Alternate Antibiotics for Use in Treatment of Acute Gonorrheal Urethritis in Males

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MANY SPECIAL problems arise in selecting a suitable antibiotic for mass therapy in a venereal disease clinic. It is difficult to get patients to return voluntarily for completion of multiple parenteral treatments. Also, when drugs are dispensed in the clinic for oral use at home, there can be no assurance that patients will follow treatment schedules exactly as prescribed. Ideally, the antibiotic should be therapeutically effective in one easily administered dose, relatively nontoxic, hypoallergenic, and reasonable in cost.

Except for increasing allergic reactions, which vary from relatively benign urticaria to severe anaphylaxis and death, penicillin most closely fits the above criteria for the treatment of gonorrhea. Immediate, severe reactions have been reported for all types of penicillin and all routes of administration (*1,2*). For patients with a history of previous allergy or drug reactions, a 3 to 10 times higher incidence of reaction to penicillin has been reported (*3*). Brown and associates, of the Public Health Service, recently reported that the incidence of penicillin reactions in venereal disease clinic patients increased from 5.95 per 1,000 in 1954 to 9.71 per 1,000 in 1959 (*4*).

Unfortunately, in recent years there has been a diminishing in vitro sensitivity of *Neisseria gonorrhoeae* to penicillin (*5*). Some cases which at first appeared to be completely penicillin resistant were found to be either concurrent infections with penicillinase-producing staphylococci or infections with bacteriologically similar, penicillin-resistant *Mimeae* (*6*). It is still clinically plausible to develop adequate blood levels of penicillin for large-scale therapy, but no one knows how much longer this will be possible.

This paper compares the effectiveness of two types of oral broad-spectrum antibiotics, demethylchlortetracycline and a phosphate complex of tetracycline (with and without amphotericin B), against that of a widely accepted, adequate dose of penicillin.

Methods and Materials

The study included 1,056 male clinic patients diagnosed clinically and bacteriologically as having acute gonorrheal urethritis. They were treated on one of four schedules as follows:

Treatment schedule	*Number patients*
900 mg. demethylchlortetracycline (6 capsules in one dose)	469
1,200,000 units procaine penicillin G in oil with 2 percent aluminum monostearate (PAM) intramuscularly	360
3 gm. tetracycline with amphotericin B (500 mg. orally every 4 hours for 24 hours)	121
3 gm. tetracycline without amphotericin B (500 mg. orally every 4 hours for 24 hours)	106

To stabilize the time factor as much as possible with respect to reinfection rates, the different schedules were given alternately in 1-week periods for 7 months. Since our supply of tetracycline was somewhat limited, tetracycline schedules were alternated into the program less frequently than the other two antibiotics.

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The patients were not told they were subjects for a study, nor were they in any way treated differently from other clinic patients. Those who returned to the clinic because their symptoms either did not subside or reappeared did so voluntarily. Second specimens from all who returned to the clinic were carefully cultured. Patients returning within 30 days whose second cultures proved positive were counted as treatment failures. Because accuracy is impossible, no attempt was made to distinguish between relapse and reinfection.

Results

Treatment failure rates are shown in the table. Patients treated with 3 gm. tetracycline with and without amphotericin B had the lowest percentage of returns after 7 days. None of those given tetracycline with amphotericin B returned, and only one patient, 0.9 percent, given tetracycline alone returned to the clinic. Those treated with demethylchlortetracycline and PAM had return rates of 3.6 percent and 3 percent respectively for the same period.

After 14 days patients treated with tetracycline with amphotericin B again had the lowest return rate, 3.3 percent, and those given tetracycline alone, 4.7 percent. For patients who received PAM and demethylchlortetracycline, the rates were 5.3 percent and 8.5 percent.

At 21 days patient returns were 7.5 percent for those given tetracycline alone; 7.7 percent, PAM; 9.1 percent, tetracycline with amphotericin B; and 10.4 percent, demethylchlortetracycline.

The total return rates for all patients varied within a range of 1.6 percent after 30 days. Those who received tetracycline with amphotericin B and PAM had a cumulative return rate of 10.8 percent, whereas for those given tetracycline alone the rate was only 0.5 percent more, and the cumulative rate was 11.3 percent. The cumulative return rate for patients given demethylchlortetracycline was only 12.4 percent.

Percentage of treatment failures in 1,056 males with acute gonococcal urethritis, by type of antibiotic received and number of days after treatment

Antibiotic	Number patients	Number days after treatment			
		7	14	21	30
Demethylchlortetracycline, 900 mg	469	3. 6	8. 5	10. 4	12. 4
PAM, 1,200,000 units	360	3. 0	5. 3	7. 7	10. 8
Tetracycline with amphotericin B, 3 gm	121	0	3. 3	9. 1	10. 8
Tetracycline without amphotericin B, 3 gm	106	. 9	4. 7	7. 5	11. 3

Comments

Ideally, second specimens from all study patients should be cultured 7 days after treatment. Also, patients should refrain from sexual intercourse during this time. However, only about 50 percent of the patients will voluntarily return to the clinic. Therefore, this drug evaluation was designed so that all conditions would be essentially constant throughout the entire study. Since these patients cannot be controlled as to sexual activity, the problem of treatment failure versus reinfection must be considered. It can be assumed that the reinfection rate is relatively constant when drugs are alternated at weekly intervals. The return rate in this study reflects both the reinfection rate and the treatment failure rate. Variations should reflect the difference in treatment failure rate.

Except for occasional nausea following the large oral dose of demethylchlortetracycline, no toxic or allergic manifestations were observed in the clinic or reported by any of the patients after the ingestion of these broad-spectrum antibiotics. Also, no problems were reported by either private physicians or members of city-county hospital staff who work in close cooperation with this clinic. It should be safe, therefore, to assume that few or no serious problems were caused by the oral drugs.

A comparison of 900 mg. demethylchlortetracycline with 3 gm. of the phosphate complex of tetracycline is perhaps somewhat weighted in favor of the tetracycline. A 6-capsule, 900-mg. dose of demethylchlortetracycline was evaluated because of the obvious advantages of a supervised single-dose oral medication. Tetra-

cycline without amphotericin B and tetracycline with amphotericin B were given in divided doses as requested by the Communicable Disease Center of the Public Health Service, which provided these antibiotics.

While the results from demethylchlortetracycline in a single 900-mg. oral dose fall a little below the other drugs evaluated, the differences were not great.

Although only about one-fourth as many patients were placed on tetracycline without amphotericin B or tetracycline with amphotericin B as the other two drugs, we believe that since the same selection methods were used and since this evaluation was carried out during the same time period, these comparative statistics are of clinical importance. Some investigators consider a 14-day followup period as optimal for evaluating therapeutic agents in acute gonorrheal urethritis of the male. If a 14-day interval is used to compare the antibiotics in this study, it would appear that the tetracycline phosphate preparations in the multiple-dose schedule employed demonstrated results somewhat superior to the other two drugs.

From the results, the alternate antibiotic preparations studied seemed to provide a cure rate similar to that yielded by the widely accepted 1,200,000 units PAM in the treatment of male gonococcal urethritis. Either tetracycline or demethylchlortetracycline should be useful for the treatment of patients with histories of penicillin allergy.

Summary

Because of an increasing incidence of allergic reactions to penicillin as well as evidence that many strains of *Neisseria gonorrhoeae* are evolving which have a diminished sensitivity to penicillin, an evaluation was made of alternate antibiotics administered to males with acute gonorrheal urethritis at a venereal disease clinic.

A comparison of return rates for patients treated with one of three oral broad-spectrum antibiotics, 3 gm. tetracycline without amphotericin B, or 3 gm. tetracycline with amphotericin B, or 900 mg. demethychlortetracycline, with the return rate of those treated with 1,200,000 units PAM, revealed that the effectiveness of these oral antibiotics closely approximated that of PAM.

NOTE: Demethylchlortetracycline was supplied for this evaluation by Lederle Laboratories, Pearl River, N.Y., and tetracycline with and without amphotericin B was supplied by the Communicable Disease Center of the Public Health Service.

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