

Using One Dose of Doxycycline or Penicillin To Treat Men With Gonococcal Urethritis

STEPHEN R. JONES, M.D., and HARRY E. GILLELAND, Jr., M.S.

THE organisms isolated in the current epidemic of gonococcal urethritis are often unresponsive to usual (1) and, at times, unusual (2) doses of penicillin. The search for another safe but effective one-dose remedy to replace penicillin as the drug of choice for the treatment of gonorrhea at

At the time of the study, the authors were with the preventive medicine service and the department of pathology, William Beaumont General Hospital, El Paso, Tex. Dr. Jones is now a research trainee in infectious diseases, department of internal medicine, University of Texas Southwestern Medical School, Dallas. Captain Gilleland, MSC, U.S. Army, is currently on active duty with the 9th medical laboratory, Long Binh, Vietnam.

Miguel Portillo, microbiology section, department of pathology, William Beaumont General Hospital, provided technical advice and assistance, and J. E. Martin, Jr., Neisseria Research Unit, Venereal Disease Research Laboratory, Center for Disease Control, HSMHA, provided antibiotic sensitivity testing.

Tearsheet requests to Editorial Assistant, Department of Medical Research and Development, William Beaumont General Hospital, El Paso, Tex. 79920.

times produces enthusiasm for a particular antibiotic. Such has been the case with doxycycline, a tetracycline derivative, first successfully used in Europe (3) and then publicized in the popular press (*Parade Magazine*, Oct. 19, 1969). American investigators have since reported doxycycline to be 96 percent effective in a single oral dose of 250 mg. (4). This report was reviewed by Rogers (5) with reserved optimism, suggesting further evaluation.

The minimal inhibitory concentration (MIC) of doxycycline for *Neisseria gonorrhoeae* closely resembles that of tetracycline and its other analogs (6, 7). For 25 strains of *N. gonorrhoeae* isolated at Boston City Hospital, the range of MIC's was 0.09 to 3.1 $\mu\text{g. per ml.}$ (6), and for 96 strains isolated at St. Thomas Hospital, London, the range was 0.09 to 6.2 $\mu\text{g. per ml.}$; only two of these strains required more than 3.1 $\mu\text{g. per ml.}$ and only eight more than 1.56 $\mu\text{g. per ml.}$ (7).

Limited studies (8) of serum levels following a single 300 mg. dose suggest that sufficient concentrations are achieved and maintained to inactivate *N. gonorrhoeae*: in two healthy young men, the mean serum levels were at or greater than 3.0 $\mu\text{g. per ml.}$ after 2 hours; they remained at this level through the eighth hour and then gradually diminished. Because of these encouraging reports, we

undertook a clinical trial of the treatment of acute gonococcal urethritis with a single oral dose of doxycycline.

The study had the following specific goals:

1. To assess the effectiveness of a single oral dose of 300 mg. of doxycycline in the treatment of acute gonococcal urethritis in men, comparing it with a single injection of 2.4 million units of procaine penicillin G (the dose currently recommended by the Public Health Service and the Armed Forces (1)).

2. To reassess the clinical response of acute gonococcal urethritis in this military community and the in vitro resistance of *N. gonorrhoeae* to penicillin G as previously evaluated by Sokoloff and Goldstein in 1963 (9).

3. To evaluate the incidence of the tribe *Mimea* as a cause of penicillin-resistant urethritis in this locale.

Materials and Methods

Study population. The study group consisted of enlisted men assigned to Fort Bliss, a large Army post on the U.S.-Mexican border. The men had reported to sick call with symptoms of urethritis and a history of recent sexual exposure and were found to have uncomplicated gonococcal urethritis. Only patients naming local (El Paso or Juárez) contacts as the source of their infection were included.

The initial diagnosis of gonococcal urethritis was made when a purulent urethral exudate, taken from the urethral meatus by a cotton swab, was present and this exudate, when smeared and Gram stained, showed intracellular gram-negative diplococci with contiguous sides appearing flattened or slightly concave. The diagnosis was confirmed by culture of the exudate on Thayer-Martin (T-M) medium.

Treatment programs. Two programs were evaluated:

1. From November 1969 through April 1970, 69 patients were given 300 mg. (three 100 mg. capsules) of doxycycline hyclate orally in one dose. Medication was dispensed by S.R. Jones, who insured that the pills were swallowed.

2. From April through May 1970, 66 patients were given 2.4 million units of procaine penicillin G intramuscularly. The injections were given at the person's troop medical clinic and, on followup, the patient was questioned to insure that it had been given. All patients were initially seen and treated on either a Monday or Tuesday and

were requested to return the following Friday for followup.

Followup. Followup consisted of questioning the patient about vomiting the medication (when appropriate) and whether any symptoms had persisted. A urine sample was collected aseptically, immediately centrifuged, and the sediment cultured.

Laboratory methods. All exudate and urine sediment were cultured on both Thayer-Martin selective medium and Mueller-Hinton (M-H) medium. Plates were incubated in CO₂ at 35° C. and were read at 48 and 72 hours.

The presumptive identification of *N. gonorrhoeae* was made (a) on ability to grow a typical colonial morphology on T-M medium, (b) a positive oxidase reaction, and (c) typical appearance on Gram stain (as described previously). Cultures taken from the group treated with penicillin were sent to the Venereal Disease Research Laboratory in Atlanta, Ga. The penicillin and tetracycline sensitivities of 32 individual cultures were determined according to the method of Thayer and co-workers (10).

Results

Of the 135 patients initially selected, 50 remained in each treatment group for final evaluation. Of the 69 treated with doxycycline, 19 patients were eliminated: eight failed to return, two vomited the medication (both between ½ and 1 hour after ingestion), and nine returned 48 hours after treatment with urethral discharge persisting, which on smear and Gram stain was again positive. They returned before the appointed culture session, so they were not seen by the investigators. Of the 66 treated with penicillin, 16 were eliminated because they failed to return for followup. Of the 50 in each group from whom culture followup was obtained, there were 19 (38 percent) treatment failures with doxycycline and five (10 percent) with penicillin (table 1).

After eliminating the two patients who vomited the medication, the results for the remaining 133 initial patients were based on the assumptions that those who failed to return were treatment successes and those with positive smears after 48 hours were treatment failures. These assumptions seem reasonable since all cases of venereal disease from this population were seen at only one interviewing section and laboratory. There were 27 failures (40.3 percent) of 67 treated with doxycycline and five failures (7.5 percent) of 66

Table 1. Comparison of failures of single oral doses of doxycycline with procaine penicillin G in treating acute gonococcal urethritis in men in El Paso and Atlanta

Drug and dose	Study group	Number of cases	Number of culture followups	Treatment failures			
				All failures		Culture followups	
				Number	Percent	Number	Percent
Doxycycline, 300 mg.....	El Paso, 1969-70....	67	50	27	40.3	19	38.0
Doxycycline, 250 mg.....	Atlanta, 1968.....	169	158	6	3.6	6	3.8
Procaine penicillin G, 2.4 million units....	El Paso, 1970.....	66	50	5	7.5	5	10.0
Procaine penicillin G, 2.5 million units....	El Paso, 1962.....		47	0	0	0	0

SOURCES: Atlanta 1968 study, reference 4; El Paso 1962 study, reference 9.

treated with penicillin (table 1). *N. gonorrhoeae* was isolated from all cultures taken from patients treated with penicillin who were treatment failures; in no culture was the tribe *Mimea* found.

The MIC values for both penicillin and tetracycline are given in table 2 for the 32 gonococcal isolates for which antibiotic sensitivity testing was performed. The average MIC for the isolates which were successfully treated with penicillin was 0.33 units per ml., whereas the penicillin treatment failures had an average MIC of 0.82 units per ml. (table 3).

Comment

Advantages of a one-dose oral medication for treating gonorrhea are significant. Oral medications are safer and more pleasant, and a single dose insures that the full treatment is administered under supervision. Although several one-dose parenteral alternatives to penicillin have been evaluated, including kanamycin (A) (11), cephaloridine (B) (12), and a combination of penicillin and probenecid (13), these drugs have the disadvantage of being administered parenterally and, in addition, they neither prevent postgonococcal urethritis nor treat the occasional case of urethritis caused by *Mimea* (14).

Of the oral antimicrobial agents, tetracycline and its analogs have most often been evaluated for effectiveness as a one-dose treatment (1, 3). It has been suggested by Holmes and co-workers (1) that only single oral doses of tetracycline in excess of 1.5 gm. will be successful in treating acute gonococcal urethritis in males.

In a study at the El Paso medical facility in 1962 (15), a single oral dose of 900 mg. of demethylchlortetracycline (C) resulted in a 36 percent failure rate. Despite the fact that 300 mg. of doxycycline hyclate (D) is the equivalent of

1.5 gm. of tetracycline or 900 mg. of demethylchlortetracycline, we chose to use this amount because the serum levels achieved seemed sufficient to inhibit *N. gonorrhoeae* and because of the reported success of Domescik and co-workers in Atlanta (4) with a somewhat lesser dose.

We met with much less success than did the Atlanta investigators (table 1). Several possible reasons for this follow.

Reinfection. We lessened the likelihood that our highly promiscuous population would rapidly become reinfected by avoiding an interposing weekend between treatment and followup. We believed that if reinfection was an important factor, it would have been reflected in the group treated with penicillin as well.

Table 2. Results of antibiotic sensitivity testing of 32 pretreatment gonococcal isolates

Drug	Number of isolates
Penicillin (units per ml. ¹):	
0.005.....	1
0.01.....	1
0.05.....	4
0.1.....	5
0.15.....	2
0.2.....	3
0.3.....	3
0.4.....	1
0.5.....	2
0.7.....	6
1.0.....	2
1.5.....	2
Tetracycline (µg. per ml. ²):	
0.125.....	3
0.25.....	5
0.5.....	7
1.0.....	9
2.0.....	8

¹ Average minimal inhibitory concentration is 0.41 unit per ml.

² Average minimal inhibitory concentration is 0.94 unit per ml.

Technique of followup culture. The method used to obtain followup cultures differed. Domesick and co-workers (4) used urethral scrapings taken with a wire loop while we used urine sediment. Although we believed, as did Fischnaller and co-workers (11), that urine sediment culture is a more reliable and accurate method of testing the male, the magnitude of difference in results between the two studies is unlikely to be caused by this alone.

Different interval between treatment and followup. Approximately half of our patients were seen at 72 hours and half at 96 hours following treatment, while all of the Atlanta patients were seen at 96 hours following treatment. However, from the data of Holmes and co-workers (1), 72 hours seems a more than adequate time for treatment to be effective.

Local variation in gonococcal sensitivity to tetracycline and its derivatives. This variation seems the most likely explanation for the difference. Specific in vitro variations of sensitivity of *N. gonorrhoeae* to tetracycline between El Paso and Atlanta (4) have not yet been documented. Evidence of variation in vitro sensitivity, however, between strains from other localities has been demonstrated (1). The background for altered sensitivity to tetracycline is present in the El Paso area. Military personnel often use others' leftover tetracycline in an attempt at self-treatment, and it can be purchased without prescription in neighboring Mexico, where it is alleged to be used regularly in self-treatment.

From our results, the one-dose therapy for acute gonococcal urethritis in men with a single 300 mg. dose of doxycycline is not an acceptable alternate for penicillin in this military community. Whether the ineffectiveness of this particular tetracycline derivative, when used in this fashion, will be noted in other areas where tetracycline is used routinely for treating gonorrhea remains to be seen. The results of this study point out the need for close local evaluation of new drugs and drug treatment schedules before their adoption for routine use.

Three important reasons for treatment failures with penicillin, as discussed by Thayer and Moore (16), are (a) increased resistance to penicillin by some gonococcal strains, (b) mistaken diagnosis of the tribe *Mimea* for *N. gonorrhoeae*, and (c) penicillinase-producing urethral flora.

In 1962, Sokoloff and Goldstein (9), treating patients from Fort Bliss, observed that 2.5 million

Table 3. Penicillin minimal inhibitory concentration (MIC) values for 27 penicillin treatment successes and 5 penicillin treatment failures

Units per ml.	Number of isolates
Treatment successes: ¹	
0.005.....	1
0.01.....	1
0.05.....	4
0.1.....	5
0.15.....	2
0.2.....	3
0.3.....	3
0.4.....	1
0.5.....	1
0.7.....	3
1.0.....	2
1.5.....	1
Treatment failures: ²	
0.5.....	1
0.7.....	3
1.5.....	1

¹ Average MIC equals 0.33 unit per ml.

² Average MIC equals 0.82 unit per ml.

units of procaine penicillin G used in 49 men with acute gonococcal urethritis was 100 percent effective (table 1), although lesser doses produced significant treatment failures. From the results of concomitant in vitro studies, they stated that their clinical discoveries correlated well with the in vitro results, and concluded, "our studies, both in vitro and in vivo, support and document the opinion that the relative resistance to penicillin *N. gonorrhoeae* now displayed is the single causative factor of its frequently reported failure to yield to the usual penicillin regimen." They found no evidence of *Mimea* infections but did not investigate the role of penicillinase-producing organisms in the urethra. Kjellander and Finland (17), however, found no evidence that the presence of penicillinase-producing bacteria in the urethra caused significant treatment failures. Therefore, Sokoloff and Goldstein's conclusions are probably correct.

In the interim 7 years, despite the continued worldwide emergence of strains of *N. gonorrhoeae* with diminished sensitivity to penicillin and the concomitant rise in treatment failures, penicillin G in an intramuscular dose of 2.4 million units, administered either once or twice separated by 24 hours, continues to be the accepted treatment at the William Beaumont General Hospital. A review of 2,492 cases treated here in 1968, diagnosed by smears alone and without close followup, revealed 187 or 8.5 percent treatment failures. Therefore, the 10 percent failure rate experienced with close followup was anticipated.

The penicillin sensitivity studies performed on 32 gonococcal isolates from penicillin-treated patients gave evidence of the increase in relative resistance to penicillin by *N. gonorrhoeae* in the El Paso area since the study performed in 1962 (9). This increase in resistance helped explain the 1970 10 percent failure rate with penicillin treatment of 2.4 million units compared with the 100 percent cure with 2.5 million units in 1962 (9). The average MIC of all 32 isolates was 0.41 units per ml. with a range of 0.005 to 1.5 units per ml. (table 2) compared with an average MIC of 0.121 units per ml. with a range of 0.01 to 0.50 units per ml. reported by Sokoloff and Goldstein (9) from a random selection series of 43 isolates. Eighty-four percent (26 of 32) of our isolates required 0.10 units per ml. or more to inhibit growth, while only 63 percent (27 of 43) of their strains required this concentration. This group was then generally defined as the "relatively resistant" category (9).

The increased failure rate, therefore, is reflected in the increased MIC values encountered in the isolates in our study. The in vitro penicillin MIC values, however, did not correlate precisely with the in vivo clinical response. Although all cases of penicillin failure did result from isolates with high MIC's (0.5 to 1.5 units per ml.) and the average MIC of the treatment failures was 0.82 units per ml. as opposed to an average MIC of 0.33 units per ml. for the successfully treated cases, there were seven isolates with MIC's in the range of 0.5 to 1.5 units per ml. which were treatment successes (table 3). Based upon their in vitro sensitivity testing, these seven isolates might have been expected to be treatment failures.

Another objective of the study was to reassess the role in acute urethritis played by *Mimea* in this community. Despite the report of a study (18) in which this organism caused two-thirds of the cases of acute urethritis, no other large series of urethritis caused by *Mimea* has been recorded, although isolated cases (14) remind us of the possibility. Sokoloff and Goldstein (10) looked for *Mimea* in 195 patients with acute urethritis in this community, but failed to isolate it from any person.

We also looked for *Mimea*. All our cultures had growth on T-M medium before 48 hours, and, although *Mimea* can grow on T-M medium, its appearance is usually retarded (14) or there is no growth whatsoever (16). Furthermore, M-H medium was included in this study primarily to

detect the growth of *Mimea* since it would probably be missed on T-M medium. In no culture, however, was there retarded or absence of growth of an organism on T-M with concomitant growth on M-H medium, which would have been indicative of *Mimea*. Finally, all organisms were taken from pure culture and examined microscopically, and neither the pleomorphism nor the altered Gram staining typical of *Mimea* were seen. It is unlikely, therefore, that *Mimea* plays an important part in acute urethritis in men in this military community.

REFERENCES

- (1) Holmes, K. K., Johnson, D. W., and Floyd, T. M.: Studies of venereal disease. I. Probenecid-procaine penicillin G combination and tetracycline hydrochloride in the treatment of "penicillin-resistant" gonorrhea in men. JAMA 202: 461-466, Nov. 6, 1967.
- (2) Berry, B. E.: Treatment of gonorrheal urethritis evaluated in 230 men. JAMA 202: 657-659, Nov. 13, 1967.
- (3) Lissus, A.: The treatment of gonorrhea with doxycycline as a single dose. Chemotherapy (Basel) 13: 366-368 (1968).
- (4) Domesick, G., McLone, D. G., Scotti, A., and Mackey, D. M.: Use of a single oral dose of doxycycline monohydrate for treating gonorrheal urethritis in men. Public Health Rep 84: 182-183, February 1969.
- (5) Rogers, D. E.: Venereal infections. Yearbook of medicine 1969, Year Book Medical Publishers, Inc, Chicago, 1969, p. 51.
- (6) Steigbigel, N. H., Reed, C. W., and Finland, M.: Susceptibility of common pathogenic bacteria to seven tetracycline antibiotics in vitro. Am J Med Sci 255: 179-195 (1968).
- (7) Phillips, I., et al.: In-vitro activity of twelve antibacterial agents against *Neisseria gonorrhoeae*. Lancet No. 7641: 263-265, Feb. 7, 1970.
- (8) Steigbigel, N. H., Reed, C. W., and Finland, M.: Absorption and excretion of five tetracycline analogues in normal young men. Am J Med Sci 255: 296-312, May 1968.
- (9) Sokoloff, B., and Goldstein, H.: Clinicolaboratory study of acute gonorrhea in men in the El Paso, Tex., area. JAMA 184: 197-200, Apr. 20, 1963.
- (10) Thayer, J. D., Samuels, S. B., Martin, J. E., Jr., and Lucas, J. B.: Comparative antibiotic susceptibility of *Neisseria gonorrhoeae* from 1955 to 1964. In Antimicrobial agents and chemotherapy, 1964, edited by J. C. Sylvester. American Society for Microbiology, Ann Arbor, Mich., 1965, pp. 433-436.
- (11) Fischnaller, J. E., et al.: Kanamycin sulfate in the treatment of acute gonorrheal urethritis in men. JAMA 203: 909-912, Mar. 11, 1968.
- (12) Lucas, J. B., et al.: Treatment of gonorrhea in males with cephaloridine. JAMA 195: 919-921, Mar. 14, 1966.

- (13) Keys, T. F., Halverson, C. W., and Clarke, E. J.: Single-dose treatment of gonorrhea with selected antibiotic agents. *JAMA* 210: 857-861, Nov. 3, 1969.
- (14) Kozub, W. R., et al.: Gonorrhea-like urethritis due to *Mima polymorpha* var. *oxidans*. Patient summary and bacteriological study. *Arch Intern Med* (Chicago) 122: 514-516, December 1968.
- (15) Sokoloff, B.: Demethylchlortetracycline therapy in acute gonococcal urethritis. *Clin Pharmacol Ther* 6: 350-353 (1965).
- (16) Thayer, T. D., and Moore, M. B., Jr.: Gonorrhea: present knowledge, research and control efforts. *Med Clin North Am* 48: 755-765 (1964).
- (17) Kjellander, J. O., and Finland, M.: Penicillin treatment of gonorrheal urethritis. *N Engl J Med* 269: 834-836 (1963).
- (18) Svihus, R. H., Lucero, E. M., Mikolajczyk, M. T., and Carter, E. E.: Gonorrhea-like syndrome caused by penicillin-resistant *Mimeae*. *JAMA* 177: 121-124, July 15, 1961.

SUPPLY REFERENCES

- (A) Kanamycin sulfate, Kantrex, Bristol Laboratories (a division of Bristol-Myers Co.), Syracuse, N.Y. 13201
- (B) Cephaloridine, Loridine, Eli Lilly and Co., 307 E. McCarty St., Indianapolis, Ind. 46206
- (C) Demethylchlortetracycline, Declomycin, Lederle Laboratories (a division of American Cyanamid Co.), Pearl River, N.Y. 10965
- (D) Doxycycline hyclate, Vibramycin, Pfizer Laboratories Division, Pfizer, Inc., 235 East 42d St., New York, N.Y. 10017

JONES, STEPHEN R. (University of Texas Southwestern Medical School, Dallas), and GILLELAND, HARRY E., Jr.: *Using one dose of doxycycline or penicillin to treat men with gonococcal urethritis. HSMHA Health Reports, Vol. 86, September 1971, pp. 849-854.*

A clinical evaluation was performed to compare the use of doxycycline with penicillin in the treatment of acute gonococcal urethritis. Fifty men were treated with single oral doses of 300 mg. of doxycycline (group D), and another 50 men were treated with 2.4 million units of procaine penicillin G intramuscularly (group P). Group D had a treatment failure rate of 38 percent compared with a rate of 10 percent for group P. Hence, the authors believe a single 300 mg. dose of doxycycline is not an acceptable alternate for penicillin therapy for acute gonococcal ure-

thritis in men in the military community studied.

In vitro testing for penicillin and tetracycline sensitivities was performed on 32 gonococcal organisms isolated from the men in group P. The range of minimal inhibitory concentrations (MIC) for these organisms was from 0.005 units per ml. to 1.5 units per ml. penicillin and from 0.25 µg. per ml., to 2.0 µg. per ml. tetracycline. The average MIC for all 32 isolates was 0.41 units per ml. penicillin and 0.94 µg. per ml. tetracycline. The average MIC for the 27 isolates success-

fully treated with penicillin was 0.33 units per ml., whereas the average MIC for the five penicillin treatment failures was 0.82 units per ml. When the results of this study were compared with the results of a study made by Sokoloff and Goldstein in El Paso, Tex., in 1962, these figures indicated an increase in relative resistance to penicillin by *Neisseria gonorrhoeae* in this area. In no case was *Mimeae* isolated; hence, the authors believe that this organism does not play a significant role in acute urethritis in this community.