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Omiganan Pentahydrochloride (MBI 226), a Topical 12-Amino-Acid Cationic Peptide: Spectrum of Antimicrobial Activity and Measurements of Bactericidal Activity

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The activity of omiganan pentahydrochloride (formerly MBI 226; a synthetic cationic peptide) was assessed against 1,437 recent clinical bacterial isolates and 214 recent clinical yeast isolates. The omiganan was highly active, and minimal bactericidal concentrations or minimal fungicidal concentrations were either equal to or two- to fourfold higher than MICs. Kill curve experiments showed a clear pattern of bactericidal activity.

Omiganan pentahydrochloride (formerly MBI 226) is a novel topical cationic peptide (sequence: ILRWPWWPWRRK-amide) analog of indolicidin that was originally purified from the cytoplasmic granules of bovine neutrophils (5). Omiganan pentahydrochloride has demonstrated in vitro activity against a wide variety of microorganisms, including gram-positive and -negative bacteria and fungi (D. J. Hoban, E. Witwicki, G. C. Zhanel, L. Palatnick, and H. D. Friedland, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. E-1647, 2002), and can be used in venous catheter care (6, 7). This compound is rapidly microbicidal and interacts with the cytoplasmic membranes of both gram-positive and -negative bacteria (3; D. Dugouard, C. Pasetka, D. Erfle, E. Rubinchik, K. Lee, H. D. Friedland, and P. McNicol, Abstr. 102nd Gen. Meet. Am. Soc. Microbiol., abstr. A-46, p. 9-10, 2002). In *Staphylococcus aureus*, omiganan pentahydrochloride acts by depolarizing the cytoplasmic membrane, resulting in cell disruption and death. This compound also shows a dose-dependent inhibitory effect on whole-cell protein, RNA, and DNA synthesis in *S. aureus* (D. Dugouard, C. Pasetka, D. Erfle, E. Rubinchik, M. Guarna, P. McNicol, and H. D. Friedland, Abstr. 102nd Gen. Meet. Am. Soc. Microbiol., abstr. A-47, p. 10, 2002). The exposure of *Escherichia coli* to omiganan pentahydrochloride resulted in outer membrane permeabilization (D. Dugouard et al., Abstr. 102nd Gen. Meet. Am. Soc. Microbiol., abstr. A-46). A topical 1% gel preparation of omiganan is currently in phase III clinical trials for the prevention of catheter-related bloodstream infections (5, 6, 7).

The purpose of this study was to evaluate the in vitro antimicrobial activity of omiganan pentahydrochloride against recent clinical isolates of bacteria and *Candida*. We also evaluated the bactericidal activity of omiganan pentahydrochloride and its stability in frozen storage after the preparation of reference broth microdilution panels.

A total of 1,651 clinical strains were tested against omiganan pentahydrochloride and other selected comparator antimicrobial agents. Bacterial strains (n = 1,437) were tested in both cation-adjusted (CA) and -unadjusted (UA) Mueller-Hinton (MH) broth. Two hundred fourteen *Candida* sp. strains were tested in RPMI 1640 broth with MOPS (morpholinepropanesulfonic acid) buffer. Approximately one-half of these isolates were obtained from the omiganan pentahydrochloride clinical trials.

For the bacterial isolates, susceptibility testing was performed by using NCCLS reference broth microdilution methods (11). Omiganan pentahydrochloride reagent grade compound was provided by Micrologix Biotech, Inc. (Vancouver, Canada). Comparator agents were purchased from Sigma Chemical Co. (St. Louis, Mo.) or obtained from their respective manufacturers in the United States. Up to 13 comparators were evaluated, depending upon the species tested. Commercially prepared frozen broth microdilution panels (Sensititre/TREK Diagnostics, Cleveland, Ohio) were thawed and inoculated with a final inoculum concentration of approximately 5×10^5 CFU/ml. The bacterial isolates were tested in CA and UA MH broth. Panels were read manually, and an endpoint of no visible growth was established as the MIC, per NCCLS criteria (12). Concurrent quality control (QC) studies were performed by testing control strains, which were *Streptococcus pneumoniae* ATCC 49619, *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *E. coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853. A study was previously performed to establish QC ranges for omiganan pentahydrochloride for five bacterial American Type Culture Collection (ATCC) strains and two yeast ATCC strains (T. R. Anderegg, T. R. Fritsche, R. N. Jones, and the Quality Control Working Group, Letter, J. Clin. Microbiol. **42:**1386-1387, 2004). Colony counts were performed weekly to ensure the inoculum of approximately 3×10^5 to 7×10^5 CFU per ml.

For the yeast isolates, a suspension equal to a 0.5 McFarland standard was made, diluted 1:500 in RPMI 1640 broth with MOPS buffer, and inoculated into the thawed panels to a final concentration of 0.5×10^3 to 2.5×10^3 CFU/ml. Panels were incubated in an ambient air environment at 35°C and were read at 24 and 48 h of growth (1, 2, 10). QC was performed by testing the following ATCC strains: *Candida parapsilosis*

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TABLE 1. Antimicrobial activities of omiganan pentahydrochloride and selected comparator antimicrobial agents against 1,651 strains of bacteria and *Candida* spp.

Organism (no. tested) and antimicrobial agent[a]	MIC (μg/ml)			% by category[b]	
	50%	90%	Range	Susceptible	Resistant
Oxacillin-susceptible CoNS (44)					
Omiganan pentahydrochloride (CA MH broth)	4	8	0.5–8	—	—
Omiganan pentahydrochloride (UA MH broth)	2	4	0.5–4	—	—
Vancomycin	1	2	0.25–2	100.0	0.0
Penicillin	0.25	4	≤0.06–>8	36.4	63.6
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	90.9	9.1
Ofloxacin	≤0.5	≤0.5	≤0.5–>4	90.9	6.8
Gentamicin	≤1	≤1	≤1	100.0	0.0
Neomycin	≤0.12	0.25	≤0.12–2	—	—
Bacitracin	32	>32	≤0.25–>32	—	—
Mupirocin	0.25	0.5	≤0.12–>256	93.2	6.8
Oxacillin-resistant CoNS (174)					
Omiganan pentahydrochloride (CA MH broth)	4	4	0.5–16	—	—
Omiganan pentahydrochloride (UA MH broth)	2	4	≤0.25–4	—	—
Vancomycin	1	2	0.5–2	100.0	0.0
Penicillin	8	>8	≤0.06–>8	1.7	98.3
Ciprofloxacin	>2	>2	≤0.25–>2	31.6	66.7
Ofloxacin	>4	>4	≤0.5–>4	32.2	66.7
Gentamicin	2	>8	≤1–>8	—	—
Neomycin	≤0.12	16	≤0.12–>16	—	—
Bacitracin	32	>32	8–>32	0.0	100.0
Mupirocin	32	>256	≤0.12–>256	48.0	30.1
Oxacillin-susceptible *S. aureus* (88)					
Omiganan pentahydrochloride (CA MH broth)	16	16	2–32	—	—
Omiganan pentahydrochloride (UA MH broth)	8	16	1–32	—	—
Vancomycin	0.5	1	0.5–1	100.0	0.0
Penicillin	8	>8	≤0.06–>8	14.8	85.2
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	90.9	9.1
Ofloxacin	≤0.5	≤0.5	≤0.5–>4	90.9	8.0
Gentamicin	≤1	≤1	≤1–>8	—	—
Neomycin	0.5	1	≤0.12–>16	—	—
Bacitracin	32	32	2–32	2.3	97.7
Mupirocin	0.25	0.25	≤0.12–>256	94.3	5.7
Oxacillin-resistant *S. aureus* (111)					
Omiganan pentahydrochloride (CA MH broth)	16	16	8–64	—	—
Omiganan pentahydrochloride (UA MH broth)	8	16	4–64	—	—
Vancomycin	1	1	0.5–2	100.0	0.0
Penicillin	>8	>8	0.5–>8	0.0	100.0
Ciprofloxacin	>2	>2	≤0.25–>2	30.0	70.0
Ofloxacin	>4	>4	≤0.5–>4	29.7	69.4
Gentamicin	≤1	>8	≤1–>8	65.8	31.5
Neomycin	>16	>16	≤0.12–>16	—	—
Bacitracin	32	>32	4–>32	—	—
Mupirocin	0.25	16	≤0.12–>256	86.5	3.6
Vancomycin-susceptible *E. faecalis* (87)					
Omiganan pentahydrochloride (CA MH broth)	64	128	16–128	—	—
Omiganan pentahydrochloride (UA MH broth)	64	128	16–128	—	—
Vancomycin	1	2	0.5–2	100.0	0.0
Penicillin	4	8	2–8	100.0	0.0
Ciprofloxacin	1	>2	≤0.25–>2	50.6	36.8
Ofloxacin	4	>4	1–>4	—	—
Gentamicin	8	>8	2–>8	—	—
Neomycin	>16	>16	8–>16	—	—
Bacitracin	32	>32	4–>32	—	—
Mupirocin	128	256	32–>256	0.0	2.3
Vancomycin-nonsusceptible *E. faecalis* (13)					
Omiganan pentahydrochloride (CA MH broth)	64	128	64–128	—	—
Omiganan pentahydrochloride (UA MH broth)	64	64	32–64	—	—
Vancomycin	>32	>32	8–>32	0.0	92.3
Penicillin	4	4	2–8	100.0	0.0
Ciprofloxacin	>2	>2	>2	0.0	100.0
Ofloxacin	>4	>4	>4	0.0	100.0
Gentamicin	>8	>8	2–>8	—	—

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TABLE 1—*Continued*

Organism (no. tested) and antimicrobial agent[a]	MIC (μg/ml)			% by category[b]	
	50%	90%	Range	Susceptible	Resistant
Neomycin	>16	>16	4–>16	—	—
Bacitracin	>32	>32	32–>32	—	—
Mupirocin	64	128	32–128	0.0	0.0
Vancomycin-susceptible *E. faecium* (44)					
Omiganan pentahydrochloride (CA MH broth)	8	16	2–16	—	—
Omiganan pentahydrochloride (UA MH broth)	8	8	2–16	—	—
Vancomycin	0.5	1	0.25–2	100.0	0.0
Penicillin	>8	>8	1–>8	15.9	84.1
Ciprofloxacin	>2	>2	0.5–>2	14.3	76.2
Ofloxacin	>4	>4	2–>4	—	—
Gentamicin	8	>8	4–>8	—	—
Neomycin	>16	>16	4–>16	—	—
Bacitracin	32	>32	16–>32	—	—
Mupirocin	0.5	1	0.25–2	100.0	0.0
Vancomycin-nonsusceptible *E. faecium* (57)					
Omiganan pentahydrochloride (CA MH broth)	8	16	2–16	—	—
Omiganan pentahydrochloride (UA MH broth)	8	8	2–16	—	—
Vancomycin	>32	>32	>32	0.0	100.0
Penicillin	>8	>8	>8	0.0	100.0
Ciprofloxacin	>2	>2	>2	0.0	100.0
Ofloxacin	>4	>4	>4	—	—
Gentamicin	>8	>8	2–>8	—	—
Neomycin	>16	>16	4–>16	—	—
Bacitracin	32	>32	8–>32	—	—
Mupirocin	1	1	0.25–4	100.0	0.0
Beta-hemolytic streptococci (102)					
Omiganan pentahydrochloride (CA MH broth)	16	32	2–128	—	—
Omiganan pentahydrochloride (UA MH broth)	16	32	1–64	—	—
Vancomycin	0.25	0.5	≤0.06–1	100.0	—
Oxacillin	≤0.25	≤0.25	≤0.25–2	—	—
Penicillin	≤0.06	≤0.06	≤0.06–0.5	99.0	—
Ciprofloxacin	0.5	1	≤0.25–>2	—	—
Ofloxacin	1	2	≤0.5–>4	99.0	1.0
Gentamicin	8	>8	≤1–>8	—	—
Neomycin	>16	>16	4–>16	—	—
Bacitracin	8	>32	≤0.25–>32	—	—
Mupirocin	≤0.12	1	≤0.12–1	100.0	0.0
Penicillin-susceptible viridans group streptococci (66)					
Omiganan pentahydrochloride (CA MH broth)	64	256	4–512	—	—
Omiganan pentahydrochloride (UA MH broth)	64	256	1–512	—	—
Vancomycin	0.5	0.5	0.12–1	100.0	—
Oxacillin	≤0.25	≤0.25	≤0.25–0.5	—	—
Penicillin	≤0.06	0.12	≤0.06–0.12	100.0	0.0
Ciprofloxacin	1	>2	≤0.25–>2	—	—
Ofloxacin	2	4	≤0.5–>4	—	—
Gentamicin	4	>8	≤1–>8	—	—
Neomycin	>16	>16	≤0.12–>16	—	—
Bacitracin	16	32	≤0.25–>32	—	—
Mupirocin	1	1	≤0.12–>256	98.5	1.5
Penicillin-nonsusceptible viridans group streptococci (34)					
Omiganan pentahydrochloride (CA MH broth)	64	256	4–256	—	—
Omiganan pentahydrochloride (UA MH broth)	64	256	2–256	—	—
Vancomycin	0.5	0.5	0.12–0.5	100.0	—
Oxacillin	1	>2	≤0.25–>2	—	—
Penicillin	0.5	4	0.25–>8	0.0	14.7
Ciprofloxacin	2	>2	0.5–>2	—	—
Ofloxacin	2	4	1–>4	—	—
Gentamicin	2	8	≤1–>8	—	—
Neomycin	16	>16	2–>16	—	—
Bacitracin	8	32	0.5–32	—	—
Mupirocin	1	32	0.25–>256	85.3	2.9
Bacillus spp. (103)					
Omiganan pentahydrochloride (CA MH broth)	16	32	≤0.25–64	—	—
Omiganan pentahydrochloride (UA MH broth)	16	32	≤0.25–64	—	—

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TABLE 1—*Continued*

Organism (no. tested) and antimicrobial agent[a]	MIC (μg/ml)			% by category[b]	
	50%	90%	Range	Susceptible	Resistant
Vancomycin	1	2	≤0.06–32	98.1	1.0
Oxacillin	>2	>2	≤0.25–>2	31.1	68.9
Penicillin	>8	>8	≤0.06–>8	26.2	73.8
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	95.1	4.9
Ofloxacin	≤0.5	1	≤0.5–>4	94.2	3.9
Gentamicin	≤1	≤1	≤1–4	100.0	0.0
Neomycin	0.5	1	≤0.12–16	—	—
Bacitracin	>32	>32	≤0.25–>32	—	—
Mupirocin	>256	>256	≤0.12–>256	14.6	76.7
Corynebacterium spp. (103)					
Omiganan pentahydrochloride (CA MH broth)	4	8	≤0.25–64	—	—
Omiganan pentahydrochloride (UA MH broth)	2	4	≤0.25–32	—	—
Vancomycin	0.5	0.5	0.12–>32	99.0	1.0
Oxacillin	>2	>2	≤0.25–>2	22.3	77.7
Penicillin	4	>8	≤0.06–>8	17.5	82.5
Ciprofloxacin	>2	>2	≤0.25–>2	35.9	62.1
Ofloxacin	>4	>4	≤0.5–>4	36.9	61.2
Gentamicin	≤1	>8	≤1–>8	75.7	19.4
Neomycin	0.5	>16	≤0.12–>16	—	—
Bacitracin	8	>32	≤0.25–>32	—	—
Mupirocin	>256	>256	≤0.12–>256	1.9	97.1
Enterobacter spp. (100)					
Omiganan pentahydrochloride (CA MH broth)	32	256	8–>512	—	—
Omiganan pentahydrochloride (UA MH broth)	16	128	4–512	—	—
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	94.0	4.0
Ofloxacin	≤0.5	1	≤0.5–>4	94.0	3.0
Gentamicin	≤1	≤1	≤1–>8	94.9	5.1
Neomycin	1	2	0.25–>16	—	—
Bacitracin	>32	>32	>32	—	—
Polymyxin B	≤0.25	16	≤0.25–>32	—	—
E. coli (108)					
Omiganan pentahydrochloride (CA MH broth)	16	32	8–64	—	—
Omiganan pentahydrochloride (UA MH broth)	8	16	4–32	—	—
Ciprofloxacin	≤0.25	>2	≤0.25–>2	84.3	15.7
Ofloxacin	≤0.5	>4	≤0.5–>4	83.3	15.7
Gentamicin	≤1	≤1	≤1–>8	91.7	8.3
Neomycin	1	2	≤0.5–>16	—	—
Bacitracin	>32	>32	32–>32	—	—
Polymyxin B	≤0.25	≤0.25	≤0.25–0.5	—	—
Klebsiella spp. (101)					
Omiganan pentahydrochloride (CA MH broth)	32	128	8–512	—	—
Omiganan pentahydrochloride (UA MH broth)	16	128	4–512	—	—
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	92.0	6.0
Ofloxacin	≤0.5	2	≤0.5–>4	92.1	5.9
Gentamicin	≤1	≤1	≤1–>8	95.0	3.0
Neomycin	1	2	≤0.12–>16	—	—
Bacitracin	>32	>32	>32	—	—
Polymyxin B	≤0.25	≤0.25	≤0.25–16	—	—
P. aeruginosa (102)					
Omiganan pentahydrochloride (CA MH broth)	128	256	16–256	—	—
Omiganan pentahydrochloride (UA MH broth)	32	64	16–256	—	—
Ciprofloxacin	≤0.25	>2	≤0.25–>2	78.4	19.6
Ofloxacin	1	>4	≤0.5–>4	69.6	22.5
Gentamicin	2	>8	≤1–>8	86.3	10.8
Neomycin	4	>16	1–>16	71.6	—
Bacitracin	>32	>32	>32	—	—
Polymyxin B	0.5	0.5	≤0.25–>32	—	—
C. albicans (104)					
Omiganan pentahydrochloride	64	64	32–>512	—	—
Nystatin	2	2	1–32	—	—

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TABLE 1—*Continued*

Organism (no. tested) and antimicrobial agent[a]	MIC (μg/ml)			% by category[b]	
	50%	90%	Range	Susceptible	Resistant
Fluconazole	≤0.25	1	≤0.25–>512	96.2	3.8
Amphotericin B	0.5	0.5	0.12–1	100.0	—
C. glabrata (27)					
Omiganan pentahydrochloride	256	512	128–512	—	—
Nystatin	2	2	1–4	—	—
Fluconazole	16	32	4–256	44.4	7.4
Amphotericin B	0.5	1	0.25–1	100.0	—
C. krusei (26)					
Omiganan pentahydrochloride	32	64	16–256	—	—
Nystatin	2	2	2–32	—	—
Fluconazole	16	32	0.5–64	11.5	3.8
Amphotericin B	1	1	0.5–1	100.0	—
C. parapsilosis (30)					
Omiganan pentahydrochloride	128	256	32–256	—	—
Nystatin	2	2	2	—	—
Fluconazole	1	2	≤0.25–32	96.7	0.0
Amphotericin B	0.5	0.5	0.5–1	—	—
C. tropicalis (27)					
Omiganan pentahydrochloride	16	32	8–64	—	—
Nystatin	2	2	1–2	—	—
Fluconazole	0.5	1	≤0.25–64	96.3	3.7
Amphotericin B	1	1	0.5–1	100.0	—

[a] With mupirocin, isolates were considered susceptible when MICs were ≤8 μg/ml and resistant (high level) when MICs were >256 μg/ml.
[b] —, no breakpoint has been established by the NCCLS (10, 12).

ATCC 22019 and *Candida krusei* ATCC 6258 (Anderegg et al., letter).

All frozen panels representing the three medium types were included in a 120-day stability study. Panels were tested in triplicate at days 0, 7, 14, 21, 28, 45, 60, 90, and 120 postmanufacture for each of five bacterial and two yeast QC strains.

Ten strains were tested by kill curve methodology to evaluate the bactericidal activity of omiganan pentahydrochloride (8, 9). Bacterial kill curve studies were performed with CA MH broth, and *Candida albicans* kill curve studies were performed with RPMI 1640 broth and MOPS buffer. Omiganan pentahydrochloride activity was tested at one, two, four, and eight times the MIC at timed intervals of 0, 0.5, 2, 6, and 24 h.

Minimal bactericidal and fungicidal concentrations (MBCs and MFCs, respectively) were assessed by plating the broth from the MIC well and from the three $\log_2$ dilutions above the MIC for each organism onto appropriate growth media. Colonies of the starting inoculum were counted at the times the MICs were determined. The lowest concentration of antimicrobial agent that kills ≥99.9% of the starting test inoculum is defined as the MBC endpoint (4). A total of eight strains, including *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *S. aureus* 24-1920A, *C. albicans* 15-10082A, and *C. albicans* 13-13547A, were selected for this experiment.

Omiganan pentahydrochloride was very active against all gram-positive species tested (Table 1). The rank order of the gram-positive pathogens according to their susceptibilities to omiganan pentahydrochloride (the MICs at which 50% of the isolates were inhibited [MIC_{50}s]) was as follows: oxacillin-susceptible coagulase-negative staphylococcus (CoNS) = oxacillin-resistant CoNS = *Corynebacterium* spp. (MIC_{50}, 4 μg/ml) > vancomycin-susceptible *Enterococcus faecium* = vancomycin-resistant *E. faecium* (MIC_{50}, 8 μg/ml) > oxacillin-susceptible *S. aureus* = oxacillin-resistant *S. aureus* = beta-hemolytic streptococci = *Bacillus* spp. (MIC_{50}, 16 μg/ml) > vancomycin-susceptible *E. faecalis* = vancomycin-nonsusceptible *E. faecalis* = penicillin-susceptible viridans group streptococci = penicillin-nonsusceptible viridans group streptococci (MIC_{50}, 64 μg/ml). Omiganan pentahydrochloride was equally active against oxacillin-susceptible and -resistant CoNS (MIC_{90}, 8 and 4 μg/ml, respectively). Omiganan pentahydrochloride MICs for *S. aureus* (MIC_{90}s, 16 μg/ml) were generally twofold higher than those for CoNS.

Omiganan pentahydrochloride was eightfold more active against *E. faecium* (MIC_{50}, 8 μg/ml) than against *E. faecalis* (MIC_{50}, 64 μg/ml), and its activity was not affected by vancomycin resistance. Against beta-hemolytic streptococci, omiganan pentahydrochloride MICs ranged from 2 to 128 μg/ml, with a MIC_{90} of 32 μg/ml. Among the gram-positive species tested, the highest omiganan pentahydrochloride MICs for both penicillin-susceptible and -nonsusceptible isolates were those for viridans group streptococci (MIC_{90}, 256 μg/ml). Omiganan pentahydrochloride showed excellent in vitro activity against *Bacillus* spp. (MIC_{50}, 16 μg/ml), and omiganan pentahydrochloride MICs were lowest for *Corynebacterium* spp., with a MIC_{50} of only 4 μg/ml.

In general, MICs with UA MH broth were equal or twofold lower than those with CA MH broth for the bacterial species evaluated in the present study (Table 1). The highest variation was seen with *P. aeruginosa*, for which the MIC_{50} dropped from 128 μg/ml in CA MH broth to 32 μg/ml in UA MH broth. This

TABLE 2. Kill curve kinetic studies in cation-deficient MH broth for 10 selected organisms with four concentrations of omiganan pentahydrochloride and monitoring at 0.5, 2, 6, and 24 h

Organism	Concn tested[d]	CFU/ml at time indicated (h)					MIC (μg/ml)
		0	0.5	2	6	24	
S. aureus ATCC 29213	Control	4.8E6	5.7E6	3.3E7	5.2E8	8.5E8	8
	MIC		2.0E6	1.3E5	1.6E4	3.2E8	
	2 × MIC		1.2E6	3.8E4	1.6E3[a]	6.2E5	
	4 × MIC		3.8E5	7.8E3	1.3E2[a]	1.1E4	
	8 × MIC		1.5E5	1.1E3[a]	1.0E2[a]	1[a]	
S. aureus MBI 105[b]	Control	2.8E6	4.8E6	2.0E7	3.7E8	7.1E8	8
	MIC		1.3E5	1.5E4	5.9E4	2.3E7	
	2 × MIC		1.8E4	1.7E3[a]	7.7E6	6.1E6	
	4 × MIC		1.2E4	2.3E2[a]	1.7E5	4.9E5	
	8 × MIC		7.5E3	2.9E2[a]	1[a]	6.0E2[a]	
Staphylococcus epidermidis 6–313A[b]	Control	1.8E5	1.3E5	1.7E5	4.7E6	1.3E8	2
	MIC		3.6E4	2.0E3	2.0E4	5.8E4	
	2 × MIC		1.7E4	8.5E2	1[a]	1.0E5	
	4 × MIC		4.7E3	1.6E2[a]	1[a]	8.0E4	
	8 × MIC		1.2E3	1[a]	1[a]	1.0E3	
E. faecium 27–308A (VSE)	Control	2.1E6	2.1E6	2.2E7	3.2E8	6.0E8	8
	MIC		9.5E5	2.0E5	1.7E4	3.3E5	
	2 × MIC		3.6E5	3.2E4	1.4E3[a]	3.1E2[a]	
	4 × MIC		4.4E4	2.7E3	1.3E2[a]	6[a]	
	8 × MIC		7.4E3	2.6E3	5[a]	1[a]	
E. faecium 15–206A[c]	Control	7.3E5	2.0E6	9.1E6	3.1E8	3.5E8	8
	MIC		3.5E5	3.4E5	1.4E5	9.8E5	
	2 × MIC		2.0E5	4.2E4	8.5E3	7.6E3	
	4 × MIC		1.2E5	2.5E3	3.2E2[a]	4.[a]	
	8 × MIC		1.4E4	6[a]	1[a]	1[a]	
E. coli ATCC 25922	Control	1.4E6	2.8E6	4.0E7	5.0E8	8.7E8	16
	MIC		1.7E6	1.4E6	1.7E6	1.9E8	
	2 × MIC		1.5E6	6.0E5	3.8E4	2.9E8	
	4 × MIC		2.2E5	5.4E4	3.4E4	5.7E2[a]	
	8 × MIC		9.0E2[a]	2.3E2[a]	1[a]	1[a]	
Klebsiella pneumoniae 21-1940A	Control	9.0E5	4.3E6	1.1E8	4.4E8	6.7E8	16
	MIC		3.5E6	1.3E7	2.3E8	7.5E8	
	2 × MIC		2.1E6	4.9E5	8.2E4	3.0E8	
	4 × MIC		2.7E5	2.3E4	1.1E4	7.3E3	
	8 × MIC		2.7E4	6.5[a]	1[a]	1[a]	
Acinetobacter baumannii 101-2823A	Control	3.2E6	4.4E6	2.7E7	7.5E7	2.2E9	8
	MIC		6.7E6	1.4E7	2.0E7	1.3E9	
	2 × MIC		4.2E6	1.6E5	7.2E4	8.2E5	
	4 × MIC		1.2E6	6.6E2[a]	1[a]	1[a]	
	8 × MIC		4.1E2[a]	1[a]	1[a]	1[a]	
P. aeruginosa ATCC 27853	Control	2.8E6	2.3E6	2.6E7	2.2E8	3.0E9	16
	MIC		3.4E6	3.2E6	1.6E8	7.5E8	
	2 × MIC		3.4E6	1.9E7	9.1E7	1.8E9	
	4 × MIC		2.5E3[a]	2.2E3[a]	1.0E5	2.1E8	
	8 × MIC		1.0E2[a]	4.3E2[a]	4.3E4	1.2E6	
C. albicans 15-10082A	Control	3.0E6	2.5E6	3.5E6	8.9E6	2.3E7	64
	MIC		2.0E6	1.9E6	3.8E6	9.3E6	
	2 × MIC		1.9E6	2.4E5	5.6E3	3.0E4	
	4 × MIC		3.5E5	9.1E2[a]	1[a]	1[a]	
	8 × MIC		9.3E3	2[a]	1[a]	1[a]	

[a] Indicates bactericidal results (≥3 $\log_{10}$ killing), usually occurring at 2 to 6 h.
[b] Oxacillin-resistant strains.
[c] Vancomycin-resistant strains.
[d] 2 × MIC, 4 × MIC, and 8 × MIC, two, four, and eight times the MIC, respectively.

trend was also observed in QC studies with *P. aeruginosa* strains.

The in vitro activity of omiganan pentahydrochloride against the gram-negative isolates is also summarized in Table 1. The rank order of susceptibilities by the MIC_{50}s of omiganan pentahydrochloride for the gram-negative organisms was as follows: *E. coli* (MIC_{50}, 16 μg/ml) > *Enterobacter* spp. = *Klebsiella* spp. (MIC_{50}, 32 μg/ml) > *P. aeruginosa* (MIC_{50}, 128 μg/ml). Omiganan pentahydrochloride MICs were highest for *Enterobacter* spp. among the bacterial pathogens tested in the present study, with a MIC_{90} of 256 μg/ml.

Omiganan pentahydrochloride demonstrated excellent in vitro activity against the *Candida* species. The rank order of in vitro activity levels according to the MIC_{50}s of omiganan pentahydrochloride for the *Candida* species was as follows: *C. tropicalis* (MIC_{50}, 16 μg/ml) > *C. krusei* (MIC_{50}, 32 μg/ml) > *C. albicans* (MIC_{50}, 64 μg/ml) > *C. parapsilosis* (MIC_{50}, 128 μg/ml) > *C. glabrata* (MIC_{50}, 256 μg/ml). All *Candida* spp. isolates evaluated showed a narrow range of omiganan pentahydrochloride MICs. MICs of 64 μg/ml were observed for 84% of the *C. albicans* spp., while the MICs for 97% of all strains were between 32 and 128 μg/ml.

When the MBC and MFC tests were performed with CA MH broth, the MBCs were the same or two- to fourfold greater than the MICs (data not shown). For tests performed with UA MH broth, the MICs were two- to fourfold lower than those observed for tests carried out with the CA MH broth, and the corresponding MBCs were either equal to the MICs or twofold higher (data not shown). For *C. albicans*, the MFCs were either equal to or twofold higher than the MICs. The highest recorded MBC or MFC for any bacterial or yeast isolate tested was 128 μg/ml.

Table 2 summarizes the time-kill curve experiments for the 10 organisms tested. A clear pattern of rapid bactericidal activity was noted within 2 to 6 h. Increased concentrations of omiganan pentahydrochloride enhanced the bactericidal effect. Excellent concentration-dependent killing by omiganan pentahydrochloride was demonstrated against strains of vancomycin-resistant enterococci and oxacillin-resistant staphylococci. However, several strains, including both oxacillin-resistant staphylococcal strains, demonstrated regrowth to baseline levels at 24 h. Omiganan pentahydrochloride was also rapidly fungicidal against the *C. albicans* strain.

Frozen panels including omiganan pentahydrochloride and comparator antimicrobial agents appeared to remain stable over the 120-day monitored period (data not shown). All results from triplicate testing recorded for seven ATCC control strains between days 7 and 120 were within the recently proposed QC range (Anderegg et al., letter).

In summary, omiganan pentahydrochloride was highly active against the bacterial and yeast isolates tested in this study. Omiganan pentahydrochloride results were slightly higher (1 to 2 $\log_2$ dilution steps) when bacteria were tested in CA MH broth than in CU MH broth. The cation concentration effect on omiganan pentahydrochloride MICs varied among the pathogens tested. Omiganan pentahydrochloride demonstrated rapid, concentration-dependent bactericidal and fungicidal activity with MBCs (or MFCs) equal to the MICs or only up to fourfold greater. The results of this study demonstrate that omiganan pentahydrochloride was active against contemporary bacteria and *Candida* spp. and indicate that this compound should be further evaluated for possible clinical use, especially for prevention of catheter-related infections and therapy for cutaneous infections (6, 7).

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