British Journal of Dermatology (1993) **129**, 437–442.

Does naftifine have anti-inflammatory properties? A double-blind comparative study with 1% clotrimazole/1% hydrocortisone in clinically diagnosed fungal infection of the skin

E.G.V.EVANS, I.G.V.JAMES,* R.A.J.SEAMAN† AND M.D.RICHARDSON‡

PHLS Mycology Reference Laboratory, Department of Microbiology, University of Leeds and General Infirmary, Leeds LS2 9JT, U.K.

**The Surgery, 555 Chorley Old Road, Bolton BL1 6AF, U.K.*

†*Stotfold Health Centre, Hitchin Road, Stotfold, Hitchin SG5 4HP, U.K.*

‡*Regional Mycology Reference Laboratory, Department of Dermatology, Robertson Building, University of Glasgow, 56 Dumbarton Road, Glasgow G11 6NU, U.K.*

Accepted for publication 15 March 1993

Summary In a multicentre, double-blind, randomized, parallel group study in general practice, 269 patients with clinically diagnosed fungal infection of the skin were treated with either naftifine (Exoderil®) or 1% clotrimazole plus 1% hydrocortisone (CHC; Canesten HC®) applied twice daily for 4 weeks. Only 115 patients were shown subsequently to have a fungal infection by laboratory tests; the others had inflammatory disease of unknown aetiology. In those with fungal disease, both treatments were equally effective in terms of mycological cure (negative microscopy and culture). Clinical results for all 265 patients showed no clinically identifiable difference between the two preparations in terms of resolution of the disease, indicating that naftifine does have anti-inflammatory activity at least equal to CHC. This study suggests that there is no clinical advantage in treating patients with clinically diagnosed fungal infection of the skin with an antimycotic/corticosteroid combination as opposed to naftifine alone.

Dermatophyte infections are frequently associated with a marked inflammatory response, and are often treated topically with a corticosteroid/antifungal combination. Studies comparing Daktacort® with its constituents, 2% miconazole and 1% hydrocortisone, and Canesten HC® (CHC) with its constituents, 1% clotrimazole and 1% hydrocortisone, showed that the combination therapies were more effective than the antifungal alone in reducing the signs and symptoms of inflammation.[1,2] However, concern has been expressed about the use of topical steroids in fungal infections of skin, on the basis that they may interfere with cutaneous defence mechanisms, or lead to systemic toxicity if absorbed through broken skin. Therefore, it would be an advantage to have a non-steroidal agent which has both anti-inflammatory and antimycotic activity.

Naftifine hydrochloride (Exoderil®) is a fungicidal, allylamine antifungal[3] which is effective both *in vitro* and *in vivo* against dermatophyte and yeast infections.[4] Its mode of action is similar to that of terbinafine (Lamisil®), namely, inhibition of ergosterol biosynthesis at the point of squalene epoxidation, resulting in a deficiency of membrane sterol production and an intracellular accumulation of squalene.[3] However, unlike terbinafine, naftifine is only formulated topically, as it is ineffective orally. Experimental and clinical studies have indicated that, in addition to its antifungal action, naftifine may also have anti-inflammatory and antihistaminic activity.[5–8]

This study was designed to investigate further the anti-inflammatory activity of naftifine, by comparing naftifine 1% cream with 1% clotrimazole plus 1% hydrocortisone (CHC; Canesten HC®) cream, in patients with clinically diagnosed fungal infection of the skin with associated inflammation, who presented in general practice. In this setting, patients are usually treated on the basis of the clinical diagnosis only, because facilities for microscopical examination of skin are not usually available, and a combined antifungal/anti-inflammatory agent is often given when the lesions are inflamed. Therefore, this study mirrors what generally occurs in general practice, by entering patients on the basis of a

clinical diagnosis alone. It provides a comparison of the performance of both products in treating a variety of inflammatory skin lesions, putatively due to fungal infection, but which in reality may or may not be fungal in origin.

Methods

Patients

Male and female patients aged 12 years or more, with a clinical diagnosis of tinea pedis, tinea corporis, or tinea cruris, and a symptom/sign score of greater than 3 (see below) were eligible for entry into the study. Pregnant or lactating women were excluded, and women of reproductive age were required to be using a reliable form of contraception. Patients who had received radiation therapy, systemic therapy with toxic or immunosuppressive drugs, or therapy with antibacterial, antifungal, antiviral or anthelminthic drugs in the previous 7 days were also excluded. Concomitant therapy of chronic conditions such as cardiac insufficiency, high blood pressure or diabetes mellitus was allowed to continue during the study, but no additional topical medication was allowed. All patients gave written informed consent, countersigned by a parent or guardian in the case of those under the age of 18.

Study design

This was a multicentre, randomized, double-blind, parallel group study, in which patients were stratified into two groups: Group I comprised patients with tinea pedis, and Group II comprised patients with tinea corporis or tinea cruris. Within each group, patients were randomly allocated to receive naftifine 1% cream twice daily, or CHC twice daily, for 4 weeks.

Study procedure and assessments

Patients were seen weekly during the 4-week treatment period, and followed-up at 2 weeks (week 6) and 8 weeks (week 12) after completing therapy. At each visit, signs and symptoms were assessed: erythema, scaling, vesiculation, pustules, crusting and pruritus were each scored on a scale of 0, absent; 1, mild; 2, moderate; 3, severe, to give a clinical score (maximum possible score 18), and a skin scraping was taken for mycological assessment. Mycological investigations, performed in Leeds or Glasgow (depending on the study centre location), consisted of direct microscopy in 20% KOH, and culture on Sabouraud glucose agar (plus chloramphenicol 0·05% and actidione 0·5% w:v) at 27–30°C for up to 3 weeks. Clinicians were not informed of the mycology results until after the patients had completed the 6-week follow-up visit, thereby preventing the withdrawal of patients who did not have a fungal infection.

The severity of any adverse events was recorded as mild, moderate or severe, and their relationship to therapy assessed as certain, probable, improbable, uncertain, or no relationship.

Statistical analysis

Statistical analysis of mycological cure (negative microscopy and culture), based on all patients entered who were initially positive by microscopy and culture, was performed at week 6 with a chi-squared test. An intent-to-treat analysis was carried out on the clinical score with an analysis of covariance, with centre, drug, group (tinea pedis vs. tinea corporis/cruris) and baseline mycology as factors, and the baseline total score as covariate. The interactions between drug, group and baseline mycology have also been included in the model, as has the covariate by drug interaction.

Results

Patients

A total of 269 patients were recruited from 28 general practice centres: 157 (58%) with a clinical diagnosis of tinea pedis, and 112 (42%) with tinea corporis or tinea cruris. Of these, 115 (42·7%) had laboratory evidence of a fungal infection (89 microscopy and culture positive): 55% (86) of those with a clinical diagnosis of tinea pedis, and only 26% (29) of the tinea corporis or cruris patients.

Patient demographics and details of the types of infection are shown in Table 1.

Mycology

All patients were infected with dermatophytes, with the exception of two with *Candida albicans*, two with *Malassezia furfur* (these four patients were in the tinea corporis/cruris group), and two with *Scopulariopsis brevicaulis* isolated (tinea pedis group) (Table 2).

The number of mycologically cured patients (Table 3) indicates that both treatments were equally effective, as the response rate was similar at each time point, and that relapse was uncommon.

Table 1. Patient demographics in relation to treatment groups and types of infection

	Canesten HC® group		Naftifine group	
	Tinea pedis	Tinea corporis/cruris	Tinea pedis	Tinea corporis/cruris
Age (years)				
Median	40	35	41	39
Range	12–77	12–81	14–76	12–77
Sex				
Male	58	35	58	40
Female	22	22	19	15
Race				
White Caucasian	74	55	70	52
Asian	3	2	5	2
Negroid	3	0	1	1
Mixed	0	0	1	0
Duration of infection (weeks)				
Median	10	6	12	6
Range	1–1000	1–520	1–1000	1–52
Number previously treated	30 (38%)	13 (23%)	25 (32%)	11 (20%)

Table 2. Causal organisms in patients with confirmed fungal infection, and positive cultures in the different treatment groups

	Canesten HC® group		Naftifine group	
Organism	Tinea pedis	Tinea corporis/cruris	Tinea pedis	Tinea corporis/cruris
Trichophyton rubrum	20	5	23	8
Trichophyton mentagrophytes	5	1	10	2
Trichophyton verrucosum	0	1	0	0
Trichophyton erinacei	0	0	0	1
Epidermophyton floccosum	2	0	0	0
Microsporum canis	0	2	0	1
Microsporum gypseum	0	0	0	1
Dermatophyte sp.	0	0	1	0
Scopulariopsis brevicaulis	1	0	1	0
Candida albicans	0	1	0	1
Malassezia furfur	0	1	0	1
Totals	28	11	35	15

Clinical scores

Of the 269 patients recruited to the study, four failed to attend after the baseline visit, and therefore the intent-to-treat analysis was based on 265 patients. For patients who withdrew during the study, the last value recorded was carried forward to each subsequent visit.

The mean total clinical score for all patients over time (Fig. 1), adjusted for the baseline score, shows a striking reduction in the total scores over the 4-week treatment period for both treatments, and at week 4 the difference was statistically significant ($P=0{\cdot}05$) in favour of CHC. However, as the mean residual score for CHC was 0·9 compared with 1·3 for naftifine, it was not a clinically identifiable and thus clinically relevant difference.

The mean total clinical scores for the tinea pedis group and the tinea corporis/cruris patients, according to the baseline mycology result, are shown in Figures 2–5. The reduction in clinical score with the two treatments was the same for all patient groups, apart from the tinea pedis mycology-negative group, in which CHC-treated patients had a tendency to lower scores at all time points.

Table 3. Patients mycologically cured (microscopy and culture negative) at each visit* (percentages in parentheses)

Indication	Treatment	Week no. 0	1	2	3	4	6	12
Tinea pedis	Canesten HC®	0/28 (0)	16/27 (59)	19/28 (68)	22/27 (81)	24/26 (92)	18/23 (78)	20/23 (87)
	Naftifine	0/35 (0)	18/34 (53)	25/35 (71)	28/33 (85)	32/34 (94)	31/34 (91)	31/33 (94)
						$P=0{\cdot}70$†		
Tinea corporis/cruris	Canesten HC®	0/11 (0)	8/10 (80)	9/10 (90)	7/8 (88)	8/10 (80)	8/8 (100)	6/7 (86)
	Naftifine	0/15 (0)	11/15 (73)	12/15 (80)	15/15 (100)	13/15 (87)	13/15 (87)	13/15 (87)
						$P=0{\cdot}82$†		
Both indications	Canesten HC®	0/39 (0)	24/37 (65)	28/38 (74)	29/35 (83)	32/36 (89)	26/31 (84)	26/30 (87)
	Naftifine	0/50 (0)	29/49 (59)	37/50 (74)	43/48 (90)	45/49 (92)	44/49 (90)	44/48 (92)
						$P=0{\cdot}84$†		

* Only includes patients who were microscopy and culture positive.
† Chi-squared test.

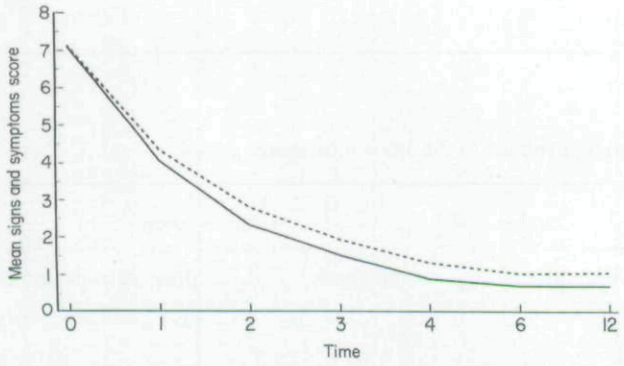

Figure 1. Mean total symptoms score for all patients* at each visit. —, Canesten HC®; – – – –, naftifine. *Weekly totals adjusted for week 0 total.

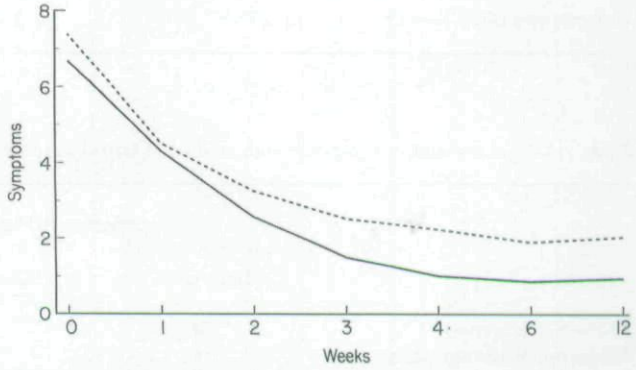

Figure 3. Mean total symptom score* for patients with clinically diagnosed tinea pedis with no laboratory evidence of a fungal infection at baseline.† ——, Canesten HC®; – – –, naftifine. * Weekly totals adjusted for week 0 total. †Positive, defined as evidence of fungal infection on microscopy or culture.

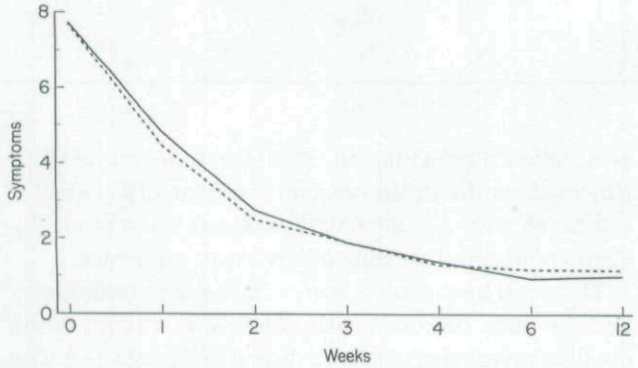

Figure 2. Mean total symptom score* for patients with clinically diagnosed tinea pedis with evidence of a fungal infection at baseline.† ——, Canesten HC®; – – –, naftifine. * Weekly totals adjusted for week 0 total. †Positive, defined as evidence of fungal infection on microscopy or culture.

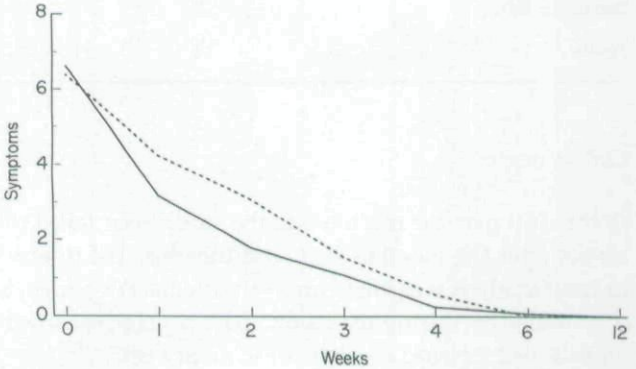

Figure 4. Mean total symptom score* for patients with clinically diagnosed tinea corporis/cruris with evidence of a fungal infection at baseline.† ——, Canesten HC®; – – –, naftifine. * Weekly totals adjusted for week 0 total. †Positive, defined as evidence of fungal infection on microscopy or culture.

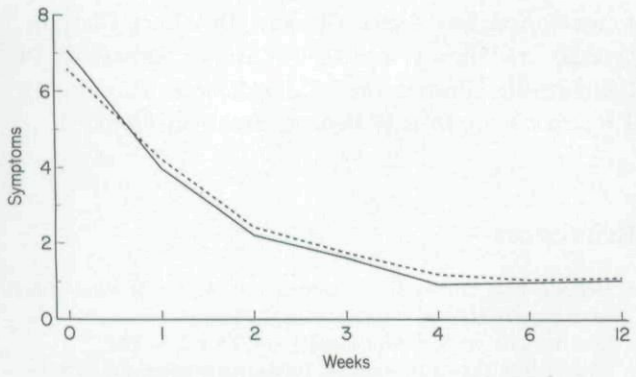

Figure 5. Mean total symptom score* for patients with tinea corporis/cruris with no evidence of fungal infection at baseline.† ——, Canesten HC®; – – –, naftifine. * Weekly totals adjusted for week 0 total. †Positive, defined as evidence of fungal infection on microscopy or culture.

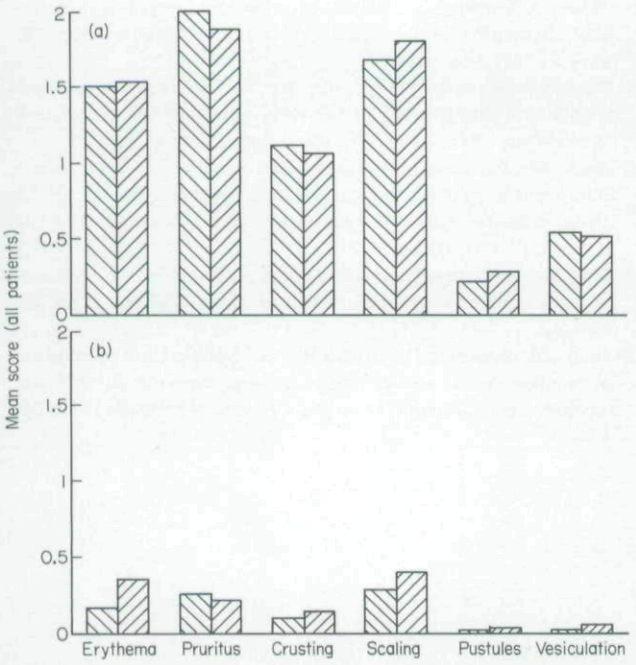

Figure 6. Individual components of clinical score for all patients (a) before (week 0), and (b) after (week 4) treatment. ▧, Canesten HC®; ▨, naftifine.

The individual components of the clinical score for all patients are shown in Figure 6, both prior to treatment (Fig. 6a) and at the end of treatment (week 4; Fig. 6b). The main components were erythema, pruritus and scaling, but all signs and symptoms improved significantly during treatment, and both treatments were equally effective.

Adverse events

Twenty (14·7%) adverse events were reported on CHC, compared with 18 (14·0%) on naftifine. Of the adverse events reported on CHC, only three (2·2%) were thought to be certainly or probably related to treatment (blisters and burning, smarting at the site of application, metallic taste); three patients had severe adverse events of uncertain relationship to therapy (inflamed, pruritic scrotum, severe itching, exacerbation of infection). Only one patient on CHC was withdrawn, because of a sensitivity reaction at the site of infection which was of uncertain relationship to treatment. Six patients (4·7%) on naftifine experienced adverse events certainly or probably related to treatment (itching, blisters, and a burning sensation); only one serious adverse event was reported (itching), and no patients on naftifine withdrew due to adverse events.

Discussion

In the treatment of superficial fungal infection with associated inflammation, it would seem advantageous to use a non-steroidal antifungal with inherent anti-inflammatory activity. This study was undertaken to investigate whether naftifine was as effective as the antimycotic/corticosteroid preparation CHC, both in terms of its antifungal and its anti-inflammatory activity.

Of the 269 patients entered, only 115 were subsequently found to have laboratory evidence of a fungal infection, and only 89 of these were culture positive. As expected, both treatments were highly effective in eradicating the fungal pathogens. Both treatments were also highly effective in rapidly reducing the signs and symptoms of inflammation, and this improvement continued until the end of treatment. At week 4, although there was a statistically significant difference in favour of CHC, due to the large number of patients enabling a small difference in clinical score (0·4) to be detected, the difference was not clinically relevant; a score of '1' was equivalent to a 'mild' for one of the six signs and symptoms, and clinically it would not be possible to distinguish a score of 0·9 from 1·3.

In patients with fungal infection, eradication of the fungus would have contributed towards the reduction in inflammation and hence the clinical score. We can obtain a better evaluation of the inherent anti-inflammatory properties of the two preparations by looking at the results in those patients who did not have a fungal infection. This group, which represents the majority in this study, were a mix of patients. Some would have had

an undetected fungal infection, but most would have been suffering from other inflammatory skin diseases. In the tinea pedis group, CHC was superior to naftifine both at week 1 and week 4, but the difference in score between the two at each time point was only '1', corresponding to a 'mild' for one of the signs and symptoms, and both topical agents were therefore highly effective in this group of patients; in the tinea corporis/cruris group no differences in response were evident. This suggests that naftifine has inherent anti-inflammatory properties.

In conclusion, this study shows that use of the antifungal/corticosteroid combination CHC conferred no advantage over treatment with the antifungal naftifine in clinically diagnosed tinea pedis, tinea corporis and tinea cruris, and it confirms similar recent findings with these two preparations in tinea pedis.[9] Naftifine is available in 30–40 countries world-wide, mainly in Europe, the Far East and in the U.S.A., although at present it is not available in the U.K.

Acknowledgments

We would like to thank Sandoz Pharmaceuticals for the management and analysis of this study, and the following colleagues who contributed patients: Dr C.S.Joshipura, Manchester; Dr R.C.Joshipura, Manchester; Dr P.S.Basu, Manchester; Dr J.M.Shah, Manchester; Dr A.K.Mishra, Bolton; Dr P.M.Baldwin, Nottingham; Dr A.White, Nottingham; Dr B.Elvy, Norwich; Dr G.MacFarlane, Glasgow; Dr J.MacKenzie, Glasgow; Dr D.L.Phillips, Caldicot; Dr D.P.Jaiswal, Dagenham; Dr J.Ham, Rugby; Dr R.Kirkpatrick, Cumbernauld; Dr L.M.Campbell, Glasgow; Dr B.K.Jaiswal, Dagenham; Dr C.Leigh, Kings Norton; Dr C.Smith, Glasgow; Dr V.Berg, Glasgow; Dr B.Silvert, Manchester; Dr R.N.Stones, Knutsford; Dr C.McIntosh, Stirling; Dr R.C.Goodfellow, Preston; Dr T.P.Jones, Hull; Dr K.W.Benson, Stoke-on-Trent.

References

1 Mertens RLJ, Morias J, Verhamme GA. A double-blind study comparing Daktacort, miconazole and hydrocortisone in inflammatory skin infections. *Dermatologica* 1976; **153**: 228–35.

2 Szarmach H, Weuta H, Stepka L. Indikationsabgrenzung zwischen Clotrimazol/Hydrocortison und seinen beiden Komponenten. Eine doppelblinde Studie. *Arzneimittelforsch* 1984; **34**: 927–30 (Ger.) (Eng. Abstr.).

3 Petranyi G, Ryder NS, Stütz A. Allylamine derivatives: new class of synthetic antifungal agents inhibiting fungal squalene epoxidase. *Science* 1984; **224**: 1239–41.

4 Weidinger G. Clinical efficacy of naftifine. In: *Recent Trends in the Discovery, Development and Evaluation of Anti-fungal Agents* (Fromtling RA, ed). Proceedings of an International Telesymposium, May 1987. JR Prous: Barcelona, 1987; 497–509.

5 Nolting S, Weidinger G. Naftifin bei schweren Dermatomykosen—kontrollierter Wirkungsvergleich mit Econazol. *Mykosen* 1985; **28**: 69–76 (Ger.) (Eng. Abstr.).

6 Friederich HC, Haes PJ, Tronnier N. Therapievergleich zwischen Naftifin und einem corticosteroidhaltigen Imidazol-Derivat. *Aktuelle Dermatologie* 1985; **11**: 77–80 (Ger.) (Eng. Abstr.).

7 Black AK, Fincham N, Greaves MW, Hensby CN. Time course changes in levels of arachidonic acid and prostaglandins D2, E2, F2 alpha in human skin following ultraviolet B irradiation. *Br J Clin Pharmacol* 1980; **10**: 453–7.

8 Jung EG. The anti-inflammatory efficacy of naftifine as evaluated from the erythema response to ultraviolet light. *Mykosen* 1985; **28**: 109–12.

9 Smith EB, Breneman DL, Griffith RF *et al.* Double-blind comparison of naftifine cream and clotrimazole/betamethasone dipropionate cream in the treatment of tinea pedis. *J Am Acad Dermatol* 1992; **26**: 125–7.