Bensal HP (BHP-410), a Novel Antimicrobial Agent with Activity against MRSA, VRE, Gram-negative MDROs, Yeasts, and Dermatophytic Fungi


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Abstract

Background: Increasing multidrug resistance and a dwindling antibiotic pipeline have created a major global health crisis. Little is known about the activity of topical agents against multidrug resistant organisms (MDROs) or about their therapeutic or infection control relevance in meeting this challenge. With this in mind, a study was designed to assess the activity of a novel topical antimicrobial BHP-410 containing salicylic acid, benzoic acid and GRB-7 (a bark extract) against a broad range of MDROs including MRSA, VRE, ESBIL and carcinobemase-producing isolates. In addition its activity against selected isolates of Mycobacterium fortuitum, Nocardia brasiliensis, yeasts and filamentous fungi was also assessed.

Materials and Methods: Activity against 161 isolates comprising 12 bacterial species (5 gram-negative, 7 gram-positive), 3 yeast species, and 3 dermatophyte species was assessed. The 129 bacterial isolates included well characterized non-MDRO and MDRO isolates of Enterobacteriaceae, P. aeruginosa, A. baumannii, S. aureus, and Enterococcus faecalis and routine clinical isolates. Inhibitory activity of BHP-410 was assessed using diffusion tests, all bacterial and fungal isolates were equally susceptible within a range of 40 to 80-fold dilutions. BHP-410 was rapidly bactericidal against P. aeruginosa and MRSA.

Results: In cylinder diffusion tests, all bacterial and fungal isolates were inhibited by BHP-410 and no resistance was detected. There was no apparent reduction in inhibition zone when comparing MDRO-isolates to non-MDRO (wild type) isolates. In MIC tests non-MDRO and MDRO isolates were equally susceptible with all gram-positive isolates were inhibited by an 80-fold dilution of BHP-410. Gram-negative isolates were all susceptible within a range of 40 to 80-fold dilutions. BHP-410 was rapidly bactericidal against P. aeruginosa and MRSA.

Conclusions: Bensal HP-410 has an extremely broad spectrum of antimicrobial activity and is unaffected by the resistance mechanisms of MDROs. Further study is warranted to investigate its full clinical utility.

Materials & Methods

Test Agent: Bensal HP marketed by EPI Health (Charleston SC)

Organisms: In vitro activity was investigated against 184 bacterial and fungal isolates from the culture collections of Creighton University, Omaha, NE, the Alegent Creighton Hospital Microbiology Laboratory, Omaha, NE, and the University of Louisville Microbiology Lab, Louisville, KY.

The isolates were from U.S. and international sources and included well characterized non-MDRO and MDRO isolates of Enterobacteriaceae (n=40), Pseudomonas aeruginosa (n=11), Acinetobacter baumannii (n=13), Staphylococcus aureus (n=23) including MRSA and methicillin-susceptible S. aureus (MSSA), and Enterococcus faecalis (n=11) including VRE. Also tested were routine clinical isolates of Group A Streptococcus (S. pyogenes, n=13), Propionibacterium acnes (n=1), Mycobacterium fortuitum (n=10) and Nocardia brasiliensis (n=10). The fungal isolates included Candida albicans (n=10), C. glabrata (n=10), Cryptococcus neoformans (n=1), Trichophyton rubrum (n=12), T. tonsurans (n=10), and T. mentagrophytes (n=10). The MDROs were previously characterized for resistance mechanisms by phenotypic, biochemical and molecular methods (1) and included isolates producing the ESBL TEM-52, SHV ESBLs, OXA-46, CTX-M-1, CTX- M-9, CTX-M-12, CTX-M-14, CTX-M-15, CTX-M-17, CTX-M-18, and CTX-M-19, chromosomal and plasmid-mediated AmpC β-lactamases that included FOX-like and CMY-2 enzymes, and carbapenemases of the IMP, VIM, KPC, and NDM families. Especially challenging MDROs include carbapenemase-producing isolates of P. aeruginosa and A. baumannii and P. aeruginosa isolates with upregulated MexAB, MexEF, and MexXY efflux pumps, and down-regulation of the OprD porin.

Investigations: Susceptibility was determined by the cylinder diffusion (2) and CLSI agar dilution (3) methods. Examples of cylinder diffusion tests are shown in Figure 1. Bacterial activity was assessed by time-kill methodology following exposure of P. aeruginosa ATCC 27853 and MRSA SA179 to concentrations of 1x and 4x the MIC.

Results: All isolates, bacterial and fungal, were inhibited by Bensal HP. No resistance was detected. No MDRO isolates exhibited cross resistance to Bensal HP. That is susceptibility was unaffected by the innate or acquired resistance mechanisms of the isolates. Zone diameters were generally larger for gram-positive bacteria and filamentous fungi than for gram-negative bacteria (Table 1). Some MDROs had larger inhibition zones than their wild type counterparts. Representative isolates exhibiting this trend are shown in Table 2.

In MIC tests with 73 selected isolates that included both MDROs and non-MDROs in each species tested, all gram-positive isolates were inhibited by an 80-fold dilution of Bensal HP (MIC of 0.375/0.75/0.75/0.75 mg/mL of salicylic acid/benzoic acid/GRB-7 respectively) and the gram-negative isolates were all susceptible to a 40-fold dilution (MIC of 0.75/1.5/1.5/0.75 mg/mL of salicylic acid/benzoic acid/GRB-7 respectively), with most gram-negatives being susceptible to an 80-fold dilution (0.375/0.75/0.75 mg/mL).

In time-kill tests, BHP-410 was rapidly bactericidal against P. aeruginosa ATCC 27853 and MRSA SA179 at 4x the MIC (1:20 dilution) with no regrowth occurring in the 24 hour incubation period (Figures 2 and 3).

Conclusions:

1. Bensal HP has an extremely broad spectrum of activity that is not compromised by mechanisms of antibiotic resistance occurring in contemporary multidrug resistant bacteria.
2. All gram-positive and gram-negative bacteria, yeasts, and filamentous fungi in this study were susceptible to the clinically used concentration of Bensal HP (i.e. inhibited by undiluted cream).  
3. No resistance to Bensal HP was detected.
4. Bensal HP was rapidly bactericidal in time-kill studies with an isolate of Pseudomonas aeruginosa and an isolate of MRSA.
5. Further study is warranted to investigate its full clinical utility.

References