GRISEOFULVIN IN TREATMENT OF PERSISTENT FUNGAL INFECTIONS OF THE SKIN

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The recent discovery that griseofulvin can be used orally as a fungistatic, effective against the dermatophytes, represents a major advance in therapy. In this country the majority of cases of ringworm are due to infection of the feet by organisms which can be controlled by topical fungicides, albeit with a high relapse rate. In recent years, however, there has been an increased incidence of infection by *Trichophyton rubrum*, a species which gives rise to resistant and intractable infections, especially when the nails are infected, and there would appear to be a small group of people in whom infection of multiple nails by this organism has hitherto been incurable. The preliminary papers of Williams, Marten, and Sarkany (1958) and Blank and Roth (1959) have shown that this organism, like the other dermatophytes, is inhibited *in vivo* by griseofulvin, and there would appear to be every likelihood that these infections may soon be controllable.

Clinical experience of the drug is as yet too limited for a great deal to be known about the effective dosage, the duration of treatment required, the long-term results, and the possibility of toxic reactions.

The following report records the experience of two independent groups of observers who have handled the drug during the last seven months. Of the 34 patients treated, 26 have had long-standing infection of multiple nails and skin by *T. rubrum*, previously resistant to numerous lines of treatment, including surgical avulsion of nails.

In each case fungus has been demonstrated microscopically in the affected site and identified by culture prior to starting treatment. All patients have been examined and scrapings checked at regular intervals, and in 12 instances blood counts have been done daily for 14 days and thereafter at weekly intervals. In the following report an area is said to have cleared only when the clinical state has returned to normal and fungus can no longer be demonstrated microscopically or by culture; in most instances photographs have been taken to compare changes in nail infection; except in the group specified, no local treatment has been carried out.

Clinical Cases and Results

Two children with candidiasis and one man with tinea versicolor showed no clinical change as a result of treatment.

Two men showing typical cattle ringworm due to *Trichophyton verrucosum* each developed an Id

reaction two days after starting treatment (2 g. daily). This settled when griseofulvin was stopped after seven days, and the primary lesions resolved over a period of three weeks. It was not felt that the duration of infection had been significantly modified.

One man showing a vesicular infection of the instep due to *Trichophyton mentagrophytes* var. *interdigitale* was given 2 g. daily for two weeks followed by 1 g. daily for two weeks. There was immediate symptomatic improvement, but scaling persisted for five weeks and viable fungus was present in the sole for six weeks. Re-examination at regular intervals during the next three months showed the soles to be clinically normal, there being no evidence of fungus microscopically.

Infection by *T. rubrum*

(a) *Infection of Smooth Skin Only.*—Two patients, each showing typical scaling patches on the legs, were given 2 g. daily for two weeks followed by 1 g. daily for one week. Each showed subjective improvement within a few days and in one patient scrapings became negative after 10 days and have remained so over a period of six months. In the other patient, scrapings still remained positive after three weeks, and this case is still under observation.

(b) *Intractable Infection of Multiple Nails and Adjacent Palms, Soles, or Smooth Skin.*—In this group 26 patients have been treated, all of whom have had chronic infection by *T. rubrum*, in most cases of many years' duration. Nearly all patients experienced symptomatic relief as regards skin: itching disappeared from the smooth-skin lesions in two to three days, and scaling became less evident within a week, from the palms and soles in about four to six weeks. In view of the different factors, influencing infection of the smooth skin, palms, soles, fingernails, and toenails, infection in each of these sites is considered separately.

Variations in Dosage

(1) 2 g. daily for two weeks, followed by 1 g. daily for one week. Two patients, each showing infection of soles and multiple toenails, were not influenced by treatment, and fungus was still present in both sites six months after completing treatment.

(2) 2 g. daily for three weeks. In this group 11 patients were treated six months ago and have been observed at regular intervals since. Most of these patients experienced clinical improvement during the period of treatment, and in many cases this was maintained for a considerable time after treatment was stopped. In 10 patients the soles and toenails were affected. In two instances the soles cleared and have remained so for six months; in the other eight, though there was objective improvement, fungus has always been present. Occasionally toenails appeared to have improved clinically, but none has cleared. Five of these patients also had palmar and fingernail infection; in two patients the palms have cleared and have remained so, but in the other three, though there was clinical improvement, scrapings have remained positive. Growth of several fingernails has appeared to be nearer to normal, but infection has persisted in three patients. In one patient in whom infection was limited to the nail of the little finger, this nail has grown out normally, whilst, in another, two fingernails out of five infected nails have cleared. These nails cleared three to four months after the completion of treatment, and have remained clear.

(3) 2 g. daily for three weeks combined with the local application of benzoic acid compound ointment, B.P.C., to the affected site. This group, consisting of 10 patients, has also been observed for six months after treatment. All patients had infection of multiple toenails, and one patient was unable to complete treatment owing to toxic effects. While in no instances did toenails clear, in five patients they appeared to improve. Seven of these patients also had infection of the adjacent sole, and in two this has persisted, but cleared in the other five. Palmar infection was present in five patients, clearing in two but persisting in three. Several fingernails were infected in four patients and all showed clinical improvement. In one patient eight affected nails, in another one out of three, and in a third an infected right thumbnail have remained clear during the period of observation.

(4) 2 g. daily for two weeks followed by 1 g. daily for five weeks. One patient who had long-standing infection of all nails, palms, soles, and most of the smooth skin improved dramatically. The lesions of the smooth skin cleared in a fortnight and the palms and soles in six weeks. Several nails, both on feet and on hands, improved during and for three months after treatment, but fungus was still present in all nails five months after completing treatment. There has in the last two months been some relapse in the smooth skin, but both palms and soles remain clear. The second patient with infection of multiple toenails and fingernails, who was still on treatment at the time of writing, showed some clinical improvement in the nails, but fungus was still present.

(5) 2 g. daily for two months followed by 1 g. daily for 12 weeks. One patient showing infection of all toenails and soles experienced immediate symptomatic improvement, and scrapings from the soles became negative after five weeks, remaining so until the twelfth week of treatment, when a positive scraping was again obtained. There has been some clinical improvement of the nails, but fungus was still present in all of them. This patient is still under treatment.

Side-Reactions

Blood Counts.—These have been done in most cases at the same time of the day and by the same technician. In 4 out of 12 patients in whom regular blood counts have been done, considerable variation in the differential blood count was noted from day to day, but in no instance did the absolute count fall below 2,000. One patient who showed the most wide variation is referred to below.

General Reactions.—Several patients complained of headaches and some malaise, but in most cases not of sufficient degree to inconvenience them. Five patients developed erythematous rashes while on treatment; in one this cleared, though the treatment was continued, but in the others the reactions disappeared only when griseofulvin was stopped. In one of these the reaction occurred after completing three weeks of treatment, and this patient had an acute recurrence when she was given griseofulvin at a later date. Another patient who became febrile nine days after starting treatment complained of dizziness, general malaise, and fainting on two occasions, in addition to developing an extensive erythematous rash on the trunk. These symptoms settled as soon as griseofulvin was stopped. Four days later she was given a lower dosage—that is, 1 g. daily

—and after five days again became febrile and vomited on several occasions. This again ceased when griseofulvin was stopped, but she had two further recurrences each time she was given the drug, in one instance when given in conjunction with antihistamines. Blood counts taken in relation to these episodes showed no significant blood changes.

Another patient developed severe headache, nausea, and dizziness within a few hours of taking the drug, and in the course of three days her absolute polymorph count fell from 8,200 to 2,200. Her symptoms cleared when treatment was discontinued but immediately recurred as soon as treatment was resumed, her count falling from 6,500 to 2,200 in 24 hours. During the next 10 days the count showed very wide variations between 5,000 and 2,000, never falling below the latter figure. Treatment had to be discontinued because of an increase in her symptoms. This patient was shown at the North of England Dermatological Society meeting in March, and after this, on the advice of Dr. J. F. Wilkinson, she was given the drug again as an in-patient. On this occasion she had no return of her symptoms or significant change in her blood count and she has now been on treatment for six weeks.

Discussion

The above results are in line with those of Williams *et al.* (1958) and Blank and Roth (1959). Griseofulvin is ineffective against infection by *Candida albicans* and *Malassezia furfur* but does influence infection by the other dermatophytes, including *T. rubrum*. In this series the periods of treatment varied from 3 to 14 weeks. There has been considerable variation in results, but in most cases lesions of the smooth skin have cleared in 10 to 14 days and palm and sole infection in 35 to 42 days. In no instance have toenails grown out normally, though many have shown clinical improvement. In several patients fingernail infection has responded and nails have grown out normally after periods of treatment of only three weeks.

It is difficult to draw conclusions from a small series, but it would appear that the results have been better in the group in which a topical fungicide was used concurrently. For example, in four patients showing between them infection of 21 fingernails, 10 nails regrew normally. This compares with an equivalent group in which there was no topical treatment: 5 patients had a total of 17 infected fingernails, of which 3 grew out normally.

Considerable variations in response to treatment are apparent, since courses of treatment lasting only three weeks have cleared fingernail infection in some instances, while periods of treatment of 7 to 14 weeks have failed to cure infection in other patients. A number of factors can account for such discrepancies, including variation in ability to absorb griseofulvin or to accumulate it in an active form at the site of fungal growth. Equally it seems possible that not only different species but also different strains of fungi may vary in their susceptibility to griseofulvin.

Since griseofulvin is fungistatic and not fungicidal, its mode of action would seem to be by inhibiting fungal growth in its mycelial stage, so that infection is carried away by the outward growth of keratins. In the smooth skin the inhibitory effect of griseofulvin will cause the fungus to lose its foothold in the normal process of desquamation of soft keratin. The exact

rate at which this occurs on the smooth skin of the trunk and limbs is uncertain, but, arguing from the above findings, it would appear that the infected layer is shed in approximately 10 to 14 days. Desquamation in palms and soles takes much longer, probably between four and six weeks.

Nail infection presents a different problem, since here keratin does not desquamate: hence it is necessary to wait for the nail to grow sufficiently for infection to be carried beyond the free edge. Rates of nail growth differ greatly, the fingernails growing approximately four times as fast as toenails (Le Gros Clark, 1958). An average rate of growth for the normal thumbnail is 3 mm. a month (Le Gros Clark and Buxton, 1938), so at least four months must be allowed for infection of fingernails to grow out, while well over a year would be required for infection to be eliminated from the nail of the big toe.

Whether it would therefore be necessary to administer griseofulvin continuously or intermittently over such a long period can be proved only by trial and error. Since the action is one of fungistasis, any temporary fall below the concentration necessary to inhibit fungal growth would allow reinvasion to take place, either from mycelium itself or from the germination of spores which are unaffected. This effect has already been observed in the hair root (J. M. Beare, 1959, personal communication), and it would seem reasonable to suppose that a similar effect could take place in the nail. Long-continued administration of the drug would in addition raise the question of resistance developing in the fungus. This has not yet been observed in the dermatophytes, but adaptation to fungicides has been observed among plant fungi (Parry and Wood, 1958).

Increasing use of griseofulvin will clarify the position about toxicity. In our series three patients were unable to tolerate the drug, but in spite of noting some variation in the differential blood count we have insufficient evidence to say that it has a toxic effect on the bone-marrow. Further patients, not included in this series, have also shown no significant haematological change. It would, however, appear important that this possibility is borne in mind, particularly in view of the report of Paget and Walpole (1958), who showed that it had a colchicine-like action on mitoses when given intravenously in large doses.

In our present state of knowledge it would seem that a combination of surgical removal of nails, with griseofulvin systemically and possibly the subsequent use of topical fungicides, would offer the patient suffering from chronic nail infection by *T. rubrum* the best chance of cure.

Summary

Thirty-four patients with fungal infections of the skin have been treated with oral griseofulvin in a dosage of 1-2 g. daily.

Two children with candidiasis and one man with tinea versicolor showed no improvement.

Two patients infected with *T. verrucosum* derived no significant benefit.

Infection by *T. mentagrophytes* in one patient cleared after four weeks' treatment.

Two cases of *T. rubrum* infection of the smooth skin were treated for three weeks; one cleared completely and the other improved.

Twenty-six patients with long-standing *T. rubrum* infection with nail involvement were treated for periods of 3-20 weeks. The majority improved, but in only one instance was the infection eradicated.

Toxic reactions are recorded and possible reasons for the wide variations in clinical response discussed.

Some of these cases were under the clinical care of Professor J. T. Ingram, Dr. F. F. Hellier, and Dr. S. T. Anning, and we would like to thank them for their co-operation and advice. We also thank the staff of the pathological department at both hospitals, and Dr. J. F. Wilkinson for his advice on haematology, Dr. Jacqueline Walker for kindly co-operating in the mycology, and Messrs. Glaxo Limited for generous supplies of griseofulvin.

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THE MUSCULAR LESION IN HYPERTHYROIDISM

BY

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The occurrence of muscular weakness in hyperthyroidism is well recognized, but it is difficult to state exactly the incidence of muscular involvement, since normal function is hardly possible to define and mild degrees of impairment are most common. Evidence of a muscular lesion can probably be demonstrated in most hyperthyroid patients, and in some it may be the most important part of the disease. Twenty-six cases of hyperthyroidism with a varying degree of muscular involvement are described (See Table). The first two patients were seen a year before the rest of the series, and are included as examples of the rare severe form of muscle lesion (Cases 1 and 2). The remaining 24 were those of some 40 unselected hyperthyroid patients in whom evidence of a muscle lesion was particularly looked for clinically, and in many cases electromyographically, and whose progress was then followed for between one and two years.

The Muscular Lesion

In three patients (Cases 1, 2, and 3) severe muscular weakness developed acutely over the course of a few days, each patient having been hyperthyroid for a few weeks. Two of these three (Cases 1 and 2) had aching in the muscles, and one (Case 2) also had paraesthesia in the legs. Two (Cases 2 and 3) had mental confusion combined with an appearance of apathy—not real, but imposed by the profound weakness; also, the facial muscles were weak and speech became faint and indistinct, and all the voluntary muscles of the trunk and limbs were involved. Swallowing and respiration remained adequate in these patients, but deaths have been reported in similar cases, probably from respiratory insufficiency. In Cases 1 and 2 the diagnosis of hyperthyroidism was not at first considered. Both these patients responded rapidly to antithyroid treatment when