In Vitro Activity of the Combination of Solithromycin and Cephalosporins against Neisseria gonorrhoeae

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Introduction

- Gonorrhea is the second most prevalent bacterial sexually transmitted infection throughout the world.
- Despite the availability of treatment options, multidrug-resistant (MDR) Neisseria gonorrhoeae has emerged, presenting a significant public health challenge.

Methods

- **Bacterial Strains**: Sixty-four N. gonorrhoeae strains (56 clinical strains and 8 WHO reference strains) were tested.
- **Antimicrobial Susceptibility Testing and Synergy Testing**: The minimum inhibitory concentrations (MICs) for each antimicrobial agent were determined by agar dilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. The Fractional Inhibitory Concentration Index (FICI) for antimicrobial combination was calculated. The FICI value of ≤0.5 was considered as synergy, >0.5 to ≤4.0 as indifference, and >4.0 as antagonism.

Results

- **Solithromycin**: MICs (0.004–32 μg/mL) were much lower than those of azithromycin (0.001–512 μg/mL), ceftriaxone (0.002–1 μg/mL), and cefixime (0.015–0.25 μg/mL), respectively. CFX MICs (0.002–1 μg/mL) were mostly ≤0.03 μg/mL, while those of solithromycin were between 0.125 and 0.25 μg/mL. CRO MICs (0.006–0.03 μg/mL) were mostly ≤0.015 μg/mL.
- **Combination Testing**: Both antimicrobial combinations produced the same median FICI of 1.00 (indifference) and a similar range of FICIs: CFX + SOL, FICI of 0.63–1.00; CRO + SOL, FICI of 0.75–1.50; and CRO + CFX, FICI of 0.75–1.50. No antagonism was observed for any of the 64 strains.

Conclusions

- The combination of ceftazidime or ceftriaxone with solithromycin produced no antagonistic effects.
- This study provides a potential strategy for delay and combat the emergence of MDR gonorrhea by incorporating combination therapy into clinical practice.

Acknowledgment: This study was supported by a grant from Ceptray Pharmaceuticals.

References

3. The Fractional Inhibitory Concentration Index (FICI) of each antimicrobial agent was determined by the MIC of the antimicrobial agent (A or B) in the combination divided by the MIC of the antimicrobial acting alone.

Table 1. Activity of Antibiotics against 64 strains of N. gonorrhoeae

<table>
<thead>
<tr>
<th>Group</th>
<th>Azithromycin MIC (μg/mL)</th>
<th>Cefixime MIC (μg/mL)</th>
<th>Ceftriaxone MIC (μg/mL)</th>
<th>CFX/SOL (FICI)</th>
<th>CRO/SOL (FICI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.004</td>
<td>0.03 0.125 0.25 1.00</td>
<td>0.03 0.06 0.125 0.25</td>
<td>0.03 0.06 0.125 0.25</td>
<td>0.63 0.75 1.00 1.50</td>
<td>0.63 0.75 1.00 1.50</td>
</tr>
<tr>
<td>0.006</td>
<td>0.03 0.125 0.25 1.00</td>
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<td>0.63 0.75 1.00 1.50</td>
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<tr>
<td>0.015</td>
<td>0.03 0.125 0.25 1.00</td>
<td>0.03 0.06 0.125 0.25</td>
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<td>0.63 0.75 1.00 1.50</td>
<td>0.63 0.75 1.00 1.50</td>
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- No antagonism was observed with the combination of solithromycin and cefixime or ceftriaxone for all the 64 strains.
- Both antimicrobial combinations produced the same median FICI of 1.00 (indifference) and a similar range of FICIs: CFX + SOL, FICI of 0.63–1.00; and CRO + SOL, FICI of 0.75–1.50; standard deviation, 0.172 for both combinations.
- MICs of antimicrobials decreased when combined: SOL, 1–4 log, dilution decrease; CFX, 1–2 log, dilution decrease.
- All strains with elevated cefixime or ceftriaxone MICs had lower solithromycin MICs and produced FICIs of indifference when solithromycin was combined with cefixime or ceftriaxone (Table 3).

- One high-level azithromycin-resistant strain (MIC 152 μg/mL) with a solithromycin MIC of 32 μg/mL was susceptible to cefixime. Solithromycin MIC decreased by 3 to 4 log, dilution when combined with cefixime or ceftriaxone (Table 3).

Table 2. Fractional Inhibitory Concentration Index (FICI) of combination of cefixime or ceftriaxone and solithromycin

<table>
<thead>
<tr>
<th>Strain</th>
<th>CFX/SOL (FICI)</th>
<th>CRO/SOL (FICI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.004</td>
<td>0.63 0.75 1.00 1.50</td>
<td>0.63 0.75 1.00 1.50</td>
</tr>
<tr>
<td>0.006</td>
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</tr>
</tbody>
</table>

- The combination of cefixime or ceftriaxone with solithromycin produced no antagonistic effects.
- These findings strengthen the potential clinical utility of solithromycin as a component of dual therapy with third generation cephalosporins for gonorrhea.
- The combination of cefixime and solithromycin would give an advantage of being oral drugs versus an injectable ceftriaxone.
- The findings from in vitro studies may not be entirely predictive of clinical outcomes, therefore, a clinical trial is warranted to evaluate the in vivo efficacy of cefixime/solithromycin and solithromycin for the treatment of gonorrhea.

Table 3. Synergy Results for N. gonorrhoeae strains with elevated MICs to solithromycin, cefixime, and ceftriaxone

<table>
<thead>
<tr>
<th>Combination</th>
<th>Range of Elevated MICs</th>
<th>Strains (n)</th>
<th>CFX/SOL (FICI)</th>
<th>CRO/SOL (FICI)</th>
<th>CFX/MIC (μg/mL)</th>
<th>CRO/MIC (μg/mL)</th>
<th>CFX/CRO (FICI)</th>
<th>CRO/CFX (FICI)</th>
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