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Review Article (Pages: 3925-3939)

Clinical Pharmacology of Meropenem in Neonates: Effects and Pharmacokinetics

*Gian Maria Pacifici[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Meropenem, a carbapenem antibiotic, has a broad-spectrum activity and is active against Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influencae, Moraxella catarrhalis, gram-negative enteric bacilli as Escherichia coli, Klebsiella, Enterobacter, Serratia and Pseudomonas aeruginosa. Meropenem has excellent penetration in body tissues and in cerebrospinal fluid (in the presence of inflammation). Meropenem is bactericidal, because it inhibits transpeptidases responsible for peptidoglycan synthesis involved in cell formation and repair.

Meropenem is approved for use in complicated intraabdominal infections, complicated skin and skin structure infections and bacterial meningitis in pediatric patients. The dose of meropenem is 20 mg/kg by slow intravenous infusion once every 12 hours in the first week of life and once every 8 hours for infants older than this. Meropenem is predominantly excreted by renal route. After an administration of 15 mg/kg meropenem twice-daily to premature infants, the mean total body clearance is 0.157 l/kg/h, the distribution volume is 0.74 l/kg, and the half-life is 3.4 hours. The %T>MIC is the percent time above minimum inhibitory concentration. After a dose of 20 mg/kg t.i.d., the target value of 50%T>MIC is achieved, indicating that 20 mg/kg is effective for susceptible bacteria. In contrast, for bacteria with higher MIC such as Pseudomonas aeruginosa (MIC ≥2 µg/ml), the probability of target attainment of 50%T>MIC is 60.7% at a dose of 40 mg/kg t.i.d. The limited amounts of meropenem that cross the placenta are insufficient to treat infection in fetuses. The aim of this study was to review the effects and pharmacokinetics of meropenem in neonates.

Key Words: Effects, Meropenem, Neonates, Pharmacokinetics.

*Please cite this article as: Maria Pacifici G. Clinical Pharmacology of Meropenem in Neonates: Effects and Pharmacokinetics. Int J Pediatr 2016; 4(11): 3925-39. DOI: **10.22038/ijp.2016.7850**

Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

Received date Oct 2, 2016 ; Accepted date: Oct 22, 2016

1-INTRODUCTION

Meropenem is a valuable broad-spectrum antibiotic. Meropenem is a carbapenem β-lactam antibiotic active against a very wide range of gram-positive and gram-negative aerobic and anaerobic bacteria that first came into general clinical use in 1985. Methicillin-resistant staphylococci and Enterococci faecium are resistant to meropenem, as are some strains of Pseudomonas aeruginosa. Approximately 70% of a meropenem dose in recovered intact in the urine, but partly is eliminated as an inert metabolite. The elimination half-life in adults is 1 hour, but a little longer in children 2-6 months old. The initial half-life in term infants is 2 hours and in the preterm infants is 3 hours, but the half-life falls significantly, irrespective of gestation, within 10-14 days of birth (1).

Meropenem has many of the same properties, and most of the adverse effects, as imipenem, but it seems to cause less nausea. It has not been in use as long as imipenem and has not been as extensively studied, but the evidence to date suggests that meropenem is less likely to induce seizures than imipenem with cilastatin. Meropenem is administered by slow intravenous infusion. It penetrates the cerebral spinal fluid of patients with bacterial meningitis, and most other body fluids, well. The limited amounts of meropenem that cross the placenta are insufficient to treat infection in the fetus. Teratogenicity studies and limited reports of use in human pregnancies are largely reassuring. Meropenem passes into breast milk, but there is no reason to withhold breastfeeding (1). Meropenem is bactericidal based on the ability to competitively inhibit the transpeptidases responsible for peptidoglycan synthesis involved in cell formation and repair (2). Meropenem does not require co-administration with cilastatin, because it is not sensitive to renal dipeptidase. Its toxicity is similar to that of imipenem except that it may be less likely to cause seizures (0.5% for meropenem; 1.5% for imipenem). Clinical experience with meropenem demonstrates therapeutic equivalence with imipenem (3).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, EMBASE, Google scholar and PubMed as search engines; August 2016 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

Combinations of search terms from three categories ("Meropenem" keyword AND "Neonetes" keyword AND "Pharmacokinetics meropenem neonate" keyword AND "Pharmacokinetics meropenem neonate" keyword AND "Infants" keyword), were used to search for the relevant literature. In addition, the book Neonatal Formulary (1) was consulted.

3-RESULTS

3-1. Treatment

Give 20 mg/kg by slow intravenous infusion once every 12 hours in the first week of life and once every 8 hours for infants older than this. The dose may be given as an intravenous injection over 5 min if required. Double the dose to 40 mg/kg in children where meningitis and serious infection of Pseudomonas aeruginosa are suspected. Intramuscular use is not recommended. Dosage frequency should be halved if there is evidence of renal failure, and treatment stopped altogether if there is anuria unless dialysis is instituted (1).

3-2. Uses

Limited to treatment of pneumococcal meningitis and other serious infections caused by susceptible gram-negative organisms resistant to other antibiotics, especially extended-spectrum β-lactamase producing Klebsiella pneumoniae (4).

Meropenem is more active against gram-negative bacilli and less active against gram-positive cocci than imipenem (5). The pharmacokinetics of meropenem are typical of those of a parenteral β-lactam antibiotics with low protein binding and predominantly renal excretion. Dosage reduction is required in patients with reduced renal function; no dosage adjustment is required for patients with hepatic impairment. Meropenem has excellent penetration in abdominal tissues, bile, blister fluid, inflammatory exudates, cerebrospinal fluid (in the presence of inflammation), gynecologic tissues, respiratory tract tissues, and urinary tract tissues; tissue levels are generally equal to or above the levels needed for the treatment of patients with susceptible pathogens (1).

In the neonatal intensive care units (NICU) the extensive use of third generation cephalosporins for therapy of neonatal sepsis may lead to rapid emergence of multiresistant gram-negative organisms. Koksal et al. (6) reported the use of meropenem in 35 infants with severe infection due to Acinetobacter baumanii and Klebsiella pneumoniae. Eighty-two percent of the cases (29/35) were born prematurely. Assisted ventilation was needed in 85.7% (30/35). Six percent (2/35) died. All gram-negative bacteria were resistant to ampicillin, amoxicillin, ticarcilin, cefazoline, cefotaxime, ceftazidime, ceftriaxone and aminoglycosides. The incidence of drug-related adverse events (mostly a slight increase in liver enzyme) was 8.5%. No adverse effects were observed. At the end of therapy, overall satisfactory clinical and bacterial response was obtained in 33/35 (94.3%) of the newborns treated with meropenem. Clinical and bacterial response rates for meropenem were 100%, for sepsis and 87.5% for nosocomial pneumonia. These findings suggest that meropenem may be a useful antimicrobial agent in neonatal infections caused by multiresistant gram-negative bacilli.

3-3. Meropenem has a wide broad activity against many microorganisms

Meropenem exhibits in vitro activity against an impressive number of community-acquired and nosocomial pediatric pathogens (2) such as the clinically relevant gram-positive organisms as Staphylococcus aureus, group A Streptococcus and Streptococcus pneumoniae, including virtually all strains of pneumococcus that have to date exhibited decreased susceptibility to penicillin. Meropenem is also active against respiratory gram-negative organisms such as Haemophilus influenzae and Moraxella catarrhalis; enteric Gram-negative bacilli such as Escherichia coli, Klebsiella, Enterobacter and Serratia and Pseudomonas aeruginosa. Meropenem demonstrates a remarkable stability against beta-lactamases, including the type I inducible β-lactamases which are responsible for third generation cephalosporin-resistant strains of Enterorobacter, Serratia, Citrobacter and Pseudomonas. These organisms pose a particular threat when responsible for nosocomial gram-negative infections. Meropenem is also highly active against anaerobes including β-lactamase-positive strains of Bacteroides fragilis.

Meropenem is approved for use in complicated intraabdominal infections, complicated skin and skin structure infections and bacterial meningitis in pediatric patients aged ≥ 3 months in the US, and in most other countries for nosocomial pneumonia, complicated intraabdominal infections, septicemia,

febrile neutropenia, complicated skin structure infections, urinary tract infections, obstetric and gynecological infections, cystic fibrosis in patients with pulmonary exacerbations, and for the treatment of severe community-acquired pneumonia (7). Meropenem has a broad spectrum of in vitro activity against gram-positive and gram-negative pathogens, including extended-spectrum β-lactamase and Enterobacteriacae. Meropenem is well tolerated and has the advantage of being suitable for administration as an intravenous bolus infusion. Its low propensity for inducing seizures means that it is suitable for treating meningitis and is the only carbapenem approved in this indication. Thus, meropenem continues to be an important option for the empirical treatment of serious bacterial infections in hospitalized patients.

3-4. Safety and effectiveness of meropenem in neonates

Two hundred neonates were enrolled; 142 (71%) were born at < 32 weeks of gestational age, and 130 (65%) were ≥2 weeks postnatal age at the time of enrollment (8).

The demographic characteristic of neonates are summarized in **Table.1**. Overall, 89% of subjects had respiratory conditions, 90% gastrointestinal conditions, and 73% cardiovascular conditions at baseline. Forty-five percent of subjects had abdominal surgery prior enrollment. Meropenem is commonly used off-label in infants < 3 months of age, despite a lack of safety and efficacy data, because of its broad range of antimicrobial activity and its stability against chromosomally encoded and plasmid-mediated Extended-spectrum beta-lactamases (ESBL) infections (9). Meropenem's spectrum includes Enterobacteriacae, Pseudomonas aeruginosa (10), and Bacteroides fragilis (11).

The potential of meropenem for adverse central nervous system side effects, particularly seizures, has been carefully studied in older children (12, 13). In the study by Cohen-Wolkowiez et al. (8), clinical seizures were reported in 10/200 (5%) infants; however, only 1 was confirmed by Electroencephalography (EEG). Additionally, 50% of infants with seizures had a central nervous system condition that could be responsible for the seizures, and Cohen-Wolkowiez et al. (8) observed no apparent difference in predicted meropenem plasma concentrations in patients with or without seizures. Because a comparator arm was not included in the trial by Cohen-Wolkowiez et al. (8) and the number of study participants was relatively small from an epidemiologic standpoint, it is difficult to know if the rate of seizures associated with meropenem is above the background seizures rate for this population. However, among infants admitted to the neonatal intensive care unit, seizures were 9% (14), and the cumulative incidence in the most premature infants (< 28 weeks of gestational age) is as high as 12%. The majority (>70%) of infants enrolled in the study by Cohen-Wolkowiez et al. (8) were < 32 weeks of gestational age and critically ill at baseline, which suggests that the seizure rate observed is similar or lower than that reported in prior studies. The most commonly reported adverse effects of meropenem from previously published pediatric study are diarrhea (3.3%-4.7%), nausea and vomiting (0.4%-1%), rash (0.8%), glossitis (1%), and oral thrush (1.9%) (12); in comparison trials, these reactions occurred with similar frequency in the comparison of cephalosporin group (12, 14). In a review of 6,154 infants receiving meropenem in 54 clinical trials, meropenem demonstrated a favorable safety profile relative to comparators including cephalosporin, imipenem/cilastatin, and

clindamycin/aminoglycoside (15). Children were given 10-40 mg/kg meropenem every 8 hours in the studies reviewed. The incidence of seizures among all subjects was 0.37%, 0.25%, 0.43%, and 0.38% in the meropenem, cephalosporin, imipenem/cilastatin, and clindamycin/aminoglycoside groups, respectively. This finding is not surprising given that meropenem has less affinity than imipenem for γ-aminobutyric acid receptors which are the potential target for central nervous system adverse effects and has been found to cause less neurotoxicity than imipenem both in animal models and during clinical trials (12, 16). In addition, higher alanine aminotransferase, aspartate aminotransferase, alkaline phosphate, and bilirubin levels were observed in 5.2%, 4.3%, 2.2%, and 0.7%, respectively (15).

Meropenem was well tolerated in the cohort of critically ill infants with suspected and/or proven intraabdominal infections. Although the study by Cohen-Wolkowiez et al. (8) was not randomized, the overall success rate was 84% (162/192), meeting the definition of therapeutic success. The success rate was highest in more mature infants (≥ 32 weeks of gestational age; 93% [51/55]). No serious adverse events probably or definitely associated with meropenem were observed. Collectively, these data support and may inform the development of comparative trials of meropenem in infants with complicated intraabdominal infections. **Table.2** shows the overall safety summary and **Table.3** summarizes the effectiveness results.

3-5. Meropenem in neonatal severe infections

Koksal et al. (6) administered meropenem intravenously at the dosage of 20 mg/kg in 20-30 min infusion. Meropenem therapy was continued for a minimum of 5 days in order to define clinical/bacterial response. The number of infants was 35, the birth weight was 1,470 ± 500 grams, the gestational age was 30.5 ± 5 weeks, the premature infants (≤ 1,500 grams) were 29 (82.8%). The causal microorganisms were Acinetobacter baumanii 18 (51%) and Klebsiella pneumonia 17 (49%). Two infants died and 33 infants survived. At the end of therapy overall satisfactory clinical and bacterial responses were obtained in 33 (94.3%) of the newborns treated with meropenem. Satisfactory bacterial and clinical response rates for nosocomial sepsis were 100%. Satisfactory bacterial and clinical response for nosocomial pneumonia were 87.5%. The clinical and bacterial responses were correlated in both groups. Failures were observed in two newborns with pneumoniae caused by Acinetobacter baumanii.

The most frequent adverse event was a slight and transient (average one week) increase in liver transaminases which was demonstrated in 3 cases (8.5%). Nosocomial Klebsiella pneumoniae infection and Acinetobacter baumanii infection were associated with a high mortality in neonates and antimicrobial therapy of these infections has been complicated by the emergence of multiresistant strains (16). Fidel-Rimon et al. (17) administered meropenem to 18 infants (51%) affected by Acinetobacter baumanii and to 17 (49%) infants affected by Klebsiella pneumoniae. Two infants died and 33 infants survived. At the end of meropenem therapy overall satisfactory clinical and bacterial response was 94.3%. Meropenem is effective and well tolerated in the newborn and can be used against multiresistant gram-negative invasive infections in newborns. Yatsky et al. (18) administrated meropenem in 15 newborns with sepsis, pneumoniae was cured in all cases. Meropenem is effective and well tolerated in the newborn and can be used effectively against multiresistant gram-negative invasive infections in newborn infants.

3-6. Pharmacokinetics of meropenem in neonates

Van Enk et al. (19) evaluated and compared the pharmacokinetics of meropenem in 7 premature neonates, the mean birth weight was 925 grams and the mean postnatal age was 21 days. The neonates received 15 mg/kg meropenem twice-daily on clinical grounds as a 1-min infusion. After the first dose and during state-state, serum levels of meropenem were measured at 12 hours after intravenous administration. Serum concentration-time curves could be described with a one-compartment model. Mean total body clearance was 0.157 l/kg/h, the distribution volume was 0.74 l/kg, and the half-life was 3.4 hours. At day 5 of steady-state, the pharmacokinetic properties did not differ significantly. No side effects were noted.

Pedari et al. (20) compared the steady-state pharmacokinetics and safety of meropenem given via short (30 min) or prolonged (4 hours) infusion to neonates with a gestational age of < 32 weeks to define the most appropriate dosing regimen for efficacy study on neonatal late-onset sepsis. Meropenem was given to 16 infants for sepsis and to 3 infants for pneumonia with no differences in the distribution of diagnoses between groups. Eleven infants (58%) had altogether 13 positive blood culture (coagulase-negative staphylococci, n=5; Enterobacteriacae Staphylococcus, n=4; Enterococcus faecalis, n=2; Staphylococcus aureus, n=1; Pseudomonas aeruginosa, n=4). Most of the infants were severely ill, with 95% requiring respiratory support and 42% requiring vasoactive treatment.

Meropenem is distributed in extracellular water and is excreted mainly by glomerular filtration (21). Therefore, changes in body water and development of renal function influence the disposition of meropenem. Bradley et al. (22) studied 37 neonates and administered single doses of 10 and 20 mg/kg of meropenem as a 30 min infusion. These authors demonstrated that an 8 hour interval may be more would provide robust coverage for their patients but that 40 mg/kg may be necessary for some infections with more resistant pathogens like Pseudomonas aeruginosa. van den Anker (21) reported the demographic pharmacokinetics of meropenem in 23 preterm (gestational age, 29 to 36 weeks, mean $\pm$ standard deviation [SD] was 32$\pm$2 weeks) and 15 full term (gestational age, 37 to 42 weeks, mean $\pm$ SD was 39$\pm$1 weeks) neonates (p-value <0.0001). Meropenem doses of 10, 20 and 40 mg/kg were administrated as single doses (30-min intravenous infusion). Blood was obtained for determining the meropenem concentration nine times. For meropenem plasma clearance, the demographic variables chosen as descriptors were as follows:

Clearance (CL) = 0.0133 x Creatinine Clearance (Clcr) + 0.1088 x weight - 0.261; where Cl_{cr} is the creatinine clearance estimate in units of ml/min/1.73 m^2 [estimated by the Schwartz formula (23)]. The resulting meropenem plasma clearance estimate is in liter/hours and the weight is in kg. It should be noted that weight along with height are included in the Schwartz formula (23). Overall, the regression was highly statistically significant. The p-value for Cl_{cr} was 0.001 and for weight was 0.036. The regression relationship explained 67.9% of the variance (i.e., r^2=0.679). The relationship was the same when performed stepwise forward or stepwise backward. For the distribution volume, the physiological/demographic variable chosen was Cl_{cr}. The clearance of meropenem was 23.2 $\pm$ 5.53 ml/min/1.73 m^2 in preterm infants and 43 $\pm$ 10.5 ml/min/1.73 m^2 in full-term infants (p-value <0.001).

Distribution $volume_c$ = 0.000278 x Cl_{cr} + 0.147. In the equation, the distribution

volume is in liters and Cl_{cr} is in units of ml/min/1.73 m^2. Again, the relationship was highly statistically significant, with p-value <0.0001. Bradley et al. (22) described the meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in neonates. Neonates < 2 months of age received a single dose of meropenem of 10 or 20 mg/kg. Meropenem serum concentrations were measured at specific times during the 24 hour post-infusion. Population pharmacokinetics were evaluated using NONMEN. Using Monte Carlo simulation, the probability of pharmacokinetic-pharmacodynamic target attainment was evaluated by computer modeling from predictions extrapolated from population pharmacokinetic data, using "virtual" dosing regimens of 10, 20, and 40 mg/kg administered every 8 or 12 hours against community- and hospital-acquired pathogens. Thirty-seven neonates were enrolled, 22 were born at < 36 weeks gestational age. Meropenem clearance was greater in neonates with older chronologic ages and in those born at later gestational ages. Serum creatinine and postconceptional age were the best overall predictors of meropenem elimination: Clearance (l/h/kg) = 0.041 + 0.040/ serum creatinine [S_{cr}] + 0.003 x (postconceptional age - 35 weeks). Monte Carlo simulation demonstrated that in infants during the first 2 weeks of life, a dosage of 20 mg/kg/dose every 8 hours achieved the desired pharmacodynamic target in 95% of preterm neonates and 91% of term neonates against Pseudomonas.

The kinetic parameters of meropenem are summarized in **Table.4** (20). Except for a higher serum Cmax in the short-infusion group (30 min) and a higher time to reach drug Cmax in serum (Tmax) in the prolonged-infusion group (4 hours), all of the pharmacokinetic parameters of the two groups were similar. Large interindividual variability was seen, especially in Cmax. All the pharmacokinetic parameters of neonates with a postnatal age <15 days (n=6) and a postnatal of ≥ 15 days (n=13) were similar in both groups. All of the patients in the short-infusion group and 8/10 in the prolonged-infusion group achieved an fT > minimum inhibitory concentrations [MIC] of 100% for an MIC of 2 µg/ml (percent time that free drug concentrations remain above the MIC). The *f*T > 6.2 x MIC value required to prevent resistance development in Pseudomonas aeruginosa was 80.2% (95% confidence interval [CI], 70.8 to 89.6) in the short-infusion group and 81.9% (95% CI, 69.6 to 94.4) in the prolonged-infusion group (not statistically significance). In all age groups, the short and prolong infusion of meropenem have not been different in terms of effect against Escherichia coli and Klebsiella species, organisms that cause a significant proportion of the gram-negative infections in neonates (24). For intermediate or resistant microorganisms (with meropenem MICs >2 mg/l) like Acinetobacter species and Pseudomonas aeruginosa, previous pharmacokinetics /pharmacodynamics simulation studies involving neonates and pediatric patients (22) have suggested better pharmacokinetics/pharmacodynamics target attainment with 4-hours infusion. Recently it has been suggested that the Cmin/MIC ratio could play a role in resistance suppression (25).

The concentration at which a maximal bactericidal effect is achieved is an important determinant of efficacy. Prolonged infusion results in a much lower Cmax and longer Tmax than administration over 30 min, potentially compromising the attainment of the 4xMIC necessary for optimum killing properties of β-lactams in critically ill infants (20). Padri et al. (20) conclude that in very low birth weight neonates, prolonged meropenem infusions is

optimal, as it balances a reasonable Cmax and *f*T>MIC for susceptible organisms with convenience of dosing with no dosing adjustment over the first month of life. Smith et al. (26) determined the pharmacokinetics of meropenem in young infants as a basis for optimizing dosing and minimizing adverse events. Premature and term infants < 91 days of age hospitalized in 24 neonatal intensive care units were studied. Limited pharmacokinetic sampling was performed following single and multiple doses of meropenem 20-30 mg/kg every 8-12 hours based on postnatal and gestational age at birth. Population and individual patient (Bayesian) pharmacokinetic parameters were estimated using NONMEM. Two hundred infants were enrolled. Their median (range) gestational age at birth and postnatal age at pharmacokinetic evaluation were 28 (23-40) weeks and 21 (1-92) days, respectively. In the final pharmacokinetic model, meropenem clearance was strongly associated with serum creatinine (S_{cr}) and postnatal age (PMA) (Clearance [l/h/kg]= 0.12*[(0.5/S_{cr})**0.27]*[PMA/32.7)**1.46]). Meropenem concentrations remained >4 µg/ml for 50% of the dose interval and >2 µg/ml for 75% of the dose interval in 96% and 92% of neonates, respectively. The estimated penetration of meropenem into the cerebral fluid was 70% (5-148 µg/ml). The median empirical Bayesian post-hoc parameter estimate for clearance, 0.119 l/h/kg, was nearly identical to the typical population model estimates of 0.122 l/h/kg. The median empirical Bayesian post-hoc parameter estimate for distribution volume, 0.468 l/kg, was also similar to the typical population model estimate of 0.460 l/kg. Nine cerebrospinal fluid meropenem concentrations (3 duplicates) were available from 6 neonates and ranged from 0.7-34.6 µg/ml. Meropenem dosing strategies based on postnatal and gestational ages achieved therapeutic drug exposure in almost all infants. A population pharmacokinetic model for meropenem in Japanese pediatric patients with various infectious diseases was developed based on 116 plasma concentrations from 50 pediatric patients Ohata et al. (27). The population pharmacokinetic parameters developed in this analysis are useful for calculation of the percent time above minimum inhibitory concentration (%T>MIC) and for optimal dosing of meropenem in pediatric patients. After dosing at 20 mg/kg t.i.d. by 0.5-hour infusion, the target value of 50% T>MIC was achieved, indicating that 20 mg/kg t.i.d. by 0.5-hours infusion is effective for susceptible bacteria. In contrast, for bacteria with higher MICs such as Pseudomonas aeruginosa (MIC ≥ 2 µg/ml), the probability of target attainment of 50%T>MIC was 60.7% at a dose of 40 mg/kg t.i.d. by 0.5-hours infusion (highest dose approved for pediatric patients in Japan). The simulations described in this article indicated that 40 mg/kg t.i.d. with a longer infusion duration (e.g. 4-hours) is more effective against bacteria with a MIC > 2 µg/ml. The predicted probability of target attainment for 50%T>MIC efficacy rate was 95.9%. Calculating %T>MIC at MICs of 0.06-16 µg/ml for each plasma meropenem profile on the 4th day (steady-state) in 1000 simulated subjects, mean and 95% prediction intervals of %T>MIC were obtained for each MIC and each dose. Target attainment rate for bacteriostatic exposures (target: 30%T>MIC) or bactericidal exposures (target: 50%T>) at each MIC were also predicted. The target attainment rate against each strain, including Escherichia coli, methicillin-susceptible Staphylococcus aureus and Pseudomonas aeruginosa, were predicted using the reported MIC distribution data of meropenem against clinically isolated strains in 2006 (26). Escherichia coli and methicillin-susceptible Staphylococcus aureus were selected as typical gram-

negative and gram-positive organisms, respectively. Pseudomonas aeruginosa was selected as a representative example of commonly associated with more severe infections.

3-7. Transmission of meropenem in breast milk

Sauberan et al. (28) reported the sequential breast milk concentrations of meropenem in a breast-feeding mother receiving intravenous meropenem therapy for a postpartum urinary tract infection caused by an extended-spectrum β-lactamase-producing strain of Escherichia coli. Five samples of milk were obtained. The highest measured value was 0.644 µg/ml, and the lowest was 0.246 µg/ml. These authors did not sample breast milk in the mother at time of presumed peak concentration (2-4 hours after a dose), and hence the presumed range of breast milk concentrations may underestimate the true maximum potential milk exposure. However, the true peak milk concentration of meropenem is unlikely to be higher than 1 µg/ml, considering that the estimated half-life of meropenem elimination from breast milk is 7.7 hours based on the second and third reported meropenem concentration values. Even an average milk concentration of 1 µg/ml would expose the breast-feeding infant to 0.150 mg/kg per day of oral meropenem, several orders of magnitude below the recommended neonatal treatment dose of intravenous meropenem of 60 mg/kg per day (22).

Table-1: Infant demographics

Gestational age < 32 weeks			Gestational age ≥ 32 weeks		
Variables	Postnatal age <2 weeks	Postnatal age ≥ 2 weeks	Postnatal age <2weeks	Postnatal age ≥2 weeks	Total
Number of infants	39	103	31	27	200
Postnatal age (days)	26.0 (22.5-31.5)	26.3 (23.0-31.5)	36.0 (32.1-40.0)	34.4 (32.1-40)	27.8 (22.5-40.0)
Male sex number (%)	24 (62)	56 (54)	22 (71)	16 (59)	118 (59)
Hispanic or Latino ethnicity	5 (13)	16 (16)	4 (13)	3 (11)	28 (14)
African-American	12 (31	33 (32)	8 (26)	6 (22)	59 (30)
White	26(67)	65 (63)	21 (68)	18(67)	130 (65)
Other	2 (5)	5 (5)	2 (6)	4 (15)	13 (7)

The figures are the median and range, by Cohen-Wolkowiez et al. (8)

Table-2: Overall safety summary

Variables	Gestational age < 2 weeks		Gestational age ≥ 2 weeks		Total
	Postnatal age < 2 weeks no. (%)	Postnatal age ≥ 2 weeks no. (%)	Postnatal age < 2 weeks no. (%)	Postnatal age ≥ 2 weeks no. (%)	
Number of infants	39	103	31	27	200
Infants with at least 1 adverse event	26 (67)	47 (46)	13 (42)	13 (48)	99 (50%)
Infants with adverse event by causality unrelated	19 (49)	37 (36)	12 (39)	10 (37)	78 (39)
Infants with possibly related infection	7 (18)	10 (10)	1 (3)	2 (7)	10 (5)
Infants with seizure	4 (10)	3 (3)	1 (3)	2 (7)	20 (10)

Level II laboratory adverse effects	2 (5)	8 (7)	0 (0)	0 (0)	10 (5)
Infants with direct bilirubin increased	2 (5)	3 (3%)	0 (0)	0 (0)	5 (2.5)
Infants with at least 1 serious adverse effects	9 (23)	18 (17)	2 (6)	5 (18)	34 (17)
Infants died	3 (8)	8 (8)	0 (0)	0 (0)	11 (5.5)
Adverse events that lead to study drug discontinuation	1 (3)	3 (3)	0 (0)	2 (7)	6 (3)

The figures are the number of infants and (%), by Cohen-Wolkowiez (8).

Table-3: Summary of effectiveness results

Variables	Gestational age < 32 weeks		Gestational age ≥ 32 weeks	
	Postnatal age < 2 weeks no. (%)	Postnatal age ≥ 2 weeks no. (%)	Postnatal age < 2 weeks no. (%)	Postnatal age ≥ 2 weeks no. (%)
Evaluable for effectiveness	39	98	28	27
Effectiveness success	29 (74)	82 (84)	26 (93)	25 (93)
Presumptive clinical cure score ≥ 7	35 (90)	90 (92)	27 (96)	97 (100)
Presumptive clinical cure score < 7	0 (0)	1 (1)	0 (0)	0 (0)
Presumptive clinical cure score missing	4 (10)	7 (7)	1 (4)	0 (0)
Change in antibiotic therapy	7 (18)	12 (12)	2 (7)	2 (7)
Cultures negative for bacteria	27 (69)	49 (50)	9 (32)	13 (48)
Culture not done	12 (31)	49 (50)	19 (68)	14 (52)

The figures are the number of infants and (%), by Cohen-Wolkowiez (8).

Table-4: Results of noncompartmental analysis of pharmacokinetic parameters in the short- and prolonged-infusion groups

Parameters	Short infusion	Prolonged infusion	P-value
Actual meropenem dose (mg/kg)	18.9±5	18.3±2.4	0.650
Cmax (mg/l)	3.4±0.9	3.3±1.7	0.436
Tmax (hours)	0.7±0.4	4.0±1.9	0.005
Cmin (mg/l)	6.5±3.7	7.2±6.1	0.780
Clss (ml/h/kg)	52.4±15.5	62.7±31.6	0.842
Vss (ml/kg)	270.6±83.3	342.9±174.3	0.447
AUC (h.µg/ml)	369±66.1	338.6±121.6	0.497
*f*T >MIC (%) (95%Cl)*	100 (100-100)	99.9 (99.6-100)	0.193

The figures are the mean± SD, by Padari et al. (20); *Calculated for the EUCAST MIC susceptibility breakpoint of 2 mg/l for Pseudomonas aeruginosa and Enterobacteriacae; Clss=clearance at steady-state. Vss=distribution volume at steady-state. CI=confidence interval.

4-DISCUSSION

Meropenem, a carbapenem β-lactam antibiotic, has a broad-spectrum of activity. It is active against a very wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. Against the clinically relevant gram-positive microorganisms, activity has been demonstrated against Staphylococcus aureus, group A Streptococcus and Streptococcus pneumoniae, including virtually all strains of pneumococcus that have to date exhibited decreased susceptibility to penicillins. Meropenem is also active against respiratory gram-negative microorganisms such as Haemophilus influenzae and Moraxella catarrhalis; enteric gram-negative bacilli such as Escherichia coli, Klebsiella, Enterobacter and Serratia; and other gram-negative microorganisms such as Pseudomonas aeruginosa (3). The carbapenem class of antibiotics demonstrates remarkable stability against beta-lactamases, including the type I inducible beta-lactamases which are responsible for third generation cephalosporin-resistant strains of Enterobacter, Serratia, Citrobacter and Pseudomonas (3). These microorganisms pose a particular threat when including beta-lactamase-positive strains of Bacteroides fragilis. Despite the benefits associated with meropenem's extended antimicrobial spectrum, there are safety concerns related to potential central nervous system side effects in young infants (11). The potential of meropenem for adverse central nervous system side effects in particular seizures, has been carefully studied in older children (12, 13). The most commonly reported adverse effects of meropenem from previously published pediatric study are diarrhea (3.3%-4.7%), nausea and vomiting (0.4%-1%), rash 0.8, glossitis (%), and oral thrush (1.9%) (12). In comparison trials, these reactions occurred with similar frequency in the comparison cephalosporin group (12, 13). The incidence of seizures among all infants was 0.37%, 0.25%, 0.43%, and 0.38% in the meropenem, cephalosporin, imipenem/cilastatin, and clindamycin/aminoglycoside groups, respectively. Meropenem does not require co-administration with cilastatin, because it is not sensitive to renal dipeptidase. Its toxicity is similar to that of imipenem except that it may be less likely to cause seizures (0.5% for meropenem; 1.5% for imipenem (3). The incidence of drug-related adverse events was a slight increase in liver enzyme in 8.5%.

At the end of therapy, overall satisfactory clinical and bacterial response was obtained in 33/35 (94.3%) cases. Clinical and bacterial response rate for meropenem was 100% for sepsis and 87% for nosocomial pneumonia. These findings suggest that meropenem may be a useful antimicrobial antibiotic in neonatal infections caused by multi-resistant gram-negative bacilli (6). A total of 200 infants was enrolled; overall, 89% of the infants had respiratory conditions, 90% gastrointestinal conditions, 73% cardiovascular conditions at baseline. Meropenem is commonly used off-label in infants < 3 months of age, despite a lack of safety and efficacy data, because of its broad range of antimicrobial activity and its stability against chromosomally encoded and plasmid-mediated extended-spectrum β-lactamase (ESBL) infections (9). The dose of meropenem is 20 mg/kg by slow intravenous infusion once every 12 hours in the first week of life and once every 8 hours for infants older than this (1). Meropenem has excellent penetration in abdominal tissues, bile, blister fluid, inflammatory exudates, cerebrospinal fluid (in the presence of inflammation), gynecologic tissues, respiratory tract tissues, and urinary tract tissues. Tissue levels are generally equal to or above the levels needed for the treatment of patients

with susceptible pathogens. Seven premature neonates with a mean birth weight of 925 grams and with a mean postnatal age of 21 days were treated with 15 mg/kg meropenem twice-daily (19). Serum meropenem concentration-time curves could be described with a one-compartment model. Mean total body clearance was 0.157 l/kg/h, the distribution volume was 0.74 l/kg, and the half-life was 3.4 hours.

Meropenem is distributed in the extracellular water and is excreted mainly by glomerular filtration (21). Therefore, change in body water and development of renal function influence the disposition of meropenem (21). The demographic pharmacokinetics of meropenem in 23 preterm and 15 full term neonates were determined by van den Anker et al. (21), the clearance of meropenem was 23.2±5.53 ml/min/1.73 m^2 in preterm infants and 43±10.5 ml/min/1.73 m^2 in full term infants p-value <0.001).

Bradley et al. (22) described the meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in neonates < 2 months of age who received 10 or 20 mg/kg meropenem. Thirty-seven infants were enrolled, 22 were born at < 36 weeks gestational age. Meropenem clearance was greater in older infants. Monte Carlo simulation demonstrated that in infants during the first 2 weeks of life, a dosage of 20 mg/kg/dose every 8 hours achieved the desired pharmacodynamic target in 95% of preterm infants and 91% of term infants against Pseudomonas aeruginosa.

Padari et al. (20) compared the pharmacokinetics of meropenem infused for 30 min and 4 hours. Except for a higher Cmax in the short-infusion group and a longer time to reach Cmax (Tmax) in the prolonged-infusion group, all pharmacokinetic parameters of the two groups were similar. All of the patients in the short-infusion group and 8/10 patients in the prolonged-infusion group achieved an *f*T>MIC of 100% for an MIC of 2 µg/ml. The *f*T>6.2xMIC, value required to prevent resistance development in Pseudomonas aeruginosa was 80.2% (95% CI, 70.8 to 89.6) in the short-infusion group and 81.9% (95% CI 69.6 to 94.4) in the prolonged-infusion group (not statistically significant). For intermediate or resistant microorganisms (with meropenem MICs of >2 µg/ml) such as Pseudomonas aeruginosa and Acinetobacter species a better pharmacokinetic/pharmacodynamic target was achieved with 4-hours infusion for (21). Ohata et al. (27) studied the population pharmacokinetics in 50 pediatric patients. After dosing meropenem at 20 mg/kg t.i.d. by 0.5-hours infusion, the target value of 50%T>MIC was achieved, indicating that 20 mg/kg t.i.d. by 0.5-hours infusion is effective for susceptible bacteria. In contrast, for bacteria with higher MICs such as Pseudomonas aeruginosa (MIC ≥ 2 µg/ml), the probability of target attainment of 50%T>MIC efficacy was 60.7% at a dose of 40 mg/kg t.i.d. meropenem by 0.5-hours infusion.

Meropenem is excreted in breast milk (28). A case is presented of a breast-feeding mother receiving meropenem treatment for a postpartum urinary tract infection caused by extended-spectrum beta-lactamase producing Escherichia coli. Five milk samples were collected in a 48-hour period during meropenem therapy. The average and maximum meropenem concentrations in milk were 0.48 and 0.64 µg/ml, respectively. Based on the maximum concentration, the calculated infant daily exposure from breast milk was 97 µg/kg/day. There were no dermatologic or gastrointestinal side effects noted in the breastfed infant. Meropenem appears to be acceptable to use during breast-feeding. The limited amounts of meropenem that

cross the placenta are insufficient to treat infection in the fetus (1).

5-CONCLUSION

In conclusion, meropenem, a carbapenem β-lactam antibiotic, is a bactericide broad-spectrum antibiotic. It is active against a very wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. Meropenem is active against Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influence, Moraxella catarrhalis, enterococci gram-negative bacilli, Klebsiella, Enterobacter and Serratia and Pseudomonas aeruginosa. Methicillin-resistant staphylococci and Enterococci faecium are resistant to meropenem. Meropenem can be given as a short (30 min) or a prolonged (4 hours) intravenous infusion, a better pharmacokinetics/pharmacodynamics target attainment was obtained with 4-hours infusion. The dose of meropenem is 20 mg/kg once every day in the first week of life and once every 8 hours for infants older than this.

Meropenem is used to treat nosocomial pneumonia, complicated intraabdominal infections, septicemia, febrile neutropenia, complicated skin structure infections, urinary tract infections, obstetric and gynecological infections, cystic fibrosis in patients with pulmonary exacerbations, and for the treatment of severe community-acquired pneumonia. Meropenem is distributed in the extracellular water and is excreted mainly by glomerular filtration, maturation of glomerular filtration increases the meropenem clearance. The clearance of meropenem (ml/min/1.73 m^2) is 23.2$\pm$5.53 in prematures and 43.0$\pm$10.5 in full term neonates (p-value is <0.0001). About 70% of meropenem dose is excreted intact in the urine. After the administration of meropenem (15 mg/kg every 12 hours) to premature neonates, the half-life is 3.4 hours, the mean total body clearance is 0.157 l/kg/h, and the distribution volume is 0.74 l/kg. After a dose of 20 mg/kg, the target value 50%T>MIC was achieved, indicating that 20 mg/kg is effective for susceptible bacteria. In contrast, for bacteria with higher MIC such as Pseudomonas aeruginosa (MIC ≥2 μg/ml), the probability of target attainment of 50%T>MIC was 60.7% at a dose of 40 mg/kg.

6-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7-ACKNOWLEGMENTS

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio of the Medical Library of the University of Pisa for retrieving the scientific literature.

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