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Meropenem: An Alternative for Broad-Spectrum Antibacterial Coverage

Marcia L. Buck, Pharm.D.

Broad-spectrum antibiotics are important components in the empiric treatment of serious infections until culture results are available. The carbapenems, imipenem-cilastatin and meropenem, have bactericidal activity against both Gram positive and Gram negative organisms, making them useful alternatives for empiric treatment. Both of these agents have been used in infants and children.[1-4] Meropenem, the newer compound, will be the focus of this review.

Spectrum of Activity

The carbapenems, like all beta-lactams, penetrate the bacterial cell wall of susceptible organisms to bind with penicillin-binding-proteins and inhibit cell wall synthesis. Meropenem has been shown to possess *in vitro* activity against many Gram positive organisms, including most Streptococci, Staphylococci, and Enterococci species. Penicillin-resistant bacterial strains, however, are typically resistant.[3,4] Gram negative coverage includes *E. coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, and strains of Acinetobacter, Citrobacter, Shigella, Pasteurella, Proteus, Providencia, and Salmonella.

Meropenem also has bactericidal activity against *Moraxella catarrhalis*, *Morganella morganii*, *Serratia marcescens*, *Yersinia enterocolitica*, and *Campylobacter jejuni*. Anaerobic coverage by meropenem includes Bacteroides, Peptostreptococcus, Clostridium, Fusobacterium, and Prevotella species.[3,4]

Indications

Meropenem has been approved by the Food and Drug Administration for the treatment of intra-abdominal infections and bacterial meningitis in patients $\geq$ 3 months of age.

Experience in Infants and Children

Despite the narrow indications approved by the FDA, meropenem has been used for a variety of pediatric conditions.[5-8] Two large-scale multicenter randomized studies have been published to date. The first of these compared meropenem to cefotaxime, with or without the addition of metronidazole or amikacin.[5] The authors enrolled 170 children between the ages of 3 months to 12 years. Antibiotics were given empirically for presumed serious bacterial infection. Satisfactory clinical response was achieved in 98% of the meropenem-treated patients and in 93% receiving one of the cefotaxime regimens.

Similar results were obtained in a study of 414 children between 1 month and 12 years given either meropenem or cefotaxime with or with out clindamycin or tobramycin.[1] Patients included those with lower respiratory tract infection, urinary tract infection, septicemia, skin infections, and intra-abdominal infections. Patients received either 10 to 20 mg/kg of meropenem every 8 hours or cefotaxime 40 mg/kg every 6 hrs with or without additional antibiotics for an average period of 5 days. In this trial, 99% of the patients in the meropenem group had a satisfactory clinical response versus 96% in the cefotaxime group.

Meropenem has also been shown to produce favorable results in the treatment of bacterial meningitis in infants and children. Studies demonstrating similar efficacy to cefotaxime and ceftriaxone have recently been published in abstract form.[7] In addition, a recent case report described the successful use of meropenem to treat a 5 year old with multiply resistant pneumococcal meningitis.[8]

Meropenem has also been studied in children with cystic fibrosis. It has activity against *Pseudomonas aeruginosa*, both mucoid and

nonmucoid strains, as well as *Burkholderia cepacia*, making it an attractive alternative to standard therapy. In a clinical trial of 40 children and adults with cystic fibrosis, meropenem provided comparable improvement in bacteriologic findings, pulmonary function tests, and general activity level to ceftazidime during pulmonary exacerbations.[1]

Pharmacokinetics

Meropenem, like imipenem, is acid labile in the stomach and requires parenteral administration. Both drugs are widely distributed throughout the body and penetrate inflamed meninges well. Neither of the carbapenems are highly bound to plasma proteins; meropenem is estimated to be only 2% protein bound.[4,9] Meropenem is primarily eliminated unchanged in the urine. The only known metabolite, ICI 213689, does not possess antibacterial activity.[9]

The pharmacokinetics of meropenem have been well described in both adult and pediatric patient populations. In 1995, Blumer and colleagues[10] performed an escalating, single-dose pharmacokinetic study of meropenem in 73 infants and children. Doses of 10, 20, and 40 mg/kg were evaluated. Mean pharmacokinetic parameters were: half-life 1.13±0.15 hrs, volume of distribution 0.43±0.06 L/kg, and total clearance 5.63±0.75 ml/min/kg. These values are similar to those found in adults. No specific age or dose-dependent effects were noted in this study.

Also in 1995, Martinkova and colleagues[11] studied the elimination of meropenem in 25 premature neonates with an average gestational age of 32.5 weeks. The authors found an average half-life of 2.92 hrs, a volume of distribution of 0.46 L/kg, and a total clearance of 2.17 ml/min/kg. Comparing these data to the results from Blumer's study, the premature neonates had a longer half-life and slower total body clearance.[9] This result was not unexpected, based on the reliance of meropenem on the maturing kidneys for elimination.

Population pharmacokinetic modelling (NONMEM) has also been used to evaluate meropenem elimination in children. In a study of 300 meropenem serum concentrations from 65 children between 2 months and 12 years of age, Parker et al[12] found that volume of distribution was related to patient body weight and that meropenem clearance could be predicted from creatinine clearance values.

Dosing

Clinical trials conducted in children with meropenem have used dosage regimens ranging from 10 to 40 mg/kg administered IV every 8 hours.[5-7] In the dose escalation study described earlier[10], a dose of 20 mg/kg given every 8 hours produced plasma meropenem concentrations above the MIC for 90% of the bacterial strains tested. Higher doses did not offer a significant improvement in killing ability.

The manufacturer recommends 20 mg/kg every 8 hours for children with intra-abdominal infections and 40 mg/kg every 8 hours for meningitis, with a maximum single dose of 2 grams. The preferred method for administration is infusion over 20 to 30 minutes; however, meropenem may be given by bolus injection over 3-5 minutes, if needed.

Meropenem has not been studied in children with renal dysfunction, but recommendations for adults include reductions in both dose and dosing interval.

Adverse Effects

The most commonly reported adverse effects in pediatric meropenem trials have been diarrhea (1-4%), nausea and vomiting (0.4 to 1%), rash (0.8-2%), glossitis (1%), oral or diaper area moniliasis (0.5%), and injection site inflammation (0.5%). In comparison trials, these reactions occurred in similar frequency in the comparison (cephalosporin) groups.[4,6] Similar results have also been observed in clinical trials of adult patients.[4]

The potential for adverse CNS effects, particularly seizures, has been carefully studied with meropenem.[12] All beta-lactam antibiotics have the potential to cause neurotoxicity. The mechanism for this adverse effect is believed to be competitive inhibition of gamma-aminobutyric acid (GABA).

Imipenem has been linked to the development of seizures for several years. In adults, the incidence of this adverse effect has been as high as 3% in some reports. In children, neurotoxicity with imipenem has also been reported. Wong and colleagues[13] began a clinical trial in which children were given imipenem 25 mg/kg every 6

hours for the treatment of bacterial meningitis. Seven of the first 21 patients enrolled in the study developed seizures, prompting the investigators to discontinue the study. Additional case reports have also been published of seizures occurring in neonates during imipenem use. It should be remembered, however, that most of these patients had documented meningitis and were already at risk for seizures as a result of their underlying disease.

Meropenem has less affinity for GABA receptors and has been found to cause less neurotoxicity than imipenem both in animal models and during clinical trials. In trials comparing meropenem to cephalosporin regimens, the incidence of seizures was not significantly different between groups. The only seizures reported in meropenem-treated pediatric patients to date have occurred during treatment for meningitis. No cases have been reported in children treated for non-CNS infections.[6]

Summary

Meropenem offers some unique advantages for empiric antibacterial therapy in children. It has a broad spectrum of activity against both Gram positive and Gram negative organisms, has good penetration into the CNS, and appears to be less likely than imipenem to cause seizures. Further research in children is needed to establish the role of meropenem in empiric therapy.

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Pharmacology Literature Review

Antibiotic Selection

The authors of this review from Boston Medical Center provide a systematic method for comparing antibiotics for the outpatient setting. They review a variety of topics, including spectrum of action, dose and duration of therapy, cost, taste, adverse effect profile, issues affecting compliance, and likelihood of treatment failure. This article will be a very useful tool not just for clinicians, but also for students and residents to review the appropriate methods for antibiotic selection in the clinic. Werk LN, Bauchner H. Practical considerations when treating children with antimicrobials in the outpatient setting. **Drugs 1998;55:779-90.**

Cross-sensitivity of Serum Sickness

Cefaclor-induced serum sickness is a well documented adverse reaction. Loracarbef, structurally very similar to cefaclor, might be expected to produce the same reaction in susceptible children. In this study, five children with serum sickness after receiving cefaclor and five controls provided serum samples to test for cross-sensitivity to loracarbef. Peripheral blood mononuclear cells were isolated and exposed to both antibiotics and their metabolites to reveal potential cytotoxic effects. In this *in vitro* model, all of the samples tested with cefaclor

metabolites demonstrated significant lymphocyte death. Loracarbef and its metabolites, however, did not cause detectable cell death. Based on these findings, the authors rechallenged three of the children known to have cefaclor serum sickness with loracarbef, and all tolerated therapy without adverse reactions. Kearns GJ, Wheeler JG, Rieder MJ, et al. Serum sickness-like reaction to cefaclor: Lack of in vitro cross-reactivity with loracarbef. **Clin Pharmacol Ther 1998;63:686-93.**

Drug Interactions at the Renal Level

The focus of this review is to identify those drug interactions caused as a result of changes in renal drug elimination. The authors provide a brief review of the role of the kidney in drug elimination, then expand upon the potential sites of drug interaction and methods to test at these sites. The authors conclude with a section discussing the potential role for these in vitro and in vivo models in drug development testing. The text is fairly detailed- this is an article for study, not light reading. Bonate PL, Reith K, Weir S. Drug interactions at the renal level: Implications for drug development. **Clin Pharmacokinet 1998;34:375-404.**

Kernicterus Prevention

This brief review covers the variety of treatment options currently available for infants with hyperbilirubinemia. The author divides the review into two sections: the first lists types of treatments, such as phototherapy, exchange transfusion, and drug therapies. The second section addresses different clinical scenarios and how these treatment options might be best utilized. Interesting features of this review include a timeline of historical methods for treating elevated bilirubin concentrations and a brief discussion of therapies still under investigation. Rubaltelli FF. Current drug treatment options in neonatal hyperbilirubin(a)emia and the prevention of kernicterus. **Drugs 1998;56:23-30.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/26/98:

1. Tolcapone (Tasmar®; Roche) was added to the formulary. This agent is a selective, reversible inhibitor of catechol-O-methyl-transferase (COMT) and is used to treat the signs and symptoms of idiopathic Parkinson's disease. It should only be used in conjunction with a levodopa/carbidopa preparation.

Editors' Note

Welcome to Our New Readers!

The staff of *Pediatric Pharmacotherapy* would like to welcome all new members of the Children's Medical Center staff. This newsletter is provided free of charge to all CMC personnel and referral physicians. If you are interested in submitting material for publication or serving on the editorial board, please contact Dr. Marcia Buck at the address listed below.

For assistance with questions related to medication use in children currently admitted to the CMC, you may contact the CMC pharmacy at 982-0920. For more in-depth consultations, you may contact Dr. Buck by phone at 982-0921 or by paging 971-6222, or one of the pediatrics pharmacy team members, Clara Jane Snipes, R.Ph., Doug Paige, R.Ph., or Lily Mulugeta, Pharm.D. by paging PIC 1775.

The University of Virginia Drug Information Center is also available to assist you with medication questions. The Center is run by Drs. Anne Hendrick and Michelle McCarthy. You may contact the Center by phone at 924-8034, Monday through Friday between the hours of 8:00 AM and 4:30 PM. The Drug Information Center can also provide assistance when requesting an addition to the formulary.

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If you have any comments or would like to be on our mailing list, please contact Marcia Buck by mail at Box 274-11, University of Virginia Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.