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Single-Dose Trospectomycin for Chlamydial Urethritis in Men

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Trospectomycin is an aminocyclitol analog of spectinomycin with significant in vitro activity against *Chlamydia trachomatis*. A single 1-g intramuscular dose was administered to 10 men with symptomatic, culture-positive chlamydial urethritis. Trospectomycin was well tolerated but failed to eradicate chlamydial infection, as determined by cultures obtained approximately 1 week after treatment.

Infection caused by *Chlamydia trachomatis* is currently considered the most common sexually transmitted disease in the United States (2). The current Centers for Disease Control recommendation for the treatment of most chlamydial infections is a 7-day regimen of doxycycline, tetracycline, or erythromycin or a 10-day regimen of sulfisoxazole, each given multiple times daily (3). Lack of compliance with similar regimens has been shown to be associated with treatment failure among patients with gonococcal urethritis (7) and can be expected to present similar problems in the control of chlamydial disease as well. Thus, optimal treatment of this infection would be an effective, well-tolerated drug which could be administered as a single dose under medical supervision.

Trospectomycin is a derivative of the aminocyclitol antibiotic spectinomycin and has been shown to have in vitro activity against *C. trachomatis* and many gram-positive and gram-negative bacteria, including *Neisseria gonorrhoeae* (19). In addition, it is approximately 10 times more active in vitro than spectinomycin against *C. trachomatis* (19), and pharmacokinetic data obtained with animals and humans (1) as well as studies with the female mouse model (10) suggest that an abbreviated course of trospectomycin might be effective treatment for chlamydial genital tract infections. On the basis of these data, the present, open study was designed to assess the efficacy and toxicity of a single 1-g dose of trospectomycin given intramuscularly in the treatment of uncomplicated *C. trachomatis* urethritis in men.

(This work was presented in part at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, Calif., 1988.)

Adult men, 18 to 60 years of age, with symptomatic chlamydial urethritis were enrolled in the study. Histories were obtained and genital examinations were performed at study entry, at days 4 to 8, and at days 21 to 28. Blood and urine samples for routine studies including complete blood count with differential, platelet count, urinalysis, and tests of hepatic and renal function were obtained at the first two visits. Urethral swabs were obtained at entry for Gram stain, direct fluorescent-antibody testing with the Syva Microtrak *Chlamydia trachomatis* Direct Specimen Test (Syva Co., Palo Alto, Calif.), and culture for *C. trachomatis* and *N. gonorrhoeae*. Culture and identification of *N. gonorrhoeae* were performed with Martin-Lewis plates as previously described (15, 17). Specimens for chlamydia cultures were transported in 2-sucrose phosphate buffer, and cultures were performed with McCoy cell monolayers as described previously (17). The MICs of trospectomycin and tetracycline were determined for chlamydial isolates obtained from each patient before and after trospectomycin administration and, in parallel, for a control strain, kindly provided by Josephine Ehret (Department of Health and Hospitals, Division of Public Health, Denver, Colo.) (5). The MIC was considered the lowest concentration of antibiotic that produced complete suppression of iodine-stained-inclusion formation. After initial cultures were obtained, all study patients were treated with 1 g of trospectomycin administered intramuscularly in a 3.3-ml volume. Patients were instructed to abstain from sexual intercourse or to use condoms while enrolled in the study. Cultures of urethral swabs were repeated at each follow-up visit.

Ten patients were enrolled. All had chlamydial elementary bodies detected by direct fluorescent-antibody testing of their urethral smears, and all had chlamydial infection confirmed by culture. Ages ranged from 18 to 42 years with a mean of 24 years. Five patients were white, five were black, and all were heterosexual. At the follow-up visit on days 4 to 8, all 10 patients remained culture positive for chlamydia, and no significant differences in the magnitude of iodine-stained-inclusion counts were observed in cultures of specimens obtained at the first two visits. However, patients frequently reported less discharge than at entry, although all complained of at least one persisting symptom, usually tingling or itching of the urethra. At the follow-up visit on days 21 to 28, cultures from six of eight patients remained positive for chlamydia. The remaining two patients had received intervening tetracycline therapy. Two patients also had *N. gonorrhoeae* isolated from their urethras at study entry. Specimens obtained from both at the next visit were culture negative. MICs for *C. trachomatis* isolates were consistently 4 to 8 μg/ml for trospectomycin and 0.1 to 0.2 μg/ml for tetracycline. No significant differences in susceptibility between isolates obtained from individual subjects before and after trospectomycin administration were observed. No serious toxicities from the administration of trospectomycin were observed. However, temporary local discomfort was associated with the intramuscular injection in nine patients, and four patients complained of perioral tingling or numbness, which resolved spontaneously within 1 to 4 h after the injection. No significant abnormalities were revealed by laboratory tests.

In this study, we were unable to demonstrate any antimicrobial effects of a single 1-g dose of trospectomycin admin-

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istered intramuscularly for *C. trachomatis* urethritis in 10 symptomatic, heterosexual men. Although there appeared to be some modification of symptoms, the lack of a placebo control group does not allow differentiation of our observations from the natural course of untreated chlamydial urethritis. The lack of efficacy which we observed could not be explained by increased resistance to trospectomycin among our clinical isolates. Trospectomycin was generally well tolerated, although self-limited facial paresthesias were seen at a frequency similar to that reported in a previously conducted phase I trial (11).

Historically, several clinical studies have examined the effectiveness of other antibiotics given in a single dose for the treatment of chlamydial urethritis (4, 8, 9, 12–14, 18). Most have been done as parts of evaluations of single-dose therapy for concomitant gonococcal urethritis. None of these studies has demonstrated efficacy rates which would allow these regimens to supplant the use of the multiple-dose schedules for routine treatment of chlamydial urethritis. The complex replication cycle of *C. trachomatis* requires approximately 48 h for completion (16) and probably represents the major factor contributing to the failure of single-dose antibiotic therapy, inasmuch as most single-dose regimens do not produce adequate levels of active drug at the site of infection for prolonged periods. More recent clinical studies of a new antibiotic of the azalide class, azithromycin, have yielded favorable results, suggesting that a single-dose regimen may be feasible (6). Our study of a single 1-g intramuscular injection of trospectomycin demonstrated that this drug is ineffective for treatment of symptomatic, uncomplicated chlamydial urethritis in men. However, further studies to evaluate alternative dosage regimens of this antibiotic in the treatment of chlamydial disease may be indicated.

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