Original article

Efficacy of topical griseofulvin in treatment of tinea corporis

Mohamed A. A. Kassem,[1] Samia Esmat,[2] Eihab R. Bendas[1] and Mohamed H. M. El-Komy[2]

[1]*Department of Pharmaceutics, Faculty of Pharmacy and* [2]*Department of Dermatology, Faculty of Medicine, Cairo University, Cairo, Egypt*

Summary

Tinea infections are among the most common dermatological conditions throughout the world. Griseofulvin is a classical oral fungistatic antibiotic, active against *Epidermophyton floccosum*, *Trichophyton* and *Microsporum* species, the causative fungi of tinea corporis. To evaluate the efficacy of topical griseofulvin in the treatment of tinea circinata using three different vehicles for drug delivery. Sixteen patients with tinea circinata were instructed to apply either griseofulvin gel form in group A or a similar placebo gel for control group; a niosomal gel formulation of griseofulvin for group B or; a liposomal gel formulation of griseofulvin for group C. Patients were evaluated both clinically and mycologically after 3 weeks. Marked improvement was seen for groups A, B and C both clinically and mycologically while no improvement was observed in the placebo group. Mild and transient irritation was reported in four patients. Our results show that topical griseofulvin preparations may be effective and safe in treating tinea circinata and that further large-scale studies may establish the high efficacy of the niosomal gel formulation.

Key words: griseofulvin, niosomes, tinea corporis, liposomes, griseofulvin gel, topical griseofulvin.

Introduction

Tinea corporis (TC) or ringworm of the glabrous skin is caused by *Epidermophyton floccosum* and many species of *Trichophyton* and *Microsporum*.[1,2] Topical antifungals may be sufficient for treatment of TC. Systemic therapy, however, may be required when the infected areas are large, macerated with a secondary infection, or in immunocompromised individuals.[3]

Griseofulvin, a classical oral antibiotic first isolated as a metabolic product from a culture of penicillium griseofulvum in 1939 by Oxford *et al.*, is active against *Trichophyton*, *Microsporum* and *Epidermophyton floccosum*, the causative fungi of TC,[2,4] therefore, we examined the efficacy and safety of topical griseofulvin preparations in the treatment of TC using three different vehicles for delivery.

Correspondence: Mohamed H. M. El-Komy, 5 Falaky Square Bab El-Louk, Cairo, Egypt. Tel.: 02 012 341 5852.
E-mail: komy_m@yahoo.com

Accepted for publication 30 November 2005

Subjects and methods

Twenty-four patients with clinically diagnosed and mycologically confirmed TC were selected. Each patient signed an informed consent to participate in the study. The patients were divided into four groups; patients of each group were advised to topically apply one of the four following preparations twice daily for 3 weeks. Group A: gel formula at a dose of 1% of griseofulvin; control group: an identical placebo gel; group B: local of niosomal gel application containing 1% of griseofulvin; and group C: liposphere formulation of 1% of griseofulvin twice daily.

The following parameters were observed for evaluation of treatment efficacy: erythaema (scores 1–3), scales (scores 1–3), itching (scores 1–3), pustules (present or absent) and size of lesions. These parameters were determined before treatment and at weekly intervals till fourth visit (3 weeks).

Skin scrapings obtained before treatment and at third follow-up visit were sent to a laboratory for mycological culture on yeast extract-agar (with cycloheximide 0.5%) in autoclave for up to 2 weeks. The dermatophytes present and proliferating in the screening culture were

counted to evaluate the effect of treatment by griseofulvin preparations.

Griseofulvin preparations

Griseofulvin gels

The gel formula consisted of 1 g of griseofulvin, solvent mixture consisting of 5 ml of DMF, 40 ml of PEG 300 and 55 ml of distilled water, 2 g of Carbopol and few drops (approximately 3–5 drops) of triethanolamine.

Griseofulvin niosomes

The niosomal formulation incorporated in Carbopol gel was prepared by lipid film hydration technique, containing 100 mg of griseofulvin, 71 mg of Span 40, 71 mg of cholesterol and 5 ml of phosphate buffered saline (PBS) adjusting hydration time for 4 h.

Griseofulvin lipospheres

The formula of griseofulvin lipospheres was prepared by solvent technique and composed of 100 mg of griseofulvin, 400 mg of stearic acid, and 5 mg of propyl paraben as oily phase and 200 mg of egg phospatidylcholine, 10 ml of PBS and 5 mg of methyl paraben as aqueous phase.

Results

Of 24 patients recruited, 16 patients completed the trial with mean age of 31.6 years. Lesions surface area ranged from 1.80 to 182 cm^2 with a mean of 37.9 cm^2. The main measure of efficacy was clinical cure, which was defined as complete disappearance of lesions. Secondary measure of efficacy was mycological cure, which was defined as no growth of dermatophytes in the culture.

Table 1 shows the degree of response to different griseofulvin formulations. The patients treated with formula 'B' showed an 80% clinical cure rate (Fig. 1a,b) and a treatment duration time of 2.25 weeks on average. The mycological count turned negative in 80% of patients.

Only one patient out of four treated with formula 'C' showed no change in lesions. Another patient using formula 'C' had residual erythaema at fourth visit. But the other two patients were cured completely within 2 weeks on average showing a 50% clinical cure rate.

Formula A showed a 75% clinical cure rate as three of four patients treated with this formula were cured within 3 weeks on average (Fig. 2a,b). None of the patients in the placebo group were cured completely. Two patients receiving formula A and one patient receiving formula B in addition to one placebo patient reported mild transient irritation after topical application of formula.

Discussion

Griseofulvin exerts its fungistatic action primarily by disrupting the cell's mitotic spindle structure, thus arresting the metaphase of cell division or by production of defective DNA, which is unable to replicate. Griseo-

Table 1 Degree of response to different grisofulvin preparations.

		Duration of treatment till clearance (in weeks)				
Pt. no.	Formula	Erythema	Scales	Itching	Pustules	Mycological count (at third visit)
1	A	3	2	2	2	Decreased
2	A	3	3	2	Absent	No count
3	A	3	3	3	Absent	No count
4	A	No change	No change	No change	No change	Decreased
5	B	1	1	3	Absent	No count
6	B	1	1	1	Absent	No count
7	B	3	2	2	Absent	No count
8	B	Decreased	Decreased	3	Absent	Decreased
9	B	2	2	2	Absent	No count
10	C	1	1	1	Absent	No count
11	C	No change	No change	No change	Absent	Decreased
12	C	Decreased	3	2	2	No count
13	C	3	2	2	2	No count
14	Control	No change	No change	No change	No change	Increased
15	Control	No change	No change	No change	No change	Increased
16	Control	No change	No change	No change	No change	Decreased

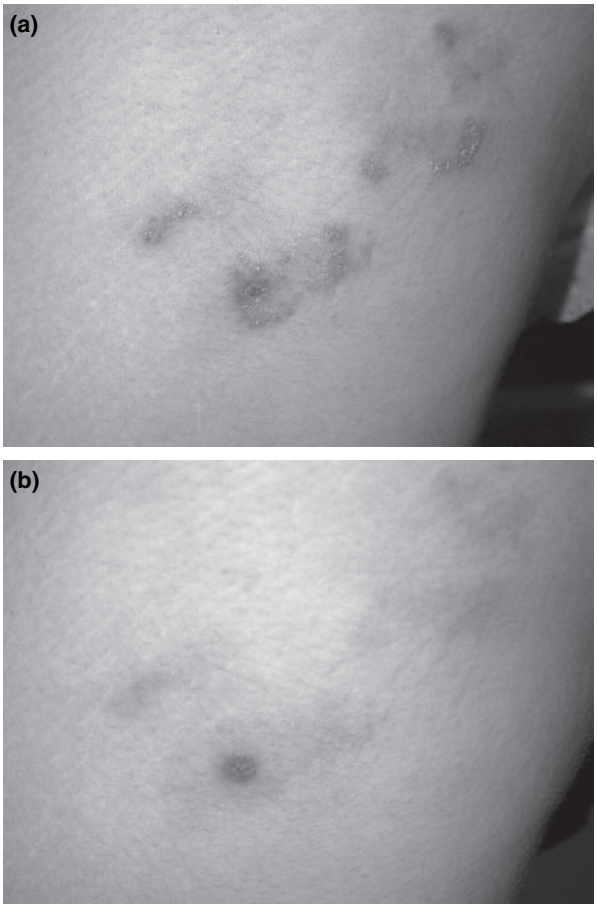

Figure 1 Patient no. 9. Tinea circinata of thigh before treatment (a). Three weeks after application of topical grisofulvin niosomal formulation (b).

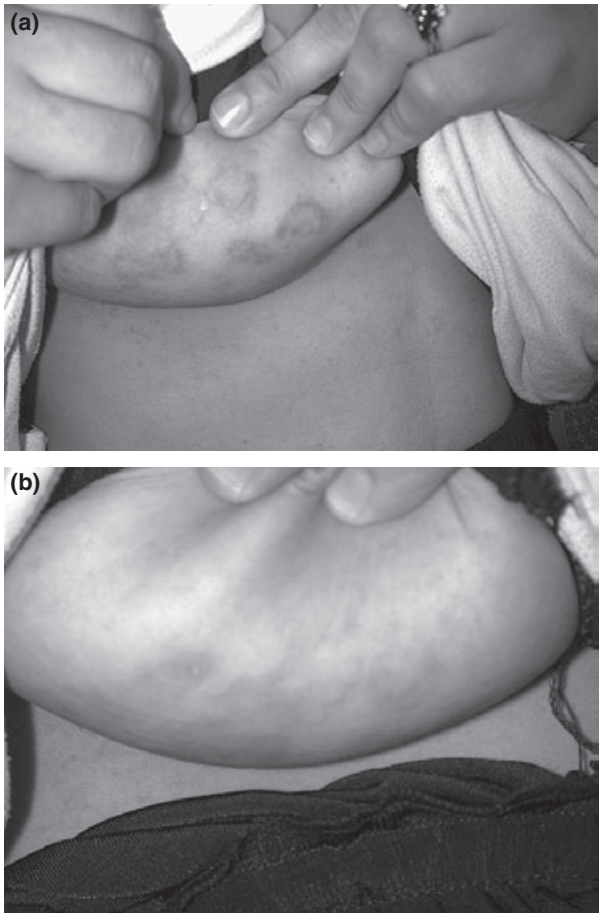

Figure 2 Patient no. 2. Tinea circinata of breast before treatment (a). Three weeks after application of topical grisofulvin gel formulation (b).

fulvin is deposited in keratin precursor cells, which renders them an unfavourable environment for fungal invasion. Infected skin is then replaced with tissue not infected with the dermatophyte.[5] Systemic griseofulvin may cause headache, fatigue, nausea and vomiting, diarrhoea, urticaria and even angioedema.[6] It is contraindicated in patients with porphyria, hepatocellular failure, or a history of hypersensitivity to the drug.[5] We thought of topical griseofulvin in order to avoid its systemic adverse effects, but still advantage from its antifungal action, guarded that the penetration of grisofulvin reaches the level of the basal KC for an appropriate antifungal effect. So in this study, the efficacy and safety of topical griseofulvin in the treatment of tinea circinata using three different vehicles for delivery was evaluated.

We used gels, liposomes and niosomes formulations, which are well-documented for transdermal drug delivery.[7] Liposomal encapsulation of a therapeutic substance enables increasing the accumulation of the active ingredient in target tissues and controlling the spread of the active ingredient to non-target tissues, where it might do harm.[8] Niosomes loaded with drugs for dermal application are aimed to preferentially show interactions with the inflamed (epidermal) tissue without exerting an immediate or strong systemic action.[9] The chemical stability of niosomes and relatively low cost of the materials make niosomes more attractive than liposomes in industry.[10–12]

The griseofulvin gel form showed a 75% clinical cure rate and 50% mycological cure within average treatment duration of 3 weeks. Moreover, the mycological count decreased even in the only patient who did not show any signs of clinical improvement, which may suggest that apparent clinical improvement may have required an extended period of treatment.

The liposphere formulation of grisofulvin, showed a 50% efficacy in clinically clearing the lesions and a 75% mycological cure rate in the shortest treatment duration time of 2 weeks on average with no side-effects reported. The discrepancy between mycological cure and clinical cure here is because of a persistent erythaema in one case, which finally resolved but after the study time limit. Like the gel formulation, the liposphere formulation decreased the mycological count in the clinically unresponsive patient. It is worth mentioning that this patient had a widespread cutaneous fungal infection and may have benefited more from systemic antifungal therapy as suggested by Gupta *et al.* [3].

The niosomal form of griseofulvin showed the highest clinical and mycological cure rates (80%) with a treatment duration time of 2.25 weeks on average. Only one patient was considered unresponsive in spite of disappearance of itching and a marked decrease in scales, erythaema, as well as mycological count at end of 3 weeks. None of the patients receiving the placebo gel showed any clinical improvement in their lesions, moreover two of the three patients showed an increase in mycological count. Mild and transient irritation after applying the preparation occurred in few patients, but none reported any of the systemic adverse effects of grisofulvin.

Only a few reports used topical griseofulvin preparations in treatment of dermatophyte infections of the skin. In one study, 1% griseofulvin spray was effective in the treatment of 100 tinea pedis patients where the mycological cure was 79.2% on the fourth week of treatment and 80.9% 2 weeks post-treatment.[13]

We could then conclude that topical preparations of 1% griseofulvin can be effective and safe in treating TC infections. Niosomal gel formulation seems to produce the best efficacy with minimal side-effects; however, larger scale comparative trials are still needed for further verification of these findings.

References

1 Hay RJ, Moore M. Mycology. In: Champion R, Burton J, Ebling F (eds), *Rook/Wilkinson/Ebling Textbook of Dermatology*, 6th edn. Oxford: Blackwell Scientific Publications, 1998: 1277–376.

2 Richardson MD, Warnock DW. Dermatophytosis. In: *Fungal Infection Diagnosis and Management*, 2nd edn. Oxford: Blackwell science Ltd, 1997: 65–6.

3 Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra, and piedra. *Dermatol Clin* 2003; **21**: 395–400.

4 Moossavi M, Bagheri B, Scher RK. Systemic antifungal therapy. In: Levine N, Thiers BH (eds), *Dermatologic Clinics Systemic Dermatologic Therapy*. Philadelphia: W.B. Saunders company 2001;**19**:35–8.

5 *Martindale The Extra Pharmacpoeia*, twenty-ninth edn. James EFR(ed.). London: The Pharmaceutical Press, 1989: 425 p.

6 Davies RR. Griseofulvin. In: Speller DCE (ed.), *Antifungal Chemotherapy*. Chichester, England: John Wiley & Sons Ltd., 1980: 150–82.

7 Shahiwala A, Misra A. Studies in topical application of niosomally entrapped nimesulide. *J Pharm Pharmaceut Sci* 2002; **5**: 220–5.

8 Steinberg FM, Raso J. Biotech pharmaceuticals and biotherapy: an overview. *J Pharm Pharmaceut Sci* 1998; **1**: 48–59.

9 Junginger HE, Hofland HEJ, Bouwstra JA. Liposomes and niosomes interactions with human skin. *Cosmet Toil* 1991; **106**: 45–50.

10 Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS. The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. *J Pharm Pharmacol* 1985; **37**: 237–42.

11 Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A. Preparation and properties of niosomes. *J Pharm Pharmacol* 1985; **37**: 863–8.

12 Schreir H, Bouwstra J. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. *J Controlled Release* 1994; **30**: 1–15.

13 Aly R, Bayles CI, Oakes RA, Bibel DJ, Maibach HI. Topical griseofulvin in the treatment of dermatophytoses. *Clin Exp Dermatol* 1994; **19**: 43–6.