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Antipneumococcal Activities of a Ketolide (HMR 3647), a Streptogramin (Quinupristin-Dalfopristin), a Macrolide (Erythromycin), and a Lincosamide (Clindamycin)

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Four different compounds belonging to the macrolide-lincosamide-streptogramin B (MLS_b) class of antimicrobial agents were tested against 611 *Streptococcus pneumoniae* strains. The ketolide (HMR 3647, previously RU66647) and the streptogramin (quinupristin-dalfopristin) were both active against pneumococci with high-level MLS_b resistance (clindamycin-resistant strains) as well as those with low-level macrolide resistance (clindamycin-susceptible strains).

Macrolide-resistant strains of *Streptococcus pneumoniae* are increasing in prevalence (1, 2, 4). Consequently, there is a need for alternative agents that might include macrolide-resistant pneumococci in their spectrum of activity. The ketolide HMR 3647 (previously RU66647) is a new addition to the macrolide-lincosamide-streptogramin B (MLS_b) class of antimicrobial agents; it is a ketolide derivative which is a semi-synthetic 14-member-ring macrolide, harboring a 3-keto group instead of an α-L-cladinose on the aglycone A (6). The purpose of this report is to compare the antipneumococcal activities of HMR 3647 and a streptogramin (quinupristin-dalfopristin) to that of erythromycin and clindamycin. Specifically, the data were examined to determine the extent of cross-resistance to the different agents among the pneumococci.

Macrolide-resistant strains of *S. pneumoniae* have been studied by other investigators in recent years (7, 10, 11). Three common phenotypes have been defined according to their resistance or susceptibility to erythromycin and clindamycin (10, 11). Pneumococci may be Ery^s $Clin^s$, Ery^r $Clin^s$, or Ery^r $Clin^r$; Ery^s $Clin^r$ strains have not been reported. Ery^r $Clin^s$ strains tend to be resistant to other 14- and 15-member-ring macrolides but susceptible to clindamycin and streptogramin B. This low-level macrolide resistance has been shown to be associated with an altered macrolide efflux system, which results in cross-resistance to other macrolide and azalide compounds (11) but not to clindamycin or streptogramin B. To date, macrolide-inactivating enzymes have not been described for pneumococci. The Ery^r $Clin^r$ phenotype presents as high-level macrolide resistance that is presumably the result of altered rRNA, which blocks binding of the macrolides to their target site. The altered target sites result in high-level resistance to the macrolides, clindamycin, and streptogramin B (8, 10, 11).

We performed in vitro studies with 611 isolates of *S. pneumoniae* using the broth microdilution procedure recommended by the National Committee for Clinical Laboratory Standards (9). The study drugs were serially diluted in cation-adjusted Mueller-Hinton broth supplemented with 2 to 3% lysed horse blood. The inocula were adjusted to provide ca. 5×10^5 CFU/ml in each well, as confirmed by periodic colony counts performed throughout the study. Microdilution trays were incubated 20 to 24 h at 35°C without added CO_2. HMR 3647 was provided by Roussel Uclaf, Romainville, France, and quinupristin-dalfopristin was obtained from Rhone-Poulenc Rorer, Collegeville, Pa. Erythromycin and clindamycin were obtained from their respective U.S. manufacturers.

The 611 isolates of *S. pneumoniae* were selected from stock cultures that originated from medical centers distributed throughout the continental United States. This included 396 penicillin-susceptible (MIC, ≤0.06 μg/ml), 138 penicillin-intermediate (MIC, 0.12 to 1.0 μg/ml), and 77 penicillin-resistant (MIC, ≥2.0 μg/ml) strains. Most (73%) of the 74 erythromycin-intermediate or -resistant strains were also resistant or intermediate in susceptibility to penicillin (1). Each isolate was categorized as being susceptible (MIC, ≤0.25 μg/ml) or resistant (MIC, ≥1.0 μg/ml) to erythromycin and/or clindamycin. For three strains, the MIC of erythromycin was intermediate (0.5 μg/ml), and those three strains were considered resistant to erythromycin for the purposes of this analysis. There were no clindamycin-intermediate strains. The 611 isolates were divided into three phenotypes: i.e., Ery^s $Clin^s$, Ery^r $Clin^s$, and Ery^r $Clin^r$. Table 1 describes the results of microdilution tests with isolates within each phenotype. Fasola et al. (5) reported a few false-susceptible test results with the National Committee for Clinical Laboratory Standards broth microdilution procedure. Those methodologic concerns were not addressed in this study. Furthermore, the possibility that inducible resistance may be overlooked was not considered since others have found it to be very uncommon among pneumococci (5, 7).

The most common phenotype was Ery^s $Clin^s$; those strains were very susceptible to all four study drugs. Quinupristin-dalfopristin was the least potent drug tested against Ery^s $Clin^s$ strains. Two-thirds of the erythromycin-resistant pneumococci were susceptible to clindamycin (Ery^r $Clin^s$ phenotype). Against that phenotype, MICs of erythromycin were elevated into the intermediate (MIC, 0.5 μg/ml) or resistant (MIC, ≥1.0 μg/ml) category. The MICs of the ketolide (HMR 3647) and of the streptogramin (quinupristin-dalfopristin) were not markedly elevated. Strains with the third phenotype (Ery^r $Clin^r$) were highly resistant to erythromycin and clindamycin, but MICs of HMR 3647 and of quinupristin-dalfopristin were not elevated. Strains in all three phenotypes were susceptible to ≤0.5 μg of HMR 3647 per ml and to ≤4.0 μg of quinupristin-dalfopristin per ml; the ketolide was consistently more potent than the streptogramin.

The high-level resistance that results from alteration of tar-

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TABLE 1. In vitro activity of a ketolide (HMR 3647) and a streptogramin (quinupristin-dalfopristin) against *S. pneumoniae*

Resistance phenotype (no. of strains)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
Ery^s $Clin^s$ (537)	HMR 3647	≤0.06–≤0.06	≤0.06	≤0.06
	Quin-Dalf[b]	≤0.06–1.0	0.25	0.5
	Erythromycin	≤0.06–0.25	≤0.06	≤0.06
	Clindamycin	≤0.06–0.12	≤0.06	≤0.06
Ery^r $Clin^s$ (50)	HMR 3647	≤0.06–0.5	0.25	0.5
	Quin-Dalf	0.12–4.0	0.5	0.5
	Erythromycin	1.0–8.0	4.0	8.0
	Clindamycin	≤0.06–0.25	≤0.06	≤0.06
Ery^r $Clin^r$ (24)	HMR 3647	≤0.06–0.25	≤0.06	≤0.06
	Quin-Dalf	0.25–1.0	0.5	0.5
	Erythromycin	1.0–>32	>32	>32
	Clindamycin	1.0–>32	>32	>32

[a] 50% and 90%, MICs at which 50 and 90% of the isolates, respectively, are inhibited.
[b] Quin-Dalf, quinupristin-dalfopristin (30:70 ratio).

get sites on rRNA should result in cross-resistance to streptogramin B as well as clindamycin and erythromycin. Our data confirm those of Biedenbach, Wanger, and Jones (3) in that the quinupristin-dalfopristin combination is not like other streptogramin compounds because it is not affected by the altered target sites responsible for the Ery^r $Clin^r$ phenotype. The ketolide HMR 3647 is also active against the Ery^r $Clin^r$ phenotype, presumably because other binding sites are involved. We cannot rule out the possibility that inducible resistance might be present but not detected by standard test methods. The Ery^r $Clin^s$ phenotype is probably caused by a multicomponent efflux system (11). Such strains show low-level resistance to erythromycin (MICs, 1.0 to 8.0 μg/ml). Those Ery^r $Clin^s$ strains should be resistant to all macrolides but not to other drugs in the MLS_b class (10, 11). The streptogramin quinupristin-dalfopristin was nearly equal in its activity against all three phenotypes of *S. pneumoniae*, and the MICs may be low enough to predict clinical efficacy, if appropriate tissue levels can be achieved during therapy. The new ketolide HMR 3647 might be useful when treating patients infected with macrolide-resistant as well as macrolide-susceptible pneumococci. Clinical efficacy is yet to be documented in humans.

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