J. Soc. Cosmetic Chemists, **17**, 575–579 (1966)

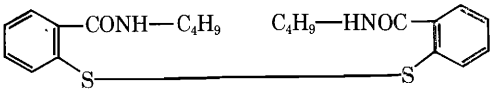
Cosmetic Uses of a New Synthetic Antifungal Agent

F. GIALDI, PROF. ORD.,* A. BARUFFINI, PROF. INC.,* R. PONCI, PROF. STRAORD.,† and P. CACCIALANZA, PROF. ORD.‡

Synopsis—It is shown that 2,2 -dithiobis (*N*-butylbenzamide) is an effective topical antifungal agent for therapeutic, prophylactic, and cosmetic use. The results of clinical tests with cosmetic products containing this agent are detailed.

Introduction

For several years, studies have been carried out toward the synthesis of antifungal agents related to aromatic sulfides (1, 2). Among the new substances synthesized, 2,2-dithiobis[*N*-butylbenzamide] (OD-507) has been found to be particularly interesting:



This substance possesses high antifungal activity and is also active against some bacteria. Table I gives some data on minimum inhibitory concentrations of this compound. Comparative microbiological tests have demonstrated that OD-507 possesses activity equal or superior to that of the best known natural or synthetic antifungal agents (2).

Pharmacological studies on the toxicity of OD-507 have revealed that this substance is very well tolerated (3). Furthermore, a series of

* Institute of Pharmaceutical Chemistry, Pavia University, Italy.
† Institute of Pharmaceutical Chemistry, Parma University, Italy.
‡ Dermatological Clinic, Perugia University, Italy.

Table I
Minimum Inhibitory Concentrations

Microorganism	MIC (mcg./ml.)
Trichophyton mentagrophytes (ATCC 8757)	1
Trichophyton mentagrophytes (ATCC 9129)	1
Epidermophyton floccosum (ATCC 10227)	2
Microsporum audouini (ATCC 9079)	5
Microsporum gypseum (ATCC 11658)	5
Microsporum canis (ATCC 10214)	2
Candida albicans (ATCC 10231)	10
Candida albicans (LCP)	5
Candida tropicalis (ATCC 1369)	1
Saccharomyces cerevisiae (ATCC 9763)	10
Saccharomyces carlsbergensis (ATCC 9080)	5
Kloeckera brevis (ATCC 977)	0.5
Cryptococcus neoformans (SKF 1110)	2
Nocardia asteroides (CBS)	5
Staphylococcus aureus (ATCC 6538)	2
Streptococcus pyogenes (C-203)	1
Streptococcus faecalis (ATCC 10541)	5
Bacillus subtilis (ATCC 6633)	2
Pseudomonas aeruginosa (ATCC 10145)	20
Mycobacterium tuberculosis (H 37 RV)	1

experimental "patch tests" and "scratch tests" in humans indicated no irritation or sensitization reactions by this substance.

In view of all these facts, the utility of OD-507 as an antifungal medication for dermatological use was studied in a preliminary clinical trial, and the results obtained have been reported (2). The substance has proved to be generally well tolerated both by healthy human skin and in areas of epidermomycotic lesions. The antifungal activity of OD-507 tested in various types of epidermomycotic infections (inguinal epidermophytosis, erythrasma, athlete's foot, etc.) has been found to be extensive and efficient, superior or comparable to that of the best-known modern therapeutic antifungal preparations.

Purpose of Study

All the results of studies so far performed emphasize the fact that OD-507 is both highly active and always well tolerated. In fact, the rare cases of intolerances noted in the earlier clinical experiments (2) have turned out to be related to the composition of the vehicle, not to the active antifungal agent. The study of OD-507 has now been extended to the cosmetic field. The basic requirement for the application of an active substance in cosmetics is its tolerance over prolonged periods

of use. In other words, the possibility of including OD-507 in a series of preparations, either as a prophylactic against widespread epidermomycotic states or as a useful adjuvant to therapeutic treatment, was studied.

Experimental

Three preparations were used: a body powder, a solid skin detergent, and a shampoo.

The body powder was formulated with 2% micronized OD-507 in a base consisting of talc, isopropyl myristate, and Carbowax 1500 to assure adhesion of the preparation.

The solid skin detergent was formulated with the objective of using detergents capable of giving aqueous solutions at weakly acid pH values. A solid skin detergent based on anionic surfactants, polyethylene glycols, alcohols, and higher fatty acids was therefore prepared. Lactic acid was used to achieve the acidic pH. OD-507 was incorporated at a concentration of 2%. This preparation, dispersed in water at 1% concentration, gives a pH of 6.5.

The shampoo was formulated at a neutral pH, choosing anionic and non-ionic surfactants as detergents. The OD-507 was incorporated at 0.5% concentration. The formulations are shown below:

Body Powder

Talc USP XVII	95.0 g
Isopropyl myristate (Italcolloid-Italy)	1.0 g
Polyethylene glycol 1500 (Carbowax 1500; Union Carbide-USA)	2.0 g
OD-507	2.0 g

Solid Skin Detergent

Sodium laurylsulfate (Empicol L.Z.G.V.; Marchon Italiana-Italy)	11.0 g
Sodium *N*-oleyl-*N*-methyltaurate (Arkopon T.; Hoechst-Germany)	31.0 g
Stearic acid	16.5 g
Stearyl alcohol	12.0 g
Polyethylene glycol (Polyglycol E 4000; Dow Chemical-USA)	11.0 g
Talc USP XVII	16.0 g
Lactic acid	0.5 g
OD-507	2.0 g

Shampoo

Sodium laurylpolyoxyethylene sulfate (Salvo E020; Chemy-Holland)	35.0 g
Polyoxyethylene stearate (Myrj 52; Atlas-U.S.A.)	5.0 g
Sodium *N*-alkyl-*N*-methyltaurate (Hostapon C.T.; Hoechst-Germany)	10.0 g
OD-507	0.5 g
Water to make	100.0 ml

Results

The cosmetic preparations under test were used by subjects suffering from a variety of clinical skin mycoses which, according to past personal history, had all chronically relapsed. The case list was, therefore, a selected one and comprised primarily refractory patients.

The *first group* consisted of 18 subjects, all suffering from dermatophytosis between the toes (athlete's foot) chronically relapsing during the spring/summer season for three to five years.

After complete clinical recovery (through use of OD-507 cream), 12 of these subjects started maintenance treatment using the solid detergent two to three times weekly and applying the talcum powder daily or on alternate days. The other six subjects were not treated with the cream but instead started prophylactic treatment with the solid detergent and the talcum powder at the start of spring, a period which, according to past personal history, consistently coincided with relapse of the mycosis. The results indicate that no fungal manifestations reappeared in any of the 18 subjects so treated. Patient tolerance of the solid detergent and the talcum powder was excellent.

The *second group* consisted of 11 subjects with inguinal epidermomycosis (bilateral in 9 cases) which had repeatedly relapsed for years. All subjects applied the detergent and talcum powder systematically every day for a long period instead of ordinary soap and bath talc. As in the first group, no relapses occurred in any of the cases.

The *third group* comprised ten subjects suffering from *pityriasis versicolor* which consistently relapsed in spite of varied and prolonged earlier treatments. In several cases the lesions still showed obvious fluorescence under ultraviolet light. All ten subjects made systematic and prolonged use of the solid detergent and talcum powder under test. None of the patients showed relapse of the chromophytosis.

The fourth group comprised seven obese subjects, suffering from relapsing candidiasis of the large body folds. Two cases suffered from

diabetes, and all subjects suffered from frequent and abundant sweating. Regular use of the solid detergent and of the talcum powder under test gave excellent, rapid and long-lasting results. As above, tolerance of the preparations was excellent.

The *fifth group* comprised six cases of severe chronic seborrheic dermatitis of the mid-chest in adults. Systematic and prolonged use of the solid detergent and talcum powder led to recovery from the symptoms.

The *sixth group* comprised six cases of so-called dry pityriasis of the scalp, nine cases of pityriasis steatoides of the scalp, and two cases of tinea amiantacea. All of these subjects, many of whom had had severe relapses or were chronic, greatly benefited from use of the shampoo. This preparation, included as an adjuvant with other routine medicaments (UV rays, corticosteroids, etc.), was found to be a practical and beneficial topical therapeutic means. After termination of clinical treatment, the regular use of the shampoo (instead of the usual shampoos) favored continuing recovery and evidently prevented the onset of the easily occurring relapses in all subjects.

Throughout these clinical studies, the use of placebos as controls was not considered necessary.

Conclusions

The clinical results obtained in the 67 cases studied confirm that OD-507 is active and well tolerated. It may be considered a synthetic antifungal agent which is perfectly suitable also for the formulation of cosmetic preparations.

Formulations such as those tested above have been shown to be extremely efficient prophylactics against several frequently relapsing mycotic states. These preparations are also believed to be useful adjuvants for use during medical treatment of mycotic infections.

(Received April 21, 1966)

References

(1) Gialdi, F., Ponci, R., and Baruffini, A., *Il. Farmaco Ed. Sci.*, **12,** 413 (1957); *Ibid.*, **14,** 15, 25, 216, 606, 648, 829 (1959); *Ibid.*, **15,** 835, 856 (1960); *Ibid.*, **16,** 411, 509 (1961); *Ibid.*, **18,** 288, 653 (1963); *Ibid.*, **19,** 76, 121, 254, 356, 437 (1964).

(2) Gialdi, F., Ponci, R., and Caccialanza, P., *Mycopathol. Mycol. Appl.*, **24,** 163 (1964).

(3) Personal communication from Prof. B. Fischetti of Perugia University.