ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May, 1993, p. 1150–1153
0066-4804/93/051150-04$02.00/0

Vol. 37, No. 5

NOTES

Comparative Susceptibilities of 173 Aerobic and Anaerobic Bite Wound Isolates to Sparfloxacin, Temafloxacin, Clarithromycin, and Older Agents

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Received 29 October 1992/Accepted 8 February 1993

The in vitro activities of sparfloxacin, temafloxacin, ciprofloxacin, ofloxacin, clarithromycin, erythromycin, tetracycline, cephalothin, penicillin G, and amoxicillin-clavulanic acid against 173 recent clinical bite wound isolates were determined by agar dilution. Sparfloxacin was active against all strains (MIC for 90% of strains tested, ≤1 μg/ml) except for most fusobacteria and one-third of the *Prevotella* spp. The other fluoroquinolones had similar activities but higher MICs, especially for streptococci. Clarithromycin was more active against many isolates including *Pasteurella multocida* than erythromycin, with MICs of ≤2 μg/ml (versus 4 μg/ml for erythromycin).

Since many laboratories are unable to perform in vitro susceptibility studies with fastidious aerobic and anaerobic bacteria, clinicians must sometimes rely on the medical literature to guide therapeutic choices, both empiric and specific, for human and animal bite wounds. Prior studies (3, 6, 8, 9) have noted a high percentage of β-lactamase-producing bacteria and the emergence of resistance to commonly used antimicrobial agents in several genera of isolates obtained from bite wounds. Consequently, information about newer alternative therapeutic agents and their in vitro activities against the full spectrum of species isolated from bite wounds is needed to help guide therapeutic choices.

The use of fluoroquinolones, such as ciprofloxacin and ofloxacin (6, 16), for treating bite wound infections has been considered. They have been noted to be active against the aerobic but not many of the anaerobic bacteria isolated from human and animal bite wounds (6, 16). Consequently, there is interest in the potential utility of other quinolones. Sparfloxacin (AT-4140, RP 64206, and PD 131501) is a new fluoroquinolone agent that has an expanded spectrum of activity against aerobic and anaerobic bacteria (1, 4, 7). Temafloxacin, recently voluntarily removed from the market by its manufacturer, was also considered potentially useful in bite wound therapy (5, 7, 10). Erythromycin, while suboptimally active against *Pasteurella multocida*, must sometimes be used, albeit cautiously, for the treatment of bite wound infections in multidrug-allergic patients, children, and pregnant women. Clarithromycin, a new macrolide, has been noted to have improved pharmacokinetics and in vitro activity compared with those of erythromycin (11, 15).

Consequently, we determined the comparative susceptibilities of 112 aerobic and 61 anaerobic bite wound isolates to these new antimicrobial agents and compared the activities of these new drugs with those of older agents.

All bacteria studied (Table 1) were recent clinical isolates and were identified by standard criteria (2, 12, 14, 18). The sources and number of isolates were as follows: dog bites, 66; cat bites, 37; human bites, 45; other animal bites, 22; and bites of unknown origin, 3.

Susceptibility powders were kindly supplied as follows: ciprofloxacin, Miles Laboratories, New Haven, Conn.; ofloxacin, R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J.; sparfloxacin, Rhone-Poulenc Rorer, Collegeville, Pa.; temafloxacin and clarithromycin, Abbott Laboratories, North Chicago, Ill.; penicillin, cephalothin, and erythromycin, Eli Lilly & Co., Indianapolis, Ind.; amoxicillin-clavulanic acid (tested in a ratio of 2:1), SmithKline Beecham, Philadelphia, Pa.; tetracycline, Pfizer Inc., New York, N.Y.

Strains were taken from frozen stock cultures and transferred twice to ensure purity and good growth. Bacteria were tested by standard procedures by the appropriate methods for the particular organism as previously described (6). Brucella blood agar supplemented with hemin, vitamin K_1, and 5% laked sheep blood was the basal medium used for anaerobic isolates.

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 *Eikenella 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. Care was taken to avoid drug carryover for the fluoroquinolones tested. Plates with aerobic isolates were incubated at 35°C in an aerobic environment for 24 h and then examined. *E. corrodens* and viridans group streptococci were incubated in 5% CO_2 for 48 h and were then examined. Anaerobic bacteria were incubated for 48 h in anaerobic jars and were then examined. Control strains of *Staphylococcus aureus* ATCC 25923, *E. corrodens* ATCC 23834, *P. multocida* ATCC 43137, *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotaomicron* ATCC 29741 were tested simultaneously with the appropriate plates and environments.

The results of this study are summarized in Table 1. *P.*

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TABLE 1. Comparative activities of sparfloxacin, ciprofloxacin, ofloxacin, penicillin G, amoxicillin-clavulanic acid, cephalothin, erythromycin, clarithromycin, and tetracycline against 173 strains of bacteria isolated from bite wounds

Organism (no. of isolates) and antimicrobial agent	MIC (μg/ml)[a]			
	Range	50%	90%	GM
Eikenella corrodens (16)				
Sparfloxacin	≤0.03–0.06	≤0.03	0.06	0.04
Temafloxacin	≤0.03–0.125	0.06	0.125	0.05
Ciprofloxacin	≤0.03–0.5	≤0.03	≤0.03	0.04
Ofloxacin	≤0.03–0.125	≤0.03	0.06	0.04
Penicillin G[b]	0.06–4	1	4	1.12
Amoxicillin-clavulanic acid	0.06–0.5	0.5	0.5	0.43
Cephalothin	0.25–32	8	16	8.48
Erythromycin	1–16	8	8	6.36
Clarithromycin	≤0.03–2	2	2	1.59
Tetracycline	1–8	2	4	1.94
Pasteurella multocida (16)				
Sparfloxacin	≤0.03–≤0.03	≤0.03	≤0.03	0.03
Temafloxacin	≤0.03–≤0.03	≤0.03	≤0.03	0.03
Ciprofloxacin	≤0.03–≤0.03	≤0.03	≤0.03	0.03
Ofloxacin	≤0.03–0.06	≤0.03	0.06	0.03
Penicillin G[b]	≤0.03–0.25	0.125	0.25	0.20
Amoxicillin-clavulanic acid	0.125–0.25	0.25	0.25	0.21
Cephalothin	0.125–0.25	0.25	0.25	0.21
Erythromycin	1–4	2	4	1.80
Clarithromycin	1–2	2	2	1.60
Tetracycline	0.25–1	0.5	0.5	0.48
EF-4 (13)				
Sparfloxacin	≤0.03–≤0.03	≤0.03	≤0.03	0.03
Temafloxacin	≤0.03–0.06	≤0.03	0.06	0.04
Ciprofloxacin	≤0.03–≤0.03	≤0.03	≤0.03	0.03
Ofloxacin	≤0.03–0.06	≤0.03	0.06	0.04
Penicillin G[b]	0.06–4	0.5	4	0.50
Amoxicillin-clavulanic acid	0.125–1	0.5	0.5	0.38
Cephalothin	0.125–32	2	32	2.0
Erythromycin	0.25–4	1	4	0.94
Clarithromycin	0.125–4	1	2	0.54
Tetracycline	0.125–1	0.25	1	0.39
Moraxella spp. (10)				
Sparfloxacin	≤0.03–≤0.06	≤0.03	≤0.03	0.03
Temafloxacin	≤0.03–0.125	≤0.03	0.06	0.04
Ciprofloxacin	≤0.03–0.25	≤0.03	0.06	0.04
Ofloxacin	≤0.03–0.25	≤0.03	0.06	0.04
Penicillin G[b]	≤0.03–1	0.5	1	0.25
Amoxicillin-clavulanic acid	≤0.03–1	0.25	0.5	0.21
Cephalothin	0.25–4	2	4	1.60
Erythromycin	1–4	1	4	1.60
Clarithromycin	≤0.03–1	0.5	1	0.27
Tetracycline	≤0.03–4	1	2	0.55
Staphylococcus aureus (13)				
Sparfloxacin	0.06–0.125	0.06	0.125	0.10
Temafloxacin	0.125–0.25	0.125	0.25	0.22
Ciprofloxacin	0.25–0.5	0.5	0.5	0.43
Ofloxacin	0.125–0.5	0.5	0.5	0.42
Penicillin G[b]	≤0.03–8	1	8	0.62
Amoxicillin-clavulanic acid	0.125–1	0.5	1	0.46
Cephalothin	0.125–0.5	0.25	0.25	0.25
Erythromycin	0.125–0.25	0.25	0.25	0.25
Clarithromycin	0.125–0.25	0.25	0.25	0.19
Tetracycline	0.5–1	0.5	1	0.60
Staphylococcus spp.[c] (21)				
Sparfloxacin	≤0.03–1	0.125	0.125	0.13
Temafloxacin	0.125–2	0.25	0.25	0.22
Ciprofloxacin	0.125–2	0.125	0.5	0.20
Ofloxacin	0.25–2	0.25	0.5	0.42
Penicillin G[b]	≤0.03–32	0.125	1	0.19

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TABLE 1—*Continued*

Organism (no. of isolates) and antimicrobial agent	MIC (μg/ml)[a]			
	Range	50%	90%	GM
Amoxicillin-clavulanic acid	≤0.03–0.5	0.125	0.25	0.11
Cephalothin	≤0.03–0.5	0.06	0.5	0.11
Erythromycin	≤0.03–>32	0.25	0.5	0.29
Clarithromycin	≤0.03–>32	0.125	0.25	0.21
Tetracycline	0.25–>32	0.5	>32	1.10
Streptococcus spp. (23)				
Sparfloxacin	≤0.03–0.5	0.25	0.5	0.22
Temafloxacin	≤0.03–1	0.5	1	0.34
Ciprofloxacin	≤0.03–4	1	2	0.65
Ofloxacin	≤0.03–2	1	2	0.83
Penicillin G[b]	≤0.03–0.125	0.06	0.125	0.07
Amoxicillin-clavulanic acid	≤0.03–0.5	0.06	0.25	0.08
Cephalothin	0.125–2	0.5	2	0.47
Erythromycin	≤0.03–8	0.06	8	0.16
Clarithromycin	≤0.03–4	≤0.03	2	0.09
Tetracycline	0.125–>32	0.5	32	1.30
Prevotella and *Porphyromonas* spp.[d] (29)				
Sparfloxacin	0.25–16	0.5	2	0.93
Temafloxacin	0.06–8	0.5	1	0.45
Ciprofloxacin	0.25–32	1	2	1.10
Ofloxacin	0.25–16	1	2	0.98
Penicillin G[b]	≤0.03–>32	0.125	16	0.26
Amoxicillin-clavulanic acid	≤0.03–0.5	0.125	0.25	0.23
Cephalothin	≤0.03–>32	1	32	1.72
Erythromycin	0.125–8	0.5	4	0.71
Clarithromycin	≤0.03–4	0.125	0.25	0.14
Tetracycline	0.5–>32	1	32	1.69
Fusobacterium spp.[e] (20)				
Sparfloxacin	0.06–>32	32	>32	10.0
Temafloxacin	≤0.03–>32	4	32	2.7
Ciprofloxacin	≤0.03–32	8	32	6.0
Ofloxacin	0.25–>32	32	>32	13.6
Penicillin G[b]	≥0.03–1	0.06	0.5	0.10
Amoxicillin-clavulanic acid	≤0.03–0.5	0.06	0.25	0.09
Cephalothin	≤0.03–2	0.06	0.25	0.12
Erythromycin	0.25–>32	8	>32	10.4
Clarithromycin	≤0.03–>32	8	>32	5.6
Tetracycline	0.25–16	0.5	2	0.65
Peptostreptococcus spp.[f] (12)				
Sparfloxacin	0.125–4	0.5	1	0.48
Temafloxacin	0.125–2	0.5	1	0.42
Ciprofloxacin	0.25–8	0.5	2	0.85
Ofloxacin	0.25–16	1	8	1.25
Penicillin G[b]	≤0.03–16	0.125	0.25	0.16
Amoxicillin-clavulanic acid	≤0.03–0.5	0.25	0.5	0.15
Cephalothin	0.06–2	0.25	2	0.34
Erythromycin	0.06–>32	1	>32	1.25
Clarithromycin	0.06–>32	0.5	>32	0.63
Tetracycline	0.25–>32	2	>32	3.0

[a] 50 and 90%, MICs for 50 and 90% of isolates tested, respectively; GM, geometric mean.
[b] Expressed in units per milliliter.
[c] *Staphylococcus epidermidis* (*n* = 7), *S. intermedius* (*n* = 3), *S. hominis* (*n* = 3), *S. cohnii* (*n* = 1), *S. warneri* (*n* = 5), and *S. capitis* (*n* = 2).
[d] *Prevotella intermedia* (*n* = 5), *Prevotella bivia* (*n* = 3), *Prevotella buccae* (*n* = 5), *Prevotella oralis* (*n* = 2), *Prevotella melaninogenica* (*n* = 4), *Prevotella loeschii* (*n* = 1), *Prevotella oris* (*n* = 1), *Prevotella* spp. (*n* = 4), *Porphyromonas asaccharolytica* (*n* = 3), and *Porphyromonas gingivalis* (*n* = 1).
[e] *Fusobacterium nucleatum* (*n* = 11), *F. necrophorum* (*n* = 2), and *Fusobacterium* spp. (*n* = 7).
[f] *Peptostreptococcus prevotii* (*n* = 2), *P. micros* (*n* = 3), *P. magnus* (*n* = 1), *P. anaerobius* (*n* = 5), and a *Peptostreptococcus* sp. (1).

multocida and *E. corrodens* isolates were susceptible to the agents tested, with the exception of erythromycin. Care should be taken in interpreting the susceptibility to cephalothin, since the breakpoint used is more applicable to parenteral than oral dosing regimens. In addition, all susceptibility determinations are currently based on achievable concentrations in serum and may not be relevant to the concentrations achieved at the site of infection, such as the

skin and soft tissue or bone affected by bites. The anaerobic isolates showed variable susceptibilities to the various agents. Sparfloxacin was generally more active than ciprofloxacin and ofloxacin, but significant resistance was seen in the *Fusobacterium* species tested. Clarithromycin was generally more active than erythromycin, including against *P. multocida* and *Prevotella* spp., but also showed poor activity against *Fusobacterium* spp.

Bite wounds are common injuries affecting one to two million Americans annually, which can be extrapolated to one of two Americans suffering a bite wound in their lifetime (13). Beta-lactam agents such as penicillin, amoxicillin-clavulanic acid, cefuroxime, and cefoxitin have generally been favored, yet a number of patients will be allergic or intolerant to beta-lactam agents and therefore will require alternative therapy.

In our prior studies (8, 9), caution has been urged when erythromycin must be employed when *P. multocida* is a potential pathogen. We previously tested roxithromycin (RU-985), a new macrolide, and showed it to be consistently less active than erythromycin against both aerobic and anaerobic bite wound isolates on a weight basis (9). Clarithromycin was consistently more active than erythromycin by 1 to 4 dilutions. Organisms that have previously been considered resistant to erythromycin, such as *P. multocida*, *E. corrodens*, and *Prevotella* spp., were susceptible to clarithromycin. However, until clinical data are available, careful clinical monitoring seems prudent with its use. Discrepancies between the disk diffusion and broth dilution methods when testing erythromycin against *P. multocida* have been noted (17). Consequently, clinicians also need to be cautious in interpreting clarithromycin disk susceptibility data for *P. multocida* until the potential differences between methodologies are examined.

Several fluoroquinolones, such as ciprofloxacin and ofloxacin, have been previously noted to possess in vitro activities against a variety of aerobic and fastidious bite wound isolates including *P. multocida* and *E. corrodens* but not streptococci (6, 16). However, against the anaerobic bite wound bacteria they were less active. Sparfloxacin was generally more active than ciprofloxacin and ofloxacin against the *Prevotella* spp. and *Peptostreptococcus* spp. studied. However, a majority of *Fusobacterium* spp. were resistant to all three fluoroquinolones. Because of its activity against all aerobic bite wound pathogens studied, it seems that sparfloxacin merits clinical evaluation for the therapy of bite wound infections.

The other agents studied exhibited susceptibilities similar to those noted in prior reports (6, 8). Tetracycline was generally active against all isolates with the exception of several strains of streptococci and peptostreptococci. Amoxicillin-clavulanic acid was active against all isolates tested. Cephalothin was more active against *P. multocida* than we have noted in previous studies (6, 8). This should be interpreted with caution since levels of first generation cephalosporins achieved with oral doses are markedly lower than those achieved with parenteral doses of cephalothin. In addition, we have previously noted many clinical failures when cephalexin has been used to treat bite wound infections due to *P. multocida* (unpublished data, personal experience).

We thank Margarita I. Ostovari for technical assistance and Alice E. Goldstein and Judee H. Knight for general assistance.

This study was supported in part by a grant from Rhone-Poulenc Rorer and the Maurice Goldstein Public Health Research Foundation.

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