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In Vitro Activity of HR 756, a New Cephalosporin, Against *Neisseria gonorrhoeae*

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The in vitro activity of HR 756 was compared with penicillin, cefamandole, cefoxitin, and tetracycline against *Neisseria gonorrhoeae*. A total of 192 randomly selected isolates (of which 23 had minimal inhibitory concentrations of ≥0.5 μg/ml for penicillin) and three β-lactamase-producing isolates were tested. HR 756 was the most active antibiotic tested, with more than 90% of the isolates inhibited by 0.008 μg/ml and all inhibited by 0.25 μg/ml.

Infection with *Neisseria gonorrhoeae* is the most commonly reported communicable disease in the United States. Although penicillin is still the best antibiotic, in recent years an increasing number of isolates of *N. gonorrhoeae* have become resistant to this agent (6, 7, 9, 12, 16). The basis of this resistance can be due to either a chromosomally mediated decrease in penicillin uptake by the bacteria (13) or the production of β-lactamase (15). This β-lactamase, which has recently been reported, is similar to the enzyme produced by many gram-negative bacilli (1). It is, therefore, clear that other antibiotics effective against penicillin-resistant *N. gonorrhoeae* are needed.

We have previously reported that HR 756, a new cephalosporin antibiotic, was very active against both gram-positive and gram-negative bacteria (14). In addition Fu and Neu (4) have shown that HR 756 was not hydrolyzed by the Richmond types I, III, IV, and V β-lactamases. In the present study, we have tested the activity of HR 756 against randomly selected clinical isolates and several β-lactamase-producing isolates of *N. gonorrhoeae* and compared the activity of this new cephalosporin with the activities of penicillin G, cefamandole, cefoxitin, and tetracycline.

MATERIALS AND METHODS

Antibiotics. HR 756 was obtained from Hoechst-Roussel Pharmaceutical Inc., Sommerville, N.J., cephalothin and cefamandole were obtained from Eli Lilly & Co., Indianapolis, Ind., cefoxitin was obtained from Merck Sharp & Dohme, West Point, Pa., and penicillin G was obtained from Wyeth Laboratories, Philadelphia, Pa.

Organisms. Recent clinical isolates of *N. gonorrhoeae* were obtained from 192 patients by the Saint Louis Public Health Department. Three β-lactamase-producing strains were provided by James Jorgensen, San Antonio, Tex.

Susceptibility tests. The minimal inhibitory concentrations (MICs) of penicillin, HR 756, cefoxitin, cefamandole, and tetracycline were determined by agar dilution testing (6). Twofold concentrations of the antibiotics, from 4 to 0.002 μg/ml, were distributed into proteose agar (Difco Laboratories, Detroit, Mich.) supplemented with 1% hemoglobin and 1% IsoVitaleX (Baltimore Biological Laboratory, Cockeysville, Md.). The test organisms were grown overnight on chocolate agar and then suspended in Mueller-Hinton broth. The suspension was adjusted to a turbidity equivalent of 0.5 of a McFarland no. 1 standard, and 1 μl of a 1:10 dilution of the adjusted suspension (10^4 colony-forming units) was inoculated onto the antibiotic-containing plates with a Steers replicator. After overnight growth at 35°C in a CO_2 atmosphere, the MIC was determined as the lowest concentration of the antibiotic that permitted the growth of no more than one colony. A faint haze was ignored.

RESULTS

Table 1 summarizes the susceptibility testing results with the five antibiotics and 192 isolates of *N. gonorrhoeae*. HR 756 was the most active antibiotic tested, with a mean MIC 16- to 43-fold lower than that of the other antibiotics. A total of 175 of the 192 isolates (91%) were inhibited by HR 756 at a concentration of 0.008 μg/ml, and 191 isolates were inhibited by ≤0.03 μg/ml. Penicillin G and cefamandole were less active than HR 756, and 0.5 μg of each antibiotic per ml was required to inhibit 90% of the isolates. Cefoxitin and tetracycline were the least active antibiotics tested.

Thornsberry et al. (16) have classified isolates of *N. gonorrhoeae* with penicillin MICs of <0.5 μg/ml as susceptible and those with MICs ≥0.5 μg/ml as relatively resistant. These criteria were used to classify the isolates tested in our study, and the mean MICs of HR 756, cefamandole, cefoxitin, and tetracycline against penicillin-susceptible and relatively resistant isolates are pre-

sented in Table 2. HR 756 was the most active antibiotic against both populations of *N. gonorrhoeae*. There was a statistically significant increase in the MICs of HR 756, cefamandole, and cefoxitin for the penicillin-resistant as compared with the penicillin-susceptible populations ($P < 0.05$), but the mean MICs of tetracycline were similar for both groups. Despite this, the MICs of HR 756 for the penicillin-resistant isolates were still approximately 20 to 70 times lower than the MICs of the other antibiotics.

The susceptibility test results from the three β-lactamase-producing isolates are summarized in Table 3. The MIC of penicillin was >4 μg/ml for all three of these isolates, but all were as highly susceptible to HR 756 as were the penicillin-susceptible isolates.

DISCUSSION

Thornsberry et al. (16) reported that from 4.4 to 20.3% of isolates of *N. gonorrhoeae* which were collected from selected geographical areas were relatively resistant to penicillin. Resistant isolates were most commonly recovered from black patients, from patients with a history of recent antibiotic usage, or from men with symptomatic urethritis. In the study reported here, with a similar population 23 of 192 isolates (12%) had penicillin MICs of ≥0.5 μg/ml. β-Lactamase-producing isolates are relatively uncommon in the United States and are generally recovered from travelers from the Far East or their sexual contacts. None of the 192 randomly selected isolates in this study produced β-lactamase.

TABLE 1. *Antibiotic activity against 192 randomly selected isolates of N. gonorrhoeae*

Antibiotic	MIC (μg/ml) required to inhibit the following percentage of isolates:			Mean MIC
	50	90	100	
HR 756	0.004	0.008	0.25	0.01
Penicillin G	0.125	0.5	1	0.16
Cefamandole	0.125	0.5	2	0.19
Cefoxitin	0.25	1	2	0.43
Tetracycline	0.25	1	4	0.36

TABLE 2. *Antibiotic activity against penicillin-susceptible and relatively resistant isolates of N. gonorrhoeae*

Antibiotic	Mean MIC (μg/ml) for isolates with a penicillin MIC of:	
	<0.25 μg/ml (169)[a]	≥0.5 μg/ml (23)
HR 756	0.006	0.011
Cefamandole	0.146	0.478
Cefoxitin	0.394	0.723
Tetracycline	0.376	0.234

[a] Numbers in parentheses are numbers of isolates with penicillin MICs of <0.5 or ≥0.5 μg/ml.

TABLE 3. *Antibiotic activity against three β-lactamase-producing isolates of N. gonorrhoeae*

Antibiotic	MIC (μg/ml) of antibiotic for the following isolates:		
	GC-1	GC-2	GC-3
Penicillin G	>4	>4	>4
HR 756	0.03	0.008	≤0.002
Cefamandole	0.5	0.25	0.25
Cefoxitin	4	1	0.5
Tetracycline	>4	1	1

Cephalosporins have not been widely tested against *N. gonorrhoeae*. The cephalosporin and cephamycin antibiotics most active against *N. gonorrhoeae* have been reported to be cefamandole, cefoxitin, and cefuroxime (2, 3, 5, 8, 10, 11). Our studies have confirmed that cefamandole and cefoxitin are effective in vitro against *N. gonorrhoeae;* however, HR 756 was much more active than either of these two antibiotics. Although cefuroxime was not tested in the present studies, Eykyn et al. (3) reported that it was eightfold more active than cefamandole in inhibiting 90% of the isolates which they studied. In the study reported herein, HR 756 was 64-fold more active than cefamandole in inhibiting 90% of the isolates of *N. gonorrhoeae*.

In summary, HR 756 was the most active of five antibiotics tested against *N. gonorrhoeae*. Because of the low MIC and good activity against strains which were either relatively resistant to penicillin or produced β-lactamase, clinical studies of the efficacy of HR 756 for the treatment of gonococcal infections appear to be warranted.

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