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ORIGINAL ARTICLES

GRISEOFULVIN - FINE PARTICLE FOR THE SYSTEMIC TREATMENT OF SUPERFICIAL DERMATOMYCOSES

By

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INTRODUCTION

Superficial dermatomycoses constitute one of the common skin diseases met with in clinical practice. In the past, the treatment of mycotic skin infection had been limited to the application of local anti-fungal agents. Cases used to relapse inspite of continuous local therapy. Fungus infection of nail was particularly resistant to local measures. The use of antibiotic Griseofulvin constitutes a major break through as regards the management of cases of superficial dermatomycoses is concerned. In this paper, an attempt has been made to evaluate clinically the efficacy of Griseofulvin-Fine Particle on different types of fungus infection met with in the Skin Department of Rajendra Hospital, Patiala.

BRIEF REVIEW OF LITERATURE

Griseofulvin, a metobolic product of Penicillium griseofulvum Dierckx, was first isolated and chemically characterised by Oxford, Raistrick and Simonart[1] in 1939. In 1946, Brian, Curtis and Hemming[2] isolated a fungistatic "Curling factor" from penicillium Janczewski. The following year, Grove and McGowan[3] established the identical nature of Griseofulvin and "Curling factor". The chemical structure of the Griseofulvin was worked out by Grove et al[4] in 1952. In 1955, scientists at Glaxo Laboratories showed that Griseofulvin was active in vitro against the pathogenic dermatophytes. Gentles[5] in 1958 was the first to show that guineapigs expermentally infected with fungi like Microsporon Canis and Trichophyton mentagrophyte responded quickly to small doses of Griseofulvin given orally. The same yaar, Lauder and O'Sullivan successfully treated experimental Trichophyton verrucosum infection in the calves. Paget and Walpole[7] doses to demonstrated the colchicine-like effect of griseofulvin administered in very heavy

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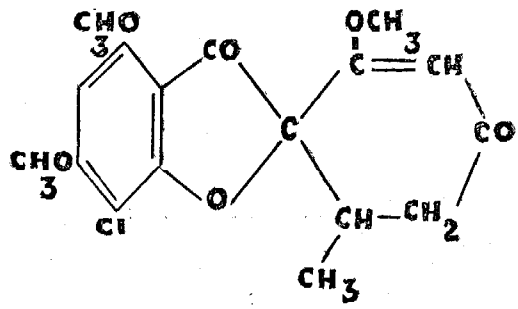
rats. William et al[8] administered griseofulvin orally, in doses of 2G daily, to patients of dermatophytosis and found 2G daily to be an effective dose without serious side effects. In 1959, S. C. Desai[9,10,11] from his preliminary experiences with griseofulvin concluded that the dosage schedule of 5 mgm./lb body weight and 7 mgm/lb body weight were inadequate. In 1962 B. N. Banerjee and A. K. Pain[12] established the clinical usefullness of griseofulvin (Fulcin) in 65 cases They noticed flareup in 5 patients during followup and three patients had mild side effects during the course of treatment. The same year, Aitkinsen, R. M. et al[13] found that the reduction in the size of the particle of griseofulvin resulted in better absorption and enabled the same blood levels to be obtained at half the dosages hitherto used with the original material. A single dose of 125 mgm. of griseofulvin in the new finer form gives approximately the same concentration of griseofulvin as a single dose of 250 mgm. of original large sized particle. The clinical trial conducted by George Harvey and J. O'D. Alexander[14] has confirmed the suggestion that a lower dose of griseofulvin in a finely divided state would be as effective as double the dose of coarser material. F. O. C. Meenan[15] administered griseofulvin F. P. to 18 children with fungus infection and reported two failures.

PHARMACOLOGY

Griseofulvin is a neutral thermostable antibiotic. Its chemical formula is given below :—



GRISEOFULVIN

(7-CHLORO-4, 6, 2 TRIMETHOXY-6 METHYLGRIS-2-EN-3, 4, DIONE)

Mode of Action: The fungi that caused ring worm live in the keratin of the skin, hair and nails. By an enzyme process, fungi can digest, live on and distort keratin. Their existance and persistence on human beings depend on their growing fast enough to avoid being cast of with the superficial keratosis and slowly enough to escape the living, lethal cells below.

Although the exact mechanism of the action of the griseofulvin is not yet known, griseofulvin from the blood stream seems to be taken by the cells destined to produce keratin so as to make newly formed keratin immune to fungal invasion. Orally administered, griseofulvin reaches the basal layer via blood stream and is

taken up by newly formed cells. Outward movement of griseofulvin protected keratin expels fungus. Gentles[5] demonstrated the formation of resistant keratin in hair of infected guineapigs after treatment with griseofulvin. Bedford et al[16] have shown that griseofulvin from the blood stream tends to give higher concentration in the skin than in other body tissues. Scott, A.[17] has demonstrated that radioactive griseofulvin concentrated particularly where fungus had accumulated.

Dosages. Adult: Four tablets (0.5 G) daily by mouth. Children: 2–3 tablets (250–375 mg.) daily by mouth or 15 mg. griseofulvin F. P./kg. body weight daily.

The length of treatment will depend on the site of infection, disappearance of clinical signs and symptoms, and absence of fungus from the infected tissue examined microscopically or tested for culture growth.

CLINICAL MATERIAL AND METHOD

Sixty two cases of common superficial dermatomycoses with varying chronicity and extent were selected for trial with Griseofulvin F. P. (Grisovin F. P.). The extent of lesion was graded from + to + + +, + for slight lesion, + + for moderate lesion and + + + extensive lesion. Care was taken to include those cases in the trial to whom the drug had not been exhibited previously at any period of their illness. Cases of Pityriasis versicolor and candidiasis were not included keeping in mind the poor results of treatment by other workers. The clinical diagnosis in each case was confirmed by cultural examination. To an adult, griseofulvin F. P. was administered in the dosage of 250 mg. twice daily. Dose for child was proportionately reduced and calculated according to 15 mg./kg. body weight daily. The duration of treatment was adjusted according to the site, extent and duration of disease. Local anti-fungal treatment was simultaneously instituted with a view to keep the concentration of fungi low on the surface of the skin, and thus minimise the chances of reinfection. Patients were told to observe hygenic precautions as far as possible.

CLINICAL OBSERVATION AND RESULT

Sixty two cases were observed during the trial and results are tabulated below:—

I. *Age and Sex:* Although age and sex has got little importance, the present study included 38 males, 24 females, including 6 children. The age varied from 4 to 60 years.

II. *Contact with pet animals*: Eight cases gave positive history of contact with pet animals, and in 54 the history of contact was negative.

III. *Aetiological Agent*: Large majority of cases of ring worm were caused by the Trichophyton, few by Epidermophyton and 1 by Microsporon group.

The spectrum of fungi treated with Griseofulvin FP is tabulated in table No. I

TABLE No. I

A. ***Single Type***

Type of fungus	No. of cases
1. TRICHOPHYTON	
i) T. interdigitale	29
ii) T. mentagrophyte	23
iii) T. schonleini	2
2. EPIDERMOPHYTON	
i) E. floccosum	5
3. MICROSPORON	
i) M. audouini	1
Total	60

B. ***Combined type***

Type of fungus	No. of cases
1. Trichophyton interdigitake + Epidermophyten flaccosum	1
2. Trichophyton mentagrophyte + Epidermophyton floccosum	1
Total	2

IV. *Type of disease*: Type of the disease, clinical pattern-single and combined with the number of cases are tabulated in Table No, 2 below.

TABLE No. 2

A. ***Single clinical pattern***

Type of disease	No. of cases
i) Tinea Capitis	2
ii) Tinea Barbae	2
iii) Tinea Corporis	14
iv) Tinea Manuum	13
v) Tinea Unguium	7
vi) Cheiropompholyx	2
vii) Tinea Cruris	6
viii) Tinea Pedis	8
Total	54

B. ***Combined clinical pattern***

	Type of disease	No. of cases
i)	Tinea Manuum and Tinea Pedis	1
ii)	Tinea Corporis and Tinea Unguium	1
iii)	Tinea Manuum and Tinea Unguium	1
iv)	Tinea Cruris and Tinea Axillaris	2
v)	Tinea Cruris and Tinea Barbae	1
vi)	Tinea Cruris and Tinea Pedis	1
vii)	Tinea Cruris and Tinea Corporis	1
	Total	8

V. *Extent of disease*: The extent of disease is graded from one to three plus. The number of cases is shown against each grade in the Table No. 3 below.

TABLE No. 3

	Extent of disease	No. of cases
i)	Slight +	17
ii)	Moderate + +	30
iii)	Extensive + + +	15
	Total	62

VI. *Duration of illness*:

Maximum — 10 years.

Minimum — 1 month

Average — 23.01 months appx.

The duration of illness with number of cases is tabulated below in Table 4.

TABLE No. 4

Duration of illness	No. of cases	Duration of illness	No. of cases
0—3 months	9	37—48 months	3
4—6 ,,	9	49—60 ,,	1
7–12 ,,	14	61—72 ,,	4
13–18 ,,	5	73—84 ,,	–
19–24 ,,	8	85—96 ,,	1
25–30 ,,	2	97–108 ,,	–
31–36 ,,	5	109–120 ,,	1
Total	62		10

VII. *Duration of Griseofulvin-FP Therapy*:

The table No. 5 below shows the duration of griseofulvin FP therapy and the number of cases treated.

Maximum — 24 weeks
Minimum — 3 weeks
Average — 7.9 weeks appx

TABLE No. 5

Duration of treatment	No. of cases	Duration of treatment	No. of cases
3 weeks	1	10 weeks	2
4 ,,	2	11 ,,	–
5 ,,	1	12 ,,	7
6 ,,	35	13 ,,	–
7 ,,	3	14 ,,	3
8 ,,	5	24 ,,	2
9 ,,	1		
Total	62		14

VIII. *Result of Therapy*: The result of therapy was assessed in terms of disappearance of signs and symptoms. Accordingly the result was graded clinically i) complete cure, ii) partial cure iii) failure and iv) recurrence.

TABLE No. 6

	Result	No. of cases	percentage
i)	Cemplete	50	80.6%
ii)	Partial	11	17.7%
iii)	Failure	1	1.6%
iv)	Recurrence	6	9.6%

IX (a) Symptomatic result in cases of fungal infection of smooth skin is tabulated in Table No. 7 (a).

(b) Symptomatic result in cases with Tinea Ungium alone and combined with Tinea Pedis and Tinea Capitis is tabulated in Table No. 7 (b).

X. *Side effects*: Side effects observed during Griseofulvin FP therapy are given in table No. 8 below.

TABLE No. 8

Symptom / No. of cases				
Headache	Gastro-intestinal discomfort	Urticaria/ allergic rash	Erythema multi-forme	Id eruption
2	5	2	1	1

TABLE No. 7 (a)

Symptom / signs	Day on which relieved / Number of cases																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
i) Itching	4	14	14	8	3	7	1	–	–	1	–	1	–	–	–	–	–	–	–	–
ii) Erythema	–	1	4	8	4	13	6	5	1	3	–	–	–	1	–	–	–	–	–	–
iii) Infiltration	–	2	2	4	8	12	9	6	2	2	–	–	–	1	–	–	–	–	–	–
iv) Scaliness	–	–	–	–	1	1	4	2	6	10	4	5	6	4	3	4	1	–	–	–
v) Nodulation	–	–	–	–	–	–	–	–	–	–	–	–	–	2	–	–	–	–	–	1
vi) Pigmentation	No change with treatment.																			

TABLE No. 7 (b)

Symptom / sign	weeks in which relieved / no. of cases.																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
i) Dystrophy of nail								1 F				4 c		2 c						1 c				1 p
ii) Growth of hair				1	2	2																		

'c' complete cure.

'p' partial cure.

'F' failure.

DISCUSSION

Although the fungi are the oldest known parasites of man and animals, the specific treatment of the disease caused by them is still far from complete. Superficial dermatomycoses varied in its response to local therapeutic measures. The time honoured Whitfield ointment held a place of pride till the discovery of griseofulvin. For the fisrt time an orally administered drug, griseofulvin, has been effective in curing superficial dermatomycoses. The drug supplied by Glaxo Laboratories was given to patients in 1958, more or less simultaneously, by three independent groups of workers, Williams & Associates[8] in London, Riehl Riehl[18] in Vienna, Harvey Blank[19] and colleagues in U. S. A. These clinical trials showed the efficacy of griseofulvin as an effective anti-fungal antibiotic.

In India clinical studies were made by S. C. Desai and associates[9,10,11] in 1959 from Bombay, Dass Gupta et al[20] in 1959, R. N. Gupta et al[21] in 1959 from Utter Pradesh, B. N. Bannerjee and Pain[12] in 1962 from Calcutta. These studies have established the value of griseofulvin as a powerful effective antifungal agent. Resistant cases of ring worm infection, which defied all local measures in the past, cleared with dramatic rapidity. Peterkin[22] showed that griseofulvin was ineffiective when applied locally.

From the medical literature published in Punjab, no reference is available on this subject. This fact provoked me to undertake this study espacially with griseofulvin fine particle. The species and incidence of fungal infection vary widely from country to country and from town to town. The social status and habits of population affect the incidence of infection. These observations further convinced me in taking up the study of the clinical effect of griseofulvin fine particle on the species of fungi prevelant in this part of the country.

AGE & SEX

Age and sex have no importance in the treatment of fungus infection but for the fact that lesser dose is required for children. The present study included 38 males, and 24 females. Age varied from 4 to 60 years, 6 being children. S. C. Desai and Bannerjee's studies were counducted with griseofulvin alone.

CONTACT WITH PET ANIMALS

In the present study 8 cases gave history of contact with pet animals, in 54 contact history was negative. No such observation has been made in previous studies reported from India.

AETIOLOGIACAL AGENT

This study contained 29 cases of Trichophyton interdigitale, 23 cases of Trichophyton mentagrophyte, 2 cases Trichophyton schonleini, 5 cases of Epidermophyton, 1 of Microspon infection. The regional prevalence of the species of the aetiological fungi is not the same as reported by other workers namely S. C. Desai,[9,10,11] B. N. Bannerjee and A. K. Pain[12].

TYPE OF DISEASE

The type of disease, in which the effect of griseofulvin FP was studied included 51 cases of smooth skin infection including the cases with disease of more than one site. Tinea Unguium 7, Tinea Capitis 2, Tinea Barbae 3, Cases of Candidiasis and Tinea versicolor were nor included keeping in mind the poor results obtained by other workers namely Bannerjee and associates[12] (1963)

DURATION OF ILLNESS

In this study the maximum duration of illness was 10 years, minimum 1 month. Maximum illness in Bannerjees[12] series was 22 years, minimum was 15 days. Preliminary observation, reported by S. C. Desal and associates in 1959 included patients with illness of 6 months to 12 years standing.

In has been concluded that the length of the treatment with griseofulvin varied with the duration of illness of the patient. Other fiindings are in general agreement with other workers.

EXTENT OF DISEASE

In the present series 30 cases were with moderate disease, 15 cases with extentsive and 17 mild. Cases with moderate to extensive disease required longer period of treatment as compared with mild cases. The daily dose griseofulvin FP was not alterad by the extent of the disease, but total amount of griseofulvin FP required to cure the disease was more in moderate to extensive cases as compared with miid cases. These findings are in agreement with other workers.

DURATION OF GRISEOFULVIN FP THERAPY

In this study the minimum duration of griseofulvin FP therapy was 3 weeks, maximum was 24 weeks and the average was 7.9 weeks appx. Most of the cases required treatment varying from 4 to 6 weeks. The duration of treatment varied with factors like chronicity, type and extent of disease. It was concluded that the cases with Tinea Unguium and Tinea Manuum required the longest period of treatment. These findings are in general conformity with those of other workers viz. S. C. Desai[9] (1959), Harvey Blank et al[23] (1959), Bannerjee and assocites[12] (1962). The average duration of treatment given to cases of this series was 7.9 weeks appreximately. This finding is at variance with other workers. The average duration of treatment is longer.

SYMPTOMATIC EFFECT OF GRISEOFULVIN FP

Itching disappeared in the majority of cases on 2nd or 3rd day. in few as late as 12th day.

Erythema took 2–14 days to disappear after the institution of griseofulvin FP therapy.

Infiltration cleared off in 2–14 days after the commencement of treatment. Majority of the cases showed clearance on 6th or 8th day of therapy.

Scaliness: scales disappeared from the lesion in 5 to 7 days. Majority showed clearance in 7 to 14 days.

Pigmentation was more marked in cases of long standing especially with cases of Tinea Cruris. It was uneffected by griseofulvin FP therapy. It is further concluded that pigmentation is unrelated to the activity of the disease.

Lystrophy of nails: Dystrophy of nails disappeard very gradually with griseofulvin FP. Healthy growth of the finger nails was seen 2–3 weeks after the commencement and was completed in about 12 weeks time. This growth was rapid in the begining, slow in later stages.

Growth of hair: Griseofulvin FP replaced the diseased hair by normal hair in four to 6 weeks time.

These clinical findings are in general agreement with other workers, (9,10,11,12,23).

RESULT OF GRISEOFULVIN FP THERAPY.

In this clinical study of 62 cases, 50 cases were completely cured, 11 cases were partially cured, 1 failure, 6 cases have recurrence after a variable period of 2–8 months after the cessation of treatment. Failure of griseofulvin FP treatment was noticed in 1 case of Tinea Unguium. In Bannerjee's series, 45 cases were completely cured, 15 failed to respond, 5 cases still on treatment, 5 relapsed after a period of 1 to 2 weeks. Cases in whom griseofulvin failed to effect cure were those of Tinea Versicolor and Candiasis.

RECURRENCE AFTER GRISEOFULVIN FP THERAPY

A large number of cases of ring worm are cured, occasionaily few cases may return with the condition. Since the follow-up period in quite a number of studies has not been sufficiently long, it would be difficult to say whether recurrence would occur quite frequently or less frequently after the cessation of treatment. In the present study, the recurrence of condition was noticed 2–8 months after cessation of treatment with griseofulvin FP. It is to be surmised that this recurrence could have been due to either fresh infection or relapse. Chances of relapse are less since the patients were given treatment for a comparatively longer period and moreover the cases in which recurrence occured it occured quite sometime after stopping the treatment. Although the topic of relapse vs reinfection is debatable; in the opinion of the author, these cases of recurrence were, in all liklihood, the cases of reinfection since the local factor and environments responsible for reinfection for that particular individual remain unaltered. It has been aptly commented by J. Walter Wilson[24] (1959) that people infected with Trichophyton rubrum are immunologically defective in some way. The griseofulvin does not change this fundamentalimmunological system, hence they are more prone to become reinfected and deserve treatment in the same manner with griseofulvin as we use insulin for diabetics. M. Beare[25] has recommended a long term maintenance dose of a tablet of griseofulveln once weekly for an indefinite

period. He was able to ward off relapses in case of Tinea Cruris and Pedis over a period of 2 years. In the personal opinion of the authour, although the above measure seems to be praiseworthy, but this use of griseofulvin as a chemo-prophylactic agent for and indefinite period seems to be impracticable in the type of cases seen by him.

SIDE EFFECTS OF GRISEOFULVIN FP THERAPY

In this study, side effects were seen in 11 cases out of 62 cases treated with griseofulvin FP. Nine cases had mild side effects which did not warrant the suspension of the treatment. One case showed erythemamultiforme like lesion, and another one with Id eruption on palms. In this series, gastrointestinal side effects like nausea, thirst, abdominal discomfort and diarrhoea were conspicuous. These findings are in agreement with the other workers (9,10,11,12,26). It is further concluded that these mild side effects require only symptomatic treatment.

SUMMARY & CONCLUSIONS

1. Sixty two cases of common superficial dermatomycoses with varying extent of disease and chronicity have been studied to assess the therapeutic efficacy of griseofulvin FP.

2. Griseofulvin FP seems to have a remarkable curing effect on a wide variety of superficial fungus infection of the skin and its appendages. It cures fungus infection completely in 80.6% of cases.

3. Follow-up was carried out in most of the cases. In one case of proved fungus infection there was no response to griseofulvin FP, Six cases showed recurrence after complete cure. Recurrence occured 2-8 months after cessation of therapy. They seem to be cases of reinfection rather than relapse, 11 cases showed complete symptomatic improvement with partial objective improvement. These cases included 5 cases of Tinea Pedis, 3 cases of Tinea Manuum, 3 cases of Tinea unguium.

4. Side effects were noticed in 11 cases out of 62, 9 had mild side effects like gastrointestinal discomfort, nausea and diarrhoea, headache, urticaria. 2 patients developed erythema multiforme and Id eruption.

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