Comparison of in Vitro Activity of Doripenem with other Carbapenems Against Clinical Isolates of Extended Spectrum Beta-Lactamase Producing Gram-Negative Bacilli

Thesis

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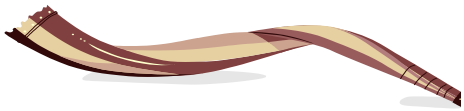

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Contents

List of Abbreviations

Abbreviation	Meaning
AMR	Antimicrobial resistance
CDC	Centers for disease control and prevention
CIAI	Complicated intraabdominal infections
CLSI	Clinical Laboratory Standards Institute
CUTI	Complicated urinary tract infections
E.coli	Escherichia coli
ESBL	Extended spectrum β-lactamase
FDA	Food and Drug Administration
K.pneumoniae	Klebsiella pneumoniae
MHA	Muller Hinton Agar
MIC	Minimal inhibitory concentration
NP	Nosocomial pneumonia
OMP	Outer membrane protein
PBP	Penicillin binding protein
TBRI	Theodor Bilharz Reasearch Institute
VAP	Ventilator associated pneumonia

List of Tables

Table No. ***Page***

List of Figures

Figure No. ***Page***

Gram-negative bacilli play a significant role in the most prevalent types of nosocomial infections including hospital-acquired pneumonia, ventilator-associated pneumonia, urinary tract infections and intra abdominal infections as well as community acquired infections ***(Gaynes and Edwards, 2005)***.

Although substantial attention has been given to develop agents that combat drug-resistant Gram-positive cocci, pursuit of antimicrobials for use in infections caused by Gram-negative bacilli has not been equally extensive ***(Livermore et al., 2005)***. This trend combined with the continued emergence and spread of Gram-negative bacilli resistant to β-lactam agents, has resulted in a growing need for new agents active against the resistant Gram-negative pathogens encountered in hospitals ***(Paterson, 2006)***.

Extended spectrum beta lactamases (ESBLs) produced by Gram-negative bacilli confer resistance to third and fourth generation cephalosporins and monobactams, and are frequently associated with co-resistance to other classes of anti-microbial drugs, such as fluoroquinolones, cotrimoxazole, tetracycline and aminoglycosides ***(Falagas et al., 2009)***.

The stability of carbapenems to a wide variety of β-lactamases produced by Gram-negative bacilli, combined with their relatively low toxicity potential, makes this class of

antibiotics good candidates for use against hospital-associated Gram-negative bacterial infections ***(Pillar et al., 2008)***.

Doripenem, a new parenteral carbapenem, has been recognized as a valuable addition to the currently available carbapenems in the treatment of serious bacterial infections ***(Keam, 2008).***

This antibiotic has a broad spectrum in vitro activity against Gram-positive and Gram-negative bacteria, including ESBL and anaerobic pathogens ***(Mendes et al., 2009***), it has a low propensity for resistance selection and is stable in solution, which provides an option for administration as a prolonged infusion that enhances achievable pharmacodynamic/ pharmacokinetic targets for bactericidal activity and therefore presumed efficacy against more resistant pathogens ***(Nakamura et al., 2009).***

Recent studies concluded that doripenem seems to be a promising agent in the treatment of nosocomial pneumonia, blood stream infections and intra abdominal infections particularly in patients who are at risk of developing antimicrobial resistance, with results comparable to and even superior to other carbapenems ***(Korten et al., 2011)***.

This work aims at studying in vitro antimicrobial activity of Doripenem in comparison with other Carbapenems against ESBLs producing Gram-negative clinical isolates. This may help in finding an alternative option for the treatment of infections with these resistant pathogens.

Bacterial Antimicrobial Resistance

Definition:

Bacterial antimicrobial resistance (AMR) is a condition in which there is no or decreased susceptibility to antimicrobial agents that ordinarily cause inhibition of bacterial cell growth or death ***(Soulsby, 2005)***.

Failure of antibiotic treatment for an infection usually leads to serious consequences for the patient and is associated with increased health care costs for society ***(Blomberg et al., 2007).***

An American study showed that the mortality rate from bacteremia and the hospital costs for surgery-related infections were nearly twice as high for patients infected with ESBL-producing bacteria than for patients infected with non ESBL bacteria ***(Janson et al., 2008).***

Increasing prevalence of resistance has been reported in many pathogens over the years in different regions of the world including developing countries ***(Byarugaba, 2008).*** This has been attributed to changing microbial characteristics, selective pressures of antimicrobial use, and societal and technological changes that enhance the development and transmission of drug-resistant organisms. Although AMR is a natural biological

phenomenon, it is often enhanced as a consequence of infectious agents' adaptation to exposure to antimicrobials used in humans or agriculture and the widespread use of disinfectants at the farm and the household levels ***(Walsh, 2008).***

It is accepted that inappropriate and irrational use of antimicrobials is the single most important factor responsible for increased AMR ***(Byarugaba, 2004 and Aarestrup et al., 2005).***

Other causes of increased AMR include inadequate national commitment to a comprehensive and coordinated response, insufficient engagement of communities, weak or absent surveillance and monitoring systems, inadequate systems to ensure quality, an uncontrolled supply of medicines, and poor infection prevention and control practices ***(Arias and Murray, 2009).***

Megha et al. (2012) reported that, AMR reduces the effectiveness of treatment because patients remain infectious for longer time spreading resistant microorganisms to others. When infections become resistant to first-line medicines, more expensive therapies must be used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and societies. Without effective

antimicrobials for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised.

The emergence and spread of resistance in Enterobacteriaceae are complicating the treatment of serious nosocomial infections and threatening to create species resistant to all currently available agents ***(WHO, 2011).***

Approximately 20% of *Klebsiella pneumoniae (K. pneumoniae)* infections, 25% of *Escherichia coli (E.coli)* infections and 31% of *Enterobacter spp* infections in intensive care units in the United States involve strains not susceptible to third generation cephalosporins ***(CDC, 2011).***

Such resistance to third-generation cephalosporins is typically caused by the acquisition of plasmids containing genes that encode for Extended-Spectrum Beta-Lactamases (ESBLs), and these plasmids often carry other resistance genes as well. ESBL-producing *Enterobacteriaceae* have now emerged in the community as well ***(Paterson, 2006).***

Genetic sources of resistance:

The genes for the resistance mechanisms may be located on either the chromosome or plasmids. Plasmids are circularized pieces of (DNA) that act independently of the chromosome. The practical significance of the difference is that

the chromosomal DNA is relatively stable, whereas the plasmid DNA is easily mobilized from one strain to another. In addition, the linking of resistance genes for multiple antimicrobial agents on a plasmid allows the bulk transfer of resistance that characterizes many newly resistant organisms ***(Florence et al., 2007).***

When resistance determinants are on plasmids, they will spread quickly within the genus and even unrelated bacterial genera. When resistance is associated with genes on chromosomes, resistant microorganisms will spread more slowly ***(Dakh, 2008).***

The mechanisms of horizontal transfer of resistance genes between bacteria are conjugation (commonest), transduction and transformation ***(Wickens and Wade, 2005)***.

Another transfer mechanism is the transposon (transposable genetic element). Transposons can carry portions of plasmids. More importantly, they can also carry a piece of the chromosome from one bacterium to another by conjugal transfer. The result may be a mosaic of genetic material from the donor and the recipient bacteria ***(Todar, 2012).***

Gupta ***(2007)*** reported that, the emergence of a phenotype resistant to antimicrobial agents depends on various factors including for example: degree of resistance expression,