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NOTES

Orally Administered Cefpodoxime Proxetil for Treatment of Uncomplicated Gonococcal Urethritis in Males: a Dose-Response Study

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An open-label, dose-response study of cefpodoxime proxetil (CPD), an expanded-spectrum cephalosporin, was conducted with 58 males with uncomplicated *Neisseria gonorrhoeae* infections with single doses of 600, 400, 200, 100, or 50 mg of CPD administered orally by tablet. CPD eradicated *N. gonorrhoeae* in all 50 evaluable patients (10 per group) at all doses studied. Eight of the isolates eradicated were β-lactamase-producing organisms. Two patients reported three side effects, nausea, vomiting, and diarrhea, which were mild and resolved without intervention or sequelae. There were no clinically remarkable drug-related changes in vital signs or clinical laboratory assays. Results show that single oral doses of CPD are an effective and well-tolerated treatment for uncomplicated *N. gonorrhoeae* infection in males at doses as low as 50 mg.

Cefpodoxime proxetil (U-76,252) (CPD), an orally administered, expanded-spectrum cephalosporin with a broad spectrum of antimicrobial activity (2, 7, 9, 11), has been shown to be active against both penicillinase-producing and non-penicillinase-producing strains of *Neisseria gonorrhoeae* (2). Cefpodoxime is resistant to most β-lactamases but is not itself a β-lactamase inhibitor. In vitro studies of the activity of CPD against multiple strains of *N. gonorrhoeae* have shown excellent activity. The MICs of CPD for β-lactamase-negative strains were ≤0.008 μg/ml for 42 strains and ≤0.06 μg/ml for 33 strains. For β-lactamase-positive isolates, the MICs of CPD were ≤0.06 μg/ml for 25 strains and 0.015 μg/ml for 24 strains (9).

The present study was an open-label, uncontrolled study in which males with uncomplicated *N. gonorrhoeae* infection were treated with single doses of 600, 400, 200, 100, or 50 mg of CPD administered orally in tablets (dose expressed in CPD equivalents).

The protocol was approved by an institutional review board, and each participant gave written informed consent. Male patients with urethral discharge and Gram stains with gram-negative intracellular diplococci were enrolled. Exclusions included patients less than 18 or more than 60 years of age, patients with known allergy to β-lactam antibiotics or probenecid, patients with coexisting syphilis (clinically or serologically diagnosed), patients who received antibiotic therapy ≤14 days prior to enrollment, patients with active symptoms of other serious illness, patients with complications of *N. gonorrhoeae* infection (e.g., epididymitis, septic arthritis, or disseminated *N. gonorrhoeae*), and patients who were previously enrolled in this study (reinfection or relapse) or who were receiving any other investigational drugs.

Beginning with the 600-mg dose group, the groups were run sequentially. The dose was reduced to the next sequential level when the bacterial eradication rate at the preceding level was ≥90% (i.e., 9 or 10 cures among 10 subjects). When the eradication rate was ≤80%, the dose was not to be reduced; rather, the subsequent group of 10 patients was to receive the same dose of CPD preceded immediately by 1.0 g of probenecid given orally. Because 100% eradication of *N. gonorrhoeae* was achieved at each planned dose, probenecid was not given, and a 50-mg dose of CPD was evaluated instead. All patients received the medication after a light snack (3–5).

A pretreatment culture for *N. gonorrhoeae* was obtained, and Gram stains were made from urethral samples. The presence or absence of *Chlamydia trachomatis* from the urethra was determined by a fluorescent-antibody test (10). When appropriate, cultures for *N. gonorrhoeae* were to be obtained from other sexually exposed sites, (i.e., the pharynx or anus). Patients were considered nonevaluable if they did not abstain from sexual intercourse or if they took any other medication effective against sexually transmitted diseases before the posttreatment evaluation. If a patient used condoms, however, he remained evaluable.

At the posttreatment visit (4 to 9 days after therapy), a test-of-cure culture was obtained from each patient to determine the presence or absence of *N. gonorrhoeae*. Those patients who were culture positive for *N. gonorrhoeae* posttreatment were to be considered treatment failures and were to be retreated with an antibiotic chosen by the investigator. The presence or absence of *C. trachomatis* infection was evaluated by a fluorescent-antibody test for all patients whose samples tested positive for *C. trachomatis* pretreatment and for those patients who had clinical signs and symptoms of postgonococcal urethritis (10). Any patient with evidence of nonspecific urethritis or with a positive test for *C. trachomatis* was to be treated accordingly after the final evaluation at the discretion of the investigator. The investigator noted whether a discharge at the site(s) of infection was present and, if so, whether it was purulent or nonpurulent.

Specimens for *N. gonorrhoeae* culture were obtained from the first 1 to 2 cm of the anterior urethra by means of a

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Calgiswab or small, smooth platinum wire loop and were streaked on modified Thayer-Martin medium or Martin-Lewis medium within 30 min and placed in CO_2.

Oxidase-positive colonies of gram-negative diplococci with a colony morphology characteristic of *N. gonorrhoeae* were accepted as presumptive identification. All isolates were tested for β-lactamase activity by using the iodometric method, although use of the chromogenic cephalosporin test of O'Callaghan was recommended (8). In addition, the MICs of CPD, amoxicillin, ceftriaxone, tetracycline, and trospectomycin for all isolates were determined by the agar plate dilution technique at a laboratory chosen by the investigator.

Fifty-eight male patients between the ages of 18 and 46 years (means for groups ranged from 24.2 to 27.4 years) enrolled in this study, and 50 were considered evaluable (10 per group). Of the evaluable patients, 48 were diagnosed with uncomplicated *N. gonorrhoeae* and two had *N. gonorrhoeae* and nongonococcal urethritis. *N. gonorrhoeae* was not isolated from any site other than the urethra among the patients enrolled. The dose groups did not differ statistically from one another with respect to age, weight, or height. Among the evaluable patients, 32% (16 men) had had one previous occurrence of *N. gonorrhoeae* infection and 14% (12 men) reported having between two and six previous occurrences. Eight patients were considered nonevaluable for the following reasons: (i) seven patients failed to return for the posttreatment evaluation, and (ii) one patient did not abstain from sex or use condoms.

Eradication of *N. gonorrhoeae* (100%) was achieved for every evaluable patient in each dose group. The one nonevaluable patient who did not abstain from sex or use a condom had a positive test-of-cure culture, which was β-lactamase positive. Eight other patients from the following dose groups had β-lactamase-positive organisms eradicated: the 50-mg group (two patients), the 200-mg group (one patient), the 400-mg group (two patients), and the 600-mg group (three patients). Two patients had *C. trachomatis* identified in their pre- and posttreatment urethral specimens, while *C. trachomatis* was present posttreatment only in five patients.

Only three side effects of mild intensity were reported by two patients. One patient in the 200-mg dose group experienced nausea and vomiting, probably not related to the study medication, for 2 h, and one patient in the 400-mg dose group had diarrhea, possibly related to the study drug, for 1 day. Otherwise, there were no clinically remarkable drug-related changes in vital signs or clinical laboratory assays.

In this study, CPD achieved 100% eradication of *N. gonorrhoeae*, including eight β-lactamase-positive strains, when administered orally in single doses as low as 50 mg. A 200-mg dose of CPD was chosen for further evaluation in treatment of gonococcal urethritis in phase III studies on the basis of the efficacy achieved in this study, the plasma half-life (2.45 h), the peak concentration in plasma (2.3 μg/ml), and the maximal reported MICs (1, 6, 9). Although lower doses (i.e., 50 and 100 mg) were also safe and effective, the 200-mg dose was chosen with the intent to delay potential development of resistant strains of GC.

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