

Single-Dose Treatment of Uncomplicated Acute Gonococcal Urethritis in Ethiopian Men: Comparison of Rosoxacin, Spectinomycin, Penicillin, and Ampicillin

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A total of 140 Ethiopian men with gonococcal urethritis were randomly assigned to treatment with aqueous procaine penicillin G (4.8×10^6 units intramuscularly [im] plus 1.0 g of oral probenecid); oral ampicillin (3.5 g plus 1.0 g of oral probenecid); spectinomycin (2.0 g im); or oral rosoxacin (Acrosoxacin; 300 mg). Failure rates were 24%, 19%, zero, and 3%, respectively. Forty-four (31.4%) patients were infected with penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and were evenly distributed in the treatment groups. All 39 PPNG strains analyzed for plasmid content possessed a 2.6-Mdalton plasmid; 28 (71.8%) had a 3.2-Mdalton β -lactamase-encoding plasmid, ten (25.6%) had a 4.4-Mdalton plasmid (three with and seven without a 24.5-Mdalton plasmid), and one had only a 24.5-Mdalton plasmid. Two patients were infected with *N. gonorrhoeae*-possessing plasmids apparently capable of encoding but not producing β -lactamase. Both spectinomycin and rosoxacin are excellent single-dose treatment regimens for gonococcal urethritis in men. All people receiving these drugs in Ethiopia should be tested serologically for syphilis, however, as eight (11.8%) of 68 men in this study also had active latent syphilis.

THE USUAL TREATMENT for uncomplicated gonococcal urethritis in Addis Ababa, Ethiopia, is penicillin aluminum monostearate (PAM); 1.2×10^6 units im. Patients not cured by penicillin are given spectinomycin (2.0 g im) when available, or oral co-trimoxazole or tetracycline. In 1974, the rate of treatment failure for the PAM regimen in 82 men with uncomplicated gonococcal urethritis was 8.5%, and all isolates of *Neisseria gonorrhoeae* had a MIC of penicillin of $<1.0 \mu\text{g/ml}$ (P. L. Perine, unpublished observation). Despite its relatively

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high rate of treatment failure, PAM continues to be the most commonly used treatment for gonorrhea and syphilis in Addis Ababa. The purpose of this study was to evaluate the efficacy of the World Health Organization's recommended single-session treatment regimens for uncomplicated gonorrhea¹ and of rosoxacin, an orally administered quinolone derivative.

Patients and Methods

In 1983, 140 of 151 men attending the Venereal Disease Clinic, Addis Ababa, Ethiopia, with complaints of urethritis were diagnosed by gram stain and culture as having gonococcal urethritis.¹ These men were randomly assigned to one of four single-session treatment regimens after giving their informed consent. Thirty-four received 4.8×10^6 units of aqueous procaine penicillin G (APPG) im together with 1.0 g of oral probenecid; 37 were given 300 mg of rosoxacin (Acrosoxacin) orally; 36 were given 3.5 g of oral ampicillin together with 1.0 g of probenecid; and 33 received 2.0 g of spectinomycin im. All patients denied taking any medication within the week preceding entry into the study.

All isolates of *N. gonorrhoeae* were tested for β -lactamase production by the rapid iodometric and Nitrocefin® (Glaxo, Inc., Research Triangle Park, NC) methods.² Plasmid analysis³ and tests of sensitivity to the antibiotics² used in the study were done on 124 gonococcal isolates that survived shipment in a trypticase soy broth-10% glycerol solution on dry ice to the Centers for Disease Control, Atlanta, Georgia.

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TABLE 1. Single-Dose Treatment of Uncomplicated Male Gonococcal Urethritis in Addis Ababa, Ethiopia

Treatment Regimen	No. Cured/No. Treated (% Cured)*		
	Nonpenicillinase Strains (n = 96, 69% of Total)	Penicillinase Strains (n = 44, 31% of Total)	Total
Aqueous procaine penicillin G (n = 34)	20/23 (87.0)	6/11 (55.0)	26/34 (76.0)
Rosoxacin (n = 37)	25/26 (96.0)	11/11 (100)	36/37 (97.0)
Ampicillin (n = 36)	23/26 (88.5)	6/10 (60.0)	29/36 (80.5)
Spectinomycin (n = 33)	21/21 (100)	12/12 (100)	33/33 (100)
Total	89/96 (93.0)	35/44 (80.0)	124/140 (89.6)

* Cure was defined as negative culture and absence of symptoms of gonorrhea on day 7 after treatment.

Results

Forty-four (31.4%) of the patients were infected with penicillinase-producing *N. gonorrhoeae* (PPNG) and were evenly distributed among the treatment groups (table 1). All 124 isolates were sensitive to rosoxacin and spectinomycin; the concentrations at which 90% of strains were inhibited (MIC₉₀) were 0.06 and 12 µg/ml, respectively. The MIC₉₀ values of penicillin and ampicillin for the 81 non-PPNG isolates were 1 and 2 µg/ml, respectively, as compared with an MIC₉₀ of 8 µg/ml for the 43 PPNG isolates tested. All 80 non-PPNG strains possessed a 2.6-Mdalton cryptic plasmid, and one strain each also possessed a 24.5-, a 3.2-, or a 4.4-Mdalton plasmid. The latter two isolates did not express sufficient β-lactamase to be detected by the rapid iodometric or Nitrocefin® tests.

All of the 39 PPNG strains tested contained a 2.6-Mdalton and additional plasmids; a 3.2-Mdalton plasmid was present in 28 (71.8%), a 4.4-Mdalton plasmid in seven (17.9%), a 24.5-Mdalton plasmid in one, and a 4.4- plus a 24.5-Mdalton plasmid in three (7.7%). The size and number of plasmids did not affect the MICs for rosoxacin or spectinomycin, but the presence of either the 3.2- or a 4.4-Mdalton β-lactamase plasmid was associated with high rates of treatment failure (40–45%) among patients given the APPG or ampicillin regimen.

Discussion

This study demonstrated the efficacy of both spectinomycin and rosoxacin for treatment of uncomplicated gonorrhea in Ethiopian men. In contrast, treatment failure rates were unacceptably high among patients treated with standard APPG or ampicillin regimens. Although the high level of resistance of PPNG strains to ampicillin and APPG was expected, the relatively high level of resistance of non-PPNG strains to these antibiotics was not. The latter type of resistance is most likely a result of chromosomally mediated mechanisms that were first documented in Ethiopia in 1972.⁴ The widespread use

of low-dose penicillins for prophylaxis or treatment of gonorrhea in Addis Ababa has undoubtedly favored the selection and dissemination of the resistant non-PPNG strains and of PPNG strains in the city.

Twelve (57.1%) of the 21 patients infected by PPNG were cured by standard treatment with APPG and ampicillin regimens. The PPNG isolated from ten of the 12 patients contained the 3.2-Mdalton plasmid. It is possible that PPNG strains possessing the 3.2-Mdalton plasmid are more susceptible to penicillin than are those containing the 4.4-Mdalton plasmid encoding for β-lactamase. This result was also unexpected because no more than 23% of uncomplicated PPNG infections from Southeast Asia are cured by these regimens.⁵ This finding could be attributable to slow or minimal production of β-lactamase by Ethiopian PPNG strains, or to surreptitious use of additional antibiotics by these patients (who all denied it).

Isolates of PPNG became prevalent at the Addis Ababa Venereal Disease Clinic sometime after 1980.⁶ The diversity of plasmids encoding for β-lactamases suggests that these strains may have been imported from both Africa and Asia.⁷ Two patients in this study were infected with strains of *N. gonorrhoeae* possessing plasmids apparently capable of encoding but not producing β-lactamase, a phenomenon not previously reported. It is possible that these plasmids were lost as the organism was subcultured.

Both spectinomycin and rosoxacin proved to be excellent single-dose treatment regimens for treatment of uncomplicated gonococcal urethritis in men. Mild but transient side effects, including nausea (28%), headache (23%), dizziness (2.7%), and vomiting (2.7%) were reported by patients treated with rosoxacin, as has been reported in other studies using this drug regimen.^{8,9} A major drawback of both of these antibiotics, however, is that they have no treponemicidal activity. Venereal syphilis is highly prevalent in Addis Ababa; the sera of eight (11.8%) of 68 men in this study were tested and revealed active latent syphilis. This diagnosis was based

on reactive rapid plasma reagin tests with titers ranging from 1:4 to 1:28. It is likely, therefore, that use of alternative, non-penicillin treatment regimens for gonorrhea in Addis Ababa will result in an increase in the reservoir of untreated early latent syphilis in the population. One of the third-generation cephalosporins, such as ceftriaxone,¹⁰ would be the ideal antibiotic to use to treat gonorrhea in Ethiopia but the current cost of these drugs is prohibitive.

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