



**PEDIATRIC INFECTIOUS
DISEASE SOCIETY OF THE
PHILIPPINES**

PIDSP JOURNAL

**Vol.13 No.2
July-Dec 2012**

Invited Review

Dengue: A Growing Global Health Threat

*Usa Thisyakorn M.D., Chule Thisyakorn, M.D. Department of Pediatrics,
Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand2*

Original Articles

A Case Control Study of the Demographic Characteristics, Risk Factors, Clinical Findings, Treatment and Outcome among Children 18 Years and Below Who are Confirmed to have Influenza A H1N1/09 Virus

*Romina D. Gerolaga, M.D., Robert Dennis Garcia, M.D.
Makati Medical Center13*

The Clinical Outcome and Antibiotic Sensitivity Pattern of Enterobacter Spp. Culture Positive Neonates Admitted at Cebu Doctors' University Hospital – Neonatal Intensive Care Unit (2005-2008)

Lalaine Amor H. Maderal, M.D., Barbra Charina V. Cavan, M.D.*
Cebu Doctors' University Hospital.....22*

Haemophilus Influenzae Type B Conjugate Vaccine (HiBCV) and Heptavalent Pneumococcal Conjugate Vaccine (PCV7) Immunization Status Of Patients 5 Years and Below Hospitalized For Pneumonia

*Lou Ver Leigh A. Manzon, M.D., Robert Dennis J. Garcia, M.D., Sally
Victoria B. King, M.D Department of Pediatrics, Makati Medical Center30*

Interim Advice

Post Disaster Interim Advice on the Prevention of Leptospirosis in Children37

Outbreak of Serratia Marcescens in the Newborn Care Unit in a Local Tertiary Hospital

*Sandra Joyce Pena, MD, Xenia Cathrine Fabay, MD
Baguio General Hospital and Medical Center.....39*

The Use of Meropenem among Neonates: A One-Year Retrospective Study in the Nursery of a Local Tertiary Hospital

*Ferdinand P. Gangangan, MD, Xenia Cathrine Fabay, MD
Baguio General Hospital and Medical Center.....47*

PIDSP Newsletter

PIDSP AT THE APAME CONGRESS 201254

PIDSP Joins the PPS Total Family Healthcare Expo56

**Vol.13 No.2
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BRIEF REPORT

THE USE OF MEROPENEM AMONG NEONATES: A ONE-YEAR RETROSPECTIVE STUDY IN THE NURSERY OF A LOCAL TERTIARY HOSPITAL

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KEYWORDS:

sepsis, neonatal sepsis, meropenem

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ABSTRACT

Objectives: This study was conducted to determine profile of neonates being treated with meropenem as well as to assess its clinical efficacy in the treatment of neonatal infections.

Methods: This is a retrospective review of the records of sick neonates admitted at the Newborn Care Unit of a tertiary hospital and treated with meropenem. Those discharged against advice were excluded. Frequency and percentage were used in comparing the following variables: sex, 5-minute APGAR score, age of gestation, birth weight, type of infection, culture results, treatment outcome, and adverse reactions.

Results: There were 34 charts available for review, but two were excluded. There were 62.5 % females and 37.5 % males: 28.1 % of them had a 5-minute APGAR score of 10; 37.5 % had 9; 21.9% had 8; and 12.5 % had 7. Sixty-two percent (62.5%) of the subjects were between 32 to 35 weeks age of gestation: 46.9 % were of low birth weight; 34.4 % were of very low birth weight; and 18.7 % had normal weights. Sepsis was the most common indication in the use of meropenem, followed by sepsis with pneumonia, pneumonia then sepsis with meningitis. Majority (68.75%) of the patients had no growth in their blood while 60% had no growth in the CSF. *Enterobacter aerogenes* (15.6%) was the most common blood isolate while *Enterobacter gergeviae* (20%) and *Klebsiella pneumoniae* (20%) were the isolates in the CSF culture. Treatment outcomes were favorable; 84.4% were improved, while 9.4% were unimproved and shifted to other antibiotics, and 6.2% died.

Conclusion: The use of meropenem is effective in the treatment of life-threatening infections among newborns.

INTRODUCTION

Infections in the newborn care unit have been steadily rising. It poses challenges not only to the general pediatrician but to neonatologists, as well. In the Baguio General Hospital and Medical Center (BGHMC), sepsis alone ranked 5th and 1st in the leading causes of morbidity and mortality, respectively, in the year 2004¹. The development of newer drugs used to battle infections did not only revolutionize the management of the sick neonate, but has also contributed, to a certain degree, to the emergence of resistant microbes in the treatment arena. Resistance to penicillins, aminoglycosides, and the lower generation cephalosporins has pushed the clinician to shift to broader spectrum antibiotics. In the local setting, cefepime, piperacillin-tazobactam and meropenem have been used to treat severe infections. Among these three broad spectrum antibiotics used in our newborn care unit, meropenem is the least studied drug for neonatal infections.

This study aims to assess the clinical efficacy of Meropenem in the treatment of neonatal infections. The specific objectives of the study were to determine the profile of neonates treated with meropenem as to age of gestation by Ballard's score, birth weight, 5-minute Apgar score, sex, type of neonatal infections responsive to meropenem and observe for adverse effects of the drug.

MATERIALS AND METHODS

Study Period and Population

All sick neonates who were admitted at the Newborn Care Unit from January to December 2004 and were treated with meropenem during their course of illness. Those who were discharged against medical advice and those transferred to other hospitals were not included in the review.

Materials and Methods: A review of the charts of all sick neonates admitted from January to December 2004 was performed to determine those who were given meropenem regardless of their treatment outcomes. Frequency and

percentage were used in determining the comparative analysis of each variable.

Limitations of the Study: Only charts available at the Medical Records Section were used. Assessment of the efficacy of meropenem was based solely on clinically assessable parameters, such as resolution or worsening of signs and symptoms, as assessed by the physician-in-charge. Other parameters, such as drug plasma concentration, half-life and clearance are beyond the scope of this study due to unavailability of such tests locally.

RESULTS

Thirty four neonates were given meropenem during their course of illness; two of them were excluded because they were discharged against medical advice.

Demographic profile

Majority of the patients treated were female (62.5%), and all had % min APGAR score of more than 7. More than 80% of the patients were between 30 and 37 weeks age of gestation and were of low birth weight. Types of infections included sepsis, sepsis-meningitis, sepsis- pneumonia and pneumonia

Culture results were noted for both blood and CSF samples. All patients had a blood culture done, while 5 patients who were suspected of meningitis had their CSF analyzed. Of the blood isolates, 22 (68.8%) revealed no growth, 5 (15.6%) revealed *Enterobacter aerogenes*, and 1 (3.1%) each for *Xanthomonas maltophilia*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. All, except for *Xanthomonas maltophilia*, were sensitive to meropenem (Table 2a).

Of the CSF isolates, 3 (60%) revealed no growth, while 1 (20%) *Enterobacter gergoviae* and 1 (20%) *Klebsiella pneumoniae*, which were all sensitive to meropenem (Table 2b).

Table 1. Demographic profile of Neonates Treated with Meropenem

Demographic Characteristic	No. of Neonates (%)
Sex	
Male	12 (37.5)
Female	20 (62.5)
5 min APGAR SCORE	
7	4 (12.5)
8	7 (21.9)
9	12 (37.5)
10	9 (28.1)
Age of Gestation (weeks)	
26-29	2 (6.25)
30-33	15 (46.87)
34-37	13 (40.63)
38-40	2 (6.25)
Birth weight (kg)	
1-1.49	11 (34.4)
1.5-2.49	15 (46.9)
>2.5	6 (18.7)
Type of Infection	
Sepsis	14 (43.8)
Sepsis-meningitis	5 (15.6)
Sepsis-pneumonia	8 (25)
Pneumonia	5 (15.6)

Table 2a. Blood Isolates and their Sensitivity to Meropenem (N=32).

Microorganism	No of isolates	Sensitivity to meropenem
No growth	22	
<i>Xanthoma maltophilia</i>	1	Resistant
<i>Acinetobacter baumannii</i>	1	sensitive
<i>Pseudomonas aeruginosa</i>	1	sensitive
<i>Enterobacter cloacae</i>	2	sensitive
<i>Enterobacter aerogenes</i>	5	sensitive

Adverse Effects

There was 1 (3%) noted adverse effect observed during the course of treatment with meropenem, which was phlebitis on the IV site.

Table 2b. Cerebrospinal Fluid Isolates and their Sensitivity to Meropenem (N=5).

Microorganism	No of isolates	Sensitivity to meropenem
No growth	3	
<i>Enterobacter gergeviae</i>	1	sensitive
<i>Klebsiella pneumoniae</i>	1	sensitive

DISCUSSION

Despite the narrow indications approved by the FDA, meropenem has been used for a variety of pediatric conditions²⁻⁵. Two large-scale, multi-center, randomized studies have been published to date. The first of these compared meropenem alone to cefotaxime, with or without the addition of metronidazole or amikacin in the empiric treatment of presumed serious bacterial infection among 170 children between the ages of 3 months to 12 years. Satisfactory clinical response was achieved in 98% of the meropenem-treated patients and in 93%, who received one of the cefotaxime regimens.

Similar results were obtained in a study of 414 children between 1 month and 12 years, who were given either meropenem or cefotaxime—with or without clindamycin or tobramycin⁶. Patients included were those with lower respiratory tract infections, urinary tract infections, septicemia, skin infections, and intra-abdominal infections. Ninety-nine per cent of the patients in the meropenem group had a satisfactory clinical response versus the 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 been recently published by Bradley, et. al.⁴. In addition, a recent case report by John CC, Aouad G, Berman B, et. al.⁵, described the successful use of meropenem in treating a 5-year old with multiple resistant pneumococcal meningitis.

Meropenem has also been studied in children with cystic fibrosis. It has activity against *Pseudomonas aeruginosa*—both mucoid and non-mucoid strains, as well as, *Burkholderia cepacia*, which makes 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.⁶

The pharmacokinetics of meropenem has been well-described in both adults and pediatric populations. Blumer and colleagues, in 1995, did a study on this and found out that the mean pharmacokinetic parameters, namely half-life (1.13 +/- 0.15 hrs.), volume of distribution (0.43 +/- 0.06 L/kg), and total clearance (5.63 +/- 0.75 ml/kg/min) were similar to those found in adults.¹⁷

Also in 1995, Martinkova¹⁸ and colleagues studied the elimination of meropenem in 25 premature neonates who had an average gestational age of 32.5 weeks. They found that meropenem an average half-life of 2.92 hours, volume of distribution of 0.46 L/kg, and a total clearance of 2.17 ml/min/kg. In comparison to the Blumer's study, the premature neonates had a longer half-life and a slower total body clearance. This result was not unexpected, based on the reliance of meropenem on the maturing kidneys for elimination.

In this study, the primary indications of meropenem were sepsis, sepsis-meningitis, pneumonia, and sepsis-pneumonia. It was observed that this drug was effective in pneumonia (100% improved), pneumonia-sepsis (87% improved), sepsis (85% improved), and sepsis- meningitis (60% improved). However, other co-morbid conditions, which may have affected the efficacy of meropenem were not taken into account.

Meropenem causes bacterial cell death by binding to penicillin-binding proteins (PBPs), thus, inhibiting cell wall biosynthesis. It is active against most gram-positive and gram-negative

aerobes and anaerobes.⁸ Meropenem is indicated for intra-abdominal infections caused by Viridans group Streptococci, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *B. fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus* species.¹⁰⁻¹² It is also indicated in bacterial meningitis in pediatric patients 3 months of age or older caused by *S. pneumoniae*, *H. influenzae* and *N. meningitidis*.¹⁰⁻¹² Both meropenem and imipenem are not active against methicillin-resistant *Staphylococci*, *E. faecium* or *Stenotrophomonas maltophilia*; but resistance to meropenem by *P. aeruginosa* has been reported.⁹ In this review, resistance to *Xanthoma maltophila* (*Stenotrophomonas maltophilia*) was seen.

The most commonly reported adverse effects in pediatric meropenem trials were 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 comparative trials, these reactions occurred in similar frequency in the comparison (cephalosporin) groups.^{3,14} Similar results had also been observed in clinical trials of adult patients.¹⁴

In this review, phlebitis on the intravenous site was noted during the course of the treatment. This phlebitis, however, was not conclusive whether meropenem was the cause because details were not noted in the chart.

Meropenem has less affinity for GABA receptors and has less neurotoxicity than imipenem in both animal models and during clinical trials comparing meropenem to cephalosporin regimens; the incidence of seizures was not significantly different between groups. The only seizure reported in meropenem-treated pediatric patients to date has occurred during treatment for meningitis. No case had been reported in children treated for non-CNS infections;³ this adverse reaction however was not noted in this review.

CONCLUSIONS

The use of meropenem in the treatment of life threatening infections among newborns is highly effective as shown in this review.

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