Efficacy of a Surfactant, Allantoin, and Benzalkonium Chloride Solution for Onychomycosis

Preliminary Results of Treatment with Periodic Debridement

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A 10-month, hospital-based, open-label clinical study was undertaken of a unique antimicrobial nail solution containing surfactant, allantoin, and benzalkonium chloride to determine its effectiveness, in conjunction with periodic debridement, against pedal onychomycosis. Forty patients with microbial infection of the nails were enrolled in this study, in which a new, objective nail-scoring system was used. At the start of the study, the mean nail score was 8.3, and 79.8% of the nails scored had severe disease (on a scale of 0 to 10, with 10 defined as total nail involvement, accompanied by pain and thickening). By the conclusion of the study, the mean score had decreased to 2.5, 32.6% of the patients’ nails were scored 0 or 1, and 90% of the patients subjectively judged their improvement as excellent or good. (J Am Podiatr Med Assoc 89(3): 124-130, 1999)

Epidemiologic studies have shown that up to 18% of the world’s population is afflicted with microbial infection of the nail plate. Of these infections, 80% to 90% are caused by dermatophyte fungal species (eg, Trichophyton, Microsporum, and Epidermophyton species), 3% to 11% by nondermatophyte molds (eg, Aspergillus species), 5% to 17% by yeasts (eg, Candida species), and 5% to 12% by bacteria (eg, Pseudomonas and Staphylococcus species).1-4 Although the pathogenic etiology varies greatly, Lubeck et al5 have suggested that longer life spans, increased therapies with antineoplastic agents, and a continually growing population of immunocompromised individuals are among the factors that have contributed to an increase in susceptibility to the disease.

Historically, treatment of these infections has had only limited success, partly because of poor patient compliance and partly because of physicians’ perception of onychomycosis as merely a cosmetic problem that is not worthy of treatment. However, there are studies that show that nail disease has a serious emotional and psychological impact on the affected individual and can negatively influence a person’s social interactions with others.6,7 Moreover, the economic impact of nail disease is great: In the 1989 fiscal year alone, Medicare claims for nail disease totaled more than $43 million for physician visits only, not including medications.6,8 The impact of onychomycosis and its increasing significance in society and in the practice of podiatric medicine are such that the Journal...
interaction with cell membranes. As a result, certain compounds have hydrophobic and hydrophilic species between two solvents, rather than diffusing into the bulk of the solution. The quaternary ammonium compounds are cationic molecules with surfactant properties. A surfactant is a substance that, when placed in solution, will congregate at the surface or the interface of the benzalkonium chloride as well as preserving the activity of the molecule in nonoptimal conditions (ie, an unfavorable aqueous environment). Nonetheless, with development of a stable delivery system, benzalkonium chloride would be expected to offer both persistent and residual activity in mammalian tissue.

The emollient allantoin protects skin cells. Allantoin is mildly keratolytic and also stimulates proliferation of skin cells. It is most commonly used to promote wound healing. Benzalkonium chloride can be formulated with surfactants and allantoin and remain antiseptically active. A surfactant- and allantoin-based delivery system has been developed that allows the molecule to remain active against pathogens while it protects the viable skin cells and enhances the rapid absorption of benzalkonium chloride into the stratum corneum and the nail matrix.

In this article, the authors report the results of a 10-month, open-label study of the clinical efficacy of this surfactant-based delivery system containing allantoin and the active ingredient benzalkonium chloride, available over the counter as Mycocide NS (Woodward Laboratories, Los Alamitos, California), for the treatment of nail-plate disease.

Materials and Methods

Patient Selection and Enrollment

A 10-month, open-label study was undertaken to evaluate the efficacy of a surfactant, allantoin, and benzalkonium chloride solution for the treatment of pedal onychomycosis. To participate in the study, patients could not have been using any other topical antifungal agent within the month prior to enrollment or have any history of oral or systemic antifungal usage, could not be sensitive to the ingredients of the medication being tested, and had to have palpable pedal pulses. Patients with psoriasis or lichen planus medication being tested, and had to have palpable pedal pulses. Patients with psoriasis or lichen planus and pregnant or lactating females were excluded from the study. No exclusion criteria were set for the number of digits involved or the extent of nail-plate infection.

At the initial visit, patients were visually assessed for the presence of pedal onychomycosis. After enrollment of the patient in the study, baseline hematologic evaluation was conducted for safety purposes. The baseline examination at Day 0 consisted of a clinical examination with focused history, objective and subjective scoring of the involved nails (as described later), and color photography of the involved nail or nails. Infected nails were mechanically debried, and patients were given the antimicrobial...
surfactant, allantoin, and benzalkonium chloride solution for use twice daily on the affected (and adjacent) nails. Patients were instructed to apply one or two drops to each nail plate and the tissue surrounding the nail twice daily and to massage the solution into the affected area until it was absorbed. Nail samples taken at Day 0 were analyzed using potassium hydroxide preparation, dermatophyte test medium, and Sabouraud’s dextrose agar culture with classification for the presence and nature of microbial infection. Complete blood count and urinalysis were performed at the initial and final clinic visits as a precautionary check for systemic toxicity. Monthly follow-up visits consisted of subjective and objective scoring of involvement of the nail plate, obtaining color photographs, and replenishing medication. The potassium hydroxide preparation, dermatophyte test medium, and Sabouraud’s dextrose agar culture evaluation were repeated on the patients’ affected nail samples at the 10-month visit.

**Diagnostic Evaluation**

**Potassium Hydroxide Preparation.** The procedure for this evaluation was performed as described elsewhere.21, 22 Dissolved nail plate was assessed for the presence of potassium hydroxide–resistant debris, which is indicative of fungal infections.

**Dermatophyte Test Medium Agar Culture.** Culture growth evaluation was also performed as described previously.21, 22 Nail fragments from patients presenting with microbially infected nails were placed in a vial containing a dermatophyte test medium agar slant (containing cycloheximide, gentamicin, and chloramphenicol and pH-based color indicator). These slants were assessed for color change and/or growth after 3 days and at 2 weeks.

**Sabouraud’s Dextrose Agar Culture.** Classification of microbial species present in the affected nails was done through standard hospital laboratory procedures. (Negative cultures were kept for 6 weeks to confirm that no fungal growth had occurred.)

**Nail Scoring.** Patients’ nails were quantitatively assessed using a version of the Woodward Laboratories, Inc, Dystrophic Nail Score Form (Fig. 1). This scoring form provides quantifiable data by using the general formula:

\[ \text{Score} = \text{Area} + \text{Pain} + \text{Thickness} \ (APT) \]

The dystrophic area score was determined by adding the numerical values for each of the areas indicated in the schematic diagram of a nail. The proximal portion of the nail—the lunula and/or eponychium—is given greater weight in the scoring because of the difficulty in eradicating nail infections in this area. One point was added to this area score if the patient reported pain or nail discomfort, and one point was added if the patient’s nails were thickened. The maximum score that may be achieved with this rating system is 10, and indicates a fully involved, thickened, and painful nail. A score of 0 indicates a clinically normal nail.

**Patient Subjective Evaluation.** The patients’ subjective impressions of their progress were assessed with a standardized interview form that was used at each patient visit (Fig. 2). As a result, a series of factors were followed from visit to visit as clinical data; owing to its subjective nature, however, the information was not included in this study.

**Results**

Forty patients from the podiatry subspecialty clinic of the Family Practice Clinic at Pacific Hospital of Long Beach with microbial nail infections were en-
rolled in the study. These infections were caused by pathogen species including *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Candida albicans*, *Epidermophyton floccosum*, and *Aspergillus versicolor* as diagnosed by the methods previously described and were treated twice daily with the surfactant, allantoin, and benzalkonium chloride solution.

Of the 40 patients enrolled in the study, 24 were female and 16 were male. The patients' ages ranged from 28 to 93 years (mean, 64.4 years). Half of the patients enrolled in the study were able to complete the course of treatment. Data on these patients are provided in Table 1. (Most of the patients dropped from the study were excluded because of noncompliance; the average age of those completing the study was 64.7 years.) The 20 patients who completed the study had a total of 123 dystrophic, infected nails. The patients presented with a full range of nail involvement, from one to ten involved nails, with a mean involvement of 6.2 nails per patient. (The median was six nails involved per patient, and the mode was all ten nails involved in six patients.) By the conclusion of the 10-month treatment period, subjective self-evaluation ratings indicated that 44.4% of the patients perceived an excellent result, 45.6% perceived a good result, 7% perceived a fair result, and 3% perceived a poor result.

For quantitative evaluation of effectiveness, an objective nail-scoring system was used in which the area of microbial involvement (assessed via nail dystrophy), pain, and thickening of patients' nails were assessed. At the initiation of the study, the mean score was 8.3. The data show a steady reduction in nail scores for most patients, with a mean nail score of 2.5 at 10 months. This represents an improvement in the nail scores that becomes statistically significant at 10 months ($P < .05$).

Most of the patients included in the study had partial nail-plate involvement. However, of the 123 nails scored and evaluated for the study, 44 had scores of 10, indicating total dystrophic onychomycosis. Although only six of those nails had "exit scores" of 0 (at the end of 10 months), there was complete clearing of totally involved nails in 14% of the patients, which is noteworthy; furthermore, the average exit score of these nails improved to 5.1. When the 52 nails with advanced, dystrophic changes indicated by a score of 9 are considered as a subset, the rate of total clearing increased to 23% and the average exit score was 3.7. Figure 3 graphically depicts the improvement in the patients' nail scores.

No significant changes were noted in any of the patients' complete blood count or urinalysis results and no adverse reactions were reported (or caused any patient to withdraw from the study).

Improvement in the general appearance of affected nails was noticeable in many of the patients after 4 months of treatment. It is noteworthy that no patient being treated with the surfactant, allantoin, and benzalkonium chloride solution experienced spreading of the onychomycosis from infected digits to any adjacent digits. After 10 months of twice-daily application of the surfactant, allantoin, and benzalkonium chloride solution to affected nails, a significant shift in the dystrophic nail scores of the patients is apparent. These results suggest that treatment with the surfactant, allantoin, and benzalkonium chloride solution is a clinically effective treatment for a wide variety of microbial pathogens of human nails.

**Discussion**

The objective of this study was to determine the degree of effectiveness of a surfactant, allantoin, and benzalkonium chloride antimicrobial nail solution for the treatment of pedal onychomycosis. The results from the 10-month assessment period indicate a
Other studies of the clinical efficacy of antimicrobial nail products have taken care to limit patients included to those with infections caused by the few pathogens that are greatly affected by the compound being studied or have set narrow conditions for patient inclusion, concurrently setting broad conditions of clinical success. As a result, another objective of the current study was to demonstrate the effectiveness of the surfactant, allantoin, and benzalkonium chloride solution in a random pool of patients varying widely in age, medical and socioeconomic status, and the extent of nail involvement. Patients with onychomycosis present with microbial infections, which include infections caused by dermatophytes, molds, and yeast, as well as some bacterial superinfection. The nail solution tested in this clinical study was found to be effective overall, indicating its efficacy as a broad-spectrum topical, antimicrobial nail treatment.

Table 1. Data on the Patients Participating in the Study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Left</th>
<th>Right</th>
<th>Number of Nails Involved</th>
<th>Average Nail Score (APT)</th>
<th>Pathogen at Enrollment</th>
<th>Fungal Culture at Final Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Start    4 Months 8 Months 10 Months</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>61</td>
<td>2</td>
<td>2</td>
<td>7.3  1.0  0.3  0.2</td>
<td>Aspergillus versicolor</td>
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</tr>
<tr>
<td>2</td>
<td>67</td>
<td>5</td>
<td>5</td>
<td>10.0 3.7  4.7  2.6</td>
<td>Candida species</td>
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<td></td>
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<tr>
<td>3</td>
<td>93</td>
<td>0</td>
<td>1</td>
<td>10.0 4.0  1.0  0.0</td>
<td>None recovered</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>5</td>
<td>5</td>
<td>9.7  7.8  6.9  6.2</td>
<td>DTM positive, no ID</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>4</td>
<td>2</td>
<td>9.5  5.5  5.8  4.3</td>
<td>DTM positive, no ID</td>
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<td></td>
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<tr>
<td>6</td>
<td>76</td>
<td>4</td>
<td>3</td>
<td>9.0  2.6  3.0  3.9</td>
<td>None recovered</td>
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<td></td>
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<td>7</td>
<td>77</td>
<td>5</td>
<td>5</td>
<td>9.0  4.7  5.7  6.1</td>
<td>None recovered</td>
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<td>8</td>
<td>50</td>
<td>1</td>
<td>1</td>
<td>9.0  3.0  0.0  0.0</td>
<td>Hyphae, no ID</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>5</td>
<td>5</td>
<td>10.0 6.4  6.4  6.8</td>
<td>Geotrichum species</td>
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<tr>
<td>10</td>
<td>41</td>
<td>1</td>
<td>4</td>
<td>7.0  3.0  2.0  2.8</td>
<td>Trichophyton mentagrophytes</td>
<td>Negative</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trichophyton rubrum</td>
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<tr>
<td>11</td>
<td>28</td>
<td>4</td>
<td>4</td>
<td>5.8  3.4  4.8  4.4</td>
<td>T rubrum; Aspergillus species</td>
<td>Negative</td>
<td></td>
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<tr>
<td>12</td>
<td>72</td>
<td>1</td>
<td>1</td>
<td>5.0  0.5  0.0  0.0</td>
<td>Candida albicans</td>
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<td>13</td>
<td>79</td>
<td>5</td>
<td>5</td>
<td>9.0  5.1  4.0  4.1</td>
<td>Alternaria species</td>
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<td>14</td>
<td>71</td>
<td>3</td>
<td>2</td>
<td>9.4  2.4  0.8  0.4</td>
<td>None recovered</td>
<td>Negative</td>
<td></td>
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<tr>
<td>15</td>
<td>82</td>
<td>3</td>
<td>3</td>
<td>8.6  5.7  4.7  3.3</td>
<td>None recovered</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>1</td>
<td>1</td>
<td>9.0  4.0  1.0  0.0</td>
<td>None recovered</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>2</td>
<td>2</td>
<td>6.8  1.0  0.2  0.2</td>
<td>A versicolor</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>79</td>
<td>3</td>
<td>3</td>
<td>5.8  1.0  0.0  0.0</td>
<td>Epidermophyton floccosum</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>3</td>
<td>2</td>
<td>6.4  3.8  0.4  0.6</td>
<td>T rubrum</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>56</td>
<td>5</td>
<td>5</td>
<td>9.1  4.3  3.5  3.4</td>
<td>None recovered</td>
<td>Negative</td>
<td></td>
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<tr>
<td>Mean</td>
<td>64.7</td>
<td>3.1</td>
<td>3.05</td>
<td>8.3  3.6  2.8  2.5</td>
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<td>SD</td>
<td>1.6</td>
<td>1.9</td>
<td>2.4</td>
<td>1.6  1.9  2.4  2.4</td>
<td></td>
<td></td>
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<tr>
<td>SEM</td>
<td>1.4</td>
<td>1.5</td>
<td>2.2</td>
<td>1.4  1.5  2.2  2.1</td>
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<tr>
<td>Chi-square</td>
<td>2.7</td>
<td>3.6</td>
<td>4.1</td>
<td>&gt;.10 &lt;.10 &lt;.05</td>
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</tbody>
</table>

Abbreviations: APT, area + pain + thickness; DTM, dermatophyte test medium; ID, identification.

marked improvement in the nails of patients suffering from onychomycosis. After 10 months of treatment, 21.1% of patients' nails appeared clinically normal, and 11.5% showed negligible involvement (as indicated by nail scores of 0 and 1, respectively). The average nail score decreased from 8.3 to 2.5 after 10 months of treatment. In addition, patient satisfaction with therapy effectiveness was quite high, as observed through the patients' subjective evaluations at each monthly clinic visit: 90% of patients rated their result as good or excellent.

Moreover, although it was not among the indices quantified in this study, the residents and clinician conducting the study noted a softening, and often a thinning, of the nail plates of almost all of the patients, presumably due to the hydrating effects of the surfactants. Consequently, debridement of the nails became easier as the study progressed.
Perhaps one of the reasons for the success of the surfactant, allantoin, and benzalkonium chloride solution is the antimicrobial spectrum of benzalkonium chloride. This broad spectrum includes fungi as well as bacteria and viruses. It has been suggested that as many as half of fungal toenails may have an associated bacterial infection. The surfactant, allantoin, and benzalkonium chloride solution would be considerably more efficacious than azoles or allylamines against this type of infection.

The topical antimicrobial nail solution studied in this clinical evaluation contained the active ingredient benzalkonium chloride in a patented surfactant delivery system coupled with a keratolytic emollient and cell proliferant/protectant, allantoin. This formulation contrasts with other topical treatments for microbially infected nails that have been found, in general, to have limited effectiveness owing to the lack of penetration into the hard, keratinized material of the nail plate and surrounding tissue. Furthermore, the antimicrobial solution studied in this work lacks the systemic toxicity and myriad drug interactions associated with oral medications for onychomycosis.

Conclusion

In conclusion, these results confirm the clinical effectiveness of the surfactant, allantoin, and benzalkonium chloride antimicrobial nail solution against microbial nail infections of widely varying etiology. The cure rate demonstrated is comparable to published data for the new generation of systemic antifungal agents. Because the solution represents a low-toxicity alternative to those oral medications currently being prescribed, it is an appropriate treatment for the many patients who cannot take oral antifungal medications for medical reasons.

Although no topical antifungal agent is now indicated for use on nails according to the current Food and Drug Administration antifungal monograph, the surfactant, allantoin, and benzalkonium chloride antimicrobial nail solution is comparable in cost to other topical antifungal medications (at approximately $2 per nail per month). In contrast, a 3- to 4-month course of treatment with the new generation of oral medications costs from $500 to $1,000. Because of its markedly lower cost, the surfactant, allantoin, and benzalkonium chloride antimicrobial solution is an economical initial therapy for the treatment of this disease.

Although the number of patients (20) was limited in this study, more than 120 nails were treated during the course of the study. In light of the promising results, the authors believe that this inexpensive, relatively innocuous treatment merits additional research on a larger scale to assess more precisely its efficacy and establish its place in the set of treatment options available for onychomycosis.

Acknowledgment. Supported in part by Woodward Laboratories Research Grant #1-NS3PHLB3.

References

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