

In-Vitro Activity of Omiganan Pentahydrochloride, a Topical Cationic Peptide, Tested Against Contemporary Bacteria and Yeast Isolates

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Abstract

Background:

Omiganan pentahydrochloride, a synthetic, linear, cationic peptide, has microbicidal activity against many bacteria and yeasts. Omiganan is currently in clinical development for prevention of topical infections. The activity of omiganan was assessed against bacterial and yeast isolates from a recent clinical trial.

Materials and Methods:

A total of 1,437 bacterial and 214 yeast strains were tested against omiganan and 15 comparators using NCCLS susceptibility (S) methods (M7-A6, M27-A2). Other tested agent classes included beta-lactams, fluoroquinolones, aminoglycosides, three topical drugs, and vancomycin (VAN) for bacteria, and amphotericin B, fluconazole, and nystatin for yeast. MICs were determined in cation-adjusted and cation-unadjusted Mueller-Hinton broth (MHB).

Results:

Omiganan MICs ($\mu\text{g/mL}$) in either cation-unadjusted MHB or RPMI 1640 broth were as follows in the table to the right

Conclusion:

The highest omiganan activity was observed against CoNS and *Corynebacterium* spp. (MIC_{50} , 4). *S. aureus* and *E. faecium* were slightly less susceptible to omiganan (MIC_{50} , 8). Resistance (R) to oxacillin, penicillin, or vancomycin did not affect omiganan activity, but MICs were slightly elevated in cation-adjusted MHB. Omiganan showed good activity against Gram-negative bacilli. The most susceptible *Candida* was *C. tropicalis* (MIC_{50} , 16). Overall, omiganan showed broad-spectrum activity against all clinically relevant organisms.

Organisms (n)	MIC ₅₀	MIC ₉₀	Range
CoNS OXA-S (44)	2	4	0.5–4
CoNS OXA-R (174)	2	4	≤0.25–4
<i>S. aureus</i> OXA-S (88)	8	16	1–32
<i>S. aureus</i> OXA-R (111)	8	16	4–64
β -hemolytic streptococci (102)	16	32	1–64
Viridans group streptococci			
PEN-S (66)	64	256	1–512
PEN non-S (34)	64	256	2–256
<i>E. faecalis</i>			
VAN-S (67)	64	128	16–128
VAN-R (13)	64	64	32–64
<i>E. faecium</i>			
VAN-S (44)	8	8	2–16
VAN-R (57)	8	8	2–16
<i>Bacillus</i> spp. (103)	16	32	≤0.25–64
<i>Corynebacterium</i> spp. (103)	2	4	≤0.25–32
<i>P. aeruginosa</i> (102)	32	64	8–64
<i>Enterobacter</i> spp. (100)	16	128	4–512
<i>E. coli</i> (108)	8	16	4–32
<i>Klebsiella</i> spp. (101)	16	128	4–512
<i>Candida albicans</i> (104)	64	64	32–>512
<i>C. glabrata</i> (27)	256	512	128–512
<i>C. krusei</i> (26)	32	64	16–256
<i>C. parapsilosis</i> (30)	128	256	32–256
<i>C. tropicalis</i> (27)	16	32	8–64

This presentation summarizes the in-vitro antimicrobial activity of omiganan against bacteria and yeast isolates from a recent clinical trial.

Introduction

Omiganan pentahydrochloride (omiganan) is a synthetic, linear, cationic peptide with demonstrated in-vitro activity against a wide variety of microorganisms, including bacteria and fungi. This rapidly microbicidal compound interacts with the cytoplasmic membranes of both Gram-positive and Gram-negative bacteria. In *Staphylococcus aureus*, omiganan acts by depolarizing the cytoplasmic membrane, resulting in cell disruption and death; in *Escherichia coli*, exposure to omiganan results in outer membrane permeabilization. A 1% gel preparation of omiganan is currently in clinical development for topical use.

Materials and Methods

Susceptibility testing. Omiganan was supplied by Micrologix Biotech Inc., Vancouver, BC; comparison drugs, by their domestic manufacturers. Antimicrobial susceptibility testing of bacteria was performed according to broth microdilution methods recommended by the NCCLS. MICs were determined in cation-adjusted and cation-unadjusted Mueller-Hinton broth (MHB). An initial 0.5 McFarland inoculum was prepared, diluted 1:29 in sterile water with polysorbate 80, then used to inoculate a commercially-prepared broth microdilution panel (frozen-form; Sensititre/TREK Diagnostics, Cleveland, OH). Final inoculum in the panel was 5×10^4 CFU/mL. Panels were incubated in ambient air at 35°C. MIC determinations were assessed at 16 to 18 hours for all Gram-negative species and at 20 to 24 hours for all Gram-positive or fastidious organisms. NCCLS M100-S13 interpretive standard tables were used to determine susceptibility and resistance rates. The bacitracin breakpoints established by the French Society for Microbiology (susceptible at $\leq 2 \mu\text{g/mL}$ and resistant at $\geq 4 \mu\text{g/mL}$) were used to assess the activity of this compound; an omiganan-susceptible breakpoint of $\leq 256 \mu\text{g/mL}$ was applied for comparative purposes only. Concurrent quality control of testing procedures and antimicrobial panels was performed using the following bacterial strains: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619.

Yeast susceptibility testing was performed according to NCCLS-recommended procedures (M27-A2, 2000). An initial 0.5 McFarland inoculum was prepared, diluted 1:500 in RPMI 1640 broth, then inoculated into a thawed, frozen-form panel to a final concentration of 0.5 to 2.5×10^3 CFU/mL. MIC results were read after 24 hours of incubation at 35°C. Quality control of testing procedures was performed using *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258.

Organisms tested. A total of 1,651 strains (1,437 bacteria and 214 yeast) was tested against omiganan and select comparators. Micrologix Biotech Inc. provided 332 bacterial and 32 yeast strains from clinical trial patients. In addition, 462 bacterial strains were collected from recent clinical infections in Canada (Dr. R. P. Rennie), and 643 bacterial and 182 yeast strains were collected from recent clinical infections in the United States.

Comments

- Omiganan MIC results were two-fold lower when bacteria were tested in cation-unadjusted MHB than when tested in cation-adjusted MHB.
- In general, omiganan was very active against the Gram-positive bacteria tested (1,026 isolates; Table 2). Only one isolate (viridans group *Streptococcus* spp.) had a MIC greater than 256 $\mu\text{g/mL}$.
- Both *S. aureus* and CoNS were very susceptible to omiganan. Resistance to oxacillin did not adversely affect omiganan activity.
- Omiganan was approximately eight-fold more active against *E. faecium* (MIC_{50} , 16 $\mu\text{g/mL}$ in cation-adjusted MHB) than against *E. faecalis* (MIC_{50} , 128 $\mu\text{g/mL}$ in cation-adjusted MHB), and its activity was not affected by vancomycin resistance patterns.
- Omiganan was very active against β -hemolytic streptococci, with a MIC_{50} of 16 $\mu\text{g/mL}$ and a MIC_{90} of 32 $\mu\text{g/mL}$ for both cation-adjusted and cation-unadjusted MHB.
- Viridans group streptococci (100 strains) showed the highest omiganan MIC values among the Gram-positive species tested, with a MIC_{50} of 64 $\mu\text{g/mL}$ and a MIC_{90} of 256 $\mu\text{g/mL}$ for penicillin-susceptible and non-susceptible isolates in both MHB media.
- *Bacillus* spp. (MIC_{50} , 16 $\mu\text{g/mL}$; MIC_{90} , 32 $\mu\text{g/mL}$) and *Corynebacterium* spp. (MIC_{50} , 2 to 4 $\mu\text{g/mL}$ and MIC_{90} , 4 to 8 $\mu\text{g/mL}$) were very susceptible to omiganan.
- Among the Gram-negative pathogens tested, *Enterobacter* spp. showed the highest omiganan MIC results, with a MIC_{50} of 128 $\mu\text{g/mL}$ in cation-unadjusted MHB and 256 $\mu\text{g/mL}$ in cation-adjusted MHB.
- *E. coli* showed the lowest omiganan MICs among the Gram-negative species (Table 3), with MIC_{50} s of 8 and 16 $\mu\text{g/mL}$, and MIC_{90} s of 16 and 32 $\mu\text{g/mL}$ in cation-unadjusted and cation-adjusted MHB, respectively.
- Omiganan exhibited good activity against *Klebsiella* spp., (MIC_{50} s of 16 and 32 $\mu\text{g/mL}$ and MIC_{90} s of 128 and 128 $\mu\text{g/mL}$ in cation-unadjusted MHB and cation-unadjusted MHB, respectively).
- Omiganan was active against *P. aeruginosa*, but MICs were approximately four-fold higher when the isolates were tested in cation-adjusted MHB (MIC_{50} s of 32 and 128 $\mu\text{g/mL}$ and MIC_{90} s of 64 and 256 $\mu\text{g/mL}$ in cation-unadjusted MHB and cation-adjusted MHB, respectively).
- The rank order of in-vitro susceptibility to omiganan among the *Candida* species (Table 4) was as follows: *C. tropicalis* (MIC_{50} , 16 $\mu\text{g/mL}$) > *C. krusei* (MIC_{50} , 32 $\mu\text{g/mL}$) > *C. albicans* (MIC_{50} , 64 $\mu\text{g/mL}$) > *C. parapsilosis* (MIC_{50} , 128 $\mu\text{g/mL}$) > *C. glabrata* (MIC_{50} , 256 $\mu\text{g/mL}$).

Results

Table 1. Antimicrobial activity of omiganan against bacteria tested in cation-unadjusted Mueller-Hinton broth.

Organism (No. Tested)	No. of Isolates (Cumulative %) Inhibited at MIC (mg/mL) of:											
	≤0.25	0.5	1	2	4	8	16	32	64	128	256	512
Coagulase-negative staphylococci												
Oxacillin-susceptible (44)	0 (0.0)	5 (11.4)	8 (29.5)	15 (63.6)	16 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
Oxacillin-resistant (174)	2 (1.1)	15 (9.8)	23 (23.0)	72 (64.4)	62 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
<i>S. aureus</i>												
Oxacillin-susceptible (88)	0 (0.0)	0 (0.0)	1 (1.1)	1 (2.3)	1 (3.4)	53 (63.6)	31 (98.9)	1 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
Oxacillin-resistant (111)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	82 (74.8)	25 (97.3)	1 (98.2)	2 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
<i>E. faecalis</i>												
Vancomycin-susceptible (87)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)	3 (5.7)	45 (57.5)	37 (100.0)	0 (100.0)	0 (100.0)
Vancomycin-resistant (13)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	12 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
<i>E. faecium</i>												
Vancomycin-susceptible (44)	0 (0.0)	0 (0.0)	0 (0.0)	5 (11.4)	9 (31.8)	28 (95.5)	2 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
Vancomycin-resistant (57)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	22 (40.4)	31 (94.7)	3 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
β -hemolytic streptococci (102)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	3 (3.9)	25 (28.4)	57 (84.3)	12 (96.1)	4 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
viridans group streptococci												
Penicillin-susceptible (66)	0 (0.0)	0 (0.0)	1 (1.5)	0 (1.5)	0 (1.5)	7 (12.1)	2 (15.2)	14 (36.4)	25 (74.2)	4 (80.3)	12 (98.5)	1 (100.0)
Penicillin-resistant (34)*	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (2.9)	2 (8.8)	3 (17.6)	7 (38.2)	11 (70.6)	3 (79.4)	7 (100.0)	0 (100.0)
<i>Bacillus</i> spp. (103)	11 (10.7)	3 (17.6)	6 (19.4)	14 (33.0)	2 (35.0)	6 (40.8)	39 (78.6)	16 (94.2)	6 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
<i>Corynebacterium</i> (103)	3 (2.9)	5 (7.8)	19 (26.2)	37 (62.1)	30 (91.3)	8 (99.0)	0 (99.0)	1 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
<i>Enterobacter</i> spp. (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	23 (24.0)	37 (61.0)	19 (80.0)	5 (85.0)	6 (91.0)	7 (98.0)	2 (100.0)
<i>E. coli</i> (108)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	59 (57.4)	41 (95.4)	5 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)
<i>Klebsiella</i> spp. (101)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	19 (20.8)	35 (55.4)	10 (65.3)	8 (73.3)	20 (93.1)	5 (98.0)	2 (100.0)
<i>P. aeruginosa</i> (102)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.9)	33 (37.3)	51 (87.7)	13 (100.0)	0 (100.0)	0 (100.0)	0 (100.0)

*Combined intermediate (0.25 – 1 $\mu\text{g/mL}$) and resistant ($\geq 2 \mu\text{g/mL}$) results.

Table 3. Antimicrobial activity of omiganan and selected agents against Gram-negative bacteria.

Antimicrobial Agent	MIC (mg/mL)			% by Category	
	50%	90%	Range	Susceptible	Resistant
<i>Enterobacter</i> spp. (100)					
Omiganan (cation-unadjusted MHB)	16	128	4–512	98.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	32	256	8–>512	90.0 ^a	--
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	94	4
Ofloxacin	≤0.5	1	≤0.5–>4	94	3
Gentamicin	≤1	2	≤1–>8	94.9	5.1
Neomycin ^c	1	2	0.25–>16	99	--
Bacitracin ^d	>32	>32	>32	--	--
Mupirocin ^e	>256	>256	16–>256	0	15.2
Polymyxin B	≤0.25	16	≤0.25–>32	--	--
<i>E. coli</i> (108)					
Omiganan (cation-unadjusted MHB)	8	16	4–32	100.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	16	32	8–64	100.0 ^a	--
Ciprofloxacin	≤0.25	>2	≤0.25–>2	84.3	15.7
Ofloxacin	≤0.5	>4	≤0.5–>4	83.3	16.7
Gentamicin	≤1	≤1	≤1–>8	91.7	8.3
Neomycin ^c	1	2	≤0.5–>16	95.4	--
Bacitracin ^d	>32	>32	>32	--	--
Mupirocin ^e	128	256	16–>256	0	5.6
Polymyxin B	≤0.25	≤0.25	≤0.25–0.5	--	--
<i>Klebsiella</i> spp. (101)					
Omiganan (cation-unadjusted MHB)	16	128	4–512	98.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	32	128	8–512	98.0 ^a	--
Ciprofloxacin	≤0.25	0.5	≤0.25–>2	92	6
Ofloxacin	≤0.5	2	≤0.5–>4	92.1	5.9
Gentamicin	≤1	≤1	≤1–>8	95	3
Neomycin ^c	1	2	≤0.12–>16	99	--
Bacitracin ^d	>32	>32	>32	--	--
Mupirocin ^e	256	>256	16–>256	0	34
Polymyxin B	≤0.25	≤0.25	≤0.25–16	--	--
<i>P. aeruginosa</i> (102)					
Omiganan (cation-unadjusted MHB)	32	64	8–64	100.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	128	256	16–256	100.0 ^a	--
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 ^c	4	>16	1–>16	71.6	--
Bacitracin ^d	>32	>32	>32	--	--
Mupirocin ^e	>256	>256	>256	0	100
Polymyxin B	0.5	0.5	≤0.25–>32	--	--

Footnote for Table 3: MHB = Mueller-Hinton broth.

^aA susceptible breakpoint of $\leq 256 \mu\text{g/mL}$ was used for comparison purposes.

^bNo breakpoint has been established by the NCCLS.

^cA susceptible breakpoint of $\leq 10 \mu\text{g/mL}$ was used as suggested by Barry (1976).

^dIsolates were categorized as susceptible or resistant according to the breakpoints established by the French Society for Microbiology.

^eIsolates were considered susceptible when MICs were $\leq 8 \mu\text{g/mL}$ and resistant (high-level) when MICs were $>256 \mu\text{g/mL}$.

Table 2. Antimicrobial activity of omiganan and selected agents against Gram-positive bacteria.

Antimicrobial Agent	MIC (mg/mL)			% by category	
	50%	90%	Range	Susceptible	Resistant
CoNS, oxacillin-susceptible (44)					
Omiganan (cation-unadjusted MHB)	2	4	0.5–4	100.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	4	8	0.5–8	100.0 ^a	--
Vancomycin	1	2	0.25–2	100	0
Oxacillin	≤0.25	≤0.25	≤0.25	100	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
Neomycin ^c	≤0.12	0.25	≤0.12–>2	100	--
Bacitracin ^d	32	>32	≤0.25–>32	2.3	97.7
Mupirocin ^e	0.25	0.5	≤0.12–>256	93.2	6.8
CoNS, oxacillin-resistant (174)					
Omiganan (cation-unadjusted MHB)	2	4	≤0.25–4	100.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	4	4	0.5–16	100.0 ^a	--
Vancomycin	1	2	0.5–2	100	0
Oxacillin	>2	>2	0.5–>2	0	100
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	58	26.4
Neomycin ^c	≤0.12	16	≤0.12–>16	85.5	--
Bacitracin ^d	32	>32	8–>32	0	100
Mupirocin ^e	32	>256	≤0.12–>256	48	30.1
<i>S. aureus</i> , oxacillin-susceptible (88)					
Omiganan (cation-unadjusted MHB)	8	16	1–32	100.0 ^a	-- ^b
Omiganan (cation-adjusted MHB)	16	16	2–32	100.0 ^a	--
Vancomycin	0.5	1	0.5–1	100	0
Oxacillin	≤0.25	0.5	≤0.25–2	100	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