ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1986, p. 945–947
0066-4804/86/050945-03$02.00/0

Vol. 29, No. 5

Antimicrobial Spectrum of Ro 15-8074/001, a New Oral Cephalosporin

MARK G. THOMAS†* AND SELWYN D. R. LANG
Middlemore Hospital, Auckland, New Zealand

Received 15 October 1985/Accepted 30 January 1986

The activity of Ro 15-8074/001 was compared with that of cefaclor, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, norfloxacin, and ceftriaxone against 225 clinical isolates. It was more active than cefaclor, amoxicillin-clavulanic acid, and trimethoprim-sulfamethoxazole against members of the family *Enterobacteriaceae* and *Haemophilus influenzae* and had activity similar to that of cefaclor against nonenterococcal streptococci. It was not usefully active against *Pseudomonas aeruginosa*, *Streptococcus faecalis*, or most isolates of staphylococci.

Ro 15-8075 (Fig. 1A) is the pivaloylomethoxyester of an aminothiazolyl cephalosporin. After oral administration and absorption the ester group is enzymatically split to produce the free acid Ro 15-8074 (Fig. 1B). Peak levels in serum of 5 μg of Ro 15-8074 per ml are achieved following oral administration of 1 g of Ro 15-8075, and 80 to 100% of the free acid is excreted in the urine over the first 24 h. When administered to mice with experimental infections due to a range of gram-positive or -negative organisms, curative doses for 50% (of mice) of Ro 15-8075 were 5 to 100 times lower than those of cephalexin (data on file, F. Hoffmann-La Roche and Co. Ltd., Basel, Switzerland). We used the sodium salt (Ro 15-8074/001) of the free acid to compare the activity of this compound with that of four other oral antibiotics and ceftriaxone against a variety of bacteria.

Ro 15-8074/001 was a gift from F. Hoffman-La Roche. All other antibiotics were donated by their respective manufacturers. Antimicrobial activity was determined by an agar dilution method with fresh serial dilutions of compounds prepared according to the instructions of the manufacturer. The inoculum was prepared from a fresh overnight broth culture adjusted to a McFarland 0.5 standard and then diluted to deliver 10^5 CFU with a replicating spot device. *Haemophilus influenzae* and nonenterococcal streptococci were tested on Mueller-Hinton agar supplemented with 5% chocolatized horse blood and 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.) incubated in 8% CO_2 at 37°C for 18 h. All other isolates were tested on Mueller-Hinton agar incubated in air at 37°C for 18 h. Serial dilutions of trimethoprim-sulfamethoxazole (TMP-SMX) were supplemented with 5% lysed horse blood. Susceptibility to amoxicillin-clavulanic acid was determined by using a constant ratio of amoxicillin to clavulanic acid of 2:1.

The MIC was defined as the lowest concentration of antibiotic that resulted in inhibition of visible growth or growth of ≤3 colonies. The strains tested were 225 isolates from specimens recently submitted to the Middlemore Hospital microbiology laboratory. All isolates were identified by standard laboratory procedures, and to avoid duplication only a single isolate per patient was tested. Control organisms were *Escherichia coli* NCTC 11560, *E. coli* ATCC 35218, *E. coli* ATCC 25922, *Staphylococcus aureus* NCTC 11561, *S. aureus* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853.

The comparative activity of the six antimicrobial agents tested are summarized in Table 1. Ro 15-8074/001 inhibited 98 isolates (79%) of members of the family *Enterobacteriaceae* at concentrations ≤1.0 μg/ml and 119 isolates (96%) at concentrations ≤8.0 μg/ml. In contrast cefaclor inhibited 35 isolates (28%) of *Enterobacteriaceae* at concentrations ≤1.0 μg/ml and 85 isolates (69%) at concentrations ≤8.0 μg/ml. Of the 39 cefaclor-resistant (MIC, ≥16 μg/ml) *Enterobacteriaceae* isolates, 34 (87%) were inhibited by ≤8.0 μg of Ro 15-8074/001 per ml. In general, Ro 15-8074/001 was more active than amoxicillin-clavulanic acid and TMP-SMX but less active than norfloxacin against the *Enterobacteriaceae*. It had a similar spectrum of activity to ceftriaxone, but MICs of ceftriaxone were usually two to three $\log_2$ dilutions lower.

Ro 15-8074/001 was not active against *P. aeruginosa* (11 isolates; MIC, ≥256). It was more active than cefaclor against *Acinetobacter* sp. and was more active than cefaclor,

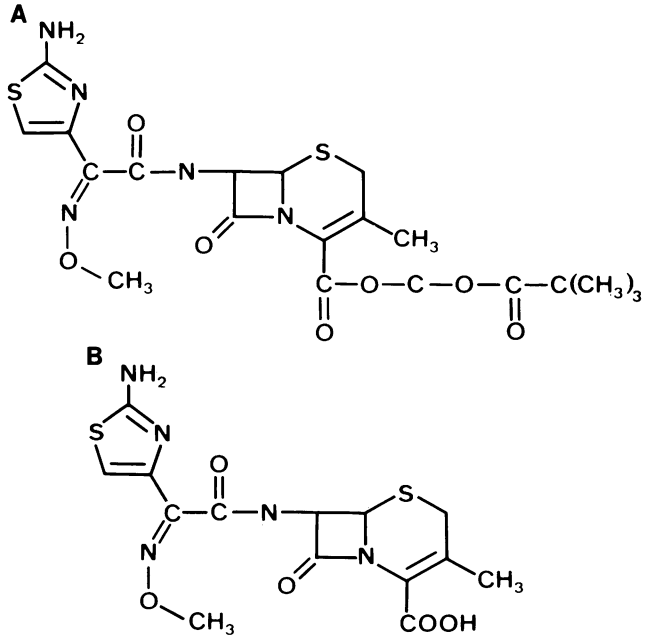

FIG. 1. Structures of Ro 15-8075 (A) and Ro 15-8074 (B).

* Corresponding author.
† Present address: Communicable Diseases Unit, St. George's Hospital, London SW17 0QT, England.

TABLE 1. Susceptibility of bacterial isolates to Ro 15-8074/001 and five other antibiotics

Organism (no. of isolates)	Compound	MIC (μg/ml)		
		Range	50%[a]	90%[b]
Escherichia coli (41)	Ro 15-8074/001	0.03–4.0	1.0	1.0
	Cefaclor	0.25–32	4.0	8.0
	Amoxicillin-clavulanic acid[c]	0.5–16	4.0	8.0
	TMP-SMX[d]	0.5–16	2.0	8.0
	Norfloxacin	0.03–1.0	0.125	0.25
	Ceftriaxone	≤0.015–0.125	0.06	0.125
Klebsiella spp. (27)	Ro 15-8074/001	0.125–≥256	0.25	1.0
	Cefaclor	0.5–≥256	1.0	≥256
	Amoxicillin-clavulanic acid	1.0–32	4.0	32
	TMP-SMX	1.0–≥256	2.0	≥256
	Norfloxacin	0.6–16	0.25	2.0
	Ceftriaxone	0.03–8.0	0.125	0.25
Proteus mirabilis (16)	Ro 15-8074/001	0.06–0.125	0.06	0.125
	Cefaclor	0.5–32	1.0	2.0
	Amoxicillin-clavulanic acid	0.5–64	1.0	4.0
	TMP-SMX	2.0–≥256	2.0	32
	Norfloxacin	0.125–1.0	0.125	0.5
	Ceftriaxone	≤0.015–0.03	≤0.015	0.03
Proteus spp. (indole positive) (8)	Ro 15-8074/001	0.06–≥256		≥256
	Cefaclor	128–≥256		≥256
	Amoxicillin-clavulanic acid	4.0–≥256		≥256
	TMP-SMX	2.0–4.0		4.0
	Norfloxacin	0.06–4.0		4.0
	Ceftriaxone	≤0.015–2.0		1.0
Enterobacter spp. (20)	Ro 15-8074/001	0.06–≥256	2.0	8.0
	Cefaclor	2.0–≥256	≥256	≥256
	Amoxicillin-clavulanic acid	4.0–128	64	128
	TMP-SMX	0.5–≥256	2.0	4.0
	Norfloxacin	0.06–2.0	0.125	1.0
	Ceftriaxone	0.03–32	0.25	8.0
Citrobacter spp. (12)	Ro 15-8074/001	0.25–2.0	1.0	2.0
	Cefaclor	0.5–128	4.0	128
	Cefaclor	0.5–128	4.0	128
	Amoxicillin-clavulanic acid	1.0–64	4.0	16
	TMP-SMX	2.0–≥256	4.0	≥256
	Norfloxacin	0.06–0.25	0.125	0.25
	Ceftriaxone	0.06–0.25	0.06	0.25
Acinetobacter spp. (6)	Ro 15-8074/001	1.0–32		32
	Cefaclor	16–≥256		128
	Amoxicillin-clavulanic acid	1.0–32		16
	TMP-SMX	1.0–≥256		8.0
	Norfloxacin	1.0–≥256		16
	Ceftriaxone	1.0–32		32
Haemophilus influenzae (12)[e]	Ro 15-8074/001	0.125–4.0	0.25	0.25
	Cefaclor	2.0–32	4.0	8.0
	Amoxicillin-clavulanic acid	0.5–4.0	0.5	1.0
	TMP-SMX	1.0–16	2.0	16
	Norfloxacin	0.06–0.25	0.06	0.125
	Ceftriaxone	≤0.015–0.125	≤0.015	≤0.015
Staphylococcus aureus (methicillin sensitive) (17)	Ro 15-8074/001	1.0–64	32	64
	Cefaclor	2.0–8.0	4.0	8.0
	Amoxicillin-clavulanic acid	≤0.015–0.25	0.125	0.25
	TMP-SMX	1.0–4.0	2.0	2.0
	Norfloxacin	0.5–2.0	1.0	2.0
	Ceftriaxone	1.0–4.0	4.0	4.0
Coagulase-negative staphylococci (three methicillin sensitive) (9)	Ro 15-8074/001	8.0–≥256		≥256
	Cefaclor	0.5–64		64
	Amoxicillin-clavulanic acid	≤0.015–32		16
	TMP-SMX	1.0–8.0		8.0
	Norfloxacin	0.5–2.0		1.0
	Ceftriaxone	1.0–≥256		≥256
Streptococcus pyogenes (12)	Ro 15-8074/001	0.03–0.125	0.06	0.06
	Cefaclor	0.03–0.06	0.06	0.06
	Amoxicillin-clavulanic acid	0.03	0.03	0.03
	TMP-SMX	2.0–8.0	8.0	8.0
	Norfloxacin	4.0–8.0	8.0	8.0
	Ceftriaxone	≤0.015–0.06	0.03	0.06

Continued on following page

TABLE 1—*Continued*

Organism (no. of isolates)	Compound	MIC (μg/ml)		
		Range	50%[a]	90%[b]
Streptococcus agalactiae (10)	Ro 15-8074/001	1.0	1.0	1.0
	Cefaclor	0.25–0.5	0.25	0.5
	Amoxicillin-clavulanic acid	0.06–0.125	0.06	0.125
	TMP-SMX	4.0–8.0	4.0	8.0
	Norfloxacin	4.0–8.0	4.0	8.0
	Ceftriaxone	0.03–0.06	0.03	0.06
Streptococcus pneumoniae (14)	Ro 15-8074/001	0.125–0.5	0.5	0.5
	Cefaclor	0.125–0.25	0.25	0.25
	Amoxicillin-clavulanic acid	≤0.015	≤0.015	≤0.015
	TMP-SMX	4.0–32	8.0	16
	Norfloxacin	4.0–16	8.0	16
	Ceftriaxone	≤0.015–0.03	≤0.015	0.03

[a] Concentration required to inhibit 50% of isolates.
[b] Concentration required to inhibit 90% of isolates.
[c] MICs of amoxicillin-elavulanic acid expressed as the concentration of amoxicillin present (amoxicillin clavulanic acid ratio = 2:1).
[d] MICs of TMP-SMX expressed as the concentration of SMX present (TMP/SMX ratio = 1:20).
[e] All isolates beta-lactamase negative.

amoxicillin-clavulanic acid, and TMP-SMX against *H. influenzae*.

Ro 15-8074/001 had poor activity against staphylococci and *Streptococcus faecalis* (10 isolates; MIC, 16 to ≥256). Its activity against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Streptococcus agalactiae* was similar to that of cefaclor and greater than that of TMP-SMX and norfloxacin. In general amoxicillin-clavulanic acid was the most active agent against staphylococci and streptococci.

MICs of Ro 15-8074/001 for control organisms were 0.5 μg/ml for *E. coli* ATCC 35218 and *E. coli* NCTC 11560; 0.5 to 1.0 μg/ml for *E. coli* ATCC 25922; 16 μg/ml for *S. aureus* ATCC 25923; 32 μg/ml for *S. aureus* NCTC 11561; and ≥256 μg/ml for *P. aeruginosa* ATCC 27853.

The results of this study indicate that Ro 15-8074/001 is an effective antimicrobial agent against routine isolates of members of the family *Enterobacteriaceae*, *H. influenzae*, and nonenterococcal streptococci. Other workers have found that Ro 15-8074/001 is more active than cefaclor, cefadroxil, ampicillin, and TMP-SMX against the *Enterobacteriaceae* (2) and more active than amoxicillin-clavulanic acid and cefaclor against pencillinase-producing and nonpenicillinase-producing *Neisseria gonorrhoeae* (1). Further studies are indicated to determine the clinical efficacy of this new oral cephalosporin.

This study was supported by a grant from F. Hoffmann-La Roche.

LITERATURE CITED

1. **Ng, W. S., P. Y. Chau, Y. K. Leung, and P. C. L. Wong.** 1985. *In vitro* activity of Ro 15-8074, a new oral cephalosporin, against *Neisseria gonorrhoeae*. Antimicrob. Agents Chemother. **28**:461–463.
2. **Peeters, M., and P. Piot.** 1985. *In vitro* activity of Ro 15-8074, a new oral cephalosporin. J. Antimicrob. Chemother. **16**:469–473.