibiotic resistance was interpreted using CLSI guidelines.

Results: Most of the isolates were resistant to more than one drug. Resistance to tigecycline was not found. Tigecycline (1ug/ml) had low MIC against organisms tested.

Conclusion: This data indicates that tigecycline, a new drug in its class, has broad-spectrum in-vitro activity against both Gram negative and positive nosocomial isolates. Therefore, it may be a suitable drug to be used for the treatment of highly resistant nosocomial infections (JPMA 59:240; 2009).

Introduction

Irrational use of antibiotics has resulted in the emergence of resistant bacteria globally. In Pakistan, lack of infection control practice and non existent formal antibiotic policies has further augmented this problem. There have been reports from all over the country on the rising trend of nosocomial pathogens producing extended spectrum beta lactamase (ESBL) and methicillin resistant Staphylococcus aureus.[1-4] Infections due to these organisms have resulted in increased mortality, morbidity and cost of treatment.[5]

Tigecycline is a new injectable glycylcycline antibacterial product. It inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains resulting in inhibition of protein synthesis.

This study was conducted to evaluate the in-vitro activity of tigecycline against nosocomial pathogens (aerobic) and compare its activity with other commonly used antibiotics in our hospitals.

Materials and Methods

Nosocomial isolates were tested at three different hospital laboratories between 2006 and 2007. The laboratories which participated were Liaquat National Hospital Karachi, Aga Khan University Hospital Karachi and Armed Forces Institute of Pathology, Rawalpindi. A total of 430 Clinical isolates of both Aerobic Gram positive (143) and Gram negative (287) aerobic bacteria were included from all types of specimens. Clinically significant isolates were identified on the basis of Gram stain, morphology and biochemical reactions. Final confirmation of isolates was also performed by Laboratories International for microbiology studies, a division of International Health Management Associates, Inc, Schaumburg, IL, USA.

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method of the Clinical and Laboratory Standards Institute (CLSI) using gram-negative broth panels (Microscan, Dade Behring, Sacramento, CA, USA). All panels were incubated for 16-20 hours aerobically at 350C as per CLSI guidelines.[6] Quality control strains used were E.coli ATCC 25922, Staphylococcus aureus ATCC 29213, E.faecalis ATCC 29212, S.pneumoniae ATCC 49619, and H.influenzae ATCC 49247. These were all sensitive strains. They were used with each batch as indicated.

Susceptibilities were determined according to the interpretive criteria of CLSI.[6] No interpretive criteria for disc diffusion method have been approved for tigecycline when testing Acinetobacter spp. E.coli and K.pneumoniae were tested for ESBL production using CLSI guidelines.

MICs and susceptibilities were determined against amoxicillin-clavulanate, piperacillin-tazobactam, levofloxacin, minocycline, ceftazidime, ceftriaxone, cefepime, imipenem, amikacin, ampicillin and tigecycline. Tigecycline, ampicillin and amoxicillin-clavulanate were not tested against Acinetobacter spp., as no interpretive criteria were available for disc diffusion methodology. Pseudomonas aeruginosa is not

reported in this study as it is intrinsically resistant to tigecycline.

Results

Results of isolates tested by both disc diffusion method and MICs are given.

Tigecycline showed no resistance by disc diffusion method against all 360 isolates included in the study (Table 1). This included both Gram positive (Enterococcus spp., Staphylococc aureus and Streptococcus spp.) and negative isolates (Enterobacter spp., Klebsiella pneumoniae., Serratia spp. and Eschericia coli). It also showed very low MIC against all isolates including Acinetobacter spp. (Table 2). Acinetobacter spp. on the other hand had higher MICs for all antibiotics including imipenem but for tigecycline MIC was very low (1 ug/ml) (Table 3).

Discussion

We report uniform activity of tigecyline against nosocomial Gram negative and positive organisms isolated in three clinical microbiology laboratories affiliated with tertiary care hospitals. We also report low MICs (1-2 ug/ml) of tigecycline for isolates we tested.

Antimicrobial resistance among Gram negative and positive pathogens in Pakistan is on the rise. A number of reports have been published showing presence of ESBL producing E.coli and Klebsiella species in the community as well as in hospitals. Recently Jabeen et al reported 40% of the 2840 isolates tested as ESBL producers. Among theses ESBL positive isolates 50% were Enterobacter species, 41% E.coli and 36% K. pneumoniae.[1] In another study conducted in 1999 the frequency of ESBL producing enterobacteriacae was 35%.[2] In a multicenter study Hafiz et al reported frequency of isolation of MRSA as 42%.[3]

Prevalence of multiresistant Acinetobacter spp. is also rising in intensive care units making treatment options much more costly and difficult. In a recent study conducted in a tertiary care hospital in Karachi, 65% isolates of Acinetobacter species. obtained from blood isolates of febrile neutropenic patients were resistant to imipenem.[7] The emergence of carbapenem resistance among Acinetobacter species is alarming. In our study imipenem resistance in Acinetobacter spp. was 63%. This study also shows high MIC 90 for several antibiotics against Acinetobacter species. However tigecycline showed low MICs of ≤2ug/ml for majority of the isolates tested. This finding is in concordance with Diane et al.[8] For MRSA and for ESBL producing Enterobacteriaceae in-vitro results of tigecycline are in full agreement with other studies reported earlier.[8,9] This drug was found uniformly active against both groups of organisms with low MIC results.

Tigecycline is the first of the glycylcyclines which has

Table: 2 MICs of tigecycline against various pathogens (n=430).

Organisms	Number	MICs ug/ml
Staphylococcus aureus	69	0.5
Acinetobacter spp.	41	1
Enterobacter spp.	48	1
E. coli	76	0.5
K. pneumoniae	71	2
Enterococcus spp.	44	0.25
Haemophilus spp.	29	0.5
Strept. pneumoniae	30	0.06
Serratia spp.	22	2

Table 3: MICs of Acinetobacter species (41) against various antibiotics.

Acinetobacter species	MICs ug/ml
Amikacin	128
Amoxicillin/clavulanic acid	64
Ampicillin	64
Cefepime	64
Ceftazidime	64
Ceftriaxone	128
Imipenem	32
Levofloxacin	16
Minocycline	4
Piperacillin/tazobactam	256
Tigecycline	1

Table: 1 Susceptibility pattern of tigecycline against various isolates by disc diffusion method (n=360).

Organisms	Number	% Susceptibility	% Intermediate	% Resistance
Enterobacter spp.	48	97.92	2.08	0
Enterococcus spp.	44	100	0	0
Eschericia coli	76	100	0	0
Klebsiella pneumoniae.	71	94.29	5.71	0
Staphylococcus aureus	69	100	0	0
Serratia spp.	23	90.91	9.09	0
Strep. pneumoniae.	30	100	0	0

been marketed recently. It has remained unaffected by bacterial resistance due to a number of defense mechanisms such as protein binding, beta-lactamase production (ESBL production, AmpC hyperproducers), DNA gyrase alterations, the van resistance genes, plus other mechanisms that are used by many of the commonly encountered isolates in community-acquired and nosocomial infections.[10-12]

A study published by Jabeen et al[1] reported that in enterobacteriaceae resistance to non-beta lactam antibiotics (fluoroquinolones, aminoglycosides and co-trimoxazole) was more frequent in ESBL producing organisms ($p<0.05$) than in non ESBL producers. Cross resistance to amikacin, gentamicin, co-trimoxazole and ofloxacin was 14%, 51%, 22%, 41% among ESBL producers than non-ESBL isolates. In this study none of the ESBL producing organisms were found resistant to imipenem, similar to our study. Authors were not able to check tigecycline as it was not available in 2005. This study showed lowest MIC for imipenem and tigecycline against Enterobacter species and K. pneumoniae and the same result was found against E.coli followed by amikacin.

ESBL producing K.pneumoniae did not show higher MICs for imipenem and tigecycline. However in USA a large scale study conducted found higher MICs against imipenem. (MIC 90 16ug/ml).[11]

Finally, it is concluded that tigecycline is not yet affected by various resistance mechanisms affecting other antibiotics since that requires research at a molecular level. It has broad spectrum activity against both Gram negative and positive nosocomial isolates. Therefore we suggest that in the current situation it can be a suitable drug for the treatment of highly resistant nosocomial infections and it should not be used for empirical treatment. For future, we recommend that to deal with the ever-increasing antimicrobial resistance, it is necessary to monitor resistance patterns carefully and continuously.

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