

# Treatment of Gonorrhea with Spectinomycin Hydrochloride: Comparison with Standard Penicillin Schedules

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Spectinomycin hydrochloride, a new parenteral antibiotic prepared from *Streptomyces spectabilis*, was compared with standard U.S. Public Health Service-recommended dosages of aqueous procaine penicillin G in the treatment of uncomplicated gonorrhea in 353 men and 314 women. Of the 314 women, 130 had a pretreatment positive rectal culture. All diagnoses were proven by culture on Thayer-Martin selective medium. Minimal inhibitory concentrations of both drugs were determined. Single doses of 2 and 4 g of spectinomycin were compared with 2.4 million units of procaine penicillin in males and with both 2.4 and 4.8 million units of procaine penicillin in females. Both spectinomycin schedules, 2.4 million units of penicillin in males and 4.8 million units of penicillin in females, resulted in cure rates in excess of 90%. There were no failures at the rectal site only in those women with positive rectal cultures. There was no advantage to using the larger amount of spectinomycin in either sex.

Gonorrhea is the most prevalent of the venereal diseases and the most common reportable bacterial infection of adults. The incidence of gonorrhea has risen steadily since 1958, and the number of cases reported annually has nearly doubled since 1965. This has been accompanied by an increased resistance of gonorrhea to penicillin therapy. Allergic reactions to penicillin also constitute a significant problem. Lentz and Nicholas found that 7.7% of 5,461 patients reporting to a large venereal disease clinic in Philadelphia were hypersensitive to penicillin as indicated by a positive skin reaction when tested with penicilloyl-polylysine (5). The foregoing factors make it imperative that new therapeutic agents be continually developed and evaluated in the treatment of gonorrhea.

Spectinomycin hydrochloride is a new parenteral antibiotic prepared from *Streptomyces spectabilis* which has shown promising results in the treatment of gonorrhea (4). It appears to be remarkably free from side effects and offers an advantage over oral preparations since it is given as a single injection in the clinic. The initially studied sulfate salt (10, 13) has subsequently been replaced by the hydrochloride salt, which is more soluble and causes less pain upon injection. It has been shown to be well tolerated and the concentrations obtained in

serum are comparable to those achieved after administration of the sulfate salt. In this report, we describe our experience in treating males and females with proven gonococcal infections with spectinomycin hydrochloride. The effectiveness of spectinomycin is compared with that of the standard aqueous procaine penicillin G schedules recommended by the U.S. Public Health Service.

## MATERIALS AND METHODS

The study was conducted on patients at the Houston Social Hygiene Clinic. A total of 400 women and 353 men proven to have gonococcal infection by culture on Thayer-Martin selective medium were selected for the study.

**Males.** All male patients presented with signs or symptoms, or both, of acute urethritis. Culture was obtained by inserting a sterile cotton-tipped applicator into the anterior urethra and streaking it onto the culture medium. The cultures were incubated overnight at 37 C in a candle jar and were observed at 24 hr for the presence of typical oxidase-positive colonies of gram-negative diplococci. Confirmation by sugar fermentation tests was obtained for all cultures. The patients were randomly assigned to one of three treatment groups. Group 1 was treated with 2.4 million units of aqueous procaine penicillin G, group 2 was treated with 2 g of spectinomycin hydrochloride, and group 3 was treated with 4 g of spectinomycin hydrochloride. Any patient giving a history of peni-

cillin hypersensitivity was assigned to the next spectinomycin protocol. All drugs were given in a single injection except for the larger dose of spectinomycin hydrochloride which was divided equally in each buttock. The patients were instructed to abstain from sexual intercourse and to return in 7 days. All patients returning did so between 5 and 8 days, and on return were questioned closely regarding any side effects and interim sexual relationships. They were reexamined for the presence of urethral discharge, and if a discharge was present a Gram stain was made. All patients, whether or not a discharge was present, were cultured on Thayer-Martin selective medium as before. A patient was classified as a treatment failure if the post-treatment culture was positive for *Neisseria gonorrhoeae*, regardless of the absence of signs or symptoms.

**Females.** The majority of women coming to the clinic are contacts of infected males; about 10% come for treatment because a positive culture has been found at some other clinic, e.g. Planned Parenthood or maternity clinics. Only 10 to 15% of the women have symptoms referable to the reproductive system. Women were cultured on Thayer-Martin selective medium by insertion of sterile cotton-tipped applicators into both the cervix and rectum. Cultures were handled as for the males. Through an administrative error, the females were initially assigned only to the same treatment schedules as the males. Group 1 received 2.4 million units of aqueous procaine penicillin G, group 2 received 2 g of spectinomycin hydrochloride, and group 3 received 4 g of spectinomycin hydrochloride intramuscularly. As the study neared completion, a fourth treatment group was added. This group received 4.8 million units of aqueous procaine penicillin G, divided equally in each buttock. In all respects, this group was identical to the others with the exception that minimal inhibitory concentrations (MIC) were not determined for culture isolates. The patients were instructed to return in 1 week for reevaluation. All patients who returned did so between 5 and 8 days after treatment. They were reexamined and recultured as before from both the cervix and rectum.

## RESULTS

**Males.** Two-thirds of the patients in each group treated returned. There were no significant differences in the cure rates among the three groups of patients (Table 1). Aqueous procaine

penicillin G, 2.4 million units, and both 2 and 4 g of spectinomycin hydrochloride cured slightly over 90% of the returning males. Four treatment failures in group 1 (aqueous procaine penicillin G) were retreated with 4 g of spectinomycin hydrochloride, and all were cured.

Of eight treatment failures in group 2 (2 g of spectinomycin), three were retreated with 4.8 million units of aqueous procaine penicillin G; two of these were cured and one failed. Two group 2 failures were retreated with 4 g of spectinomycin hydrochloride; both failed to respond to the larger dose as well.

In group 3 (4 g of spectinomycin), there were five treatment failures. Three of these were retreated with aqueous procaine penicillin G, 4.8 million units; two were cured and one was classified as a failure when seen 1 week later. One group 3 failure was retreated with 9 g of tetracycline in divided doses and was negative upon culture 1 week later.

No post-treatment nongonococcal urethritis was observed in the three treatment groups. If signs or symptoms persisted, *N. gonorrhoeae* was invariably found by culture.

**Females.** Of 400 women presenting at the Houston Social Hygiene Clinic with cervical gonorrhea, 169 (42%) were also found to have a positive rectal culture for gonorrhea. Only nine (2.2%) of those with positive rectal cultures did not have a positive cervical culture as well. Of 400 patients treated, 314 (79%) returned for follow-up evaluation; 130 of the 314 (41%) patients who returned had a pretreatment positive rectal culture.

Spectinomycin in dosages of both 2 and 4 g resulted in bacteriological cures in approximately 96% of the patients (Table 2). In the patients with rectal gonorrhea, there was no significant difference in the failure rate of those treated with 2 g (1 of 36) and of those treated with 4 g (2 of 33). The higher dose of penicillin (4.8 million units) was equivalent to the spectinomycin schedules as demonstrated by  $X^2$  analysis; 5 of 70 cervical and 4 of 40 rectal infections were

TABLE 1. Results of treatment of uncomplicated gonococcal urethritis in males

Treatment	Treated	Followed	Cures <sup>a</sup>	Failures <sup>a</sup>
Aqueous procaine penicillin G, 2.4 million units . . . . .	121	76	69 (90.8%)	7 (9.2%)
Spectinomycin hydrochloride, 2 g . . . . .	122	82	74 (90.2%)	8 (9.8%)
Spectinomycin hydrochloride, 4 g . . . . .	110	70	65 (92.9%)	5 (7.1%)

<sup>a</sup> In those followed.

classified as treatment failures. All of the rectal failures were also cervical failures. Aqueous procaine penicillin in a dose of 2.4 million units was clearly inferior to both spectinomycin schedules, having an overall patient failure rate of 21.3% among returnees. Among infections treated with 2.4 million units of penicillin, 16 of 74 cervical infections were classified as treatment failures, and 7 of 24 rectal infections persisted. There were no failures at the rectal site only in any of the groups.

**Susceptibility studies.** The MIC of both spectinomycin and penicillin was determined for initial and follow-up cultures from all patients with a positive follow-up culture. Additionally, initial MIC values were selected at random from patients who were treatment successes. The agar plate dilution method described by Thayer et al. (11) was used to determine the MIC of spectinomycin and penicillin on cultures from a total of 86 patients. The initial MIC values

for the penicillin treatment groups are shown in Fig. 1. Of the 81 tested strains, 60 were "sensitive," 9 were "moderately sensitive," 10 were classified as "resistant," and only 2 were "highly resistant" (0.0025–0.2 units/ml, sensitive; 0.2–0.5 units/ml, moderately sensitive; 0.5–1.0 units/ml, resistant; and 1.0 units/ml, highly resistant; *oral communication*, John E. Martin, Center for Disease Control, Atlanta, Ga.). Gonococcal resistance is only relative, and these classifications apply primarily to single-dose treatment schedules. The initial mean MIC of penicillin (0.09 units/ml) for penicillin-treated patients who were cured is statistically different ( $P < 0.02$ ) from the initial mean MIC of penicillin (0.47 units/ml) for penicillin treatment failures (Table 3).

The MIC of spectinomycin ranged from 5.0 to 15.0  $\mu\text{g/ml}$  (Fig. 2), and thus fell well within the average concentrations attained in serum after administration of spectinomycin (12;

TABLE 2. Results of treatment of females with uncomplicated gonorrhea

Treatment	Treated	Followed	Cures	Failures <sup>a</sup>
Aqueous procaine penicillin G				
2,400,000 units .....	92	75	59 (78.7%)	16 (21.3%)
4,800,000 units .....	123	73	67 (91.8%)	6 (8.2%)
Spectinomycin hydrochloride				
2 g .....	90	77	74 (96.1%)	3 (3.9%)
4 g .....	95	89	85 (95.5%)	4 (4.5%)

<sup>a</sup> Patients were considered a treatment failure if the culture was positive for gonorrhea from either the cervix or rectum.

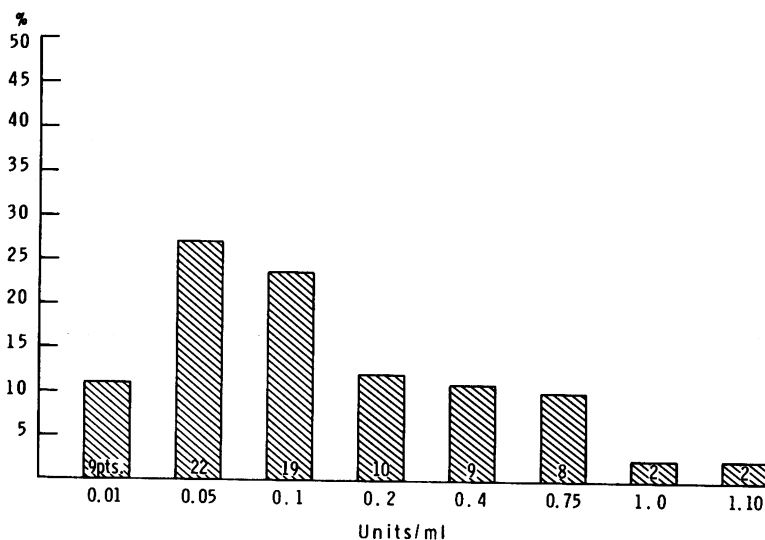


FIG. 1. Initial minimal inhibitory concentrations of penicillin for cultures from 81 patients. The number of patients is shown on each bar.

TABLE 3. Initial MIC of penicillin for cultures from penicillin treatment failures

Treatment group	Initial MIC of penicillin (units/ml)							
	0.01	0.05	0.1	0.2	0.4	0.75	1.0	1.10
Male, 2.4 million units.....	0	0	3	0	1	2	0	1
Female, <sup>a</sup> 2.4 million units.....	1	4	4	3	3	0	1	

<sup>a</sup> Initial MIC values were not obtained for three patients: follow-up MIC values were 0.20, 0.40 and 1.10 units/ml.

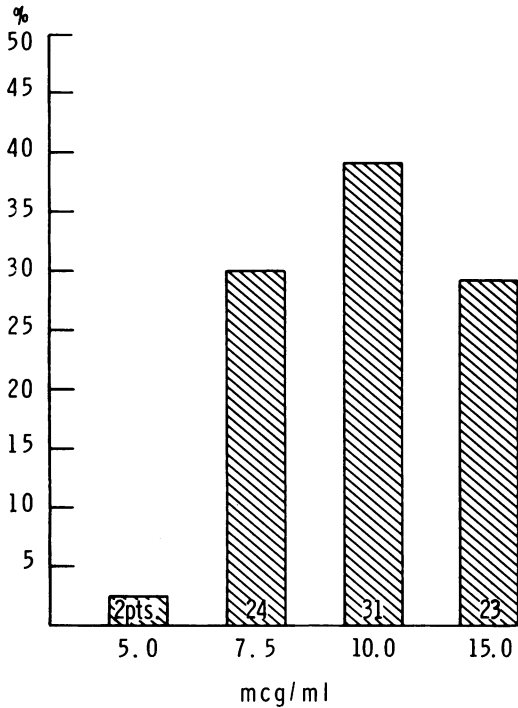


FIG. 2. Initial minimal inhibitory concentrations of spectinomycin for cultures from 80 patients. The number of patients is shown on each bar.

personal communication, T. R. Pyke, The Upjohn Co.). The MIC values for isolates from spectinomycin failures (Table 4) were within the same range, and there were no significant differences between the initial MIC values of the cured patients and those of the failed patients for spectinomycin.

These data indicate that 15% of gonococci isolated from this area are "resistant" to penicillin as defined above. Multiple doses of penicillin would produce concentrations in the blood sufficient to kill these "resistant" gonococci; however, multiple doses are not feasible in venereal disease clinics. Susceptibility or resistance to spectinomycin has not been defined. The correlation

TABLE 4. Initial MIC of spectinomycin for cultures from spectinomycin treatment failures

Treatment group	Initial MIC (µg/ml)			
	5.0	7.5	10	15
Male				
2.0 g <sup>a</sup> .....	0	1	2	3
4.0 g.....	0	0	4	2
Female				
2.0 g.....	0	2	0	0
4.0 g.....	0	1	2	0

<sup>a</sup> Initial MIC was not obtained for one patient; follow-up MIC was 7.5 µg/ml.

coefficient between the initial MIC of spectinomycin and that of penicillin for the 82 patients who had both determinations was 0.24, indicating that an organism with a high spectinomycin MIC is more likely to have a high than a low penicillin MIC.

There were no side effects among the groups treated with either spectinomycin or penicillin. Thirty-two of the patients treated with spectinomycin had a definite past history of penicillin allergy; none of these had any side effects or reactions related to spectinomycin hydrochloride.

DISCUSSION

Results of the present study indicate that spectinomycin hydrochloride is an effective alternate antibiotic to penicillin in the treatment of uncomplicated gonorrhea in both males and females. A 2-g dose of spectinomycin is equivalent to the U.S. Public Health Service-recommended doses of aqueous procaine penicillin G in the treatment of acute gonorrhea in both males and females and appears to be the optimal dosage. It is evident that increasing the dosage of spectinomycin from 2 to 4 g does not result in a higher cure rate.

Spectinomycin appears to be remarkably free from side effects, and there appears to be no cross-reactivity (hypersensitivity) to penicillin. A salient feature of this drug is its effectiveness in a

single dose. This is a preferred feature in venereology because it insures that the patient has received a curative dose.

Shapiro and Lentz, treating urogenital gonorrhea, reported that spectinomycin sulfate in a dose of 4 g was effective in only 78% of 51 females, and they considered this dosage comparable to 2.4 million units of aqueous procaine penicillin (9). Cornelius and Domesick found both 2 and 4 g of spectinomycin hydrochloride effective in 96% of women with uncomplicated gonorrhea (4).

The problem of rectal gonorrhea is not new. It has been discussed since the early 1900's (6) and does not seem to have changed significantly since then. Although early workers did not have the advantages offered by modern culture media, Jesionek cultured the gonococcus from the rectum in 1898 and established the entity of gonococcal proctitis (6). Early investigators stated that infection of the rectum occurred in about 30% of all female gonorrhea (6), a figure that compares favorably with recent surveys (1, 7).

Rectal cultures pre- and post-treatment added little to our ability to diagnose or determine the cure of gonorrhea in the female. Rectal cultures increased our diagnosis of gonorrhea by only 2.2%. In view of the added expense, reluctance on the part of the patient and physicians concerned, and the poor yield, we do not advocate routine rectal cultures for the diagnosis of and determination of cure of gonorrhea in the female. Scott and Stone stated that rectal gonorrhea requires a larger dose of penicillin for adequate treatment than does urogenital gonorrhea, possibly because the concentration of penicillin in the rectum is not high and its action may be impaired by penicillinase produced by intestinal organisms (8). Sparling et al., however, found that rectal gonorrhea in the female was no more difficult to cure than cervical infection, and they obtained cure rates of over 90% with 3 g of spectinomycin sulfate or 2.4 million units of aqueous procaine penicillin (10). We did not find any patient failing at the rectal site only, and we do not think that a larger dose of spectinomycin or penicillin is required for gonococcal proctitis than for urogenital gonococcal infection.

Spectinomycin's effect upon syphilis is not precisely known. Wilcox treated two patients with dark-field positive syphilis with a single injection

of spectinomycin sulfate. Motile *Treponema pallidum* cells were recovered at 16 hr in one patient but were absent in the other patient 38 hr after treatment (13). Clark and Yobs, however, reported that spectinomycin sulfate treatment of rabbits with incubating syphilis delayed the appearance of the primary lesion at a low dosage level (3) but cured syphilis at an extremely high level (2). Until more clinical experience is gained, some uncertainty must apply to spectinomycin's possible effect upon incubating syphilis, and serological follow-up must be obtained because syphilis may have been contracted at the same time and from the same source as gonorrhea.

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