A double-blind clinical trial of griseofulvin in patients with Raynaud's phenomenon

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Summary

Twenty-four patients with Raynaud's phenomenon were treated with griseofulvin and a placebo in a double-blind cross-over clinical trial. The results were assessed subjectively and plotted sequentially. The number of patients able to distinguish the active from the placebo treatment was statistically significant ($P=0.05$). There were indications that the response was dose dependent. Further studies are needed to establish whether griseofulvin offers useful clinical improvement in this condition.

Introduction

The treatment of Raynaud's disease and Raynaud's phenomenon remains unsatisfactory. The oral administration or local application of vasodilators (Kleckner *et al.*, 1951) and the intramuscular injection of oestrogens (Klinefelter, 1936) have been used, but with inconclusive results. The effects of sympathectomy, although often good over the first 6 months, may not be lasting: Johnston *et al.* (1965) have shown that on follow-up many of these patients relapse, and this is especially so in those patients with scleroderma and other connective tissue disorders.

There are a number of references in the literature to the successful use of griseofulvin in Raynaud's phenomenon. However, most of these report the treatment of sporadic cases (Giordano, 1967; Bour & Cremer, 1963; Charles & Carmick, 1970; Hasker, 1970) and none a controlled study. It was felt that a controlled study of griseofulvin in patients with Raynaud's phenomenon was worth attempting.*

* Allen (1971) has since published an account of a controlled trial in twelve patients.

Method and material

All patients had Raynaud's phenomenon according to the criteria of Allen & Brown (1932) and of a severity sufficient to make it feasible to assess subjective changes after 4-week treatment periods. The patients were divided into two groups; Group A consisting of those who had severe ischaemic pain, even when they were indoors and in bed, as well as those patients who had had sympathectomy without benefit, and Group B, which comprised all others.

On admission to the trial patients were assigned to the appropriate group and issued with their first 4 weeks' treatment. This consisted of either griseofulvin or a placebo. After 4 weeks patients had a week's rest during which no tablets were taken; they then took tablets for a second 4-week period, this time the alternative treatment to that given during the first 4 weeks. The two types of tablet, which were identical in appearance, were allotted to the first or second treatment periods according to a random code. Neither the patient nor the physician was aware of the order in which the tablets were given.

Group A patients took 2 g of griseofulvin BP (i.e. fine particle) daily, as 2×500 mg tablets night and morning (or two placebo tablets night and morning); Group B patients took 1 g of griseofulvin daily as 1×500 mg tablet night and morning (or one placebo tablet night and morning). All the patients were instructed to take their tablets with a meal which, if possible, included fat, as this is known to enhance the absorption of griseofulvin. No patient was having other treatment for his Raynaud's disease and a careful record was kept of concurrent drug therapy, particularly in respect of drugs such as phenobarbitone, phenytoin or oral contraceptives,

which are known or thought to influence the metabolism of griseofulvin.

After the initial assessment on entry to the trial patients were seen on a minimum of three occasions. At each visit general progress and volunteered side effects were recorded. At the end of the trial period the patient was asked to express a preference for one or other of the two treatment periods; if he felt unable to this was recorded as 'no difference'. The doctor also recorded his view of which treatment period, if either, had appeared to benefit the patient the more. As each patient completed the trial his record card was sent to an independent observer who decoded the treatments and plotted the choices, using a restricted sequential design ($1-\beta=0.95$, $2\alpha=0.05$, $\theta_1=0.85$), corresponding to a 5% probability. The trial took place between December and March.

Results

Twenty-four patients were studied, fourteen in Group A and ten in Group B. Seven of the patients had scleroderma.

In Group A nine patients chose griseofulvin in preference to the placebo, and the remaining five patients could not differentiate between the effects of drug and placebo.

Five patients in Group B preferred griseofulvin, three preferred the placebo and two were unable to choose between the two.

The results when plotted sequentially showed a significant preference for griseofulvin both in the Group A patients and when both groups were analysed as a whole (Fig. 1).

FIG. 1. Preferences for griseofulvin or placebo:

- , Group A 2 g/day (patient's choice);
- o o o o o o o o, Groups A and B (patient's choice);
- - - - - , Groups A and B (doctor's choice).

The doctor's assessment of which regimen was of most benefit did not always agree with the patient's. When his 'choices' were plotted there was no significant difference between griseofulvin and the placebo.

Side effects

Twelve patients reported side effects while on active treatment and four while on placebo. Of those complaints recorded during griseofulvin therapy three were of diarrhoea (including one patient who had diarrhoea during the preceding placebo treatment), four headache, two indigestion, two dizziness and one sleepiness. Half the patients in each group had side effects, which may indicate that side effects are not dose dependent. Except for one patient, on 2 g/day, who stopped taking her tablets because of diarrhoea, all side effects resolved on continued treatment.

A review of the case records showed that mild analgesics taken by two or three patients were the only other drugs used during the trial period.

Discussion

Since 1958 the antibiotic griseofulvin has been widely used for its activity when given orally against dermatophyte infections. Soon after its introduction Cohen *et al.* (1960) reported significant benefit after griseofulvin therapy in patients with shoulder-hand syndrome. There followed sporadic reports of the value of the drug in Raynaud's disease (Haskett 1970) and in Raynaud's phenomenon in patients with scleroderma (Giordano, 1967; Bour & Cremer, 1963), as well as in angina pectoris (DePasquale *et al.*, 1963).

The mechanism involved would seem to be an effect on vascular tone. Plethysmographic studies indicated increased blood flow in the small arteries following griseofulvin (Sforza & Mossa, 1964). Rubin (1963) showed that griseofulvin can increase coronary arterial blood flow and that this effect was not altered by blocking autonomic ganglia or the adrenergic, cholinergic or histamine receptors. He thus concluded that the drug had a direct action on vascular smooth muscle. Recently Charles & Camick (1970) measured the digital temperature response following 1 min exposure to stirred ice water at 0°C. The temperature curves following griseofulvin therapy showed almost normal recovery in six out of seven patients with Raynaud's disease.

In our study patients were frequently able to distinguish griseofulvin from a placebo. One patient felt sensation in her fingers for the first time for 20 years, another was able to wash his car on a cold day, and a woman who had not previously been able to do so could take money out of her purse herself to pay the bus conductor on a very cold day. The symptomatic relief achieved appeared to be dose

dependent; a greater number of patients in the higher dose group were benefited despite the fact that this group comprised the more severely affected. Some patients who had not improved on 1 g/day during the trial responded afterwards when their dose was increased to 1.5 or 2 g daily. As may have been expected, in patients with scleroderma the response to griseofulvin was less marked.

Further long-term studies are necessary to establish whether griseofulvin offers lasting clinical benefit in Raynaud's phenomenon and whether any such benefit is dependent upon continuous high dose therapy.

References

- ALLEN, B.R. (1971) Griseofulvin in Raynaud's phenomenon. *Lancet*, **ii**, 840.
- ALLEN, E.V. & BROWN, G.E. (1932) Raynaud's disease: a critical review of minimal requisites for diagnosis. *American Journal of Medical Science*, **183**, 187.
- BOUR, D.J.H. & CREMER, G. (1963) Succesvolle behandeling van sclerodermie met griseofulvine. *Nederlands tijdschrift voor geneeskunde*, 107. II. **46**, 2145.
- CHARLES, C.R. & CARMICK, E.S. (1970) Skin temperature changes in Raynaud's disease after griseofulvin. *Archives of Dermatology*, **101**, 331.
- COHEN, A., GOLDMAN, J., DANIELS, R. & KANENSON, W. (1960) Treatment of shoulder hand syndrome with griseofulvin. *Journal of the American Medical Association*, **173**, 542.
- DEPASQUALE, N.P., BURKS, J.W. & BURCH, G.E. (1963) The treatment of angina pectoris with griseofulvin. *Journal of the American Medical Association*, **184**, 421.
- GIORDONO, M. (1967) Griseofulvin for scleroderma. *Lancet*, **ii**, 260.
- HASKER, W.E.S. (1970) Griseofulvin in Raynaud's disease. *Lancet*, **ii**, 1136.
- JOHNSTON, E.N.M., SUMMERLY, R. & BIRENSTINGL, M. (1965) Prognosis in Raynaud's phenomenon after sympathectomy. *British Medical Journal*, **1**, 962.
- KLECKNER, M.S. JR, ALLEN, E.V. & WAKIM, K.G. (1951) The effect of local application of glyceryl trinitrate (nitroglycerine) on Raynaud's disease and Raynaud's phenomenon. *Circulation*, **3**, 681.
- KLINEFELTER, E.W. (1936) Successful treatment of Raynaud's disease with estrogenic substance. *Archives of Dermatology and Syphilology*, **34**, 887.
- RUBIN, A.A. (1963) Coronary vascular effects of griseofulvin. *Journal of the American Medical Association*, **185**, 871.
- SFORZA, F. & MOSSA, L. (1964) Clinical observations on the use of griseofulvin in chronic obliterative disorders of peripheral arteries. *Rassegna medica sarda*, No. 10, 129.