Comparative Study of Cefoperazone and Spectinomycin for Treatment of Uncomplicated Gonorrhea in Men

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Beta-lactamase-negative Neisseria gonorrhoeae infections were treated with single-dose cefoperazone (0.5 or 1.0 g) or spectinomycin (2.0 g). Anogenital infections were cured in 36 (83%) of 43 volunteers given 0.5 g of cefoperazone, 61 of 61 volunteers given 1.0 g of cefoperazone, and 99 of 100 volunteers given spectinomycin. The cefoperazone geometric mean MIC for 242 isolates was 0.028 μg/mL. Cefoperazone (1.0 g) and spectinomycin (2.0 g) are comparable for the therapy of anogenital gonorrhea in men.

Since 1976, appreciation of the increasing prevalence of beta-lactamase-producing Neisseria gonorrhoeae (3, 10) has stimulated investigation of the efficacy of new antibiotics for the treatment of gonorrhea. More recently, the recognition of outbreaks of gonorrhea caused by N. gonorrhoeae with chromosomally mediated, high-level resistance to the antibiotics commonly used for gonorrhea therapy have added to this concern (4, 7). In addition, even for gonorrhea caused by readily susceptible strains, each of the single-dose regimens recommended by the U.S. Public Health Service for the treatment of uncomplicated gonorrhea has shortcomings in terms of toxicity or tolerance, unacceptable efficacy at some anatomic sites, or cost, and none is effective for the treatment of coexistent infection with Chlamydia trachomatis (5).

Cefoperazone is a broad-spectrum cephalosporin with activity against a wide range of organisms and is widely used for the treatment of serious infections. Cefoperazone is active in vitro against both beta-lactamase-producing and beta-lactamase-negative N. gonorrhoeae, with MICs ranging from 0.004 to 0.25 μg/ml (1, 13), has a serum half-life of over 2 h, and has peak levels in serum of 33 and 73 μg/ml after intramuscular injections of 0.5 and 1.0 g, respectively (16). These features suggest that cefoperazone may be useful for the treatment of uncomplicated gonorrhea. In this study, single intramuscular doses of 0.5 or 1.0 g of cefoperazone were compared with a single dose of 2.0 g of spectinomycin for the treatment of uncomplicated gonorrhea in men.


Men ≥18 years of age were recruited from among patients attending the Seattle-King County or Denver Metro Sexually Transmitted Disease clinics who had either a smear of urethral or rectal exudate showing gram-negative intracellular diplococci or culture isolation of N. gonorrhoeae. Volunteers with complicated gonococcal infection, with a history of allergy to spectinomycin or beta-lactam antibiotics, or who had taken antimicrobial therapy active against N. gonorrhoeae within 2 weeks of enrollment were excluded from participation. Volunteers with negative initial cultures for N. gonorrhoeae were excluded from analysis. The subjects were classified as to age and sexual preference according to self-description.

Urethral specimens for the isolation of N. gonorrhoeae were obtained from all the men by insertion of calcium alginate-tipped urethral genital swabs 2 to 3 cm beyond the meatus; pharyngeal (all subjects) and rectal (homosexual and bisexual men only) specimens were collected with cotton-tipped swabs. All specimens were directly inoculated onto modified Thayer-Martin medium and immediately incubated at 36°C in an atmosphere containing 4 to 7% CO2 for 36 to 48 h. All isolates were identified and tested for beta-lactamase production by standard methods (14, 18).

Specimens for the isolation of C. trachomatis were obtained by passage of a second calcium alginate swab 3 to 4 cm into the urethra (all subjects) and anal canal (homosexual and bisexual men only). The swabs were stored in 0.2 M sucrose-phosphate buffer for transport at 4°C. Within 24 h, the specimens were inoculated into tissue culture, and identification of chlamydial inclusions was done by using fluorescein-conjugated monoclonal antibodies (Microtrak; Syva Corp., Palo Alto, Calif.) (17).

N. gonorrhoeae isolates were frozen at −70°C in 1:1 Trypticase (BBL Microbiology Systems, Cockeysville, Md.) soy-yeast broth–horse serum for subsequent testing for susceptibility to antimicrobial agents. The MICs of cefoperazone, penicillin G (Seattle isolates), ampicillin (Denver isolates), tetracycline hydrochloride, and spectinomycin were determined by the agar dilution method on gonococcal agar base (Difco Laboratories, Detroit, Mich.) containing 1% IsoVitalex (BBL) and twofold dilutions of antibiotic (19).

In the initial phase of the study, the volunteers were randomly assigned to treatment with 0.5 g of cefoperazone or 2.0 g of spectinomycin. In phase 2, the volunteers were randomized to treatment with 1.0 g of cefoperazone or 2.0 g of spectinomycin. Cefoperazone was diluted in 0.5%...
gonorrhea of groups. Table treated was patients, including infections; populations from respectively.

Some patients were infected at both sites.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Antimicrobial agent (dose [g])</th>
<th>Cefoperazone (0.5)</th>
<th>Cefoperazone (1.0)</th>
<th>Spectinomycin (2.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. treated</td>
<td></td>
<td>48</td>
<td>68</td>
<td>117</td>
</tr>
<tr>
<td>No. (%) evaluable</td>
<td></td>
<td>43 (90)</td>
<td>61 (90)</td>
<td>100 (93)</td>
</tr>
<tr>
<td>Sexual orientation [no. (%)]</td>
<td>Heterosexual</td>
<td>14 (33)</td>
<td>16 (26)</td>
<td>28 (28)</td>
</tr>
<tr>
<td></td>
<td>Homosexual or bisexual</td>
<td>29 (67)</td>
<td>45 (74)</td>
<td>72 (72)</td>
</tr>
<tr>
<td>Eradication of N. gonorrhoea [no. cured/no. treated (%)]</td>
<td>Urethral</td>
<td>26/30 (87)</td>
<td>44/44 (100)</td>
<td>78/79 (99)</td>
</tr>
<tr>
<td></td>
<td>Rectal</td>
<td>14/17 (82)</td>
<td>22/22 (100)</td>
<td>33/33 (100)</td>
</tr>
<tr>
<td></td>
<td>Anogenital*</td>
<td>36/43 (83)</td>
<td>61/61 (100)</td>
<td>99/100 (99)</td>
</tr>
<tr>
<td></td>
<td>Pharyngeal</td>
<td>1/8 (13)</td>
<td>6/9 (67)</td>
<td>10/15 (67)</td>
</tr>
</tbody>
</table>

* Some patients were infected at both sites.


The results of therapy and characteristics of the study populations from Seattle and Denver are summarized in Table 1. In Seattle, heterosexual, homosexual, and bisexual men were enrolled, whereas in Denver only homosexual and bisexual men were enrolled; no other significant differences were observed among volunteers enrolled in Seattle or Denver (data not shown); of 233 volunteers enrolled, N. gonorrhoea was not isolated from 17 and 12 failed to return for follow-up, leaving 204 (88%) evaluable subjects. The age (mean, 27.2 ± 6.2 years) and racial distribution of volunteers was typical for men seen at the two clinics, and no significant differences were observed among the three treatment groups.

Cefoperazone at 1.0 g cured anogenital gonorrhoea in all 61 evaluable patients, compared with 36 (83%) of 43 patients given the 0.5-g dose (P = 0.003). Spectinomycin (2.0 g) was comparable to 1.0 g of cefoperazone, eradicating anogenital gonorrhoea in 99 of 100 men. Concomitant pharyngeal infection was eradicated in only one (13%) of eight volunteers treated with the 0.5-g dose of cefoperazone, compared with 67% of those treated with either 1.0 g of cefoperazone (P = 0.07) or spectinomycin (P = 0.04). When all infected sites (urethra, rectum, and pharynx) are considered, 0.5 g of cefoperazone cured 30 (70%) of 43 volunteers, compared with 58 (95%) of 61 volunteers for 1.0 g of cefoperazone and 94 of 100 volunteers for spectinomycin.

Infection with C. trachomatis was documented in 36 (18%) patients, including 19 with urethral infections and 17 with rectal infections; there were no significant differences in coinfection rates among the treatment groups (data not shown). After treatment with cefoperazone (0.5 and 1.0 g), C. trachomatis persisted in 5 (71%) of 7 and 9 (75%) of 12 volunteers, respectively. Seven (41%) of 17 chlamydial infections persisted after spectinomycin therapy.

All three regimens were well tolerated. Among the volun-

ters receiving cefoperazone, one (2%) treated with 0.5 g and seven (11%) treated with 1.0 g reported self-limited episodes of diarrhea (≥ three loose stools per day) after therapy. No other significant clinical toxicity or side effects were noted.

All N. gonorrhoeae isolates in this study were beta-lactamase negative. The antimicrobial susceptibilities of all pretreatment isolates are shown in Table 2. The cefoperazone geometric mean MIC for all isolates was 0.028 µg/ml. The geometric mean MICs of cefoperazone were higher for the 16 isolates with chromosomally mediated resistance (MIC, ≥1.0 µg/ml) to ampicillin or penicillin (geometric mean MIC of cefoperazone, 0.19 µg/ml) than for strains susceptible (MIC, <1.0 µg/ml) to the antibiotics (geometric mean MIC of cefoperazone, 0.02 µg/ml; P < 0.001). Similarly, for the seven gonococcal isolates with tetracycline MICs of ≥4.0 µg/ml, the MICs of cefoperazone were higher (geometric mean MIC, 0.07 µg/ml) than for more susceptible isolates (geometric mean MIC, 0.03 µg/ml; P = 0.02). In general, the MICs for isolates from patients who failed treatment tended to be higher for all antimicrobial agents tested than the MICs for isolates from patients who were cured, although these differences were not significant.

In this study, cefoperazone in a single dose of 1.0 but not 0.5 g was as effective as spectinomycin for the treatment of uncomplicated gonorrhoea. The 1.0-g dose cured anogenital gonorrhoea in all 61 patients treated and eradicated pharyngeal infection in 6 of 9 patients; the 0.5-g dose, which could be used with slightly less discomfort for the patient and virtually no side effects, cured only 83% of the patients with anogenital gonorrhoea and only 1 (13%) of 8 patients with pharyngeal infections. The in vitro susceptibility data and successful treatment of four patients with chromosomally

TABLE 2. MICs for 242 isolates of beta-lactamase-negative N. gonorrhoeae

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Geometric mean (range)</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefoperazone</td>
<td>0.028 (0.002–0.5)</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>0.19 (0.015–2.0)</td>
<td>0.25</td>
<td>1.0</td>
</tr>
<tr>
<td>Ampicillin G</td>
<td>0.10 (0.015–1.0)</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.84 (0.125–32)</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>20.8 (8–32)</td>
<td>16</td>
<td>32</td>
</tr>
</tbody>
</table>

* 50 and 90%. Antimicrobial concentrations required to inhibit 50 and 90% of isolates, respectively.
- Penicillin G and ampicillin MICs were determined for Seattle (n = 118) or Denver (n = 158) isolates, respectively.
mediated resistance to penicillin (MIC, $\geq 1.0 \mu g/ml$) suggest that the 1.0-g dose of cefoperazone offers an alternative treatment for patients with these relatively resistant strains of *N. gonorrhoeae*. In vitro studies done by others (1, 13) suggest that beta-lactamase-producing gonococci are also susceptible to levels of cefoperazone in serum that are readily attainable with the 1.0-g dose. Although we are unaware of data on the treatment of penicillinase-producing *N. gonorrhoeae* infections with 1.0 g of cefoperazone, in a small study done in Korea (13), 27 (93%) of 29 urethral infections caused by penicillinase-producing *N. gonorrhoeae* were cured after treatment with 0.5 g of the drug. Thus, cefoperazone at 1.0 g intramuscularly should be efficacious for uncomplicated anogenital gonorrhea, irrespective of local variations in the prevalence of penicillinase-producing *N. gonorrhoeae* or gonococci with chromosomally mediated antimicrobial resistance.

As is true for other single-dose regimens for gonorrhea (6, 8, 9), cefoperazone was not effective in the eradication of coexisting anogenital infection with *C. trachomatis*. The apparent eradication of 59% of chlamydial infections by spectinomycin in this study conflicts with extensive clinical and published experience and is difficult to explain. No single-dose antimicrobial regimen has ever reliably eradicated *C. trachomatis*; as recommended by the Centers for Disease Control (5), heterosexual men and women with gonorrhea should receive a 7-day course of tetracycline in addition to single-dose treatment with a beta-lactam or spectinomycin. Newer antimicrobial agents, such as the quinolones, are active in vitro against *N. gonorrhoeae* and *C. trachomatis* (2, 11) and are promising as future therapeutic agents for sexually transmitted diseases. Like many other agents tested to date, although single doses reliably cure uncomplicated gonorrhea, the quinolones are not effective in single doses for the treatment of infections caused by *C. trachomatis* (15).

The role of cefoperazone in the routine therapy of uncomplicated gonococcal infection is unclear. Although the 1.0-g dose of cefoperazone appears effective for urethral and rectal gonorrhea in men, it has no important advantages over other single-dose treatments for gonorrhea and is considerably more expensive per dose (cost, approximately $9.60/g). In addition, among the cephaloridine tested to date, only ceftriaxone has been documented to be effective for pharyngeal gonorrhea (12) and has been extensively tested in women.

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**LITERATURE CITED**


