EVALUATION OF CLOTRIMAZOLE, A NEW BROAD-SPECTRUM ANTIFUNGAL AGENT FOR DERMATOMYCOSES

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Summary

A clinical investigation with clotrimazole cream and solution was conducted in 60 patients with dermatomycosis. 10 had candidiasis, 41 had dermatophytosis and 9 had tinea versicolor infection.All the 10 patients with candidiasis were cured, the average duration of therapy being 1–2 weeks. Clotrimazole was also effective in dermatophyte infection, resulting in cure in 25 and improvement in 13, there being only 3 failures. Whereas the clinical evidence of disease disappears within 3 weeks in acute dermatomycoses of less than 6 months duration, it required 4–6 weeks of therapy for chronic infection. We found it difficult to assess the efficacy in pityriasis versicolor infection.

Both the cream as well as solution produced identical results and tolerance was very satisfactory in over 95% of patients. Clotrimazole is notable for its remarkable quick effect on both dermatophytes and candidiasis as confirmed by us and also in erythrasma and tinea versicolor infections as reported by other workers. Its well documented persistence in all the layers of epidermis and its utility in subjects clinically resistant to griseofulvin adds to its usefulness. It is a valuable addition to the range of topical antifungal drugs particularly in developing countries where there is a lack of proper dermatological and mycological expertise for diagnosis and therapy.

Superficial fungal infections (dermatomycoses) of the skin are world-wide in distribution and involve vast population groups. They cause significant morbidity [1,2] and should be considered as of high communicability[2,3,4,5]. Superficial dermatomycoses is mainly comprised of 3 groups viz., (a) candidiasis (b) dermatophytosis (c) tinea versicolor. As yet, there is no single therapeutic agent for all of them, and they require proper dermatological and mycological expertise for diagnosis and therapy which is generally not available in developing countries. Hence, any new introduction in this field always merits investigation.

Recently, Bayer Germany has developed a new antimycotic agent, clotrimazole i.e. bis-phenyl -(2-chlorophenyl)-1-imidazolyl methane, under the trade name canesten.

Experimental as well as clinical investigations have shown that the drug is well tolerated. Thus single and repeated local applications of the solution and cream to the skin of the rabbit[6] as well as a clinical evaluation in 721 patients[7] have shown that the tolerance on topical administration is excellent. Using patch

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testing by the occlusion technique, Wahlerg[8] tested 465 patients with clotrimazole, the test concentrations in 166 patients being 16 times and in 293 patients 32 times greater than the therapeutic concentration normally employed. No cases of skin reactions were obeserved in any patient. Clotrimazole has also been adminis tered with success orally with few side-effects[9].

The drug is reported to have a wide spectrum of activity. In vitro studies[10] have shown activity against dermatophytes, budding fungi, biphasic fungi and moulds. The spectrum of action thus encompasses that of amphotericin B and nystatin, as well as griseofulvin and tolnaftate. On the basis of their experiments using a strain of Candida albicans, Iwata et al[11] concluded that clotrimazole acts primarily by damaging the permeability barrier, possibly through reaction with the cell membrane of sensitive organisms.

Clotrimazole is reported to have a good skin-penetrating power. Duhm et al[12] using C14 - labelled drug, demonstrated that 6 hours after local application, the minimum inhibitory concentrations for most fungi or even higher levels were attained in the epidermis. (Fig. Page No. 21).

This is a report on our screening programme of clotrimazole cream and solution in 60 patients of dermatomycosis, in order to study its efficacy, tolerance and duration of therapy required in various infections. We also tried to ascertain the comparative therapeutic efficacy of the 2 bases namely, cream and solution. Topical medicaments with formulations of a base derived from experience in cold climates, may not always produce equivalent clinical results when used in tropical countries. Several factors such as humidity and heat with the resultant increased sweating and lowered pH of the skin may interfere with the release of the active drug from the base and affect its stability. Besides, ingredients of the base itself may interfere with stability of the drug under different ambient conditions[13].

Material and Method

Patients with clinicaliy diagnosed fungus infection confirmed by direct microscopic examination and/or culture were selected for the study. Previous history of other medicaments taken was noted and these were discontinued. Patients were given a tube of clotrimazole cream (1%) and/or bottle of clotrimazole solution (1%) and instructed to use it twice a day after bath in the following manner. A drop of solution or a small pellet of cream, about the size of a pea, was to be placed at about 2 inches distance from each other in the affected area. The patient was asked to rub the medicament thinly over the affected area till it disappeared. The area of application was extended to 1-2 inches outside the affected area to prevent contiguous substantial extensions of the disease.

The patients were examined twice a week for 2 weeks and weekly thereafter for a minimum of 4 weeks and wherever possible upto 8 weeks. During these visits the patient's subjective evaluation by way of his symptoms and the physician's objective evaluation by way of subsidence of erythema, vesiculation or scaling, were recorded.

Absence of lesions on clinical examination as well as negative KOH preparation and/or culture examination were taken as criteria of cure. In some patients, although the lesions had objectively subsided, itching persisted in localised areas in or around the lesion. This was particularly noted with tinea cruris or tinea corporis on hairy regions, and signified bacterial folliculitis or follicular trichophytosis Desai[14] has emphasized this event as a cause of recurrence. These patients were evaluated as improved.

Clotrimazole cream was used in 37 patients and solution in 8 patients. In 15 patients with bilateral lesions, clotrimazole cream was used on one side, and clotrimazole solution on the other and the efficacy assessed.

Results

Clotrimazole was tested in 60 patients of all age groups (Table 1). These included 10 cases of candidiasis, 9 of T. versicolor infection and 41 of dermatophytes infection. Of the latter, 17 were acute with duration of less than 6 months and 24 were chronic with duration of more than 6 months and even upto 20 years with repeated recurrences. The need to understand any defect in immunologic status in these groups was brought out by Desai [15,16] and Desai et al.[17] as immunologic status will condition the recurrence and the final outcome of any therapy.

Of the 60 patients, 41 were earlier treated by their doctors or had practised self-medication with unsatisfactory results as follows: topical antifungal 5; topical corticosteroid 7; topical antifungals + corticosteroids 5; systemic corticosteroids 6; griseofulvin 13 and griseofulvin with topical corticosteroids 5. Of these, 5 were clinically griseofulvin resistant cases with persistent lesions despite taking adequate dosage.

Candidiasis

Clotrimazole was effective in all 10 patients (Table 2) comprising 6 with candidial intertrigo, 1 with vulvovaginitis, 1 with intertrigo and balanitis, 1 with candidiasis of the body and 1, a child of 15 days of age with disseminate candidiasis. As indicated in Table 3, clinical as well as laboratory cure was obtained within the 1st week of treatment in 5 patients, in the 2nd week in 3 and in the 4th week in 1 patient. The remaining patient with disseminate candidiasis was free of lesions within 3 weeks of therapy. All the patients remained symptom-free up to 6 weeks of observation.

Dermatophytosis

The 41 patients with dermatophyte infection had the following distribution of lesions: corporis 16 of whom 6 had disseminate lesions, cruris 20 of whom 3 had extensive cruris with corporis and 2 with tinea pedis and intertrigo. There were no patients with tinea mannum. Clotrimazole was effective in this condition also resulting in cure in 25, improvement in 13, and failures in only 3 patients (Table 2). As is evident from

TABLE 1

No. of patients in each age group

AGE Group (In years)	< 1	1 – 10	11 – 20	21 – 30	31 – 40	41 – 50	51 – 60	61 – 70	71 – 80
No. of patients	1	1	10	7	21	10	5	4	1

TABLE 2

Therapeutic results with clotrimazole cream and solution in different indications

Disease	Total number of patients	Cure	Improvement	No change
Candidiasis	10	10	0	0
Dermatophytosis:				
Acute (upto 6 months)	17	12	3	2
Chronic (6 months – 2 yrs.)	12	7	4	1
Chronic (> 2 years)	12	6	6	0
T. versicolor	9	0	5	4

the table, results were particularly good in patients with acute infection with period of infection up to 6 months as compared to chronic infection with periods of infection above 6 months and even to several years. However, even in chronic infection, a cure in 13 out of 24 patients was quite encouraging. These included 5 cases which were clinically resistant to griseofulvin. Whereas the clinical evidence of disease disappeared within 3 weeks in acute dermatophytosis, it disappeared only after 4–6 weeks of therapy in chronic infection. (Table 3).

On discontinuation of clotrimazole, recurrences were observed in 7 patients who responded to a further course of treatment with the drug. Clotrimazole proved to be very satisfactory in ameliorating objective lesions. In 5 patients, even though the lesions had disappeared after therapy, itching persisted and these were categorised as improved. In one patient itching was secondary to superadded pyoderma and in another due to scabies infection. In 2 patients itching was thought to be the result of sensitization as the lesions were mildly eczematoid. Itching cleared up on appropriate additional therapy.

T. versicolor

It is usually difficult to assess the efficacy of antifungal drugs in this condition in the coloured patients since in the majority of them the predominant symptom is only secondary hypopigmentation. It is our experience that disappearance of hypopigmentation takes at least 6–10 weeks and needs additional phototherapy. Nine cases were taken up in the trial. Clotrimazole produced relief of symptoms such as itching when present, and scaling but hypopigmentation was persistent in four. In five patients some improvement (Table 2) of hypopigmentation was noticed especially in those parts of the body which were exposed to sunlight. Judging from the symptomatic improvement, clotrimazole appears to be of value in this condition. However, a clinical trial on a larger sample is necessary for confirmation.

Lotion or cream

Comparative efficacy of clotrimazole cream and solution were assessed by using these simultaneously on the left and right sides of the body in 15 subjects. Both cream and solution were found equally effective in 14 patients. In the remaining subject with disseminate trichophytosis the cream proved therapeutically superior. 4 patients felt that cream gave better results, but 3 opined that the solution was superior. The remaining 8 felt that both preparations were equally effective but considered that the cream was cosmetically more acceptable.

Tolerance

The tolerance of clotrimazole cream and solution on topical application was satisfactory in 57 patients. 3 patients had irritation necessitating discontinuaton of treatment. A 15-day old child

TABLE 3

Duration of therapy required for disappearance of symptoms in different indications

Disease	Total number of patients	1st week	2nd week	3rd week	4th week & more	No change
Candidiasis	10	5	3	1	1	0
Dermatophytosis						
Acute (upto 6 months)	17	3	3	9	0	2
Chronic (6 months – 2 years)	12	2	4	3	2	1
Chronic (> 2 years)	12	2	3	2	5	0
T. versicolor	9	0	0	0	5	4

with disseminate candidiasis also showed good tolerance to clotrimazole. It was also well tolerated in the subprepeutial transitional mucosa in subjects with balanitis.

Discussion

Dermatomycosis is a very common condition in this country being more prevalent in summer and monsoon seasons with significant morbidity resulting in loss of considerable man-hours (1). As yet, there is no single remedy which is effective in all the 4 common diseases i.e., candidiasis, dermatomycoses, t. versicolor and erythrasma, which are caused by a variety of organisms belonging to many species of superficial fungi or bacteria. Clotrimazole, a new antimycotic agent, is claimed to be well tolerated and to have a very broad action spectrum. This is confirmed by us. Weuta[18] reporting therapeutic results of clotrimazole cream and solution in 1021 and 647 patients respectively suffering from various fungal infections reported favourable response in 90% using the cream and 91% of patients using the solution. These are favourable figures. Our experience shows that results in chronic dermatophytosis may not be as good as in acute conditions. Itani[19] used clotrimazole solution for treatment of 60 patients with different dermatomycoses, out of which 54 were eligible for evaluation. He reported a cure in 49 and improvement in the other 5, there being no therapeutic failures. Fredriksson[20] found clotrimazole solution effective in both candidiasis and tinea. He reported clinical healing in 57% of cases and marked improvement in an additional 33% following 3 weeks treatment.

Polemann[21] reporting his experience over a 3 year period with clotrimazole solution or cream reported 100% cure in 65 patients of pityriasis versicolor, 51.5% cure and 36.4% improvement in 33 cases of erythrasma, 58.7% cure and 30.5% improvement in 325 patients with dermatophyte infections and 64.4% cure and 22.9% improvement in 371 patients with candidiasis. While our results for candidiasis and dermatophytosis confirm this, we wonder if 100% cure could be achieved in a condition such as P. versicolor which signifies immunologic anergy and extensive parasitoses without inflammatory response. As such, there is inadequate knowledge on the pathogenesis of this condition.

Clayton & Coonoor[22] have shown that clotrimazole cream is as effective as Waitfield's ointment for treatment of ringworm infection of the glabrous skin, pityriasis versicolor and erythrasma. Further, they reported that clotrimazole proved as effective as nystatin for treatment of candida skin infections. In our opinion, the results do not show adequate evaluation of subjective and objective symptomatology. Whitfield's ointment certainly is ineffective in many situations such as tinea pedis, athletes' foot, and chronic disseminate tinea corporis. Hence judgement based on positive microscopic and/or culture findings alone do not signify the result nor the 'disease' Desai[14] had shown persistence of microscopic fungal elements even up to 90 days from a clinically healed and normal area. This phenomenon signifies a state of 'parasitosis' or a 'Carrier' state rather than that of a 'disease' with invasive or inflammatory concordance. Not all the reports mentioned above are from tropical countries. Our results are similar to those reported by other workers except for T. versicolor infections in which the difficulties are already mentioned above. Clotrimazole appears to be very effective for candidiasis. Diabetes, steroid or antibiotic therapy, malnutrition etc., can predispose a person to candidal infection. Recurrences are common as candida are commensals in the gastro-intestinal tract in many healthy subjects. They can be secondary invadars on other skin

lesions. Clotrimazole would prove a therapeutic agent of first choice in all dermatomycoses because of its favourable skin penetrating property, possible depot action and good tolerance by majority of patients. Its wide spectrum of activity against common different pathogens make it eminently suitable for tropical areas with lack of diagnostic expertise or laboratory facilities. Clotrimazole is superior to other agents such as nystatin and hamycin for candidiasis and tolnaftate for dermatophytoses, which have efficacy against certain pathogens only.

Further experience is needed for assessment of its value for treatment of chronic and recurrent dermatophytoses. The following factors also need to be ascertained.

(a) Since clotrimazole does not produce irritation even in concentrations 32 times greater than that normally used (8) it may be interesting to find out if higher concentrations of clotrimazole would cure chronic dermatomycoses of the palms and soles as this is the area of failure of most topical antimycotic agents as well as griseofulvin. (b) Concentration in stratum corneum at various intervals after stoppage of therapy. If the drug can remain for a week or more, it would be an excellent "all purpose" fungicide which may then be used as a prophylactic in susceptible individuals.

Our preliminary experience with clotrimazole in *tinea versicolor* infections show necessity for (a) use of higher concentrations because there is no inflammatory support from the body defences (b) longer duration of therapy, possibly for more than 6-8 weeks (c) combination with melanocyte-stimulating measures such as use of tarderivatives and ultra-violet or tanning agents such as Psoralens to help early restoration of the normal pigmentation.

We do not recommend a combination of antifungal agents with steroids. We have repeatedly observed in patients who have used corticosteroids or an antifungal-corticosteroid combination that even though there is a subjective relief of itching, the drug actually helps the maintenance and growth of the organism. This becomes evident from miscroscopic examinations of the lesions which show persistent or active mycelia in apparently healed lesions. Further, as soon as this therapy is discontinued, the lesions reappear with double vigour.

To summarise, we have found clotrimazole a very useful fungicidal agent. Our favourable results with clotrimazole are all the more significant since 68% of patients had received prior treatment with questionable success. In our experience, both the cream and solution are equally suitable for treatment since they produced identical results and equal tolerance. In only three patients, it was necessary to discontinue the treatment because of irritation. Our results as regards tolerance are in line with those reported by Freis[7], Weuta[18] and Itani[19] all of whom had figures over 93%.

Acknowledgment

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PRIMARY SELF HEALING SQUAMOUS EPITHELIOMA—F. Handa, et al.

Fig. 1 Showing malignant squamous cells under high power.

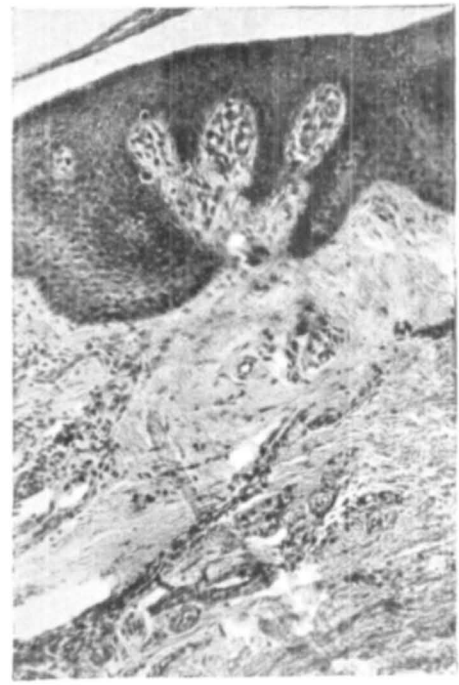
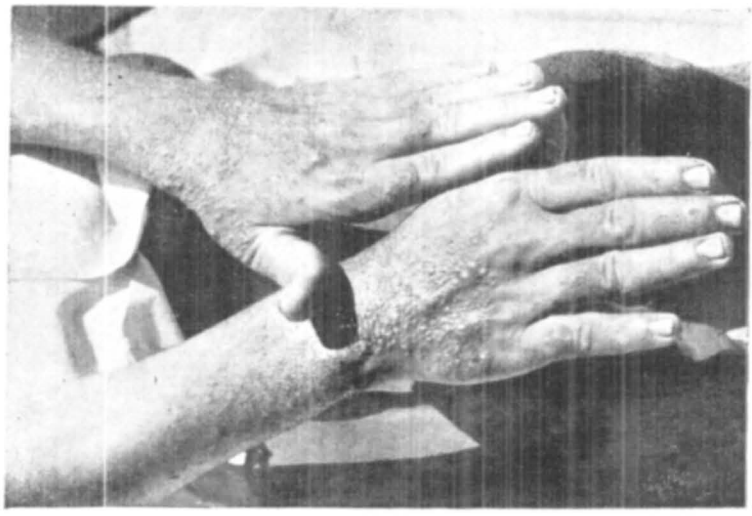
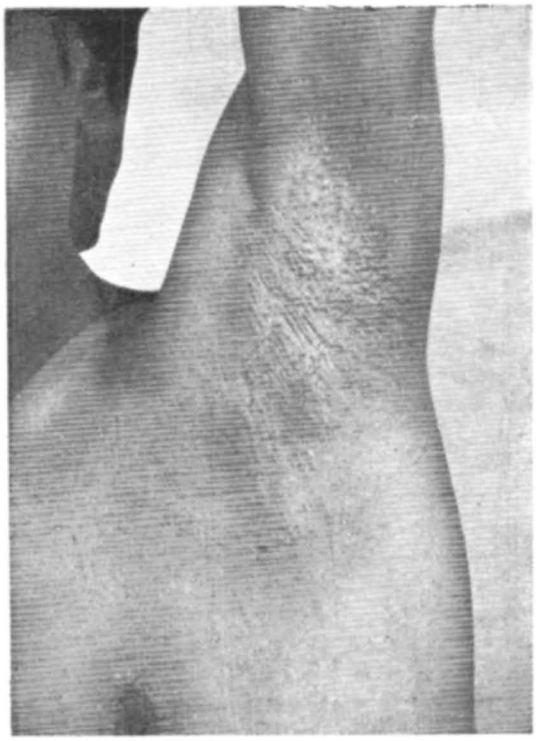


Fig. 2 Showing chronic inflammatory cells and fibrous tissue in the healed scar region.

ACNE CORNEA OR OIL-ACNE SIMULATING PITYRIASIS RUBRA PILARIS—Raghubir Singh, et al.



Shows hyperkeratotic follicular papules on the extensor aspect of both forearms, wrists, dorsum of hands and fingers.



FOX FORDYCE DISEASE —
C. F. Shah, et al.

Axilla and areola showing follicular papular lesions.

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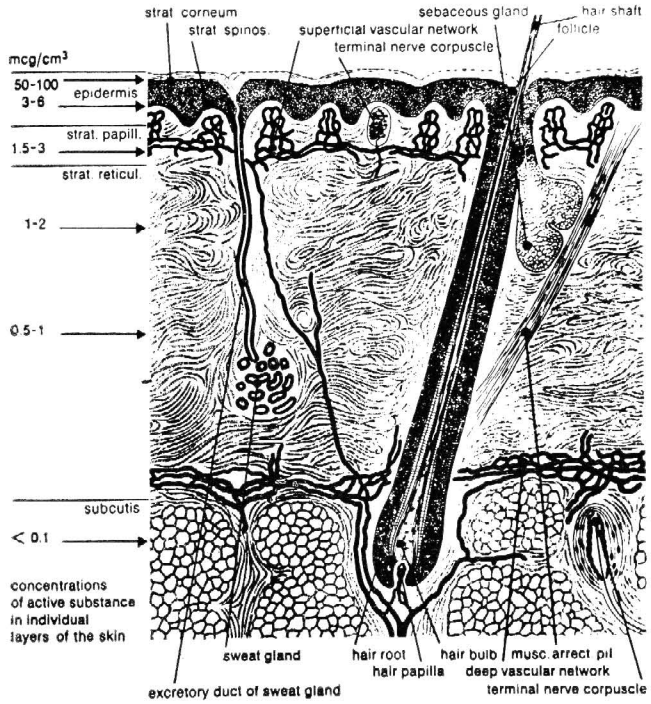

Figure 1. Concentrations of Clotrimazole in individual skin layers (Duhm et al 1972). Figures represent average values.