ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1990, p. 371–372
0066-4804/90/020371-02$02.00/0

Vol. 34, No. 2

In Vitro Activity of Cefpodoxime Proxetil (U-76,252; CS-807) against *Neisseria gonorrhoeae*

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Received 31 July 1989/Accepted 26 October 1989

Cefpodoxime proxetil is an oral cephalosporin antibiotic. The in vitro activities of cefpodoxime (the active metabolite of cefpodoxime proxetil), ceftriaxone, and cefuroxime against both antibiotic-susceptible and antibiotic-resistant clinical isolates of *Neisseria gonorrhoeae* were determined. Cefpodoxime inhibited all penicillin-susceptible strains and penicillinase-producing strains at ≤0.015 μg/ml; chromosomally resistant strains were inhibited by cefpodoxime at ≤0.125 μg/ml.

The emergence of antibiotic-resistant *Neisseria gonorrhoeae* is a significant worldwide problem. The Centers for Disease Control, Atlanta, Ga., have recently established policy guidelines for the detection, management, and control of resistant strains (1). Their recommendations include the use of the parenterally administered, β-lactamase-stable ceftriaxone as the drug of choice in areas where penicillinase-producing *N. gonorrhoeae* (PPNG) accounts for 1% or more of all gonorrheal isolates. New cephalosporins have been synthesized that are highly potent, β-lactamase stable, and well absorbed when given orally. These may provide alternatives to parenteral cephalosporin therapy for infections caused by resistant strains of gonococci (R. N. Jones, Antimicrob. Newsl. 5:1–7, 1988).

Two such agents are cefpodoxime proxetil (U-76,252; CS-807), a new broad-spectrum, esterified cephalosporin antibiotic which is well absorbed when given orally, and cefuroxime axetil, the oral-dosage form of cefuroxime sodium. After oral administration, cefpodoxime proxetil is hydrolyzed to its active metabolite, cefpodoxime (U-76,253), by the intestinal wall esterases (2). The β-lactamase stability of cefpodoxime (4; Jones, Antimicrob. Newsl., 1988) and its potent activity against both PPNG and non-PPNG (B. H. Yagi and G. E. Zurenko, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 657, 1987) prompted us to evaluate the in vitro activity of cefpodoxime against antibiotic-resistant strains of *N. gonorrhoeae* and compare it with those of ceftriaxone and cefuroxime.

A total of 105 *N. gonorrhoeae* clinical cultures was obtained from the following sources: Centers for Disease Control (20 strains); *Neisseria* Reference Laboratory, Harborview Medical Center, Seattle, Wash. (62 strains); Kalamazoo County Department of Public Health and Bronson Methodist Hospital, Kalamazoo, Mich. (14 strains); and a small number of miscellaneous strains. Isolates were grouped according to their antibiotic resistance on the basis of Centers for Disease Control susceptibility guidelines (1). Isolates resistant to penicillin (MIC, ≥1 μg/ml) included PPNG and chromosomally resistant *N. gonorrhoeae* (CMRNG). The tetracycline-resistant strains demonstrated chromosomal-type resistance (MIC, ≥1 μg/ml); spectinomycin-resistant strains were of the typical high-level resistance type (MIC, ≥64 μg/ml).

The following antimicrobial agents were tested: cefpodoxime proxetil (tested as cefpodoxime sodium [U-76,253A]; The Upjohn Co., Kalamazoo, Mich.); cefuroxime axetil (tested as cefuroxime sodium; Glaxo Pharmaceuticals, Research Triangle Park, N.C.); ceftriaxone (Roche Laboratories, Nutley, N.J.); tetracycline (tetracycline hydrochloride; Sigma Chemical Co., St. Louis, Mo.); and spectinomycin hydrochloride (The Upjohn Co.).

MICs were determined by using a twofold serial agar dilution method (5) with supplemented Proteose agar medium (Proteose no. 3 agar [Difco Laboratories, Detroit, Mich.] supplemented with 1% bovine hemoglobin [BBL Microbiology Systems, Cockeysville, Md.] and 1% IsoVitaleX [BBL]). The inoculum was prepared from cultures which were grown overnight in a candle jar at 35°C on supplemented Proteose agar. Cell suspensions were prepared in Trypticase soy broth (BBL) so that the final inoculum delivered to each plate were approximately 10^4 to 10^5 CFU per spot. The plates were incubated in a jar with CO_2 GasPaks (BBL) at 35°C for 20 h.

Table 1 presents the MIC range and the MICs for 50 and 90% of strains tested (MIC_{50} and MIC_{90}, respectively) of each antibiotic for comparison of susceptibility among the four groups of isolates. All three cephalosporins demonstrated potent activity against penicillin-susceptible isolates (Table 1). Cefpodoxime and ceftriaxone were the most active compounds (MIC_{90}, ≤0.008 μg/ml), while cefuroxime was significantly less active (MIC_{90}, 0.125 μg/ml). The activities of these penicillinase-stable cephalosporins against PPNG are shown (Table 1). Both cefpodoxime and ceftriaxone were highly active against PPNG isolates, with MIC_{90}s of 0.015 and ≤0.008 μg/ml, respectively; cefuroxime, with an MIC_{90} of 0.125 μg/ml, was considerably less active against this group of isolates, although this value is still well within the cefuroxime-susceptible range. All of the cephalosporins were active against CMRNG isolates. Ceftriaxone (MIC_{90}, 0.03 μg/ml) was the most active compound, followed by cefpodoxime (MIC_{90}, 0.125 μg/ml) and cefuroxime (MIC_{90}, 1.0 μg/ml). A comparison of MIC_{90}s for the penicillin-susceptible and CMRNG groups demonstrated a significant increase in the MIC_{90} of each of the three cephalosporins for CMRNG. However, these results still fall within the susceptible range of these drugs. The results for a group of 13 spectinomycin-resistant strains, which were universally susceptible to the cephalosporins tested, are summarized in Table 1. Cefpodoxime, ceftriaxone, and cefuroxime yielded MIC_{90}s of 0.015, ≤0.008, and 0.125 μg/ml, respectively.

Cefpodoxime exhibited activity comparable to, or slightly less than, the activity of the parenteral drug ceftriaxone

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TABLE 1. Antibiotic susceptibility of *N. gonorrhoeae*

Susceptibility group (no. of isolates)[a]	Antibiotic	MIC (μg/ml)[b]		
		Range	50%	90%
PenS (28)	Cefpodoxime	≤0.008–0.015	≤0.008	≤0.008
	Cefuroxime	≤0.008–0.125	≤0.008	0.125
	Ceftriaxone	≤0.008	≤0.008	≤0.008
	Tetracycline	0.125–1	0.25	0.5
PPNG (32)	Cefpodoxime	≤0.008–0.015	≤0.008	0.015
	Cefuroxime	≤0.008–0.25	0.03	0.125
	Ceftriaxone	≤0.008	≤0.008	≤0.008
	Tetracycline	0.125–4	1	4
CMRNG (32)	Cefpodoxime	≤0.008–0.125	0.03	0.125
	Cefuroxime	≤0.008–1	0.25	1.0
	Ceftriaxone	≤0.008–0.03	≤0.008	0.03
	Tetracycline	1–8	4	4
SPR (13)	Cefpodoxime	≤0.008–0.015	≤0.008	0.015
	Cefuroxime	≤0.008–0.5	0.015	0.125
	Ceftriaxone	≤0.008	≤0.008	≤0.008
	Tetracycline	0.125–8	1	2
	Spectinomycin	>256	>256	>256

[a] PenS, Penicillin susceptible; CMRNG, chromosomally resistant to tetracycline or to both tetracycline and penicillin; SPR, spectinomycin resistant.
[b] 50% and 90%, MIC for 50 and 90% of isolates, respectively.

against all susceptibility groups. Potent activity against antibiotic-resistant *N. gonorrhoeae* was demonstrated by cefpodoxime and cefuroxime, the two oral drugs; however, the MIC_{90}s of cefpodoxime were eightfold lower than those for cefuroxime. Cefpodoxime inhibited all CMRNG at 0.125 μg/ml or less and 90% of PPNG, penicillin-susceptible isolates, and spectinomycin-resistant isolates at 0.015 μg/ml or less. The MIC range of cefixime, the recently marketed oral cephalosporin, for PPNG has been reported in the literature as ≤0.01 to 0.1 μg/ml (3).

Clinical pharmacokinetic studies with 200-mg oral doses of cefpodoxime proxetil demonstrated peak cefpodoxime concentrations in plasma of 2.4 ± 0.75 μg/ml, with a half-life of 2.7 h (data on file; The Upjohn Co.). Concentrations in plasma in excess of the highest MIC_{90} recorded in our in vitro study (0.125 μg/ml for CMRNG) were maintained for approximately 15 h following a single dose, making cefpodoxime proxetil a candidate for oral treatment of resistant gonorrhea. The 200-mg single-oral-dose regimen is being evaluated in phase II clinical trials of gonorrhea.

We thank J. Biddle (Centers for Disease Control), H. Larsen (Kalamazoo County Department of Health), A. Erlandson (Bronson Methodist Hospital), and R. Rice (*Neisseria* Reference Laboratory) for providing the *Neisseria* isolates used in this study and V. Taylor, R. Clarke, and M. Meissner for assistance in manuscript preparation.

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