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Activities of HMR 3004 (RU 64004) and HMR 3647 (RU 66647) Compared to Those of Erythromycin, Azithromycin, Clarithromycin, Roxithromycin, and Eight Other Antimicrobial Agents against Unusual Aerobic and Anaerobic Human and Animal Bite Pathogens Isolated from Skin and Soft Tissue Infections in Humans

ELLIE J. C. GOLDSTEIN,[1,2]* DIANE M. CITRON,[1] SHARON HUNT GERARDO,[1] MARIE HUDSPETH,[1] AND C. VRENI MERRIAM[1]

The R. M. Alden Research Laboratory, Santa Monica-University of California, Los Angeles Medical Center, Santa Monica, California 90404,[1] and University of California, Los Angeles School of Medicine, Los Angeles, California 90024[2]

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The activities of HMR 3004 and HMR 3647 and comparator agents, especially macrolides, were determined by the agar dilution method against 262 aerobic and 120 anaerobic strains isolated from skin and soft tissue infections associated with human and animal bite wounds. HMR 3004 and HMR 3647 were active against almost all aerobic and fastidious facultative isolates (MIC at which 90% of the isolates are inhibited [MIC_{90}], ≤0.5 and 1 μg/ml, respectively) and against all anaerobes [*Bacteroides tectum*, *Porphyromonas macacae* (*salivosa*), *Prevotella heparinolytica*, *Porphyromonas* sp., *Prevotella* sp., and peptostreptococci] at ≤0.25 and ≤0.5 μg/ml, respectively, except *Fusobacterium nucleatum* (HMR 3004, MIC_{90} = 16 μg/ml; HMR 3647, MIC_{90} = 8 μg/ml) and other *Fusobacterium* species (MIC_{90}, 1 and 2 μg/ml, respectively). In general, HMR 3004 and HMR 3647 were more active than any of the macrolides tested. Azithromycin was more active than clarithromycin against all *Pasteurella* species, including *Pasteurella multocida* subsp. *multocida*, *Eikenella corrodens*, and *Fusobacterium* species, while clarithromycin was more active than azithromycin against *Corynebacterium* species, *Weeksella zoohelcum*, *B. tectum*, and *P. heparinolytica*.

While premarket in vitro testing of new antimicrobial compounds is often extensive, these studies focus on typical bacterial pathogens. Little or no data are available about the activities of these new agents against the unusual veterinary pathogens affecting the 4.5 million Americans who are bitten annually by animals (2, 27) and the variety of aerobic and anaerobic veterinary species encountered in their infectious complications (3, 10, 13, 14). Recent advances in molecular microbiological methods have allowed the recognition of many new species, including *Pasteurella* species and subspecies of *Pasteurella multocida* that have different ecological niches and varied host prevalences (17, 23). New anaerobic species associated with bites, such as *Bacteroides tectum*, *Prevotella heparinolytica*, and *Porphyromonas macacae* ("*Porphyromonas salivosa*" [4]) have been recognized and frequently isolated from animal bite wound infections (1, 4). Microbiologists are faced with many challenges when identifying the bacteria isolated from human and animal bite wounds. These isolates may even differ from the same species obtained from other types of human infection (1). Prior susceptibility studies of new and older compounds (11, 12) did not differentiate many of the *Pasteurella* species and subspecies or the *Prevotella* and *Porphyromonas* species, and therefore scant data is available to the clinician on which to base the selection of empirical therapy.

Consequently, the clinician must depend on published studies to guide both empirical and subsequent specific antimicrobial therapeutic choices. While erythromycin is frequently used as an alternative agent for the penicillin-allergic patient, there have been reports of its limited utility in vitro against some bite wound pathogens and clinical reports of its therapeutic failure (19, 21, 26).

HMR 3004 (RU-64004) and HMR 3647 (RU-66647) are new ketolide agents under development. Ketolides are new semisynthetic 14-membered-ring macrolides derived from erythromycin A. They are characterized by having a 3-keto group on the erythronolide A ring instead of a L-cladinose moiety (20, 28). HMR 3647 is characterized by a C_{11-12} carbamate which is linked by an alkyl chain to an imidazolium and pyridinium nucleus. These compounds have been demonstrated to be more active than existing macrolides against common pathogens and also against erythromycin A-resistant gram-positive cocci (efflux and inducible macrolides-lincosamides-streptogramin B) and to have improved antianaerobic activity (5, 6, 18, 28). HMR 3004 and HMR 3647 could therefore offer therapeutic alternatives to treat bite wound infections. In order to determine their activities against the large variety of pathogenic species encountered in bite wound infections, we compared the susceptibilities of 381 recently isolated clinical human and animal bite wound isolates to HMR 3404 and HMR 3647 to their susceptibilities to other commonly used agents.

MATERIALS AND METHODS

The strains used were isolated from bite wounds between 1990 and 1997 and were identified by standard criteria (15–17, 22, 29). The specific sources were dog

* Corresponding author. Mailing address: 2021 Santa Monica Blvd., Suite 640E, Santa Monica, CA 90404. Phone: (310) 315-1511. Fax: (310) 315-3662. E-mail: EJCGMD@aol.com.

TABLE 1. In vitro activities of HMR 3004 (RU-64004), HMR 3647 (RU-66647), and other agents against 382 aerobic and anaerobic animal and human bite pathogens

Organism (no. of isolates) and agent[a]	MIC (μg/ml)		
	Range	50%	90%
Aerobes			
Pasteurella multocida subsp. *multocida* (13)			
HMR 3004	0.125–1	0.5	0.5
HMR 3647	0.25–1	1	1
Erythromycin	1–4	4	4
Azithromycin	0.25–1	1	1
Clarithromycin	0.5–2	2	2
Roxithromycin	1–8	4	4
Cefpodoxime	<0.016–0.06	0.03	0.03
Cefotaxime	<0.016	<0.016	<0.016
Ampicillin	0.06–0.125	0.125	0.125
Ampicillin-sulbactam	0.06–0.125	0.125	0.125
Tetracycline	0.125–0.5	0.25	0.25
Levofloxacin	0.016–0.03	0.016	0.03
Pasteurella multocida subsp. *septica* (14)			
HMR 3004	0.5–1	0.5	1
HMR 3647	1–2	1	1
Erythromycin	1–4	2	4
Azithromycin	0.5–1	1	1
Clarithromycin	1–4	2	4
Roxithromycin	4–8	4	8
Cefpodoxime	<0.016–0.125	0.03	0.125
Cefotaxime	<0.016–0.03	<0.016	0.03
Ampicillin	0.03–0.25	0.125	0.125
Ampicillin-sulbactam	0.06–0.25	0.125	0.25
Tetracycline	0.25–0.5	0.25	0.5
Levofloxacin	0.016–0.03	0.016	0.03
Pasteurella canis (14)			
HMR 3004	0.5	0.5	0.5
HMR 3647	0.5–1	0.5	1
Erythromycin	0.5–4	1	2
Azithromycin	0.125–1	0.5	0.5
Clarithromycin	1–4	2	2
Roxithromycin	2–8	4	4
Cefpodoxime	<0.016–0.06	<0.016	<0.016
Cefotaxime	<0.016	<0.016	<0.016
Ampicillin	<0.016–0.125	0.03	0.06
Ampicillin-sulbactam	<0.016–0.125	0.06	0.125
Tetracycline	<0.016–1	0.25	0.5
Levofloxacin	<0.008–0.03	0.016	0.03
Pasteurella stomatis (11)			
HMR 3004	0.25–1	0.5	1
HMR 3647	0.125–1	0.5	1
Erythromycin	0.25–4	1	2
Azithromycin	0.125–1	0.5	1
Clarithromycin	0.5–4	2	4
Roxithromycin	0.5–8	2	4
Cefpodoxime	<0.016	<0.016	<0.016
Cefotaxime	<0.016	<0.016	<0.016
Ampicillin	<0.016–0.125	0.06	0.125
Ampicillin-sulbactam	0.03–0.125	0.125	0.125
Tetracycline	0.125–2	1	2
Levofloxacin	<0.008–0.03	0.016	0.016
Other *Pasteurella* spp.[b] (11)			
HMR 3004	0.125–2	0.25	1
HMR 3647	0.125–2	0.25	2
Erythromycin	0.25–8	2	4
Azithromycin	0.06–2	0.125	1
Clarithromycin	0.25–8	1	4
Roxithromycin	0.5–16	2	8
Cefpodoxime	<0.016–0.06	<0.016	0.06
Cefotaxime	<0.016	<0.016	<0.016
Ampicillin	<0.016–0.25	0.06	0.125
Ampicillin-sulbactam	0.06–0.25	0.125	0.125
Tetracycline	0.125–2	0.5	1
Levofloxacin	0.016–0.125	0.016	0.03
Actinobacillus and *Haemophilus* spp.[c] (9)			
HMR 3004	<0.016–8	0.25	
HMR 3647	<0.016–8	0.25	
Erythromycin	<0.016–16	1	
Azithromycin	<0.016–8	0.25	
Clarithromycin	<0.016–32	0.5	
Roxithromycin	<0.016–32	1	
Cefpodoxime	<0.016–0.125	0.06	
Cefotaxime	<0.016–0.06	<0.016	
Ampicillin	<0.016–1	0.125	
Ampicillin-sulbactam	0.03–1	0.125	
Tetracycline	<0.016–4	1	
Levofloxacin	<0.008–0.125	0.016	
Corynebacterium aquaticum (9)			
HMR 3004	≤0.016	0.016	
HMR 3647	<0.016–0.03	0.03	
Erythromycin	0.03–0.125	0.03	
Azithromycin	0.03–0.06	0.03	
Clarithromycin	≤0.016–0.03	≤0.016	
Roxithromycin	<0.016–0.06	0.06	
Cefpodoxime	32	32	
Cefotaxime	0.12–16	16	
Ampicillin	2–4	2	
Ampicillin-sulbactam	2	2	
Tetracycline	4–8	8	
Levofloxacin	2	2	
Corynebacterium spp.[d] (17)			
HMR 3004	<0.016–0.06	<0.016	<0.016
HMR 3647	<0.016–0.06	<0.016	<0.016
Erythromycin	<0.016–32	0.03	8
Azithromycin	<0.016–>32	0.06	>32
Clarithromycin	<0.016–2	<0.016	2
Roxithromycin	<0.016–>32	0.03	16
Cefpodoxime	<0.016–32	1	8
Cefotaxime	<0.016–8	0.25	4
Ampicillin	<0.016–4	0.25	2
Ampicillin-sulbactam	<0.016–4	0.25	2
Tetracycline	<0.016–32	0.25	4
Levofloxacin	<0.008–16	0.125	8
EF-4b (20)			
HMR 3004	0.125–1	0.25	0.5
HMR 3647	0.125–1	0.25	1
Erythromycin	0.125–2	0.25	1
Azithromycin	0.06–0.5	0.06	0.25
Clarithromycin	0.06–1	0.125	0.5
Roxithromycin	0.25–4	0.5	1
Cefpodoxime	<0.016–0.5	0.06	0.125
Cefotaxime	<0.016–0.25	0.06	0.06
Ampicillin	0.125–0.5	0.125	0.25
Ampicillin-sulbactam	0.03–0.5	0.125	0.25
Tetracycline	0.125–0.5	0.25	0.25
Levofloxacin	<0.008–0.06	<0.008	0.06
Eikenella corrodens (19)			
HMR 3004	0.03–1	0.25	0.5

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TABLE 1—*Continued*

Organism (no. of isolates) and agent[a]	MIC (μg/ml)		
	Range	50%	90%
HMR 3647	0.03–1	0.5	1
Erythromycin	0.25–16	4	8
Azithromycin	0.125–8	1	4
Clarithromycin	0.25–8	4	4
Roxithromycin	2–16	8	16
Cefpodoxime	<0.016–4	0.125	2
Cefotaxime	0.03–0.5	0.5	0.5
Ampicillin	0.25–1	0.5	0.5
Ampicillin-sulbactam	0.125–0.5	0.5	0.5
Tetracycline	0.125–2	0.5	2
Levofloxacin	<0.008–0.03	0.016	0.03
Moraxella catarrhalis (11)			
HMR 3004	<0.016–1	0.25	0.25
HMR 3647	<0.016–1	0.125	0.25
Erythromycin	<0.016–1	0.25	1
Azithromycin	<0.016–1	0.06	0.125
Clarithromycin	<0.016–1	0.25	0.5
Roxithromycin	<0.016–4	1	1
Cefpodoxime	<0.016–0.5	<0.016	0.06
Cefotaxime	<0.016–0.25	<0.016	0.03
Ampicillin	<0.016–0.5	0.03	0.25
Ampicillin-sulbactam	<0.016–0.125	0.03	0.125
Tetracycline	<0.016–1	0.5	0.5
Levofloxacin	<0.008–0.125	<0.008	0.125
Moraxella spp.[e] (11)			
HMR 3004	<0.016–8	0.125	4
HMR 3647	<0.016–8	0.125	4
Erythromycin	<0.016–8	1	4
Azithromycin	<0.016–1	0.25	1
Clarithromycin	<0.016–8	0.5	4
Roxithromycin	<0.016–16	1	8
Cefpodoxime	<0.016–4	<0.016	2
Cefotaxime	<0.016–4	<0.016	2
Ampicillin	<0.016–2	0.25	0.5
Ampicillin-sulbactam	<0.016–0.25	0.125	0.250%
Tetracycline	<0.016–2	0.25	2
Levofloxacin	<0.008–0.125	<0.008	0.125
Neisseria weaveri (15)			
HMR 3004	<0.016–0.5	0.125	0.25
HMR 3647	<0.016–1	0.125	0.25
Erythromycin	<0.016–1	0.5	1
Azithromycin	<0.016–0.5	0.03	0.125
Clarithromycin	0.25–1	0.5	1
Roxithromycin	<0.016–2	0.125	2
Cefpodoxime	<0.016–0.3	<0.016	<0.016
Cefotaxime	<0.016–0.03	<0.016	0.03
Ampicillin	<0.016–0.25	0.125	0.25
Ampicillin-sulbactam	0.016–0.125	0.06	0.125
Tetracycline	<0.016–0.5	<0.016	0.25
Levofloxacin	<0.008–0.125	<0.008	0.06
Weeksella zoohelcum (10)			
HMR 3004	0.06–0.125	0.06	0.125
HMR 3647	0.25–1	0.5	0.5
Erythromycin	0.125–1	0.5	0.5
Azithromycin	0.5–2	1	1
Clarithromycin	0.06–0.125	0.125	0.125
Roxithromycin	0.125–0.5	0.5	0.5
Cefpodoxime	<0.016–0.25	<0.016	0.03
Cefotaxime	<0.016–0.25	<0.016	0.03
Ampicillin	<0.016–2	0.125	0.125
Ampicillin-sulbactam	<0.016–0.5	0.03	0.125
Tetracycline	1–2	2	2
Levofloxacin	0.03–0.125	0.06	0.125

Continued

TABLE 1—*Continued*

Organism (no. of isolates) and agent[a]	MIC (μg/ml)		
	Range	50%	90%
Staphylococcus aureus (18)			
HMR 3004	0.03–0.06	0.06	0.06
HMR 3647	0.03–0.125	0.06	0.06
Erythromycin	0.06–0.25	0.25	0.25
Azithromycin	0.25–0.5	0.5	0.5
Clarithromycin	0.06–0.25	0.125	0.25
Roxithromycin	0.25–0.5	0.5	0.5
Cefpodoxime	0.25–2	2	2
Cefotaxime	0.25–2	1	2
Ampicillin	0.03–16	1	4
Ampicillin-sulbactam	0.03–4	1	2
Tetracycline	0.25–>32	0.5	16
Levofloxacin	0.016–0.125	0.125	0.125
Staphylococcus epidermidis (10)			
HMR 3004	0.03–>32	0.06	0.125
HMR 3647	0.06–>32	0.06	0.25
Erythromycin	0.125–>32	0.125	32
Azithromycin	0.25–>32	0.25	>32
Clarithromycin	0.25–>32	0.125	32
Roxithromycin	0.25–>32	0.5	>32
Cefpodoxime	0.125–16	0.5	4
Cefotaxime	0.125–8	0.5	4
Ampicillin	0.03–4	0.125	4
Ampicillin-sulbactam	0.06–2	0.25	2
Tetracycline	0.25–>32	0.5	32
Levofloxacin	0.125–0.25	0.125	0.125
Other *Staphylococcus* spp.[f] (18)			
HMR 3004	0.03–>32	0.06	0.06
HMR 3647	0.03–>32	0.06	0.125
Erythromycin	0.125–>32	0.125	>32
Azithromycin	0.06–>32	0.25	>32
Clarithromycin	0.06–>32	0.125	4
Roxithromycin	0.125–>32	0.25	>32
Cefpodoxime	0.125–16	1	4
Cefotaxime	0.125–8	1	4
Ampicillin	0.03–16	0.25	8
Ampicillin-sulbactam	0.03–4	0.125	2
Tetracycline	0.125–>32	0.125	>32
Levofloxacin	0.125–0.5	0.125	0.25
Streptococcus mitis(11)			
HMR 3004	<0.016–0.03	<0.016	<0.016
HMR 3647	<0.016–0.03	<0.016	<0.016
Erythromycin	<0.016–0.25	0.03	0.03
Azithromycin	<0.016–1	0.03	0.06
Clarithromycin	<0.016–1	<0.016	0.03
Roxithromycin	<0.016–4	0.06	0.06
Cefpodoxime	<0.016–0.25	0.125	0.25
Cefotaxime	<0.016–0.25	0.125	0.25
Ampicillin	<0.016–0.5	0.5	0.5
Ampicillin-sulbactam	<0.016–0.5	0.5	0.5
Tetracycline	<0.016–2	0.5	2
Levofloxacin	0.5–1	1	1
Streptococcus spp.[g](17)			
HMR 3004	<0.016	<0.016	<0.016
HMR3647	<0.016–0.03	<0.016	<0.016
Erythromycin	<0.016–0.03	0.03	0.03
Azithromycin	<0.016–0.06	0.03	0.06
Clarithromycin	<0.016–0.25	<0.016	0.03
Roxithromycin	<0.016–1	0.03	0.06
Cefpodoxime	<0.016–0.25	0.125	0.25
Cefotaxime	<0.016–0.125	0.06	0.125
Ampicillin	<0.016–0.125	0.06	0.125
Ampicillin-sulbactam	0.03–0.5	0.06	0.125

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TABLE 1—*Continued*

Organism (no. of isolates) and agent[a]	MIC (μg/ml)		
	Range	50%	90%
Tetracycline	0.25–>32	1	32
Levofloxacin	0.125–1	1	1
Anaerobes			
Bacteroides tectum (11)			
HMR 3004	0.06–0.25	0.125	0.25
HMR 3647	0.5–1	0.5	1
Erythromycin	0.5–1	1	1
Azithromycin	1–2	2	2
Clarithromycin	0.125–0.25	0.125	0.125
Roxithromycin	0.5–1	1	1
Cefpodoxime	<0.016–8	0.125	0.25
Cefotaxime	<0.016–4	0.125	0.125
Ampicillin	<0.016–8	0.03	0.03
Ampicillin-sulbactam	0.03–0.5	0.03	0.06
Tetracycline	0.25–8	0.25	0.5
Levofloxacin	0.06–0.25	0.25	0.25
Clindamycin	<0.016	<0.016	<0.016
Metronidazole	<0.06–0.5	0.5	0.5
Bacteroides forsythus (3)			
HMR 3004	<0.016–0.06		
HMR 3647	0.125–0.25		
Erythromycin	0.5		
Azithromycin	0.5–1		
Clarithromycin	0.06		
Roxithromycin	0.25		
Cefpodoxime	<0.016		
Cefotaxime	<0.016		
Ampicillin	<0.016–0.03		
Ampicillin-sulbactam	0.03		
Tetracycline	0.25		
Levofloxacin	0.125–0.25		
Clindamycin	<0.016–0.03		
Metronidazole	<0.06		
Fusobacterium nucleatum (12)			
HMR 3004	<0.016–16	1	16
HMR 3647	<0.016–8	2	8
Erythromycin	<0.016–>32	4	>32
Azithromycin	0.125–8	0.5	2
Clarithromycin	<0.016–32	4	32
Roxithromycin	<0.016–>32	8	>32
Cefpodoxime	<0.016–32	0.06	2
Cefotaxime	<0.016–>32	0.06	2
Ampicillin	<0.016–>32	<0.016	0.5
Ampicillin-sulbactam	<0.016–0.5	0.125	0.5
Tetracycline	0.125–2	0.25	2
Levofloxacin	0.5–>8	0.5	>8
Clindamycin	<0.016–0.125	0.03	0.125
Metronidazole	<0.06–0.25	<0.06	0.125
Fusobacterium spp.[h] (10)			
HMR 3004	<0.016–4	0.5	1
HMR 3647	<0.016–2	0.5	2
Erythromycin	<0.016–16	2	16
Azithromycin	0.125–2	0.25	1
Clarithromycin	0.06–32	2	8
Roxithromycin	0.06–32	8	16
Cefpodoxime	<0.016–0.25	0.06	0.25
Cefotaxime	<0.016–0.25	0.06	0.25
Ampicillin	<0.016–32	0.06	0.5
Ampicillin-sulbactam	<0.016–1	0.06	0.125
Tetracycline	0.03–1	0.25	0.5
Levofloxacin	<0.016–>8	2	>8

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TABLE 1—*Continued*

Organism (no. of isolates) and agent[a]	MIC (μg/ml)		
	Range	50%	90%
Clindamycin	<0.016–0.06	0.03	0.06
Metronidazole	<0.06–0.5	0.125	0.5
Peptostreptococcus spp.[i] (15)			
HMR 3004	<0.016–0.125	<0.016	0.06
HMR 3647	<0.016–0.25	0.03	0.06
Erythromycin	0.06–>32	1	>32
Azithromycin	0.5–>32	1	>32
Clarithromycin	0.06–>32	0.5	>32
Roxithromycin	0.125–>32	1	>32
Cefpodoxime	0.06–16	1	4
Cefotaxime	0.03–32	0.25	2
Ampicillin	<0.016–1	0.125	0.5
Ampicillin-sulbactam	<0.016–0.5	0.125	0.5
Tetracycline	0.125–32	0.25	32
Levofloxacin	0.06–4	0.5	1
Clindamycin	<0.016–2	0.125	0.5
Metronidazole	0.25–8	0.5	2
Porphyromonas salivosa (12)			
HMR 3004	<0.016	<0.016	<0.016
HMR 3647	0.03–0.125	0.06	0.06
Erythromycin	0.06–0.25	0.25	0.25
Azithromycin	0.25–1	0.5	0.5
Clarithromycin	0.03–0.125	0.06	0.125
Roxithromycin	0.125–0.25	0.25	0.25
Cefpodoxime	<0.016–2	1	2
Cefotaxime	0.03–2	2	2
Ampicillin	<0.016–2	1	1
Ampicillin-sulbactam	<0.016–0.06	0.03	0.06
Tetracycline	0.25–32	0.5	0.5
Levofloxacin	0.06–0.5	0.25	0.5
Clindamycin	<0.016	<0.016	<0.016
Metronidazole	<0.06–0.5	0.125	0.5
Porphyromonas gingivalis (9)			
HMR 3004	<0.016	<0.016	
HMR 3647	0.03–0.125	0.06	
Erythromycin	0.06–1	0.5	
Azithromycin	0.06–1	0.5	
Clarithromycin	0.03–0.06	0.06	
Roxithromycin	0.125–0.25	0.125	
Cefpodoxime	<0.016–0.03	<0.016	
Cefotaxime	<0.016–0.06	0.03	
Ampicillin	<0.016–0.03	<0.016	
Ampicillin-sulbactam	<0.016–0.03	0.03	
Tetracycline	0.125–0.5	0.25	
Levofloxacin	0.06–0.25	0.125	
Clindamycin	<0.016	<0.016	
Metronidazole	<0.06–0.25	<0.06	
Porphyromonas spp.[j] (13)			
HMR 3004	<0.016	<0.016	<0.016
HMR 3647	<0.016–0.25	0.03	0.06
Erythromycin	0.06–>32	0.125	0.25
Azithromycin	0.06–32	0.25	0.5
Clarithromycin	0.03–>32	0.06	0.125
Roxithromycin	0.03–>32	0.125	0.25
Cefpodoxime	<0.016–0.25	0.03	0.06
Cefotaxime	<0.016–0.25	0.03	0.25
Ampicillin	<0.016–0.25	0.016	0.25
Ampicillin-sulbactam	<0.016–0.125	<0.016	0.03
Tetracycline	0.06–2	0.25	1
Levofloxacin	0.06–2	1	2
Clindamycin	<0.016–0.125	<0.016	<0.016
Metronidazole	0.06–2	0.25	1

Continued on the following page

TABLE 1—*Continued*

Organism (no. of isolates) and agent[a]	MIC (μg/ml)		
	Range	50%	90%
Prevotella heparinolytica (12)			
HMR 3004	0.03–0.125	0.06	0.125
HMR 3647	0.06–0.5	0.125	0.25
Erythromycin	0.25–0.5	0.25	0.5
Azithromycin	0.5	0.5	0.5
Clarithromycin	0.06–0.125	0.125	0.125
Roxithromycin	0.5–1	0.5	0.5
Cefpodoxime	0.25–1	0.5	1
Cefotaxime	0.25–0.5	0.25	0.5
Ampicillin	0.06–0.125	0.125	0.125
Ampicillin-sulbactam	0.06–0.25	0.125	0.125
Tetracycline	0.25–16	0.25	8
Levofloxacin	0.5–1	0.5	1
Clindamycin	<0.016	<0.016	<0.016
Metronidazole	0.125–0.25	0.25	0.25
Prevotella spp.[k] (21)			
HMR 3004	<0.016–0.25	0.03	0.125
HMR 3647	<0.016–1	0.25	0.5
Erythromycin	0.06–4	1	2
Azithromycin	0.125–4	0.5	2
Clarithromycin	0.03–0.25	0.125	0.125
Roxithromycin	0.06–2	0.5	1
Cefpodoxime	0.06–>8	0.25	8
Cefotaxime	0.03–16	0.5	4
Ampicillin	0.03–16	0.25	8
Ampicillin-sulbactam	0.03–1	0.25	0.5
Tetracycline	0.25–>32	0.5	16
Levofloxacin	0.016–1	0.5	1
Clindamycin	<0.016–0.06	<0.016	0.03
Metronidazole	<0.06–2	0.5	2

[a] The following isolates and susceptibilities are not included in the table: *Brevibacterium* sp. (1), *Rothia* sp. (1), and *Flavobacterium* sp. (2), all of which were susceptible to ≤0.016 μg/ml of HMR 3304 or HMR 3467; and *Eubacterium* sp. (2), for which the MICs were <0.03 μg/ml (HMR 3004) and 0.125 μg/ml (HMR 3467).

[b] *Pasteurella* species include *P. dagmatis*, 7; *P. haemolytica*, 1; *P. multocida* subsp. *gallicida*, 2; and *P. testudinis*, 1.

[c] *Actinobacillus* and *Haemophilus* species include *A. actinomycetemcomitans*, 2; *A. seminis*, 2; and *Haemophilus* species, 5.

[d] *Corynebacterium* species include *C. xerosis*, 1; *C. minutissimum*, 9; *C. jeikeium*, 2; and other *Corynebacterium* species, 5.

[e] *Moraxella* species include *M. osloensis*, 3; *M. atlantae*, 1; *M. nonliquefaciens*, 1; other *Moraxella* species, 6.

[f] *Staphylococcus* species include *S. capitis*, 1; *S. haemolyticus*, 1; *S. hominis*, 2; *S. hyicus*, 2; *S. intermedius*, 6; *S. warneri*, 4; *S. sciuri* subsp. *lentus*, 2.

[g] *Streptococcus* species include viridans streptococci, 2; *S. constellatus*, 2; *S. equinus*, 1; *S. intermedius*, 1; *S. mutans*, 2; *S. sanguis* I, 5; and *S. sanguis* II, 4.

[h] *Fusobacterium* species include *F. necrophorum*, 1; *F. russii*, 6 (including one beta-lactamase-producing strain); and other fusobacteria, 3.

[i] *Peptostreptococcus* species include *P. anaerobius*, 7; *P. micros*, 3; *P. magnus*, 1; *P. prevotii*, 1; *P. asaccharolyticus*, 1; and other *Peptostreptococcus* species, 2.

[j] *Porphyromonas* species include *P. cangingivalis*, 5; *P. canoris*, 4; *P. cansulci*, 1; *P. circumdentaria*, 2; and *Porphyromonas levii*, 1.

[k] *Prevotella* species include *P. bivia*, 4; *P. buccae*, 3; *P. intermedia*, 4; *P. melaninogenica*, 4; *P. denticola*, 1; *P. loescheii*, 1; *P. zoogleoformans*, 3; and *P. oralis*, 1.

bites (n = 156), cat bites (n = 164), human bites (n = 39), and bites of other or unknown animal origin (n = 23). Twelve ATCC strains and five control strains were also tested. The numbers and species of isolates tested are given in Table 1.

Standard laboratory powders were obtained from the following suppliers: HMR 3404, HMR 3647, cefotaxime, and roxithromycin from Roussel Uclaf, Paris, France; azithromycin and ampicillin-sulbactam from Pfizer Inc., New York, N.Y.; levofloxacin from R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J.; clarithromycin from Abbott Laboratories, Abbott Park, Ill.; tetracycline from Lederle Laboratories, Pearl River, N.Y.; cefpodoxime and clindamycin from Pharmacia & Upjohn, Kalamazoo, Mich.; and metronidazole from Searle Research and Development, Skokie, Ill.

Frozen cultures were transferred at least twice, on Trypticase soy agar supplemented with 5% sheep blood or chocolate agar for the aerobes and on brucella agar supplemented with hemin, vitamin K_1, and 5% sheep blood for the anaerobes, to ensure purity and good growth. Susceptibility testing was performed according to National Committee for Clinical Laboratory Standards standards (24, 25). Brucella agar supplemented with hemin, vitamin K_1, and 5% laked sheep blood was the basal medium used for anaerobic species and for *Eikenella corrodens* and *Weeksella zoohelcum*. Mueller-Hinton agar was used for staphylococci, and Mueller-Hinton agar supplemented with 5% sheep blood was used for the remainder of the organisms. Antimicrobial agents were reconstituted according to the manufacturers' instructions. Serial twofold dilutions of antimicrobial agents were prepared on the day of the test and added to the media in various concentrations (micrograms per milliliter).

The agar plates were inoculated with a Steers replicator (Craft Machine Inc., Chester, Pa.). The inoculum used for aerobic bacteria was 10^4 CFU per spot, and the inoculum used for *E. corrodens* and anaerobic bacteria was 10^5 CFU per spot. Control plates without antimicrobial agents were inoculated before and after each set of drug-containing plates. Plates with aerobic isolates were incubated at 35°C in an aerobic environment for 24 h and then examined. *E. corrodens* and streptococci were incubated in 5% CO_2 for 48 h and were then examined.

Control strains tested included *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Bacteroides fragilis* ATCC 25285, and *Eubacterium lentum* ATCC 43055. In addition, *E. corrodens* ATCC 23834, *Pasteurella multocida* subsp. *multocida* ATCC 43137 and 12947, *Pasteurella haemolytica* ATCC 33396, *Pasteurella multocida* subsp. *gallicida* ATCC 51689, *Pasteurella multocida* subsp *septica* ATCC 51688, *Pasteurella stomatis* ATCC 43327, *Pasteurella dagmatis* ATCC 43325, *Pasteurella canis* ATCC 43326, *Pasteurella testudinis* ATCC 33688, *Moraxella osloensis* ATCC 19976, and *Moraxella lacunata* ATCC 17967 were tested simultaneously with the appropriate plates and environments. The MIC was defined as the lowest concentration of an agent that yielded no growth or a marked change in the appearance of growth compared to that on the growth control plate.

RESULTS AND DISCUSSION

The activities of HMR 3004, HMR 3647, and the comparator agents against the bite wound isolates tested are shown in Table 1. The susceptibilities of the control strains tested were within reference ranges. HMR 3004 was the most active macrolide-ketolide compound tested. HMR 3647 was active either at the same concentrations (micrograms per milliliter) as HMR 3004 or generally within one to two doubling dilutions.

Results for *P. multocida* subsp. *multocida* showed that HMR 3004 (MIC at which 90% of the isolates are inhibited [MIC_{90}], 0.5 μg/ml) was more active than HMR 3647 (MIC_{90}, 1 μg/ml), azithromycin (MIC_{90}, 1 μg/ml), and clarithromycin (MIC_{90}, 2 μg/ml) and eight times more active than erythromycin (MIC_{90}, 4 μg/ml) and roxithromycin (MIC_{90}, 4 μg/ml). Against *P. multocida* subsp. *septica*, *P. canis*, *P. stomatis*, and *P. dagmatis*, HMR 3004 was two to eight times more active than erythromycin, clarithromycin, and roxithromycin and equivalent to HMR 3647 and azithromycin.

Schulin et al. (28) noted that HMR 3004 was active against gram-positive organisms, including multiply resistant staphylococci and streptococci. In our study HMR 3004 was active against *S. aureus* (MIC_{90} ≤ 0.06 μg/ml) and *Staphylococcus epidermidis* (MIC_{90} ≤ 0.125 μg/ml), including two of four macrolide-resistant staphylococci (MICs for one strain each of *S. epidermidis* and *Staphylococcus warneri* were 32 μg/ml). Both Schulin et al. (28) and Jamjian et al. (18) noted only an occasional strain of coagulase-negative staphylococci to be resistant to HMR 3004. In our study, the MIC_{90}s for all other fastidious aerobic bite pathogens were ≤0.5 μg/ml. Of the 262 aerobic isolates tested, the MICs for two strains of *M. osloensis* and two strains of *Actinobacillus actinomycetemcomitans* were 4 to 8 μg/ml.

Against the various other *Pasteurella* species susceptibility differences occurred with azithromycin (MIC_{90}, ≤1 μg/ml) and clarithromycin (MIC_{90}, ≤4.0 μg/ml) (Table 1). All *Pasteurella* species were susceptible to the beta-lactams tested as well as to levofloxacin and tetracycline.

All anaerobes were susceptible to ≤0.25-μg/ml HMR 3004 and to ≤0.5-μg/ml HMR 3647 except for 5 of 22 *Fusobacterium*

nucleatum and *Fusobacterium* species, for which the MICs of HMR 3004 were ≥4.0 μg/ml. HMR 3647 was one to two dilutions more active than HMR 3004 against *F. nucleatum* and other *Fusobacterium* species. Ednie et al. (5, 6) tested HMR 3004 and HMR 3647 against a variety of clinical anaerobic isolates, most of which were different species than those tested in our study. In one study (5) all of their *F. nucleatum* isolates were susceptible to ≤4 μg of HMR 3004/ml, while the MICs for two of our isolates were 16 μg/ml. This difference might be accounted for by the different sources of our isolates, or it might be due to their use of Oxyrase added to the test medium for macrolides and consequent incubation in an aerobic rather than a CO_2-containing anaerobic environment. It has been shown that the CO_2 in the atmosphere of incubation can variably effect the in vitro activity of some macrolides against the isolates tested due to a pH effect (7–9). However, in their second study (5), they tested nine strains of *F. nucleatum* (it is unclear if these fusobacteria were the same as those used in the first study, as they noted that 60% of all isolates were new strains but did not further specify changes). They noted that the MICs for at least two isolates of *F. nucleatum* were 8 or 16 μg/ml. In the second study (5), they used Wilkins-Chalgren agar supplemented with 5% sheep blood and Oxyrase and adjusted to pH 8.0. They incubated strains that grew poorly without CO_2 supplementation, including the fusobacteria, in a CO_2 environment, while we used supplemented brucella blood agar in an anaerobic environment containing CO_2 to assure luxuriant growth.

HMR 3004 and HMR 3647 appear to have improved activities compared to those of the macrolides tested against the full spectrum of pathogens isolated from human and animal bite wounds and merit further evaluation.

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