Therapeutic Trial and Pharmacokinetics of Sulbactam for Uncomplicated Gonorrhea in Men

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The efficacy of intramuscular sulbactam for uncomplicated gonorrhea was assessed in 20 men infected with β-lactamase-negative Neisseria gonorrhoeae. Ten subjects received 2.0 g of sulbactam given in a single intramuscular dose with 1.0 g of probenecid orally; 4 of 10 urethral infections persisted, as did one rectal infection. Ten subjects were treated with 0.5 g of intramuscular sulbactam given twice, 4 h apart; 3 of 10 urethral infections and 2 of 2 rectal infections persisted. The geometric mean MIC of sulbactam for 20 pretreatment isolates of N. gonorrhoeae was 1.37 μg/ml (range, 0.25 to 8.0 μg/ml). Serum levels of sulbactam, determined for nine subjects in the two treatment groups, fell below the MIC of some gonococci after <6 h with both regimens. In the regimens studied, sulbactam alone is not suitable as therapy for uncomplicated gonorrhea.

The emergence of penicillinase-producing strains of Neisseria gonorrhoeae (2, 6) has stimulated investigation of alternative treatments for gonorrhea. Sulbactam (CP-45899) is a β-lactamase inhibitor that enhances the activity of the β-lactamase-sensitive penicillins against penicillinase-producing N. gonorrhoeae or other β-lactamase-producing organisms. In addition, sulbactam itself has significant in vitro activity against β-lactamase-positive and -negative N. gonorrhoeae, with reported MICs of 0.15 to 2.5 μg/ml (4, 8). This study was designed to assess the efficacy of sulbactam alone as single-session therapy for men with acute uncomplicated gonorrhea due to β-lactamase-negative N. gonorrhoeae and to correlate the results with serum levels of the drug.

MATERIALS AND METHODS

The study population consisted of men ≥17 years of age with acute uncomplicated gonococcal urethritis. Infection was initially documented by Gram-stained smears of urethral exudate and subsequently confirmed by isolation of N. gonorrhoeae. Anorectal and pharyngeal cultures also were performed on all subjects.

Two regimens were studied. Regimen A (12 subjects) was 2.0 g of sulbactam given in two simultaneous intramuscular (i.m.) injections (1.0 g each) plus probenecid (1.0 g orally). Regimen B (11 subjects) was two 0.5-g i.m. doses of sulbactam given 4 h apart, without probenecid. In five subjects treated with regimen A and four subjects given regimen B, blood specimens for determination of sulbactam serum levels were obtained at standardized intervals for 10 h. Smears and cultures of the urethra and cultures of the anal canal and pharynx were repeated 2 and 7 days after treatment. Subjects with persistent gonococcal infection were retreated with aqueous procaine penicillin G (4.8 MU i.m.) plus probenecid (1.0 g orally) or with spectinomycin (2.0 g i.m.).

Specimens for isolation of N. gonorrhoeae were inoculated directly onto modified Thayer-Martin medium and incubated at 35°C in an atmosphere of 5% CO₂. N. gonorrhoeae was identified by routine methods, and isolates were stored at −70°C in horse serum and tryptic soy-yeast broth (1:1, vol/vol) for later antimicrobial susceptibility testing. β-Lactamase production was tested by the acidometric method (9). Agar dilution MICs of sulbactam, penicillin G, and tetracycline hydrochloride were determined by using twofold dilutions of antibiotic in GC agar base (Difco Laboratories, Detroit, Mich.) containing 1% hemoglobin and 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.) as described previously (10). Serum specimens for the pharmacokinetic studies were stored at −20°C. Serum levels of sulbactam were determined by gas chromatography of the methyl ester with detection by mass spectrometry, as described elsewhere (5). The limit of detection of sulbactam with this method is approximately 0.3 μg/ml.

Written informed consent was obtained from all subjects. Statistical methods included Student’s t test and the two-tailed Fisher exact test.

RESULTS

Ten of 12 patients treated with regimen A and 10 of 11 treated with regimen B returned for follow-up examinations. These 20 men had a mean age of 30.3 years (range, 17 to 47 years). There were no significant differences in these characteristics between subjects treated with regimen A or regimen B. N. gonorrhoeae was eradicated from all infected sites in 5 of 10 patients treated with regimen A and 6 of 10 treated with regimen B (Table 1). All nine treatment failures were detected by culture at the first follow-up visit. All subjects denied intersex sexual exposure.

The serial serum concentrations of sulbactam in five subjects treated with regimen A and four subjects given regimen B are shown in Table 2. The serum concentrations observed in patients who were cured were not significantly higher than in those whose treatment failed. The serum half-life (t_{1/2}) of sulbactam (mean ± 1 standard deviation) was 1.57 ± 0.47 h after regimen A and 1.12 ± 0.53 h after the second 0.5-g dose of regimen B.

Table 3 shows the MICs of sulbactam and penicillin G for 20 pretreatment urethral isolates of N. gonorrhoeae. The geometric mean MIC of sulbactam was 1.37 μg/ml, and that for penicillin 0.17 μg/ml. The geometric mean MIC of
TABLE 1. Results of treatment of uncomplicated gonorrhoea in men with sulbactam

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. treated</th>
<th>No. returned for follow-up</th>
<th>Cure rate (no. cured/no. followed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12</td>
<td>10</td>
<td>6/10</td>
</tr>
<tr>
<td>B</td>
<td>11</td>
<td>10</td>
<td>7/10</td>
</tr>
</tbody>
</table>

α Regimen A: sulbactam (2.0 g i.m.) plus probenecid (1.0 g orally).
β Regimen B: sulbactam (two 0.5-g doses i.m. 4 h apart).

TABLE 2. Levels of sulbactam in serum

<table>
<thead>
<tr>
<th>Time after initial dose (h)</th>
<th>Sulbactam (µg/ml) in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen A* (n = 5)</td>
</tr>
<tr>
<td></td>
<td>Mean ± 1 SD</td>
</tr>
<tr>
<td>1</td>
<td>35.2 ± 14.7</td>
</tr>
<tr>
<td>4</td>
<td>7.5 ± 4.3</td>
</tr>
<tr>
<td>5</td>
<td>ND**</td>
</tr>
<tr>
<td>6</td>
<td>4.3 ± 2.4</td>
</tr>
<tr>
<td>8</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>0.9 ± 0.9</td>
</tr>
</tbody>
</table>

α Regimen A: sulbactam (2.0 g i.m.) plus probenecid (1.0 g orally).
β Regimen B: sulbactam (two 0.5-g doses i.m. 4 h apart).
** ND, Not determined.

definite relationship between the MIC of sulbactam for the infecting gonococcus and the response to treatment.

The combination of sulbactam or a related β-lactamase inhibitor with penicillin, ampicillin, or amoxicillin may have value for the treatment of penicillinase-producing \( N.\) gonorrhoeae infections. Using a single-dose regimen of 2.0 g of sulbactam (a congener of sulbactam and ampicillin) with 1.0 g of probenecid, Atia et al. (1) cured 91 (97%) of 94 men with gonococcal urethritis, including 6 of 6 infected with penicillinase-producing strains of \( N.\) gonorrhoeae. In the regimens that we studied, however, sulbactam alone is not suitable for the treatment of gonorrhoea.

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LITERATURE CITED


