Use of Meropenem in the Treatment of Serious Infections in Children: Review of the Current Literature

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Meropenem is a new β-lactam carbapenem antibiotic that appears to be promising in the treatment of hospitalized infants and children with serious infections. It has broad-spectrum activity against microorganisms, including most of the major aerobic (gram-negative and gram-positive) and anaerobic pathogens that cause serious bacterial infections in neonates and children. In addition, its pharmacokinetic profile makes possible parenteral administration every 8 hours. Several studies have demonstrated that meropenem is an effective and safe treatment for infants and children with serious pediatric infections (e.g., urinary tract infections, pneumonia, sepsis, intraabdominal infections, and skin and soft-tissue infections), bacterial meningitis, and cystic fibrosis. The results of further studies of the use of meropenem in the treatment of high-risk seriously ill infants and children are awaited with interest.

The initial clinical experience with the β-lactam carbapenem antibiotics suggested that they may represent a major breakthrough in the management of infections in infants and children. These compounds have broad-spectrum activity; when administered as single-drug therapy, they attain bactericidal concentrations that are comparable with those achieved with combination therapy, thus resulting in greater ease of administration and potential reductions in toxic effects, patient monitoring, and cost [1–3].

Until recently, imipenem was the only carbapenem approved for use in the United States. It has been used to treat infants and children with moderate to severe infections. Imipenem may not, however, fulfill some of the criteria that would comprise an “ideal” antimicrobial therapy for the management of infections in infants and children. The use of imipenem is associated with adverse reactions that range from nausea, diarrhea, and vomiting to more serious side effects such as seizures [4, 5]. One study of imipenem/cilastatin treatment of bacterial meningitis in infants and children [6] was terminated when seven (33%) of the 21 treated children had seizures after administration of therapy. Because it has limited stability against degradation by the human renal enzyme dehydropeptidase-I (DHP-I), imipenem must be given with cilastatin. In addition, it requires four-times-daily dosing. Meropenem was recently approved for the use in infants and children with intraabdominal infections and bacterial meningitis.

Meropenem, a new carbapenem antibiotic, has undergone extensive investigation at centers around the world and appears to be highly promising in the treatment of moderate to serious bacterial infections in infants and children. Meropenem has broad-spectrum antimicrobial activity; it has been shown to be active in vitro against aerobic gram-negative and gram-positive bacteria as well as anaerobic organisms, such as Bacteroides species [7–11]. It is highly stable against β-lactamase hydrolysis and is more resistant than imipenem to DHP-I [4, 9, 12–14].

When meropenem was compared with numerous single- and multiple-drug regimens consisting of second- and third-generation cephalosporins (e.g., ceftazidime, ceftriaxone, cefotaxime, and cefoxitin), gentamicin and other aminoglycosides, piperacillin, clindamycin, ciprofloxacin, and/or metronidazole, it consistently demonstrated a broader spectrum of activity and was generally found to be more potent [7, 9–11, 15, 16].

In this article, recent literature regarding the pharmacokinetics and antimicrobial activity of meropenem (with particular emphasis on its clinical use in the management of serious infections in children) is reviewed. Future applications of meropenem, which remain to be investigated, are also explored.

Pharmacokinetics of Meropenem

A large body of data describes the pharmacokinetic properties of meropenem in adults [13, 17–23]. To establish dosing guidelines for the use of meropenem in children, an escalating single-dose pharmacokinetic study was conducted with 73 infants and children between the ages of 2 months and 12 years who received 10, 20, and 40 mg/kg of meropenem daily as a 30-minute infusion; the subjects were divided into four age groups [24]. Blood samples were obtained immediately before infusion, at the end of infusion, and at 60, 120, 240, 360, and 480 minutes after the start of dosing.

As shown in figure 1, there was a proportional increase in the peak plasma concentration and area under the curve when the dose was increased from 10 to 20 mg, but a somewhat lesser effect was noted when the dose was increased from 20...
Antimicrobial Activity of Meropenem

Meropenem is a bactericidal drug with an MIC:MBC ratio of 1:1 or 1:2 [4]. It penetrates into the cell and binds to penicillin-binding proteins (particularly penicillin-binding proteins 2 and 3), thus interfering with the synthesis of vital cell wall components and causing cell death [4, 26]. Meropenem is stable against hydrolysis by most plasmid- or chromosome-encoded \( \beta \)-lactamases [7, 9, 13, 27–29]. Its in vitro activity is unaffected by changes in pH, inoculum size, or the presence of human sera in culture media [7, 28]. Meropenem is less likely than imipenem to induce type 1 \( \beta \)-lactamases, although it is more likely than ceftazidime, cefoxitin, or piperacillin to do so [14].

Meropenem has been shown to be highly potent against a broad spectrum of aerobic and anaerobic bacteria [3, 7, 8, 14, 15, 25, 30–33]. For the purposes of this discussion, susceptibility, intermediate or moderate susceptibility, and resistance to meropenem are provisionally defined as MICs of \( \leq 4 \) mg/L, \( \leq 8 \) mg/L, and \( \geq 16 \) mg/L, respectively. In vitro activity of meropenem against anaerobes, gram-negative aerobic organisms, most Enterobacteriaceae, and nonfermentative gram-negative bacteria is superior to that of imipenem [11, 14, 15, 25, 33, 34]. However, the in vitro activity of imipenem against gram-positive aerobes is equal to or slightly greater than that of meropenem.

The activity of meropenem appears to make it uniquely well suited to the treatment of serious infections in children. Meropenem has been shown to be highly active against the pathogens frequently associated with many serious infections in this age group. These organisms include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pyogenes* [7, 14, 15, 25, 31]. Meropenem is also highly active against many pathogens associated with serious gastrointestinal infections in children, including *Salmonella* species [7, 33], *Shigella* species [7, 33], *Yersinia enterocolitica* [7], and *Campylobacter jejuni* [25].

In vitro studies have shown that meropenem has excellent activity against the pathogens isolated from sputum samples from patients with cystic fibrosis. The MIC \(_{50}\) and MIC \(_{90}\) values for common bacterial isolates from patients with cystic fibrosis are as follows: *Pseudomonas aeruginosa*—0.25 and 0.5 mg/L, respectively; multiresistant *P. aeruginosa*—0.15 and 0.5 mg/L, respectively; *Burkholderia cepacia*—2 and 16 mg/L, respectively; *Escherichia coli*—<0.032 and 0.063 mg/L, respectively; *Staphylococcus aureus*—0.125 and 0.25 mg/L, respectively; and *H. influenzae*—0.125 and 0.25 mg/L, respectively. The antimicrobial activity of meropenem is not affected by alterations in the inoculum size of the bacterium or the addition of serum to media [9, 10, 35].

Efficacy of Meropenem Treatment for Pediatric Patients

Several studies evaluating the usefulness of meropenem treatment for hospitalized infants and children with serious bacterial infections, bacterial meningitis, and cystic fibrosis have been conducted. The results of these investigations are discussed below.

**Serious infections in infants and children.** Two multicenter randomized studies evaluating the efficacy and safety of meropenem vs. cefotaxime in the treatment of infants and children with clinical signs and symptoms of bacterial infections serious enough to require hospitalization and to be treated with parenteral antibiotics have been conducted [36]. The protocols of the two studies were similar; however, one was conducted in the United States and Canada, while the other was conducted in Europe and South Africa. The North American study compared meropenem with cefotaxime alone or in combination with clindamycin and/or tobramycin. The European/South African study compared meropenem with cefotaxime alone or in combination with metronidazole or amikacin.

A total of 414 children were evaluated: 243 in the meropenem treatment group and 171 in the cefotaxime treatment group. The ages of the children ranged from 1 month to 12 years. Their diagnoses included lower respiratory tract infection, urinary tract infection, septicemia, skin and skin structure infections, and intraabdominal infections. The patients received 10 to 20 mg/kg of iv meropenem q8h or 40 mg/kg of iv cefotaxime q6h. The average duration of treatment was 5.6 days for meropenem and 5.3 days for cefotaxime. The additional anti-
Table 1. Clinical responses of infants and children with serious infection who were treated with meropenem or cefotaxime.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Meropenem* (%)</th>
<th>Cefotaxime* (%)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>133/134 (99)</td>
<td>94/98 (96)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>73/73 (100)</td>
<td>58/61 (95)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>23/23 (100)</td>
<td>7/8 (88)</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>13/13 (100)</td>
<td>9/9 (100)</td>
</tr>
<tr>
<td>Skin and skin structures</td>
<td>18/19 (95)</td>
<td>16/16 (100)</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>6/6 (100)</td>
<td>4/4 (100)</td>
</tr>
</tbody>
</table>

NOTE. Data were adapted from [35].
* With or without amikacin, clindamycin, metronidazole, or tobramycin.

As shown in table 1, both treatment regimens produced favorable clinical outcomes at the end of treatment. A total of 99% of patients treated with meropenem had a satisfactory clinical response, as did 96% of patients treated with cefotaxime. Meropenem was particularly effective in treating lower respiratory tract infections, urinary tract infections, septicemia, and intraabdominal infections (100% response rates). It was also highly effective in treating skin and skin structure infections (95% response rate). Both treatments were well tolerated, and no clinical or laboratory adverse events were reported for >2% of patients in either treatment group.

Bacterial meningitis. Carabepenem antibiotics have been shown to be highly effective in vitro against the major pathogens responsible for meningitis in children [7, 37, 38]. In the case of meropenem, its MIC50 value is lower than that of imipenem for most H. influenzae isolates, and it has marked activity against N. meningitidis [39]. In addition, meropenem has been shown to penetrate the CSF of children with inflammation associated with acute meningitis [40]. The clinical experience with meropenem suggests that its clinical and bacteriologic efficacies are comparable with those of cefotaxime, and there appear to be no significant differences in their toxicity profiles [39, 41].

Several randomized studies comparing meropenem with either cefotaxime or ceftriaxone as treatment for infants and children with bacterial meningitis due to H. influenzae, S. pneumoniae, or N. meningitidis have been completed in Europe, Latin America, South Africa, and Israel [40, 42]. The study participants received either 40 mg/kg of meropenem q8h or standard doses of a comparable antibiotic (i.e., cefotaxime or ceftriaxone). Most patients received dexamethasone as adjuvant therapy.

As shown in table 2, the clinical outcomes and bacteriologic findings for all three treatment groups were comparable, and there was complete (100%) eradication of H. influenzae (type b), N. meningitidis, and S. pneumoniae isolates in all treatment groups. Meropenem was well tolerated; the incidence of seizures in patients treated with meropenem (including patients who had a history of seizures and those who had seizures immediately before treatment with meropenem) was similar to that in patients treated with cephalosporins. These findings are consistent with the preliminary results of a multicenter study currently being conducted in the United States and Central America [43].

Cystic fibrosis. Although patients with cystic fibrosis typically require multiple courses of treatment, there appears to be a minimal risk of spontaneous resistance to meropenem at present. In one study [44], the mutational frequency of single-step resistance to meropenem was <10^{-9} cfu for B. cepacia, 10^{-6} cfu for mucoid P. aeruginosa, and 10^{-5} cfu for nonmucoid P. aeruginosa.

A clinical trial was conducted in the United Kingdom to assess the clinical efficacy of meropenem vs. ceftazidime in the treatment of respiratory infections caused by susceptible pathogens in patients with cystic fibrosis [45, 46]. Forty children and adults were randomized to treatment with either meropenem (27 patients) or ceftazidime (13 patients). A total of 81 infections were treated: 60 in the meropenem treatment group and 21 in the ceftazidime treatment group.

The patients' response to treatment was assessed according to changes in bacteriologic parameters, results of pulmonary function tests (forced expiratory volume in 1 second and forced vital capacity), sputum volume, body weight, and Shwachman

Table 2. Demographics, clinical responses, and bacteriologic findings for infants and children with bacterial meningitis who were treated with meropenem, cefotaxime, or ceftriaxone.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meropenem* (n = 136)</th>
<th>Cefotaxime* (n = 99 or 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>10.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Percent of patients 3 mo to 12 y of age</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>No. of treated patients with indicated response/no. of treated patients (%)</td>
<td>134/136 (98)</td>
<td>122/131 (93)</td>
</tr>
<tr>
<td>Clinical response</td>
<td>115/115 (100)</td>
<td>109/110 (99)</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>31/31 (100)</td>
<td>49/49 (100)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>25/25 (100)</td>
<td>32/32 (100)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>21/21 (100)</td>
<td>22/22 (100)</td>
</tr>
<tr>
<td>Hearing loss* at 6-w follow-up</td>
<td>20/129 (16)</td>
<td>13/120 (11)</td>
</tr>
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</table>

NOTE. Of 292 patients initially enrolled in this study, all but 25 patients received dexamethasone therapy. Data were adapted from [40].

* 40 mg/kg iv every 8 hours.
* 75 to 100 mg/kg iv every 8 hours.
* 80 to 100 mg/kg iv every 24 hours.
* 20 dB or greater unilaterally or bilaterally.
Table 3. Demographics, clinical responses, and bacteriologic findings for children and adults with pulmonary infections associated with cystic fibrosis who were treated with meropenem or ceftazidime.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meropenem</th>
<th>Ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>No. of treatment courses</td>
<td>60*</td>
<td>21</td>
</tr>
<tr>
<td>Percent of patients with indicated response</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>Improved clinical response at end of treatment</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>Increase in FEV₁</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>Increase in FVC</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Decreased bacterial count</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>Decrease in sputum volume (mL)</td>
<td>15.8</td>
<td>12.7</td>
</tr>
</tbody>
</table>

NOTE. FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity. Data were adapted from [44].

* Fifty-four treatment courses were clinically evaluable.

score (a reliable clinically validated assessment of general activity in patients with cystic fibrosis) [47].

As shown in table 3, the overall bacteriologic findings and clinical outcomes at the end of treatment were comparable for the two groups. Virtually all (98%) of the meropenem-treated patients had a satisfactory clinical response, and bacteriologic findings for 73% of these patients were satisfactory (i.e., decreased bacterial counts). The respective rates for the ceftazidime treatment group were 90% and 65%. Similar results were observed at follow-up, when 86% of meropenem-treated patients and 85% of ceftazidime-treated patients still demonstrated a favorable clinical response. Meropenem was well tolerated.

Specimens obtained from each patient throughout the duration of the study were cultured for bacteria, and patients who were treated repeatedly were followed up for up to 1 year. There was little emergence of resistance to meropenem, even in isolates from three patients who received a total of five, seven, and eight courses of therapy, respectively [45].

Patients from whom at least one pathogen sensitive to treatment was isolated were eligible for enrollment into the study; *P. aeruginosa* was the predominant organism. One meropenem-treated patient with *B. cepacia* infection failed to respond to treatment and subsequently died 10 days after treatment with ceftazidime. Two patients failed to respond to ceftazidime treatment; one of these patients then received meropenem therapy and responded clinically. Emergence of resistance to ceftazidime in *P. aeruginosa* and *B. cepacia* isolates from patients with cystic fibrosis has been noted in other investigations [48–51].

Safety of Meropenem Treatment for Children

The safety of meropenem treatment has been evaluated for 417 children (unpublished data, Zeneca Pharmaceuticals, Wilmington, DE). This analysis also included data for 330 patients treated with comparative drugs (iv cefotaxime alone or in combination with metronidazole, amikacin, clindamycin, tobramycin, or clindamycin plus tobramycin). The frequency of clinical adverse events was similar in the meropenem and comparative drug treatment groups. Diarrhea was the most frequent adverse effect in both groups; it occurred in 6.2% of the meropenem-treated patients and in 5.5% of the comparative drug–treated patients. Vomiting (3.4% vs. 2.4%, respectively) and rash (2.6% vs. 3%, respectively) were also observed. The most frequent laboratory adverse events were thrombocytopenia (8% vs. 5.4%, respectively) and increases in levels of aspartate aminotransferase (3.7% vs. 3.9%, respectively) and alanine aminotransferase (3.4% vs. 4.2%, respectively).

Discussion

The advent of new therapeutic modalities has increased the survival rate among patients with chronic debilitating diseases such as cancer and HIV infection. In addition, advances in the care of critically ill neonates and children have improved the outcome for these high-risk patients. Unfortunately, many of these medical milestones have resulted in a large population of hosts with increased susceptibility to infections, particularly those due to resistant pathogens. Furthermore, the indiscriminate use of antibiotic therapy for infants and children has resulted in the emergence of bacteria resistant to many of the most widely used agents.

Hence, the search has continued for new antibiotics for use in the treatment of children with serious bacterial infections that are simple and convenient to administer, that are effective in eradicating the major pathogens involved in these infections, and that do not incur additional costs.

Evidence to date suggests that the new β-lactam carbapenem meropenem is a valuable alternative to parenteral cephalosporins (which are used alone or in combination with other agents) for the treatment of hospitalized infants and children with severe infections [36, 45]. Because of its spectrum of activity, meropenem is particularly well suited to the treatment of infections caused by multiple and/or resistant organisms. In addition, because meropenem does not cause significant toxic effects and because routine monitoring of serum levels is not required, the drug may simplify home therapy for patients who are in stable condition.

The two studies reviewed in this paper in which meropenem was used to treat infants and children with serious bacterial infections (e.g., lower respiratory tract infection, urinary tract infection, septicemia, skin and skin structure infections, and intraabdominal infections) demonstrated that it was a safe and effective alternative to cefotaxime for this population [36]. An evaluation of the pharmacokinetics of meropenem in hospitalized infants and children [24] indicated that a dosage of 20 mg/kg q8h will maintain plasma meropenem concentrations
above the MIC\textsubscript{90} value for virtually all potentially susceptible pathogens responsible for pediatric bacterial infections.

Bacterial meningitis is still frequently diagnosed for children and can cause significant morbidity and mortality. Meropenem reaches high concentrations in the CSF. In limited trials [40-42], meropenem has been shown to have an efficacy comparable with those of the third-generation cephalosporins in the treatment of meningitis. Patients with cystic fibrosis have frequent exacerbations of endobronchitis. \textit{P. aeruginosa} plays a major role in this process, but other bacterial pathogens, like \textit{H. influenzae} and \textit{S. aureus}, are frequently involved.

Additional studies comparing meropenem with other antibiotics are needed to define the role of meropenem in the management of serious infections in infants and children. The most important role for meropenem may be in the treatment of infections due to resistant gram-negative bacteria and possibly infections due to resistant pneumococci. Other areas of interest for future study include whether meropenem may replace more toxic compounds, such as chloramphenicol or the aminoglycosides, or replace multiple-drug therapy.

Because of its broad-spectrum antimicrobial activity, meropenem holds the greatest promise for those patients with cancer, neonatal sepsis, nosocomial infections, bone and joint infections, and intraabdominal infections who require empirical antibiotic therapy before the availability of culture results. For those patients whose conditions are stable, meropenem could facilitate home therapy because of its convenient three-times-daily dosing regimen.

In conclusion, meropenem is distinguished by a unique pharmacokinetic, microbiological, and clinical profile that should make it a valuable addition to the antibiotic armamentarium for infections in infants and children.

References