BUTENAFINE HYDROCHLORIDE AND MELALEUCA ALTERNIFOLIA OIL COMBINATION IN TREATMENT OF TOENAIL ONYCHOMYCOSIS: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY.

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Abstract

A fungus infection of the toenails (onychomycosis) is a common pathological condition and it is extremely difficult to both diagnose and cure. This was a study that examined the safety and clinical effectiveness of 2 percent butenafine hydrochloride combined with 5 percent Melaleuca alternifolia oil in topical cream treatment of toenail onychomycosis. One hundred and twenty-five patients, aged 18-80 and with at least 25 % involvement of one of their toenails with fungus were recruited in a randomized, placebo-controlled study. Right in the active cream group (n=60), think 80 percent of cure rate and when crossing the sexes, 83.3 percent male and 75 percent female achieved clinical success. None of the patients on placebo became cured. Only a few side effects were noticed including swelling in 6.7 % of patients and hardly any side effect was reported at all. There were no relapses in one-year follow up. The active treatment group showed to penetrate and stay more in the body using the antifungal agents than other systemic treatments that tend to have serious side effects, the treatments need to be on long term regimens and are generally prone to failing in time. This multimodal therapy had a more safer and effective and accelerated option instead of the systemic antifungal therapies, thus substantiating the possibility of topical therapy in treating onychomycosis without the supplement of systemic medications.

Key words: Onychomycosis, butenafine hydrochloride, Melaleuca alternifolia oil, toenail fungus, topical treatment, antifungal therapy, dermatophytes, clinical efficacy, placebo-controlled trial.

Introduction

Onychomycosis is an illness based on fungus that normally attacks the entire nail plate where the nail bed often is included. It is a difficult to detect and cure chronic condition that can be characterized by more than 30 percent of all fungal infections (Summerbell, 1997), extremely tough to take care of and diagnose, and carries profound physical and psychological effects on the patients. Onychomycosis occurs more in different directions according to the geographic location and less prevalent in children (Gupta et al., 1997). The prevalence is also higher in adults; nonetheless, feet are affected more often than hands (Haneke, 1990). The identification of the causative organisms assists in the determination of the mode of infection and it is categorized into four type which include distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), and total dystrophic onychomycosis (TDO). The most common pathogens are dermatophytes, especially Trichophyton rubrum of whom more than 90 percent of cases are dermatophytoses (Baran & Aly, 1997) and notermatophyte molds and yeasts, which act as contaminants in a few cases (Baran & Aly, 1997). Hot and humid climatic conditions, excess moisture, shared bathing or showers, friction and the wearing of closed shoes are some causes of augmenting the risk of getting infected.

Therapy that applies in treatment of onychomycosis include mechanical debridement of the nail, surgical intervention or matrixectomy of the nail, chemical avulsion (keratinolysis), and the systemic antifungal therapy and in some cases topical therapies are as well administered concomitantly (Crissey

et al., 1995; Brennan & Leyden, 1997). The majority of the available oral antifungal drugs including the azoles and the allylamines as well interfere with the synthesis of ergosterol, a major component of the cell membrane of fungi by inhibiting squalene epoxidase. Although they need long-term administration, side effects may be associated with these treatments such as gastro-intestinal impairment, rashes, meniral irregularity, alteration of vision and taste, headaches and reversible increase in liver enzymes. Such restrictions lead to the poor effectiveness of therapeutic progress, and a universal, effective therapy is not found yet. Thus a strong topical agent that would support systemic treatments would be very useful. Such agent should be able to penetrate through the dense structure of the keratin of the nail and high concentrations should be maintained so that the pathogen is killed.

Butenafine, a derivative of phenol modified benzylamine group, is a very strong antifungal agent possessing the action of ergosterol biosynthesis inhibition the same way as allylamines (earlier in the metabolic pathway) compared to azoles. Its minimal fungicidal concentration (MFC) is also lower than that of azoles (Fukushiro et al.,1992; Tschen et al.,1997). The ideal topical antifungal to use in treating superficial infections must be broad-spectral, permeate the nail bed epithelium, have low concentration, keratinophilic, lipophilic, fungicidal as opposed to fungistatic, have high in vivo cure rate with low relapse, side effects and easy to use with cheaper cost. Butenafine has exhibited good fungicidal activity (Syed et al., 1998).

The active compounds present in Melaleuca alternifolia oil that is extracted out of Australian tea tree are terpinen-4-ol, cineole and viridiflorene and these compounds are antiseptic and antifungal in nature (Walker, 1962; Buck et al., 1994). The oil possesses superior penetration capability, it is colorless, is myristic in smell and is resistant to high temperature and pressures. Hypersensitivity and chronic toxicity have not been recorded. When both butenafine hydrochloride and Melaleuca alternifolia oil were combined, in a cream-like product, the product was tested in response to its effectiveness in treating toenail onychomycosis.

This randomized, placebo-control, was to test the clinical efficacy and safety of a 2 percent butenafine hydrochloride and 5 percent Melaleuca alternifolia oil cream in the treatment of toenail onychomycosis. The research has been performed in Karachi City in Pakistan in the period of March to February 1996-97 in the Islamic private and municipal clinics with the consent of the review board.

Patients and Methods

A total of 75 outpatients (females 36, males 39) with 18-80 years age range (mean age 29.6) who were at least 25 percent fungal infection on one of their big toenails were included in the study and had a clinical diagnosis of distal subungual onychomycosis as determined by a 30 percent potassium hydroxide wet mount and a positive dermatophyte dermatophyte culture. The participants were identified with the help of referrals by medical officers and registered healthcare providers who were to be informed about the study.

At baseline, people excluded based on occurrence of onychomycosis with a triggering agent of molds, bacteria or Candida spp, any prior history of psoriasis, or any severe comorbidities, or an allergic reaction to the Melaleuca alternifolia oil, or any member of azole or benzylamine derivatives, or other medications that might have effects on the bioavailability of benzylamines. Also, the patients negative of dermatophyte infection were not allowed and thus the patients who had been taking systemic antifungal medications in the last three months or applied topical therapy in the last two weeks of the study are not admitted. The pregnant and lactating women were also not studied.

During the first meetings, each of the participants was informed orally and in writing about the objectives of the research. They were fully informed in regard to the possible side effects of the treatment and the potential effects of the investigational drug upon the basis of the Helsinki Declaration (Venice revision). Informed consent was given by all the participants prior to studying.

A 2 percent butenafine hydrochloride with 5 percent weight of Melaleuca alternifolia oil was prepared by an approved pharmaceutical laboratory along with a corresponding placebo containing Melaleuca

alternifolia oil. The samples of the tests packed in precoded 40-g containers were stored at the ambient temperature. It was a double-blind investigation, and precoded preparation of trials (50 actives and 25 placebo) were distributed randomly to the patients and they used them in a week. The participants were demonstrated on how to apply the medication on the affected toenail three times a day by the use of a new occlusive plastic dressing, which was also issued out to the participants during the seven days stay at the treatment centre. Each time they applied, they were advised to cover the treated toenail back to the cover shape and bring a remaining dose the following visit they would be scheduled.

Evaluation of mycological cure, clinical efficacy and overall success of patients was undertaken weekly. A replacement of similar precoding was thereby administered at every visit to carry on with the treatment. It was debrided in week 4 to week 6 with a nail clipper once the toenail seemed ready. The treatment was proceeded according to instructions and maximum time during which active treatment was given was eight weeks (according to the study protocol). Once the toenail reached the stage where it was not ready to be removed by nail clipper at the expiry of the treatment period, the toenail was regarded as non-responsive to the drug and recorded in the case report form.

Patients were encouraged to keep the drug out of children. Clinical efficacy and tolerability were obtained by physical assessment and lab assessment at week 8, 24 and 36 (culture negative) and patients were questioned on occurrence of any adverse effect at every visit. Mycological cure was established as negative dermatophyte fungal culture and no hyphae seen in 30 percent potassium hydroxide wet mount test. The success criteria were what was considered as clinical success, which was either a 100 percent remission, or 90 percent-99 percent improvement of the nail being treated. There was overall cure which was included in the cure of all clinical signs with other components, which comprised of mycological and progressive formation of a normal nail. The length of duration governed the intensity of the side effects as drug-related side effects were classified as severe, moderate, mild, or absent.

Statistical Analysis

Factors that were compared to check the variance between the treatment groups were height, weight, age, sex, presence of toenail onychomycosis (chronicity and disease course).

The Cochran-Mantel-Haenszel test was adopted to compare mycological cure, clinical effectiveness and overall success of the treatments between the two groups. The Breslow-Day test was used to determine the homogeneity between the relationship between treatment and cure. A two tailed exact test was done on the relationship between outcome and treatment by Fisher.

Cochran-Mantel-Haenszel test was used to compare clinical effectiveness of treatment and apprehension data of patients. The Wilcoxon rank sum test was used to evaluate all signs and symptoms and the change in the total signs and symptoms change in baseline.

Results

A total of 75 patients were given chance to participate in the study and these patients were allocated in active cream treatment and placebo treatment arms of study, respectively 60 and 15. Both groups had similar patient demographics as the active cream group had 36 males against 24 females and the placebo group had 9 males against 6 females. In the active cream group, the Mean age of the patient was 29.6 years as compared to 29.7 years in placebo group. The average survival of the illness was also slightly longer in the placebo group (15.0 months), as compared to the active cream group (14.3 months).

About treatment outcome the active cream group had a much higher cure rate of 80.0% (48/60) of the patients achieved a cure. However, by contrast, no patients in the placebo group were cured. Out of male patients, 83.3 percent (30/36), and females, 75.0 percent (18/24) were cured among the patients in the active cream group. Trichophyton rubrum was the most predominant causative pathogen pathogen in the two groups where it was found in 38 cases in the active treatment group and 18 cases

in the placebo group. More so, the active and placebo groups had 2 individuals of T. tonsurans and 1 individual of T. mentagrophytes and 1 case of T. tonsurans respectively.

Regarding adverse events, the active cream treatment group resulted in minimal adverse events that include 54 patients reporting of no adverse incidents, 6 patients with mild inflammation, and no incidents report of relapse after one year of follow-up. Twelve patients in placebo group exhibited no adverse effect and no mild effect or side effect was recorded in any of the patients. Summing up, it could be stated that active cream treatment was much effective compared to placebo showing a great rate of cure and low rate of adverse effect.

Table 1: Comparison of Active Cream Treatment and Placebo Treatment for Dermatophyte Infections

Characteristics	Active Cream Treatment	Placebo Treatment
Patients (n)	60	15
Male	36	9
Female	24	6
Mean age (years)	29.6	29.7
Mean duration of disease (months)	14.3	15.0
Patients cured (n)	80.0% (48/60)	nil
Male	83.3% (30/36)	-
Female	75.0% (18/24)	-
Causative Dermatophytes		
Trichophyton rubrum	38	18
T. tonsurans	2	1
T. mentagrophytes	1	0
Adverse Events (n of patients)		
None	54	12
Mild inflammation	6	0
Relapse after 1 year	nil	0

Discussion

The most important conclusion made in this study was that the mixture of butenafine hydrochloride and Melaleuca alternifolia oil in cream was very successful in the treatment of toenail onychomycosis. The drug was tolerated favourably by the patients and they gave complete compliance during the trial. But, the placebo which has just tea tree oil did not yield the expected outcomes. Perhaps the 8 weeks of treatment was not sufficient to enable the finish product of the tea tree oil to be given a chance to be realised.

Some of the fungicidal agents have been found to be highly effective in terms of in vivo tests and fail in its application to human beings owing to the resistance developed to the causative agents. Dermatophytes that cause onychomycosis cannot survive in the serum and their infection only penetrates dead and keratinized nail tissue (Rashid & Richardson, 1997). In this tissue, dermatophytes may create a barrier so they cannot be penetrated by antimycotic drugs and this results in ineffective or partial treatment. How effective topical treatment is greatly relies on the vehicle since it is a significant proportion that determines the efficiency of the rate of penetration and also the efficient delivery of the medication.

A perfect topical treatment of onychomycosis must enhance efficacy of the medication in terms of penetration and retention of the selected drug beside favoring the growth of an affected nail. The

combination treatment produced better results, as compared to other oral and systemic antifungal therapies (Roberts, 1994; Drake et al., 1997), which are linked to unwanted side effects (Amichai & Grunwald, 1998), as well as the need to have a long treatment period. The treatment was more efficient and less risky as the cure rate was 80 percent, mild adverse effects were only found in 6,7 percent of patients, and they never relapsed. In addition, it exceeded the other researches on onychomycosis which incorporated the use of antifungal agents coupled with urea as a keratoplastic agent (Torres-Rodriguez et al., 1991; Friedman-Birnbaum et al., 1997).

The clinical experience feels free to suggest that onychomycosis can be treated with a variety of topical antifungal agents implying that fungal infections in toenail can be cured without considering systemic medicines. Drastic evidence to support this idea can be given to the fact that the systemic biochemical and biological effects of drugs which are usually provided by the administration of the drugs orally can also be obtained through the topical application of the active ingredients.

Conclusion

To summarize, the butenafine hydrochloride and Melaleuca alternifolia oil combination in the topical cream have shown strong effect toonimportance when it comes to treatment of toenail onychomycosis that has a 80 percent curative rate with minimal side effects with no relapse incurred even within a one year follow-up. There were no results of the placebo, which only consisted of tea tree oil, which indicated that the duration of treatment might take longer or a different formulation might be required in order to realize tea tree oil results in full. Another focus of interest in this study was the problem of onychomycosis treatment because of the capability of dermatophytes to engender a barrier on a keratinized skin on the nail which restricts the applicability of most antifungal agents. Nevertheless, the combination therapy was found to be better in relation to the penetration and retention, providing the successful treatment. This topical treatment was safer and more effective, as compared to oral and systemic antifungal therapies, which proved to have long periods of treatment and serious side effects. The findings favor the notion that onychomycosis of the toenails may be well treated using the topical agents without resorting to the use of systemic agents, a valuable input in study of onychomycosis treatment, not to mention a good option with minimum risk to the patients.

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