

Safety of Topical Oleozon® in the Treatment of Tinea Pedis: Phase IV Clinical Trial

S. MENÉNDEZ*, L. RE**, L. FALCÓN***, M.B. ARGOTE***, I. MÉNDEZ* D. FERNÁNDEZ****, B. ELÍAS-CALLE*****, M. VALERO*****

* Ozone Research Center; Havana, Cuba

** Molecular Pharmacology, Ancona University; Ancona, Italy

*** Dr. Carlos J. Finlay, Hospital; Havana, Cuba

**** FINE, Military Hospital; Cárdenas, Matanzas, Cuba

***** Dr. Agostinho Neto, General Hospital; Guantánamo, Cuba

Key words: ozonized vegetable oils, phase IV clinical trial, safety, tinea pedis, adverse drug reactions, Oleozon®

SUMMARY - *The efficacy of topical OLEOZON® against tinea pedis has already been demonstrated. The aim of the present study was to assess the adverse reactions associated with topical OLEOZON® in patients with tinea pedis. A multicenter, open, phase IV clinical trial was carried out. An adverse drug reaction report form specifying the reactions most commonly associated with topical OLEOZON® was designed. This study lasted three years. Patients were treated with topical OLEOZON® twice a day for six weeks. Of the total of 2596 patients admitted to the study, 2165 (83.4%) patients finished the treatment. The main cause of drop out of the 431 patients (16.6 %), was the scant attendance at the clinical evaluation. Six patients (0.3%) showed adverse reactions. The most frequently reported adverse reactions were skin burning sensation, pruritus and erythema of mild intensity. Skin burning sensation was considered, according to the causal relationship, as definite; pruritus and erythema were considered probable. Taking into account the number of patients that finished the treatment, an efficacy of 92.7% (2007 patients cured) was achieved. The favourable safety profile achieved with topical OLEOZON® in this study, together with its demonstrated efficacy and its low cost justify the extension of this treatment in clinical practice for patients with tinea pedis, particularly in developing countries.*

Introduction

Tinea pedis is a very common and often chronic foot infection caused by fungi of the genera *Trichophyton*, *Microsporum* or *Epidermophyton*¹⁻³. Topical and oral OLEOZON® (ozonized sunflower oil) is a medication produced in Cuba which has been evaluated previously in different clinical trials⁴⁻⁷. It is already registered for the treatment of tinea pedis, impetigo and giardiasis. Its remarkable germicidal action has been well documented⁸⁻¹⁰, as well as its lack of toxicity and low cost¹¹⁻¹³.

Topical OLEOZON® was evaluated in a controlled randomized phase III assay, using ketoconazole (Nizoral®) as the comparing group⁴. The results demonstrated that no significant differences were found between the two medications, nor were any side-effects or bacterial superinfection observed in the study.

Adequate safety profiles for tinea pedis treatment were observed in different clinical trials¹⁴⁻¹⁶, as for topical OLEOZON®⁴, but it was not known whether a similar profile would be found in routine clinical practice conditions using a large

number of patients. Therefore, taking into account the characteristics of OLEOZON® and the need to find effective, low-cost safe antimycotic drugs, the aim of this study was to perform a multicenter open phase IV clinical assay to evaluate the true picture of adverse drug reactions (ADRs) and the drug's effectiveness in routine clinical practice.

Patients and Methods

A multicenter, open, phase IV clinical assay was carried out aimed at evaluating the possible ADRs during the treatment of patients with tinea pedis using topical OLEOZON®. An ADR report form, specifying the reactions most commonly associated with OLEOZON® was designed. This study lasted three years. Four hospitals from different provinces of Cuba participated. All the patients 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. They were aged over 15 years, of either gender and any race and without previous treatment or with more than five days without any topical or systemic medication. From the study were excluded patients with decompensated diseases, hypersensitivity to the medication and those being treated with antibiotics, corticoids, cytostatics or immunedepressant drugs.

Treatment

Patients were treated with topical OLEOZON® (each 100 ml contains 8-12 % hydroxyperoxides of unsaturated triglycerides as active oxygen^{17,18}), twice per day, for six weeks.

ADR Evaluation

An ADR is defined as any noxious and undesired effect to a drug observed at doses usually administered therapeutically in humans. The severity of ADR was classified in four levels:

- 1) Mild, when the side-effect did not significantly interfere with the normal functions of the patient, no therapy was necessary;
- 2) Moderate, when the side-effect produced an impairment of the normal functions of the patient, without being a risk to his/her health, but needed specific treatment;
- 3) Severe, when the side-effect produced a significant impairment of the normal functions of the patient, without being a risk to his/her life, but hospitalization was required;
- 4) Very severe, if a reaction was potentially life-threatening or contributed to the patient's death.

A qualitative assessment was used to classify the causal relationship as definite, probable, possible or doubtful¹⁹. According to this method, a reaction was classified as definite if it (A) followed a reasonable temporal sequence after drug administration; (B) followed a known pattern of response to the suspected drug; (C) could not be explained by concurrent disease or other drugs; and (D) was confirmed by improvement upon removal of the drug and by reappearance on rechallenge. It was considered probable if it had the criteria (A), (B), (C) and was confirmed on suspension of the drug but not on rechallenge. A reaction was defined as possible if it followed a reasonable time sequence to the application of the drug, but could also be explained by concurrent disease or other drugs. Finally, a reaction that was more likely related to factors other than the suspected drug was classified as doubtful.

Clinical Efficacy Evaluation

As a second aspect of this clinical assay, the efficacy of topical OLEOZON® was measured in all the patients studied, and also with respect to the different clinical forms present in tinea pedis. The efficacy was evaluated as clinical cure (disappearance of all lesions, for that reason no mycological diagnosis was needed) before or in six weeks. If a patient was clinically cured before six weeks of treatment, the medication was continued until six weeks. If a clinical cure was not achieved at the end of the treatment, this was considered a failure.

Patients were submitted to clinical and ADR evaluation every two weeks and at the end of the study (six weeks). If any side-effects appeared in the meantime, patients would immediately inform the physician to classify the severity of ADR and to determine the causal relationship. After finishing the treatment, all patients had a follow-up at six months to check for relapse.

The study was approved by the Scientific Committee of the Ozone Research Center. As the study only involved the usual medical procedures (this is a medication already registered in Cuba for the treatment of tinea pedis, with its license to use it) and confidentiality of the subjects was maintained, ethics approval and patient informed consent were not required.

Statistical Analysis

Univariate analyses were performed to identify the variables that could influence ADRs. The analysis was assessed by χ^2 test or Fisher's exact test, depending on the minimum expected values. For the efficacy evaluation, data were analyzed by one-way analysis of variance (ANOVA) followed by a multiple comparison test.

Results

In this study, the mean value of the evolution time of the disease was 60 months with five relapses per year. The mean age was 35 years, 85% were male and 55% were white. Interdigital lesions were the most common symptom in more than 90%; the plantar lesion was present in less than 50% of cases.

A total of 2596 patients suffering from tinea pedis were included in this study, but only 2165 patients (83.4%) finished the treatment because 431 (16.6%) dropped out due to scant attendance at the clinical evaluation (every 2 weeks). Taking into account the number of patients that finished

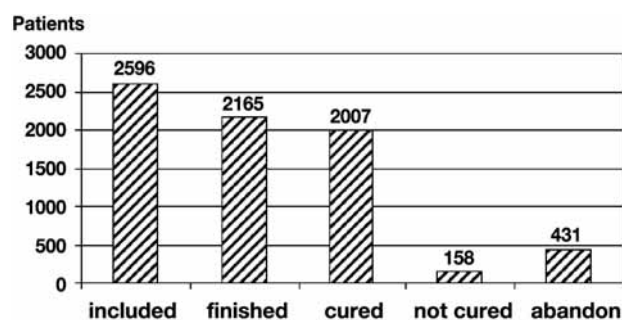


Figure 1 General results of tinea pedis treatment with topical OLEOZON®.

Table 1 Classification of ADRs and their qualitative assessment in this study

ADRs classification	Qualitative Assessment			
	Definite	Probable	Possible	Doubtful
Mild	Skin burning sensation (6)	Pruritus (1) Erythema (1)	-	-
Moderate	-	-	-	-
Severe	-	-	-	-
Very severe	-	-	-	-

In brackets is the number of patients that presented ADRs. One patient presented skin burning sensation and pruritus and another one presented skin burning sensation and erythema.

Table 2 Behavior of the patients that finished the topical OLEOZON® treatment in relation to the different clinical forms of tinea pedis and their evaluation.

Clinical forms	Total patients that finished the treatment	Cured patients (%)	Not cured patients (%)
Scaly	1085 (50.1%) ^a	1062 (97.9) ^a	23 (2.1)
Vesicular	130 (6.0%) ^b	85 (65.4) ^c	45 (34.6)
Macerated	690 (31.9%) ^c	655 (94.9) ^{a,b}	35 (5.1)
Mixed	260 (12%) ^d	205 (78.8) ^{b,c}	55 (21.2)
Total of patients	2165	2007	158

Different letters signify statistical differences ($p < 0.05$).

the topical OLEOZON® treatment, an efficacy of 92.7% (2007 patients cured) was achieved and only 7.3% (158 patients) were not cured (figure 1). However, if we consider as failure the number of patients that abandoned the treatment the effectiveness decreases to 77.3% (analysis by intention to treat). Only six patients (0.3%) presented ADRs. The most frequently reported ADRs were skin burning sensation, pruritus and erythema of mild intensity. Four patients presented skin burning sensation, one patient presented skin burning sensation and pruritus and the other one also had skin burning sensation but with erythema. Once the ADRs appeared in these six patients, the treatment was suspended for 24h. Patients were evaluated during this period to confirm their improve-

ment upon removal of OLEOZON® and the reappearance or not of the ADRs on rechallenge. Skin burning sensation was considered definite according to the causal relationship; pruritus and erythema were considered probable. No causal relationship considered as possible or doubtful was found in this study (table 1).

Considering the number of patients that finished the treatment, a major incidence (50.1%) of the scaly form of tinea pedis, followed by the macerated form (31.9%), were present in this study. The scaly and macerated forms demonstrated a high percentage of cured patients, with 97.9 and 94.9%, respectively (table 2).

No relapses were found in six months of follow-up.

Discussion

The results of this study suggest that topical OLEOZON® is a safe drug with an excellent post-marketing safety profile. Post-marketing monitoring is an important procedure to detect reactions that can become apparent only when the drug is used in a large and varied population. Indeed, those observed in clinical trials for tinea pedis¹⁴⁻¹⁶ do not reflect the true behaviour of ADRs due to the limited number of patients.

Active surveillance provides a vital service to the healthcare system by identifying and assessing early warning signals, and when appropriate, taking preventive action to minimize the deleterious effects of drugs. In Cuba this has a special relevance because the information generated in clinical trials can be limited by the patients' recruitment rate.

The most frequent ADRs associated with topical OLEOZON® therapy were skin-burning sensation, pruritus and erythema. These ADRs had also been reported in the treatment of impetigo with topical OLEOZON®⁵ in a phase III clinical trial carried out in 136 children. However, some contradictions are present with respect to ADRs. In the study²⁰, no ADRs were reported with the use of topical OLEOZON® in adults with different diseases (tinea pedis, pyoderma, onychomycosis, simplex herpes). Also, another study (unpublished observations) carried out in 80 children with impetigo reported no ADRs. In this study only 0.3% of ADRs were found.

Skin burning sensation could be a consequence of topical OLEOZON® application, due to the active metabolites that are formed^{17,18} (aldehydes, acids, ozonides and hydroperoxides) in the reaction of the ozone with the sunflower oil and the patient's sensitivity. For that reason, skin burning sensation can be classified as definite, according to the causal relationship, however, erythema and pruritus were in the group of probable ADRs (confirmed on suspension of the drug but not on rechallenge).

A high efficacy (92.7%) was obtained when all the patients that finished the treatment are considered. However, with respect to the analysis by intention to treat, where all the patients included in the study are considered, the effectiveness decreased to 77.3%, similar to that obtained in the phase III clinical trial⁴. This is an important point

to take into account, since in daily practice patients sometimes interrupt treatment, this result being a truer figure of medication efficacy. The incidence in respect to the different clinical forms, is similar to that already reported², where the scaly form occupied the first on the list. Also, the scaly form responds best to different treatments.

Another aspect to highlight is that topical OLEOZON® exhibits an antifungal and antibacterial activity^{4,5,8-10} as well as an anti-inflammatory property²¹⁻²². Normally, the severity of tinea pedis infection determines the course of treatment required. Mild infections may be resolved using a topical agent, but are commonly associated with high relapse rates. However, more severe cases (eg, dermatophytosis complex) may require oral and topical treatment that eliminates the bacterial and fungal infection and sometimes if inflammation is present an agent with a known anti-inflammatory action may be needed. All these drugs can be accompanied by side-effects such as gastrointestinal distress, headache, and hepatic toxicity, among others. In our study, the mean value of the evolution time of the disease was 60 months with five relapses per year, then, we can consider that we are studying chronic patients. This six weeks topical OLEOZON® treatment guaranteed the absence of relapses (at least in the six months of follow-up), and the presence of superinfection due to bacteria and the associated inflammation. In this case OLEOZON® will be the best choice due to its germicidal and anti-inflammatory properties, its low cost, safety and tolerability (favourable cost/benefit ratio).

Conclusions

The favourable safety profile achieved with topical OLEOZON® in this study together with its demonstrated efficacy and low cost justify the extension of this treatment in clinical practice for patients with tinea pedis, particularly in developing countries.

Acknowledgements

This study was sponsored by the Ozone Research Center and the Health Ministry of Cuba.

References

- 1 Fauci AS, Braunwald E, Isselbacher KJ et Al: Principles of Internal Medicine. 14th Edition. McGraw-Hill Companies Inc 1: 301-302, 1998.
- 2 Brooks KE, Bender JF: Tinea pedis: diagnosis and treatment. Clin Podiatr Med Surg 13: 31-46, 1996.
- 3 Lester M: Ketoconazole 2 percent cream in the treatment

- of tinea pedis, tinea cruris and tinea corporis. *Cutis* 55: 181-183, 1995.
- 4 Menéndez S, Falcón L, Simón DR et Al: Ozonized sunflower oil in the treatment of tinea pedis. *Mycoses* 45: 329-32, 2002.
 - 5 Menéndez S, Fernández M, Amoroto M et Al: Eficacia y seguridad del OLEOZON® tópico en el tratamiento de pacientes con impétigo. *Rev Panam Infectol* 9: 23-29, 2007.
 - 6 Amoroto M, Fernández M, González ME et Al: Eficacia del aceite ozonizado (Oleozone®) en el tratamiento de la giardiasis. Ensayo clínico fase III, aleatorizado, abierto y controlado. *Rev Cubana de Farmacia* 36: 173-175, 2002.
 - 7 Vigna I, Menéndez S: Eficacia de la ozonoterapia en gatos con diferentes enfermedades oftalmológicas. *RECVET* 11: 11, 2007. <http://www.veterinaria.org/revistas/recvet/n111107.html>.
 - 8 Sechi LA, Lezcano I, Nuñez N et Al: Antibacterial activity of ozonized sunflower oil (Oleozone®), *J Appl Microbiology* 90: 279-284, 2001.
 - 9 Lezcano I, Nuñez N, Espino M et Al: Antibacterial activity of ozonized sunflower oil, Oleozone®, against *Staphylococcus aureus* and *Staphylococcus epidermidis*. *Ozone Sci & Eng* 22: 207-214, 2000.
 - 10 Lezcano I, Molerio J, Gómez M et Al: Actividad in vitro del OLEOZON® frente a agentes etiológicos de infecciones de la piel. *Revista CENIC Ciencias Biológicas* 29: 209-212, 1998.
 - 11 Acevedo F, González J, Moleiro J et Al: Ensayo de toxicidad dérmica de 120 días del aceite ozonizado, OLEOZON®, en ratas Cnp. SPRD. *Avances en Biotecnología Moderna* 4: T4-T10, 1997.
 - 12 Arteaga ME, Molerio J, Bada A et Al: Clasificación toxicológica del OLEOZON®. *Revista CENIC Ciencias Biológicas* 32: 57-9, 2001.
 - 13 Llerena C, García G, Molerio J et Al: Irritabilidad dérmica del Oleozone®. *Revista CENIC Ciencias Biológicas* 26: 104-9, 1995.
 - 14 Saple DG, Amar AK, Ravichandran G et Al: Efficacy and safety of butenafine in superficial dermatophytoses (tinea pedis, tinea cruris, tinea corporis). *J Indian Med Assoc* 99: 274-5, 2001.
 - 15 Lebwohl M, Elewski B, Eisen D et Al: Efficacy and safety of terbinafine 1% solution in the treatment of interdigital tinea pedis and tinea corporis or tinea cruris. *Cutis* 67: 261-6, 2001.
 - 16 Svejgaard E, Avnstorp C, Wanscher B et Al: Efficacy and safety of short-term itraconazole in tinea pedis: a double-blind, randomized, placebo-controlled trial. *Dermatolog* 197: 368-72, 1998.
 - 17 Díaz M, Lezcano I, Molerio J et Al: Spectroscopic characterization of ozonides with biological activity. *Ozone Sci & Eng*: 35-40, 2001.
 - 18 Ledea O, Correa T, Molerio J et Al: Volatile Components of Ozonized Sunflower Oil (OLEOZON®). *Ozone Sci & Eng* 23: 121-6, 2001.
 - 19 Naranjo CA, Shear NH, Busto U: Adverse drug reaction. In: Kalant H. & Roschlau W. H. E. (eds) *Principles Medical Pharmacology*, 6th ed. New York: Oxford University Press 1998: 791-800.
 - 20 Falcón L, Menéndez S, Simón R et Al: Aceite ozonizado en dermatología. Experiencia de 9 años. *Revista CENIC Ciencias Biológicas* 29: 165-8, 1998.
 - 21 Martínez G, Merino N, Sam S et Al: Efecto histológico y bioquímico del OLEOZON® en el modelo de la cola de ratón. *Revista CENIC Ciencias Biológicas* 28: 31-4, 1997.
 - 22 Tamoto K, Yamazaki A, Nochi H et Al: Ozononides of olive oil and methyl oleate inhibit the expression of cyclooxygenase-2 through the suppression of I κ B/NF κ B-dependent pathway in lipopolysaccharide-stimulate macrophage-like THP-1 cells. In: *Proceedings of the 17th World Ozone Congress. Ozone in Medicine*. Strasbourg, France: International Ozone Association 3: 1-5, 2005.

Dr Silvia Menéndez Cepero
Centro Nacional de Investigaciones Científicas
Centro de Investigaciones del Ozono
POBox 6414, Playa
Habana, Cuba
Tel.: +53 7 271 9264
Fax: +53 7 208 0497
E-mail: silviamenendez@infomed.sld.cu

