Research Journal of Chemical Sciences _____ ISSN 2231-606X
Vol. **5(4),** 85-88, April **(2015)** *Res. J. Chem. Sci.*

Review Paper

A New Threat of Bacterial Resistance towards Life Saving Carbapenem Antibiotics

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Available online at: www.isca.in, www.isca.me
Received 16th December 2014, revised 2nd February 2015, accepted 17th March 2015

Abstract

Carbapenems are new class of beta lactum antibiotics which are known for their broad spectrum of clinical activities to counter gram positive and gram negative bacteria thus named as agents of last line antibiotics or last resort antibiotics. There are n numbers of carbapenem antibiotic brands available in market with different formulations to treat various severe infection. More and uncontrollable usage of these antibiotics leads to formation of resistant pathogens which later changes to serious and complicated health issues. The main threat of these life saving drugs in entire antibiotic armamentarium is its resistance international organization conducted a research by CDDEP , illustrated that carbapenem retailed sale has been increased from past several years which predicts that carbapenems are used in inflating rate by health professionals. The present study is an attempt which has been made to study the factors responsible for inflating carbapenems resistance.

Keywords: Carbapenems, Beta lactum, armamentarium.

Introduction

Human health care took a charismatic term about 70 years ago when wonder drugs 'antibiotics' were introduced.It was like revolution in the medical science and since then new generation antibiotics are been invented and used to treat deadly infections. Carbapenems are the new class of antibiotics usage of which are versatile, and particulary used as last potent defender against multi resistant bacterial sepsis. Six fold increases has been occurred for uses and misuses of antibiotics, which includes carbapenems sale -a powerful life saving beta lactum antibiotic used to treat dangerous infections occurred by MDR (multi drug resistant) and gram negative and positive pathogens. Centre for disease dynamics, economics and policy in Washington D.C. conducted a research which states that carbapenem sale has been increased from 0.21-1.23 unit per million in years 2005-2010 resulting in raising antibiotic resistance[1]. This study has also revealed that resistance to carbapenems is developing very fast. In the present article the attempt has been made to look for various factors responsible for carbapenem resistance, and precautions required overcoming this intimidation.

Chemistry of Carbapenems

From the literature it has been found that in previous carbapenems, the carbon atom which is located at the C-1 position plays a vital model role in its potency and in its stability against beta –lactamases from other beta-lactam antibiotics like penicillin and cephalosporins.

Mechanism of Action

Since carbapenems belongs to beta-lactams which do not diffuse easily through bacteria cell wall. Carbapenems enter through porins (Outer membrane proteins) into gram negative bacteria. Plasma binding proteins are acylated permanently by entering into periplasmic space. PBP enzymes the transglycolases, transpeplidases and caboxypeptidases enhance the activity of forming peptidoglycan in the bacterial cell wall.

Carbapenems action mechanism is based on the inhibition of peptidase, peptidase cross linking and peptidase reaction of protein binding proteins. Carbapenems have an ability of binding to multiple PBP's. As bacterial call wall formation is continues process, autolysis occurs at the same time, it continues at time if inhibition of PBP's in the end peptidoglycan weakens and results into bursting of cell wall due to osmotic pressure[2].

The genesis of this review is based on the survey conducted in New Delhi, the capital of India where in hospitals have been surveyed to find out the resistance, uses and misuses of carbapenems.

Table-1
Cases reported for Carbapenem resistance in various Hospitals

Hospital Name	Cases reported for carbpenem resistance
Safdarjung Hospital	4
Chest and Heart Hospital	6

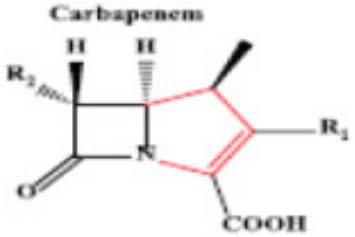

Figure-1(A)
Showing atom in Carbapenems at C-1 position

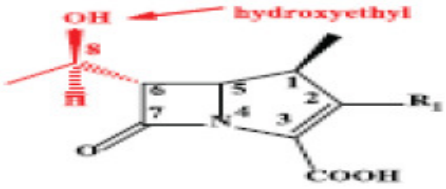

Figure-1(B)
The strategically spaced hydroxyethyl group at side chain of R-2 provides hydrolytic resistance by beta lactamases

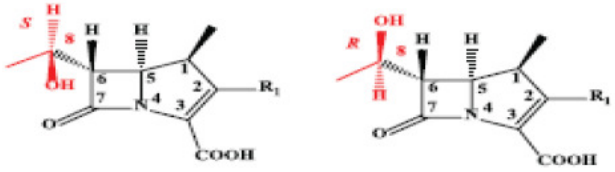

Figure-1(C)
Configuration of R at C-8 positioned are one of very strong carbapenem

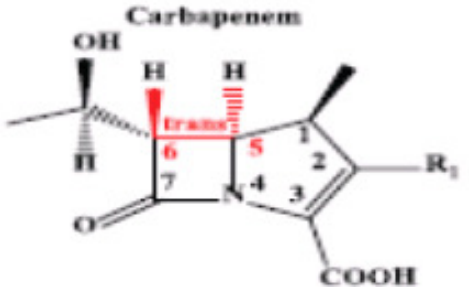

Figure 1 (D)
In Thienamycin, R is at position of C-8 and is trans for about C-50- C-6 bond
Carbapenems, tetrahydropyrrole (CH2)4NH with moiety like (doripenem, meropenem, eratapenem etc) shows in no. of side chain cyclic amines having a broad spectrum of antimicrobial activities

Above hospitals were surveyed wherein ICU Critical Care patients were 11 out of which 4 in Safdarjung hospital and 6 in Chest and Heart hospital shows resistance to carbapenems.

Mechanism of Resistance of Carbapenems

Various gram negative and positive bacterias are posing serious threat towards public by getting resistant to last resort carbapenem antibiotics.

Resistance mechanism of carbapenem is due to: production of beta lactamses, efflux pumps, mutations that alter expressions

Productions of beta lactamases which hydrolyses carbapenems, certain outer membrane proteins shows impaired expressions as due to diminished permeability, efflux pumps crosses drug across outer membranes, production of an altered expressions or low affinity targets are relevant characteristics of gram positive bacteria.

Gram negative bacteria show frank resistance through enhanced efflux, impairment in permeability.

Hydrolysation of carbapenems are readily done by class B beta lactamases, these are zinc dependent metalloenzymes. stenotrophomonas maltophilia and Elizabeth kingiea are species which are resistant to carbapenems due to beta lactamases (B class) production.

Carbapenems of KPC type have shown features as important carbapenem resistant in gram negative bacteria. Also, absence of Opr D porin protein is responsible for carbapenem resistance in P. aeruginosa in combination with production of Amp C-Beta lactamases.

Imipenem is substrate of Opr D and it gets effected most whereas its effect is seen less in meropenem and doripenem. These meropenem and doripenem shows characterstic features as tripartite multi drug efflux system i.e MeXA-MeXB-Opr M where MeXB is a cytoplasmic protein, and MeXA is a protein for fusion of membranes by linking them together and Opr M is component of outer membrane to form channels.

Gram negative bacteria like PBP2a, PBP5 in oxacillin resistant staphylocii and enterococcus faecium shows carbapenem resistance due to production of low affinity PBPS.

Causes of threatning carbapenem resistance: Misuse of antibiotics: study on Indian population has revealed that 90% of people in a country misuse antibiotics due to over cautiousness of health .as believes of past experiences people take antibiotic at first onset of symptoms for fast cure which leads resistance as body will get prone of that particular drug[3].

Over usage of drugs: antibiotics are taken without consulting the health professionals for certain period of time, even if the disease has been cured, due to lack of knowledge of antibiotic treatment and its course people do take it for months and years[4].

Health ministry of India is anxious about overuses of antibiotic due to which it is planned to forbid the availability of latest generation of antibiotics from general pharmacies[5].

Table-2
Uses of different Carbapenems against infections and there side effects

S. NO	Site	Infection by pathogens	Carbapenem used
1	Intra abdominal	Bacteroids thetaomicron, eubacterium lentum, bacteroides fragilis, clostridium clostridiforme, bacteroides uniformis, bacteroids ovatus, bacteroids distasonis, Escherichia coli.	Eratapenem Commom side effects: i. Bleeding, blistering, burning, coldness ii. Discolouration of skin, Skin rash, soreness, tenderness, iii. inflammation iv. Redness of skin
2	Skin and Skin Structure	prevotella bivia, klebsiella pneumoniae, streptococcus agalactiae, proteus mirabilis, porphyromonas asaccharolytica, staphyloccus aureus, Escherichia coli	
3	Infections of respiratory tract	Haemophilus influenzae (beta-lactamase negative isolates only) Streptococcus pneumoniae (penicillin susceptible isolates only) ,Haemophilus influenzae or Moraxella catarrhalis.	
4	Infections of Lower respiratory tract	Streptococcus agalactiae, Escherichia coli,Proteus mirabilis, or Prevotella bivia, Staphylococcus aureus (methicillin susceptible isolates only), Streptococcus pyogenes, Klebsiella pneumonia, Bacteroides fragilis, Peptostreptococcus species, Porphyromonas asaccharolytica	
5	Infections of Urinary tract	Enterobacter species,Staphylococcus aureus (penicillinase-producing strains), Klebsiella species , Escherichia coli, Morganella morganii	
6	Gynecologic infections.	Pseudomonas aeruginosa , escherichia coli, staphyloccus aureus, serratia species, bacteroides species, bacteroid fragilis, enterobacter species.	Imipenem/cilastatin and meropenem. Common side effects: i. Redness and swelling at injection site. ii. Chills, itching of skin. iii. Rapid, shallow breathing iv. Sweating, confusing v. Bluish lips or skin
7	Bacterial septicemia**.**	Staphyloccus epidermidis , pseudomonas aeruginosa, enterobacter species, staphyloccus aureus (penciilinase producing strain), streptococcus faecalis.	
8	Bone and joint infections.	Peptostreptococcus species, klebsiella pneumoniae, escherchia coli, pseudomonas aeruginosa , bacteroides fragilis, bacteroids thetaiotomicron, viridians group.	

Usage of expired antibiotics: This is common practice that while buying the medicine we never check the manufacturing date and expiry period of an drug we do take medicine which are expired ones resulting a disease to be inoperable .

Ecological factors: Once the antimicrobial treatment cease, resistant forms can occur after treatment or it may develop during treatment due to which antibiotic residues found in environment for long period of time[6].

Beside antibiotic there are other antibacterials in house hold products, these too enter in the environment thus resulting in altered ecology of microbes.

Deficient diagnosis: Incomplete or imperfect information to diagnose infection and prescribing of antimicrobials of broad spectrum instead of giving specific antibiotic leads to multi drug resistance to various pathogens.

Vetinary use: Concern is for rapid use of antimicrobials for animals for therapeutic uses, can lead to development of drug resistant pathogens which transfers to humans via food products[7].

Agricultural use: It has been reported that animals which are treated with anti microbials their fecal matter used in composition of fertilizers leads in contamination of environment

with developing resistance[8].

Precaution to avoid carbapenem resistance

Do not Medicate ownself: People should be aware of antibiotics with their classes and their mode of actions without knowing one should not medicate themselves.

Lack of Awrenesses: Since carbapenem is being a broad spectrum antibiotic people do take them for long period of time at onset of early symptoms which will results in developing a slow resistance to carbapenems

Avoid Prolong use of Drug: People do take medicine regularly as when they were taking it at time of infections, in a fear that if they cease themselves to take medicines it leads to reoccurrence of infection this unmeaningful assumption made by people leads various adverse reactions in the body with complications of resistance.

Health professionals should minimize unnecessary prescribing and over prescribing of antibiotics this situation occurs when people pressurize doctor to prescribe antibiotic for the conditions that is not required.

Use of clean, neat and contaimination free infection control procedures, Practice of good hygiene.

Conclusion

Mortality of carbapenems is decreasing very slowly; causes are due to many factors like their inflated use, their misuse, their overuse, self medications etc. Since carbapenem is a broad class of clinical spectrum activities in order to kill or inhibit the growth of bacteria, any misuse leads to strengthens the bacteria which can be neutralize by impact of antibiotics.

Painter has discussed about mechanism of antibiotic resistance, he illustrated that when any microbe is exposed to any antibiotic, the most vulnerable will die quickly and leaving the strong harder bacteria to survive, doage and administration frequencies permit these harder bacteria to kill[9]. Moreover, if single bacteria survives it multiplies and produce billions again, and if none of bacterium survives, the mutation of this bacterial DNA generates no of genetic alterations which later confer antibiotic resistance[10]. WHO warned entire world about post antibiotic era, where it states that common infections will not be cure for longer as antibiotics introduced in 1940s known as wonder drugs now are extensively used however, now situation is atrocious because of developing resistance.

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