Bacterial meningitis in adults
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Citation for published version (APA):
van de Beek, D. (2004). Bacterial meningitis in adults

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CHAPTER 5

Meropenem susceptibility of *Neisseria meningitidis* and *Streptococcus pneumoniae* from meningitis patients in the Netherlands

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Journal of Antimicrobial Chemotherapy 1997; 40: 895-7
Chapter 5

ABSTRACT

In vitro susceptibility of 299 Neisseria meningitidis and 157 Streptococcus pneumoniae strains from meningitis patients in The Netherlands in 1993 and 1994 to meropenem was determined using the Etest. Susceptibility to penicillin, ceftriaxone, chloramphenicol was also determined. Rifampicin susceptibility was additionally tested for N. meningitidis. Of the meningococci, 4.3 percent were of intermediate resistance to penicillin and 0.3 percent were resistant to rifampicin. One pneumococcal isolate (0.6 percent) was of intermediate resistance to penicillin. All strains were susceptible to meropenem. We conclude that meropenem is in vitro highly active against N. meningitidis and S. pneumoniae.

INTRODUCTION

Bacterial meningitis in The Netherlands is caused predominantly by Neisseria meningitidis and Streptococcus pneumoniae. The incidence of Haemophilus influenzae type b meningitis decreased strongly as a result of vaccination against this bacterium during the last 3.5 years.1 Although the prevalence of resistance of N. meningitidis and S. pneumoniae to penicillin, chloramphenicol, or cephalosporins in The Netherlands is low,1 resistance of these organisms to antibiotics commonly used in the treatment of meningitis is increasing globally.2-3 The prevalence of penicillin resistant N. meningitidis is low in The Netherlands,1 the UK (3 percent)4 and the USA (4 percent).5 The prevalence of such strains in Spain, however, is 20 to 50 percent.6 Pneumococcal resistance to penicillin due to changes in its penicillin binding proteins was first reported in 1965.3 The prevalence of such resistance was limited until an epidemic of highly resistant pneumococci occurred in South Africa in 1977.3 Since then, resistance has developed worldwide and in some regions it occurs in a frequency up to 70 percent.7 Reports of reduced susceptibility of pneumococci to several antibiotics, including broad-spectrum cephalosporins have also recently been published.7 Therefore it is essential to investigate the bacterial susceptibility of meningitis isolates to other classes of antibiotics appropriate for the treatment of patients with meningitis. The carbapenem meropenem excels in in vitro activity against a broad range of bacteria including penicillin resistant pneumococci,8 is stable to the majority of β-lactamases and penetrates well into the cerebrospinal fluid.9 Furthermore, meropenem seems to lack the potential of causing seizures as has been reported for imipenem-cilastatin, a structurally related carbapenem.9 We tested in vitro susceptibility to meropenem of 299 N. meningitidis and 157 S. pneumoniae strains, isolated from patients with meningitis.

METHODS

N. meningitidis and S. pneumoniae isolates were collected by the Netherlands Reference Laboratory for Bacterial Meningitis of the Academic Medical Center (Amsterdam, The Netherlands) and of the National Institute of Public Health and the Environment (Bilthoven, The Netherlands), during 1993 and 1994. Approximately 85 percent of all bacterial meningitis isolates are sent by the clinical microbiology laboratories to the reference laboratory. In total 1136 meningococcal strains and 398 cerebrospinal fluid pneumococcal strains were received in 1993 and 1994.1 From
Meropenem susceptibility

this collection 456 strains, 299 N. meningitidis and 157 S. pneumoniae strains were used to determine in vitro susceptibility. All S. pneumoniae isolates were obtained from cerebrospinal fluid. Of N. meningitidis isolates, 126 were obtained from patients with meningitis. The remaining 173 N. meningitidis isolates were isolated from blood cultures of patients having meningococcal septicaemia.

All isolates were identified upon receipt using standard procedures, were stored at -70°C in glycerol-based medium on glass beads. One or two beads were removed from stock cultures, subcultured on to chocolate agar plates (N. meningitidis) or blood agar plates (S. pneumoniae), and incubated for 18-24 h at 35°C in air with 5 percent CO₂. Quality control (QC) strains used in this study were Escherichia coli ATCC 4922, Staphylococcus aureus ATCC 29213, H. influenzae ATCC 49247 and S. pneumoniae ATCC 49619, as recommended by the National Committee for Laboratory Standards (NCCLS, Villanova, PA, USA). QC testing was performed daily for 3 days and then weekly.

For susceptibility testing the Etest was used. The inoculation procedure was performed according to the NCCLS guidelines. The inocula were prepared by suspending bacteria in phosphate-buffered saline to achieve a turbidity equivalent to a 0.5 McFarland standard. A sterile, cotton swab was dipped into the bacterial suspension and the entire surface of an agar plate was swabbed four times, resulting in a confluent lawn of growth. For meningococci chocolate Mueller-Hinton agar (Oxoid Ltd, Basingstoke, UK) was used and for pneumococci Mueller-Hinton 5 percent sheep blood agar (Oxoid Ltd). All plates were incubated at 35°C in 95 percent air and 5 percent CO₂ for 18-24 h. The MIC value was read where bacterial growth intersected the Etest strip. The MIC criteria used for the Etest were those used for microorganisms tested by dilution susceptibility test methods (NCCLS). Criteria for susceptibility to penicillin and rifampicin for meningococcal isolates have been suggested elsewhere, and results for chloramphenicol and ceftriaxone were interpreted according to the strictest NCCLS criteria for other microorganisms. For determination of the susceptibility category, the Etest results were rounded up to the nearest two-fold dilution value, as recommended by the manufacturer. The susceptibility of N. meningitidis to meropenem, penicillin, ceftriaxone, chloramphenicol and rifampicin, and of S. pneumoniae to meropenem, penicillin, ceftriaxone and chloramphenicol was tested.

RESULTS

The penicillin, ceftriaxone and chloramphenicol susceptibility data for N. meningitidis and S. pneumoniae, as well as the rifampicin susceptibility data for N. meningitidis are shown in the Table. Thirteen N. meningitidis isolates (4.3 percent) were of intermediate resistance to penicillin (MIC 0.1-1 mg/L); all were susceptible to ceftriaxone (MIC ≤0.25 mg/L) and chloramphenicol (MIC ≤2 mg/L). One meningococcal strain (0.3 percent) was resistant to rifampicin (MIC ≥4 mg/L) and one S. pneumoniae strain (0.6 percent) was of intermediate resistance (MIC 0.1-1 mg/L) to penicillin. The 456 tested strains have been included in a previous report of the antimicrobial susceptibility of isolates.
Table. Antimicrobial susceptibility of 299 CSF and blood isolates of *N. meningitidis* and 157 CSF isolates of *S. pneumoniae*.

<table>
<thead>
<tr>
<th></th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (mg/L)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Range (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N. meningitidis</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.032</td>
<td>0.064</td>
<td>0.006-0.190</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000-0.003</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.750</td>
<td>1.00</td>
<td>0.038-2.00</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.012</td>
<td>0.023</td>
<td>0.000-0.012*</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.016</td>
<td>0.023</td>
<td>0.006-0.250</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.016</td>
<td>0.023</td>
<td>0.003-0.094</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2.00</td>
<td>3.00</td>
<td>0.250-4.00</td>
</tr>
</tbody>
</table>

*One meningococcal strain was resistant to rifampicin with MIC>256 mg/L.*

All strains of *N. meningitidis* and *S. pneumoniae* were susceptible to meropenem. The distribution of MICs for *N. meningitidis* and *S. pneumoniae* of meropenem is shown in the Figure. There was no difference in the MIC values of meropenem for *N. meningitidis* (MIC<sub>50</sub> of 0.006 and MIC<sub>90</sub> of 0.012 mg/L in 1993; MIC<sub>50</sub> of 0.006 and of 0.008 mg/L in 1994) or *S. pneumoniae* (MIC<sub>50</sub> of 0.012, and MIC<sub>90</sub> of 0.016 mg/L) between 1993 and 1994. Furthermore, no difference was found between MIC values of cerebrospinal fluid and blood isolates of *N. meningitidis* (MIC<sub>50</sub> of 0.006 and MIC<sub>90</sub> of 0.008 mg/L for cerebrospinal fluid isolates; MIC<sub>50</sub> of 0.006 and MIC<sub>90</sub> 0.012 mg/L for blood isolates). The MIC<sub>50</sub> and MIC<sub>90</sub> of meropenem for meningococcal strains intermediate resistant to penicillin were 0.012 and 0.023 mg/L, respectively. The MIC of meropenem for the meningococcal strain resistant to rifampicin was 0.003 mg/L. The MIC of meropenem for the pneumococcal strain intermediate resistant to penicillin was 0.047 mg/L.

**DISCUSSION**

Meropenem appears to be a rational addition to the therapeutic options for the treatment of patients with bacterial meningitis. It is, *in vitro*, highly effective against *N. meningitidis* and *S. pneumoniae* isolates causing meningitis and has, in contrast to third-generation cephalosporins,
activity against some of the more unusual pathogens causing meningitis, particularly \textit{Listeria monocytogenes}.

Previously we reported the susceptibility of \textit{N. meningitidis}, \textit{S. pneumoniae} and \textit{H. influenzae} isolates from meningitis cases to various antimicrobials. The frequency of resistance to penicillin, ceftriaxone, chloramphenicol, and rifampicin among these isolates is very low. The strains tested for meropenem have been included in this previous survey.

All tested \textit{N. meningitidis} and \textit{S. pneumoniae} strains were susceptible to meropenem, including thirteen \textit{N. meningitidis} strains of intermediate resistance to penicillin, the \textit{N. meningitidis} strain resistant to rifampicin, and the \textit{S. pneumoniae} strain of intermediate resistance to penicillin. As meropenem may be especially useful in the management of meningitis caused by meningococcal and pneumococcal strains resistant to these antibiotics, ideally a larger number of resistant strains should have been tested for susceptibility to meropenem. However, in a recent report the MICs of meropenem for three pneumococcal strains of intermediate resistance (MIC values of penicillin 0.125-1 mg/L) and twelve penicillin resistant strains (MIC values of penicillin \geq 2 mg/L) were low, with MICs of meropenem ranging from 0.015 to 0.5 mg/L. Interestingly, in our study MICs of penicillin resistant isolates to meropenem were somewhat higher than MICs of penicillin susceptible strains.

We conclude that meropenem is, \textit{in vitro}, highly active against \textit{N. meningitidis} and \textit{S. pneumoniae} isolates from cerebrospinal fluid and may emerge as an effective antimicrobial treatment of patients with bacterial meningitis. 
