Treatment of Superficial Fungal Infections

Value and Limitations of Systemic Administration of Griseofulvin

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The development of an antibiotic, griseofulvin, that has been used successfully in systemic treatment of superficial fungal infections has revolutionized dermatologic therapy in this field in the short time it has been available. While superficial fungal infections are not a cause of death, the incidence is high, many cases are extremely chronic, especially when involving hair, nails, and feet, and they can cause considerable annoyance and disability.

As with any new drug, improper use will tend to discredit it. It is timely therefore to review briefly the extensive literature that has accumulated in a very short time with reference to the conditions in which it is effective, its proper dosage, the results of treatment, side effects and some personal observations.

Blank and Roth of the Dermatology Department of the University of Miami were the first in this country to report the successful use of griseofulvin in fungous diseases of humans. Dr. Blank and the Department of Dermatology of the University of Miami were hosts to an international symposium on griseofulvin and dermatomycosis in October 1959, and the proceedings of this symposium are contained in the May 1960 issue of the A.M.A. Archives of Dermatology which is devoted exclusively to this subject.

Conditions Benefited by Griseofulvin

Oral administration of griseofulvin has been reported effective, in general, against the large class of chronic superficial fungal infections of the "ringworm" group. The drug is completely ineffective against fungi of the yeast group, such as candida (monilia), microsporon furfur which causes tinea versicolor, all of the bacterial infections and most of the deep mycotic infections. Acute inflammatory superficial fungal infections respond more readily to topical treatment. Griseofulvin has revolutionized the treatment of scalp ringworm of all types, and of nail, foot and hand conditions caused by the extremely resistant Trichophyton rubrum.

Comprehensive studies and numerous clinical reports have shown that griseofulvin orally in a dose of 1 gm. daily is an effective treatment for superficial fungal infections of the skin, hair and nails. The drug is not effective against yeast infections (moniliais), bacterial infections or most of the deep fungous infections.

Duration of treatment varies with the site of infection, glabrous skin, crotch and scalp responding within four to five weeks. Infections of palms, soles and nails require a considerably longer time, palms healing more quickly than soles and fingernails more quickly than toenails, which may require up to a year of continuous treatment.

Auxiliary measures such as clipping hair, removing infected nail tissue and topical fungicides shorten the duration of treatment.

No serious side effects have been reported. Minor discomforts such as headaches and mild rashes occur in some cases.

Observations of a series of 49 patients with superficial fungous infections, especially hand, foot and nail infections due to Trichophyton rubrum, confirmed these reports taken from the literature. Attempts to use a reduced dosage schedule did not prove satisfactory.

It is necessary, therefore, that a diagnosis be established before treatment is begun, since it would be a waste of time and money to attempt to treat conditions which might superficially resemble fungous infections, such as psoriasis, especially of the nails, or contact dermatitis or intertrigo or chronic paronychia due to yeasts. Cultures and direct microscopic examination of scrapings after maceration in 40 per cent potassium hydroxide are invaluable guides for proper treatment as well as for confirmatory evidence of cure.

Mode of Action of Griseofulvin

The reason many superficial fungous infections are resistant to external therapy is that the organisms are embedded deep in keratinous material where topical applications do not reach. Furthermore, the fungi grow downward at the same rate that epidermis, nails and hairs grow upward, thereby staying beyond the range of surface treatment.

Griseofulvin is a fungistatic but not fungicidal antibiotic derived from at least four species of peni-
cillium. When administered orally, it is carried by the bloodstream and is deposited within the lower corneous layers, thus placing it in direct contact with the infecting organisms. Experiments suggest that griseofulvin directly intervenes with the synthesis of nucleic acid in the growing hyphae that are in contact with the drug but that the drug is not diffused through the older, more dormant portions of the fungi. Hence, downward growth is halted and the dormant fungous elements are gradually pushed to the surface. If treatment is discontinued too soon, these dormant elements may resume downward growth and the infection becomes reestablished. In patients who have been treated with griseofulvin, spores and abnormal bits of hyphae have been found to persist for as long as 90 days on clinically healed areas. These phenomena and the observation that griseofulvin is gradually leached out of the upper epidermal layers by perspiration and other means, leaving very little near the surface, suggest the advisability of using topical fungicides concomitantly, especially those containing salicylic acid which mechanically assists in removing the attenuated fungi.

**DOSEAGE**

Various dosage schedules have been tried, but the consensus favors 1 gm. daily in divided doses of 250 mg. each over a period of four weeks to twelve months or more, depending upon the location of the infection. The dosage should be reduced proportionally for children under 12 (10 mg. per pound of body weight).

Scalp, glabrous skin and crotch infections clear the most rapidly, cure often being obtained within four or five weeks. Areas with thicker keratin such as palms, soles and nails require much longer periods for clinical and mycological cure, palms responding more quickly than soles or sides of heels, and fingernails more quickly than toenails. Goldfarb and Sulzberger reported only 2 out of 48 patients with toenail involvement were cured at the end of 10 months' continuous treatment with griseofulvin.

Auxiliary measures reduce the length of treatment. In scalp ringworm, the infected hairs should be cut close or shaved within one or two weeks after beginning treatment. Removal of infected nails should be carried out by scraping, clipping or grinding with a portable dental drill, by softening with strong keratolytic agents or by surgical avulsion.

One exception to the standard schedule of 4 tablets (1 gm.) a day is scalp ringworm. It has been found that, especially in clinic practice where large numbers of children are affected, a single dose of 3 gm. of griseofulvin at one time is an effective procedure. According to Derbes, the "loading dose" method assures adequate treatment at the clinic, is more economical in both time and money, is equally effective and is no more likely to produce side effects. Derbes advised clipping or shaving the hair close within two weeks of administering the single dose, and he reported that 22 out of 23 patients were cured within a period of observation of 12 weeks after such a single dose. Even extremely chronic and resistant types of scalp infections such as favus and Trichophyton tonsurans respond readily to griseofulvin.

Fluorescence of hairs when examined under filtered ultraviolet (Wood's) light is altered by griseofulvin and is not a reliable criterion in determining whether infection has been eliminated from the scalp.

Evidence regarding the development of resistance to griseofulvin is conflicting. Most in vitro experiments indicate that resistance to the drug does not occur, but several clinical observations of patients receiving inadequate dosage suggest that it can.

**TOXICITY AND SIDE EFFECTS**

Experiments with rats demonstrated that, when administered orally, griseofulvin did not have toxic effects even in large doses, but when given parenterally it is a mitotic poison, affecting mitosis much as colchicine does. Human spermatogenesis is not affected.

No serious reactions have been reported. Minor side effects occurred in approximately 20 to 30 per cent of several fairly large series of cases, but in many cases they were transitory, often developing early in the course of treatment and disappearing without discontinuance of therapy. They include headache, nausea, vomiting, diarrhea, gastric discomfort, pharyngitis, dizziness, drowsiness, fatigue, insomnia, pruritus, morbilliform eruptions, urticaria, purpura, mild albuminuria, slight depression of the number of leukocytes, especially of the polymorphonuclear forms, menstrual disturbances, muscle cramps, urinary frequency, aphthous stomatitis, photosensitivity and loss of memory. There is usually no cross-sensitivity to penicillin. No changes in liver function or kidney function or in chemical components of the blood have been noted. In five patients who were taking steroids for other conditions, the fungous infection did not respond to griseofulvin. Moniliasis developed in a few patients while they were taking griseofulvin for other fungous infections.

When administered to patients with fungous infections who also had other diseases, griseofulvin had no effect either favorable or unfavorable on the other diseases, which included active tuberculosis, rheumatoid arthritis, cholecystitis, hypertension, arteriosclerosis, coronary thrombosis, pulmonary tu-
berculosis, gout, ulcerative colitis, chronic glomerulonephritis, sarcoidosis and myelogenous and lymphatic leukemia.\textsuperscript{10}

On the other hand, Cohen and coworkers\textsuperscript{5} reported beneficial results, at times striking, in 12 patients with shoulder-hand syndrome unaccompanied by fungous infection. The cases included postcoronary, posthemiplegic and idiopathic types. The observations were controlled with placebos. The authors were unable to offer a scientific explanation for the results.\textsuperscript{5}

**PRESENT SERIES**

We administered griseofulvin therapy to 49 patients with superficial fungous infections, most of whom had chronic, dry, scaly eruptions characteristic of Trichophyton rubrum infections. In most cases the infection was of many years' duration and involved the soles, sides of the feet, one or both palms and usually fingernails and/or toenails. In all cases the diagnosis was confirmed by direct microscopic examination of scrapings macerated in 40 per cent potassium hydroxide, and by culture also in 25 cases.

One patient, a woman with generalized scleroderma, had a single lesion on the scalp due to Trichophyton tonsurans which healed completely in five weeks.

The dosage schedule for the first six months was four 250 mg. tablets every day for two to four weeks, then either three tablets every day or four tablets a day for two or three days a week. As it soon became apparent that while improvement usually occurred, the infection was not controlled, the dosage was restored to four tablets daily; and later, in addition to the griseofulvin, externally applied fungicides such as Whitfield's ointment, which has a desirable exfoliating effect, were used. Also added to the regimen was grinding the nails with a portable dental burr and instructing patients to keep the nails scraped.

Of 45 patients with chronic hand, foot or nail involvement, 11 were cured in periods ranging from seven months to a year or more. Twenty-three patients discontinued treatment within periods of three months or less, after showing varying degrees of improvement. Recrudescence is probable. No serious side effects were observed. Fine rashes developed in two patients, one had swelling of the face and eyelids and one had a persistent bluish discoloration of the previously affected fingernails after all clinical and microscopic evidence of infection had disappeared. Moniliasis between the toes and in the crotch developed in one patient while under treatment for Trichiliasis between the toes and in the crotch developed in one patient while under treatment for Trichophyton rubrum infection of the feet and nails. One patient with chronic dry, scaly lesions of Trichophyton rubrum developed vesicles after starting to take griseofulvin. Three patients complained of headache, one of them while taking four tablets a day but not with three a day; one patient had headaches during the first course of treatment but not with a second course; one person had both headache and backache, and one patient complained of pain in the neck and shoulders. Diarrhea occurred in one patient and lasted until he discontinued the drug after four weeks.

2007 Wilshire Boulevard, Los Angeles 57 (Ayres, Jr.). McNeil Laboratories, a subsidiary of Johnson and Johnson, supplied Grifulvin\textsuperscript{9} and Schering Laboratories supplied Fulvicin\textsuperscript{9} for this study.

**REFERENCES**