Comparative Efficacy of Piperacillin and Penicillin G in Treatment of Gonococcal Urethritis

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The comparative efficacy of 2 g of piperacillin and 4.8 \times 10^6 \text{U} of penicillin G in the treatment of uncomplicated gonococcal urethritis was assessed in a randomized prospective study. Sixty-five evaluable patients received piperacillin, and 55 received penicillin G. All patients received 1 g of probenecid before therapy. All of the evaluable patients receiving either therapy were cured of gonorrhea. We conclude that piperacillin is as efficacious as aqueous procaine penicillin G in the therapy of uncomplicated gonococcal urethritis.

Piperacillin is a new semisynthetic penicillin with a wide spectrum of antibacterial activity against gram-negative and gram-positive aerobic and anaerobic bacteria (7). Thornsberry et al. (4) showed that piperacillin was the most active \(\beta\)-lactamase-resistant antibiotic against gonococci. There have been no clinical studies published to date, however, which assess the efficacy of piperacillin in the treatment of gonococcal urethritis. This study was designed in a prospective, randomized manner to compare the effectiveness of piperacillin and procaine penicillin G in the treatment of uncomplicated gonococcal urethritis in men.

Male patients with symptoms and signs compatible with uncomplicated gonococcal urethritis were solicited for entry into this study at the Alachua County Venereal Diseases Clinic in Gainesville, Fla. Those with a urethral exudate positive for intracellular diplococci by Gram stain (later confirmed by culture) were enrolled in the study unless concomitant syphilis or complicated gonorrhea were suspected or there was a history of penicillin allergy. After informed consent was obtained, the patients were randomly assigned by computer to one of two treatment groups. Group I received 2 g of piperacillin in 6.6 ml of 0.5% lidocaine administered intramuscularly in two sites. Group II received 4.8 \times 10^6 \text{U} of procaine penicillin G, also administered in two sites. Both groups received 1 g of probenecid orally before therapy. Patients were re-evaluated at 7 to 10 days after therapy for clinical and bacteriological cure.

Pre- and posttherapy urethral specimens were plated on Thayer-Martin medium. Gonococci were identified by oxidase test and appropriate carbohydrate utilization tests. Additional laboratory studies before therapy and at follow-up visit included serum hemoglobin, total leukocyte count, differential, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, serum alkaline phosphatase, blood urea nitrogen, serum creatinine, and urinalysis.

Minimal inhibitory concentrations (MICs) of penicillin G and piperacillin for each isolate were determined by the agar dilution technique (6) and the Steers replicator (3), using GC medium base supplemented with 1% hemoglobin and 1% supplement B (Difco Laboratories, Detroit, Mich.). Each isolate was examined for \(\beta\)-lactamase production by using Beta-Lactam Reagent Disks (Marion Scientific Corp., Kansas City, Mo.).

A total of 142 courses of therapy were given to 127 patients. Recurrent infections occurred in 11 patients who received two courses and in 2 patients who received three courses. Both treatment groups were comparable with respect to race, mean age (25 years versus 24 years), and length of time to onset of clinical symptoms from last sexual contact (3.8 days versus 3.9 days).

All patients who returned for test of cure and who denied new sexual contacts during the follow-up period achieved clinical cure and bacteriological eradication of Neisseria gonorrhoeae. Calculation of the 95% limits of the failure rates revealed these to be 5 per 100 for each antibiotic. Patients who did not return for test of cure were considered non-evaluable. In addition, patients who showed persistence of susceptible \textit{N. gonorrhoeae}, but who admitted to reexposure before the follow-up visit, were also considered non-evaluable. The duration of time to complete resolution of clinical symptoms was comparable in both treatment groups (2.4 versus 2.0 days).
There were cases of postgonococcal urethritis in both treatment groups (seven patients in group I versus three patients in group II) as defined by continued symptoms of urethritis, thin discharge containing inflammatory cells, and negative smear and culture for *N. gonorrhoeae*. No adverse or toxic drug reactions were encountered in either group. Piperacillin was well tolerated and produced no undue local pain. In general, it may have been slightly less painful than penicillin G. There were no abnormal laboratory results noted at follow-up, and there was no difference in the clinical course with either regimen. No β-lactamase-producing organisms were found. A summary of the results of treatment with these regimens is shown in Table 1.

The in vitro inhibitory activity of piperacillin compared with penicillin G against the clinical isolates is shown in Fig. 1. Piperacillin (mean MIC, 0.007 μg/ml) had a 10- to 16-fold greater activity than penicillin G (mean MIC, 0.102 μg/ml) against *N. gonorrhoeae*.

A previous in vitro study showed that piperacillin is generally more active than other penicillins against both β-lactamase-negative and β-lactamase-positive gonococci (4). In addition, pharmacokinetic studies in normal human subjects showed that a single intramuscular 2-g dose of piperacillin alone achieves high mean peak serum levels (30 μg/ml at 1 h postinjection) which are greatly in excess of the MIC for *N. gonorrhoeae*. As with penicillin G, oral probenecid given before piperacillin administration increases the peak serum concentration and prolongs the serum half-life of piperacillin (5). In a recent trial, Viray-Zarbo et al. (L. Viray-Zarbo, M. Del Casal, and P. G. Gooding, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 482, 1980) prospectively studied the use of a single intramuscular 2-g dose of piperacillin in 200 female subjects with β-lactamase-negative and β-lactamase-positive *N. gonorrhoeae*. They noted that 148 of 148 cases with β-lactamase-negative infection and 50 of 52 cases with β-lactamase-positive infection were cured. The two remaining cases were suspected of reexposure and reinfection.

We have shown that parenteral piperacillin is as efficacious as parenteral procaine penicillin G in producing clinical and bacteriological cure of gonorrhea. The MICs, however, indicate 10- to 16-fold greater activity of piperacillin as compared to penicillin G against isolates of *N. gonorrhoeae*. These in vitro results compare favorably with those of Thornsberry et al. (4).

An increase in number of cases of penicillinase-producing *N. gonorrhoeae* has been reported from Los Angeles County, Calif. (2) and the United States in general (1). The data from the Philippine study (Viray-Zarbo et al., 20th ICAAC, abstr. no. 482, 1980) suggest that piperacillin should be studied as a suitable alternative to spectinomycin in the treatment of penicillinase-producing *N. gonorrhoeae*. It is likely that the cost of a 2-g dose of piperacillin will be higher than the standard recommended dose of procaine penicillin G. Since piperacillin shows 10- to 16-fold greater in vitro activity against gonococci, however, it may be possible to reduce the therapeutic dose of piperacillin without compromising clinical efficacy.

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**LITERATURE CITED**


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