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Antibacterial Activity of WY-49605 Compared with Those of Six Other Oral Agents and Selection of Disk Content for Disk Diffusion Susceptibility Testing

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The in vitro antimicrobial activity of an oral penem, WY-49605, was compared with those of six other oral antimicrobial agents against 598 bacterial isolates representing 51 different species. WY-49605 exhibited good activity against most gram-positive bacteria and members of the family *Enterobacteriaceae*. It had little activity against nonfermenting gram-negative bacilli, *Enterobacter* spp., *Serratia* spp., enterococci, *Staphylococcus haemolyticus*, and methicillin-resistant *Staphylococcus aureus*. Its activity was unaffected by the β-lactamases of *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and staphylococci. Disk diffusion susceptibility tests were performed with 5-, 10-, 15-, and 30-μg WY-49605 disks. The 5-μg disk is recommended, with tentative breakpoints of ≥16 mm for susceptibility (MIC, ≤2.0 μg/ml) and ≤12 mm for resistance (MIC, ≥8.0 μg/ml).

WY-49605 (previously SUN5555, SY5555, or ALP-201) is an orally administered penem that exhibits a broad in vitro antibacterial spectrum against both anaerobic and aerobic bacteria (1, 4–6). It has also been shown to be highly resistant to the actions of a variety of β-lactamase enzymes (1, 4).

In this report, we describe the results of two separate studies. The first study compared the in vitro antibacterial activity of WY-49605 with those of six other oral antibiotics currently available in the United States against a wide range of bacterial isolates. A second study determined the optimal disk content of WY-49605 for disk diffusion susceptibility testing.

MATERIALS AND METHODS

In the first study, 598 stock cultures that had been derived from clinical specimens over the past 15 years were selected to represent the 51 different species that are listed in Table 1. WY-49605 was provided as a standardized powder by Wyeth-Ayerst Research, Philadelphia, Pa. The drugs used for comparison, amoxicillin, amoxicillin-clavulanate, cefaclor, cefuroxime, cefixime, and ciprofloxacin, were procured from their respective U.S. manufacturers. Susceptibility tests were performed by the broth microdilution method outlined by the National Committee for Clinical Laboratory Standards (NCCLS) (2). The antibiotic concentrations tested were serial twofold dilutions ranging from 16 to 0.03 μg/ml for all drugs except ciprofloxacin, which was tested at concentrations of from 4.0 to 0.008 μg/ml.

In the second study, 490 bacterial isolates representing 32 different species were selected from the first culture collection for which there was a wide range of WY-49605 MICs. The week before the second study was initiated, filter paper disks were prepared at the Clinical Microbiology Institute to contain WY-49605 at 110% of the following potencies: 5, 10, 15, and 30 μg. The compound has been shown to be stable for up to 2 years at room temperature (7), and there was no change in zone diameters with control strains for the duration of the study. Commercially prepared 30-μg ceftriaxone disks (lot no. 204657; B-D Microbiology Systems) were also tested for control purposes. Disk diffusion susceptibility tests were performed with all five disks as outlined by NCCLS (3). Broth microdilution susceptibility tests were performed simultaneously with both WY-49605 (32 to 0.016 μg/ml) and ceftriaxone (128 to 0.06 μg/ml) as outlined by NCCLS (3). For *Neisseria gonorrhoeae* and *Haemophilus influenzae*, WY-49605 MICs were determined by the agar dilution methods outlined by NCCLS (3) and were compared only with those of amoxicillin-clavulanic acid.

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RESULTS AND DISCUSSION

Comparative study. Table 1 summarizes the in vitro susceptibility data for WY-49605 in comparison with those for six other oral antimicrobial agents. On the basis of preliminary pharmacokinetic data, with the clinical formula an oral dose containing 150 mg of WY-49605 should give peak concentrations in plasma of about 8.0 μg of WY-49605 per ml (7). Thus, 2.0 μg/ml was tentatively selected as the susceptibility breakpoint for WY-49605. All 30 isolates of *Neisseria gonorrhoeae* were susceptible to WY-49605, although the MICs for β-lactamase-negative, penicillin-resistant strains were generally fourfold higher than those for the other strains. Ampicillin-susceptible and β-lactamase-producing *Haemophilus influenzae* strains were susceptible to WY-49605, but only half of the β-lactamase-negative, ampicillin-resistant strains were inhibited by 2.0 μg of WY-49605 per ml. Likewise, methicillin-susceptible *Staphylococcus aureus* strains were highly susceptible to WY-49605, but only 60% of methicillin-resistant *Staphylococcus aureus* strains were susceptible to 2.0 μg/ml. Those data support the β-lactamase stability of WY-49605 (1, 4), but they also indicate that its activity is reduced by the penicillin-binding protein alterations, accounting for the resistance to penicillin, ampicillin, and methicillin by those three organisms, respectively.

Ciprofloxacin was the most active of the test drugs against members of the family *Enterobacteriaceae*. WY-49605 had good activity against most enteric bacilli other than *Enterobacter* spp., *Serratia* spp., and *Citrobacter freundii*. However, it was more active than the other β-lactam compounds against *Citrobacter freundii* and most *Enterobacter* spp. Against the other enteric species, WY-49605 and cefixime were the most active β-lactams tested. WY-49605 was more active than cefixime against *Hafnia alvei* and *Morganella morganii*, and cefixime was more active than WY-49605 against *Providencia* spp. and *Proteus* spp. Like the other β-lactams tested, WY-49605 had no appreciable activity against nonfermenting gram-negative bacilli.

With the exception of some *Enterococcus* spp., *Staphylococcus haemolyticus*, and methicillin-resistant *Staphylococcus au-*

TABLE 1. Susceptibilities of 598 bacterial isolates to WY-49605 and six comparative oral antibiotics

Organism (no. tested)	Antibiotic	MIC (μg/ml)[a]			% Susceptible[b]
		Range	50%	90%	
Acinetobacter anitratus (10)	WY-49605	4.0–>16	8.0	16	(0)
	Amoxicillin	4.0–>16	16	>16	20
	Amox-clav[c]	4.0–>16	8.0	>16	80
	Cefaclor	16–>16	>16	>16	0
	Cefuroxime	16–>16	>16	>16	0
	Cefixime	4.0–>16	16	16	0
	Ciprofloxacin	0.06–1.0	0.5	1.0	100
Acinetobacter lwoffi (10)	WY-49605	0.5–>16	4.0	8.0	(20)
	Amoxicillin	1.0–>16	4.0	16	80
	Amox-clav	1.0–16	2.0	8.0	90
	Cefaclor	2.0–>16	16	>16	30
	Cefuroxime	2.0–>16	16	>16	40
	Cefixime	2.0–>16	8.0	>16	0
	Ciprofloxacin	0.06–0.25	0.25	0.25	100
Aeromonas spp. (5)	WY-49605	0.25–>16	0.25		(60)
	Amoxicillin	>16	>16		0
	Amox-clav	16	16		0
	Cefaclor	4.0–>16	>16		20
	Cefuroxime	0.25–2.0	2.0		100
	Cefixime	≤0.03–1.0	≤0.03		100
	Ciprofloxacin	≤0.008	≤0.008		100
Citrobacter diversus (10)	WY-49605	0.25–0.5	0.25	0.5	(100)
	Amoxicillin	>16	>16	>16	0
	Amox-clav	2.0–8.0	2.0	2.0	100
	Cefaclor	≤0.03–0.5	0.5	0.5	100
	Cefuroxime	2.0–4.0	4.0	4.0	100
	Cefixime	≤0.03–0.5	≤0.03	0.06	100
	Ciprofloxacin	≤0.008	≤0.008	≤0.008	100
Citrobacter freundii (21)	WY-49605	0.25–4.0	2.0	4.0	(76)
	Amoxicillin	8.0–>16	>16	>16	5
	Amox-clav	8.0–>16	>16	>16	5
	Cefaclor	0.5–>16	>16	>16	10
	Cefuroxime	2.0–>16	>16	>16	43
	Cefixime	0.06–>16	>16	>16	29
	Ciprofloxacin	≤0.008–0.12	0.016	0.06	100
Enterobacter aerogenes (16)	WY-49605	0.25–>16	1.0	16	(56)
	Amoxicillin	>16	>16	>16	0
	Amox-clav	16–>16	>16	>16	0
	Cefaclor	2.0–>16	>16	>16	6
	Cefuroxime	2.0–>16	4.0	>16	56
	Cefixime	0.06–>16	2.0	>16	44
	Ciprofloxacin	≤0.008–0.12	0.016	0.03	100
Enterobacter agglomerans (10)	WY-49605	0.25–16	1.0	8.0	(50)
	Amoxicillin	4.0–>16	>16	>16	20
	Amox-clav	1.0–>16	8.0	>16	50
	Cefaclor	0.5–>16	>16	>16	40
	Cefuroxime	1.0–>16	8.0	>16	70
	Cefixime	0.03–>16	1.0	8.0	60
	Ciprofloxacin	≤0.008–0.06	≤0.008	0.03	100
Enterobacter cloacae (21)	WY-49605	1.0–8.0	2.0	8.0	(57)
	Amoxicillin	4.0–>16	>16	>16	5
	Amox-clav	4.0–>16	>16	>16	5
	Cefaclor	8.0–>16	>16	>16	5
	Cefuroxime	4.0–>16	8.0	>16	52
	Cefixime	0.06–>16	>16	>16	33
	Ciprofloxacin	≤0.008–1.0	0.016	0.12	100

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TABLE 1—*Continued*

Organism (no. tested)	Antibiotic	MIC (μg/ml)[a]			% Susceptible[b]
		Range	50%	90%	
Enterococcus durans (10)	WY-49605	0.06–>16	2.0	16	(50)
	Amoxicillin	≤0.006–2.0	0.25	1.0	100
	Amox-clav	≤0.006–2.0	0.25	1.0	100
	Cefaclor	0.25–>16	8.0	>16	70
	Cefuroxime	0.12–>16	>16	>16	30
	Cefixime	2.0–>16	>16	>16	0
	Ciprofloxacin	0.12–2.0	0.25	0.5	90
Enterococcus faecalis (10)	WY-49605	1.0	1.0	1.0	(100)
	Amoxicillin	0.25–0.5	0.5	0.5	100
	Amox-clav	0.25–0.5	0.5	0.5	100
	Cefaclor	16–>16	>16	>16	0
	Cefuroxime	8.0–>16	>16	>16	10
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	0.5–2.0	1.0	1.0	90
Enterococcus faecium (10)	WY-49605	1.0–>16	8.0	>16	(10)
	Amoxicillin	0.12–4.0	0.5	4.0	100
	Amox-clav	0.12–4.0	0.5	4.0	100
	Cefaclor	8.0–>16	>16	>16	30
	Cefuroxime	16–>16	>16	>16	0
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	1.0–4.0	2.0	4.0	40
Escherichia coli (25)	WY-49605	0.25–2.0	0.5	0.5	(100)
	Amoxicillin	1.0–>16	2.0	>16	68
	Amox-clav	1.0–16	2.0	8.0	96
	Cefaclor	0.5–>16	1.0	4.0	96
	Cefuroxime	1.0–8.0	2.0	4.0	100
	Cefixime	0.12–1.0	0.25	0.5	100
	Ciprofloxacin	≤0.008–0.5	0.016	0.03	100
Haemophilus influenzae, β-lactamase negative, ampicillin susceptible (10)	WY-49605	0.25–2.0	0.5	1.0	(100)
	Amox-clav	0.5–2.0	0.5	1.0	100
Haemophilus influenzae, β-lactamase negative, ampicillin resistant (10)	WY-49605	1.0–4.0	2.0	4.0	(50)
	Amox-clav	4.0–8.0	4.0	8.0	100
Haemophilus influenzae, β-lactamase positive (10)	WY-49605	0.25–0.5	0.25	0.5	(100)
	Amox-clav	0.5–1.0	0.5	1.0	100
Hafnia alvei (10)	WY-49605	1.0–2.0	2.0	2.0	(100)
	Amoxicillin	>16	>16	>16	0
	Amox-clav	>16	>16	>16	0
	Cefaclor	>16	>16	>16	0
	Cefuroxime	4.0–>16	>16	>16	20
	Cefixime	1.0–>16	8.0	>16	10
	Ciprofloxacin	≤0.008–0.016	0.016	0.016	100
Klebsiella spp. (25)	WY-49605	0.25–4.0	0.5	2.0	(92)
	Amoxicillin	16–>16	>16	>16	0
	Amox-clav	1.0–16	2.0	16	88
	Cefaclor	0.5–>16	1.0	2.0	92
	Cefuroxime	1.0–>16	2.0	16	84
	Cefixime	≤0.03–0.25	≤0.03	0.25	100
	Ciprofloxacin	0.016–>4.0	0.03	0.5	92
Listeria monocytogenes (10)	WY-49605	0.06–0.12	0.12	0.12	(100)
	Amoxicillin	0.06–0.25	0.25	0.25	100
	Amox-clav	0.06–0.25	0.25	0.25	100
	Cefaclor	4.0–8.0	8.0	8.0	100
	Cefuroxime	>16	>16	>16	0
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	0.5–>4.0	1.0	1.0	90

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TABLE 1—*Continued*

Organism (no. tested)	Antibiotic	MIC (μg/ml)[a]			% Susceptible[b]
		Range	50%	90%	
Moraxella catarrhalis (15)	WY-49605	≤0.03–0.5	0.12	0.5	(100)
	Amoxicillin	≤0.06–8.0	1.0	4.0	100
	Amox-clav	≤0.06–0.25	≤0.06	0.12	100
	Cefaclor	0.5–4.0	1.0	2.0	100
	Cefuroxime	0.5–2.0	1.0	1.0	100
	Cefixime	≤0.03–0.5	0.25	0.25	100
	Ciprofloxacin	≤0.008–0.03	0.016	0.03	100
Morganella morganii (10)	WY-49605	2.0–4.0	2.0	2.0	(90)
	Amoxicillin	>16	>16	>16	0
	Amox-clav	>16	>16	>16	0
	Cefaclor	>16	>16	>16	0
	Cefuroxime	16–>16	>16	>16	0
	Cefixime	0.25–>16	2.0	>16	30
	Ciprofloxacin	≤0.008–0.06	≤0.008	0.016	100
Neisseria gonorrhoeae, penicillinase negative (10)	WY-49605	≤0.03–0.06	≤0.03	≤0.03	(100)
	Amox-clav	≤0.06–1.0	0.25	0.5	100
Neisseria gonorrhoeae, penicillinase positive (10)	WY-49605	≤0.03–0.12	≤0.03	0.06	(100)
	Amox-clav	0.5–4.0	1.0	2.0	100
Neisseria gonorrhoeae, penicillinase negative, penicillin resistant (10)	WY-49605	0.06–0.5	0.12	0.25	(100)
	Amox-clav	0.5–4.0	1.0	2.0	100
Neisseria meningitidis (10)	WY-49605	≤0.03	≤0.03	≤0.03	(100)
	Amoxicillin	≤0.06–0.12	0.12	0.12	100
	Amox-clav	≤0.06–0.12	0.12	0.12	100
	Cefaclor	0.06–0.25	0.12	0.25	100
	Cefuroxime	≤0.03–0.12	≤0.03	0.12	100
	Cefixime	≤0.03	≤0.03	≤0.03	100
	Ciprofloxacin	≤0.008	≤0.008	≤0.008	100
Proteus mirabilis (10)	WY-49605	1.0–2.0	2.0	2.0	(100)
	Amoxicillin	0.25–1.0	0.5	1.0	100
	Amox-clav	0.25–1.0	0.5	1.0	100
	Cefaclor	0.5–2.0	1.0	2.0	100
	Cefuroxime	0.5–4.0	1.0	1.0	100
	Cefixime	≤0.03	≤0.03	≤0.03	100
	Ciprofloxacin	0.016–0.03	0.016	0.03	100
Proteus vulgaris (10)	WY-49605	1.0–2.0	2.0	2.0	(100)
	Amoxicillin	>16	>16	>16	0
	Amox-clav	4.0–16	4.0	8.0	90
	Cefaclor	>16	>16	>16	0
	Cefuroxime	>16	>16	>16	0
	Cefixime	≤0.03–0.06	≤0.03	0.06	100
	Ciprofloxacin	≤0.008–0.06	0.016	0.03	100
Providencia rettgeri (10)	WY-49605	1.0–4.0	1.0	2.0	(90)
	Amoxicillin	2.0–>16	>16	>16	10
	Amox-clav	2.0–>16	>16	>16	10
	Cefaclor	0.25–>16	>16	>16	10
	Cefuroxime	0.06–>16	1.0	8.0	90
	Cefixime	≤0.03–0.5	≤0.03	0.25	100
	Ciprofloxacin	0.03–1.0	0.03	1.0	100
Providencia stuartii (10)	WY-49605	0.25–>16	1.0	2.0	(90)
	Amoxicillin	0.5–>16	>16	>16	10
	Amox-clav	0.5–>16	>16	>16	10
	Cefaclor	0.25–>16	>16	>16	10
	Cefuroxime	1.0–>16	4.0	>16	70
	Cefixime	≤0.03–1.0	0.06	0.12	100
	Ciprofloxacin	0.03–4.0	0.06	4.0	80

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TABLE 1—*Continued*

Organism (no. tested)	Antibiotic	MIC (μg/ml)[a]			% Susceptible[b]
		Range	50%	90%	
Pseudomonas aeruginosa (15)	WY-49605	>16	>16	>16	(0)
	Amoxicillin	>16	>16	>16	0
	Amox-clav	>16	>16	>16	0
	Cefaclor	>16	>16	>16	0
	Cefuroxime	>16	>16	>16	0
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	0.12–6.0	0.25	1.0	100
Pseudomonas spp.[d] (20)	WY-49605	16–>16	>16	>16	(0)
	Amoxicillin	1.0–>16	>16	>16	25
	Amox-clav	1.0–>16	>16	>16	25
	Cefaclor	>16	>16	>16	0
	Cefuroxime	>16	>16	>16	0
	Cefixime	4.0–>16	>16	>16	0
	Ciprofloxacin	0.016–4.0	0.12	4.0	55
Salmonella spp.[e] (15)	WY-49605	0.12–1.0	0.5	0.5	(100)
	Amoxicillin	0.25–>16	0.5	>16	80
	Amox-clav	0.25–>16	0.5	>16	87
	Cefaclor	0.25–>16	0.5	16	87
	Cefuroxime	2.0–16	4.0	8.0	93
	Cefixime	≤0.03–0.25	0.12	0.25	100
	Ciprofloxacin	≤0.008–0.03	0.016	0.016	100
Serratia marcescens (31)	WY-49605	2.0–>16	16	>16	(3)
	Amoxicillin	16–>16	>16	>16	0
	Amox-clav	16–>16	>16	>16	0
	Cefaclor	>16	>16	>16	0
	Cefuroxime	>16	>16	>16	0
	Cefixime	0.12–>16	1.0	>16	55
	Ciprofloxacin	0.03–>4	0.06	>4	84
Shigella spp.[f] (20)	WY-49605	0.12–1.0	0.25	0.5	(100)
	Amoxicillin	1.0–>16	2.0	>16	75
	Amox-clav	1.0–16	2.0	8.0	90
	Cefaclor	0.5–4.0	0.5	2.0	100
	Cefuroxime	0.25–4.0	1.0	2.0	100
	Cefixime	0.12–1.0	0.25	0.5	100
	Ciprofloxacin	≤0.008–0.016	≤0.008	0.016	100
Staphylococcus aureus, methicillin susceptible (20)	WY-49605	0.06–0.12	0.06	0.12	(100)
	Amoxicillin	0.12–>16	2.0	16	30
	Amox-clav	0.12–1.0	0.5	1.0	100
	Cefaclor	1.0–4.0	1.0	2.0	100
	Cefuroxime	1.0–2.0	1.0	1.0	100
	Cefixime	8.0–16	8.0	16	0
	Ciprofloxacin	0.06–1.0	0.25	0.5	100
Staphylococcus aureus, methicillin resistant (10)	WY-49605	0.25–>16	1.0	>16	(60)
	Amoxicillin	16–>16	>16	>16	0
	Amox-clav	4.0–16	8.0	16	(60)
	Cefaclor	16–>16	>16	>16	0
	Cefuroxime	1.0–>16	16	>16	30
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	0.25–1.0	0.25	1.0	100
Staphylococcus epidermidis[g] (12)	WY-49605	0.06–>16	0.06	0.25	(92)
	Amoxicillin	≤0.06–16	0.5	16	83
	Amox-clav	≤0.06–8.0	0.25	2.0	100
	Cefaclor	0.5–>16	0.5	8.0	92
	Cefuroxime	0.25–>16	0.25	4.0	92
	Cefixime	2.0–>16	4.0	>16	0
	Ciprofloxacin	0.12–0.25	0.25	0.25	100

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TABLE 1—*Continued*

Organism (no. tested)	Antibiotic	MIC (μg/ml)[a]			% Susceptible[b]
		Range	50%	90%	
Staphylococcus haemolyticus (10)	WY-49605	0.12–>16	4.0	>16	(40)
	Amoxicillin	4.0–>16	>16	>16	10
	Amox-clav	1.0–>16	16	>16	30
	Cefaclor	8.0–>16	>16	>16	10
	Cefuroxime	2.0–>16	>16	>16	10
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	0.12–0.25	0.12	0.25	100
Staphylococcus saprophyticus (10)	WY-49605	0.25–0.5	0.5	0.5	(100)
	Amoxicillin	0.25–0.5	0.25	0.25	100
	Amox-clav	0.25–0.5	0.25	0.25	100
	Cefaclor	1.0–2.0	2.0	2.0	100
	Cefuroxime	1.0–4.0	2.0	2.0	100
	Cefixime	>16	>16	>16	0
	Ciprofloxacin	0.25–0.5	0.25	0.25	100
Staphylococcus spp.[h] (7)	WY-49605	0.06–0.25	0.12		(100)
	Amoxicillin	≤0.06–2.0	≤0.12		100
	Amox-clav	≤0.06–0.25	≤0.12		100
	Cefaclor	0.5–2.0	1.0		100
	Cefuroxime	0.5–1.0	0.5		100
	Cefixime	8.0–>16	16		0
	Ciprofloxacin	0.12–0.25	0.12		100
Streptococcus spp. (15)	WY-49605	≤0.03	≤0.03	≤0.03	(100)
	Amoxicillin	≤0.06	≤0.06	≤0.06	100
	Amox-clav	≤0.06	≤0.06	≤0.06	100
	Cefaclor	0.06–0.12	0.12	0.12	100
	Cefuroxime	≤0.03	≤0.03	≤0.03	100
	Cefixime	0.06–0.12	0.12	0.12	100
	Ciprofloxacin	0.25–2.0	0.5	2.0	87
Streptococcus agalactiae (15)	WY-49605	≤0.03–0.06	0.06	0.06	(100)
	Amoxicillin	≤0.06–0.12	≤0.06	≤0.06	100
	Amox-clav	≤0.06–0.12	≤0.06	≤0.06	100
	Cefaclor	0.12–4.0	1.0	2.0	100
	Cefuroxime	≤0.03–0.12	0.06	0.06	100
	Cefixime	0.25–1.0	0.5	0.5	100
	Ciprofloxacin	0.5–1.0	0.5	1.0	100
Streptococcus groups C and G (20)	WY-49605	≤0.03	≤0.03	≤0.03	(100)
	Amoxicillin	≤0.06	≤0.06	≤0.06	100
	Amox-clav	≤0.06	≤0.06	≤0.06	100
	Cefaclor	0.06–0.25	0.12	0.12	100
	Cefuroxime	≤0.03	≤0.03	≤0.03	100
	Cefixime	0.06–0.25	0.12	0.25	100
	Ciprofloxacin	0.25–1.0	0.5	0.5	100
Streptococcus pneumoniae[i] (15)	WY-49605	≤0.03–0.5	0.06	0.25	(100)
	Amoxicillin	≤0.06–1.0	≤0.06	1.0	100
	Amox-clav	≤0.06–1.0	≤0.06	0.5	100
	Cefaclor	0.25–>16	0.25	16	87
	Cefuroxime	≤0.03–4.0	0.25	2.0	100
	Cefixime	0.12–>16	2.0	4.0	47
	Ciprofloxacin	0.5–1.0	1.0	1.0	100
Viridans group streptococci (10)	WY-49605	≤0.03–0.5	0.06	0.25	(100)
	Amoxicillin	≤0.06–2.0	0.12	1.0	100
	Amox-clav	≤0.06–2.0	0.12	1.0	100
	Cefaclor	0.5–16	1.0	4.0	90
	Cefuroxime	≤0.03–2.0	0.12	1.0	100
	Cefixime	0.12–>16	1.0	4.0	70
	Ciprofloxacin	1.0–4.0	2.0	4.0	10

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TABLE 1—*Continued*

Organism (no. tested)	Antibiotic	MIC (μg/ml)[a]			% Susceptible[b]
		Range	50%	90%	
Xanthomonas maltophilia (10)	WY-49605	>16	>16	>16	(0)
	Amoxicillin	8–>16	>16	>16	10
	Amox-clav	16–>16	>16	>16	0
	Cefaclor	>16	>16	>16	0
	Cefuroxime	>16	>16	>16	0
	Cefixime	16–>16	>16	>16	0
	Ciprofloxacin	1.0–4.0	2.0	4.0	40
Yersinia enterocolitica (5)	WY-49605	0.5–1.0	1.0		(100)
	Amoxicillin	2.0–>16	>16		20
	Amox-clav	1.0–>16	8.0		60
	Cefaclor	1.0–8.0	2.0		100
	Cefuroxime	0.25–4.0	4.0		100
	Cefixime	0.25–1.0	1.0		100
	Ciprofloxacin	0.016	0.016		100

[a] 50% and 90%, MICs at which 50 and 90% of isolates were inhibited, respectively.
[b] Percentage of isolates inhibited by each drug at or below the susceptibility breakpoint MIC as recommended by NCCLS (2). Since a breakpoint for susceptibility has not yet been established for WY-49605, the percentage of isolates inhibited by ≤2.0 μg/ml is noted parenthetically.
[c] Amox-clav, amoxicillin plus clavulanic acid (2:1 ratio; expressed as micrograms of amoxicillin in the combination).
[d] Includes *Pseudomonas cepacia* (n = 5), *Pseudomonas fluorescens* (n = 6), *Pseudomonas putida* (n = 4), and *Pseudomonas stutzeri* (n = 5).
[e] Includes *Salmonella enteritidis* (n = 10) and *Salmonella typhi* (n = 5).
[f] Includes five strains each of *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei.*
[g] Five strains were methicillin resistant.
[h] Includes *Staphylococcus hominis* (n = 2), *Staphylococcus simulans* (n = 3), and *Staphylococcus warneri* (n = 2).
[i] Includes 2 penicillin-intermediate and 13 penicillin-susceptible strains.

reus strains, gram-positive bacteria were uniformly susceptible to WY-49605. Against *Listeria monocytogenes*, WY-49605 was the most active compound tested.

Disk diffusion test. With the control ceftriaxone disks, there were 11 (2.2%) very major (false-susceptible) errors. These represented tests with 8 of 10 *Proteus vulgaris*, 2 of 15 *Enterobacter cloacae*, and 1 of 15 *Pseudomonas cepacia* strains. These errors persisted when the strains were retested. No major errors (false resistant) and 57 (12%) minor discrepancies were found. Considering the unusually high prevalence of antibiotic-resistant strains in this challenge collection, these error rates were not entirely unexpected.

For analyses of the WY-49605 data, MIC breakpoints of ≤2.0 μg/ml for susceptibility and ≥8.0 μg/ml for resistance were used. For the WY-49605 disks of each potency, the inhibitory zone diameter breakpoints were calculated and then adjusted to minimize interpretive discrepancies. The regression analyses were limited to those strains for which WY-49605 MICs were in the range of 0.5 to 32 μg/ml to avoid the parabolic skewing caused by the more susceptible strains.

There were eight very major discrepancies (five *Proteus mirabilis*, two *Proteus vulgaris*, and 1 *Providencia rettgeri* strain) with all four disks of each potency, and these were not resolved on retesting. Three additional isolates gave very major errors with the 30-μg disk. The calculated zone diameter breakpoints for all four disks of each potency and the resulting error rates are summarized in Table 2. The major error rate was the same (0.4%) with all disks of each potency, but the minor error rate was somewhat lower (6.0%) with the 5-μg disk than with the other disks (7.2 to 7.6%). The organisms giving minor discrepancies were distributed among 11 different species and included 5 of 10 *Morganella morganii* and 5 of 10 *Proteus mirabilis* strains. On the basis of these data, we recommend the use of the 5-μg disk, with breakpoints of ≤12 mm for resistance and ≥16 mm for susceptibility (Fig. 1). The disk potency and breakpoints should remain tentative until subsequent pharmacokinetic and clinical data are available to support (or refute) the 2.0-μg/ml MIC breakpoint for susceptibility and until the present data are confirmed with commercially prepared disks.

TABLE 2. Regression statistics and interpretive error rates for tests with disks containing different amounts of WY-49605

Disk content (μg)	Regression formula[a]	Correlation coefficient	Breakpoint (mm)		No. of interpretive errors (n = 489)			% Complete agreement
			Susceptibility	Resistance	Minor	Major	Very major	
5	$y = 14.0 - 0.21x$	0.72	≥16	≤12	29	2	8	92
10	$y = 15.3 - 0.24x$	0.79	≥20	≤16	37	2	8	90
15	$y = 15.6 - 0.23x$	0.81	≥22	≤18	37	2	8	90
30	$y = 16.3 - 0.23x$	0.78	≥25	≤21	35	2	11	90

[a] $y = \log_2 + 9$ MIC (in micrograms per milliliter) and x is the diameter of the zone of inhibition (in millimeters). Strains for which MICs were ≤0.25 μg/ml were excluded in order to avoid the parabolic portions of the regression curve.

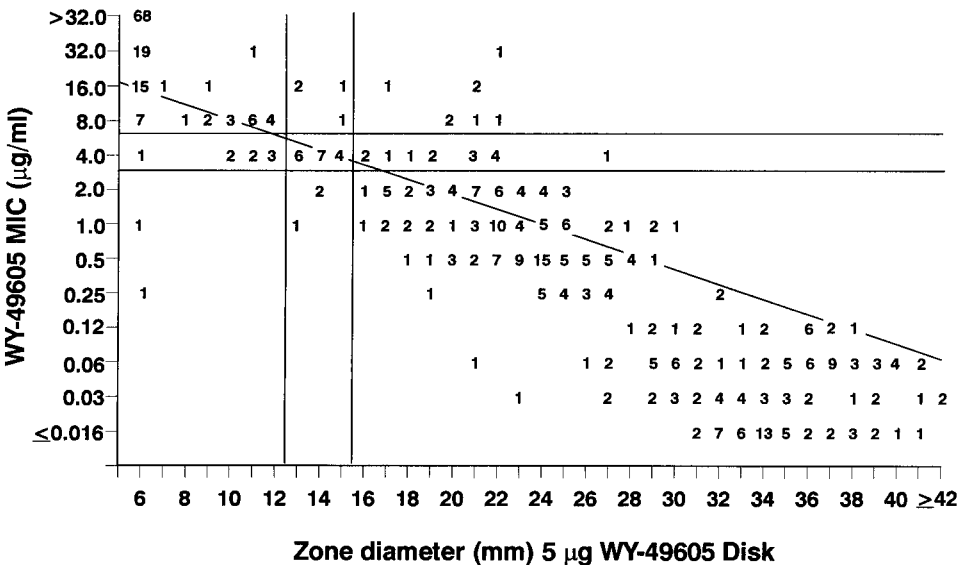

FIG. 1. Scattergram correlating MICs of WY-49605 to zones of inhibition around 5-μg WY-49605 disks. Horizontal and vertical lines represent tentative breakpoints for the susceptible and resistant categories for dilution and disk diffusion tests, respectively.

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