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In Vitro Activity of Ceftriaxone, Cefetamet (Ro 15-8074), Ceftetrame (Ro 19-5247; T-2588), and Fleroxacin (Ro 23-6240; AM-833) versus *Neisseria gonorrhoeae* and *Haemophilus ducreyi*

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We examined 300 strains of *Neisseria gonorrhoeae* and 100 strains of *Haemophilus ducreyi* to determine their in vitro susceptibility to two new cephalosporins, cefetamet (Ro 15-8074) and ceftetrame (Ro 19-5247; T-2588), and a new fluroquinolone, fleroxacin (Ro 23-6240; AM-833). Their activity was compared with that of ceftriaxone, penicillin, spectinomycin, tetracycline, and erythromycin. Cefetamet, ceftetrame, and fleroxacin had excellent in vitro activity against both groups of microorganisms. β-Lactamase production did not significantly affect the MICs of these agents. The Mtr phenotype of *N. gonorrhoeae* raised the MICs two- to fourfold, but the MICs remained within the range of achievable levels in serum. These newer compounds have a distinct advantage over existing therapeutic agents in that they can be administered orally. Clinical trials are warranted to assess their usefulness in the therapy of gonorrhea and chancroid.

Neisseria gonorrhoeae and *Haemophilus ducreyi* are two major sexually transmitted bacterial pathogens that cause frequent infections in many developing areas of the world. Their antimicrobial resistance patterns appear to be interrelated. They share a portion of the same β-lactamase-specifying plasmid. Furthermore, *H. ducreyi* is speculated to have acted as a vehicle for the transfer of β-lactamase plasmids from *Haemophilus* species to *N. gonorrhoeae* (6). In developing areas of the world, both agents presently have multiple resistance patterns partly due to plasmid-specified enzymes and partly due to chromosomal resistance (2, 4, 5).

We tested two new cephalosporins, cefetamet and ceftetrame, and a new orally administrable fluoroquinolone, fleroxacin, for their activity against 300 strains of *N. gonorrhoeae* and 100 strains of *H. ducreyi*. Their activity was compared with that of ceftriaxone, penicillin, erythromycin, tetracycline, and spectinomycin.

A total of 400 clinical isolates of bacteria were examined. Of these, 200 isolates of *N. gonorrhoeae* were from Nairobi, Kenya; 100 of these were β-lactamase positive, and 100 were β-lactamase negative. A further 100 isolates of β-lactamase-negative *N. gonorrhoeae* were collected from patients in Winnipeg, Manitoba, Canada. In addition, 100 isolates of β-lactamase-positive *H. ducreyi* collected in Nairobi, Kenya, were tested. All isolates were recovered in 1984.

The antibiotics tested were ceftriaxone, cefetamet, ceftetrame, fleroxacin, penicillin, tetracycline, spectinomycin, and erythromycin. The MIC of each antibiotic was determined by agar dilution on chocolate agar by accepted methodology (1, 3).

Cell envelope phenotypes of *N. gonorrhoeae* were presumptively identified as wild type when the MICs of erythromycin fell between 0.12 and 1.0 μg/ml. The Mtr phenotype was presumptively identified when the erythromycin MICs were ≥2 μg/ml and the Triton X-100 MICs were ≥2 μg/ml. The Env phenotype was characterized by erythromycin and Triton X-100 MICs of <0.06 and <0.5 μg/ml, respectively.

A Wilcoxon rank sum test was applied to the data. A Bonferonni correction was applied to correct for multiple comparisons.

The MICs for *N. gonorrhoeae* were lowest for ceftriaxone, ranging from 0.0005 to 0.15 μg/ml for β-lactamase-negative strains from Winnipeg (MIC for 90% of strains [MIC_{90}], 0.015 μg/ml). The ceftriaxone MIC range for β-lactamase-negative Kenya strains was 0.0005 to 0.06 μg/ml (MIC_{90}, 0.06 μg/ml). The two cephalosporins, cefetamet and ceftetrame, had similar low MICs, ranging from 0.0005 to 0.06 μg/ml for the Winnipeg isolates (MIC_{90}, 0.03 μg/ml for cefetamet and 0.06 μg/ml for ceftetrame). The range of MICs for β-lactamase-negative Kenya strains was 0.002 to 0.25 μg/ml for both antimicrobial agents, while the MIC_{90}s were 0.12 μg/ml for cefetamet and 0.06 μg/ml for ceftetrame. Fleroxacin had MICs ranging from 0.015 to 0.03 μg/ml for Winnipeg strains (MIC_{90}, 0.015 μg/ml) and 0.008 to 0.12 μg/ml for β-lactamase-negative Kenya strains (MIC_{90}, 0.06 μg/ml).

The *N. gonorrhoeae* strains from Kenya were further analyzed to determine the effect of β-lactamase production on antimicrobial susceptibility results (Table 1). The MIC_{90}s of cefetamet, ceftetrame, and fleroxacin for β-lactamase-negative strains were 0.06, 0.12, and 0.06 μg/ml, respectively. There was no significant difference between these MICs and those for β-lactamase-positive strains (0.03, 0.06, and 0.06 μg/ml, respectively (Table 1). The only significant difference in activity occurred with penicillin.

The Mtr phenotype was detected in 5% of Winnipeg *N. gonorrhoeae* strains and 39% of β-lactamase-negative Kenya *N. gonorrhoeae* strains. The Mtr phenotype significantly increased by two- to fourfold the MIC_{90} of all antibiotics tested except spectinomycin. The increase in the MIC_{90} was most pronounced for penicillin and cefetamet (Table 1).

Of the 100 *H. ducreyi* strains tested, all were β-lactamase positive. The MIC range, MIC for 50% of strains (MIC_{50}), and MIC_{90} for *H. ducreyi* are shown in Table 2. Ceftriaxone, ceftetrame, and fleroxacin were the most active compounds tested, with MIC_{90}s of 0.004, 0.03, and 0.06 μg/ml, respec-

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TABLE 1. MIC_{90}s of antimicrobial agents against Kenya *N. gonorrhoeae* strains grouped by β-lactamase production and membrane phenotype

Drug	MIC_{90} (μg/ml) for:		
	β-Lactamase-positive strains (n = 100)	β-Lactamase-negative strains[a]	
		Wild type (n = 61)	Mtr (n = 39)
Ceftriaxone	0.03	0.03	0.06
Cefetamet	0.03	0.03	0.12
Ceftetrame	0.06	0.06	0.12
Fleroxacin	0.06	0.03	0.06
Penicillin	32.0	1	4
Spectinomycin	16.0	16	16
Tetracycline	8.0	4	8
Erythromycin	4.0	1	4

[a] When the two phenotypes were compared, the P value (determined by the Wilcoxon test) was 0.0001 for all drugs except spectinomycin, for which the P value was not significant.

tively. The MIC_{90} of cefetamet, by comparison, was 0.5 μg/ml.

The evolution of antimicrobial resistance in *N. gonorrhoeae* and *H. ducreyi* is an area of active study (2, 5–7). Evaluation of new antimicrobial agents is necessary because of the ongoing nature of acquired resistance found in these microorganisms.

The in vitro data indicate that the two new cephalosporins, cefetamet and ceftetrame, and the new fluoroquinolone, fleroxacin, are very active against both *N. gonorrhoeae* and *H. ducreyi*. A prior study also reported the excellent activity of cefetamet against *N. gonorrhoeae* (8). β-Lactamase production had no deleterious effect on the activity of these agents against *N. gonorrhoeae*. For non-β-lactamase-producing *N. gonorrhoeae* strains, the Mtr phenotype modestly (two- to fourfold) raised the MIC_{90} of the experimental compounds. Cefetamet was approximately twice as active against *N. gonorrhoeae* as ceftetrame was.

TABLE 2. Antimicrobial susceptibility of 100 *H. ducreyi* strains

Drug	MIC (μg/ml)		
	50%	90%	Range
Ceftriaxone	0.004	0.004	<0.0005–0.03
Cefetamet	0.25	0.5	0.015–0.5
Ceftetrame	0.015	0.03	0.001–0.03
Fleroxacin	0.03	0.06	0.015–0.06
Penicillin	128.0	128.0	4–>128
Spectinomycin	8.0	10.0	<1–16
Tetracycline	16.0	32.0	0.5–32
Erythromycin	0.06	0.12	0.004–0.12

All these drugs under investigation can be administered orally and, hence, offer an important advantage in terms of therapy. Preliminary pharmacokinetic data in normal human volunteers indicate that fleroxacin has a long serum half-life, approximately 9 h. After oral administration, the half-life of cefetamet appears to be shorter (2.3 h) and that of ceftetrame is approximately 1 h. Peak concentrations of ceftetrame in serum are between 1.83 and 3.63 μg/ml. The levels of cefetamet and fleroxacin are 5.0 to 7.6 and 4.5 μg/ml, respectively (data on file, Hoffman-La Roche Inc.). Single oral doses of fleroxacin for uncomplicated gonococcal infections may be feasible because of its long half-life and good levels in serum. Clinical trials with these compounds seem warranted to assess their potential role in the therapy of sexually transmitted diseases caused by *N. gonorrhoeae* and *H. ducreyi*.

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