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In Vitro Activity of Ro 23-9424, a Dual-Action Antibacterial Agent, against Bacterial Isolates from Cancer Patients Compared with Those of Other Agents

KENNETH V. I. ROLSTON,* HIEU T. NGUYEN, DAI H. HO, BARBARA LEBLANC, AND GERALD P. BODEY

Section of Infectious Diseases, Department of Medical Specialties, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

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The in vitro activity of Ro 23-9424 against bacterial isolates from patients with cancer was compared with those of fleroxacin, ciprofloxacin, cefoperazone, and ceftazidime. Ro 23-9424 inhibited the majority of the members of the family *Enterobacteriaceae* and all *Aeromonas* isolates at a concentration of ≤1.0 μg/ml. It was also active against *Acinetobacter* spp. and *Haemophilus influenzae*, including β-lactamase-producing strains. The MIC for 90% of isolates (MIC_{90}) of *Pseudomonas aeruginosa* was 16.0 μg/ml. All group A and B streptococci were inhibited by ≤0.25 μg/ml, and 90% of group G streptococci and *Streptococcus pneumoniae* were inhibited by 1.0 μg/ml. All methicillin-susceptible strains of *Staphylococcus aureus* and 60% of methicillin-resistant strains were susceptible to 2.0 μg of Ro 23-9424 per ml, whereas the MIC_{90} for *Staphylococcus epidermidis* and *Staphylococcus hominis* isolates was 4.0 μg/ml. *Staphylococcus haemolyticus* and *Enterococcus* spp. were less susceptible; MIC_{90}s for them were 16.0 and 32.0 μg/ml. Ro 23-9424 has a broad antibacterial spectrum and potential utility for therapy of infections in cancer patients.

Bacterial infections remain an important cause of morbidity and mortality in neutropenic patients (3). Until recently, most infections in such patients were caused by enteric, aerobic, gram-negative bacilli (2). Gram-positive infections have reemerged in most cancer treatment centers and now account for 50 to 70% of microbiologically documented infections (17). Extended-spectrum cephalosporins have been used extensively for the empiric therapy of febrile episodes in neutropenic patients (8, 13, 14). Since 1980, a number of new quinolone-carboxylic acid compounds have been synthesized, and some of these have been evaluated for prophylaxis and therapy of infections in cancer patients (5, 10, 11, 15, 16). Ro 23-9424 is a novel antibacterial agent in which the microbiologically active metabolite of cefotaxime, desacetylcefotaxime, has been linked by an ester bond at the C-3 position to the carboxy group of the long-acting quinolone fleroxacin (6). We determined the activity of Ro 23-9424 against clinical isolates obtained from cancer patients and compared its activity with those of cefoperazone and ceftazidime, the most commonly used extended-spectrum cephalosporins at our institution. Fleroxacin and ciprofloxacin were also used for comparison.

All bacterial strains were isolated from cancer patients admitted to the University of Texas M. D. Anderson Cancer Center during the past 5 years. Greater than 90% of these isolates were from blood culture specimens. The rest were from various sites, including sputum, urine, wounds, cerebrospinal fluid, and bile. Only a single isolate per patient was used to avoid duplication. Many isolates came from patients who were treated with cephalosporins, carbapenems, monobactams, or quinolones. The isolates were stored in our laboratory by use of ultrafreezing techniques.

Ro 23-9424 and fleroxacin were gifts from Hoffmann-La Roche Inc., Nutley, N.J. Ciprofloxacin, cefoperazone, and ceftazidime were obtained from their respective U.S. manufacturers. Susceptibility testing was performed by a previously described microtiter broth dilution method and in accordance with guidelines established by the National Committee for Clinical Laboratory Standards (12, 16). Organisms were inoculated into broth and incubated overnight at 37°C. Appropriate dilutions were made so that the final inoculum tested was 5×10^5 CFU/ml. The test medium was cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) for all organisms except *Corynebacterium jeikeium*, which was tested in brain heart infusion broth with 5% rabbit serum, and the streptococci, which were tested in cation-adjusted Mueller-Hinton broth with 2% lysed horse blood. The antibiotic concentrations tested ranged between 64.0 and 0.03 μg/ml. *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212 were used as control strains. The MIC was defined as the lowest concentration of each drug that inhibited visible growth after incubation at 35°C for 16 to 20 h.

A total of 793 isolates representing 36 bacterial species were tested. The overall results are shown in Table 1. Ro 23-9424 inhibited all *Aeromonas* isolates and 90% of the members of the family *Enterobacteriaceae* (with the exception of *Citrobacter freundii* and *Enterobacter cloacae*) at ≤1.0 μg/ml. The MIC for 90% of isolates (MIC_{90}) of *Acinetobacter* spp. was 4.0 μg/ml. *Alcaligenes denitrificans* subsp. *xylosoxidans* isolates were relatively resistant. Ro 23-9424 inhibited 90% of the *Haemophilus influenzae* isolates, including β-lactamase-producing isolates, at a concentration of ≤0.12 μg/ml. Its activity against *P. aeruginosa*, *Xanthomonas maltophilia*, *Pseudomonas fluorescens* and *Pseudomonas putida* was moderate (MIC_{90}, 8.0 to 16.0 μg/ml).

Ro 23-9424 inhibited 100% of *Bacillus cereus* isolates and >90% of *C. jeikeium* isolates at a concentration of 4.0 μg/ml. The MIC_{90} for *E. faecalis* was 16.0 μg/ml, and that for *Enterococcus faecium* was 32.0 μg/ml. For *Listeria monocytogenes* isolates, the MIC_{90} was 16.0 μg/ml. Ro 23-9424 was two- to fourfold more active against methicillin-suscep-

* Corresponding author.

TABLE 1. In vitro activities of Ro 23-9424 and comparative drugs

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml) 50%	MIC (μg/ml) 90%
Acinetobacter anitratus (20)	Ro 23-9424	2.0	2.0
	Fleroxacin	0.25	1.0
	Ciprofloxacin	0.25	0.5
	Cefoperazone	4.0	8.0
	Ceftazidime	4.0	8.0
Acinetobacter lwoffii (20)	Ro 23-9424	2.0	4.0
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.06	0.25
	Cefoperazone	2.0	8.0
	Ceftazidime	2.0	4.0
Aeromonas spp. (20)	Ro 23-9424	0.12	0.5
	Fleroxacin	0.03	0.12
	Ciprofloxacin	≤0.03	0.12
	Cefoperazone	0.25	2.0
	Ceftazidime	0.25	2.0
Alcaligenes denitrificans subsp. *xylosoxidans* (15)	Ro 23-9424	16.0	16.0
	Fleroxacin	4.0	4.0
	Ciprofloxacin	2.05	4.0
	Cefoperazone	4.0	>64.0
	Ceftazidime	4.0	>64.0
Citrobacter diversus (20)	Ro 23-9424	0.25	0.5
	Fleroxacin	0.06	0.12
	Ciprofloxacin	≤0.03	≤0.03
	Cefoperazone	0.5	32.0
	Ceftazidime	0.25	32.0
Citrobacter freundii (25)	Ro 23-9424	2.0	4.0
	Fleroxacin	0.06	1.0
	Ciprofloxacin	0.06	0.5
	Cefoperazone	16.0	64.0
	Ceftazidime	32.0	>64.0
Enterobacter aerogenes (20)	Ro 23-9424	0.5	1.0
	Fleroxacin	0.12	0.5
	Ciprofloxacin	≤0.03	0.06
	Cefoperazone	2.0	4.0
	Ceftazidime	4.0	4.0
Enterobacter agglomerans (20)	Ro 23-9424	0.5	1.0
	Fleroxacin	0.06	0.12
	Ciprofloxacin	≤0.03	0.06
	Cefoperazone	4.0	4.0
	Ceftazidime	0.5	1.0
Enterobacter cloacae (20)	Ro 23-9424	0.25	2.0
	Fleroxacin	0.12	0.5
	Ciprofloxacin	≤0.03	0.5
	Cefoperazone	8.0	64.0
	Ceftazidime	2.0	64.0
Escherichia coli (40)	Ro 23-9424	0.25	0.5
	Fleroxacin	0.06	0.12
	Ciprofloxacin	≤0.03	≤0.03
	Cefoperazone	0.25	0.5
	Ceftazidime	0.12	0.5
Haemophilus influenzae (14)	Ro 23-9424	0.06	0.12
	Fleroxacin	≤0.03	0.06
	Ciprofloxacin	≤0.03	≤0.03
	Cefoperazone	0.06	0.5
	Ceftazidime	0.12	1.0
Klebsiella pneumoniae (25)	Ro 23-9424	0.25	1.0
	Fleroxacin	0.12	0.25
	Ciprofloxacin	≤0.03	0.12
	Cefoperazone	0.25	1.0
	Ceftazidime	0.5	1.0
Klebsiella oxytoca (20)	Ro 23-9424	0.25	0.5
	Fleroxacin	0.12	0.12
	Ciprofloxacin	≤0.03	≤0.03
	Cefoperazone	0.12	1.0
	Ceftazidime	0.06	0.5
Morganella morganii (13)	Ro 23-9424	0.25	0.5
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.25	0.5
	Cefoperazone	0.5	2.0
	Ceftazidime	0.06	1.0
Proteus mirabilis (20)	Ro 23-9424	0.25	1.0
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.12	0.12
	Cefoperazone	0.06	0.5
	Ceftazidime	≤0.03	0.06
Proteus vulgaris (20)	Ro 23-9424	0.25	1.0
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.12	0.12
	Cefoperazone	0.06	0.5
	Ceftazidime	≤0.03	0.06
Pseudomonas aeruginosa (40)	Ro 23-9424	4.0	16.0
	Fleroxacin	1.0	4.0
	Ciprofloxacin	0.12	1.0
	Cefoperazone	4.0	32.0
	Ceftazidime	2.0	8.0
Pseudomonas fluorescens (20)	Ro 23-9424	4.0	16.0
	Fleroxacin	2.0	4.0
	Ciprofloxacin	0.12	0.25
	Cefoperazone	8.0	16.0
	Ceftazidime	4.0	16.0
Pseudomonas putida (20)	Ro 23-9424	4.0	16.0
	Fleroxacin	4.0	8.0
	Ciprofloxacin	0.12	0.5
	Cefoperazone	4.0	16.0
	Ceftazidime	4.0	32.0
Salmonella spp. (15)	Ro 23-9424	0.25	0.5
	Fleroxacin	≤0.03	2.0
	Ciprofloxacin	≤0.03	1.0
	Cefoperazone	0.03	0.12
	Ceftazidime	0.03	0.5
Serratia marcescens (20)	Ro 23-9424	1.0	1.0
	Fleroxacin	0.25	0.25
	Ciprofloxacin	0.12	0.25
	Cefoperazone	1.0	8.0
	Ceftazidime	1.0	4.0
Xanthomonas maltophilia (20)	Ro 23-9424	4.0	8.0
	Fleroxacin	2.0	8.0
	Ciprofloxacin	2.0	8.0
	Cefoperazone	8.0	64.0
	Ceftazidime	32.0	>64.0

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TABLE 1—*Continued*

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TABLE 1—*Continued*

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml) 50%	MIC (μg/ml) 90%
Bacillus cereus (20)	Ro 23-9424	1.0	2.0
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.06	0.12
	Cefoperazone	2.0	16.0
	Ceftazidime	4.0	32.0
Corynebacterium jeikeium (20)	Ro 23-9424	4.0	4.0
	Fleroxacin	1.0	1.0
	Ciprofloxacin	0.5	1.0
	Cefoperazone	32.0	64.0
	Ceftazidime	32.0	>64.0
Enterococcus faecalis (25)	Ro 23-9424	4.0	16.0
	Fleroxacin	4.0	8.0
	Ciprofloxacin	1.0	2.0
	Cefoperazone	16.0	32.0
	Ceftazidime	>64.0	>64.0
Enterococcus faecium (14)	Ro 23-9424	8.0	32.0
	Fleroxacin	8.0	16.0
	Ciprofloxacin	1.0	2.0
	Cefoperazone	>64.0	>64.0
	Ceftazidime	>64.0	>64.0
Listeria monocytogenes (15)	Ro 23-9424	8.0	16.0
	Fleroxacin	4.0	4.0
	Ciprofloxacin	1.0	2.0
	Cefoperazone	2.0	16.0
	Ceftazidime	4.0	16.0
Staphylococcus aureus (20), penicillin G susceptible	Ro 23-9424	1.0	2.0
	Fleroxacin	0.5	1.0
	Ciprofloxacin	0.25	0.5
	Cefoperazone	1.0	2.0
	Ceftazidime	2.0	4.0
Staphylococcus aureus (35), methicillin susceptible	Ro 23-9424	2.0	2.0
	Fleroxacin	0.5	0.5
	Ciprofloxacin	0.25	0.5
	Cefoperazone	1.0	4.0
	Ceftazidime	2.0	16.0
Staphylococcus aureus (20), methicillin resistant (1987–1990)	Ro 23-9424	2.0	16.0
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.25	0.5
	Cefoperazone	>64.0	>64.0
	Ceftazidime	>64.0	>64.0
Staphylococcus aureus (20), methicillin resistant (1991)	Ro 23-9424	2.0	16.0
	Fleroxacin	2.0	16.0
	Ciprofloxacin	1.0	16.0
	Cefoperazone	>64.0	>64.0
	Ceftazidime	>64.0	>64.0
Staphylococcus epidermidis (15), methicillin susceptible	Ro 23-9424	2.0	4.0
	Fleroxacin	1.0	1.0
	Ciprofloxacin	0.25	0.25
	Cefoperazone	8.0	32.0
	Ceftazidime	32.0	>64.0
Staphylococcus epidermidis (10), methicillin resistant (1987–1990)	Ro 23-9424	2.0	4.0
	Fleroxacin	1.0	1.0
	Ciprofloxacin	0.25	0.25
	Cefoperazone	8.0	32.0
	Ceftazidime	32.0	>64.0
Staphylococcus epidermidis (10), methicillin resistant (1991)	Ro 23-9424	2.0	8.0
	Fleroxacin	1.0	8.0
	Ciprofloxacin	1.0	8.0
	Cefoperazone	>64.0	>64.0
	Ceftazidime	>64.0	>64.0
Staphylococcus haemolyticus (20), methicillin resistant	Ro 23-9424	2.0	16.0
	Fleroxacin	0.5	1.0
	Ciprofloxacin	0.25	0.5
	Cefoperazone	>64.0	>64.0
	Ceftazidime	>64.0	>64.0
Staphylococcus hominis (20)	Ro 23-9424	2.0	4.0
	Fleroxacin	0.5	1.0
	Ciprofloxacin	0.25	0.25
	Cefoperazone	8.0	32.0
	Ceftazidime	32.0	>64.0
Staphylococcus saprophyticus (12)	Ro 23-9424	0.5	1.0
	Fleroxacin	0.25	0.5
	Ciprofloxacin	0.12	0.5
	Cefoperazone	8.0	16.0
	Ceftazidime	16.0	32.0
Streptococcus pyogenes (20)	Ro 23-9424	0.06	0.25
	Fleroxacin	2.0	4.0
	Ciprofloxacin	0.5	2.0
	Cefoperazone	0.5	1.0
	Ceftazidime	1.0	4.0
Streptococcus agalactiae (20)	Ro 23-9424	0.12	0.25
	Fleroxacin	4.0	8.0
	Ciprofloxacin	2.0	2.0
	Cefoperazone	0.5	0.5
	Ceftazidime	1.0	4.0
Streptococcus spp., group G (20)	Ro 23-9424	0.12	1.0
	Fleroxacin	4.0	8.0
	Ciprofloxacin	0.5	2.0
	Cefoperazone	0.5	1.0
	Ceftazidime	1.0	4.0
Streptococcus pneumoniae (20)	Ro 23-9424	0.25	1.0
	Fleroxacin	8.0	16.0
	Ciprofloxacin	2.0	4.0
	Cefoperazone	0.5	2.0
	Ceftazidime	0.5	2.0

tible *Staphylococcus* isolates (including coagulase-negative staphylococci) than against methicillin-resistant isolates. All streptococcal isolates were susceptible to 1.0 μg of Ro 23-9424 per ml.

Ro 23-9424 was less active than ciprofloxacin against the majority of gram-negative organisms tested. It was consistently four- to eightfold more active than ceftazidime and cefoperazone against gram-negative isolates except *E. coli*, *Klebsiella* spp., *Proteus* spp., and *Salmonella* spp., for which similar MIC_{90}s were obtained.

Ro 23-9424 was more active than cefoperazone and ceftazidime against most gram-positive isolates. Ciprofloxacin and fleroxacin were more active than Ro 23-9424 against *Enterococcus* spp. and methicillin-susceptible and methicillin-resistant *Staphylococcus* spp. isolated before the end of 1990 but were less active against most *Streptococcus* spp.

Quinolone-resistant staphylococcal isolates have appeared at our institution since the beginning of 1991, but the activity of Ro 23-9424 does not appear to be significantly different against these organisms. Ro 23-9424 was active against >95% of isolates that were resistant to the cephalosporins ceftazidime and cefoperazone.

With the resurgence of gram-positive infections and the continuing association of gram-negative infections with neutropenic patients, the search for potent, extended-spectrum antimicrobial agents continues. To provide broad coverage, empiric antibiotic regimens generally consist of an aminoglycoside and a beta-lactam (an antipseudomonal penicillin or an extended-spectrum cephalosporin) in combination (2). Recently, the extended-spectrum cephalosporins cefoperazone and ceftazidime and the quinolone ciprofloxacin were used as single agents for this group of patients (11, 13–15). The extended-spectrum cephalosporins were associated with response rates ranging from 75 to 95% for gram-negative, aerobic bacterial infections. They were also effective against streptococci but were less effective against many other gram-positive pathogens. Antimicrobial prophylaxis with newer quinolones such as norfloxacin and ciprofloxacin has been shown to reduce the incidence of gram-negative infections in patients with hematologic malignancies but either has had no effect on or occasionally has led to an increase in the frequency of gram-positive infections, presumably because of the poor activity of these agents against streptococci (5, 10, 18). The quinolones alone are also not very effective for the therapy of gram-positive infections in neutropenic patients (11).

Ro 23-9424 is representative of a new class of antimicrobial agents with a dual mechanism of action and potent, extended-spectrum activity. This study shows that Ro 23-9424 has excellent activity against the majority of gram-positive and gram-negative organisms isolated from cancer patients. These results are similar to those of Beskid et al. (1), Jones et al. (9), and Gu and Neu (7), who evaluated the activity of Ro 23-9424 against clinical isolates from various sources. The potential advantages of this type of dual action compound include the possibility of preventing or delaying the development of bacterial resistance, activity against β-lactamase-producing organisms because of the quinolone moiety, and activity against streptococci because of the cephalosporin moiety. The compound has been shown to be extremely active in experimental infections in animal models. Results of pharmacokinetic studies in animals suggest that Ro 23-9424 is eliminated primarily in the urine by excretion of the intact molecule, rather than by hydrolysis to fleroxacin and desacetylcefotaxime (4). This pattern of elimination is typical of cephalosporins. In summary, Ro 23-9424 is a promising new compound with a dual mechanism of action and a broad antimicrobial spectrum. If human pharmacokinetic and toxicologic properties of Ro 23-9424 are found to be favorable, it will deserve to be clinically evaluated for a variety of indications, including initial empiric antimicrobial coverage in neutropenic cancer patients.

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