ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1997, p. 1033–1036 Vol. 41, No. 5
0066-4804/97/$04.00+0

Susceptibilities of 228 Penicillin- and Erythromycin-Susceptible and -Resistant Pneumococci to RU 64004, a New Ketolide, Compared with Susceptibilities to 16 Other Agents

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Received 27 September 1996/Returned for modification 4 February 1997/Accepted 20 February 1997

The susceptibilities of 228 penicillin- and erythromycin-susceptible and -resistant pneumococci to RU 64004, a new ketolide, were tested by agar dilution, and the results were compared with those for penicillin G, erythromycin, azithromycin, clarithromycin, rokitamycin, clindamycin, pristinamycin, ciprofloxacin, sparfloxacin, trimethoprim-sulfamethoxazole, doxycycline, chloramphenicol, cefuroxime, ceftriaxone, imipenem, and vancomycin. RU 64004 was very active against all strains tested, with MICs at which 90% of the isolates are inhibited (MIC_{90}s) of 0.016 μg/ml for erythromycin-susceptible strains (MIC, ≤0.25 μg/ml) and 0.25 μg/ml for erythromycin-resistant strains (MIC, ≥0.5 μg/ml). All other macrolides had MIC_{90}s of 0.03 to 0.25 and ≥128 μg/ml for erythromycin-susceptible and -resistant strains, respectively. Among erythromycin-resistant strains, clindamycin MICs for 28 of 91 (30.7%) were ≤0.125 μg/ml. Pristinamycin MICs for all strains were ≤1.0 μg/ml. MIC_{90}s of ciprofloxacin and sparfloxacin were 4.0 and 0.25 μg/ml, respectively, and were unaffected by susceptibility to penicillin or erythromycin. Vancomycin and imipenem inhibited all strains at ≤0.5 and ≤0.25 μg/ml, respectively. MICs of cefuroxime and cefotaxime rose with those of penicillin G. MICs of trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol were variable but were generally higher for penicillin- and erythromycin-resistant strains. RU 64004 is the first member of the macrolide group which has low MICs for erythromycin-resistant pneumococci.

The worldwide incidence of infections caused by pneumococci resistant to penicillin G and other antimicrobials has increased at an alarming rate during the past 2 decades and in particular during the past 5 years (4, 9). The main foci of penicillin-resistant pneumococci are currently South Africa, Spain, and eastern Europe. However, resistant strains are found almost universally wherever susceptibility testing is performed by appropriate methods (4). The spread of penicillin-resistant clones from country to country and from continent to continent demonstrates the capability of these strains to spread rapidly throughout the world (15). In the United States, one recent survey (7) has shown an increase in resistance to penicillin from <5% before 1989 (including MICs of ≥2.0 μg/ml for <0.02% of isolates) to 6.6% in 1991 to 1992 (including MICs of ≥2.0 μg/ml for 1.3% of isolates).

The distribution of penicillin-resistant strains is highly variable in the United States. Block and coworkers (6) have recently reported a 28% incidence rate of penicillin-resistant pneumococci in middle ear fluid from children with acute otitis media in Kentucky and a 29% incidence rate of these strains in nasopharyngeal cultures from children with otitis media in Tennessee.

Pneumococcal strains with intermediate and especially with full resistance to penicillin G are often resistant to erythromycin. In the United States in 1991 to 1992, Breiman and coworkers demonstrated erythromycin resistance rates of 3.7 and 2.2% in patients 1 to 2 and ≥4 years of age, respectively (7). In Europe, erythromycin resistance rates are generally higher. For example, 27.5% of all pneumococci studied in France during 1992 (63% of penicillin-resistant strains) were erythromycin resistant (10). Although clarithromycin MICs for pneumococci are generally 1 or 2 dilutions lower than those of other macrolides (5, 12, 14, 17), erythromycin-resistant pneumococci are resistant to all other existing macrolides (12). Until now, the only member of the macrolide-lincosamide-streptogramin group which is consistently active against all pneumococci, irrespective of their penicillin or erythromycin susceptibility status, has been RP 59500 (quinupristin-dalfopristin), a parenteral streptogramin (18).

RU 64004, a new ketolide, is a semisynthetic macrolide characterized by a 3-keto function which replaces the cladinose moiety of other members of the macrolide group. Previous preliminary studies have documented activity of this group of compounds against pneumococci (1–3). In the present study, we compared the susceptibilities of 228 penicillin-and erythromycin-susceptible and -resistant pneumococci to RU 64004 with their susceptibilities to penicillin G, erythromycin, azithromycin, clarithromycin, clindamycin, rokitamycin, pristinamycin (related to RP 59500), trimethoprim-sulfamethoxazole, ciprofloxacin, sparfloxacin, doxycycline, chloramphenicol, cefuroxime, ceftriaxone, imipenem, and vancomycin.

MATERIALS AND METHODS

Bacterial strains. A total of 228 isolates of *Streptococcus pneumoniae* isolated from blood, cerebrospinal fluid, the ear, the nasopharynx, or sputum were examined. Seventy-three strains susceptible to penicillin (MICs, <0.1 μg/ml) were isolated from various hospitals in the United States. Ninety-one isolates resistant to penicillin (MICs, ≥2.0 μg/ml) and most of the 64 intermediate strains (MICs, 0.1 to 1.0 μg/ml) were isolated in the United States, South Africa, France, Spain, eastern Europe (Hungary, Slovakia, and Bulgaria), Japan, and Korea. Most of the 91 erythromycin-resistant strains (MICs, ≥0.5 μg/ml) were isolated in the latter sites. It has previously been recommended (11) that strains classified as "intermediate" on the basis of MICs be classified as resistant because of the bimodal nature of erythromycin susceptibility in pneumococci.

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TABLE 1. Susceptibility of pneumococci to antimicrobial agents by penicillin susceptibility

Antimicrobial and penicillin susceptibility[a]	MIC (μg/ml)		
	Range	50%	90%
Penicillin			
S	0.016–0.06	0.016	0.06
I	0.125–1.0	0.5	1.0
R	2.0–8.0	4.0	4.0
RU 64004			
S	0.008–0.125	0.016	0.06
I	0.004–2.0	0.016	0.06
R	0.004–1.0	0.06	0.25
Erythromycin			
S	0.004–≥128.0	0.06	4.0
I	0.03–≥128.0	0.06	≥128.0
R	0.016–≥128.0	≥128.0	≥128.0
Azithromycin			
S	0.03–≥128.0	0.06	4.0
I	0.03–≥128.0	0.125	≥128.0
R	0.06–≥128.0	≥128.0	≥128.0
Clarithromycin			
S	0.008–≥128.0	0.03	2.0
I	0.008–≥128.0	0.03	≥128.0
R	0.016–≥128.0	2.0	≥128.0
Rokitamycin			
S	0.03–≥128.0	0.25	0.25
I	0.03–≥128.0	0.25	≥128.0
R	0.03–≥128.0	≥128.0	≥128.0
Clindamycin			
S	0.016–≥64.0	0.06	0.06
I	0.016–≥64.0	0.06	≥64.0
R	0.016–≥64.0	0.06	≥64.0
Pristinamycin			
S	0.125–0.5	0.25	0.5
I	0.125–1.0	0.5	0.5
R	0.125–1.0	0.5	1.0
Trimethoprim-sulfamethoxazole			
S	0.06–≥16.0	0.25	4.0
I	0.125–≥16.0	1.0	8.0
R	0.125–≥16.0	4.0	≥16.0
Ciprofloxacin			
S	0.125–2.0	0.5	2.0
I	0.125–4.0	1.0	4.0
R	0.5–4.0	2.0	4.0
Sparfloxacin			
S	0.016–0.25	0.06	0.125
I	0.016–0.25	0.06	0.25
R	0.03–1.0	0.25	0.25
Doxycycline			
S	0.03–≥32.0	0.125	4.0
I	0.03–≥32.0	0.25	16.0
R	0.03–16.0	4.0	16.0
Chloramphenicol			
S	≤2.0–≥16.0	≤2.0	8.0
I	≤2.0–≥16.0	4.0	≥16.0
R	≤2.0–≥16.0	4.0	≥16.0
Cefuroxime			
S	≤0.016–1.0	0.03	0.125
I	0.125–≥16.0	1.0	4.0
R	0.25–≥16.0	4.0	8.0
Ceftriaxone			
S	≤0.016–0.25	0.016	0.125
I	0.06–4.0	0.5	1.0
R	0.125–4.0	2.0	2.0
Imipenem			
S	≤0.008–0.125	≤0.008	≤0.008
I	≤0.008–0.25	0.03	0.06
R	0.016–0.25	0.06	0.125
Vancomycin			
S	0.03–0.5	0.25	0.25
I	0.06–0.5	0.25	0.5
R	0.06–0.5	0.25	0.5

[a] S, susceptible (≤0.06 μg/ml); I, intermediate (0.125 to 1.0 μg/ml); R, resistant (≥2.0 μg/ml).

Antimicrobial agents. Antimicrobial agents were supplied as laboratory powders of known potency, as follows: RU 64004, rokitamycin, and pristinamycin (Roussel Uclaf, Paris, France); erythromycin and clarithromycin (Abbott Laboratories, North Chicago, Ill.); azithromycin (Pfizer Inc., New York, N.Y.); clindamycin (The Upjohn Co., Kalamazoo, Mich.); trimethoprim, sulfamethoxazole, penicillin G, doxycycline, and chloramphenicol (Sigma Chemical Co., St. Louis, Mo.); ciprofloxacin (Miles, Inc., West Haven, Conn.); sparfloxacin (Rhône-Poulenc Rorer, Collegeville, Pa.); cefuroxime and vancomycin (Eli Lilly & Co., Indianapolis, Ind.); ceftriaxone (Roche Laboratories, Nutley, N.J.); and imipenem (Merck & Co., Rahway, N.J.).

MIC testing. MICs were determined by the agar dilution method with Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 5% sheep blood (11). For MIC determinations, suspensions with a turbidity equivalent to that of a 0.5 McFarland standard were prepared by suspending growth from blood agar plates in 2 ml of Mueller-Hinton broth (BBL). Suspensions were further diluted 1:10 to obtain a final inoculum of 10^4 CFU/spot. Plates were inoculated with a Steers replicator and incubated overnight in ambient air at 37°C. Standard quality control strains (16) were included in each run. Additionally, MICs of RU 64004, erythromycin, azithromycin, clarithromycin, rokitamycin, clindamycin, and pristinamycin were read after an additional 24 h of incubation. Unless otherwise specified, all data presented are from the overnight incubation.

RESULTS

Results of the MIC testing (standard overnight incubation) are presented in Tables 1 and 2. In Table 1, MICs are shown by penicillin susceptibility. Macrolide and clindamycin resistance was found mainly in penicillin-intermediate and -resistant strains. In all cases, however, RU 64004 MICs were ≤2.0 μg/ml, with MICs at which 90% of the isolates are inhibited (MIC_{90}s) of 0.06, 0.06, and 0.25 μg/ml for penicillin-susceptible, -intermediate and -resistant strains, respectively. In contrast, MIC_{90}s of erythromycin, azithromycin, clarithromycin, and rokitamycin were 0.25 to 4.0, ≥128.0, ≥128.0, and ≥128.0 μg/ml, respectively, for the above three groups. All strains were susceptible to pristinamycin at empirically chosen MICs of ≤1.0 μg/ml. Quinolone activity was independent of penicillin susceptibility, with sparfloxacin being more active than ciprofloxacin (MIC_{90}s = 0.25 and 4.0 μg/ml, respectively). MICs of cefuroxime, ceftriaxone, and imipenem rose with those of penicillin G. However, all strains were inhibited by ceftriaxone at MICs of ≤4.0 μg/ml and by imipenem at MICs of ≤0.25 μg/ml. Susceptibilities of strains to trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol were variable. As in the case of the macrolides, however, resistance to the latter three drugs was seen more often in penicillin-intermediate and -resistant strains. All strains were susceptible to vancomycin at MICs of ≤0.5 μg/ml.

Results analyzed by erythromycin susceptibility are presented in Table 2. For erythromycin-susceptible strains, MICs of azithromycin, clarithromycin, and rokitamycin were low (≤0.25 μg/ml), with clarithromycin MICs being 1 to 3 dilutions lower than those of erythromycin, azithromycin, and rokitamycin. RU 64004 yielded the lowest MICs of all the macrolides tested for erythromycin-susceptible strains (MIC_{90}, 0.016 μg/ml). MICs of azithromycin, clarithromycin, and rokitamycin were also higher for strains which were resistant to erythromycin (≥0.5 μg/ml). In comparison, RU 64004 MICs, although higher than those for erythromycin-susceptible strains, were all ≤2.0 μg/ml (MIC_{90}, 0.25 μg/ml). Although most macrolide-resistant strains were also resistant to clindamycin, 28 of 91 strains (30.7%) were susceptible to clindamycin (MICs, ≤0.125 μg/ml) but resistant to erythromycin. Pristinamycin and quinolone MICs were identical for erythromycin-susceptible and -resistant strains. MICs of β-lactams, trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol were generally higher for erythromycin-resistant than for erythromycin-susceptible strains.

No significant changes in clindamycin or pristinamycin MICs (1- to 2-dilution difference) were observed when results after overnight incubation were compared with those after an additional 24 h. Macrolide MIC increases (≥3 dilutions) that occurred after an additional 24 h were mainly for strains for which erythromycin MICs were ≥4.0 μg/ml. Increased RU 64004 MICs after an additional 24 h did not exceed 1.0 μg/ml. In most cases, increased macrolide MICs occurred for strains which were already resistant after overnight incubation. However, in eight cases, one doubling dilution increase after an additional 24 h made these strains erythromycin resistant by National Committee for Laboratory Standards (NCCLS) criteria (16). The latter strains were also susceptible or intermediate to azithromycin and clarithromycin after overnight incubation and intermediate or resistant after an additional 24 h of incubation, by NCCLS MIC criteria.

TABLE 2. Susceptibility of pneumococci to antimicrobial agents by erythromycin susceptibility

Antimicrobial and erythromycin susceptibility[a]	MIC (μg/ml)		
	Range	50%	90%
Penicillin			
S	0.016–8.0	0.125	4.0
R	0.016–8.0	2.0	4.0
RU 64004			
S	0.004–0.06	0.016	0.016
R	0.016–2.0	0.06	0.25
Erythromycin			
S	0.004–0.25	0.06	0.06
R	1.0–≥128.0	≥128.0	≥128.0
Azithromycin			
S	0.016–0.5	0.06	0.125
R	0.25–≥128.0	≥128.0	≥128.0
Clarithromycin			
S	0.008–0.125	0.03	0.03
R	0.25–≥128.0	32.0	≥128.0
Rokitamycin			
S	0.03–0.5	0.25	0.25
R	0.06–≥128.0	≥128.0	≥128.0
Clindamycin			
S	0.016–0.125	0.06	0.06
R	0.016–≥64.0	≥64.0	≥64.0
Pristinamycin			
S	0.125–0.5	0.25	0.5
R	0.125–1.0	0.5	1.0
Trimethoprim-sulfamethoxazole			
S	0.06–≥16.0	0.5	8.0
R	0.125–≥16.0	4.0	≥16.0
Ciprofloxacin			
S	0.125–4.0	1.0	4.0
R	0.125–4.0	1.0	2.0
Sparfloxacin			
S	0.016–0.5	0.125	0.25
R	0.016–1.0	0.125	0.25
Doxycycline			
S	0.03–16.0	0.125	4.0
R	0.03–≥32.0	4.0	16.0
Chloramphenicol			
S	≤2.0–≥16.0	≤2.0	8.0
R	≤2.0–≥16.0	4.0	≥16.0
Cefuroxime			
S	≤0.016–8.0	0.25	4.0
R	0.03–≥16.0	4.0	8.0
Ceftriaxone			
S	≤0.016–4.0	0.125	2.0
R	0.03–4.0	1.0	2.0
Imipenem			
S	≤0.008–0.25	≤0.008	0.125
R	≤0.008–0.25	0.03	0.125
Vancomycin			
S	0.03–0.5	0.25	0.5
R	0.06–0.5	0.25	0.5

[a] S, susceptible (≤0.25 μg/ml); R, resistant (≥0.5 μg/ml [includes NCCLS intermediate category]).

DISCUSSION

The results of this study confirm the excellent activity of RU 64004 against pneumococci, irrespective of penicillin or erythromycin susceptibility status, and reflect previous preliminary findings (1–3). RU 64004 has a broad spectrum of activity against pneumococci, β-lactamase-positive and -negative *Haemophilus influenzae*, beta-hemolytic and alpha-hemolytic streptococci, enterococci, and *Enterobacteriaceae* (1–3). Although RU 64004 MICs were a few dilutions higher for erythromycin-resistant than for erythromycin-susceptible strains, they were still significantly lower than those of other macrolides. This study confirms the cross-resistance of erythromycin-resistant pneumococci to other macrolides as well as the slightly improved activity of clarithromycin compared to those of erythromycin and azithromycin (5, 12, 14, 17). However, with an NCCLS resistance breakpoint of ≥1.0 μg/ml for both erythromycin and clarithromycin (16), all macrolide-resistant pneumococci would also be expected to be clinically clarithromycin resistant.

It has previously been shown that macrolide-resistant pneumococci are also resistant to clindamycin. Although this is usually the case, this study confirms the existence of macrolide-resistant but clindamycin-susceptible pneumococci (17). Some previous reports of this phenomenon were probably due to the use of microdilution techniques and the interpretation of results after overnight incubation, with concomitant poor growth leading to falsely low MICs. Fasola and coworkers have demonstrated that incubation in CO_2 or prolonged aerobic incu-

bation of microdilution trays is necessary in order to obtain accurate results with clindamycin (8). Incubation of MIC plates for an additional day did not lead to significant differences in clindamycin MICs, providing further support for the phenomenon of dissociated clindamycin and macrolide susceptibility in pneumococci.

Pristinamycin, a streptogramin analog, yielded results which were identical to those of RP 59500 (18). Quinolone MICs were similar to those described previously (18, 20), as were those of β-lactams and vancomycin (13, 19, 21). A significant percentage of penicillin-intermediate and -resistant strains were also resistant to trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol.

In summary, RU 64004 shows great potential for the treatment of infections caused by pneumococci, irrespective of their penicillin or erythromycin susceptibility status. Clinical studies will be necessary in order to test this hypothesis.

ACKNOWLEDGMENTS

This study was supported in part by a grant from Hoechst-Marion-Roussel, Clinical Pharmacology and Anti-Infectives, Paris, France.

We thank J. Liñares (Barcelona, Spain), P. Geslin (Paris, France), A. Marton (Budapest, Hungary), F. Mihalcu (Bucharest, Romania), J. Trupl (Bratislava, Slovakia), L. Setchanova (Sofia, Bulgaria), R. Yoshida (Nagasaki, Japan), and J.-H. Song (Seoul, Korea) for their kind provision of cultures.

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