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Meropenem: Current perspective

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REVIEW ARTICLE

ABSTRACT

Meropenem is an ultra broad spectrum parenteral carbapenem with excellent safety profile and minimal drug interactions. It is effective in a variety of tissue infections. But to prevent emerging drug resistance, its use should be restricted to complicated/serious infections not amenable to other antimicrobials.

Key Words

Carbapenem, meropenem, drug resistant enterobacteriaceae (DRE).

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INTRODUCTION

Meropenem, a member of the carbapenem family, is an ultra broad-spectrum β-lactam antimicrobial that has been in use clinically since 1994. It covers broad range of Gram-negative, Gram-positive and anerobic bacteria. It continues to be an important option for empirical treatment of serious bacterial infections and also considered as a last resort against ESBL (extended spectrum β lactamase) producing bacilli in intensive care settings.

Pharmacology - Like other carbapenems, meropenem is stable against chromosomal and extended-spectrum β-lactamases. But unlike imipenem, it does not require concomitant administration of cilastatin to inhibit human dehydropeptidase.[1,2]

Meropenem is not absorbed orally. It is administered intravenously as an infusion (over 15-30 minutes) or bolus injection (over 3-5 minutes). It can be given intramuscularly also. It rapidly achieves therapeutic level in various tissues (colon, gall bladder, fascia, muscle, omentum, skin, lungs, heart, kidney, and gynaecological organs) and body fluids (CSF, skin blister fluids and peritoneal fluid). [1,2,3]

It is widely distributed in humans, with a volume of distribution (V D) at steady rate on the order of 15-20 L. Only 2% drug is bound to plasma protein. Its elimination $t_{1/2}$ in an adult with normal renal function is approximately one hour and in children less than 2 years of age, it is around one and half hour. It is rapidly excreted by the kidney (by both glomerular filtration and tubular secretion) with 80 % of excretion occurring within 3 hours and increasing to 95% within 8 hours of administration. In urine, 60-80% of drug is excreted as such with only 15-25 % as an inactive open β-lactam metabolite (ICI 213,689). Around 2% of drug is excreted in faeces. [1,2]

Mechanism of action - Meropenem is a bactericidal agent. By binding to the serine residue of transpeptidase (Penicillin binding protein) and rendering it inactive, meropenem interferes with bacterial cell wall synthesis. Marked affinity for multiple different PBPs, and resistance to all serine beta-lactamases explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria.[4,5]

Antibacterial Spectrum - Meropenem is active against wide range of Gram-negative (including ESBL producing) , Gram positive and anaerobic bacteria. Its in-vitro susceptibility pattern include [2,5]-

Gram-negative group - Escherichia coli , Haemophilus influenzae , Klebsiella pneumoniae , Neisseria meningitidis , Pseudomonas aeruginosa , Proteus mirabilis, Proteus vulgaris, Enterobacter, Citrobacter, and Acinatobacter. Stenotrophomonas maltophilia are inherently resistant to the carbapenems including meropenem.

Gram-positive group - Enterococcus faecalis, Penicillin susceptible staphylococcus aureus, Penicillin susceptible

staphylococcus epidemidis, Streptococcus viridians (penicillin-susceptible isolates only) and Corynebacterium diphtheriae. It is not active against E. Faecium, and MRSA.

Anaerobes- Bacteroides fragilis, Fusobacteria, Propionibacteria, Peptostreptococcus and Clostridium group.

Emerging drug resistance –Recently Gram negative rods resistant to carbapenems have been reported. Mechanisms of resistance included modified penicillin-binding protein affinity, decreased uptake of β-lactams, production of carbapenem-hydrolyzing β-lactamases, and decreased outer membrane permeability.[4,6]

Comparison of meropenem with other carbapenems and piperacillin/tazobactam – Meropenem is 2 to 4 fold more potent than imipenem against Enterobacteriaceae, including strains producing ESBLs or AmpC. Doripenem is the most potent carbapenem against Pseudomonas. Ertapenem is not avtive against pseudomonas. Piperacillin/tazobactam is more potent than carbapenems against P.aeruginosa (90% of susceptible strains versus 84% for carbapenems).[7]

Ranking of meropenem against gram-negative isolates – The overall rank order of susceptibility is: meropenem (98%) > imipenem (97%) > cefepime (95%) > tobramycin (93%) > piperacillin/tazobactam = gentamicin (92%) > ceftazidime (91%) > ciprofloxacin (87%) > aztreonam (86%) > ceftriaxone (74%). [8]

Dosage – It depends up on age group affected, severity of infection and susceptibility pattern of organism. [5,9]

Types of infection Age group	Complicated skin and skin structure infections	Complicated intra-abdominal infections	Severe infections (Meningitis, severe sepsis), Cystic fibrosis
Adults	500mg per 8 hour	1000mg per 8 hour	2000mg per 8 hour
Infants (>3months) and children	10mg/kg per 8 hour	20mg/kg per 8 hour	40mg/kg per 8 hour

Dosage adjustments

Renal failure - Plasma clearance of meropenem correlates with creatinine clearance, mandating dosage adjustments in renal impairment.

Recommended dosage in patient with impaired renal function. [2]

Creatinine clearance (ml/min)	Dose (dependent on type of infection)	Dosing interval
26 – 50	Recommended dose	Every 12 hours
10 – 25	½ of recommended dose	Every 12 hours
< 10	½ of recommended dose	Every 24 hours

Hepatic impairment – Dose adjustment is not required, as liver disease has no effect on the pK of meropenem.

Geriatric patients - . In elderly patients, age-related decline in renal function leads to delayed and decreased clearance of meropenem. So dosage adjustment is required when creatinine clearance is less than 50ml/min.

Hemodialysis – A certain amount of meropenem and its metabolite is lost through hemodialysis, requiring supplemental dose after the procedure.

Therapeutic use - To reduce the development of drug-resistant bacteria and to maintain the effectiveness of meropenem, it should only be used to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

Meropenem is approved for use in complicated intra-abdominal infection, complicated skin and skin structure infection, bacterial meningitis, nosocomial pneumonia, community-acquired pneumonia septicaemia, febrile neutropenia, complicated urinary tract infection (UTI), obstetric and gynaecological infections, and in cystic fibrosis patients with pulmonary exacerbations. [10]

Adverse drug reactions - In a review of over 6000 patients treated with meropenem, the most common adverse events were diarrhoea (2.5%), rash (1.4%) and nausea/vomiting (1.2%). Overall incidence of adverse events was less than 3%. Initially meropenem was thought to provoke seizure in CNS disorder patients especially meningitis. But in recent studies no new cases of drug related seizure were reported. The most frequent meropenem-related laboratory adverse events were thrombocytosis (1.6%) and increased hepatic enzymes (1.5-4.3%). [11,12]

Penicillin allergy and Meropenem - In individuals sensitive to β lactam group, there is a risk of fatal anaphylaxis with meropenem. But Cunha et al in their study done in 110 penicillin allergic patients reported little or no potential cross reactivity between meropenem and penicillins even in patients with a definite history of anaphylactic reactions to penicillins.[13]

Drug interactions-

Aminoglycosides and meropenem- Uually an additive or synergistic effect is observed against Gram-negative species when meropenem is used in combination with an aminoglycoside.[14]

Vancomycin or Teicoplanin and meropenem – Synergism is observed against Staphylococcus aureus (MSSA), MRSA and Staphylococcus epidermidis. [14]

Rifampicin, cotrimoxazole or ciprofloxacin and meropenem – Synrgism or addition is observed against MSSA, MRSA, and Staphylococcus epidermidis. [14]

Valproic acid and meropenem– Like other carbapenems, meropenem rapidly decreases serum level of Valproic acid to subtherapeutic level. Concomitant administration of both drugs should be avoided, and if unavoidable serum level of Valproic acid should be monitored and therapeutic level should be maintained.[15]

Clavulanic acid and meropenem- The combination of meropenem with clavulanate has high in vitro

antimycobacterial activity against extensively drug-resistant Mycobacterium tuberculosis strains. This combination along with linezolid has been successfully used to treat an advanced extensively drug-resistant tuberculosis disease with complex second-line drug resistance in a case report. [16]
Probenecid and meropenem– Probencid increases $t_{1/2}$ of meroepenem by around 33% by competitively inhibiting tubular secretion of meropenem. [17]

CONCLUSION

Despite in clinical use for around two decades, meropenem has excellent activity against wide range of bacteria especially ESBL producing gram negative bacilli. But recently few strains of gram negative bacilli have developed resistance to it, so it should be reserved for serious bacterial infections. Its use as initial empirical therapy should be implemented only after consideration of local surveillance data and patient characteristics, and once the susceptibility results are available, therapy should be narrowed.

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