Drug Therapy

Meropenem

Dheeraj Shah
Manish Narang

Meropenem is a new carbapenem antibacterial agent with wide spectrum of activity against Gram-negative, Gram-positive and anerobic organisms. It is stable against most β-lactamases produced by Gram-negative bacteria and has greatest utility in treating severe infections in hospitalized children. It has good CSF penetrability and useful in treatment of childhood meningitis and infections in neutropenic children. Due to concern relating to emergence of resistance, it should be used as a reserve drug in difficult-to-treat infections caused by resistant organisms or when conventional treatment fails.

Meropenem belongs to 'Carbapenem' group of antibacterial agents with a broad spectrum of activity against gram-negative, gram-positive and anerobic microorganisms. Meropenem has clinical and bacteriological efficacy in treatment of various serious infections in adults and children. With easy availability, the use of Meropenem is likely to increase and it is essential to keep ourselves abreast of its therapeutic role and safety profile for pediatric patients.

From the Department of Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital, Dilshad Garden, Delhi 110 095, India.

Correspondence: Dr. Dheeraj Shah, 7184 Birla Officers Flats, Kamla Nagar, Delhi 110 007, India.
E-mail: shahdheeraj@hotmail.com

Pharmacokinetics

Meropenem penetrates rapidly and widely into a range of body fluids and tissues(1,2). Meropenem also penetrates into CSF although, as with other β-lactam agents, permeability is greater in patients with meningeal inflammation(2).

Meropenem is primarily excreted by the kidney with about half to three-fourths of dose excreted unchanged in the urine and a further one-fourth excreted as a microbiologically inactive open β-lactam metabolite(3,4). Unlike Imipenem, Meropenem is stable against hydrolysis by human renal dehydropeptidase (DHP-1) and concomitant administration of cilastatin (DHP inhibitor) is not required(5,6).

Spectrum of Activity

Meropenem exerts its bactericidal action by interfering with vital bacterial cell wall synthesis. The ease with which it penetrates bacterial cell walls, its high level of stability to all serine β-lactamases and its marked activity for the penicillin binding proteins (PBPs) explain the potent bactericidal action of meropenem against a broad spectrum of aerobic and anaerobic bacteria. The activity profile of meropenem has been well established in *in vitro* studies and more recently in large surveillance studies(7,8). *In vitro* antibacterial spectrum of meropenem includes the majority of clinically significant Gram-positive and Gram-negative, aerobic and anaerobic strains of bacteria including methicillin-sensitive *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Moraxella catarrhalis, Enterococcus faecalis, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Pseudomonas aeruginosa, Burkholderia*

cepacia, Acinetobacter spp., *Hemophilus influenzae*, and *Bacteroides fragilis* (9,10). As the spectrum of activity of Meropenem extends to over 200 clinically significant bacterial species, only those commonly seen in pediatric infections would be further discussed.

Gram-negative Aerobes

Nearly all Gram-negative bacteria including those producing extended spectrum β-lactamases (ESBL) are susceptible to Meropenem. Pfaller and Jones(7) documented that 99 to 100% of isolates of Gram negative bacteria were susceptible to Meropenem, a performance significantly better than imipenem, ciprofloxacin, piperacillin β–tazobactum, cetotaxime and ceftazidime. Gram-negative bacteria considered to be highly susceptible to meropenem included Hemophilus influenzae and Neisseria meningitis. Meropenem was more effective than imipenem against *P. aeroginosa*(7).

A recent Indian multicentric surveillance study(8) documented Meropenem to be the most active of the ten antimicrobial agents tested against a total of 212 Gram-negative isolates of which 125 were confirmed by reference methods to be extended spectrum β-lactamase (ESBL) producers. The rank order of susceptibility was meropenem (99% susceptible) > piperacillin/tazobactam (77%) > ciprofloxacin (43%) > aminoglycosides and other β-lactams (30-40%). Of the tested strains only two (Acinetobacter spp. and *Pseudomonas putida*) showed an intermediate susceptibility to Meropenem. *Escherichia coli* and Klebsiella had high levels of resistance against other drugs but were susceptible to Meropenem.

Gram-positive Aerobes

Gram-positive bacteria that are highly susceptible to meropenem include Staphylococci (penicillinase negative and positive), coagulase-negative staphylococci (CONS), Streptococci, Enterococcus and *Corynebacterium diphtheriae*. However, as with other *β*-lactam antibiotics, most methicillin resistant strains of Staphylococci and CONS are not susceptible to Meropenem. Compared with imipenem, meropenem is less active against most gram-positive organisms

Anaerobic Bacteria

A wide variety of anaerobic bacteria like Clostridia (including *Clostridium perfringens*), Bacteriodes, Fusobacteria, Propionibacteria and Peptostreptococci are susceptible to Meropenem(7).

Clinical Efficacy

Meropenem appears to be promising in the treatment of hospitalized infants and children with serious infections because of its broad spectrum of antibacterial activity. It is the only carbapenem which has been approved by United States Food and Drug Administration (US-FDA) for use in pediatric meningitis and severe infections in intensive care settings. It has also been used to treat septicemia, febrile neutropenia, lower respiratory tract infections including those in cystic fibrosis, and urinary tract infections(11-14).

Neonatal Infections

Prevalence of multidrug resistant Gram-negative bacterial infections is increasing in neonatal units particularly from developing countries and is an important cause of neonatal mortality(15,16). This resistance is mainly because of production of extended spectrum β–lactamases (ESBL) rendering commonly used first and second line agents ineffective(17). High levels of resistance to β-lactams agents in India has been reported especially for Klebsiella and *Escherichia coli*(8). Due to the growing problem of

infection with ESBL-producing bacteria, which are frequently resistant to many classes of antibiotics resulting in difficult-to-treat infections, clinicians need to be familiar with potent strategies for dealing with them.

Although ciprofloxacin and the aminoglycosides still remain an option for treatment of severe neonatal infections caused by ESBL producing bacteria, their utility is limited because of poor CSF penetrability. Also, high levels of co-resistance has been demonstrated between the other β-lactam agents and ciprofloxacin and aminoglycosides(8). Clinical experience with use of Meropenem in neonates is limited. Several reports and small-scale studies have demonstrated an overall satisfactory clinical and bacterial response in most of the newborns treated with Meropenem(18-20). Most or all of the neonates involved in these studies had failed to respond to previous antibacterial therapy.

In our institution, a clinical cure was demonstrated in 90% neonates treated with meropenem in a dose of 25 mg/Kg for presumed or culture proven sepsis with multi-drug resistant bacteria(21). A comparable cure rate (90-100%) has been reported in earlier studies(18-20). Overall, Meropenem has great potential in treating sick newborns with serious infections especially after failure of conventional therapy or when multidrug resistance has been demonstrated.

Febrile neutropenia

Gram-positive organisms such as Staphylococci and Streptococci account for 50% of infections in patients with neutropenia, while enterobacteriacae are also frequently encountered. Meropenem has superior antibacterial activity compared with Ceftazidime against Staphylococci and Streptococci as well as many gram-negative bacteria, suggesting the possible value of Meropenem in empirical monotherapy for infections in these patients. In a prospective randomized study comparing Ceftazidime and Meropenem in febrile neutropenic children, the later proved to be more effective in reducing the duration of fever and antibiotic treatment in cases with fever of unknown origin(22). However, the efficacy was comparable in children with documented infections.

CNS Infections

The broad antibacterial spectrum together with its ability to penetrate into the CSF makes Meropenem a drug likely to be useful in meningitis. Absence of neurotoxicity and epileptogenecity with Meropenem also makes it superior in CNS infections in comparison to imipenem. Few small scale studies evaluating use of Meropenem in severe infections have documented a high cure rate in childhood meningitis(23,24). The benefit is likely to be greatest in the treatment of infections resistant to current treatment regimens including penicillin resistant *S. pneumoniae*, ampicilin resistant β-lactamase negative *H. influenzae* (25) and gram-negative pathogens producing extended spectrum β-lactamase such as *H. influenzae*, Klebsiella and other enterobacteriaceae.

The experience of meropenem use in childhood ventriculitis and brain abscess is scarce. Few case reports in children and adults reporting successful use of meropenem along with other adjuvant therapies in these infections are available(26-28).

Intensive-care settings

Several studies have demonstrated that meropenem is an effective and safe treatment for infants and children with serious pediatric infections (*e.g.*, urinary tract infections, pneumonia, sepsis, intraabdominal infections,

and skin and soft-tissue infections) including nosocomial infections(11-14,23,24). Meropenem monotherapy was as effective as imipenem/cilastatin in 4 comparative trials in terms of satisfactory clinical and bacteriological responses. Meropenem monotherapy was significantly more effective than ceftazidime-based combination treatments in 2 trials in patients with nosocomial lower respiratory tract infections (LRTIs) in terms of both clinical and bacteriological responses. However, 2 studies in patients with a range of serious infections found meropenem to be as effective as cephalosporin-based treatments in terms of clinical or bacteriological response(29).

Dosage and Administration

For children over 3 months, the recommended dose is 10-20 mg/kg every 8 hours depending on the type and severity of infection. In children over 50 Kg weight, adult dosage (500 mg to 1g 8 hourly) should be used. In meningitis, the recommended dose is 40 mg/Kg every 8 hours. The experience with the use of Meropenem in neonates is limited and its safety not fully established. In most of the studies in neonates, a dose similar to that recommended for children over 3 months has been successfully used. Limited pharmacokinetics data in preterm neonates demonstrated adequate serum concentrations with twice-daily administration of 15 mg/kg of meropenem(30). The possibility of twice-daily administration of meropenem in neonates requires further pharmacokinetics and efficacy studies.

Meropenem is recommended to be used intravenously (IV) and can be given as an intravenous bolus injection over approximately 5 minutes or by intravenous infusion over approximately 15 to 30 minutes. For bolus injection, the drug should be reconstituted with sterile water and for IV infusion, it may be reconstituted with compatible intravenous fluids like glucose or saline solutions. Drug reconstituted with sterile water maintains its potency at room temperature (up to 25ºC) up to 8 hours and under refrigeration (4ºC) for 48 hours. The drug should be used with caution in patients with history of hypersensitivity reactions to β-lactam antibiotics.

Patients with renal failure (Creatinine clearance less than 50 mL/min) require lower dosages. The frequency should be reduced to 12 hourly in those having creatinine clearance between 26 and 50 mL/min. At creatinine clearance of 10-25 mL/min, one-half of the unit dose should be given 12 hourly whereas for values below 10 mL/min, one-half of the unit dose should be administered once a day.

Hepatic impairment has no significant effect on pharmacokinetics of meropenem. However, the use in patients with hepatic disease should be made with careful monitoring of transaminase and bilirubin levels. The experience with meropenem use in children with altered hepatic or renal function is extremely limited.

Adverse Effects

The most frequently related adverse events in meropenem were diarrhea (2.3%), rash (1.4%), nausea and vomiting (1.4%) and inflammation at injection site (1.1%). The incidence of nausea and vomiting with meropenem is less than that with Imipenem/cilastatin but more in comparison to cephalosporins(31). Other reported adverse events are headaches, abdominal pain, oral thrush and mid prutitus(32).

Drug related elevations in hepatic enzymes and thrombocytopenia has also been observed. With regard to CNS, meropenem appears to be well tolerated and is therefore safely used in

meningitis(33). Impenem/cilastatin on the other hand is associated with a risk of seizure, particularly in those with predisposing factors such as renal dysfunction or underlying CNS pathology.

Safety of meropenem in neonates has not been established. In a study involving 20 neonates in our hospital, reversible thrombocytopenia was demonstrated in 50% babies with 10% babies having severe thrombocytopenia requiring platelet transfusion. 45% babies had mild asymptomatic deviation of renal function tests and alteration of LFT or cholestasis occurred in 30%. Oral candidiasis occurred in 30% babies and none developed seizures or neurotoxicity with meropenem. Similar side effects were also reported in other studies but the frequency of side effects was much more in our group of children.

The safety of meropenem in pregnancy and lactation has not been evaluated and it should not be used in pregnancy and lactation unless the potential benefit justifies the potential risk to the fetus.

Meropenem may reduce serum valproic acid levels and sub-therapeutic levels may be reached in some patients.

Comparison with other Newer β-Lactams

Recent *in-vitro* sensitivity studies have consistently shown the better susceptibility of gram negative isolates to meropenem over other new beta lactams such as Aztreonam, piperacillin+tazobactam and newer cephalosporins(7-9). These differences are shown to widen if only resistant organisms were included demonstrating better susceptibility of ESBL producing gram-negative bacteria to meropenem. The susceptibility of most resistant bacterial isolates to imipenem is comparable(10). However, a better safety profile of meropenem makes it a superior agent in treatment of pediatric infections.

Important differences in these drugs are highlighted in *Table I.* However, there is paucity of data directly comparing these antibiotics in a true clinical setting. Meropenem monotherapy was as effective as imipenem/cilastatin in 4 comparative trials in terms of satisfactory clinical and bacteriological responses in intensive care settings(29). However, these trials included mainly adult patients.

There is no trial comparing meropenem with either of these antibiotics in neonatal infections as most of these drugs are not FDA approved for use in neonates. Regarding severe infections in older children, the data is again lacking comparing meropenem with other newer β-lactams such as cefpirome or piperacillin+ tazobactam. Meropenem was as effective as cephalosporin-based treatments in few comparative trials in children with serious infections(29). There is an urgent need to conduct comparative trials evaluating the relative efficacy of these drugs in neonatal infections and other severe pediatric infections to rationalize antibiotic therapy. With increasing experience of meropenem use in neonates and children, it might be possible in near future to ethically conduct such trials.

Current Therapeutic Status of Meropenem

Meropenem is likely to be most useful in treatment of serious (including nosocomial) bacterial infections in intensive care settings and neonatal units (if safety confirmed by further studies). The utility is likely to be greatest in resistant and difficult-to-treat gram-negative infections. Its CSF penetrability and lack of neurotoxicity makes it suitable for childhood meningitis. It can also be used as a monotherapy for treatment of infections in febrile neutropenic patients.

TABLE I–*Comparison of Newer* β*-Lactams*

Drug	Spectrum of ultra-broad spectrum (Gram +ve, Gram –ve and anaerobes)	Efficacy very good (> 90%)	Bacteria stable for 8 hours in room temperature (up to 25ºC) and 48 hours at refrigeration (4ºC) stability impaired at temp. > 30ºC	Safety documented in children (Approved by FDA)	Expensive Not approved for use in neonates due to lack of available safety data
Meropenem					
Imipenem	Similar to meropenem (Better efficacy against Gram +ve but lesser against Gram –ve bacteria)	Very Good (>90%)	To be used immediately after reconstitution	Not approved for use in children	Expensive (especially for childre because of poor shelf life after reconstitution) Risk of neurotoxicity restricting use in CNS infections
Piperacillin + Tazobactam	Broad spectrum (Most Gram +ve, Gram – ve anaerobic bacteria)	Lesser (70-80%)	Stable for 24 hours at room temperature and 48 hours at refrigeration	Although studied in children but not approved by FDA	Limited role in CNS infections
Aztreonam	Narrower spectrum (only Gram – ve aerobes)	Lesser (70-80%)	Stable for 24 hours at room temperature and 48 hours at refrigeration	Safe in children and neonates	Not suitable for monotherapy in seriously ill patients due to narrow spectrum
Cefepime/ Cefpirome	Broad spectrum (Most Gram +ve, Gram –ve and some anaerobic bacteria)	Good (90%)	Stable for 24 hours at room temperature up to 25ºC. Stability impaired at temp >30ºC	Data unavailable to recommend use	Cross resistance with other cephalosporins common

As Meropenem is not effective against methicillin resistant staphylococci (including MRSA) and enterococcus, it should not be depended upon for treating suspected staphylococcal infections after failure of conventional anti-staphylococcal agents.

However, the drug should only be used as a reserve agent when the conventional therapy fails or when resistance to other antibiotics has been documented. This strategy is important to prevent the emergence of resistant strains against this useful antibiotic. Resistance to the tune of 12% has already been documented in Pseudomonas aeuruginosa strains isolated from hospitalized patients(34). Also, the high cost of the drug currently restricts its use to selected situations.

Funding: None.

Competing interests: None

REFERENCES

1. Blumer JL. Meropenem: evaluation of a new generation carbapenem. Int J Antimicrob Agents 1997; 8: 73-92.
2. Fish DN, Singletary TJ. Meropenem: A new carbapenem antibiotic. Pharmacotherapy 1997; 17: 644-669.
3. Drusano GL, Hutchison M. The pharmacokinetics of meropenem. Scand J Infect Dis 1995; 96: 11-16.
4. Kelly HC, Hutchison M, Haworth SJ. A comparison of the pharmacokinetics of meropenem after administration by intravenous injection over 5 min and intravenous infusion over 30 min. J Antimicrob Chemother 1995; 36: 35-41.
5. Hikida M, Kawashima K, Yoshida M, Mitsuhashi S. Inactivation of new carbapenem antibiotics by dehydropeptiase I from porcine and human renal cortex. J Antimicrob Chemother 1992; 30: 129-134.
6. Fukaswa M, Sumita Y, Harabe ET, *et al.* Stability of meropenem and effect of 1b-methylsubstitution on its stability in the presence of renal dehydropeptidase I. Antimicob Agents Chemother 1992; 36: 1577-1579.
7. Pfaller MA, Jones RN. A review of the in vitro activity of meropenem and comparative antimicrobial agents tested against 30,254 aerobic and anaerobic pathogens isolated worldwide. Diagn Microbiol Infect Dis 1997; 28: 157-163.
8. Jones RN, Rhomberg PR, Varnam DJ, Mathai D. A comparison of the antimicrobial activity of meropenem and selected broad-spectrum antimicrobials tested against multi-drug resistant Gram-negative bacilli including bacteraemic Salmonella spp.: initial studies for the MYSTIC program in India. Int J Antimicrob Agents 2002; 20: 426-431.
9. Chang SC, Fang CT, Chen YC, Hsueh PR, Luh KT, Hsieh WC. *In vitro* activity of meropenem against common pathogenic bacteria isolated in Taiwan. Diagn Microbiol Infect Dis 1998; 32: 273-279.
10. Watanabe A, Tokue Y, Takahashi H, Kikuchi T, Kobayashi T, Gomi K, *et al*. Comparative in-vitro activity of carbapenem antibiotics against respiratory pathogens isolated between 1999 and 2000. J Infect Chemother 2001; 7: 267-271.
11. Huizinga WKJ, Warren BL. Baker LW, Valleur P, Pezet DM, Hoogkamp-Korstanjep JA, *et al*. Antibiotic monotherapy with meropenem in the surgical management of intraabdominal infections. J Antimicrob Chemother 1995; 36: 179-189.
12. Hamacher J, Vogel F, Lichy J, Kohl FE, Diwok K, Wender H, *et al*. Treatment of acute bacterial exacerbations of chronic obstructive pulmonary disease in hospitalised patients - a comparison of meropenem and imipenem/cilastatin. J Antimicrob Chemother 1995; 36: 121-133.
13. Romaneilli G, Cravarezza, P, Italian Intramuscular Meropenem Study Group. Intramuscular meropenem in the treatment of bacterial infections of the urinary and lower respiratory tract. J Antimicrob Chemother 1995; 36: 109-119.
14. Mouton YJ, Beuscart C, Meropenem Study Group. Empirical monotherapy with meropenem in serious bacterial infections. J Antimicob Chemother 1995; 36: 145-156.
15. Ayan M, Kuzucu C, Durmaz R, Aktas E, Cizmeci Z. Analysis of three outbreaks due to

Klebsiella species in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2003; 24: 495-500.

16. Mahmood A, Karamat KA, Butt T. Neonatal sepsis: high antibiotic resistance of the bacterial pathogens in a neonatal intensive care unit in Karachi. J Pak Med Assoc 2002; 52: 348-350.

17. Aktas E, Yigit N, Yazgi H, Ayyildiz A. Detection of antimicrobial resistance and extended-spectrum beta-lactamase production in Klebsiella pneumoniae strains from infected neonates. Int Med Res 2002; 30: 445-448.

18. Godula-Stuglik U, Mikusz G. Clinical efficacy of meropenem in the management of severe nosocomial infections in neonates. J Antimicrob Chemother 1999; 44: 63-64.

19. Beloborodova NV, Biryukov AV. Using meropenem ("Meronem" Zenca) in neonates. Clin Microbiol Infect 1997; 2: 124.

20. Koksal N, Hacimustafaoglu M, Bagci S, Celebi S. Meropenem in neonatal severe infections due to multiresistant gram-negative bacteria. Indian J Pediatr 2001; 68: 15-19.

21. Shah D, Narang M, Faridi MMA. Efficacy and safety of meropenem in neonatal sepsis. *In:* Abstracts: 42nd National Conference of the Indian Academy of Pediatrics; 2005 Jan 6-9; Kolkata, India. p.129.

22. Fleischhack G, Hartmann C, Simon A, Wulff B, Havers W, Marklein G, *et al*. Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer. J Antimicrob Chemother 2001; 47: 841-853.

23. Arrieta A. Use of meropenem in the treatment of serious infections in children: review of the current literature. Clin Infect Dis 1997; 24 (Suppl 2): S207-S212.

24. Hsu HL, Lu CY, Tseng HY, Lee PI, Lai HP, Lin WC, *et al.* Empirical monotherapy with meropenem in serious bacterial infections in children. Microbiol Immunol Infect 2001; 34: 275-280.

25. Hasegawa K, Chiba N, Kobayashi R, Murayama SY, Iwata S, Sunakawa K, *et al.* Rapidly increasing prevalence of beta-lactamase-nonproducing, ampicillin-resistant Haemophilus influenzae type b in patients with meningitis. Antimicrob Agents Chemother 2004; 48: 1509-1514.

26. Sonntag J, Kaczmarek D, Brinkmann G, Kammler G, Hellwege HH. Complicating neonatal Escherichia coli meningitis. Z Geburtshilfe Neonatol 2004; 208: 32-35.

27. Segal-Maurer S, Mariano N, Qavi A, Urban C, Rahal JJ Jr. Successful treatment of ceftazidime-resistant Klebsiella pneumoniae ventriculitis with intravenous meropenem and intra-ventricular polymyxin B: Case report and review. Clin Infect Dis 1999; 28: 1134-1138.

28. Paffetti A, D'Aviera L, Le Foche F, Mannozzi P, Mastropietro C, Croce GF, *et al*. Successful meropenem therapy of a brain abscess and meningitis arising from acute purulent otomastoiditis: Case report. Chemother 1998; 10: 132-135.

29. Hurst M, Lamb HM. Meropenem: a review of its use in patients in intensive care. Drugs 2000; 59: 653-680.

30. van Enk JG, Touw DJ, Lafeber HN. Pharmacokinetics of meropenem in preterm neonates. Ther Drug Monit 2001; 23: 198-201.

31. Norrby SR, Gildon KM. Safety profile of meropenem: a review of nearly 5,000 patients treated with meropenem. Scand Infect Dis 1999; 31: 3-10.

32. Del Favero A. Clinically important aspects of carbapenem safety. Curr Opin Infect Dis 1994; 7: S38-S42.

33. Noorby SR, Faulkner KL, Newell PA. Differentiating meropenem and imipenem/ cilastatin. Infect Dis Clin Pract 1997; 6: 291-303.

34. Navaneeth BV, Sridaran D, Sahay D, Belwadi MR. A preliminary study on metallo-beta-lactamase producing Pseudomonas aeruginosa in hospitalized patients. Indian J Med Res 2002; 116: 264-267.