Gonorrheal Urethritis in Males Treated With a Single Oral Dose of Minocycline

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THE EFFICACY of penicillin for the treatment of gonorrhea is waning. Increasing resistance of the gonococcus to penicillin during the past 20 years has forced escalation of the recommended dose from 160,000 units to 2,400,000 units for males and 4,800,000 units for females.

Sulfonamides were widely used to treat gonorrhea at the end of the 1930's. Resistance of gonococci to sulfonamides today, however, is so great that by themselves they are no longer useful.

We believe it is essential to try new drugs as the incidence of gonorrhea in the United States continues to increase, and the susceptibility of the gonococcus to penicillin continues to decrease.

Minocycline, manufactured by Lederle Laboratories, is composed of 7-dimethylamino-6-deoxy-6-dimethyltetracycline. Steigbigel and co-workers (*1*) stated that average serum concentrations in normal subjects after a single oral dose of 150 mg. or 300 mg. of minocycline were as follows.

Hours after dose	*Serum level in μg. per ml. after—*	
	150 mg. in 8 subjects	*300 mg. in 2 subjects*
2	2. 19	4. 01
4	1. 85	3. 95
8	1. 40	3. 08
24	. 53	1. 15
48	. 19	. 56

During in vitro studies of 25 *Neisseria gonorrhoeae* strains, these investigators noted that minocycline had a susceptibility range of 0.19–3.1 μg. per ml. with a median of 0.39 μg. per ml. Among the tetracycline antibiotics which included methacycline, doxycycline, chlortetracycline, demethylchlortetracycline, oxytetracycline, and tetracycline, minocycline was the most active with 20 of the 25 strains being inhibited at 0.4 μg. per ml. or less (*2*).

Martin, using 45 gonococcal strains isolated from persons whose therapy with penicillin had failed, showed that minocycline had a susceptibility range of 0.125 to 1.0 μg. per ml. with an approximate mean of 0.225 μg. per ml. Both tetracycline and doxycycline had the same range of 0.125 to 2.0 μg. per ml., but their approximate means were 0.25 μg. per ml. for tetracycline and 0.35 μg. per ml. for doxycycline (*3*).

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Susceptibility (μg. per ml.) of 45 penicillin resistant gonococcal strains was as follows.

Drug	Range	Approximate mean
Minocycline	0. 125–1. 0	0. 225
Tetracycline	. 125–2. 0	. 25
Doxycycline	. 125–2. 0	. 35

Complete inhibition occurred at 1.0 μg. per ml. of minocycline in all cultures that required 2.0 μg per ml. of both tetracycline and doxycycline (*3*).

Based on the previously mentioned in vivo blood levels and in vitro sensitivity data, a clinical trial of a single oral dose of 200–300 mg. should show minocycline to be highly effective against *N. gonorrhoeae.*

Methods and Procedures

Two hundred seventy-two consecutive male patients coming for treatment of a urethral discharge at the Fulton County Health Department, Atlanta, Ga., during July and August 1968 were selected for this study.

The urethral exudate from each patient was initially gram stained and observed for typical intracellular gram-negative diplococci. Presence of the typical diplococci was considered presumptive evidence of gonorrheal urethritis.

The exudate from each patient was cultured on Thayer-Martin selective medium. The cultures were incubated in a candle jar at 37° C. and examined in 24 hours. Identification of *N. gonorrhoeae* was made by typical colonies growing on Thayer-Martin medium that had a positive oxidase reaction showing characteristic gram-negative diplococci (*4*).

Patients who had a presumptive diagnosis of gonorrheal urethritis by a positive gram stain were given a 200 mg., 300 mg., or 400 mg. single oral dose of minocycline.

Each patient given minocycline was instructed to return to the clinic in 48 hours. Patients who returned between 48 and 96 hours after treatment were questioned carefully and examined for signs and symptoms of gonorrheal urethritis. Any ill effects of the drug were carefully noted. Patients returning after 96 hours were excluded from the study.

An intraurethral scraping was obtained from all returning patients who had a positive pretreatment culture by use of a 2 mm. platinum wire loop. Culture plates of Thayer-Martin selective medium were immediately inoculated with the scrapings. A culture with negative results was considered evidence of cure. A positive culture was considered a treatment failure even if the patient had no discharge.

Results

Results of treating 272 patients with 200 mg., 300 mg., and 400 mg. doses of minocycline were as follows.

Single oral dose	Patients treated	Failures	Returnees	Percent cure of returnees
200 mg	100	5	64	92. 2
300 mg	137	5	110	95. 5
400 mg	35	1	22	95. 5

The 200 mg. dose was given to 100 patients whose cultures were positive, of whom 64 returned. Treatment of five persons failed, and 92.2 percent were considered cured. No side effects were observed at this level.

The 300 mg. dose was given to 137 patients with positive cultures, of whom 110 returned. Treatment of five failed, and 95.5 percent were considered cured. Fifteen of the 110 returnees had mild nausea several hours after treatment. No other side effects were observed.

The 400 mg. dose was given to 35 patients with positive cultures, of whom 22 returned. Treatment of one failed, and 95.5 percent were considered cured. Eleven of the 22 returnees noticed mild to moderate nausea several hours after treatment; nine of these also noticed mild lightheadedness.

None of the patients vomited at any of the three dose levels. Several patients at all three dose levels had a slight clearing discharge that was culture negative.

Discussion

In the treatment of gonorrhea, it is important to have an agent that is effective in a single-dose form since venereal disease patients are unreliable in keeping return appointments and in taking medication at home at prescribed times. Also, oral medication is preferred by many physicians because of its ease of handling and patient acceptance.

Tetracycline has been shown to be more than 90 percent effective in the treatment of gonococcal urethritis in men (*5*); however, followup doses every 4 to 6 hours for 4 days after an initial 1.5 gram dose is recommended by the Public Health Service (*6*).

Certain penicillins have been shown to be more than 90 percent effective in a single-dose regimen. These penicillins must be given by injection, however, and approximately 1 percent of venereal disease patients have severe or fatal reactions to them (*7*). The risk of such reactions must be weighed when many patients are treated daily with penicillin.

Minocycline was given to the 272 male patients with uncomplicated gonococcal urethritis. It has the advantage of being a nonpenicillin drug that is 92.2 to 95.5 percent effective when given in a single oral dose of 200 mg. to 300 mg. At these dosage levels minimal side effects were noticed. Increasing the dosage to 400 mg. increased both the incidence and the severity of these side effects. In this study, those patients treated who did not return were not included in the percentage of those cured. Assuming that many of these nonreturnees were cured, which has been the authors' experience in the past, the cure rate would be higher than 92.2 to 95.5 percent.

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Tearsheet Requests

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