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GR-20263: a New Aminothiazolyl Cephalosporin with High Activity Against *Pseudomonas* and *Enterobacteriaceae*

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The in vitro activity of GR-20263, a new aminothiazolyl cephalosporin, was compared with the activities of other β-lactam antibiotics by using 800 clinical bacterial isolates. GR-20263 was highly active (inhibition of 90% of the isolates between 0.03 and 1 μg/ml) against the common *Enterobacteriaceae* and 5 to 20 times more active than cefuroxime, cefoxitin, and cephalothin. GR-20263 was three to six times less active than cefotaxime against *Escherichia coli, Klebsiella pneumoniae, Salmonella,* and *Shigella,* but three to four times more active than cefotaxime against *Proteus vulgaris* and *Serratia marcescens.* The activity of GR-20263 against *Pseudomonas aeruginosa* (with minimal inhibitory concentrations of 2 and 8 μg/ml for 90 and 100% of the isolates, respectively) was similar to that of tobramycin, 2 times that of cefsulodin, 5 times that of piperacillin, and 10 times that of cefotaxime. Against *Haemophilus influenzae* GR-20263 was three times more active than ampicillin. The beta-lactamase-producing strains were as susceptible to GR-20263 as the beta-lactamase-negative strains. GR-20263 was less active than cefotaxime and ampicillin against *Staphylococcus aureus.*

Recent research in the development of the cephalosporins has produced a third generation, consisting of compounds like cefotaxime and moxalactam, the 1-oxa-β-lactam LY-127935. These new antibiotics are distinguished from their predecessors cefamandole, cefuroxime, and cefoxitin by the fact that they combine a very high stability to beta-lactamases with a much broader spectrum of activity and a greater potency against gram-negative organisms (1-3, 5-8). The only gap in their spectrum is their moderate activity against *Pseudomonas aeruginosa* and other *Pseudomonas* species. GR-20263, a new aminothiazolyl cephalosporin (Fig. 1) developed by Glaxo Group Research Ltd., Greenford, England, promises to fill that gap (P. B. Harper, S. M. Kirby, and C. H. O'Callaghan, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 559, 1979). In the present study we compared the in vitro activities of GR-20263 and other β-lactam antibiotics against a wide range of species cultured from clinical isolates. In the investigations of the *Pseudomonas* strains the most active cephalosporin (cefsulodin) and the most effective aminoglycoside (tobramycin) were included in the comparison.

MATERIALS AND METHODS

Antibiotics. GR-20263 and cefuroxime were supplied by Glaxo Laboratories, cephalothin and tobramycin were provided by Eli Lilly Research Laboratories, and cefoxitin was supplied by Merck Sharp & Dohme. Cefotaxime was obtained from Hoechst A. G., piperacillin was from American Cyanamid Co., Lederle Laboratories, cefsulodin was from Ciba-Geigy, and ampicillin was a gift from Beecham Research Laboratories.

Strains. The strains examined in this study were clinical isolates from specimens submitted to the Diagnostic Microbiology Laboratory, University Hospital St Rafaël, Leuven, Belgium. The isolates listed in Tables 1 and 2 without further specification were unselected within each species. In addition, a number of isolates were selected for resistance to ampicillin or cephalothin, as indicated below.

Susceptibility tests. A total of 731 strains of gram-negative bacilli and 70 strains of gram-positive cocci were tested for antimicrobial susceptibility by using an agar dilution technique with DST agar (Oxoid). The DST agar was supplemented with 5% horse blood to support the growth of streptococci and with 5% lysed blood to support the growth of *Haemophilus influenzae.* Overnight cultures in Trypticase soy broth (BBL Microbiology Systems) were further diluted and inoculated with an automatic multipoint inoculator, which delivered spots of broth with final inocula of 10^4 to 10^5 colony-forming units (CFU). The plates with twofold serial dilutions of the antibiotics were pre-

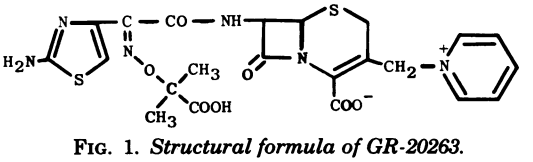

FIG. 1. *Structural formula of GR-20263.*

TABLE 1. *Comparative activities of GR-20263 and other β-lactams against gram-positive bacteria*

Species	Antibiotic	MIC (μg/ml) needed to inhibit: 50% of strains	MIC (μg/ml) needed to inhibit: 100% of strains	MIC range (μg/ml)
S. pyogenes (15)[a]	GR-20263	0.12	0.5	0.06–0.5
	Cefotaxime	0.015	0.25	0.015–0.25
	Ampicillin	0.015	0.12	0.015–0.12
S. agalactiae (14)	GR-20263	0.5	0.5	0.5
	Cefotaxime	0.06	0.06	0.03–0.06
	Ampicillin	0.12	0.12	0.06–0.12
S. pneumoniae (11)	GR-20263	0.12	0.25	0.06–0.25
	Cefotaxime	0.015	0.015	0.015
	Ampicillin	0.06	0.12	0.03–0.12
S. faecalis (12)	GR-20263	>128	>128	>128
	Cefotaxime	128	>128	128–>128
	Ampicillin	2	4	2–4
S. aureus (12)[b]	GR-20263	8	8	4–8
	Cefotaxime	2	2	0.5–2
	Ampicillin	2	16	0.25–16
S. aureus (6)[c]	GR-20263	64	>128	32–>128
	Cefotaxime	64	>128	16–>128
	Ampicillin	32	64	16–64

[a] Numbers in parentheses are numbers of strains tested.
[b] Six isolates were penicillin G susceptible and six were penicillin G resistant.
[c] Isolates were resistant to oxacillin.

TABLE 2. *Comparative activities of GR-20263 and other antibiotics against gram-negative bacteria*

Species	Antibiotic	MIC (μg/ml) needed to inhibit: 50% of strains	75% of strains	90% of strains	100% of strains	Geometric mean MIC (μg/ml)
E. coli (57)[a]	GR-20263	0.25	0.25	0.5	8	0.29
	Cefotaxime	0.06	0.12	0.12	2	0.10
	Cefuroxime	4	8	8	32	4.69
	Cephalothin	16	32	64	>128	17.00
K. pneumoniae (54)	GR-20263	0.25	0.5	1	2	0.41
	Cefotaxime	0.06	0.06	0.25	0.5	0.07
	Cefuroxime	2	4	8	16	3.26
	Cephalothin	8	32	64	>128	12.38
Enterobacter spp. (51)	GR-20263	0.25	0.5	8	32	0.51
	Cefotaxime	0.25	0.5	16	128	0.51
	Cefuroxime	8	32	>128		15.15
	Cephalothin	>128				
C. freundii (25)	GR-20263	0.5	0.5	1	1	0.48
	Cefotaxime	0.25	0.5	1	2	0.27
	Cefuroxime	4	8	32	128	8.00
	Cephalothin	>128				
Salmonella spp. (30)	GR-20263	0.5	0.5	0.5	2	0.41
	Cefotaxime	0.12	0.12	0.25	0.5	0.11
	Cefuroxime	4	8	8	16	5.04
	Cephalothin	2	4	4	128	2.76
Shigella spp. (25)	GR-20263	0.12	0.25	0.25	0.25	0.15
	Cefotaxime	0.03	0.03	0.06	0.06	0.03
	Cefuroxime	1	2	4	4	1.56
	Cephalothin	8	8	8	16	4.99
Y. enterocolitica (26)	GR-20263	0.06	0.12	1	8	0.09
	Cefotaxime	0.03	0.06	0.5	4	0.05
	Cefuroxime	2	2	4	64	1.90
	Cephalothin	64	128	>128		94.47
P. mirabilis (69)	GR-20263	0.03	0.03	0.06	0.5	0.03
	Cefotaxime	0.015	0.015	0.015	0.5	0.02
	Cefuroxime	1	1	2	64	0.93
	Cephalothin	4	4	8	>128	4.33

TABLE 2—*Continued*

Species	Antibiotic	MIC (μg/ml) needed to inhibit: 50% of strains	75% of strains	90% of strains	100% of strains	Geometric mean MIC (μg/ml)
P. vulgaris (34)	GR-20263	0.06	0.06	0.12	0.5	0.05
	Cefotaxime	0.12	0.5	2	4	0.19
	Cefuroxime	>128				
	Cefoxitin	2	2	2	4	2.04
Proteus morganii (31)	GR-20263	0.06	0.12	0.5	8	0.12
	Cefotaxime	0.03	0.06	0.5	8	0.07
	Cefuroxime	32	64	64	>128	39.13
	Cefoxitin	8	16	16	16	9.78
Proteus rettgeri (19)	GR-20263	0.06	0.25	0.5	2	0.08
	Cefotaxime	0.015	0.03	0.12	1	0.03
	Cefuroxime	1	2	8	32	1.20
	Cephalothin	64	>128			24.79
Proteus inconstans (28)	GR-20263	0.5	0.5	1	2	0.25
	Cefotaxime	0.12	0.5	1	2	0.12
	Cefuroxime	4	8	32	64	3.12
	Cephalothin	>128				67.25
S. marcescens (40)	GR-2063	0.25	0.5	0.5	1	0.28
	Cefotaxime	0.5	1	2	8	0.76
	Cefuroxime	128	128	>128		128
	Cefoxitin	16	32	64	128	25.99
Acinetobacter spp. (26)	GR-20263	4	8	8	8	2.75
	Cefotaxime	8	16	32	32	5.51
	Cefuroxime	16	64	128	>128	10.44
	Piperacillin	4	16	16	128	6.82
	Tobramycin	1	4	16	32	1.45
P. aeruginosa (76)	GR-20263	1	2	2	8	1.22
	Cefotaxime	16	16	32	128	13.70
	Cefsulodin	2	4	32	128	2.75
	Piperacillin	4	8	128	>128	5.60
	Tobramycin	0.5	8	32	64	1.54
Pseudomonas spp. (45)	GR-20263	2	4	8	128	1.82
	Cefotaxime	8	16	64	128	6.85
	Cefsulodin	32	64	128	>128	32.50
	Piperacillin	4	32	64	128	7.29
	Tobramycin	1	64	128	128	1.69
H. influenzae (ampicillin susceptible)	GR-20263	0.12	0.12	0.12	0.25	0.11
	Cefotaxime	0.015	0.015	0.03	0.5	0.02
	Cefuroxime	1	1	1	2	0.90
	Cephalothin	2	4	4	8	2.52
	Ampicillin	0.25	0.25	0.5	1	0.29
H. influenzae (ampicillin resistant)	GR-20263	0.06	0.12	0.12	0.12	0.06
	Cefotaxime	0.015	0.03	0.03	0.03	0.02
	Cefuroxime	2	2	2	2	1.30
	Cephalothin	8	8	8	8	5.19
	Ampicillin	8	16	16	16	8.00

[a] Numbers in parentheses are numbers of strains.

pared fresh daily and were used on the day of preparation. For *Proteus* strains, *p*-nitrophenyl-β-D-glucoside (final concentration 50 μg/ml) was added to the medium to avoid swarming. After incubation at 36°C for 18 h, the minimal inhibitory concentration (MIC) was taken as the lowest concentration of antibiotic which allowed no visible growth or less than five discrete colonies.

With 16 selected isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Serratia marcescens*, and *P. aeruginosa*, minimal bactericidal concentrations (MBC) were determined in Trypticase soy broth with microtiter plates and inocula of approximately 10^5 CFU/ml. After overnight incubation each MIC was determined, and 5 μl of the contents of all wells containing trace growth or no discernible growth were subcultured onto Trypticase soy agar by using a calibrated loop. The MBC was defined as the lowest concentration producing no growth or colonies equal in number to less than 0.1% of the inoculum. With four isolates of the same five species, inoculum effects on the MICs and MBCs of GR-20263 and cefotaxime were determined by using inocula of approximately 10^3, 10^5, and 10^7 CFU ml.

RESULTS

The comparative inhibitory activities of GR-20263, cefotaxime, and ampicillin against gram-positive cocci are shown in Table 1. Against gram-positive cocci, GR-20263 did not have an advantage over the other β-lactams. Ampicillin was the most active antibiotic tested against *Streptococcus pyogenes* and *Streptococcus pneumoniae* and the only antibiotic effective against *Streptococcus faecalis*. *Staphylococcus aureus* isolates which were susceptible or resistant to penicillin G or ampicillin were inhibited by 4 to 8 μg of GR-20263 per ml and by 0.5 to 2 μg of cefotaxime per ml. All staphylococci resistant to oxacillin were also resistant to the other β-lactams.

The activities of GR-20263 and other antibiotics against gram-negative bacilli are shown in Table 2. The activity of GR-20263 against *Enterobacteriaceae* was superior to the activities of cephalothin, cefuroxime, and cefoxitin, but against most species it was less active than cefotaxime. This was particularly true with *E. coli*, *K. pneumoniae*, *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, and *Citrobacter freundii*. Against most *Proteus* spp. cefotaxime was only slightly more effective than GR-20263, but GR-20263 was the most effective antibiotic against *Proteus vulgaris* and *S. marcescens*. The activity against multiresistant *S. marcescens* was extraordinary; all isolates were inhibited by 1 μg of GR-20263 per ml.

Against *Enterobacter* spp. GR-20263 and cefotaxime were equally active. *Enterobacter* was the only genus containing isolates which were inhibited only at concentrations above 16 μg/ml; four isolates were inhibited by 32 μg of GR-20263 per ml, whereas two isolates were inhibited by 32 μg of cefotaxime per ml, two were inhibited by 64 μg/ml, and one was inhibited by 128 μg of cefotaxime per ml. Taking into account all 489 *Enterobacteriaceae* isolates tested, the differences in the activities of cefotaxime and GR-20263 were minimal and only obvious at very low concentrations. Indeed, at a concentration of 0.06 μg/ml 52.8% of the isolates were inhibited by cefotaxime, compared with 30.7% inhibited by GR-20263. At a concentration of 0.25 μg/ml, cefotaxime inhibited 78.9% of the isolates and GR-20263 inhibited 71.0%, but at a concentration of 0.5 μg/ml there was no difference (89.4% of the isolates were inhibited by cefotaxime and 88.8% were inhibited by GR-20263).

The activity of GR-20263 against *P. aeruginosa* (Table 2) was remarkable; 65% of the isolates were inhibited by GR-20263 at 1 μg/ml, 92% of the isolates were inhibited by 2 μg/ml, and all isolates were inhibited by 8 μg/ml. That made GR-20263 the most effective antibiotic thus far known against *P. aeruginosa*. It was slightly more active than tobramycin, twice as active as cefsulodin, and four times as active as piperacillin, the three drugs among the aminoglycosides, cephalosporins, and penicillins, respectively, known to be the most effective compounds against *P. aeruginosa*. There was no relationship between the resistance of *P. aeruginosa* to other antibiotics and its susceptibility to GR-20263. The MICs of GR-20263 against seven isolates which were resistant to piperacillin (128 μg/ml), tobramycin (32 μg/ml), and cefsulodin (32 μg/ml) varied between 1 and 8 μg/ml.

Against the other *Pseudomonas* species GR-20263 was also the most effective antibiotic, with good activity against *Pseudomonas maltophilia* and *Pseudomonas cepacia*, two species that are in general resistant to tobramycin and gentamicin. GR-20263 inhibited 14 of 16 *P. maltophilia* isolates at concentrations between 2 and 16 μg/ml and the remaining two isolates at concentrations of 64 and 128 μg/ml (geometric mean MIC, 6.7 μg/ml). For comparison, the geometric mean MICs against *P. maltophilia* were 33.4 μg of cefotaxime per ml, 47.2 μg of piperacillin per ml, 49.4 μg of cefsulodin per ml, and 94.5 μg of tobramycin per ml.

Acinetobacter spp. were most susceptible to tobramycin, but GR-20263 was the antibiotic with the most uniform activity; all isolates were inhibited by 8 μg of GR-20263 per ml.

H. influenzae was more susceptible to cefotaxime and GR-20263 than to ampicillin, and the isolates resistant to ampicillin (MIC, ≥4 μg/ml) were at least as susceptible to GR-20263 and cefotaxime as the ampicillin-susceptible isolates.

GR-20263 was active against bacilli with acquired resistance to cephalothin. Table 3 shows the geometric mean MICs of cefuroxime, cefotaxime, and GR-20263 against isolates of *E. coli*, *K. pneumoniae*, and *P. mirabilis*, which were divided into groups with increasing resistance to cephalothin. The resistant strains were shown to produce β-lactamase by using nitrocefin, a chromogenic cephalosporin substrate (4) (a gift from Glaxo Research Laboratories). Table 3 shows that the isolates of *P. mirabilis* and *K. pneumoniae* with highest resistance to cephalothin required for inhibition about the same MICs of GR-20263 as the cephalothin-susceptible isolates, whereas the same cephalothin-resistant isolates were substantially less susceptible to cefuroxime. Only the *E. coli* isolates with cephalothin MICs of ≥256 μg/ml required about 20-fold-higher MICs of GR-20263 and cefotaxime for inhibition than the cephalothin-susceptible isolates; nevertheless, they still were inhibited at

TABLE 3. *Comparison of the mean MICs of the newer cephalosporins against isolates with increasing MICs of cephalothin*

Species	MIC range of cephalothin (μg/ml)	No. of isolates	Geometric mean MIC (μg/ml)			
			Cephalothin	Cefuroxime	Cefotaxime	GR-20263
E. coli	≤8	25	7.16	3.68	0.07	0.20
	16–128	36	33.90	4.66	0.11	0.31
	≥256	15	≥256	27.86	1.74	3.65
K. pneumoniae	≤8	27	3.52	2.59	0.06	0.27
	16–128	27	41.37	3.90	0.09	0.58
	≥256	25	≥256	16.86	0.31	0.42
P. mirabilis	≤8	67	4.00	0.86	0.02	0.03
	16–128	20	19.70	2.37	0.03	0.08
	≥256	9	≥256	23.52	0.03	0.04

TABLE 4. *MICs and MBCs of GR-20263 in Trypticase soy broth*

Species	MIC (μg/ml)		MBC (μg/ml)	
	Geometric mean	Range	Geometric mean	Range
E. coli (16)[a]	0.19	0.06–0.5	0.19	0.06–5
K. pneumoniae (16)	0.22	0.06–1.0	0.22	0.06–1.0
P. mirabilis (16)	0.04	0.015–0.12	0.05	0.015–0.25
S. marcescens (16)	0.44	0.12–2.0	0.46	0.25–2.0
P. aeruginosa (16)	1.92	0.5–4.0	2.38	1.0–8.0

[a] Numbers in parentheses are numbers of strains.

concentrations between 0.25 and 8 μg/ml.

The MBCs of GR-20263 in Trypticase soy broth against isolates of *E. coli*, *K. pneumoniae*, *P. mirabilis*, *S. marcescens*, and *P. aeruginosa* were almost the same as their MICs, when an inoculum of 10^5 CFU/ml was used (Table 4).

The effect of inoculum size on the MICs and MBCs of GR-20263 and cefotaxime was studied with four isolates each of the same five species, with the inocula varying between 10^3 and 10^7 CFU/ml (Table 5). With inocula between 10^3 and 10^5 CFU/ml the differences were small for both antibiotics with all species tested. With inocula between 10^3 and 10^7 CFU/ml we found moderate and parallel increases in the MICs and MBCs of GR-20263 and also of cefotaxime with *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*, except with one *P. mirabilis* strain for which the MBC of cefotaxime jumped from 0.015 to 8 μg/ml. Only with *S. marcescens* isolates was there a marked increase in the MICs and MBCs of both antibiotics with an inoculum of 10^7 CFU/ml.

DISCUSSION

GR-20263, a novel substituted methoxyiminocephalosporin, possesses all of the properties of the cephalosporins of the third generation, namely in vitro activity at very low concentrations against a very wide variety of gram-negative organisms and high stability to β-lactamases. This study demonstrates that GR-20263 is highly active against *S. pyogenes*, *Streptococcus agalactiae*, and *S. pneumoniae*. GR-20263 shows only poor activity against *S. aureus*, and it is completely ineffective against *S. faecalis*, like all other cephalosporins.

GR-20263 has enhanced activity against gram-negative bacilli and is substantially more active against all *Enterobacteriaceae* species than cephalothin, cefuroxime, and cefoxitin. It is three- to fivefold less active than cefotaxime against *E. coli*, *K. pneumoniae*, *Salmonella*, and *Shigella*. On the other hand, it is threefold more effective than cefotaxime against the multiresistant *S. marcescens*, a rebellious nosocomial pathogen; all isolates of *S. marcescens* were inhibited by 1 μg of GR-20263 per ml.

A further advantage of GR-20263 over cefotaxime and the new compound moxalactam (LY 127935) is its extremely high activity against *P. aeruginosa*. Indeed, it is the most effective and most reliable antibiotic against this species, with 100% of the isolates inhibited by GR-20263 at 8 μg/ml, whether they are susceptible or resistant to carbenicillin, gentamicin, tobramycin, and piperacillin, or even resistant to cefsulodin, the only cephalosporin with a selective activity against *P. aeruginosa*. GR-20263 is also more effective than cefotaxime, piperacillin, and cefsulodin against the other *Pseudomonas* species and is notably effective against *P. maltophilia*

TABLE 5. *Effect of inoculum on activity of GR-20263 and cefotaxime*

Species	Antibiotic	MIC			MBC		
		Geometric mean MIC with inoculum of 10^3 CFU/ml (μg/ml)	Geometric mean MIC with inoculum of 10^7 CFU/ml (μg/ml)	-Fold increase[a]	Geometric mean MBC with inoculum of 10^3 CFU/ml (μg/ml)	Geometric mean MBC with inoculum of 10^7 CFU/ml (μg/ml)	-Fold increase[a]
E. coli (4)[b]	GR-20263	0.12	0.29	2–4	0.15	0.35	2–4
	Cefotaxime	0.04	0.15	2–8	0.04	0.21	2–16
K. pneumoniae (4)	GR-20263	0.15	0.71	2–8	0.15	0.71	2–8
	Cefotaxime	0.03	0.12	2–8	0.03	0.12	2–8
P. mirabilis (4)	GR-20263	0.015	0.05	0–16	0.015	0.05	0–16
	Cefotaxime	0.017	0.12	0–512	0.017	0.12	0–512
S. marcescens (4)	GR-20263	0.21	8.0	32–64	0.21	11.3	32–64
	Cefotaxime	0.59	16.0	4–64	0.59	26.9	8–128
P. aeruginosa (4)	GR-20263	1.0	4.0	4	1.41	4.0	2–8
	Cefotaxime	5.66	22.6	2–8	5.66	32.0	2–16

[a] Ratio between value when inoculum size was 10^7 (FU/ml and value when inoculum size was 10^3 CFU/ml in individual isolates.
[b] Numbers in parentheses are numbers of strains.

and *P. cepacia*, the two species within the genus *Pseudomonas* which (besides *P. aeruginosa*) are most often recovered from blood cultures and which are in general resistant to the aminoglycosides.

GR-20263 is also more effective than ampicillin against *H. influenzae* and is as effective against the beta-lactamase-producing isolates as against the isolates susceptible to ampicillin. This property may be appreciated in the near future, since the spread of beta-lactamase-producing isolates is increasing. A survey in our own hospital revealed that over the last 1 year, according to monthly records, 5 to 20% of the *H. influenzae* isolates cultured from sputum were beta-lactamase producers and resistant to ampicillin (unpublished data); 2 years ago a similar survey showed that less than 0.5% were beta-lactamase-producing *Haemophilus*.

Studies in experimental animals confirmed the outstanding in vivo activity of GR-20263 in intraperitoneal mouse infections when *P. aeruginosa* was used as the infecting organism (P. Acred, D. M. Ryan, and P. W. Muggleton, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th ICAAC, Boston, Mass. abstr. no. 560, 1979). Preliminary data in humans (P. Acred, personal communication) indicate that high serum levels can be obtained and that the serum half-life may surpass 90 min.

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