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Clinical pharmacology of meropenem in infants and children

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Abstract

Meropenem is a carbapenem β-lactam antibiotic active against a very wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. Meropenem is used to treat pneumococcal meningitis and other serious infections caused by susceptible gram-negative organisms resistant to other antibiotics, especially extended-spectrum β-lactamase producing Klebsiella pneumoniae. Meropenem is mainly excreted unchanged in the urine. The half-life in term neonates is 2 hours and in preterm neonates is 3 hours, but the half-life falls significantly within 10-14 of birth life. Meropenem penetrates well into the cerebrospinal fluid and most body tissues. This drug exhibits time-dependent killing of gram-negative and gram-positive pathogens (particular Enterococcus), and the goal of therapy is to keep free drug concentrations above the MIC for at least 40% of the dosing interval. The clearance of meropenem is directly related to renal function and hepatic function does not affect meropenem pharmacokinetics. Prolonged infusion (4 hours) instead of short infusion of 30 min results in a significantly higher rate of clinical improvement and microbiologic eradication 7 days after starting meropenem therapy compared with the short infusion. At a meropenem dose of 20 mg/kg by 0.5 hours of infusion the target value of 50% T > MIC is achieved indicating that this dosage is effective for susceptible bacteria. Bacteria resistant to meropenem has been described in various studies. The aim of this study is to review the published data on effects, pharmacokinetics, and resistance of meropenem in infants and children.

Introduction

Meropenem is a valuable broad-spectrum antibiotic. It 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 Enterococcus faecium are resistant to meropenem, as are some strains of Pseudomonas aeruginosa. Meropenem is excreted in the urine, mostly unchanged, but partly as an inert metabolite. The elimination half-life in adults is only 1 hour but a little longer in children 2-6 months old. The initial half-life in term neonates is 2 hours and in the preterm neonates is 3 hours, but the half-life falls significantly, irrespective of gestation, within 10-14 days of life of birth. Meropenem has many of the same properties, and most of the same adverse effects, as imipenem, but it seems to cause less nausea. It is also stable to the renal human dehydropetidase that inactivates imipenem and does not need, therefore, to be given with cilastatin. 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 can also be given as a short (30 min) or prolonged (4 hours) intravenous infusion. It penetrates into the cerebrospinal 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 foetus. Teratogenic 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].

The goal of meropenem is to keep free drug concentrations above the MIC for at least 40% of the dosing interval. Plasma protein binding is minimal, and the clearance is directly related to renal function, and 70% of a dose is recovered intact in the urine. The use of meropenem is the 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. For sepsis give 20 mg/kg intravenously less than 32 gestational weeks, less than or equal to 14 days postnatal age. Administer every 12 hours after 14 postnatal age. For meningitis and infections caused by Pseudomonas species give 40 mg/kg intravenously, all ages. Meropenem is incompatible with acyclovir, amphotericin B, calcium gluconate, metronidazole, sodium bicarbonate, and zidovudine [2].

Meropenem is a derivate of thienamycin. Compared to imipenem, it is somewhat less active against gram-positive organisms (particular Enterococcus) and more active against gram-negative organisms. Its toxicity is similar to that of imipenem except that it may be less likely to cause seizures; thus it is preferred for treatment of meningitis when carbapenem therapy is required [MacDougal 2018].

Literature search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was January 2019. The following key words "meropenem infants effects", "meropenem children effects", "meropenem infants metabolism", "meropenem children metabolism", "meropenem infants pharmacokinetics", "meropenem children pharmacokinetics", "meropenem infants resistance", and "meropenem children resistance" were used. In addition the books Neonatal Formulary [1] and NEOFAX by Young and Mangum [2] were

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consulted. The manuscript was prepared according to the "Instructions for Authors".

Results

Effects of meropenem in infants and children

The efficacy and safety profile of meropenem were analyzed according to data collected from hospitalized paediatric patients aged 4 days to 20 years who had serious bacterial infections and were treated in a major teaching hospital in Taipei [3,4]. Of 53 patients enrolled, 47 were analyzed for clinical efficacy and 53 for safety. The satisfactory clinical response was 57% in lower respiratory tract infection, 58% in septicaemia, 100% in complicated urinary tract infection, osteomyelitis, and central nervous system infection, 83% in skin and soft tissue infection, and 93 in intra-abdominal infection. Eleven (21%) patients experienced adverse events related to meropenem. The most commonly observed adverse reactions were elevated hepatic enzymes (7.5%), increased alkaline phosphate (3.8%), and thrombocytosis (3.8%). There was no meropenem-related seizure, withdrawal, or death. The present results suggest that meropenem is well tolerated even in young infants and is effective in treating serious childhood bacterial infection. However, this study also identified a proportion of hospitalized paediatric patients with isolates that were resistant to meropenem. The trends in meropenem resistance among nosocomial acquired bacterial should be monitored closely.

Intra-abdominal infections are common in young infants and lead to morbidity and mortality. Meropenem is a broad-spectrum antimicrobial with excellent activity against pathogens associated with intra-abdominal infections. Cohen-Wolkowiez, *et al.* [5] determined the safety and effectiveness of meropenem in young infants with suspected or complicated intra-abdominal infections. Preterm and term infants aged < 91 days with suspected or confirmed intra-abdominal infections hospitalized in 24 neonatal intensive care units were studied in an open-label, multiple-dose study. Of 200 infants enrolled in the study, 99 (50%) experienced an adverse event, and 34 (17%) had serious adverse events; no adverse events were probably or definitely related to meropenem. The most commonly reported adverse events were sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), and hypokalemia (5%). Only 2 of the serious adverse events were determined to be possibly related to meropenem (isolated ileal perforation and episode of fungal sepsis). Effectiveness was evaluable in 192 (96%) infants, and overall treatment success was 84%. Meropenem was well tolerated in this cohort of critically ill infants, and the majority of infants treated with meropenem met definition of therapeutic success.

Meropenem is a promising carbapenem antibiotic as an empirical monotherapy in children with febrile neutropenia. Pancharoen *et al.* [6] conducted a study to evaluate the efficacy and safety of meropenem as empirical antibiotic therapy in 30 paediatric cancer patients with febrile neutropenia (mean age = 7.5 years), who were admitted to King Chulalongkorn Memorial Hospital from May 2000 to December 2001. Meropenem 60 mg/kg per day was given intravenously ever 8 hours. The efficacy of meropenem was assessed as successful, inconclusive and failure on days 3 and 5 of the therapy and compared to that of other empirical antibiotics used from January 1997 to April 2000. The study showed that six blood culture specimens (20%) grew organisms, half of which were considered to be contaminants, and six urine culture specimens (20%) grew gram-negative rod bacteria. On days 3 and 5 of the therapy, the success rate of meropenem was higher than that of comparatives (30% versus 17.6% on day 3, 50.0% versus 39.3% on day 5). The use of meropenem appeared safe, with minimal side effects. In conclusion, the present results showed that meropenem is a safe and tolerable antibiotic in children. The efficacy as an empirical monotherapy in paediatric cancer patients with febrile neutropenia was satisfactory, with a failure rate of 23.3% on day 5 of treatment.

Chemotherapy related neutropenia developing in oncologic patients is a significant condition and major cause of morbidity and mortality. Erbey *et al.* [7] investigated the efficacy and safety of meropenem in the treatment of febrile neutropenia in children with cancer. Twenty-four children who had a febrile neutropenic episode followed by initiation of empirical meropenem therapy were included in the study. Of all patients, 13 (54.2%) had solid tumours, while 11 (45.8%) were diagnosed to have acute leukaemia. Among all, 7 (29.2%) and 15 (62.5%) infections were identified microbiologically and clinically, respectively. Fever of unknown origin was observed in 2 (8.3%) children. The mean duration of neutropenia was 7.2+3.1 (4 to 17) days in children with solid tumours, and 9.3+4.7 (2 to 17) days in the group with leukaemia. This difference was not statistically significant. Average time of stay in hospital was 10.1+6.4 (4 to 21) days for children with solid tumours, and 15.9+11.7 (5 to 37) days for children with leukaemia (p-level = 0.041). Febrile neutropenia duration was observed to be longer in children with absolute neutrophil count of less than 100/mm^3 and even those with an absolute neutrophil count of less than 200/mm^3, and in children who were not in remission for the underlying malign disease (p-level < 0.05). While 22 (91.7%) of the children were discharged from the hospital, 2 died. The success rate of empirical therapy started with meropenem was 87.5%:

Buckingham *et al.* [8] investigated pneumococcal susceptibility to meropenem in isolates from a tertiary children's hospital where pneumococci were commonly resistant to penicillin and cefotaxime. From July 1998 to August 1999, meropenem susceptibilities were determined by E-test for all Streptococcus pneumoniae isolates from blood or cerebrospinal fluid and for penicillin-nonsusceptible pneumococcal isolates from other sites. Isolates that were penicillin-susceptible or penicillin-intermediate were all susceptible to meropenem (13 intermediate, 14 resistant). Cefotaxime-susceptible isolates were all susceptible to meropenem. Of 29 penicillin-resistant isolates, 27 were susceptible to meropenem. Of 11 cefotaxime-intermediate isolates, 10 were nonsusceptible to meropenem (9 intermediate, 1 resistant). Of 20 cefotaxime-resistant isolates, 17 were nonsusceptible to meropenem (4 intermediate, 13 resistant). Meropenem resistance is common among pneumococci with decreased susceptibility to penicillin or cefotaxime. The role of this agent in the treatment of invasive infections caused by pneumococci that are resistant to penicillin and cefotaxime may be limited.

Recently, new broad spectrum carbapenem has been investigated on a world-wide scale for the treatment of moderate to severe infections. In the neonatal intensive care units, 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.* [9] reported the use of meropenem in 35 infants with severe infections due to Acinetobacter baumanii and Klebsiella pneumoniae. All gram-negative bacteria were resistant to ampicillin, amoxicillin, ticarcillin, cefazolin, cefotaxime, ceftazidime, ceftriaxone, and aminoglycosides. Eight-two percent of cases (29/35) were born prematurely. Assisted ventilation was needed in 87.5% (30/35). All infants deteriorated during their conventional treatment and were changed to monotherapy. Six percent (2/35) died. The incidence of drug-related adverse events (mostly slight increase in liver enzymes) was 8.5%. No adverse effects such as diarrhoea, vomiting, rash, glossitis,

oral or diaper area moniliasis, thrombocytosis, thrombocytopenia, eosinophilia, and seizures were observed. At the end of therapy, overall satisfactory clinical and bacterial response was obtained in 33/35 (94.3%) of newborns treated with meropenem. Clinical and bacterial response rates for meropenem were 100% for sepsis and 87.5% for nosocomial pneumoniae. These present findings suggest that meropenem may be a useful antimicrobial agent in neonatal infections caused by multiresistant gram-negative bacilli.

Carbapenems are broad-spectrum β-lactam antibiotics with activity against most organisms encountered in the paediatric intensive care unit. Sustained meropenem was used on the pattern of gram-negative bacillus colonization in children admitted to a tertiary care paediatric intensive care unit [10]. After a 6 months baseline period, all children with serious infections admitted to a paediatric intensive care unit during the subsequent 2 years were administered meropenem. The incidence of colonization by gram-negative bacilli resistant to one of a battery of broad-spectrum parenteral agents, and by organisms resistant specifically to meropenem, during the baseline period was compared with the period of preferred meropenem use. During the period of preferred meropenem use, the amount of meropenem use increased > seven-fold, whereas the use of other advanced generation β-lactams was reduced by nearly 80%. The mean prevalence of colonization by antibiotic-resistant bacilli in general was not statistically altered during the period of meropenem prevalence (7.3 organisms/patient-days versus 9.4 organisms/100 patient-days at baseline). The prevalence of colonization by gram-negative organisms resistant specifically to meropenem was 0.61 organisms/100 patient-days during the baseline period versus 1.04 organisms/100 patient-days during the period of meropenem preference. The incidence of nosocomial infections did not change, and the prevalence of nosocomial infections caused by meropenem-resistant organisms was always < 1% of all admissions during the period of meropenem prevalence. There was no statistically detectable effect on the prevalence of colonization by gram-negative organisms resistant to one or more classes of broad-spectrum parenteral antibiotics, or to colonization by organisms resistant specifically to meropenem, when meropenem was the preferred antibiotic in a paediatric intensive care unit.

Short versus long infusion of meropenem in infants

Gram-negative bacteria are associated with significant morbidity and mortality in preterm and term newborns. Meropenem has widespread efficacy and often allows for monotherapy in this group. Prolonged infusion (4 hours) instead of short infusion (30 min) has been suggested to result in higher clinical and microbiologic efficacy and safety [11]. Infants were randomly assigned to receive either prolonged (4 hours) or short (30 min, conventional group) at a dosing regimen of 20 mg/kg per dose every 8 hours or 40 mg/kg per dose every 8 hours in meningitis and Pseudomonas infection. A total of 102 infants (51 in each group) were recruited. The 4 hours infusion group demonstrated a significantly higher rate of clinical improvement and microbiologic eradication 7 days after starting meropenem therapy compared with the conventional group. Mortality and duration of respiratory support were significantly less in the infusion group compared with the conventional group. Acute kidney injury after meropenem treatment was significantly less in the infusion group. Prolonged infusion of meropenem in neonates with gram-negative late-onset sepsis is associated with higher clinical improvement, microbiologic eradication, less neonatal mortality, shorter duration of respiratory support and less acute kidney injury compared with the conventional strategy.

Prolonged infusion of meropenem has been suggested in studies with population pharmacokinetic but has not been tested in neonates. Padari *et al.* [12] compared the steady-state pharmacokinetics of meropenem given as a short (30 min) or prolonged (4 hours) infusion to very-low-birth-weight (gestational age < 32 weeks; birth weight < 1,200 grams) neonates to define the appropriate dosing regimen for a phase 3 efficacy study. Short (N = 9) or prolonged (N = 10) infusions of meropenem were given at a dose of 20 mg/kg every 12 hours. Immediately before and 0.5, 1.5, 4, 8, and 12 hours after the 4th to 7th doses of meropenem, blood samples were collected. Pharmacokinetic analysis was performed with WinNonlin software. A short infusion resulted in a higher mean drug concentration in serum than a prolonged infusion (Cmax= 89 versus 54 μg/ml, respectively). In all but two infants in the prolonged-infusion group, the free serum drug concentration was above the MIC (2 μg/ml) 100% of the time. Meropenem clearance was not influenced by postnatal or postmenstrual age. In population pharmacokinetic analysis, a one-compartment model provided the best fit and the steady-state distribution volume was scaled with body weight and clearance with a published renal maturation function. The covariates serum creatinine and postnatal ages did not improve the model fit. The final parameter estimates at steady-state were a distribution volume of 0.301 l/kg and a clearance of 0.061 l/h/kg. Meropenem infusion of 30 min are acceptable as they balance a reasonably high Cmax with convenience of dosing. In very-low-birth-weight neonates, no dosing adjustment is needed over the first month of life.

Dosage regimen of meropenem in infants and children

A population pharmacokinetic model for meropenem in Japanese paediatric patients with various infectious diseases was developed based on 116 plasma concentrations from 50 paediatric patients [13]. The population pharmacokinetic parameters developed in these patients are useful for calculation of the percent time above MIC (T > MIC) and for optimal dosing of meropenem in paediatric patients. After a meropenem dosing at 20 mg/kg t.i.d. by 0.5 hours infusion (approved standard dose for paediatric patients in Japan), the target value of 50% T > MIC was achieved, indicating that 20 mg/kg t.i.d. by 0.5 hours infusion of meropenem 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 of meropenem (highest dose approved for paediatric patients in Japan). The simultaneous described in the present study 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 higher than 2 μg/ml. The predicted probability of target attainment for 50% T > MIC (97.0%) was well correlated not only to the microbiological efficacy rate (97.0%) but also to the clinical efficacy rate (95.9%) in present phase 3 study.

Adverse events associated with meropenem in infants and children

Hornik *et al.* [14] conducted a retrospective cohort study of 5,566 infants treated with meropenem or imipenem/cilastatin in neonatal intensive care units managed by the Pediatrix Medical Group between 1997 and 2010. Multivariable conditional logistic regression was performed to evaluate the association between carbapenem therapy and adverse events, controlling for infant factors and severity of illness. Adverse events were more common with the use of meropenem compared with imipenem/cilastatin (62.8/1,000 infant days versus 40.7/1,000 infant days, p-level < 0.001). There was no difference in

seizures with meropenem versus imipenem/cilastatin (adjusted odds ratio 0.96, 95% confidence interval = 0.68-1.32). The incidence of death, as well as the combined outcome of death or seizure, was lower with meropenem use (odds ratio = 0.68 (95% confidence interval = 0.50-0.88) and odds ratio = 0.77 (95% confidence interval = 0.62-0.95), respectively. In this cohort of infants, meropenem was associated with more frequent but less severe events when compared with imipenem/cilastatin.

Meropenem is mainly excreted unchanged with the urine [2,3]. In literature, there are no studies of meropenem metabolism in infants and children.

Pharmacokinetics of meropenem in infants and children

In order to define meropenem dosing guidelines for children, an escalating, single-dose, pharmacokinetic study at 10, 20, and 40 mg/kg was performed by Blumer *et al.* [15]. A total of 73 infants and children in four age groups were enrolled: 2 to 5 months, 6 to 23 months, 2 to 5 years, and 6 to 12 years. Each group consisted of six patients per dose. A multicenter, open-label, sequential, parallel-group trial was performed. Blood samples for meropenem analysis were taken at 30 min (end of infusion), 60, 120, 240, 360, and 480 min after dosing. Plasma was isolated from blood and used for meropenem analysis. Urine samples were collected for determination of meropenem before dosing over four intervals: 0 to 2, 2 to 4, 4 to 8, and 8 to 12 hours after dosing. Plasma concentration-time curves for these three groups showed that the peak Cmax and AUC increased proportionally from 10 to 20 mg/kg of meropenem. The increments in Cmax from 20 to 40 mg meropenem per kg were somewhat blunted, changing from 56.9 to 92.1 μg/ml and 72.4 to 133.7 μg.h/ml, respectively. This blunting may reflect both number of patients studied in each dose group as well as the setting of the maximal dose. No dose-depended differences were in half-life, distribution volume, clearance, or renal clearance among the doses studied. There were no statistically significant differences in the urinary recovery of meropenem among the three doses, with approximately 55% of the administered dose recovered as parent drug and 12% recovered as metabolite in the first 12 hours following drug administered. The renal clearance accounted for almost half of the meropenem clearance. Table 1 shows the effect of dose on meropenem pharmacokinetics. Patients enrolled were initially stratified into four groups by age. Between 2 months and 12 years of age, the half-life fell from 1.67 to 0.88 hours (p-level = 0.0003), respectively. Changes in distribution volume at steady-state showed the expected decreasing trend with age, but this trend failed to achieve statistical significance. In contrast, the clearance showed the kind of pattern frequently seen with renally eliminated drugs. Clearance appeared to increase gradually from 2 months through 5 years of age and then declined. None of these changes were statistically significant. Urinary recovery of meropenem and its metabolite as a fraction of the administered dose was also independent of age. However, the fraction of clearance attributed to renal clearance showed a decreasing trend with increasing age. Table 2 shows the effect of age on meropenem pharmacokinetics. Infusions of meropenem were well tolerated by virtually all patients; one child appeared to have some redness at the injection site. Clinical adverse events were limited, and some may not have been entirely drug related. The following adverse events were noted during the study: chest pain (N = 3), vomiting (N = 3), rash (N = 2), fever (N = 1), nausea (N = 1), injection site reaction (N = 1), and hypotension (N = 1). No laboratory abnormities were reported as a result of drug exposure in any patient. The spectrum of activity of meropenem includes all the bacterial pathogens that commonly cause infections in infants and children. Therefore, meropenem would seem to be a valuable addition to the paediatric antimicrobial armamentarium. By using this and the premise that, for β-lactam antibiotics, drug must be present at inhibitory concentrations at the site of infection throughout the dosing interval, a dosing recommendation can be made on a pharmacokinetic basis. This involves an examination of the time that serum drug concentration is above the MIC for the infecting organism. With this approach, at any given dose a dosing interval can be ascertained by projecting the plasma concentration-versus-time curve onto the MIC for a susceptible organism. Such an integrated pharmacokinetic-pharmacodynamic analysis was performed for meropenem analysis administered at 20 mg/kg every 8 or 12 hours. At this dose all organisms listed in Table 3 should be effectively treated with dosing every 8 hours. In fact, with the exception of Serratia marcescens, and Pseudomonas aeruginosa, 20 mg/kg meropenem every 12 hours would be expected to be an

Table 1. Effect of dose on meropenem pharmacokinetics in 71 infants and children aged from 2 months to 12 years receiving 3 different doses of meropenem. The figures are the mean±SD, by Blumer, *et al*. [15]

Meropenem dose (mg/kg)	Half-life (hours)	Distribution volume (l/kg)	Distribution volume* (l/kg)	Mean residence time (hours)	Clearance (ml/min/kg)	Renal clearance (ml/min/kg)	Renal clearance to clearance ratio	Bioavailability from 0-12 hours (%dose)
10 (N = 28)	1.0±0.4	0.4±0.1	0.4±0.1	1.5±0.4	5.2±1.3	2.6±1.0	0.53±0.19	0.61±0.08
20 (N = 25)	1.1±0.5	0.4±0.1	0.4±0.1	1.5±0.5	5.2±1.6	2.0±1.3	0.39±0.21	0.52±0.14
40 (N = 18)	1.3±0.6	0.6±0.2	0.5±0.1	1.7±0.7	6.5±2.0	3.0±2.1	0.46±0.28	0.48±0.26

*Steady-state.

Table 2. Effect of age on meropenem pharmacokinetics in 63 infants and children receiving 20 mg/kg of meropenem. The figures are the mean±SD, by Blumer, *et al*. [15]

Patient age	Half-life (hours)	Distribution volume (l/kg)	Distribution volume* (l/kg)	Mean residence time (hours)	Clearance (ml/min/kg)	Renal clearance (ml/min/kg)	Renal clearance to clearance ratio	Fe from 0 to 12 hours (%dose)	FeM from 0 to 12 hours (%dose)
2-5 months (N = 17)	1.6±0.6	0.5±0.1	0.4±0.1	2.2±0.4	4.3±1.6	2.6±2.0	0.54±0.26	59±13	12±5
6-23 months (N = 17)	1.3±0.4	0.6±0.2	0.4±0.1	1.6±0.4	5.3±1.4	2.4±1.0	0.48±0.18	47±20	16±10
2-5 years (N = 19)	1.0±0.4	0.5±0.2	0.4±0.1	1.4±0.4	6.2±1.9	2.8±1.7	0.46±0.23	57±15	10±4.0
6-12 years (N = 18)	0.8±0.2	0.4±0.1	0.3±0.1	1.3±0.2	5.8±1.5	2.1±1.4	0.38±0.25	64±1.0	8.0±1.0

*Steady-state. Fe and FeM are the fraction of meropenem excreted from 0 to 12 hours expressed as percentage of dose and fraction of metabolite excreted from 0 to 12 hours expressed as percentage of meropenem dose administered.

optimal dose on pharmacological principles. On the basis of the pharmacokinetic parameters, meropenem can be given at doses up to 40 mg/kg at 8-intrvals to infants and children without the risk of drug accumulation. The favourable safety and tolerance profile, as well as the predicted clinical efficacy of the drug, supports its further evaluation for the treatment of infections in children (Table 4).

Cojutti *et al.* [16] explored the pharmacokinetics and pharmacodynamics of continuous-infusion meropenem in a population of paediatric hematopoietic stem cell transplant patients who underwent therapeutic drug monitoring. The relationship between meropenem clearance and estimated creatinine was assessed by nonlinear regression. A Monte Carlo simulation was performed to investigate the predictive performance of five dosing regimens (15 to 90 mg/kg per day) for the empirical treatment of severe gram-negative-related infections in relation to four categories of renal function. Febrile neutropenia and bloodstream infections accounted for most of indications of meropenem use (77.8%). In 37.0% (10/27) of courses, microbiological isolates were identified. The most frequently identified was Escherichia coli, followed by Pseudomonas aeruginosa and Klebsiella pneumoniae. Overall, 44 meropenem concentrations at steady-state measurements were retrieved for analysis. The median meropenem concentration at steady-state was 29.8 μg/ml after a median dose of 29.8 mg/kg in children with a median of creatinine clearance estimate of 189.5 ml//min/1.73 m^2. The optimal target was defined as a probability of target attainment of ≥ 90% at steady-state concentration-MIC ratios (Css/MIC) of ≥ 1 and ≥ 4 for MICs of up to 8 μg/ml. A total of 21 children with 44 meropenem Css were included. A good relationship between meropenem clearance and estimated creatinine clearance was observed (r^2 = 0.733). Simulations showed that at an MIC of 2 μg/ml, the administration of continuous-infusion meropenem at doses of 15, 30, 45, and 60 mg/kg per day may be a probability target attainment of ≥ 90% at Css/MIC ratio of ≥ 4 in the creatinine clearance categories of 40 to < 80, 80 to < 120, 120 < 200, and 200 to < 300 ml/min/1.73 m^2, respectively. At an MIC of 8 μg/ml, doses, of up 90 mg/kg per day by continuous infusion may achieve the optimal probability target attainment only in the creatinine clearance categories of 40 to < 80, and 80 < 120 ml/min/1.73 m^2. Continuous-infusion meropenem at dosages up to 90 mg/kg per day might be effective for optimal treatment of severe gram-negative-related infections in paediatric hematopoietic stem cell transplant patients, even when caused by carbapenem-resistant pathogens on MIC of up to 8 μg/ml. A standard meropenem dosage of 20 to 40 mg/kg every 8 hours infused over 30 min is deemed effective for attainment a pharmacodynamic target of plasma meropenem concentration above MIC (time above the MIC [T > MIC] for around 40% of the dosing interval clinical stable children.

van Enk *et al.* [17] evaluated and compared the pharmacokinetics of meropenem in premature neonates, both after the first dose and during steady-state at day 5, after a 1-min intravenous administration to evaluate the possibility of twice-daily administration. Seven premature neonates receiving 15 mg/kg meropenem and during steady-state at day 5, serum levels of meropenem were measured for 12 hours intervals after intravenous administration of meropenem. Meropenem pharmacokinetics at the first dose were studied in seven neonates (mean birth weight was 925 grams, and the mean postnatal age was 21 days). Meropenem was administered as a 1 min intravenous infusion at a dosage of 15 mg/kg twice-daily. Blood samples were collected before the dose was given and 0.08, 1, 3, 5, 8, and 12 hours after the first dose. The same procedure was followed on day 5 of treatment. Serum was isolated from blood and used to measure meropenem concentrations. The pharmacokinetic parameters are summarized in Table 5.

Table 3. Predicted duration of effect expressed as time above the minimum inhibitory concentration (MIC) for meropenem administered at 20 mg/kg per dose. By Blumer, *et al*. [15]

		Time above the MIC (hours)	
	MIC (μg/ml)	8 hours after dosing	12 hours after dosing
Streptococcus pyogenes	0.01	17	15
Neisseria meningitis	0.25	16	14
Streptococcus pneumoniae, Neisseria gonorrhoea, Salmonella Spp.	0.05	14.2	12
Staphylococcus aureus, group B streptococci	0.10	13	11
Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Listeria monocytogenes	0.25	11.5	9.5
Enterobacter cloache, Bacteroides fragilis	0.50	10.2	8.3
Serratia marcescens	1.00	9	7.1
Pseudomonas aeruginosa	2.00	7.8	5.7

Table 4. Pharmacokinetic and pharmacodynamic target attainment of continuous-infusion meropenem in cases with identified clinical isolates (N = 11), by Cojutti, *et al.* [16]

Age (years)	Sex[a]	Bacteria isolate[c]	Type of infection[b]	MIC (μg/ml)	Css (μg/ml)[d]	Css/MIC[d]	Anti-gram-negative cotreatment(s)	Treatment duration (days)	Outcome[c]
3	M	Pseudomonas aeruginosa	BSI	≤ 0.25	23.95	≥ 0.2595	Amikacin	8	Cured
3	F	Klebsiella pneumoniae KPC$^+$	BSI[f]	≥ 16	50.15	≤ 3.13	Tigecycline+colistin	12	Failed
3	F	Pseudomonas aeruginosa	BSI	1.0	50.15	50.15	None	15	Cured
6	M	Klebsiella pneumoniae	BSI	0.25	57.99	231.9	Amikacin	12	Cured
12	M	Escherichia coli (porin-R)	BSI[f]	8	23.69	2.96	Amikacin	11	Cured
15	F	Escherichia coli	BSI[g]	≤ 0.25	23.69	≥ 0.2595	Amikacin	9	Cored
15	F	Escherichia coli ESBL$^+$	BSI	≤ 0.25	18.02	≥ 0.2595	Amikacin	11	Cured
15	F	Escherichia coli ESBL$^+$	BSI[h]	≤ 0.25	40.81	≥ 0.2516	None	15	Cured
15	F	Escherichia coli	UTI[i]	1.0	14.43	≥ 0.2558	None	10	Cured
16	M	Escherichia coli	BSI	≤ 0.25	7.81	≥ 0.531	Amikacin	8	Cured
16	M	Pseudomonas aeruginosa	HAP	0.5	36.13	72.26	None	5	Failed

[a]M = male, F = female. [b]BSI = bloodstream infection. [c]KPC$^+$ = Klebsiella pneumoniae carbapenase producer. [d]Mediaa and IQR are reported when two or more Css assessment were available. [e]AML = acute myeloid leukaemia. [f]Same course of treatment. [h]Second course of treatmnt. [i]Third course of treatment. UTI = urinary tract infection. HAP = hospital-acquired pneumoniae. KPC+ = Klebsiella pneumoniae carbapenemase producer. Porin-R = porin mediated resistance. ESBL = extended-spectrum β-lactamase. f = Same course of treatment. g = First course of treatment. h = Second course of treatment. i = third course of treatment.

Table 5. Mean pharmacokinetic parameters of meropenem at the first dose* and at day 5** of meropenem administration, by van Enk, *et al*. [17]

	First day of meropenem administration					Fifth day of meropenem administration				
	AUC (mg/h/l)	Clearance (l/kg/h)	Distribution Volume (l/kg)	Half-life (hours)	Mean residence time (hours)	AUC (mg/h/l)	Clearance (l/kg/h)	Distribution volume (l/kg)	Half-life (hours)	Mean residence time (hours)
Infant										
1	89.6	0.160	1.10	4.6	6.6	129	0.111	0.38	2.4	3.5
2	115	0.125	0.24	1.3	1.5	76.1	0.175	0.52	2.0	2.8
3	58.7	0.238	0.67	2.0	2.8	63.3	0.221	1.14	3.6	4.3
4	97.2	0.150	0.30	1.4	2.0	59.5	0.225	0.58	1.8	2.6
5	104	0.142	0.94	4.6	5.9	n.d.	n.d.	n.d.	n.d.	n.d.
6	78.9	0.188	1.20	4.5	6.3	171	0.077	0.44	4.0	5.7
7	150	0.093	0.72	5.4	6.6	n.d.	n.d.	n.d.	n.d.	n.d.
Mean	99.1	0.157	0.74	3.40	4.5	99.8	0.162	0.61	2.8	3.8
±SD	28.9	0.046	0.046	1.08	2.3	48.5	0.066	0.30	1.0	1.3

n.d. = not data. *N = 7. **N = 5

Bacterial resistant to meropenem in infants and children

Serotypes and patterns of antibiotic resistance of Streptococcus pneumoniae strains that cause invasive pneumococcal disease in infants were analyzed to provide guidance for clinical disease prevention and treatment [18]. The clinical features of confirmed invasive pneumococcal disease were evaluated in 61 children aged less than 5 years, who were admitted to the hospital between January 2009 and December 2011. Serotypes and antibiotic resistance of strains of Streptococcus pneumoniae were determined using the capsular swelling method and E-test. A total of 61 invasive strains were isolated. The serotype distribution of those isolates were 19A (41.o%), 14 (19.7%), 19F (11.5%), 23F (9.8%), 8 (4.9%), 9V (4.9%), 1 (3.3%), and 4, 6B, and 20 (each 1.6%). The percentage of Streptococcus pneumoniae strains resistant to meropenem were 36.1%. The percentage of multidrug-resistant strains was 95.6%. Strains with serotype 19A had the highest rate of resistance. Serotype 19A strains were most frequently isolated in children with invasive Streptococcus pneumoniae treated in the hospital. The strains causing invasive Streptococcus pneumoniae are highly resistant to antibiotics.

Infection with resistant gram-negative bacteria is a growing threat to hospitalized patients. Velaphi *et al*. [19] determined factors associated with mortality among infants infected by extended-spectrum β-lactamase-producing Klebsiella species and to assess whether selective empirical use of meropenem is associated with high rate of mortality. Medical records of neonates admitted from January 2002 to December 2003 who had positive blood and or cerebrospinal fluid culture with Klebsiella species-extended-spectrum β-lactamase were reviewed for clinical, management and outcome information. Univariate and multivariate logistic regression analyses were performed to determine factors associated with mortality rate among infants with culture-proven Klebsiella species-extended-spectrum β-lactamase. A hundred patients had positive blood (N = 97) and or cerebrospinal fluid cultures (N = 9) owing to Klebsiella species-extended-spectrum β-lactamase. Overall mortality rate was 30%. The mortality rates among those who were empirically started on a combination of piperacillin-tazobactam and amikacin (N = 48), meropenem (N = 40) and in those not started on meropenem or piperacillin-tazobactam plus amikacin (N = 12) were 25%, 32%, and 42%, respectively. Non-survivors were younger (p-level = 0.01), had cardio-respiratory compromise or required assisted ventilation at presentation (p-level < 0.001), and were not started on antibiotics, meropenem or piperacillin-tazobactam plus amikacin. On multivariate analysis, factors associated with mortality were vaginal delivery (odds ratio = -7.07, 95% confidence interval = 2.14-23.39), a need for assisted ventilation at onset of illness (odds ratio = - 4.94, 95% confidence interval = 1.12-21.86) and not starting empirical meropenem or piperacillin-tazobactam plus amikacin (odds ratio -17.01, 95% confidence interval = 2.41-120.23). While empirical use of carbapenems for nosocomial sepsis might be appropriate in areas where Klebsiella species- extended-spectrum β-lactamase is prevalent, their use can be restricted to those with cardio-respiratory compromise or severe sepsis without an increase in mortality rate.

Devrim *et al*. [20] evaluated the distribution and antibiotic susceptibility patters of pathogens causing healthcare-associated urinary tract infections in paediatric setting in children. Most common isolated organisms was Klebsiella pneumoniae (34.1%) and Escherichia coli (26.8%). Among the Pseudomonas aeruginosa, meropenem and imipenem resistance rates were 46.2% and 38.5%, respectively. Extended-spectrum β-lactamase production was present in 48 Klebsiella species (82.8%). Among extended-spectrum β-lactamase positive Klebsiella species, the rate of meropenem and imipenem resistance was 18.8%, and ertapenem resistance was 45.9%. Extended spectrum β-lactamase production was present in 27 (72.9%) Escherichia coli species. Among extended-spectrum β-lactamase positive Escherichia coli, the rate of meropenem and imipenem resistance was 7.4%, and ertapenem resistance was 14.8%. Emerging meropenem resistance in Pseudomonas aeruginosa, higher rates of ertapenem resistance in extended-spectrum β-lactamase positive ones in Escherichia coli and Klebsiella species in paediatric nosocomial urinary tract infections are important notify signs for superbug infections.

The retrospective study analyzed 1,025 bacterial isolates from blood cultures collected from paediatric patients admitted in a tertiary-care hospital in New Delhi to find out drug sensitivity patterns [21]. Staphylococcus was isolated from approximate 70% of the cultures, with 63.7% of them being methicillin-resistant. Meropenem resistance among Acinetobacter was 28.6%.

Wolkowicz *et al*. [22] analyzed the distribution of carbapenem resistance mechanisms among Pseudomonas aeruginosa clinical isolates. Fifty-five Pseudomonas aeruginosa isolates, resistant both to imipenem and meropenem, from children hospitalized in 2009-2010 were studied. All strains were genotyped by pulse-field gel electrophoresis. Mutations in the oprD gene and the occurrence of insertion sequences were determined by DNA sequencing. Mex efflux systems were determined by analysis using the efflux pump inhibitor Phe-Arg β-naphthylamide. Metallo-β-lactamase production was determined with E-test metallo-β-lactamase strips and PCR for bla_{imp}. Pulsed-field gel electrophoresis showed high genetic diversity among the isolates. Mutations inactivating the oprD gene were detected in

44 strains (80%). Frameshift mutations determined in 20 isolates were the most common cause of inactivation of the oprD gene. Point mutations leading to premature stop codons were found in 12 isolates, and various substitutions were found in 6 isolates. Disruption of the coding sequence of oprD by ISs was found in 6 isolates. Two novel ISs (ISPa51 and ISPa52) were detected. Increased activity of different Mex system was observed in 27 isolates (49%). Ten isolates simultaneously overexpressed two (N = 3) or three (N = 7) of Mex efflux system. Seven (13%) Pseudomonas aeruginosa strains were found to have minimum inhibitory concentrations (MICs) of > 64 μg/ml both for imipenem and meropenem (two VIM-4, four VIM-2 and one IMP-1). These results show a significant diversity of Pseudomonas aeruginosa strategies for resistance development. Noteworthy, a variety of ISs were found to disrupt the oprD gene.

Infections caused by antibiotics-resistant gram-positive bacteria have been reported from many paediatric haematology-oncology centres. The susceptibility profiles to meropenem, piperacillin, and vancomycin among oral flora isolates of α-haemolytic streptococci obtained from six children with cancer who received several empirical therapies against febrile neutropenia were investigated [23]. Meropenem MIC of α-haemolytic streptococci isolated from empirical therapies children was 2.167+0.258 μg/ml, which was significantly higher than MIC of α-haemolytic streptococci isolated from control groups. Intriguingly, α-haemolytic streptococci isolated approximately 6 months after hospital discharge indicated recovery of susceptibility to meropenem. α-Haemolytic streptococci isolates from neutropenic children with cancer should be checked for antibiotic susceptibility, even against carbapenems.

Zhu *et al.* [24] identified the mechanism of in-vivo development of carbapenem resistance in Klebsiella pneumoniae. Seven sequential isolates of Klebsiella pneumoniae were obtained from twin infants with pneumonia. Antimicrobial susceptibility testing was performed by agar dilution method. Plasmids of all clinical isolates and conjugates of resistant isolates were determined by pulsed-field gel electrophoresis. Molecular typing were conducted by pulsed-field gel electrophoresis of Xbal-digested genomic DNA and multilocus sequence typing. For old brother, the first and third isolates were susceptible to meropenem, whereas the second and fourth isolates was resistant. All the resistant isolates produced NDM-1 metallo-β-lactamase. Pulsed-field gel electrophoresis of Xbal-digested DNA revealed almost identical patterns with similarity indices of above 92% for all seven isolates. All the isolates had the same sequence type named sequence type 37 (ST37).

Penicillin-resistant oral streptococci constitute the genetic reservoir for β-lactam resistance in Streptococcus pneumoniae. Konig *et al.* [25] reported the isolation of clinical strains of Streptococcus mitis with unusually high MIC values for β-lactam compounds tested, only the carbapenems imipenem and meropenem showed MICs below 32 μg/ml. Pulsed-field mapping of chromosomal DNA revealed identical patterns in both strains, indicating clonal identity of the two isolates. Using chromosomal Streptococcus mitis DNA, the laboratory strain Streptococcus pneumoniae R6 could be transformed in four successive steps to cefotaxime and benzylpenicillin resistance of 64 μg/ml. These results exemplify the importance of commensal streptococci for the development of cefotaxime resistance in Streptococcus pneumoniae.

Discussion

Meropenem is a broad-spectrum antibiotic. It is a carbapenem β-lactam antibiotic active against a very wide range of gram-positive aerobic and anaerobic bacteria. Meropenem is used for the treatment of pneumococcal meningitis and other serious infections caused by susceptible organisms resistant to other antibiotics, especially extended-spectrum β-lactamase producing Klebsiella pneumoniae. The elimination half-life in term neonates is 2 hours and in preterm neonates it is 3 hours, but the half-life falls significantly within 10-14 days of life of birth [1]. Meropenem penetrates well into the cerebrospinal fluid and most body tissues. It exhibits time-depended killing of gram-negative and gram-positive pathogens, and the goal of therapy is to keep free drug concentrations above MIC for at least 40% of the dosing interval. Meropenem is stable to inactivation by human renal dehydropetidase, thus not cilastatin administration is necessary. The clearance of meropenem is directly related to renal function, and 70% of a dose is recovered intact in the urine. For sepsis give 20 mg/kg intravenously every 12 hours [2].

Hsu *et al.* [4] assessed the efficacy and safety of meropenem in paediatric patients aged 4 days to 20 years. The satisfactory clinical response was 57% in lower respiratory infection, 58% in septicaemia, 100% in complicated urinary infection, 83% in skin and soft tissue infection, and 93% in intra-abdominal infection. Meropenem is well tolerated even in young infants and is effective in treating serious childhood bacterial infections. Intra-abdominal infections are common in young infants and lead to morbidity and mortality. Cohen-Wolkowiez *et al.* [5] determined the safety and effectiveness of meropenem in 200 preterm and term infants aged < 91 days of life. A total of 99 (50%) infants experienced adverse events, and 34 (17%) had serious adverse events. The adverse events were not related to meropenem. Effectiveness was evaluable in 192 (96%) infants, and the overall treatment success was found in 84% of infants. Pancharoen *et al.* [6] evaluated the efficacy and safety of meropenem in 30 paediatric cancer children (mean age =7.5 years) with febrile neutropenia. Meropenem 60 mg/kg per day was administered intravenously every 8 hours. The use of meropenem appeared safe, with minimal side effects. The efficacy of meropenem as an empirical monotherapy in children with febrile neutropenia was satisfactory, with a failure rate of 23.3% on day 5 of treatment. Erbey *et al.* [7] investigated the efficacy and safety of meropenem in 42 children with cancer who had febrile neutropenia. The success rate 87.5%. Buckingham *et al.* [8] investigated pneumococcal susceptibility to meropenem in isolates from blood or cerebrospinal fluid in children resistant to penicillin and cefotaxime. Of 29 penicillin-resistant isolates, 27 (93.1%) children were susceptible to meropenem. Koksal *et al.* [9] reported the use of meropenem in 35 infants with severe infections due to Acinetobacter baumanii and Klebsiella pneumoniae. At the end of therapy, overall satisfactory clinical and bacterial response was obtained in 33/35 (94.3%) of newborns treated with meropenem. Clinical and bacterial response rates for meropenem were 100% for sepsis and 87%.5% for nosocomial pneumoniae. Meropenem may be a useful antimicrobial agent in neonatal infections caused by multiresistant gram-negative bacilli. Toltizis *et al.* [10] investigated the sustained meropenem use on the pattern of the colonization in gram-negative bacilli in children. There was no statistically significant effect on the prevalence of colonization by gram-negative organisms resistant to one or more classes of broad-spectrum parenteral antibiotics, or to colonization by organisms resistant specifically to meropenem, when meropenem was the preferred antibiotic in a paediatric intensive care unit.

Shabaan *et al.* [11] compared the clinical and microbiologic efficacy and safety of prolonged (4 hours) infusion versus short (30 min) infusion of meropenem in 102 children (51 children in each group). The prolonged meropenem infusion demonstrated a significantly

higher rate of clinical improvement and microbiologic eradication 7 days after starting meropenem therapy compared with the short infusion. The dosing regimen of meropenem was 20 mg/kg per dose every 8 hours and 40 mg/kg per dose every 8 hours in meningitis and Pseudomonas infection. Padari *et al.* [12] compared the steady-state pharmacokinetics of meropenem given as a short (30 min, N = 9) or prolonged (4 hours, N=10) infusion in very-low-birth-weight neonates. Meropenem was given at a dose of 20 mg/kg every 12 hours. A short infusion resulted in a higher mean meropenem serum concentration. Meropenem infusion of 30 min is acceptable in very-low-birth-weight neonates and no dosing adjustment is needed over the first month of life.

A population pharmacokinetic model for meropenem was developed in 50 paediatric patients [13]. The population pharmacokinetic parameters are useful for calculation of the percent time above MIC (%T > MIC) and for optimal dosing of meropenem in paediatric patients. After meropenem dosing at 20 mg/kg, the target value of 50% T > MIC was achieved, thus this meropenem dosage is effective for susceptible bacteria. For bacteria with higher MICs 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.

Hornik *et al.* [14] conducted a retrospective cohort study of 5,566 infants treated with meropenem or imipenem/cilastatin. Adverse event were more common with the use of meropenem compared with imipenem/cilastatin. There was no difference in seizures with meropenem versus imipenem/cilastatin. The incidence of death or seizures was lower with meropenem use. Meropenem was associated with more frequent but less severe events when compared with imipenem/cilastatin.

Blumer *et al.* [15] Studied the pharmacokinetics of meropenem in 71 infants and children receiving the meropenem doses of 10, 20, and 40 mg/kg. There were no differences in pharmacokinetic parameters with these doses. The meropenem half-life, clearance, and distribution volume values ranged from 1.0+0.4 to 1.3+0.6 hours, 5.2+1.3 to 6.5+0.2 ml/min/kg, and from 0.3+0.1 to 0.4+0.1 l/kg, respectively. These authors studied the effect of age on 63 infants and children. The half-life was 1.6+0.6 and 0.8+0.2 in infants 2-5 months old in children 6-12 years old, respectively. The half-life was shorter in children than in infants. The clearance was 4.3+1.6 and 5.8+1.5 ml/min/kg in infants and children, respectively. The clearance was smaller in infants than in children. The renal clearance was 4.3+1.6 and 5.8+1.5 ml/min/kg in infants and children, respectively. The renal clearance was shorter in infants than in children. The renal clearance to clearance ratio was 0.54+0.26 and 0.38+0.25 in infants than children, respectively. The distribution volume was not affected by age.

Cojutti *et al.* [16] explored the pharmacokinetics and pharmacodynamics of continuous-infusion meropenem in a population of paediatric hematopoietic stem cell transplant patients who underwent therapeutic drug monitoring. A Monte Carlo simulation was performed to investigate the predictive performance of five dosing regimens (15 to 90 mg/kg). The optimal target was defined as a probability of target regimen attainment (PTA) of ≥ 90% at steady-state concentration to-MIC ratios (Css/MIC) of ≥ 1 and ≥ 4 for MICs of up to 8 μg/ml. Continuous-infusion meropenem at dosages up to 90 mg/kg/day might be effective for optimal treatment of severe gram-negative-related infections in paediatric patients, even when caused by carbapenem-resistant pathogens with an MIC of up to 8 μg/ml.

Van Enk *et al.* [17] evaluated and compared the pharmacokinetics of meropenem in premature neonates, both after the first dose and during steady-state at 5 days after 15 mg/kg intravenously administration of meropenem. The mean body clearance, the distribution volume, and the half-life were not significantly different in the two meropenem dose regimens.

Liu *et al.* [18] investigated the clinical features of confirmed invasive pneumococcal disease in 61 children aged less than 5 years. The percentage of Streptococcus pneumoniae resistant to meropenem was 36.1%. Velaphi *et al.* [19] determined factors associated with mortality among infants infected by extended-spectrum β-lactamase-producing Klebsiella species and to assess whether selective empirical use of meropenem is associated with high rate of mortality. The mortality rate of children treated with meropenem was 32%. Devrim *et al.* [20] evaluated the antibiotic susceptibility patterns in children. Among the Pseudomonas aeruginosa, meropenem up to 38.5%. A total of 1,025 were isolated from children blood by Roy *et al.* [21]. Meropenem resistance among Acinetobacter was 28.8%. Wolkowicz *et al.* [22] analyzed the distribution of carbapenem resistance among Pseudomonas aeruginosa of clinical isolates from children. Fifty-five Pseudomonas aeruginosa isolates were resistant to imipenem and meropenem. The susceptibility of meropenem among oral flora isolates of α-haemolytic streptococci were obtained from 6 children with cancer [23]. Meropenem MIC of α-haemolytic streptococci isolated from empirical therapy in children was 2.167+0.258 μg/ml which was significantly higher than MIC of α-haemolytic streptococci isolated from control group. Zhu *et al.* [24] identified the in-vivo development of carbapenem resistant in Klebsiella pneumoniae. Seven sequential isolates of Klebsiella pneumoniae were obtained from twins infants with pneumoniae. Molecular typing were conducted by pulsed-field gel electrophoresis of Xbal-digested genomic DNA and multilocus sequence typing. For old brother, the first and third isolates were susceptible to meropenem, whereas the second and fourth isolates were resistant to meropenem. Konig *et al.* [25] reported the isolation of clinical strains of Streptococcus mitis with unusual high MIC values for β-lactam compounds tested only the carbapenems imipenem and meropenem showed MICs below 32 μg/ml. Using chromosomal Streptococcus mitis DNA, the laboratory strains Streptococcus pneumoniae R6 could be transformed in four successive steps to cefotaxime and benzylpenicillin resistant of 64 μg/ml.

In conclusion, meropenem is a valuable broad-spectrum antibiotic, it is a carbapenem β-lactam antibiotic active against a very wide range of gram-positive and gram-negative aerobic and anaerobic bacteria. The use of meropenem is the treatment of pneumococcal meningitis and other serious infections caused by susceptible gram-negative bacteria resistant to other antibiotics, especially extended-spectrum β-lactamase producing Klebsiella pneumoniae. Meropenem is excreted in the urine, mostly unchanged, but partly as an inert metabolite. The elimination half-life is 2 hours in term neonates and 3 hours in preterm neonates, but it falls significantly within 10-14 days of birth life. Meropenem penetrates into the cerebrospinal fluid of patients with bacterial meningitis, and most other body fluids, well. Meropenem is stable to inactivation by human renal dehydropetidase. This antibiotic is effective and safe drug in patients aged 4 days to 20 years. The gram-negative bacteria resistant to ampicillin, amoxicillin, ticarcillin, cefazolin, cefotaxime, ceftazidime ceftriaxone, and aminoglycosides were susceptible to meropenem and at the end of therapy, overall satisfactory clinical and bacterial response was obtained in 94.3% of newborns treated with meropenem. Meropenem may be a useful antimicrobial agent in neonatal infections caused by multiresistant gram-negative bacilli. Prolonged infusion (4 hours)

instead of short infusion (30 min) results in higher clinical and microbiologic efficacy and safety. After meropenem dosing at 20 mg/kg, the target value of 50% T > MIC is achieved. 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 meropenem dose of 40 mg/kg. Some bacteria may become resistant to meropenem. Meropenem is an effective and safe drug for the treatment of serious infections in infants and children.

Conflicts of interest

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

This article is a review and drugs have not been administered to men or animals.

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