COMPARATIVE ACTIVITY OF DORIPENEM, IMIPENEM AND MEROPENEM AGAINST GRAM NEGATIVE PATHOGENS: A PRELIMINARY STUDY

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ABSTRACT

BACKGROUND AND OBJECTIVE

Doripenem is a new parenteral carbapenems, which has beta-lactamase stability and is not inactivated by renal dehydropeptidases. Doripenem has a spectrum of activity similar to imipenem and ertapenem against Gram-positive cocci and similar to meropenem against Gram-negative pathogens. In this study, we summarize the activity of doripenem against Gram negative bacilli in comparison with other carbapenems (Imipenem, meropenem) and select group of antimicrobial drugs by disk diffusion.

SETTINGS AND DESIGN

A retrospective study was conducted over a period of 3 months (December 2013 to February 2014) in the Department of Microbiology of a tertiary care hospital in Northern India.

METHODS AND MATERIAL

Gram negative bacillary isolates were subjected to antimicrobial susceptibility with the following antibiotics: imipenem, meropenem, doripenem, ceftazidime, ceftriaxone, amikacin, ciprofloxacin, piperacillin/tazobactam, and trimethoprim-sulphamethoxazole by employing the Kirby-Bauer disk diffusion method. The results were interpreted as per CLSI guidelines.

RESULTS

A total of 498 isolates obtained from urine, skin and soft tissue specimens and lower respiratory specimens were included in the study. The most frequent Gram-negative bacilli isolated were E. coli (31.5%), Acinetobacter spp. (20.1%), Klebsiella spp. (19.5%), P. aeruginosa (16.7%), Enterobacter spp. (8.2%), Proteus spp. (3%) and Citrobacter spp. (1%). The isolates showed highest rates of susceptibility to meropenem (65.5%) followed by imipenem (63.7%), doripenem (55.8%), amikacin (53.4%), piperacillin/tazobactam (48.7%), trimethoprim-sulphamethoxazole (38.3%), ceftazidime (26.9%), ceftriaxone (23.9%) and ciprofloxacin (25.3%).

CONCLUSIONS

In this study, the activity of doripenem was found to be lower than meropenem and imipenem against all the isolates tested. Further detailed evaluation of doripenem is required with in-vitro MIC studies and their correlation with clinical outcomes.

KEYWORDS

Doripenem, Carbapenemases, Gram Negative Bacilli.

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INTRODUCTION

Carbapenems are a class of antimicrobials that are structurally related to penicillin. They continue to be one of the most active classes of antibiotics against many resistant pathogens. However, resistance to carbapenems is steadily increasing over the last decade according to various reports.[1] Doripenem (Formerly S-4661) is a new parenteral carbapenems, which has beta-lactamase stability and is not inactivated by renal dehydropeptidases.

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Doripenem binds to and inactivates Penicillin Binding Proteins (PBP) like other carbapenems, thus inhibiting bacterial cell wall synthesis and causing cell death. Doripenem binds to PBP2 and PBP3 in P. aeruginosa, PBP2 in Escherichia coli. PBP1, PBP2 and PBP4 of Staphylococcus aureus.[2] Doripenem has a spectrum of activity similar to imipenem and ertapenem against Gram-positive cocci, and similar to meropenem against Gram-negative pathogens.[3,4] Doripenem was recently approved by the Food and Drug Administration to treat complicated intra-abdominal infections and complicated urinary tract infections including pyelonephritis caused by susceptible bacteria. In this study, we summarize the activity of doripenem in comparison with other carbapenems (Imipenem, meropenem) and select group of antimicrobial drugs by disk diffusion.

MATERIALS AND METHODS

The study was conducted in the Microbiology Department of a tertiary care teaching hospital in North India. A retrospective

analysis of 498 gram negative bacterial isolates was conducted over a period of three months from December 2013 to February 2014. Consecutive, non-duplicate isolates from patients visiting the outpatient department as well as patients admitted to surgical, medical and ICU wards were included in the study. The isolates were predominantly obtained from patients with documented respiratory tract, skin and soft tissue and urinary tract infections. Blood agar, chocolate agar and MacConkey agar plates were used as the primary plating media. Samples were processed and isolates were identified by standard microbiological techniques.[5]

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed by the Kirby-Bauer disk diffusion method on Mueller-Hinton agar. The isolates were tested with the following antibiotics (HiMedia Laboratories, Mumbai, India): Ceftazidime (30 mcg), Amikacin (30 mcg), Ciprofloxacin (5 mcg), Piperacillin/Tazobactam (100/10 mcg), Imipenem (10 mcg), Doripenem (10 mcg), Meropenem (10 mcg) and Trimethoprim-sulphamethoxazole (1.25/23.75 µg). The antimicrobial susceptibility pattern was interpreted as per the Clinical and Laboratory Standards Institute (CLSI) guidelines.[6] E. coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 were used for the quality control.

RESULTS

A total of 498 isolates were included as part of the study. These isolates were obtained from the following samples: urine (35.1%), soft tissue specimens (28.1%), lower respiratory specimens (29.8%) and other samples (7%) like cerebrospinal fluid, ascitic fluid, central line tip, external prostatic secretions. The most frequent Gram-negative bacilli collected were E. coli (31.5%), Acinetobacter spp. (20.1%), Klebsiella spp. (19.5%); P. aeruginosa (16.7 %); Enterobacter spp. (8.2%); Proteus spp. (3%) and Citrobacter spp. (1%).

Table 1 shows the susceptibility rates of doripenem and comparator agents against all the Gram negative bacterial isolates. The isolates showed highest rates of susceptibility to carbapenems with 65.5% of the isolates being susceptible to meropenem followed by imipenem (63.7%) and doripenem (55.8%). Among the other antimicrobials tested, 48.7% of the isolates were susceptible to piperacillin/tazobactam. The isolates showed lowest rates of susceptibility to ceftriaxone (23.9%) and ciprofloxacin (25.3%).

The species wise in vitro activity of doripenem in comparison with comparator agents is shown in Table 2. The activity of doripenem against E. coli was comparable to imipenem and meropenem. Susceptibility rates to amikacin (82.8 %) and piperacillin/tazobactam (75%) were also found to be high, while the activities of cephalosporins, ciprofloxacin and trimethoprim-sulphamethoxazole were found to be variable. The susceptibility rates of Klebsiella spp. to doripenem was 40.2%, when compared to meropenem (64.9%) and imipenem (59.8%). Trimethoprim-sulphamethoxazole was the most active antimicrobial agent against Klebsiella spp. with susceptibility rates of 93.8%. Against Enterobacter spp., the potency of doripenem was comparable with imipenem with 75.6% of the isolates being susceptible, while meropenem exhibited lower activity (68.3%).

Among P. aeruginosa isolates, 53% were sensitive to doripenem, 51.8% to imipenem and 50.6% to meropenem. Amikacin was the most active drug against P. aeruginosa with 59% of the isolates being sensitive. Resistance to carbapenems was most pronounced amongst Acinetobacter spp. with only 14.1% of the isolates being susceptible to doripenem, 33% to imipenem and 31% to meropenem. Table 3 shows the antimicrobial susceptibility rates of doripenem and other antimicrobial agents against Gram negative bacilli isolated from Intensive Care Units (ICU).

The activities of doripenem and other antimicrobials against cephalosporin-susceptible and resistant Gram negative bacilli are presented in the Figure. Among E. coli isolates, doripenem had susceptibility rates of 100% and 76.2% against ceftazidime-susceptible and non-susceptible isolates respectively, compared to meropenem (100% and 70.5%, respectively) and imipenem (100% and 79.1% respectively). In Klebsiella spp., doripenem had susceptibility rates of 100% and 29.6% against ceftazidime-susceptible and non-susceptible isolates respectively, compared to meropenem (87.5% and 61.7% respectively) and imipenem (100% and 53.1% respectively).

In Enterobacter spp., doripenem had susceptibility rates of 100% and 65.5% against ceftazidime-susceptible and non-susceptible isolates respectively, compared to meropenem (100% and 55.2% respectively) and imipenem (100% and 58.6% respectively). Among P. aeruginosa isolates, doripenem had susceptibility rates of 84.2% and 26.7% against ceftazidime-susceptible and non-susceptible isolates respectively, compared to meropenem (89.5% and 20% respectively) and imipenem (94.7% and 20% respectively). In Acinetobacter spp., doripenem had susceptibility rates of 84.2% and 26.7% against ceftazidime-susceptible and non-susceptible isolates respectively, compared to meropenem (89.5% and 20% respectively) and imipenem (94.7% and 20% respectively).

Antimicrobial Agent Tested	% S*	% I†	% R‡
Doripenem	55.8	0.4	43.8
Imipenem	63.7	3.2	33.1
Meropenem	65.5	4.8	29.7
Piperacillin tazobactam	48.7	3.3	48
Ceftazidime	26.9	4.0	69.1
Ceftriaxone	23.9	1.8	74.3
Amikacin	53.4	1.8	44.8
Ciprofloxacin	25.3	0.8	73.9
Trimethoprim-sulphamethoxazole	38.3	0.4	61.3

Table 1: Antimicrobial Susceptibility Patterns of Gram Negative Bacteria

*S Susceptible, †I Intermediate, ‡ R Resistant

Antimicrobials	E. coli (n=157) (%)	Klebsiella spp. (n=97) (%)	Enterobacter spp. (n=41) (%)	P. aeruginosa (n=83) (%)	Acinetobacter spp. (n=100) (%)	Proteus spp. (n=15) (%)	Citrobacter spp. (n=5) (%)
Doripenem	83.4	40.2	75.6	53.0	14.1	86.7	80
Imipenem	85.4	59.8	73.2	51.8	33,0	100	60
Meropenem	89.2	64.9	68.3	50.6	31.0	93.3	100
Pip/taz*	75.0	26.6	51.4	53.1	15.2	93.3	80
Ceftazidime	31.8	16.5	29.3	45.8	05.0	66.7	60
Ceftriaxone	29.3	14.4	22.0	39.8	04.0	66.7	60
Amikacin	82.8	35.1	61.0	59.0	11.0	86.7	80
Ciprofloxacin	21.7	23.7	22.0	45.8	04.0	80.0	40
Tmp-smx†	33.8	93.8	24.4	10.8	06.0	20.0	20

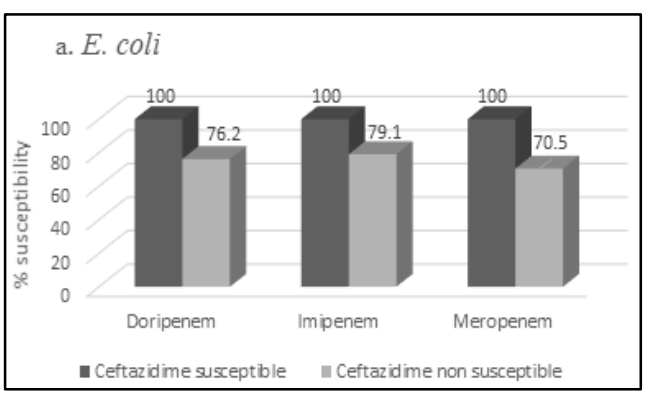
*Pip/taz-Piperacillin-tazobactam,†Tmp-smx- Trimethoprim-sulphamethoxazole

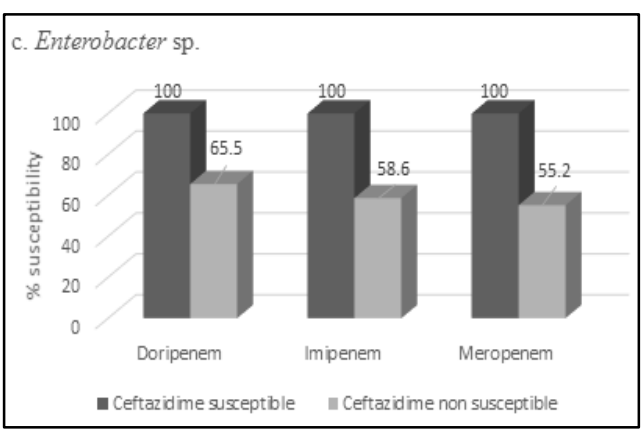
Table 2: Antimicrobial Susceptibility Rates of Doripenem in Comparison with Selected Antimicrobial Agents Against Gram Negative Bacilli

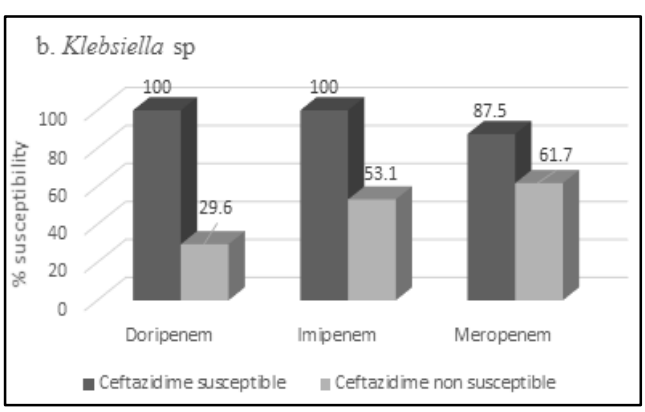
	Total (n=71)	E. coli (n=4) (%)	Klebsiella spp. (n=21) (%)	Enterobacter spp. (n=7) (%)	Pseudomonas spp. (n=9) (%)	Acinetobacter spp. (n=30) (%)
Doripenem	26.8	75	33.3	57.1	11.1	13.3
Imipenem	39.4	75	57.1	57.1	22.2	23.3
Meropenem	45.1	75	47.6	57.1	66.7	30
Piperacillin tazobactam	18.8	100	15	42.9	33.3	6.7
Ceftazidime	12.7	50	9.5	28.6	22.2	3.3
Ceftriaxone	8.5	25	9.5	14.3	11.1	3.3
Amikacin	22.5	75	23.8	14.3	55.6	3.3
Trimethoprim-sulphamethoxazole	9.9	0	23.8	14.3	0	3.3
Ciprofloxacin	7.1	25	10	14.3	11.1	0

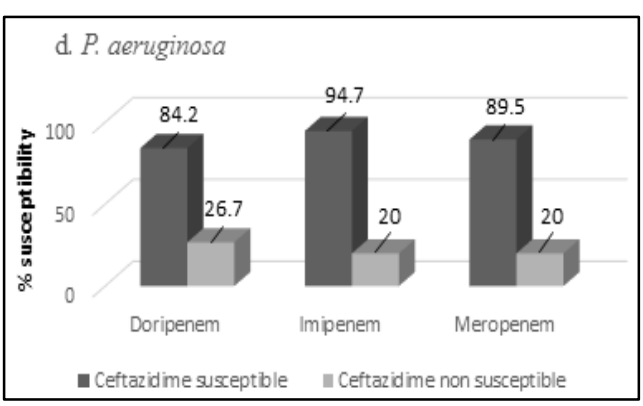
Table 3: Antimicrobial Susceptibility Rates of Doripenem and Other Antimicrobial Agents Against Gram Negative Bacilli Isolated from Intensive Care Units (ICU)

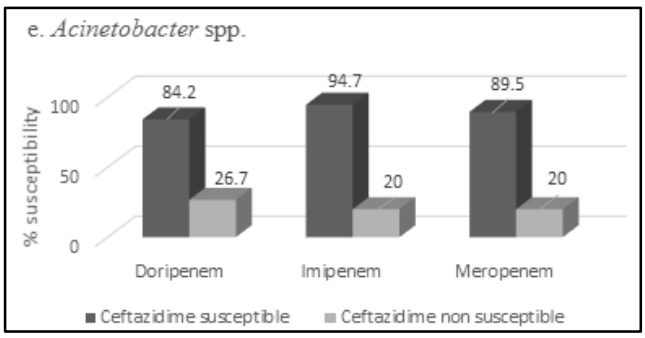
Figure: Antimicrobial activity of doripenem, imipenem and meropenem against Ceftazidime susceptible and non-susceptible isolates











DISCUSSION

This retrospective study demonstrated that doripenem has similar or slightly lower activity than imipenem and meropenem against all the gram negative bacterial isolates tested except for Klebsiella pneumoniae and Acinetobacter spp. This pattern of activity for doripenem was similar to that observed in previous studies.[7-10] The rates of susceptibility to carbapenems seen in this study were low, which is comparable to other studies conducted in India. Wattal et al reported resistance rates of 13%, 51%, 59% and 80% among E. coli, Klebsiella spp., Pseudomonas spp. and Acinetobacter spp. respectively in Delhi.[11] Another study from a tertiary care hospital in North India reported resistance rates ranging from 17-22% among Enterobacteriaceae, Pseudomonas spp. and Acinetobacter spp.[12]

Among the Enterobacteriaceae, majority of isolates of E. coli (83.4%) and Enterobacter spp. (75.6%) showed good susceptibility to doripenem, while lower rates of sensitivity were observed in Klebsiella spp. (40.2%). According to CDC, the resistance rates in isolates belonging to Enterobacteriaceae to carbapenems increased from 0% in 2001 to 1·4% in 2010.[1,13] There is scarcity of studies reporting prevalence of carbapenem resistance among Enterobacteriaceae in India. In this study, 59.8% and 64.9% of Klebsiella spp. showed susceptibility to imipenem and meropenem respectively. In a study conducted among 105 Enterobacteriaceae isolates from blood of septicaemic neonates, 74% of E. coli and 91% of Klebsiella pneumoniae were found to be susceptible to meropenem.[14] Shraddha et al reported resistance rates of 58.82% and 8.82% to meropenem and imipenem among E. coli and resistance rates of 53.84% and 30.76% to meropenem and imipenem among Klebsiella pneumoniae respectively.[15] In a study from Korea, Choi et al reported low resistance rates among Enterobacteriaceae (E. coli – 0%, Klebsiella spp. - 5.1% and Enterobacter spp. – 0%) to doripenem.[16]

The activity of all the three carbapenems against Pseudomonas spp. was comparable to each other. The non-susceptible (Intermediate and resistant) rate of 48.2% for P. aeruginosa to imipenem observed in this study is higher than that observed in other studies.[17-19] There was a significant difference in activity of doripenem, imipenem and meropenem against ceftazidime susceptible and ceftazidime non-susceptible isolates of Pseudomonas spp. This illustrates that some but not all of the mechanisms conferring resistance to cephalosporins in P. aeruginosa also confer resistance to carbapenems. In P. aeruginosa, resistance to doripenem can arise from a combination of loss of OprD protein and increased expression of pump efflux. None of the 3 carbapenems showed good activity against Acinetobacter spp.

In a study conducted in South India, high resistance rates of 100% and 89% to imipenem and meropenem in 55 isolates of A. baumannii were reported.[20] In North India, Sinha et al reported 14% meropenem resistance, Taneja et al reported 18.5% imipenem resistance and Mahajan et al reported 31.81% meropenem resistance in Acinetobacter isolates.[17,21,22] Castanheira et al reported higher susceptibility rates among 3,844 A. baumannii complex isolates to imipenem and meropenem in comparison with doripenem (Imipenem-69.4%, meropenem-66.6% and doripenem 49.9%).[23] Production of metallo-beta-lactamase or OXA-type carbapenemases in Acinetobacter spp. may be responsible for reduced susceptibility to doripenem as well as other carbapenems in this study.[23,24]

Few publications have reported the comparative activity of doripenem in comparison with meropenem and imipenem against commonly isolated Gram negative bacilli from India. In this study, the activity of doripenem was lower than meropenem against all the isolates tested. Further detailed evaluation of doripenem is required with in-vitro MIC studies and their correlation with clinical outcomes.

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