Comparative Synergistic Activity of Ceftriaxone-Piperacillin versus Ceftriaxone-Netilmicin

K. Machka*, R. Dietz

The effect of combination of ceftriaxone with piperacillin or netilmicin was studied in a total of 119 clinical isolates using the checkerboard titration technique. The isolates included *Pseudomonas aeruginosa*, *Staphylococcus aureus*, enterococci and various *Enterobacteriaceae*. Synergy was observed in all *Streptococcus faecalis* strains with both combinations. Whereas the ceftriaxone/netilmicin combination showed a higher rate of synergy against *Pseudomonas aeruginosa*, the rate of synergy against *Enterobacteriaceae* was the same for the two combinations. In no instance was antagonism encountered.

A number of new cephalosporins have been developed which have a broad spectrum of antibacterial activity. The combination of these new cephalosporins with either a broad spectrum penicillin or an aminoglycoside is recommended for the treatment of serious bacterial infections (1). A number of in vitro studies have demonstrated synergistic interaction of the beta-lactam/aminoglycoside combinations (2, 3), whereas for the double beta-lactam combinations both synergistic and antagonistic interaction has been observed (4). Clinical studies and animal trials have indicated that combinations which act synergistically in vitro are more effective in therapy of patients with impaired host defence than non-synergistic combinations (5, 6).

Ceftriaxone is a parenteral cephalosporin with a plasma half-life of approximately eight hours in humans (7). The excellent antibacterial activity is well documented (8–11), but there would appear to be no information published on the interaction of ceftriaxone in combination with either the penicillin piperacillin or the aminoglycoside netilmicin. We therefore studied the interaction and antibacterial activity of these two ceftriaxone combinations in vitro.

Materials and Methods

*Antibiotics.* The following antibiotics were used: ceftriaxone (Hoffmann-La Roche, Basel), piperacillin (Lederle/Cyanamid, Wolfratshausen) and netilmicin (Byk-Essex, Munich).

*Bacterial Strains.* A total of 119 clinical strains isolated from urine, wounds, sputum and blood were tested. They included 19 strains of gram-positive cocci, 89 strains of various *Enterobacteriaceae* species, and 11 *Pseudomonas aeruginosa* strains.

*Susceptibility Testing.* The MICs of the antibiotics were determined in Mueller Hinton broth (Difco) using the microdilution method. Twofold dilutions of the antibiotics in Mueller Hinton broth were dispensed in the wells with an 96-channel-pipettor (Dyntach). An inoculum of 10⁵ CFU was used, prepared by dilution of a 4 h shake culture. The microtiter plates were incubated in a moist chamber at 37 °C for 18 h.

*Synergy Tests.* The synergy study was done by checkerboard titration using the same technique as for the MIC determinations. The results were analyzed by calculating the fractional inhibitory concentration (FIC) of each substance at the point of maximal interaction. Synergy was defined as an FIC index of < 0.5, which represents an at least fourfold decrease in the MIC of each single drug. Partial synergy was defined as an FIC index of > 0.5 to 0.75 which represents a fourfold or greater reduction in the MIC of one drug and a twofold decrease in the MIC of the other drug. Indifference was defined as an FIC index of > 0.75 to 4, and antagonism as an FIC index of > 4.

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Table 1: Comparative in vitro activity of ceftriaxone, netilmicin and piperacillin against gram-positive cocci and gram-negative bacilli.

<table>
<thead>
<tr>
<th>Organism (no. of strains)</th>
<th>Antibiotic</th>
<th>MIC (mg/l)</th>
<th>for 50 % inhibition</th>
<th>for 90 % inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus (11)</td>
<td>ceftriaxone</td>
<td>1–4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>netilmicin</td>
<td>0.03–0.25</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>0.5 –16</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Streptococcus faecalis (8)</td>
<td>ceftriaxone</td>
<td>128– &gt; 1024</td>
<td>512</td>
<td>&gt; 1024</td>
</tr>
<tr>
<td></td>
<td>netilmicin</td>
<td>1–4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>2–4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Proteus mirabilis (9)</td>
<td>ceftriaxone</td>
<td>&lt; 0.004</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>netilmicin</td>
<td>0.06 –2</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>0.125–0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Indole-positive Proteus spp. (16)</td>
<td>ceftriaxone</td>
<td>&lt; 0.004–0.5</td>
<td>0.007</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>netilmicin</td>
<td>0.06 – &gt; 128</td>
<td>0.125</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>0.03 – &gt; 1024</td>
<td>0.5</td>
<td>128</td>
</tr>
<tr>
<td>Enterobacter spp. (16)</td>
<td>ceftriaxone</td>
<td>0.03 –256</td>
<td>0.125</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>netilmicin</td>
<td>0.06 –0.25</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>0.5 – &gt; 1024</td>
<td>2</td>
<td>&gt; 512</td>
</tr>
<tr>
<td>Escherichia coli (12)</td>
<td>ceftriaxone</td>
<td>0.015–0.25</td>
<td>0.03</td>
<td>0.06</td>
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<tr>
<td></td>
<td>netilmicin</td>
<td>0.06 –0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>0.06 –512</td>
<td>1</td>
<td>256</td>
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<tr>
<td>Klebsiella spp. (16)</td>
<td>ceftriaxone</td>
<td>0.007–0.125</td>
<td>0.03</td>
<td>0.125</td>
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<td></td>
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<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>2–1024</td>
<td>4</td>
<td>1024</td>
</tr>
<tr>
<td>Citrobacter spp. (8)</td>
<td>ceftriaxone</td>
<td>0.125–128</td>
<td>0.125</td>
<td>16</td>
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<td></td>
<td>netilmicin</td>
<td>0.125–8</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>piperacillin</td>
<td>1–128</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Serratia spp. (12)</td>
<td>ceftriaxone</td>
<td>0.06 –2</td>
<td>0.25</td>
<td>0.5</td>
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<td></td>
<td>netilmicin</td>
<td>0.125–16</td>
<td>0.5</td>
<td>4</td>
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<tr>
<td></td>
<td>piperacillin</td>
<td>0.5 – &gt; 1024</td>
<td>4</td>
<td>&gt; 1024</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (11)</td>
<td>ceftriaxone</td>
<td>4–32</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>netilmicin</td>
<td>0.25 –128</td>
<td>0.5</td>
<td>2</td>
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<td></td>
<td>piperacillin</td>
<td>2–32</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Results

The antibacterial activity of ceftriaxone, netilmicin and piperacillin used alone is summarized in Table 1. Ceftriaxone demonstrated excellent activity, superior to that of netilmicin or piperacillin, against Proteus mirabilis, indole-positive Proteus spp., Escherichia coli, Klebsiella and Serratia spp., and good activity against Enterobacter and Citrobacter spp. Piperacillin and ceftriaxone were similar in activity against Pseudomonas aeruginosa. In comparison to netilmicin, ceftriaxone was less active against staphylococci. Piperacillin was superior in activity against Streptococcus faecalis. The results of checkerboard titration are shown in Table 2. The double beta-lactam combination ceftriaxone/piperacillin showed synergy against 13 (17 %) and the ceftriaxone/netilmicin combination synergy against 14 (18 %) of the 77 Enterobacteriaceae strains, from which it was possible to calculate the FIC indices. Both combinations acted synergistically against all eight Streptococcus faecalis strains, but against none of the staphylococci strains. Ceftriaxone/netilmicin was synergistic against six of 11 Pseudomonas aeruginosa isolates, whereas the double beta-lactam combination showed synergy against only two of these strains.