

In Vitro Activities of Ketolides HRM 3647 and HRM 3004, Levofloxacin, and Other Quinolones and Macrolides against *Neisseria* spp. and *Moraxella catarrhalis*

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In vitro activities of the ketolides HRM 3647 and HRM 3004 against pathogenic *Neisseria gonorrhoeae* and *N. meningitidis*, saprophytic *Neisseria* isolates, and *Moraxella catarrhalis* were determined. The comparison of ketolide activities with those of the other macrolides shows a much better activity in the majority of species, with macrolide MICs at which 90% of the isolates are inhibited between 8- and 10-fold higher.

Ketolides are a new class of semisynthetic 14-member ring macrolides which differ from erythromycin A in that they have a 3-keto group on the erythronolide A ring instead of an L-cladinose (2). Ketolides have in vitro activities against many multi-drug-resistant (especially erythromycin-resistant strains) gram-positive organisms, including staphylococci, enterococci, and pneumococci; some anaerobes; *Haemophilus* spp.; and other fastidious strains (1, 3-6, 8).

In this study we compare the in vitro activities of ketolides HRM 3647 and HRM 3004 with those of erythromycin, other macrolides, and quinolones against pathogenic *Neisseria gonorrhoeae* and *N. meningitidis* and saprophytic *Neisseria* isolates and *Moraxella catarrhalis*. A total of 600 isolates of *Neisseria* spp. and *M. catarrhalis* received from the collection of the National Center for Microbiology of Spain or from hospital laboratories between 1994 and 1997 were studied.

Antimicrobial agents supplied as laboratory powders of known potency were as follows: HRM 3004, HRM 3647, erythromycin, clarithromycin, roxithromycin, azithromycin, ciprofloxacin, ofloxacin, levofloxacin (Hoecht-Marion-Roussel, Romainville, France) and sparfloxacin (Rhône-Poulenc-Rorer, Vitry, France). In vitro activities were determined by the agar dilution method according to National Committee for Clinical Laboratory Standards guidelines (7). The medium employed was Mueller-Hinton agar, except for gonococci, for which GC medium (Difco) was used. The inocula were directly prepared from an overnight culture in Mueller-Hinton agar or GC medium (gonococci). A standard inoculum to obtain 10⁴ to 10⁵ CFU/spot was prepared and applied to agar plates containing antibiotics by using a Denley multipoint inoculator (Cultek, Madrid, Spain). All plates were incubated at 37°C for 18 h in a 5% CO₂ atmosphere. The MIC was defined as the lowest concentration at which no growth was visible on agar plates. The following reference organisms were included for quality control: *Staphylococcus aureus* ATCC 29213 and *N. gonorrhoeae* ATCC 49226.

Table 1 shows the antimicrobial activities of ketolides (HRM 3004 and HRM 3647) compared with those of other antibiotics (macrolides and quinolones) tested against 600 strains of *Neisseria* spp. and *M. catarrhalis*.

TABLE 1. Activities of HMR 3004 and HMR 3647 compared to those of levofloxacin and other quinolones and macrolides against *Neisseria* spp. and *Moraxella catarrhalis*

Organism (no. of isolates) and drug	MIC (µg/ml)		
	Range	50%	90%
<i>Neisseria meningitidis</i> (200) ^a			
HMR 3004	0.007-0.25	0.06	0.12
HMR 3647	0.03-0.5	0.12	0.12
Erythromycin	0.06-2	1	1
Roxithromycin	0.06-4	0.5	1
Clarithromycin	0.003-1	0.12	0.5
Azithromycin	0.25-2	0.5	1
Ciprofloxacin	≤0.003-0.03	0.007	0.007
Ofloxacin	0.007-0.03	0.03	0.03
Levofloxacin	≤0.003-0.03	0.007	0.015
Sparfloxacin	≤0.003-0.015	≤0.003	0.007
<i>Neisseria gonorrhoeae</i> (200) ^b			
HMR 3004	≤0.003-0.5	0.06	0.12
HMR 3647	≤0.003-0.5	0.06	0.12
Erythromycin	0.06-2	0.5	2
Roxithromycin	0.06-4	1	2
Clarithromycin	0.03-2	0.25	1
Azithromycin	0.015-0.5	0.12	0.25
Ciprofloxacin	≤0.003-0.06	≤0.003	0.007
Ofloxacin	0.007-0.25	0.03	0.06
Levofloxacin	≤0.003-0.12	0.007	0.015
Sparfloxacin	≤0.003-0.03	≤0.003	0.007
<i>Neisseria polysaccharea</i> (10)			
HMR 3004	0.007-0.25	0.12	0.25
HMR 3647	0.007-0.25	0.12	0.25
Erythromycin	0.06-4	1	2
Roxithromycin	0.06-2	0.5	2
Clarithromycin	0.007-1	0.12	1
Azithromycin	0.03-0.25	0.06	0.25
Ciprofloxacin	≤0.003	≤0.003	≤0.003
Ofloxacin	0.007-0.015	0.007	0.015
Levofloxacin	≤0.003	≤0.003	≤0.003
Sparfloxacin	≤0.003-0.007	≤0.003	≤0.003

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TABLE 1—Continued

Organism (no. of isolates) and drug	MIC ($\mu\text{g/ml}$)		
	Range	50%	90%
<i>Neisseria lactamica</i> (10)			
HMR 3004	≤ 0.003 –1	0.03	1
HMR 3647	0.007–0.5	0.06	0.5
Erythromycin	2–4	4	4
Roxithromycin	4–8	4	8
Clarithromycin	2–4	2	4
Azithromycin	1–2	2	2
Ciprofloxacin	≤ 0.003 –0.007	≤ 0.003	0.007
Ofloxacin	0.015–0.03	0.03	0.03
Levofloxacin	≤ 0.003 –0.015	≤ 0.003	0.015
Sparfloxacin	≤ 0.003	≤ 0.003	≤ 0.003
<i>Neisseria mucosa</i> (10)			
HMR 3004	0.015–4	2	4
HMR 3647	0.06–4	0.5	4
Erythromycin	0.25–8	4	8
Roxithromycin	0.25–16	8	16
Clarithromycin	0.06–8	4	8
Azithromycin	0.06–8	2	8
Ciprofloxacin	≤ 0.003 –0.007	0.007	0.007
Ofloxacin	0.015–0.06	0.03	0.06
Levofloxacin	0.007–0.03	0.015	0.03
Sparfloxacin	≤ 0.003 –0.015	≤ 0.003	0.007
<i>Neisseria cinerea</i> (10)			
HMR 3004	0.015–1	0.5	1
HMR 3647	0.015–1	0.5	1
Erythromycin	1–8	4	8
Roxithromycin	2–8	8	8
Clarithromycin	0.5–4	4	4
Azithromycin	0.5–4	2	2
Ciprofloxacin	≤ 0.003 –0.12	0.007	0.015
Ofloxacin	0.015–0.25	0.03	0.06
Levofloxacin	0.007–0.12	0.015	0.03
Sparfloxacin	0.007–0.015	0.007	0.015
<i>Neisseria perflava/sicca</i> (10)			
HMR 3004	0.03–4	0.5	4
HMR 3647	0.06–4	0.5	4
Erythromycin	0.5–16	8	8
Roxithromycin	1–16	8	16
Clarithromycin	0.25–16	4	8
Azithromycin	0.25–4	4	4
Ciprofloxacin	≤ 0.003 –0.06	0.015	0.03
Ofloxacin	0.015–0.12	0.06	0.12
Levofloxacin	≤ 0.003 –0.12	0.03	0.03
Sparfloxacin	≤ 0.003 –0.03	0.007	0.03
<i>Moraxella catarrhalis</i> (150) ^c			
HMR 3004	0.06–0.25	0.12	0.12
HMR 3647	0.06–0.25	0.12	0.12
Erythromycin	0.06–0.5	0.25	0.25
Roxithromycin	0.12–1	0.5	0.5
Clarithromycin	0.03–0.25	0.12	0.12
Azithromycin	0.015–0.12	0.06	0.06
Ciprofloxacin	0.015–0.12	0.06	0.06
Ofloxacin	0.06–0.5	0.06	0.06
Levofloxacin	0.03–0.12	0.06	0.06
Sparfloxacin	≤ 0.003 –0.06	0.015	0.03

^a *Neisseria meningitidis* isolates include 50 penicillin-susceptible–rifampin-susceptible strains, 15 strains susceptible to penicillin and moderately resistant to rifampin, 5 strains moderately resistant to penicillin and resistant to rifampin, 100 strains moderately resistant to penicillin and susceptible to rifampin, and 30 strains moderately resistant to rifampin and to penicillin.

^b *Neisseria gonorrhoeae* isolates include 56 penicillin-susceptible strains, 10 strains moderately resistant to penicillin (β -lactamase negative), 64 penicillin-resistant (chromosomal) strains, and 70 penicillin-resistant (β -lactamase-positive) strains.

^c *Moraxella catarrhalis* isolates include 120 β -lactamase-producing and 30 β -lactamase-nonproducing strains.

N. gonorrhoeae and *N. meningitidis* were very susceptible to the ketolides (MICs at which 90% of the isolates are inhibited [$\text{MIC}_{90\text{s}}$], 0.12 $\mu\text{g/ml}$). *M. catarrhalis* shows similar features, whereas saprophytic *Neisseria* isolates, for which $\text{MIC}_{90\text{s}}$ were 4 $\mu\text{g/ml}$ (range, 0.25 [*N. polysaccharea*] to 4 [*N. mucosa*, *N. perflava/sicca*]), showed significantly decreased susceptibility. The MICs of the two ketolides for the different species were similar, and no significant differences were encountered between the various patterns of isolates studied in each species. Also, no differences were found between ketolide MICs for β -lactamase-producing or -nonproducing *M. catarrhalis* and those for pathogenic *Neisseria* isolates moderately resistant or susceptible to penicillin.

Comparison of ketolide activity with those of the other macrolides showed a much better activity in the majority of species, with macrolide $\text{MIC}_{90\text{s}}$ between 8- and 10-fold higher, except MICs for *M. catarrhalis*, which were similar to those of the ketolides. The ketolide MICs obtained by us for *Neisseria* isolates and *M. catarrhalis* were similar to those reported by other researchers (4–6). All the species tested except *M. catarrhalis* were more susceptible to quinolones than to ketolides and macrolides. The $\text{MIC}_{90\text{s}}$ of the two types of compounds for *M. catarrhalis* were very similar.

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