ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2004, p. 4898–4902 Vol. 48, No. 12
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.12.4898–4902.2004

In Vitro Activities of OPT-80 and Comparator Drugs against Intestinal Bacteria

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Received 4 July 2004/Returned for modification 28 July 2004/Accepted 31 August 2004

The activities of OPT-80 against 453 intestinal bacteria were compared with those of seven other drugs. OPT-80 showed good activity against most clostridia, staphylococci, and enterococci, but streptococci, aerobic and facultative gram-negative rods, anaerobic gram-negative rods, and *Clostridium ramosum* were resistant. Poor activity against anaerobic gram-negative rods may maintain colonization resistance.

Drugs that are poorly absorbed orally may have a place in therapy for intestinal infections and in certain other situations in which intestinal bacteria may play a role (7). It is also important to note the activity of such drugs against members of the bowel flora that might confer colonization resistance (19). Vancomycin is used systemically for therapy of severe or multiresistant gram-positive infections and orally for *Clostridium difficile* infections. Although the drug is highly effective against those infections, vancomycin resistance has been observed in various organisms, including enterococci, *Lactobacillus* spp., *Leuconostoc* spp., *Pediococcus* spp., and staphylococci (4, 9, 15, 17). Such gram-positive organisms are often resistant to other agents as well (8).

OPT-80 is an 18-membered macrocyclic antibiotic, also known as tiacumicin B, that, like vancomycin, targets gram-positive organisms (16, 18). It is currently under development as a new, narrow-spectrum antibacterial agent to treat *C. difficile*-associated diarrhea (CDAD) and colitis. Toxigenic *C. difficile* is the causative agent in 20% of cases of antibiotic-associated diarrhea (2) and is the principal cause of antibiotic-associated colitis. Current treatments for this disease include oral vancomycin and metronidazole, but both of these drugs have a relatively broad spectrum and may exacerbate disruption of gut flora that led to CDAD originally. Indeed, a major drawback to both treatments is the incidence of recurrence of CDAD, which is approximately 20% (5). A unique feature of OPT-80 is its selectivity for *Clostridium*, particularly *C. difficile* and *Clostridium perfringens*; previous work has shown that the MIC for *C. difficile* is approximately 10- to 100-fold lower than those for other organisms, including other gram-positive organisms (1, 16, 18). OPT-80 is also primarily retained in the gut, with low levels in serum following oral administration in hamsters (16), rats, monkeys, and humans (Optimer Pharmaceuticals, personal communication).

This study was designed to evaluate the in vitro activity of OPT-80 and comparator agents against intestinal bacteria. Antimicrobial concentration ranges were selected to encompass or surpass the levels that would be achieved in the gut (to the extent that this information is available), subject to the limitations of solubility of the drugs in the testing medium. Table 1 is a summary of the range of concentrations of antimicrobial agents used during testing and the levels achieved in the bowel or feces (6, 11, 12).

The bacteria included in this study were mostly recent isolates representative of the indigenous bowel flora. Bacteria were identified according to established procedures (10), supplemented in a number of cases by 16S rRNA sequence analysis. Drug MICs for anaerobes were determined by the NCCLS-approved Wadsworth agar dilution technique (14). Aerobic and facultative bacteria were tested according to NCCLS guidelines (13), using Mueller-Hinton (Sigma, St. Louis, Mo.) agar without blood except for *Streptococcus mitis* and *Streptococcus sanguinis*, for which 5% fresh sheep blood was added. The antimicrobial agents tested were obtained as powders from the following companies: amoxicillin, clindamycin, metronidazole, tobramycin, and vancomycin from Sigma; lithium clavulanate from GlaxoSmithKline (King of Prussia, Pa.); linezolid from Pfizer (Groton, Conn.); ciprofloxacin from ICN Biomedicals (Irvine, Calif.); and OPT-80 from Optimer Pharmaceuticals, Inc. (San Diego, Calif.).

TABLE 1. Summary of drug concentrations tested and fecal drug levels reported previously[a]

Drug	Fecal drug levels (μg/g)[b]	Range of conc tested
Amoxicillin-clavulanate	25–250 (?)	0.03–128
Ciprofloxacin	890	0.03–512
Clindamycin	>200 (increases up to day 5 of therapy)	0.03–512
Linezolid	9% of dose excreted in feces as inactive metabolites	0.25–128
Metronidazole	0–23; 2–3	0.25–128
OPT-80	3,000 on 450-mg/day dose[c]; dosage not yet finalized	0.03–1,024
Tobramycin	1,000–3,000 (?)	0.25–1,024
Vancomycin	1,000–8,000	0.5–1,024

[a] See references 3, 8, and 11.
[b] ?, data not solid.
[c] Optimer Pharmaceuticals, Inc., personal communication.

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TABLE 2. In vitro activity of Optimer-80 and six comparative agents against 453 bacterial isolates

Bacterial group (n[a])	Antimicrobial agent	MIC[c]		Range
		50%	90%	
Bacteroides fragilis group spp.[b] (50)	Amoxicillin-clavulanate	1	16	0.50–32
	Ciprofloxacin	16	128	8–256
	Clindamycin	4	>128	0.50–>128
	Linezolid	4	8	2.0–8
	Metronidazole	1	4	0.25–16
	Optimer-80	256	>1,024	256–>1,024
	Tobramycin	256	>1,024	256–>1,024
	Vancomycin	64	128	16–256
Veillonella spp. (10)	Amoxicillin-clavulanate	0.5	1	0.25–1
	Clindamycin	0.5	0.5	0.5
	Linezolid	2	2	1.0–2
	Metronidazole	2	2	2
	Optimer-80	32	128	16–128
	Tobramycin	16	64	8.0–64
	Vancomycin	512	512	128–>1,024
Other anaerobic gram-negative rods[d] (51)	Amoxicillin-clavulanate	1	2	0.12–16
	Ciprofloxacin	1	8	0.25–32
	Clindamycin	0.5	8	0.5–>128
	Linezolid	1	2	0.5–4
	Metronidazole	0.25	4	0.25–>128
	Optimer-80	1,024	>1,024	0.06–>1,024
	Tobramycin	128	>1,024	1–>1,024
	Vancomycin	512	>1,024	0.5–>1,024
All anaerobic gram-negative species (111)	Amoxicillin-clavulanate	1	8	0.12–32
	Ciprofloxacin	1	32	0.25–256
	Clindamycin	0.5	>128	0.5–>128
	Linezolid	4	4	0.5–8
	Metronidazole	1	4	0.25–>128
	Optimer-80	256	>1,024	0.06–>1,024
	Tobramycin	256	>1,024	1–>1,024
	Vancomycin	128	>1,024	0.5–>1,024
Clostridium bifermentans (9)	Amoxicillin-clavulanate			0.25–0.5
	Ciprofloxacin			2.0–8
	Clindamycin			0.5
	Linezolid			1.0
	Metronidazole			0.25–1
	Optimer-80			0.06
	Tobramycin			4–256
	Vancomycin			1.0
Clostridium bolteae (7)	Amoxicillin-clavulanate			0.5–32
	Ciprofloxacin			8.0–64
	Clindamycin			0.5–2
	Linezolid			4.0
	Metronidazole			0.25–1
	Optimer-80			1–64
	Tobramycin			8–128
	Vancomycin			1.0–16
Clostridium clostridioforme (4)	Amoxicillin-clavulanate			1.0–16
	Ciprofloxacin			32
	Clindamycin			0.5
	Linezolid			4.0
	Metronidazole			0.25
	Optimer-80			4.0–128
	Tobramycin			16–1,024
	Vancomycin			1.0–8
Clostridium difficile (23)	Amoxicillin-clavulanate	2	4	0.5–8
	Ciprofloxacin	8	32	1.0–64
	Clindamycin	2	>128	0.5–>128
	Linezolid	4	32	1.0–32
	Metronidazole	0.25	0.5	0.25–1
	Optimer-80	0.12	0.25	0.06–2
	Tobramycin	512	>1,024	64–>1,024
	Vancomycin	1	2	0.5–4
Clostridium glycolicum (9)	Amoxicillin-clavulanate			0.25–1
	Ciprofloxacin			1.0–16
	Clindamycin			0.5
	Linezolid			1.0
	Metronidazole			0.25–0.5
	Optimer-80			0.06–1
	Tobramycin			16–256
	Vancomycin			0.5–1

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TABLE 2—*Continued*

Bacterial group (n^a)	Antimicrobial agent	MIC[c]		Range
		50%	90%	
Clostridium innocuum (9)	Amoxicillin-clavulanate			0.5–1
	Ciprofloxacin			2.0–8
	Clindamycin			0.5–>128
	Linezolid			2.0–4
	Metronidazole			0.25–1
	Optimer-80			32–128
	Tobramycin			>1,024
	Vancomycin			8.0–16
Clostridium paraputrificum (8)	Amoxicillin-clavulanate			0.25–2
	Ciprofloxacin			1.0–4
	Clindamycin			0.5–4
	Linezolid			0.5
	Metronidazole			0.25–1
	Optimer-80			0.06–8
	Tobramycin			32–512
	Vancomycin			1–2
Clostridium perfringens (14)	Amoxicillin-clavulanate	0.25	0.25	0.25–0.5
	Ciprofloxacin	0.5	1	0.25–1
	Clindamycin	0.5	2	0.5–2
	Linezolid	2	4	1.0–4
	Metronidazole	0.5	2	0.25–2
	Optimer-80	0.062	0.062	0.06
	Tobramycin	256	1,024	1.0–1,024
	Vancomycin	1	1	0.5–1
Clostridium ramosum (10)	Amoxicillin-clavulanate	0.5	0.5	0.25–0.5
	Ciprofloxacin	16	16	4.0–16
	Clindamycin	1	4	1.0–8
	Linezolid	8	16	8.0–16
	Metronidazole	0.5	1	0.5–2
	Optimer-80	512	512	256–512
	Tobramycin	256	256	128–256
	Vancomycin	4	8	4.0–8
Clostridium sordellii (5)	Amoxicillin-clavulanate			0.25
	Ciprofloxacin			0.25
	Clindamycin			0.5–2
	Linezolid			1.0
	Metronidazole			0.5
	Optimer-80			0.06
	Tobramycin			2.0–256
	Vancomycin			1.0
Other clostridial species[e] (9)	Amoxicillin-clavulanate			0.25–2
	Ciprofloxacin			0.25–32
	Clindamycin			0.5–2
	Linezolid			1.0–4
	Metronidazole			0.25–>128
	Optimer-80			0.06–>1,024
	Tobramycin			0.25–>1,024
	Vancomycin			1.0–64
All *Clostridium* species (107)	Amoxicillin-clavulanate	0.5	4	0.25–32
	Ciprofloxacin	8	32	0.25–64
	Clindamycin	0.5	8	0.5–>128
	Linezolid	2	4	0.5–32
	Metronidazole	0.5	1	0.25–>128
	Optimer-80	0.062	128	0.06–>1,024
	Tobramycin	256	>1,024	0.25–>1,024
	Vancomycin	1	16	0.5–64
Anaerobic non-spore-forming gram-positive rods[f] (63)	Amoxicillin-clavulanate	0.25	1	0.25–4
	Ciprofloxacin	2	32	0.25–128
	Clindamycin	0.5	4	0.25–>128
	Linezolid	0.5	2	0.5–4
	Metronidazole	4	>128	0.25–>128
	Optimer-80	1	32	0.06–>1,024
	Tobramycin	64	512	1.0–>1,024
	Vancomycin	1	2	0.5–>1,024
Anaerobic gram-positive cocci[g] (49)	Amoxicillin-clavulanate	0.25	1	0.25–32
	Ciprofloxacin	1	32	0.25–64
	Clindamycin	0.5	4	0.5–>128
	Linezolid	1	4	0.5–4
	Metronidazole	0.25	1	0.25–2
	Optimer-80	0.5	2	0.06–1,024
	Tobramycin	16	256	1.0–1,024
	Vancomycin	1	1	0.5–8

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TABLE 2—*Continued*

Bacterial group (n[a])	Antimicrobial agent	MIC[c]		Range
		50%	90%	
All anaerobic gram-positive species (219)	Amoxicillin-clavulanate	0.5	2	0.25–32
	Ciprofloxacin	4	32	0.25–128
	Clindamycin	0.5	4	0.25–>128
	Linezolid	1	4	0.5–32
	Metronidazole	0.5	128	0.25–>128
	Optimer-80	0.12	64	0.06–>1,024
	Tobramycin	128	>1,024	0.25–>1,024
	Vancomycin	1	8	0.5–>1,024
Streptococcus, formerly *S. milleri* group[h] (14)	Amoxicillin-clavulanate	0.5	1	0.25–1
	Ciprofloxacin	0.5	0.5	0.5
	Clindamycin	1	4	0.5–4
	Metronidazole	64	128	64–128
	Optimer-80	32	32	16–64
	Tobramycin	128	256	32–256
	Vancomycin	1	1	1.0
Other *Streptococcus* species[i] (9)	Amoxicillin-clavulanate			0.03–4
	Ciprofloxacin			0.5–4
	Clindamycin			0.03–>128
	Metronidazole			256–>256
	Optimer-80			16–128
	Tobramycin			8.0–16
	Vancomycin			0.5–1
Enterococcus species[j] (21)	Amoxicillin-clavulanate	1	2	0.5–128
	Ciprofloxacin	4	128	2.0–>128
	Clindamycin	16	512	8.0–>512
	Metronidazole	>1,024	>1,024	>1,024
	Optimer-80	8	8	2.0–16
	Tobramycin	32	>1,024	16–>1,024
	Vancomycin	1	4	0.5–4
Staphylococcus aureus and *Staphylococcus epidermidis*[k] (19)	Amoxicillin-clavulanate	0.5	2	0.12–16
	Ciprofloxacin	0.5	1	0.03–16
	Clindamycin	0.25	0.25	0.12–>512
	Metronidazole	256	>1,024	128–>1,024
	Optimer-80	0.5	2	0.25–2
	Tobramycin	0.5	1	0.25–2
	Vancomycin	2	4	1.0–4
Total for all strains (453)[l]	Amoxicillin-clavulanate	1	16	0.03–>128
	Ciprofloxacin	2	32	0.03–512
	Clindamycin	0.5	512	0.03–>512
	Linezolid	2	4	0.5–32
	Metronidazole	1	>1,024	0.25–>1,024
	Optimer-80	8	1,024	0.06–>1,024
	Tobramycin	64	>1,024	0.25–>1,024
	Vancomycin	2	>1,024	0.5–>1,024

[a] n, number of strains tested.
[b] *Bacteroides distasonis* (7), *Bacteroides fragilis* (13), *Bacteroides ovatus* (10), *Bacteroides thetaiotaomicron* (10), *Bacteroides vulgatus* (10).
[c] Minimum inhibitory concentrations (MICs) are listed in micrograms/milliliter. 50%, MIC at which 50% of isolates tested were inhibited; 90%, MIC at which 90% of isolates tested were inhibited.
[d] *Bilophila wadsworthia* (10), *Fusobacterium mortiferum* (3), *Fusobacterium necrophorum* (3), *Fusobacterium nucleatum* (4), *Fusobacterium varium* (2), *Porphyromonas* spp. (11), *Prevotella* spp. (8), *Sutterella wadsworthensis* (10).
[e] *Clostridium bartlettii* (1), *Clostridium butyricum* (2), *Clostridium disporicum* (1), *Clostridium hypermegas* (1), *Clostridium orbiscindens* (1), *Clostridium subterminale* (1), *Clostridium* species (1), *Clostridium tertium* (1).
[f] *Actinomyces meyeri* (1), *Actinomyces odontolyticus* (5), *Actinomyces viscosus* (2), *Atopobium minutum* (3), *Bifidobacterium adolescentis* (3), *Bifidobacterium breve* (1), *Bifidobacterium dentium* (2), *Bifidobacterium* species (3), *Collinsella aerofaciens* (7), *Eggerthella lenta* (5), *Eubacterium biforme* (1), *Eubacterium cylindroides* (1), *Eubacterium limosum* (5), *Eubacterium saburreum* (3), *Lactobacillus catenaforme* (1), *Lactobacillus jensenii* (4), *Lactobactillus fermentum* (1), *Lactobacillus* species (4), *Propionibacterium avidum* (1), *Propionibacterium acnes* (7), *Propionibacterium propionicus* (1), *Propionibacterium* species (2).
[g] *Anaerococcus prevotii* (7), *Anaerococcus tetradius* (6), *Finegoldia magna* (7), *Peptoniphilus asaccharolyticus* (6), *Peptostreptococcus anaerobius* (7), *Peptostreptococcus micros* (6), *Ruminococcus gnavus* (4), *Ruminococcus* species (5), *Ruminococcus torques* (1).
[h] *Streptococcus anginosus* (7), *Streptococcus constellatus* (4), *Streptococcus intermedius* (3).
[i] *Streptococcus mitis* (3), *Streptococcus salivarius* (3), *Streptococcus sanguinis* (3).
[j] *Enterococcus avium* (1), *Enterococcus faecalis* (14), *Enterococcus faecium* (6).
[k] *Staphylococcus aureus* (9), *Staphylococcus epidermidis* (10).
[l] Not all data are shown (data for 60 strains of aerobic or facultatively gram-negative bacilli are not shown).

For analysis, the bacteria tested were generally placed into genus, species, or other groups with at least 10 isolates. The ranges and the MICs at which 50 and 90% of isolates were inhibited were determined except for organisms with fewer than 10 strains tested, for which only the ranges are reported (Table 2).

Although vancomycin showed relatively poor activity against gram-negative anaerobes, including the *Bacteroides fragilis*

group, these organisms are usually suppressed in the intestinal tract by the very high levels achieved in the bowel by oral administration (Finegold et al., unpublished data).

OPT-80 was distinctly less active against the *B. fragilis* group than vancomycin. Vancomycin had good activity against all clostridia, whereas OPT-80 had fairly good activity against *Clostridium bolteae* and *Clostridium clostridioforme*, fair activity against *Clostridium innocuum*, and relatively poor activity against *C. ramosum*. It is interesting that among the clostridia studied, susceptibility or resistance to OPT-80 correlated with the taxonomic clusters of clostridia (3) to which they belong. Clostridia that were very sensitive to OPT-80 were all in clostridial clusters I and XI; those that were less susceptible belong to clusters XIVa, XVI, and XVIII. Both OPT-80 and vancomycin had good activity against most anaerobic gram-positive non-spore-forming rods and anaerobic gram-positive cocci. Vancomycin had better activity against streptococci, both showed good activity against enterococci and staphylococci, and both had poor activity against nonanaerobic gram-negative bacilli (data for the latter group not shown).

C. difficile-associated colitis has generally responded well to therapy with vancomycin, metronidazole, or bacitracin, all administered orally; the current data indicate that it should respond well to oral OPT-80 as well, but studies on this are not available yet. Additional indications for therapy with some or all of the drugs in this study include neutropenic enterocolitis, intestinal colonization with vancomycin-resistant enterococci and staphylococci or antibiotic-resistant viridans group streptococci in an immunocompromised host, preoperative bowel preparation, D-lactic acidosis, bowel bacterial overgrowth syndrome, and investigational use in late-onset autism (7).

Factors that would help determine the relative utility of these various agents would include such things as usefulness of the compounds for therapy of serious systemic infections, levels of drug achieved in the gastrointestinal tract, maintenance of colonization resistance in the bowel, bactericidal activity, drug allergy, absorbability of the drugs with oral administration, gastrointestinal and systemic toxicity, frequency with which resistance develops, cross-resistance with other compounds (particularly those that are used systemically), frequency of dosage required, patient tolerance of the medication (over prolonged periods in the case of autism), palatability, ease of administration to young children (liquid preparation preferred), and cost. Clinical studies are needed to assess the clinical utility of the various drugs with good activity against intestinal bacteria in these situations.

This study was funded by Optimer Pharmaceuticals, Inc., San Diego, Calif., and Veterans Administration Merit Review research funds.

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