CARBAPENEMS COMPARATIVE ANALYSIS: A COMPREHENSIVE REVIEW

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Abstract
Carbapenems are the very vast group of β-lactam antibiotics containing a very broad spectrum for clinical isolates. Some of the carbapenem like Imipenem have a tendency to rapidly degrade by renal tubular enzyme present in proximal tubules DHP-1 therefore they can't produce their action therefore they should administer with the DHP inhibitors in combination it contain cilstatin with imipenem, meropenem and other carbapenem drugs are not vulnerable to DHP degradation so could be used as a single entity. Carbapenems produce their action by inhibiting cell wall synthesis through its binding with PBP (penicillin binding proteins). All carbapenems have different affinity to bind with PBP sub proteins like imipenem prefer to bind with PBP2, PBP1a and PBP2a while meropenem instead of PBP2,1a and 1b binds with PBP3. Carbapenems have a broad spectrum of activity against gram positive strains, gram negative negative strains and ESBL while it have no activity against pseudomonas species, enterococci species, acenitobacs species. The drugs Meropenem, Imipenem and doripenem have about half life of 1 hour approximately while the only carbapenem that containig a half life of about 4 hr is ertapenem so it allows once daily administration of ertapenem. Meropenem is the only carbapenem approved by FDA in treatment of meningitis. Other carbapenems including doripenem Imipenem and meropenem approved by FDA for the treatment of intra abdominal infections, skin infections, febrile neutropenia, urinary tract infections, lower respiratory tract infections, nosocomial infections etc. In short meropenem, doripenem and Imipenem/cilastatin is very efficiently treat various polymicrobial infections and nosocomial infections while ertapenem according to its structural variations more prefer to treat community acquire infections rather than nosocomial one.

Keywords: Carbapenems, comparison, their mechanism of action nd resistance, pharmacokinetic and Pharmacodynamics, indication and contraindication, adverse effects and drug interaction of carbapenems.

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INTRODUCTION

Beta lactamas are the very most frequent antibiotics having a versatilevareity of group of drugs and carbapenems are one of them. From 1940 scarbapenems are using in medical field. itinclude very most common anti-infective drugs including meropenem, imipenem, doripenem etc. globally the carbapenems are using in the treatment of severe polymicrobial infections and nosocomial infections. Theinamycin was the first carbapenem introduced in 1970s the compound theinomycin that is produced by streptomycescattleya. Imipenem is the member of this class which have the unstable nature because it forms the N-formimidoyl derivatives. However imipenem undergoes to a rapid degradation by a proximal renal tubule enzyme i:e. DHP-1 (dehydropeptidase-1). So for this reason imipenem is always used in a combination with DHP-1 inhibitor that is cilastatin.

The use of this combination (imipenem/cilastatin) has two advantages as it decrease the risk of nephrotoxicity and also prevent degradation of imipenem from proximal renal tubules. After the discovery of theinamycin next carbapenemmeropenem is the second drug introduce in America [1-3].

Heeding to the microbiological studies the meropenem have slight more active against gram positive strains while imipenem is quite more active against gram negative isolates.Ertapenem is the another member of this class having long half life and requires once a daily dose and its only used for the treatment of serious infections.

Doripenem is the newer agent of this class and still passing from clinical trials. Doripenem have same spectrum of activity as that of meropenem and imipenem instead it is slight more active against pseudomonas aeriginosa.

The purpose of this review is to compare many carbapenems activity in comparison with respect to their pharmacokinetics, pharmacodynamics, chemistry, microbiological studies, indication etc.. [4-5].

Faropenem is not actually a carbapenem but could study under beta lactams drugs it is only disscuss here in details because it’s not in actual to be consider in carbapenem class of drug.

Feropenem (medoxomil) is the new drug orally administer and have activity against isolates.it have chiral tetrahuydrofuran substitute at position C2 which is responsible for its antibacterial activity and also reduce its CNS effect as imipenem could develop seizures. It was observed that feropenem have antimicrobial activity against many gram positive and gram negative strains.
It has one beneficial point that it is resistant to the hydrolysis of beta-lactams ring by beta lactamase enzyme. Clinical trials suggest that feropenem have the same activity as that of cefuroxime, clarithromycin, azithromycin, amoxicillin, augmentin and cefpodoxime. The drug feropenem is not active against MRSA, ESBL, vancomycin resistant sp. And some *pseudomonas aeruginosa* sp.

Currently the FDA and American health care professionals not accepted feropenem because it does not have that broad kind of spectrum against clinical isolates [6-9].

The objective of this study was the comparative review of carbapenems and the study was based on previous published data collected from PubMed and other publications of last 10 years.

**Chemistry**

Carbapenems differ from penicillins in a way that it have sulphur group instead of carbon at position 1 and an unsaturated bond is present between the position C2 and C3 in the 5 member ring structure. As shown in **figure 1**.

The older one carbapenems Imipenem and panipenem could undergoes DHP-1 degradation hence given in the combination of DHP-1 inhibitors like cilastatin is given with Imipenem and betamipron is given with panipenem. Meropenem are different from Imipenem in a way that they have pyrrolidinyl substitute present at position 2 as shown in **figure 2** [10-13].

This prefer its activity against *gramnegative pathogens* and *pseudomonas aeruginosa* while comparing with Imipenem ertapenem is just similar to meropenem but there is a difference that it have benzoic acid group at position 2 as shown in **figure 2** [14-15].

Due to this substitution ertapenem have high molecular weight and increase its lipophilicity and at physiological pH it creates a negative charge on benzene ring.

Ertapenem have longer half life due to this ionized benzene ring presence in its structure it have the unique antimicrobial spectrum in a manner that it have ionized molecule and have activity against gram negative strains.

Doripenem is another new agent of this group it is effective against fermentative gram negative bacilli because it have sulfamoylami-noethyl-pyrrolidinylthio group in chain at the position 2. Tebipenempivoxil, new oral carbapenem it has 1 (1,3-thiozolin-2yl)azetidin-3-ylthio group at position 2.

Tebipenem is converted to its active metabolite by the intestinal enzyme esterase and then absorb in blood stream and it is highly stable on DHP-1 degradation [16].
Mechanism of action

All beta lactam antibiotics produce their action through penicillin binding protein (PBP). The binding of β-lactam molecule to PBPs prevent the bacterial cell wall synthesis by blocking the cross linkages of transpeptides to peptidoglycan strands. All the carbapenems have different intensities to binds with PBP therefore meropenem and doripenem as compared to imipenem are more effective against gram negative strains. Imipenem preferentially binds with PBP2 followed by PBP1a and PBP1b and has less intensity to binds with PBP3. While on the other hand meropenem and ertapenem most prefer to binds with PBP2 followed by PBP3 but they also affinitive for PBP1a and PBP1b [17-19]. Doripenem is differ from other carbapenems in a way that it have species specific intensities for binding with PBPs e.g. PBP3 in p. aeruginosa, PBPs 1,2 and 4 in s. aureus and PBP2 in E. coli. Tebipenem have strong affinities for PBPs 1a,2b and 3 in clinical isolates of streptococcus pneumonia. In gram negative isolates carbapenems have more bactericidal activity because of
their great affinity to binds with PBP 1a, 1b and 2 rather than the PBP 3 that consider to be the primary target for penicillin and aminoglycosides. The drugs that binds to PBP 3 first done filamentation of bacterial cell wall then cause lysis but carbapenemautolyse bacterial cells without causing filamentation [20-21].

**Mechanism of resistance**

The gram negative strains that are resistant to β-lactams(e.g third generation cephalosporin) are known to be sensitized by carbapenems because of their stability towards β-lactamases including ESBL &AmpC β-lactamases.despite of these ESBL producing isolates are also sensitive to ertapenem heeding to the clinical and laboratory standard institute (CLSI) [2005] breakpoints. Along with membrane permeability defects ESBL could confer resistant to *k.pneumonia*.heeding to the studies ertapenem is less stable to β-lactamases as compared to other carbapenems. Despite of broad spectrum of carbapenems some organisms demonstrated the intrinsic resistance. Resistance mostly develop due to the poor binding affinity of all β-lactams including carbapenems to PBP2a in MRSA (methicillin resistant staph. Aureus) and PBP5 in *E.faecium*.*p.aeroginosa* is the most common pathogen and is resistant to the β-lactams but still these are sensitive to carbapenems. Ertapenem has no anti-pseudomonal activity but still are not resistant with *p.aeroginosabecause it reduced membrane permeability and it also increase efflux pumps possibly. Imipenem isn’t subjected to efflux while meropenem and doripenem over expression of efflux pump of multi drug may also be confer resistance.

As compared with Imipenem doripenem and meropenem have slightly more anti-pseudomonal activity because Imipenem require multidrug efflux pump and membrane permeability defects for conferring resistance [22].

**Pharmacokinetics**

Carbapenems globally administer through parientral route because they cannot absorb from intestine. Meropenem is administering through IV route 15-30 min for IV infusion and 2-3 min for IV bolus. Intramuscular administration could also give. It rapidly diffuse in body tissues like soft tissues, gynecological tissues, muscle, omentum, lungs and body fluids including peritoneal fluid, CSF and blister fluid. In an order of 15-20L meropenem distributes in the body. only 2% of drug is bound to plasma protein in case of meropenem, Imipenem 20% bounds to plasma proteins and ertapenem bounds to plasma proteins very extensively. The only carbapenemertapenem have the
long half life as compared to all other carbapenem. They are excreted from kidney. Most of the drug recover unchanged in urine.[23-24]

**Distribution**

Imipenem could be penetrate in many tissues compartment while meropenem penetrates in various body fluids. After a 500mg dose IV infusion Imipenem reaches to body tissues in following concentrations: 2.2mg/kg in tonsillar tissues, 14-102 mg/kg in renal medulla. 5.3 mg/kg in prostatic tissue.

While that of meropenem after a 1000mg of IV infusion at 1.5-2.5 hr distributes to tissues and fluid in following concentrations: 1.4-8.2mg/kg in colon, 3.9mg/kg in skin and 0.6-4.5 mg/kg in gall bladder.

The distribution of ertapenem was observed in suction induced skin blister and it was seen that after 1g Od IV infusion till 3 days the plasma concentration of drug 24.4mg/L in 8 hours and 7.8mg/L after 24 hours.

The entire concentration of ertapenem in tissues is 16mg/kg in gall bladder, 12mg/kg in colon and 7.02 mg/kg in small intestine [25-27].

**Metabolism and elimination**

Imipenem is rapidly metabolized by DHP-1 enzyme in proximal renal tubule so that’s a reason they should administer with cilastatin the DHP-1 inhibitor both of the drugs Imipenem and cilastatin have approximately the same 1 hour half life. 60-70% of Imipenem excreted unchanged in the cilastatin presence.

Meropenem and ertapenem however stable to DHP-1 enzyme hence could be administer alone about 70% meropenem excreted in urine as a parent compound.

Glomerular filtration and secretory process are responsible for ertapenem excretion.

Dosage adjustment is require for renal compromise patient as carbapenems are extensively excreted form renal route as shown in table 1.

Heeding to observational studies the Imipenem half life increases 4 hours in case of patients whom creatinine clearance is more than 10 and the half life of meropenem increases 7 hours for that patients while ertapenems'shalf life increases 14 hours. Among the 1000mg of ertapenem 30% of drug is remove during 4 hours of hemodialysis.

So supplemental ertapenem dose is require in that case about 150mg [28-30].
Table 1: recommended meropenem dosage schedule for adult renal impaired patients

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dose (depend on type of infection)</th>
<th>Dose interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>Recommended dose (500mg cSSI &amp; 1g intra abdominal)</td>
<td>8 hours</td>
</tr>
<tr>
<td>&gt;25-50</td>
<td>recommended dose</td>
<td>12 hours</td>
</tr>
<tr>
<td>10-25</td>
<td>One half recommend dose</td>
<td>12 hours</td>
</tr>
<tr>
<td>&lt;10</td>
<td>One half recommend dose</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Pharmacodynamics

All of the β-lactams specially carbapenemshaving the dominenentpost antibiotic effects (PAE) for both gram negative and positive strains. the range of PAE for E.coli and p.aeroginosa is 2-4 hours respectively with Imipenem. While with meropenem the PAE for E.coli and pseudomonas aeroginosa is 4-5 hours. On S.aureus the ertapenem and Imipenem exhibit the PAE effects of 1.5-3.5 hours respectively after ten times exposure to MIC (minimum inhibitory concentration). The mechanism of action is discussed as above.[31-32]

Indications

Carbapenems are used for various infectious disease since decades. The data about clinical trials and indication of meropenem, Imipenem and ertapenem was based on previous published data obtained from PubMed last 10 years. The doripenem have no clinical trials been performed yet it is still in controversy.

Complicated intra abdominal infection

Imipenem/clistatin is the combination of drug use with cefepime in the treatment of complicated intra abdominal infection. In a clinical trial it was examined that meropenem and cefotaxime with metronidazole treated the infection in 161 patients the patients were suggested to take 1g meropenem thrice a day daily and some patients suggested to take combination of cefotaxime/metronidazole after 8 weeks the results shows that the patients group whom taken only meropenem till 8 weeks have 93% positive results while other group of patients declare 92% of the results. The prevalence of adverse effects for meropenem group is 32% and that of cefotaxime/metronidazole have 25% adverse effects. The clinical trials for ertapenem used in complicated intra abdominal infections is 84%. the intra abdominal infection mostly caused by klebsiellapneumonia, s.aureus, pseudomonas aeroginosa, E.coli etc and carbapenems have great spectrum of activity against these gram positive and negative pathogens. The usual dose of doripenem require to treat intra abdominal infection is 500mg every 8 hours [33].
Urinary tract infection

In the treatment of UTI ertapenem 1g and ceftriaxime 1g both administered to the patients. the urinary tract infection including polynephritis it is caused by *E.coli*, *klebsiella pneumonia*, *proteus mirabilis* and *pseudomonas aeroginosa* the carbapenems like doripenem 500mg every 8 hours could efficaciously treat urinary tract infection and polynephritis.

Complicated skin and skin structure infection

Ertapenem is approved by FDA to treat skin and skin structure infections that is caused by mostly *S.aureus*(methylene susceptible strains only), *streptococcus pyogens*, *E.coli* etc. the usual dose of 1g once daily  ertapenem is approved for skin infections the spectrum of activity is not approved for acinetobacter species or pseudomonas species. the spectrum of activity makes it more suitable for community acquired pneumonia rather than nosocomial infections [34].

Appendicitis and peritonitis

Meropenem in a usual dose of 500mg to 1gm every 8 hours could treat appendicitis and peritonitis. appendicitis is the infection of appendix and peritonitis is the inflammation or infection of peritoneal cavity. The infection caused by *viridans streptococci*, *E.coli*, *Klebsiella pneumonia*, *pseudomonas aeroginosa*, *B.fragillis*.

Meningitis

In childrens of 3 months of age and older could suffer from meningitis. The infection of meninges is due to *streptococcus pneumonia*, *Neisseria meningitides* or *h.influenza*. themonotherapy in this case in yet not established. Meropenem is the only carbapenem approved to treat meningitis. the dose of meropenem for meningitis is same that of appendicitis and peritonitis i.e. 500mg to 1g every 8 hours depending on the patient condition. Dose adjustment is required in case of renal compromised patients.

Diabetic foot infection

The patients of diabetes are more vulnerable to foot infection and for that purpose carbapenems efficiently used in diabetic foot infection or gangrenous conditions. According to the clinical trial studies the ertapenem and piperacillin/tazobactam both have the same level of cure in diabetic foot infectious conditions.

Community acquired pneumonia

For the treatment of community acquired pneumonia 1g ertapenem is combinely studied with ceftriaxone 1g during clinical trials studies. The adverse effects mostly observed including diarrhea and nausea elevated serum transaminase level may also observed during this therapy.

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CAP is mainly caused by *streptococcus pneumonia*, *influenza* and *moroxellacatharlis*. The global dose of ertapenem is 1 gm once daily for community acquired pneumonia.[35]

**Nosocomial pneumonia**

The most commonly nosocomial infections caused by gram negative isolates includes *pseudomonas aeroginosa* the therapy choice depends on the local resistance pattern. Carbapenems have less spectrum of activity for nosocomial infections.

**Febrile neutropenia**

In cancerous patients the condition of febrile neutropenia could control by given carbapenem but cefuroxime is more better choice to encounter febrile neutropenia.

**Other indications**

Imipenem is used to treat lower respiratory infection, sepsis, endocarditis and in gynecological infections at the dose of 500mg to 6 and 8 hours. Imipenem have a risk to develop seizure so should be used under clinical consideration.

**Contraindication**

The carbapenems are not active against acenitobacter species, pseudomonas species and enterococci species so contra indicated in that infections. Imipenem/cilastatin is contraindicated in CNS patients, stroke and dose adjustment require for renal impaired patients in case of meropenem.carbapenems should also be avoided in some type of allergies.[36-38]

**Adverse effects**

Diarrhea , rash, nausea , vomiting and local irritation at the injection site are the most common adverse effects of meropenem and Imipenem/cilastatin. These all are mild adverse effects and could be the major determinant leads to discontinuation of therapy in 1.4% patients. Nausea, diarrhea, infused vein complications are the main adverse effects of ertapenem the determinant that leads to discontinuation therapy of ertapenem in 1.2% patient is due to rash or gastrointestinal disturbanes.

Like the other antibiotics of beta-lactam group the Imipenem/cilastatin, meropenem, ertapenem can also evaluate some lab test like alanine amino transferase, lactate dehydrogenase and alkaline phosphatase etc. the serum creatinine and serum urea level also observed to increase by meropenem and Imipenem/cilastatin and some hematological distrubances was also observed including thrombocytopenia , eosinophilia.ertapenem could develop the drug induced neutropenia.
Imipenem have a high risk to develop seizure in vulnerable patients. The patients of renal impaired function, pre-existing CNS disease, stroke and high dose of Imipenem/cilastatin could also make person susceptible to drug induced seizures. Meropenem is the only drug to treat meningitis and have less chances to develop seizures. The comparative study of indications of carbapenems is shown in table 2.[39-41]

**Drug interaction**

Renal clearance of Imipenem/cilastatin could decrease 30% by use of probenecid with it. As compared to Imipenem cilastatin is more disturbed by probenecid. The patients who receives ganciclovir therapy and Imipenem/cilastatin are more vulnerable to develop generalized seizures. The plasma half life of ertapenem is increase by probenecid use because it can inhibit its renal tubular secretion and increase its half life from 4 hours to 4.8 hours. Meropenem is observed to increase valproic acid plasma concentration. The drug interaction related to ertapenem metabolism by cytochrome p450 enzyme is not approved for any drug interaction [42-43].

**Table 2: comparative study of carbapenems**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approved indications</th>
<th>Usual adult dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doripenem (doribax)</td>
<td>Complicated UTI, Complicated intra-abdominal infections, Community acquired pneumonia</td>
<td>500mg every 8 hours</td>
<td>Spectrum of activity similar to Imipenem/cilastatin and meropenem</td>
</tr>
<tr>
<td>Ertapenem (invanz)</td>
<td>Complicated intra-abdominal infection, Complicated skin infection, Complicated UTI, Community acquired pneumonia, Acute pelvic infection</td>
<td>1 gm once daily</td>
<td>Spectrum of activity makes it more active against community acquired infections compared to nosocomial infections.</td>
</tr>
<tr>
<td>Imipenem/cilastatin (primaxin)</td>
<td>Lower respiratory tract infection, UTI, Gynecological infection, Sepsis, Endocarditis, Polymicrobial infections, Skin infections, Intra-abdominal infections</td>
<td>500mg to 1g every 6 to 8 hours (depending on indication)</td>
<td>Not active against MRSA</td>
</tr>
<tr>
<td>Meropenem (merrem)</td>
<td>Skin infection, Appendicitis meningitis</td>
<td>500mg to 1g every 8 hours (depend on indication)</td>
<td>The single carbapenem approved for meningitis.</td>
</tr>
</tbody>
</table>
Role in therapy

Carbapenems have broad spectrum of activity as compared to other β-lactams antibiotics even it could also be used to treat infections caused by ESBL &AmpC beta lactamases. Imipenem have high risk of seizure development so never could given a psychological disturb patients while meropenem have no any risk relate to CNS and meropenem is the only drug used to treat meningitis. All of the carbapenems could used in various nosocomial and poly microbial infections. Ertapenem have less activity against nonfermentative gram negative pathogens like enterococci and aeroginosa species. Ertapenem isn’t approved for the treatment of nosocomial infections as compared to other carbapenems. The long half life of ertapenem allows it single dose daily administration. Tebipenem is the new oral carbapenem have a broad spectrum and stability than other beta-lactams. Ertapenem is clinicallylook after and compared with piperacillin/tazobactam and it shows same activity so efficiently treat moderate to severe ill infectious diseases like community acquired pneumonia, abdominal infections, lower respiratory tract infections, gynecological infections etc. [44-47].

DISCUSSION

Carbapenems comes under the group of beta-lactam antibiotics. it included meropenem , imipenem, ertapenem , tobipenem, panipenem, doripenem etc. heeding to the ling literature review it was proved that carbapenema have very much efficacy against many gram positive and negative strains and could be treat a variety of polymicrobial and nosocomial infections also could be indicated in community acquired infections in case of ertapenem. they have not too much seriously adverse effects except imipenem that have a adverse effect of development of seizures.one more negative point about imipenem is that DHP inhibitor is required for the administration of imipenem in order to decrease its nephrotoxixity and DHP degradation by renal.tubules.but it is consider to be treat a variety of pathological conditions including urinary tract infection, skin infection ,intra abdominalinfections,febrileneutropenia.The purpose of this study was to comparative review of carbapenems with respect to their pharmacokinetic, pharmacodynamics, indication and contra incation, structural differences and their comparison etc. carbapenems are the first of choice in the infection of ESBL which is very resistant to other beta lactam antibiotics this make carbapenem more efficacious for the treatment of severe infections.according to above studies dose adjustment is require for meropenem in case if renal
insufficienypatients. ertapenem have a very long half life so the dose not to exceed once daily administration. probenecid and imipenem.couldn't administer simultaneously because it may interact to each other and decrease 30% renal clearance of imipenem/ cilastatin as it is meropenem could not administer with valproic acid because its plasma concentration increases by meropenem.the whole review comparative studues suggest the use of carbapenems in various moderate to severe infectious diseases. but these drugs should never taken as a self medication.

CONCLUSION

heeding to the whole reveiw study it was concluded that carbapenems have a very broad spectrum of activity and indicated in various infectious diseases. imipenem and meropenem are the most commonly use drugs of thus group while ertapenem and doripenem not used frequently.

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCE


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