Dermatophyte infections

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Summary

The newer antifungal agents, clotrimazole, miconazole and haloprogin are considered for their efficacy and acceptability, and are compared with other topical agents used for the treatment of dermatophyte infections of the skin.

THE dermatophytes are a closely related group of fungi that cause infections of the keratinized tissues – the stratum corneum of the skin, hair and nails. The keratin is colonized but there is no penetration of the epidermal layers composed of living cells. A wide variety of clinical conditions is produced depending on the site of the infection and on the species of fungus responsible. The choice of treatment may well be dictated by either or both of these factors. Topical therapy alone will usually be successful in eradicating lesions of the glabrous skin, although widespread and chronic infections, particularly those caused by *Trichophyton rubrum*, and the more severe types of granulomatous lesions produced by *T. verrucosum* and other fungi of animal origin may require systemic therapy. Systemic therapy is essential for infections of the nails and hair.

A wide variety of topical preparations are in use for the treatment of dermatophyte infections. Whitfield's ointment (benzoic acid compound ointment) is still widely used in the U.K. It is effective and inexpensive but may be irritant particularly on raw and tender skin. Tolnaftate was one of the first synthetic chemical agents to show antifungal activity when used topically. It is effective against skin infections and only very few toxic or hypersensitivity reactions to it have been reported. Pecilocin is the only clinically available antibiotic, apart from griseofulvin, effective against dermatophytes but, unlike griseofulvin, it can only be used topically.

Haloprogin, an iodinated trichlorophenol compound, is one of the newer synthetic antifungal agents available for topical use. It differs from the 3 compounds mentioned above in that it is not only effective for dermatophyte infections but also for pityriasis versicolor and *Candida* infections of the

skin. This broad spectrum of activity is also shown by the imidazole derivatives, clotrimazole, miconazole and econazole, all of which are available as topical agents for the treatment of superficial fungal infections of the skin. These imidazoles also show activity against some Gram-positive bacteria so that they may also be used for the treatment of erythrasma. This broad spectrum of activity may be of particular value when facilities for laboratory mycological diagnosis are not readily available.

Many open and controlled comparative clinical investigations have been carried out to try to determine whether one topical agent is likely to be more effective or more acceptable than another. Variations in the type of infection, causative fungus, length of treatment, numbers of patients and different methods of assessing results make comparisons of reports of such studies difficult. However, a few examples are given to show that the more recently introduced imidazoles and haloprogin appear to be as efficient as other topical agents in current use.

Keczkes, Leighton and Good (1975), in a study of 41 patients with dermatophyte infections of the skin, compared 4 weeks' topical application of tolnaftate with a similar period of clotrimazole therapy. They found that, as judged by negative culture results, tolnaftate produced a cure rate of 93% compared with 95% for the group of patients treated with clotrimazole. In a double-blind trial comparing Whitfield's ointment with clotrimazole cream, Clayton and Connor (1973) found that after 4 weeks' therapy 88% of the patients in each treatment group were cured as assessed by negative culture results. In a similarly conducted trial comparing 4 weeks of treatment with clotrimazole or with miconazole, 79% of patients treated with clotrimazole were found to be mycologically free from infection compared with 83% of those treated with miconazole (Clayton and Knight, 1976). This difference was not statistically significant. Another clinical study comparing haloprogin with miconazole recorded no significant superiority for either compound when cure was assessed by negative culture results (Clayton *et al.*, 1979).

A controlled study on the comparative efficacy of tolnaftate and haloprogin in tinea pedis (Carter, 1972) found that when cure was assessed by negative laboratory findings, haloprogin gave a significantly higher cure rate than did tolnaftate. This difference was not revealed by the less objective clinical observations on improvement. The more accurate assessment of cure by mycological results compared to clinical judgement alone was also noted by Keczkcs *et al.* (1975). Only about 50% of the patients receiving tolnaftate or clotrimazole appeared to be clinically cured, whilst over 90% in each treatment group were free from infection as judged by negative culture results.

Relapse, or re-infection, still remains a problem in the treatment of dermatophyte infections. The follow-up period in many studies is too short to determine whether one antifungal compound is superior to another in completely eradicating the causative fungus.

The possibility of the development of resistance by the fungus to the drug being used for treatment should be considered. In a clinical trial comparing the topical use of clotrimazole and miconazole, all strains of fungi isolated were tested before therapy was started for their sensitivity to the drugs (Clayton, 1976). Any fungi isolated during treatment were similarly assessed for their sensitivity to these compounds (Table 1). None of the strains isolated at any stage during therapy had developed resistance to

TABLE 1. Sensitivity pattern of 53 strains of *Trichophyton rubrum* isolated from patients during a trial comparing clotrimazole with miconazole

Site	No. of weeks' treatment		
	0	2	4
Minimal inhibitory concentration (mg/l)			
Clotrimazole			
Toe webs	0.75	0.75	—
Sole	0.75	0.75	—
Hand	0.18	—	0.37
Miconazole			
Toe webs	0.75	—	0.37
Sole	0.37	0.75	0.75
Hand	0.75	0.75	—

either clotrimazole or miconazole. The emergence of resistant strains of dermatophytes during treatment with the imidazoles or other antifungal compounds used topically has not yet been reported.

The efficacy of a topical agent will depend on a high activity *in vitro* against the dermatophytes and on its ability to penetrate the skin so that an adequate concentration of the drug reaches the infecting fungus. The *in vitro* inhibitory effect on dermatophytes of the imidazoles, tolnaftate and haloprogin

was shown by Haller and Plempel (1978) to be very similar, the majority of strains being inhibited at concentrations of 4 mg/l or less. The ability to penetrate into the skin shown by the imidazoles so that even in the lower layers of the epidermis concentrations are obtained which are $\geq$ the minimal inhibitory values found *in vitro*, accounts for their success in eliminating the causative fungus.

The acceptability of the preparation will also play an important part in ensuring that it is used correctly and regularly. The majority of the topical agents now in use are non-staining and odourless. The irritant properties of Whitfield's ointment have already been mentioned. Tolnaftate appears relatively free from any side effects and this also applies to the imidazoles. Transient burning and irritation mostly occurring immediately after application and only during the first few days of treatment have been noted by a few patients using clotrimazole and miconazole. Reports of sensitization to these compounds are uncommon.

Although there are now many effective antifungal drugs available for topical therapy, griseofulvin still remains the most important therapeutic agent in the systemic treatment of dermatophyte infections, and is specific for them. It is effective against all dermatophytes and is readily absorbed when given by mouth. Long courses of therapy are almost invariably well tolerated and side effects are rare. The dosage of griseofulvin for adults is generally 500 mg to one g daily and the length of treatment is determined largely by the site involved. Scalp infections usually require 4 to 8 weeks' therapy, whilst nail infections need several months of treatment. Finger nails may be free from infection after 6 to 12 months of therapy, but the control of toe nail infections is far less certain requiring in many cases over one year's continuous treatment, even then the relapse rate is very high. The development of *in vitro* resistance to this antibiotic by fungi has not been shown to be a cause of treatment failure.

The search for new and more effective antifungal agents for use both topically and systemically will continue. These infections are still among the commonest fungal diseases encountered in medical practice. There exists a range of antifungal drugs available for their treatment, which have been shown to be effective both by their *in vitro* activity and as assessed by clinical studies. Patients' acceptance of such factors as the length of treatment and the form in which the compound is introduced may, however, ultimately decide which drug is most successful.

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