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Efficacy of ozonized sunflower oil in the treatment of tinea pedis

Die Wirksamkeit von ozonisiertem Sonnenblumenöl bei Tinea pedis

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Key words. Tinea pedis, antimycotic therapy, ozonized vegetable oils, Oleozon®.
Schlüsselwörter. Tínea pedis, antimykotische Chemotherapie, Ozonisierte Pflanzenöle, Oleozon®.

2 **Summary.** Ozonized sunflower oil, Oleozon®, has a remarkable germicidal action. In the present study, the efficacy of Oleozon® in the treatment of tinea pedis was demonstrated in a controlled randomized phase III assay, comparing topical Oleozon® with ketoconazole cream 2% (Nizoral) in 200 patients (100 in each group). The treatment administered was twice per day for a period of 6 weeks. The efficacy was evaluated clinically (disappearance of all lesions, with or without negative mycological results) and mycologically (negative culture results). A complete clinical and mycological cure was obtained in 75 and 81% for Oleozon® and Nizoral, respectively, with no significant differences between both groups. No side-effects or bacterial super-infections were observed. Patients were evaluated 6 months after the end of the treatment and no recurrence was observed in the Oleozon® group. Oleozon® can be an effective alternative low-cost antimycotic drug.

3 **Zusammenfassung.** Ozonisiertes Sonnenblumenöl (Oleozon®) hat bemerkenswerte keimtötende Eigenschaften. In dieser Studie wird die Wirksamkeit von Oleozon® in einer randomisierten, kontrollierten Phase-III-Studie geprüft, bei der topisches Oleozon® an 200 Patienten (100 je Gruppe) mit Ketoconazol-2%-Creme (Nizoral®) verglichen wird. Die Behandlung wurde zweimal täglich über 6 Wochen durchgeführt. Die Wirkung wurde klinisch (Verschwinden aller Läsionen mit oder ohne negative mykologische Resultate) und mykologisch (negatives Kulturresultat) bewertet. Komplette klinische und mykologische Heilung wurde bei 75% mit Oleozon® und bei 81% mit Nizoral® erreicht; die Differenz war statistisch micht signifikant. Nebenwirkungen oder bakterielle Superinfektionen wurden nicht beobachtet. Die Patienten wurden 6 Monate nach Therapieende erneut untersucht, Rückfälle wurden nicht beobachtet. Oleozon® könnte als effektive therapeutische Alternative bei geringen Kosten angesehen werden.

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Introduction

Tinea pedis is a frequently occurring disease which produces different tissue lesions such as maceration, desquamation, fissures, erythema, oedema and/or pruritus. This skin infection is caused by fungi of the genera *Trichophyton*, *Epidermophyton* and *Microsporum*. This clinical syndrome is often resistant to treatment and there can be frequent relapses. For that reason, it is important to find effective, low-cost antimycotic drugs for its treatment [1, 2], especially for use in developing countries.

Among the natural products, ajoene cream (0.4% w/w) has been demonstrated, in 34 patients, to be an effective and low-cost antimycotic drug for short-term therapy [3].

Oleozon® is obtained from the reaction between ozone and sunflower oil in appropriate

conditions, producing aldehydes and carboxylic acids, together with hydroperoxides, ozonides and other peroxide species [4]. It has been already registered in Cuba for the treatment of tinea pedis. This product has a remarkable germicidal action and its antimicrobial effects against viruses, bacteria and fungi [5, 6] and also in the treatment of infections produced by multi-resistant strains [7] have been verified *in vitro* and *in vivo*. On the other hand, toxicological studies have demonstrated that this product is not mutagenic or genotoxic and does not have side-effects in human patients [8–10]. It has been also demonstrated that vegetable oils that have not been ozonized do not have a germicidal action [11, 12].

Taking into account the properties of Oleozon® and the need to find effective antimycotic agents, a controlled clinical evaluation, comparing this product with ketaconazole in the treatment of tinea pedis was performed.

Patients and methods

A controlled randomized phase III assay was carried out, comparing Oleozon® with the recognized antimycotic drug ketoconazole (Nizoral®). Two hundred outpatients were clinically (presence of maceration, desquamation, fissures, erythema, vesicles and/or pruritus) and mycologically (positive culture of skin scrapings of the affected areas in Sabouraud glucose agar–chloramphenicol) diagnosed as suffering from tinea pedis. The number of patients was calculated using the Medstat system (2.1 version, 1989). Patients were divided into two groups of 100 patients each, using a randomized list:

Group A. Patients treated with Oleozon® topical (each 100 ml contains 8–12% hydroxiperoxides of unsaturated triglycerides as active oxygen), twice per day, for 6 weeks.

Group B: Patients treated with ketoconazole cream 2% (Nizoral®), twice per day, for 6 weeks, taking into account the spore life and the optimal time of treatment [13].

Inclusion criteria

The inclusion criteria were:

Positive clinical and microbiological diagnosis of tinea pedis, without superinfection.

Aged over 15 years and of any gender and race.

Patients without previous treatment or with more than 5 days without any topical or systemic treatment.

Patients' written acceptance to participate in the study.

Exclusion criteria

The exclusion criteria were:

Patients with: decompensated diabetes mellitus, cancer in advanced stage, severe septic stage, hepatopathy, nephropathy, pregnancy.

Hypersensitivity to the medications.

Use of corticoids, cytostatics, antibiotics or immunodepressing drugs.

Efficacy evaluation

The efficacy was evaluated clinically and mycologically using the following criteria:

Clinical cure before or in 6 weeks.

Mycological cure in 6 weeks.

Both cures in 6 weeks (optimal criterion).

A clinical cure was defined as the disappearance of all lesions, with or without negative mycological results. It was evaluated once per week.

Mycological cure was defined as negative mycological cultures. It was evaluated after 6 weeks of treatment.

To consider a patient cured it was necessary that both parameters were satisfied. If a patient was clinically cured before 6 weeks of treatment, the medication was continued until 6 weeks. If a clinical cure but not a mycological cure had been achieved at the end of treatment, this was considered a failure.

Statistical analysis

Analysis was performed using the Pearson chi-square, the M–L chi-square and the Fisher's exact tests, to compare the number of cured patients in both groups.

Results

In the sample studied (200 patients), the mean age was 28 years, 87% were male and 62% were white. The mean value of the evolution time of the disease was 55 months with four relapses per year. Left and right feet were affected in 96 and 95%, interdigital lesions were found in 91 and 93% and plantar lesions in 59 and 54% of patients, respectively. The fungal species isolated from the lesions were as follows: *Trichophyton rubrum* (59%), *Trichophyton mentagrophytes* (10%), *Epidermophyton floccosum* (8%) and *Candida albicans* (14%). Clinically, simple desquamation was present in 69% of patients, followed by desquamation and maceration in 16%, desquamation and vesicles in 8%, maceration in 5% and desquamation, maceration and fissures in less than 1% of cases.

Table 1. Mycological cure in both groups according the fungal species

Micro-organism	Oleozon® Patients with negative culture (%)	Nizoral® Patients with negative culture (%)	Significance (Fisher's exact test)
Trychophyton rubrum	87	82	0.629
Trichophyton mentagrophytes	67	92	0.445
Epidermophyton floccosum	60	80	0.804
Candida albicans	65	56	0.548

Table 2. General evaluation of both treatments at the end of the study

Treatment	Cured patients (%)	Not cured patients (%)
Oleozon®	75	25
Nizoral®	81	19

P (Pearson chi-square) = 0.571; P (M–L chi-square) = 0.570.

In order to demonstrate the homogeneity between both groups, age, gender, race, evolution time of the disease and fungal species isolated were studied in each group. No statistical difference was obtained between the groups (Pearson chi-square and M–L chi-square: $P > 0.05$). In both groups simple desquamation predominated.

Evolution, according to the fungal species isolated from the lesions, is shown in Table 1. No significant differences were obtained between both groups ($P > 0.05$).

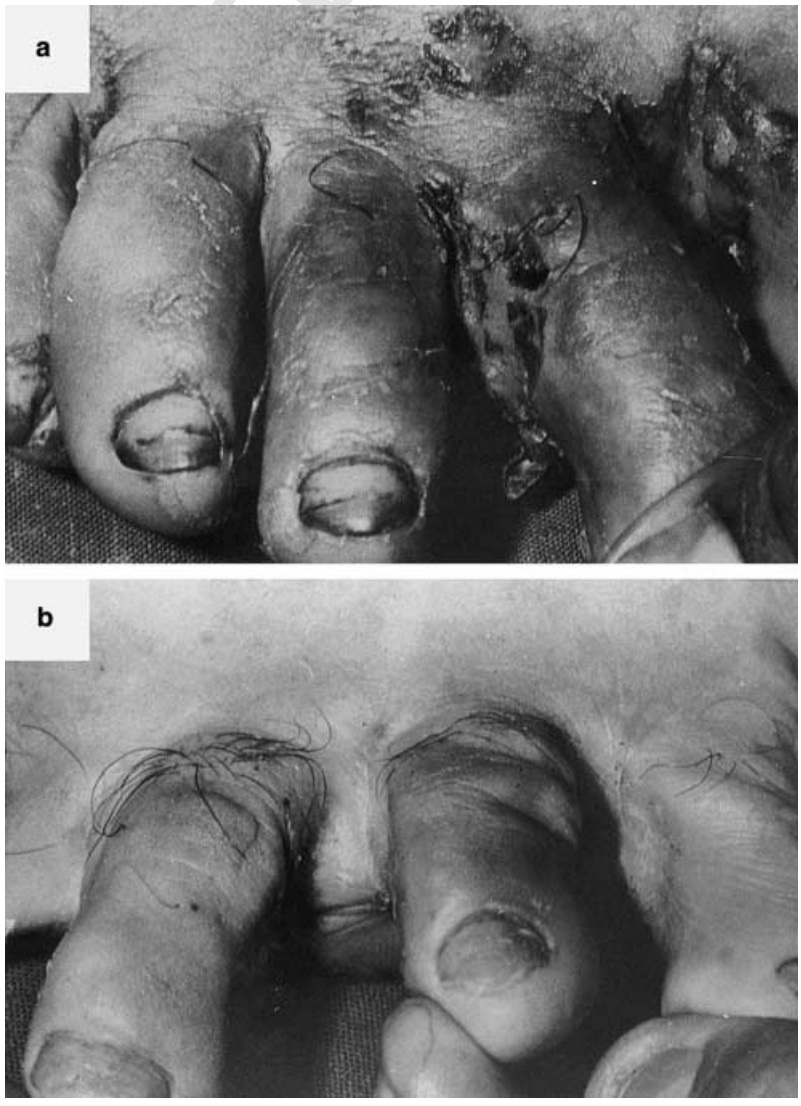

Figure 1. Representative results of tinea pedis treatment with Oleozon®. (a) Before treatment; (b) after 6 weeks treatment.

The general evaluation of the study at the end of the 6 weeks of treatment, taking into account the presence of non-clinical signs of infection and negative mycological cultures that were used to determine whether a patient was cured, is shown in Table 2 No significant differences were found between Oleozon® and Nizoral®; both treatments can be useful for the treatment of tinea pedis. No side-effects or bacterial superinfection were observed in the study.

Mycological cultures performed 6 months after the end of the treatment were negative in all patients treated with Oleozon®, whereas patients treated with Nizoral® had 4% recurrence. This is an important result because 90% of the patients in each group were soldiers, wearing boots that favour sweating and fungal proliferation. Figure 1 shows the results obtained after 6 weeks treatment with Oleozon®.

Discussion

This study has demonstrated the antimycotic properties of Oleozon®, which are similar to those of Nizoral®, in 200 patients affected with tinea pedis. The number of subjects studied, calculated by the Medstat system, showed that the difference between both groups was statistically significant. Age and gender were in agreement with the studied subjects, of which a high percentage were young, male cadets. In terms of race, the homogeneity between the two groups guaranteed that black patients, who normally have a more joined interdigital space and a greater predisposition to fungal infection [14], were in equal proportion in both groups. The time of evolution of the disease (it can be chronic in some cases) was proportional in both groups. The lack of relapses in patients treated with Oleozon® during the 6 months of follow-up are encouraging results and suggest that Oleozon® is superior to Nizoral® and other commonly used topical antimycotics [15–17], taking into account that these patients had a mean value of four relapses per year. The results obtained with Nizoral® were similar to those reported in the literature [18]. All these results and the need to find effective antimycotic agents make Oleozon® a good alternative for superficial fungus infection, for its fungicidal capacity, lack of side-effects and low-cost therapy.

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