Comparison of Spectinomycin Hydrochloride and Aqueous Procaine Penicillin G in the Treatment of Uncomplicated Gonorrhea

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Men and women with uncomplicated gonorrhea were randomly assigned to receive aqueous procaine penicillin G (2,400,000 U for men; 2,400,000 U daily for 2 days for women) or spectinomycin hydrochloride (2.0 g for men; 4.0 g for women). Among men who returned for post-treatment evaluation within 10 days, treatment failures were noted among 16 (20.3%) of 79 men who received penicillin and 8 (9.5%) of 84 men who received spectinomycin ($P < 0.1$). Similarly, 6 (13.3%) of 45 women who received penicillin and 3 (6.5%) of 46 women who received spectinomycin had positive endocervical cultures for *Neisseria gonorrhoeae* at the time of the post-treatment examination ($P =$ not significant).

Over 6% of patients who require treatment for gonorrhea give a history of hypersensitivity to penicillin (7). Tetracycline is an effective alternative to penicillin or ampicillin under these circumstances (4), but tetracycline must be taken for several days and some clinicians are concerned that noncompliance and/or sharing of medications with sexual partners may result in ineffective therapy. Thus, there exists a need for a safe, effective, single-dose treatment for patients who cannot be given penicillin. It would appear that this need has for the present been met with the introduction of spectinomycin hydrochloride. This report describes our experience with this drug in a controlled study in which it was compared with the dosage schedules of aqueous procaine penicillin G that were recommended by the Massachusetts Department of Public Health in early 1972.

MATERIALS AND METHODS

Men who presented to the Boston City Hospital with acute urethritis and whose urethral discharge contained gram-negative intracellular diplococci were invited to participate in the study. Written informed consent was obtained from those who agreed to participate, and they were randomized on the basis of the last digit in their hospital number to receive either 2.4 million U of aqueous procaine penicillin G or 2.0 g of spectinomycin hydrochloride as a single intramuscular injection. A sample of the urethral exudate obtained before treatment was inoculated

onto Thayer-Martin agar and incubated in a candle jar for 48 h at 37.5 C.

Women who were suspected on clinical or epidemiological grounds of having uncomplicated gonococcal infection and who gave written informed consent were randomized as above to receive 2.4 million U of aqueous procaine penicillin G daily for 2 days or 4.0 g of spectinomycin hydrochloride in a single divided intramuscular dose. Endocervical cultures were obtained with a sterile cotton-tipped swab and placed into 1 ml of proteose no. 3 broth (Difco) for transport to the laboratory, where they were inoculated onto Thayer-Martin agar within 2 h of collection and incubated as outlined above.

Excluded from the study were pregnant women, patients who gave a history of sensitivity to penicillin, and patients who had received other antimicrobial therapy during the preceding week. Patients who were included in the study whose cultures did not contain gonococci were not included in the analysis of the data.

All participants were asked to return for an examination 1 week after treatment, at which time they were asked about side effects from the drugs and about sexual re-exposure. Male urethral and endocervical cultures for gonococci were obtained as part of these follow-up examinations. Patients who returned more than 30 days after treatment were not included in the analysis of the data.

Colonies of typical morphology on Thayer-Martin agar that gave a positive oxidase reaction with *N,N*-dimethyl-*p*-phenylene diamine hydrochloride and that contained gram-negative cocci were considered to be *Neisseria gonorrhoeae*. Sugar fermentation reactions were not used, since over 99% of genital isolates

that meet these criteria will be confirmed as *N. gonorrhoeae* if subjected to sugar fermentation tests (C. Thornsberry, personal communication). Minimal inhibitory concentrations of penicillin and of spectinomycin were determined for some gonococcal isolates with the agar plate dilution method using the inocula replicator of Steers et. al. (9).

Chi-square analysis was used to compare the efficacy of the antimicrobial agents. The Fisher exact test was used to compare the incidence of side effects accompanying each of the drugs. The Mann-Whitney U test was used to compare the distributions of the minimal inhibitory concentrations, and a Pearson correlation co-efficient was computed to test the relation of the log of the minimal inhibitory concentrations of the antimicrobial agents.

RESULTS

We treated 392 men with documented gonococcal urethritis between January and September 1972. Of these 392 men, 184 (46.9%) returned to the clinic within 30 days and are included in the evaluation of the two treatment schedules (Table 1). Any patient who had gonococci isolated from the urethral culture obtained during the second visit was considered to be a treatment failure; no attempt was made to differentiate reinfection from relapse. Treatment with 2.0 g of spectinomycin appeared to result in fewer treatment failures than treatment with 2.4 million U of procaine penicillin G. Among those who returned to the clinic within 10 days, treatment failures were noted

TABLE 1. Comparison of aqueous procaine penicillin G and spectinomycin hydrochloride in the treatment of men with uncomplicated gonococcal urethritis

Treatment received	No. treated	Re-examined within 10 days			Re-examined within 30 days		
		No.	Treatment failures ^a		No.	Treatment failures ^b	
			No.	%		No.	%
Aqueous procaine penicillin G (2,400,000 U)	193	79	16	20.3	91	21	23.1
Spectinomycin hydrochloride (2.0 g)	199	84	8	9.5	93	14	15.1

^a Five of the 16 men who had positive cultures after penicillin treatment and three of the eight men who had positive cultures after treatment with spectinomycin acknowledged that they had had intercourse between visits to the clinic.

^b Intercourse between clinic visits was reported by 8 of 21 treatment failures who received penicillin and 8 of the 14 treatment failures who received spectinomycin.

among 16 (20.3%) of 79 men who received procaine penicillin G and among 8 (9.5%) of 84 men who received spectinomycin ($X^2 = 2.93$; $P < 0.10$).

We treated 276 women who were suspected of having uncomplicated gonococcal infection, 128 of whom had *N. gonorrhoeae* isolated from their endocervical cultures. Ninety-one of the 128 women who had documented gonococcal infection and 35 of the women who did not have gonococci isolated from their endocervical culture returned to the clinic within 30 days (Table 2). There were fewer treatment failures among the women who received spectinomycin hydrochloride, but the difference is not statistically significant ($X^2 = 0.54$; $P =$ not significant).

Of the 310 patients who returned to the clinic, 293 (124 women and 169 men) were specifically asked if they had experienced any of the symptoms listed in Table 3. The other 17 patients were not asked about side effects because of errors or other administrative difficulties. About 5% of the patients who received spectinomycin said that they had experienced fever and/or chills after treatment, whereas only one patient who received penicillin reported chills. Seven of the eight patients who noted chills and five of the seven patients who noted fever after treatment with spectinomycin were women.

The agar plate dilution method was used to estimate the sensitivity of 170 pretreatment gonococcal isolates to spectinomycin and of 176 pretreatment isolates to penicillin G. Tables 4 and 5 list the distribution of these values for all patients as well as for the patients whose cultures contained gonococci after treatment with each of the antibiotics. There were more treatment failures among the patients whose pretreatment isolates had relatively high mini-

TABLE 2. Comparison of aqueous procaine penicillin G and spectinomycin hydrochloride in the treatment of women with uncomplicated gonorrhea

Treatment	No. treated	No. re-examined within 10 days	Treatment failures ^a	
			No.	%
Aqueous procaine penicillin G (2,400,000 U daily for 2 days)	60	45	6	13.3
Spectinomycin hydrochloride (4.0 g)	68	46	3	6.5

^a One woman who had a positive culture after treatment with procaine penicillin G indicated that she had had intercourse between visits. All six women who had positive cultures after treatment received both injections of procaine penicillin G.

TABLE 3. *Adverse effects after treatment with aqueous procaine penicillin G and spectinomycin*

Symptoms	Penicillin (143 patients)		Spectinomycin (150 patients)	
	No.	%	No.	%
Nausea	7	4.9	8	5.3
Vomiting	3	2.1	3	2.0
Rash	7	4.9	4	2.7
Chills	0 ^a	0	8 ^a	5.3
Fever	1 ^b	0.7	7 ^b	4.7
Insomnia	5	3.5	4	2.7
Pain at site of injection	23	16.1	30	20.0

^a $P < 0.005$.^b $P < 0.05$.TABLE 4. *Distribution of in vitro sensitivities of pretreatment gonococcal isolates to penicillin G*

MIC ($\mu\text{g/ml}$)	All pretreatment isolates		Pretreatment isolates from penicillin treat- ment failures	
	No.	%	No.	%
0.078 or less	93	52.8	5	29.4
0.156–0.313	74	42.0	10	58.8
0.625 or more	9	5.1	2	11.8

TABLE 5. *Distribution of in vitro sensitivities of pretreatment gonococcal isolates to spectinomycin*

MIC ($\mu\text{g/ml}$)	All pretreatment isolates		Pretreatment isolates from spectinomycin treatment failures	
	No.	%	No.	%
5 or less	21	12.4	0	0
10	99	58.2	3	42.9
20 or more	50	29.4	4	57.1

mal inhibitory concentrations (MICs) to the antibiotic that they received, but these differences are not statistically significant.

Table 6 shows the relationship between the MICs of penicillin G and spectinomycin for the 165 pretreatment isolates for which both values were available. There is a positive correlation between the MIC values for penicillin and for spectinomycin, but the correlation is not statistically significant.

DISCUSSION

Several well-controlled studies have found spectinomycin hydrochloride to be useful in the

treatment of uncomplicated gonorrhea (3, 5, 8). This study confirms the utility of spectinomycin hydrochloride in the treatment of uncomplicated gonococcal infections. The results obtained with spectinomycin hydrochloride compared favorably with the results obtained with the dosage schedule of aqueous procaine penicillin G that we were using to treat men in our clinics in 1972. After we had initiated this study, new recommendations for the treatment of uncomplicated gonococcal infection were formulated. The Public Health Service (1) now recommends that the treatment of choice for uncomplicated gonococcal infection is aqueous procaine penicillin G, 4,800,000 U, divided into at least two doses and injected intramuscularly at different sites at one visit, together with 1 g of oral probenecid. Alternative effective regimens include oral ampicillin, 3.5 g, together with 1.0 g of oral probenecid; oral tetracycline, 1.5 g, initially followed by 0.5 g four times a day for 4 days; and intramuscular spectinomycin hydrochloride, 2.0 g, for both men and women.

The treatment schedules recommended by the Massachusetts Department of Public Health have also been changed. We now treat both men and women who have uncomplicated gonococcal infection with aqueous procaine penicillin G, 2,400,000 U, by intramuscular injection on 2 successive days. Although the dosage schedules of aqueous procaine penicillin G that we used to treat men and of spectinomycin that we used to treat women in this study are now obsolete, we feel that it is useful to report these data since they further confirm the efficacy and safety of spectinomycin hydrochloride.

We consider spectinomycin hydrochloride to be the drug of choice for the treatment of uncomplicated gonococcal infections in patients

TABLE 6. *Correlation of MICs of penicillin G and spectinomycin for 165 gonococcal strains isolated before treatment*

MIC of penicillin G ($\mu\text{g/ml}$)	MIC of spectinomycin hydrochloride ($\mu\text{g/ml}$)				
	2.5	5	10	20	40
1.25			2		
0.625			2		1
0.313		3	12	4	2
0.156	1	6	23	9	
0.078		4	19	5	2
0.039		1	16	7	1
0.019		1	6	3	1
0.008			9	2	
0.004		1	8	3	
0.002	1				

who are allergic to penicillin. There are of course some disadvantages associated with the use of spectinomycin hydrochloride. It is considerably more expensive than aqueous procaine penicillin G and, unlike penicillin, probably does not cure incubating syphilis (2). More significantly, strains of gonococci that are highly resistant to spectinomycin have been induced in the laboratory (5) and have been reported from clinical isolates in Denmark (6). Careful surveillance will have to be maintained for the appearance of highly resistant isolates in other areas.

A curious finding was the occurrence of a subjective sensation of fever and/or chills in about 5% of the patients who received spectinomycin hydrochloride. Although no temperature recordings or other objective data are available, all of the patients who were interviewed as part of their post-treatment evaluation were specifically asked about each of the symptoms listed in Table 3, and only one patient who received penicillin reported fever after therapy. Most of the patients who noted fever and/or chills after treatment with spectinomycin were women, suggesting that this occurrence may have been dose related since the women received twice as much of the antibiotic as the men. None of the other symptoms, most of which are listed in the spectinomycin package insert as having been associated with the drug, were reported significantly more often by patients who received spectinomycin than by patients who received aqueous procaine penicillin G.

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