Poster #502

POTENCY OF OMIGANAN PENTAHYDROCHLORIDE: EVIDENCE FOR RETAINED OR ENHANCED ACTIVITY WHEN FORMULATED IN A GEL MATRIX

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IDSA 2007
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AMENDED ABSTRACT

Background: OMI is a peptide antimicrobial being developed for topical use to prevent catheter-associated infections (CAI). In clinical trials, OMI is administered in a 1% gel formulation at the catheter insertion site. Stability of OMI in a gel matrix has not been reported but is a critical factor for routine storage. We compared potency of OMI 1% gel stored for ≥12 months at room temperature in single-use ampoules with that of freshly made 1% OMI gel and 1% OMI in broth media.

Methods: CLSI MIC microdilution methods with Mueller-Hinton and RPMI broth media were used; organisms tested included *S. aureus* ATCC 29213 (SA), *E. coli* ATCC 25922 (EC) and *C. krusei* ATCC 6258 (CK). Aqueous OMI stock solutions were prepared of 1% OMI-containing gel from ampoules, fresh OMI and gel, and fresh OMI in broth only. All OMI QC results were within published ranges.

Results: SA MIC values for 1% OMI gel from ampoules and freshly prepared 1% OMI gel were all ≥6 µg/ml (Table); these MIC values were less than for OMI prepared in broth alone (all 10 µg/ml). This represents a 2-fold SA MIC decrease (10 µg/ml to ≤6 µg/ml; equivalent to a one $\log_2$ dilution step change from 16 to ≤8 µg/ml). EC MIC modal values for 1% OMI gel from ampoules and freshly prepared 1% OMI gel were 22 and 28 µg/ml, respectively, lower than MIC values for OMI prepared in broth. CK MIC modal values for the two OMI gel-containing preparations were 14 and 20 µg/ml (within expected variation) and those from the ampoule gel were equivalent to those for OMI prepared in broth alone (no change). Gel matrix alone had no measurable effect on organism growth.

Organism/results for four replicates	OMI MIC µg/ml: 1% in broth (fresh solution)	1% in gel (stored ampoule)	1% in gel (fresh solution)	Gel only [a]
S. aureus ATCC 29213				
Mode (range)	10 (10)	≤6 (<6)	≤6 (<6)	>500 (>500)
E. coli ATCC 25922				
Mode (range)	32 (32)	22 (22)	28 (24-28)	>500 (>500)
C. krusei ATCC 6258				
Mode (range)	14 (14)	14 (14)	20 (20)	>500 (>500)

a. Dilution of gel in equivalent omiganan+gel concentrations

Conclusions: No change in potency was detected for the 1% OMI gel stored in ampoules for a year or more compared with equivalent freshly prepared solutions. Extended shelf life is a critical attribute for a topical agent being developed for prevention of CAI.

INTRODUCTION

Omiganan is a rapidly bactericidal and fungicidal cationic peptide analog of indolicidin that is known to significantly reduce normal skin flora counts following topical applications. This agent is currently in a Phase III USA and European clinical trial for prevention of catheter-associated infections, including local catheter-site infections and catheter-related blood stream infections, that are thought to arise from colonization of the catheter and infection of tissues at the site of catheter placement. Data from the National Nosocomial Infections Surveillance (NNIS) system has shown that the most commonly occurring organisms include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus* (including oxacillin- [methicillin]-resistant strains; MRSA), *Pseudomonas* spp., *Enterococcus* spp., *Enterobacteriaceae* and *Candida* spp., among others.

In clinical trials, omiganan is administered in a 1% gel formulation at the catheter-insertion site following primary insertion and during subsequent dressing changes. Stability of omiganan in a gel matrix has not been reported on previously but is a critical factor given the product may be expected to be stored routinely for extended periods in hospital stores and near nursing stations. We compared potency of 1% omiganan gel in single-use ampoules stored for ≥12 months at room temperature with that of freshly made 1% omiganan gel and 1% omiganan in broth media to examine for temporal changes.

MATERIALS AND METHODS

To characterize the potency of omiganan following ≥12 months room temperature storage, the following antimicrobial/matrices were tested and included:1% omiganan pentahydrochloride-containing gel in ampoules provided by sponsor; 1% omiganan pentahydrochloride-containing gel prepared with fresh omiganan powder and placebo gel; and 1% omiganan pentahydrochloride (no gel) prepared with Mueller-Hinton broth (for bacteria) or RPMI 1640 broth (for yeast). Isolates were also tested with 'placebo' gel containing no omiganan (gel matrix provided by sponsor).

Omiganan and placebo gel combinations were prepared as follows: 1) 1 ml of omiganan pentahydrochloride 1% gel as provided by the sponsor in ampoules was added to a conical tube with 8.33 ml of H_2O and mixed thoroughly to prepare a 1000 µg/ml test concentration; 2) fresh diluted omiganan pentahydrochloride 1% gel was prepared by adding 0.01 grams of omiganan powder to 8.33 ml of H2O in a conical tube, mixing thoroughly, and then adding 1 ml of placebo gel and mixing again to a uniform consistency, producing a 1000 µg/ml test concentration; 3) fresh 1000 µg/ml omiganan pentahydrochloride was prepared by adding 0.01 grams of omiganan powder to 9.33 ml of H_2O in a conical tube (no gel) and mixing thoroughly; 4) diluted placebo gel (no omiganan) was prepared by adding 1 ml of gel to 8.33 ml of H_20 and mixing thoroughly (to equal the gel concentration in the omiganan-containing product provided by the sponsor).

Broth microdilution assay panels were prepared by diluting the three omiganan 1000 µg/ml stock solutions and the placebo gel in Mueller-Hinton and RPMI broths to achieve the required testing ranges (6 to 500 µg/ml). Each organism (ATCC quality control [QC] strains *S. aureus* 29213, *E. coli* 25922 and *C. krusei* 6258) was tested in quadruplicate against the four test combinations. All MIC testing methods and QC parameters were as specified the Clinical and Laboratory Standards Institute (CLSI; M7-A7 [2006]; M27-A2 [2002]; and M100-S17 [2007]).

RESULTS

- QC results (four replicates each, Table 1) when testing *S. aureus* ATCC 29213, *E. coli* ATCC 25922 and *C. krusei* ATCC 6258 were all 10, 32 and 14 µg/ml, respectively, within ranges as specified by Anderegg et al [2004].
- When testing *S. aureus* MIC values for 1% omiganan gel from sponsor-supplied ampoules AND freshly prepared 1% omiganan gel, all values were ≤6 µg/ml, the lowest concentration tested, compared with 10 µg/ml for omiganan prepared in Mueller-Hinton broth alone (equivalent to a one $\log_2$ dilution step change; Table 1).
- *E. coli* MIC modal values for 1% omiganan gel from sponsor-supplied ampoules and freshly prepared 1% omiganan gel were 22 and 28 µg/ml, respectively; both values were lower than the MIC values (all 32 µg/ml) for omiganan prepared in Mueller-Hinton broth alone, but were within expected variation.
- *C. krusei* ATCC 6258 MIC modal values for 1% omiganan gel from sponsor-supplied ampoules AND freshly prepared 1% omiganan gel were 14 and 20 µg/ml, respectively (Table 1).
- Omiganan MIC values from the ampoule gel were equivalent to those for omiganan prepared in RPMI 1640 broth alone (no change); MIC values from the freshly prepared gel-containing media were slightly higher (equivalent to one doubling dilution) than the MIC values for omiganan prepared in RPMI 1640 broth alone but, again, were within expected variation.

Table 1. In vitro activity of omiganan pentahydrochloride comparing results from freshly prepared 1% omiganan in broth with those of 1% omiganan gel (hydroxy-ethyl-cellulose) stored in ampoules (Lot# 01805A as provided by Cadence Pharmaceuticals) and 1% omiganan gel that has been freshly prepared.

Organism/Replicate	Omiganan MIC µg/ml: 1% in broth (fresh solution)	1% in gel (stored ampoule)	1% in gel (fresh solution)	Gel only
S. aureus ATCC 29213				
1	10	≤6	≤6	>500[a]
2	10	≤6	≤6	>500
3	10	≤6	≤6	>500
4	10	≤6	≤6	>500
Mode	10	≤6	≤6	>500
E. coli ATCC 25922				
1	32	22	28	>500
2	32	22	28	>500
3	32	22	28	>500
4	32	22	24	>500
Mode	32	22	28	>500
C. krusei ATCC 6258				
1	14	14	20	>500
2	14	14	20	>500
3	14	14	20	>500
4	14	14	20	>500
Mode	14	14	20	>500

a. Dilution of gel in equivalent omiganan+gel concentration.

CONCLUSIONS

- Potency of omiganan powder was as expected with all strains testing within defined QC ranges as specified by Anderegg et al [2004]; the gel matrix alone had no measurable effect on bacterial growth.
- No change in potency was detected in the 1% omiganan gel supplied by the sponsor in single-use ampoules (stored for ≥12 months) for any of the tested strains (*S. aureus, E. coli and C. krusei*).
- Extended shelf-life is a critical attribute for a topical agent such as omiganan being developed for prevention of catheter-associated infections; these results demonstrate that potency of the active ingredient was not affected following packaging and storage for at least 12 months.

SELECTED REFERENCES

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