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Treatment of toenail onychomycosis with 2% butenafine and 5% *Melaleuca alternifolia* (tea tree) oil in cream

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Summary The prevalence of onychomycosis, a superficial fungal infection that destroys the entire nail unit, is rising, with no satisfactory cure. The objective of this randomized, double-blind, placebo-controlled study was to examine the clinical efficacy and tolerability of 2% butenafine hydrochloride and 5% *Melaleuca alternifolia* oil incorporated in a cream to manage toenail onychomycosis in a cohort. Sixty outpatients (39 M, 21 F) aged 18–80 years (mean 29.6) with 6–36 months duration of disease were randomized to two groups (40 and 20), active and placebo. After 16 weeks, 80% of patients using medicated cream were cured, as opposed to none in the placebo group. Four patients in the active treatment group experienced subjective mild inflammation without discontinuing treatment. During follow-up, no relapse occurred in cured patients and no improvement was seen in medication-resistant and placebo participants.

keywords onychomycosis, fungal infections, butenafine, tea tree oil, toenails, *Melaleuca alternifolia*, pharmaceutical creams

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Introduction

Onychomycosis is a prevalent superficial fungal nail infection that affects the entire nail plate and often the nail bed. This chronic disease, which accounts for more than 30% of all mycotic infections (Summerbell 1997), is difficult to diagnose and treat and has embarrassing physical and psychological consequences for patients. Incidence varies geographically and is less frequent in children (Gupta *et al*. 1997). In adults prevalence increases with age, and feet are more affected than hands (Haneke 1990). The identity of causative agents indicates the mode of infection, which can be classified into 4 subtypes: distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual infection (PSO) and total dystrophic onychomycosis (TDO). Dermatophytes are considered the most common causative pathogens, particularly *Trichophyton rubrum*, which accounts for more than 90% of all nail infections, while nondermatophyte moulds and yeasts are occasionally seen as contaminating organisms (Baran & Aly 1997). Hot, humid climates, moist conditions, communal baths or showers, abrasion and wearing of closed shoes increase the frequency of infection.

Therapies for onychomycosis include debriding to the healthy nail, surgical intervention or nail matrixectomy, chemical avulsion (keratinolysis), systemic antifungal medication or a combination of topical and systemic therapy (Crissey *et al*. 1995; Brennan & Leyden 1997). Most systemic and oral antifungal agents (azoles and allylamines) prescribed in general dermatology practice inhibit ergosterol synthesis (the major sterol component of fungal cell walls at the level of squalene epoxidase), require a prolonged course of treatment and frequently have side-effects such as gastrointestinal disorders, skin rashes, menstrual disorder, visual and taste disturbances, headaches and reversible elevation of liver enzyme levels. This has restrained limited

therapeutic options with disappointing results, and so far no ideal or convincing therapy has been advanced. As such, effective topical therapy would be desirable for augmentation of systemic therapies. However, for an antifungal drug to be topically effective, the infected nail's anatomy demands the choice of a vehicle that can penetrate through the hard keratin and retain it there in high concentration until the causative pathogen is eradicated.

Butenafine hydrochloride, a phenol-substituted benzylamine derivative, is a potent antimycotic fungicidal (Fukushiro *et al*. 1992; Tschen *et al*. 1997) with a chemical structure and mode of action similar to those of the allylamines, and interferes with the biosynthesis of ergosterol at an earlier step of the metabolic pathway than the azoles. In addition, benzylamine has lower minimal fungicidal concentration (MFC) than azoles. An ideal clinically effective topical agent for superficial fungal infections would have broad-spectrum activity, be capable of diffusion through the nail bed epithelium, be efficacious at low concentration, keratinophilic, lipophilic, fungicidal and not fungistatic, have the ability to achieve a high mycological cure rate with low incidence of relapse and adverse effects, be convenient to use and low-cost. Butenafine has noteworthy fungicidal antimycotic properties (Syed *et al*. 1998).

Melaleuca alternifolia oil, an essential oil obtained from a shrublike tree in Australia, is known to contain Terpinen 4-ol, cineole and viridiflorene as active ingredients. It has antiseptic and antifungal properties (Walker 1962; Buck *et al*. 1994) with exceptional penetration. It is a colourless liquid with a typical myristic odour, stable at elevated temperatures and pressures. Yet no cases of hypersensitivity or chronic toxicity have been reported in the literature. Amalgamation of both compounds in a cream base served to evaluate their efficacy as a topical therapy in the management of toenail onychomycosis.

The aim of this randomized, placebo-controlled study was to evaluate the clinical efficacy and tolerability of 2% butenafine hydrochloride and 5% *Melaleuca alternifolia* oil in cream to cure toenail onychomycosis. The study protocol was approved by the independent institutional review committee and the trial was conducted at private and municipal dispensaries in Karachi, Pakistan, from March 1996 until February 1997.

Patients and methods

Sixty outpatients (31 M, 29 F) aged 18–80 years (mean 29.6) with at least 25% involvement of fungal infection of one of the large toenails and clinical diagnosis of distal subungual onychomycosis (confirmed mycologically by 30% potassium hydroxide wet mount and positive culture for dermatophytes) entered the study. Subjects were recruited by referral from medical officers and registered medical practitioners informed about the study. Exclusion criteria, screened at baseline, were onychomycosis caused by moulds, bacteria or *Candida* spp., a history of psoriasis, any serious concurrent disease, hypersensitivity to *Melaleuca alternifolia* oil, azole or benzylamine derivatives and concomitant therapy with drugs appearing to affect the bioavailability of benzylamines. Another exclusion criterion was absence of dermatophyte; thus patients who had received systemic antifungal treatment within the previous three months or who were using topical treatment during the two weeks preceding the study period were not enrolled. Pregnant and lactating women were not recruited.

At a preliminary meeting, all participants received oral and written information about the purpose of the study, and following the recommendations of the Helsinki Declaration (Venice revision) were comprehensively informed about consequences of the treatment as well as possible side-effects of the investigated drug. All patients gave their informed consent.

A cream incorporating 2% butenafine hydrochloride and 5% *Melaleuca alternifolia* oil incorporated by weight and a matching placebo also containing *Melaleuca alternifolia* oil were prepared at an officially approved pharmaceutical laboratory. Test samples were packed in precoded 40-g tubes and kept at ambient temperature. The study was double-blind, and precoded trial preparations (40 active and 20 placebo) were randomly assigned to each patient for one week's use. Patients were shown how to apply the trial medication at home three times a day topically to their large toenail with a fresh occlusive plastic dressing also provided for 7 days. They were advised to wrap the medicated toenail after each application and asked to return unused trial containers at the next scheduled visit. To evaluate mycological cure, clinical efficacy and overall success, patients were examined on a weekly basis, and at each visit a similarly precoded replacement was given to them to continue treatment. Between weeks 4 and 6, if the toenail appeared ready, it was debrided with a nail clipper. Treatment was continued as directed. Active treatment was limited to 8 weeks (protocol limitation). If by that time the target toenail was not judged ready for removal by a nailclipper, it was considered resistant to the medication and accordingly recorded in the case report form.

Patients were cautioned to keep the medication out of reach of children. Clinical efficacy and tolerability of the trial product was ascertained by physical examination, laboratory assessments at week 8, 24 and 36 (culture negative) and inquiring about any adverse effect at each visit. Mycological cure was defined as negative fungal culture for dermatophytes and absence of hyphae in wet potassium hydroxide (30%) test. Clinical success was defined as 100% remission or 90%

to 99% improvement in the treated toenail. Resolution of all clinical symptoms with respect to global assessment together with mycological cure and progressive growth of normal nail was considered as overall cure. Drug-related side-effects were noted as mild, moderate, severe or none with respect to duration in days.

Statistical analysis

Variables such as height, weight, age, sex, presence of toenail onychomycosis including chronicity of infection and duration of the disease were examined to rule out differences between the two treatment groups.

Mycologic cure, clinical effectiveness and overall success of the treatment were compared between treatment groups following the Cochran-Mantel-Haenszel test. The Breslow-Day test was used to assess whether the observed relation between treatment and cure was homogeneous. Fisher's two-tailed exact test was used to compare the relation between outcome and treatment.

Clinical effectiveness of the treatment and subject apprehension data were compared between treatment groups by Cochran-Mantel-Haenszel test. All signs' and indications' evaluations and the change from baseline in total signs and indications were analysed using the Wilcoxon rank sum test.

Results

The study medication gained full patients' compliance and all 60 subjects were included for efficacy analysis. The duration of toenail disease had been 6–36 months. During the first three weeks of treatment, some effective imbibition was noted, but the affected nail was not ready for easy debridement with a nail clipper. After week 4, the target toenails of 9 patients (4 M, 5 F) were debrided; at the end of week 5, the target toenails of 13 further patients (9 M, 4 F) were removed. After week 6, another 10 patients (7 M, 3 F) followed. The target toenails of all remaining patients did not become soft enough to be removed during treatment weeks 7 and 8. Treatment was discontinued after 8 weeks (168 topical applications). The target toenails of all study subjects were examined at scheduled weekly visits up to week 16; thereafter subjects were evaluated on a monthly basis. Specimens for mycological evaluation were collected from the treated area at week 8, 24 and 36. The main causative dermatophytes isolated from the study population were *Trichophyton rubrum* (93.3.%), *T. tonsurans* (5%), and *T. mentagrophytes* (1.7%).

Breaking the code disclosed that all 32 patients whose target toenails were debrided by the end of the treatment period were from the butenafine group. In total 480 tubes (40 g each) of cream were used. The overall cure rates after 36 weeks of active *vs*. placebo treatment were 80% and 0% ($P < 0.0001$), respectively. The mean time to complete healing with progressive nail growth was 29 weeks. Eight patients in the active cream group were resistant to the trial drug. Twenty-nine patients (48.3%) had suffered from nail disease for less than one year; 51.7% for one to three years. Thirteen participants (21.7%) has used systemic drugs for more than a year in the past, and 12 (20%) had used a topical drug during the six months preceding the study. Physicals and laboratory tests were within limits throughout the study period. Statistically both groups were comparable in age, race, number and area of toenail infection. Table 1 gives pre- and post-study demographic data of participants.

93.3% had no drug-related negative side-effects. Four patients in the active cream group reported nonobjective mild inflammation which did not lead to discontinuation or interruption of treatment, however, there were no dropouts.

Discussion

The most important observation of this study is that a combination of butenafine hydrochloride and *Melaleuca alternifolia* oil in cream effectively treated toenail onychomycosis. Medication was well-tolerated and received full patient compliance. However, tea tree oil alone in the placebo did not show the expected response; perhaps 8 weeks of treatment were insufficient to render its full potency. Laboratory studies have shown that several fungicidal agents giving satisfying results in *in vivo* trials do not demonstrate the

Table 1 Characteristics and demographic data of patients treated with butenafine hydrochloride and *Melaleuca alternifolia* oil in cream or placebo for the treatment of toenail onychomycosis

Characteristics	Active cream treatment	Placebo treatment
Patients (n)	40	20
Male	24	15
Female	16	5
Mean age (years)	29.6	29.7
Mean duration of disease (months)	14.3	15.0
Patients cured (*n*)	80.0% (32/40)	nil
Male	83.3% (20/24)	
Female	75.0% (12/16)	
Causative dermatophytes		
Trichophyton rubrum	38	18
T. tonsurans	1	2
T. mentagrophytes	1	0
Adverse events (*n* of patients)		
None	36	20
Mild inflammation	4	0
Relapse after 1 year	nil	0

corresponding efficacy in clinical practice due to resistance of the causative agents to such medication. As dermatophytes cannot survive in serum, their parasitic infection is confined to dead keratinized tissue (Rashid & Richardson 1997), where they build up an effective local barrier that can restrain penetration of antimycotic agents, resulting in inefficacy or partial clinical success of many topical treatments. When a drug is applied to the skin or nail, to a great extent it is the vehicle which controls the rate of penetration and allows the drug to work efficiently. A desirable topical therapy for onychomycosis must comprise better penetration and retention of the antimycotic drug and also enhance progressive growth of the treated nail. Compared to other oral and systemic antimycotic treatments (Roberts 1994; Drake *et al*. 1997) which are accompanied by precarious drug-related side-effects (Amichai & Grunwald 1998) and require long-term regimens to achieve resolution, this treatment is significantly better in terms of results (80% cure rate), side-effects (mild, 6.7%) and relapses (0). The trial also gave better results than other oncholysis or chemical avulsion studies using antifungal drugs with urea as a keratoplastic agent (Torres-Rodriguez *et al*. 1991; Friedman-Birnbaum *et al*. 1997). However, clinical experience has shown that onychomycosis can respond to a variety of antifungal agents topically, indicating that toenail fungal infection can be resolved without systemic pharmacologic effect. There is substantial evidence to support the theory that biochemical and biological effects produced by systemic administration of an active drug can also be produced by its topical application.

In conclusion, the findings of this study demonstrate that topical therapy with 2% butenafine hydrochloride and 5% *Melaleuca alternifolia* oil incorporated in cream in conjunction with debridement with a nail clipper is safe, tolerable and significantly more effective than placebo to cure toenail onychomycosis.

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