Influence of Griseofulvin upon Acute Gouty Arthritis

By ROBERTE R. SLONIM, DAVID S. HOWELL AND HARVEY E. BROWN, JR.

Antiphlogistic properties of griseofulvin, a fungistatic antibiotic, were demonstrated in patients with acute gouty arthritis. By use of moderate-to-high dosages, complete remissions appeared in 14 patients and partial remissions in 2 within 24 to 48 hours. Side effects of the drug were negligible.

Le proprietates antiphlogistic del antibiotico fungistatic griseofulvina esseva demonstrate in patientes con acute arthritis guttose. Le administration de doses moderate o elevate esseva sequite, intra 24 a 48 horas, de remissiones complete in dece-quatro patientes e de remissiones partial in duo. Le adverse effectos secundari del esseva negligibile.

ALTHOUGH COLCHICINE, phenylbutazone and adrenocorticosteroid derivatives effectively reduce or abolish manifestations of acute gouty arthritis, they are not ideal remedies because of well known side effects which may attend their usage.[1-4] Interest in other compounds worthy of clinical trial led to consideration of griseofulvin. Antiphlogistic action of griseofulvin in animals under a variety of experimental conditions has been documented.[1,8] Its isolation from penicillium griseofulvum[6] was originally described in 1939 by Oxford, Raistrick and Simonet, with subsequent identification as a spirane derivative (fig. 1).[7,8] Potent antifungal properties in plants,[9] animals[10] and man[11] have been amply demonstrated. The current study was designed to evaluate the effect of griseofulvin in management of acute gouty attacks.

METHODS

Patient selection. Of the 23 patients with acute gouty arthritis in the series, 21 were males; 19 had arthritis exceeding one year's duration (table 1). Basis for the diagnosis of gout consisted of observations made between November 1958 and May 1961 at the Jackson Memorial Arthritis Clinic. Included were histologic demonstration of tophi in 15 patients; dramatic clinical improvement in 22 patients during colchicine trial administered by standard technic for a previous acute attack;[12] two or more serum uric acid levels greater than 6.5 mg. per cent in 22 cases: and x-ray evidence of bone destruction in 17 of the group. At least once during the course of the disease, podagra was recorded for all; nocturnal occurrence of acute attacks in 20 and hypertension in 11. Negative tests for the rheumatoid factor by the method of Singer and Plotz,[13] as well as negative LE preps by the Conley technic,[14] were demonstrated for all. At the beginning of griseofulvin treatment, the 23 patients were undergoing acute attacks of gouty arthritis; 7.3 days average duration (range 1 to 21 days). Heat, erythema, swelling and tenderness were recorded for all in 1 to 3 joints, including the tarsals in 4 patients; metatarsals in 8; ankles, 13; knees, 8; wrists, 5; and elbow, 1. Response to griseofulvin was observed and arbitrarily graded by the authors according to a point system based on improvement in the above findings: complete remis-

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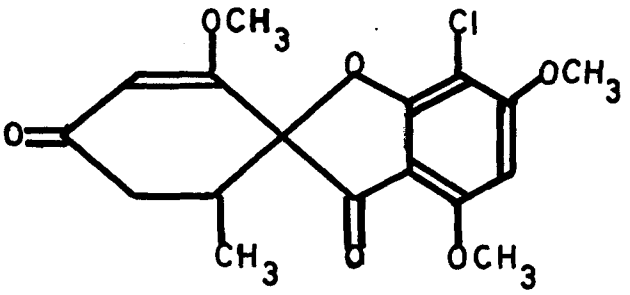
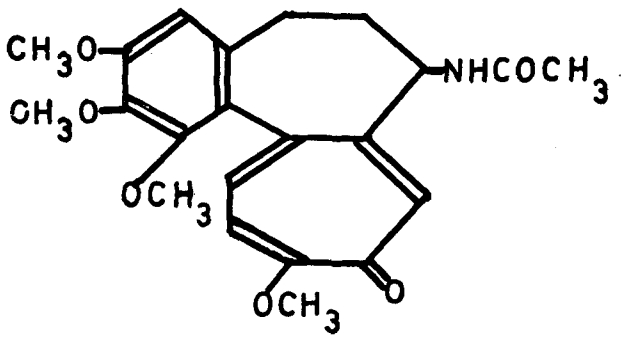


GRISEOFULVIN



COLCHICINE

Fig. 1.—Currently accepted structure of colchicine and griseofulvin. The compounds are unrelated chemically.

sion (90 to 100 per cent), moderate improvement (50 to 89 per cent), slight or no improvement (0 to 49 per cent) (table 3). A control group, patients with painful arthritis of nongouty origin, was studied for analgesic and nonspecific antiphlogistic effects of the drug (table 4).

Dosage schedule. One-to-four Gm. of griseofulvin was given orally at the onset of the study to the gouty patients, with further dosage at 6 hour spacings (table 2). Eighteen of these patients received 4 to 10 Gm. total dosage during the first day and 0 to 6 Gm. on the second. Higher doses were prescribed for 5 patients to demonstrate, if possible, an effect on serum and urine uric acid concentrations (table 5). Nineteen control patients received 3 to 4 Gm. of griseofulvin and 8 additional patients with acute rheumatoid arthritis had daily doses of 6 to 8 Gm. administered during an experimental period. Except for the latter patients, who received small maintenance dosages of adrenal corticosteroid derivatives, no other drugs were given concurrently with griseofulvin.

Laboratory methods. Serum and 24 hour urine uric acid concentrations before and after treatment were determined by a modified Folin's colorimetric method.[15] Serum levels of griseofulvin (fig. 2) were analyzed by the spectrophotofluormetric assay method of Bedford, Child and Tomich[16] with further details of procedure reported by Weinstein and Blank.[17]

Table 1.—*Clinical Characteristics of 23 Patients with Gouty Arthritis

Description	No. of patients
Male	21
Female	2
Duration of arthritis > 1 year	19
Intermittent attacks in early clinical course	20
History of nocturnal attacks	20
Podagra	23
"Diagnostic" response to colchicine (> "90% improvement" after 24 hours of treatment)	22
Serum uric acid > 6.5 mg.%	22
Biopsy of tophi	15
X-ray evidence of bone destruction	17
Hypertension B. P. > 170/90 mm.Hg.	11
Negative F-II latex test and LE prep	23

*Their ages averaged 58 years.

Table 2.—*Dosage Schedule of Griseofulvin for Patients with Gout*

No.of patients	Initial (Gm.)	Additional 1st 24 hours Gm./day	Additional 2nd 24 hours Gm./day
5	1	3	0
13	4	2–6	2–6
5	4	7–12	6–8

Table 3.—*Clinical Course during Griseofulvin Treatment of Group Afflicted with Gout

Grade of response (Reduction of acute symptoms and signs)	No. of patients	
	Duration of griseofulvin administration	
	24 hours	48 hours
Remission (90–100%)	10	14
Moderate improvement (50–89%)	5	2
Slight or no change (0–49%)	8	7

*Six of the 7 patients who failed to improve by 48 hours were no better following a course of colchicine received during the same gouty attack.

Results

Within 48 hours of commencing griseofulvin treatment, 14 patients were in complete remission and another 2 were moderately improved (table 3). Seven patients had slight or no amelioration; however, all but one of these suffered gastrointestinal distress prior to treatment and vomited an unknown fraction of the griseofulvin tablets. Six of the latter patients received a 24 hour course of colchicine (4.8 to 7.2 mg.) without benefit during the current attack. The remainder of the series had no gastrointestinal complaints. One patient (W. E.) developed a generalized maculopapular eruption 7 days following the griseofulvin trial, but received the same drug for a subsequent gouty attack with no dermatologic mishaps.

Table 4.—*Brief Doubleblind Trial of Griseofulvin in 27 Control Patients with Nongouty Arthritis**

	No. of patients exhibiting grade of symptomatic improvement		
	None	Slight	Moderate
Rheumatoid arthritis (acute)	5	7	3
Osteoarthritis	5	6	1

*Colchicine was administered, 7.2 mg. the first day and 1.2 mg. daily for 3 days; a lactose placebo and griseofulvin were given in doses of 3–8 Gm. daily. Results listed are for griseofulvin in comparison to the placebo, evaluated compositely by a point system in respect to duration of morning stiffness, grip strength and pain relief. Eight of these patients with rheumatoid arthritis were unable to complete the colchicine trial and are excluded from this phase of the comparison.

Table 5.—*Survey of Serum Concentration and Urine Content of Uric Acid Obtained from Patients with Gouty Arthritis**

		Effect of griseofulvin on uric acid mobilization		
Test	n	Initial	48 hours after onset of treatment	T-test
Serum uric acid (average—mg. %)	23	8.8	8.2	$P > 0.1$
Urine uric acid (Gm./24 hours)	6	0.68	0.54	$P\ 0.4 > 0.5$

*Uric acid alterations did not reach a level of significance.

The control groups consisted of 12 patients with painful osteoarthritis and 15 with acute rheumatoid arthritis. Griseofulvin, colchicine and placebo were administered in tablets of identical appearance over 4 day periods separated by 2 day intervals of no medication. Application of the chi-square method to the data on both these sub groups failed to reveal a significant difference in response to griseofulvin, colchicine or placebo ($P > .05$) (table 4). Also, neither at low nor high dosage was there a significant effect of griseofulvin on serum uric acid levels after 48 hours of treatment, and no evidence of uricosuric action (table 5).

In spite of the massive dosages, 5 subjects (fig. 2) who received 8 to 20 Gm. over a 48 hour period revealed peak blood levels only 2- to 4-fold greater than those of dermatologic patients receiving a dose of 1 to 2 Gm. (Crounse, R. G. and Blank, H.—personal communication). The range of peak blood levels was 4.9–9.2 μg. per milliliter for subjects receiving 8 to 20 Gm. in spaced doses and 0.4–2.5 μg. per milliliter for those receiving 1 to 2 Gm. of griseofulvin in a single initial dose. In these cases only minimal gastrointestinal intolerance was experienced by 2 individuals (H. B. and L. M.).

Discussion

Present data affirm a potent response to griseofulvin in acute gouty arthritis. Objective evidence of inflammation disappeared dramatically within 48 hours of commencing drug therapy—too brief an interval to be judged fortuitous in 16 of 23 patients. Such findings would indicate an antiphlogistic action, which might be transmitted either locally or through some systemic mechanism,

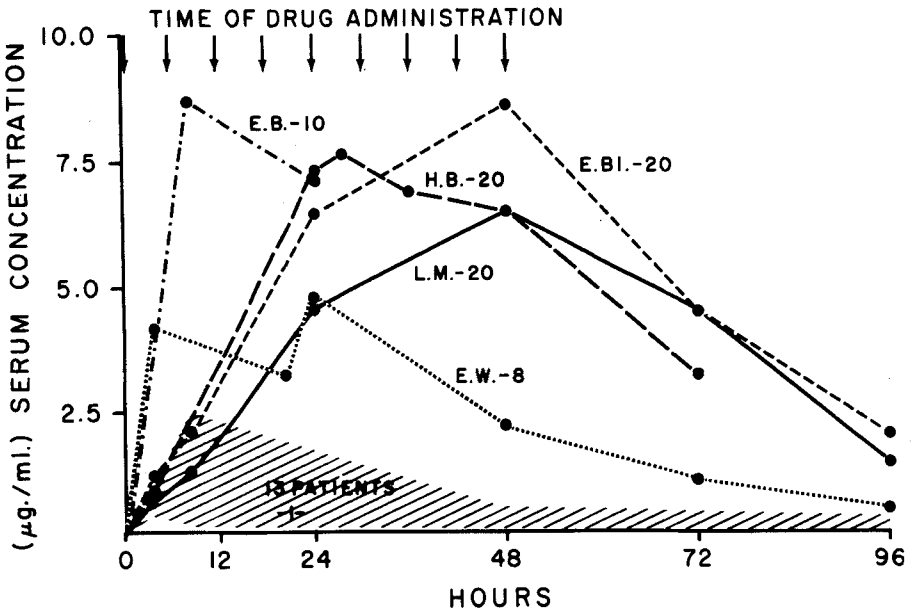


Fig. 2.—Effect of average and large oral doses of griseofulvin on its serum concentration. Two normal subjects and 3 gouty patients (E. B., E. B. L., L. M.) received 8–20 Gm. over a 2 day period—4 Gm. initially and the remainder at 6 hour spacings. Shaded area indicates range of response of dermatologic patients who received a single oral dose of 1–2 Gm.

such as the pituitary-adrenal axis, and might be either specific for gout (e.g., colchicine) or nonspecific (e.g., adrenocortical oxysteroids). Although the present preliminary data provide no conclusions on these points, they highlight interesting relevant information.

The response to griseofulvin of control patients with acute rheumatoid arthritis did not reach a level of significance (table 4), yet 2 of them (E. B. and C. B.) showed prompt substantial improvement in both symptoms and objective signs of inflammation and relapsed following the drug's discontinuation. Possibly a larger, more suitable control series (difficult to obtain in the current geriatric clinical population) might have revealed significant alterations in patients with nongouty rheumatism.

Support for a nonspecific antiphlogistic action of griseofulvin was observed for the first time in a study by D'Arcy and coworkers.[18] These investigators compared the antiinflammatory and granulation-inhibiting properties of griseofulvin to those of cortisone in guinea pigs and mice. In a dosage range of 15.6 to 500 mg. per kilogram, griseofulvin induced graded reductions of granulation growth in cotton pellets; inhibition was comparable to that of controls treated with cortisone at approximately one-tenth the dosage per unit body weight. Reduction of inflammation in tuberculin skin tests on guinea pigs also was demonstrated for griseofulvin which revealed about one-third the potency of cortisone. The antibiotic caused only weak and irregular inhibition of formalin-induced inflammations. In other experiments the effect of

this agent differed from that of cortisone in the following respects: (1) failure to protect normal and adrenalectomized mice from a cold stress, (2) absence of glycogen deposition in the livers of fasted adrenalectomized mice, (3) no alteration in either adrenal weight or histologic details of the adrenal cortex after prolonged treatment of normal mice, (and 4) no inhibition of the histamine sensitization reaction. It was concluded[18] that neither the adrenal cortex, *per se,* nor the pituitary-adrenal axis was the mediator of griseofulvin's effect which involved, "some direct action of unknown nature at the site of inflammation." These data are in need of confirmation but provide a stimulating lead on the nature of the antibiotic's influence on inflammation. It is also of interest that Cohen recorded a successful symptomatic response of patients with shoulder-hand syndrome during treatment with this drug, a phenomenon potentially linked to general antiphlogism.[19]

Another consideration is the possible relationship between actions of colchicine and griseofulvin in acute gouty arthritis. In contrast to other known agents effective in this pathologic state, such as adrenocortical steroid derivatives, phenylbutazone, and large doses of aspirin,[12] griseofulvin like colchicine induced no detectable uricosuria (table 5).[3] Both griseofulvin[20] and colchicine[21,22] arrest cell division in the metaphase, as measured by standard techniques in mice and rats. Dissimilarities in the behavior of these drugs also should be noted. The two compounds are structurally unrelated (fig. 1), except for methoxy groups on their respective benzene rings. Biochemical studies on the in vitro action of these drugs so far do not indicate any overlap. Whereas the currently favored major metabolic action of griseofulvin is an inhibitory effect on nucleic acid synthesis demonstrable in fungi,[5,28] colchicine inhibition of nucleic acid formation under other in vitro experimental conditions has not yet been found.[23,24] Finally, the antimitotic and antiarthritic actions of colchicine may be completely separate functions, a situation which by analogy might also be true of griseofulvin. Trimethylcolchicinic acid in small doses was found by Wallace to be an effective colchicine analogue in the treatment of acute gouty arthritis, but this agent displayed no effect on cell division in vitro, except in massive dosage, under special circumstances.[3,4,25] Thus, any positive connection between the action of griseofulvin and colchicine awaits further investigation.*

Regardless of the mode of action, griseofulvin's prompt induction of clinical remissions encourages extended exploration of its behavior in management of acute gout, as well as other rheumatic inflammatory states. The present data agree with extensive observations from the dermatologic literature on griseofulvin administration to man; in these reports, a low frequency of toxic effects—usually of a minor nature—were encountered.[26] Impairment of spermatogenesis observed with massive parenteral dosage of griseofulvin in rodents[20] has not been found in two careful studies† of man.[26,27] Despite promising fea-

*Since acceptance of this paper, S. L. Wallace and A. W. Nissen report similar improvement of gouty patients treated with griseofulvin (New England J. Med. 266:1099, 1962).

†Sperm counts performed at appropriate intervals in two patients receiving 10 to 16 Gm. of griseofulvin over 48 hours in this series showed no alteration from the drug.

tures of griseofulvin as an antirheumatic drug, its expense and high dosage requirements in addition to the possibility of untoward events when administered chronically indicate caution in its widespread usage for this purpose at the present.

Summary

The effect of a fungistatic antibiotic, griseofulvin, on acute gouty arthritis in 23 patients was documented. Within 48 hours of treatment, 16 had marked-to-moderately-good response, with minor or no toxicity. Six of 7 patients who failed to improve with griseofulvin did not respond to colchicine treatment during the same attack. Evidence for a general antiphlogistic action of griseofulvin in contrast to a specific one like that of colchicine is briefly discussed.

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