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Oral terbinafine in tinea capitis in children

Orale Terbinafin-Behandlung der kindlichen Tinea capitis

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Summary. Tinea capitis is a disease that frequently affects children. In most cases systemic antimycotic treatment is necessary. Griseofulvin is still the drug of choice, but requires prolonged periods of treatment (several months). To estimate the efficiency and tolerability of terbinafine for treatment of tinea capitis in children, four patients (aged 3–9 years) with tinea capitis proven by culture were treated with terbinafine at a dose of 125 mg a day for different periods (4–10 weeks). Isolates were subjected to minimal inhibitory concentration testing against terbinafine and griseofulvin. In all four cases terbinafine treatment resulted in complete remission. The clinical response was accompanied by negative culture results on follow-up. Terbinafine was well tolerated in each case. Determination of the minimal inhibitory concentration confirmed the excellent *in vitro* activity of terbinafine against dermatophytes. Controlled studies involving a larger number of children are necessary to answer questions concerning dose and duration of terbinafine treatment as well as the frequency and severity of drug-related side-effects.

Zusammenfassung. Tinea capitis ist eine bevorzugt im Kindesalter auftretende Erkrankung, die in der Regel lediglich durch eine systemisch geführte antimykotische Behandlung zur Abheilung gebracht werden kann. Im Kindesalter wird Griseofulvin bislang als Mittel der Wahl eingesetzt, obgleich aufgrund der fungistatischen Wirkung von Griseofulvin die Einnahme über einen langen Zeitraum (mehrere Monate) erfolgen muß. Um die Wirksamkeit und Verträglichkeit und Toleranz von Terbinafin bei der Therapie der kindlichen Tinea capitis einzuschätzen, führten wir eine klinische Anwendungsbeobachtung durch. Vier Kinder im Alter von 3 und 9 Jahren mit kulturell gesicherter Tinea capitis wurden mit Terbinafin in der Dosierung von 125 mg täglich über unterschiedlich lange Zeiträume (4 Wochen bis 10 Wochen) behandelt. In allen vier Fällen zeigte sich bei Therapieende ein vollständiges Fehlen von Entzündungszeichen sowie im weiteren Nachbeobachtungszeitraum eine vollständige Abheilung bei negativen Kontrollen in der Dermatophytenkultur. Terbinafin wurde problemlos vertragen. Die Bestimmung der minimalen Hemmkonzentrationen konnte die bekannte gute *in vitro*-Empfindlichkeit der isolierten Erreger gegenüber Terbinafin bestätigen. Für die Zukunft ist die Durchführung kontrollierter klinischer Studien unter Einschluß höherer Patientenzahlen zu fordern, um Fragen nach Dosis und Therapiedauer sowie nach Häufigkeit und Qualität möglicher Nebenwirkungen beantworten zu können.

Introduction

Tinea capitis occurs worldwide but is most prevalent in Africa, Asia and southern and eastern Europe, where it is the most common type of dermatophytosis. It is primarily a disease of childhood affecting mostly children between 6 and 10 years of age, predominantly boys. In recent years, however, tinea capitis has become increasingly common in adults, infants and neonates [1]. Tinea capitis is caused by a number of *Trichophyton* and *Microsporum* species. Several reports have described *Microsporum canis* as the most prevalent species or

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ranking second followed by other fungal species as *Trichophyton rubrum* [2–6]. The prevalence of tinea capitis-inducing species can change within any particular region over a period of time, as occurred in north-west Europe [7]. *T. verrucosum* was the most frequently isolated species between 1963 and 1967 (64.5%). By 1988–92 this percentage had decreased to 4.5 with *T. violaceum* becoming the most prevalent species (29.6%).

Clinical manifestations of tinea capitis vary, depending on the source of infection. In the case of an infection with a zoophilic dermatophyte, highly inflammatory suppurating lesions may predominate (kerion). Infections acquired from infected humans often cause milder inflammation and are characterized by irregular erythematous patches with mild scaling leading, if untreated, to alopecia. Diagnosis relies on the cultural detection of the aetiological agent, which can be isolated from scales, pus and hair. In cases of *M. canis* infection, a characteristic greenish fluorescence under Wood's light can provide further diagnostic evidence even before the results of culture are available.

Oral griseofulvin is still the drug of choice for the treatment of tinea capitis [8]. However, long periods of treatment are often necessary, ranging from 6 weeks up to or even longer than 4 months. The recommended dose for children weighing less than 25 kg is 10 mg kg day^{-1}, 250–500 mg day for children over 25 kg. Reducing the durations is systemic treatment is desirable as this increases patient compliance and reduces side-effects. For this reason terbinafine seems to be an appropriate drug.

Case reports

The relevant clinical data from the four children treated with terbinafine are shown in Table 1. Positive fluorescence was seen in cases no. 2 and 4 on examination of skin lesions by Wood's light.

Laboratory investigations

Isolation of strains and growth conditions

Clinical material was cultured on Kimmig's agar with and without the addition of cycloheximide.

Identification of strains

All isolates were identified according to the regulations of the Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM) and include identification based on the macroscopic and microscopic characteristics of strains when grown in culture and some additional tests for further differentiation [9]. These tests differentiated isolates by their ability to produce a red pigment when grown on potato-glucose agar, their capacity to produce urease and their behaviour in the hair perforation test. Results of culture are shown in Table 2.

Antimicrobial susceptibility testing

The minimal inhibitory concentrations (MICs) for terbinafine and griseofulvin were determined using the microdilution test as described by Granade & Artis [10]. The concentrations chosen for the microdilution test were 2, 1, 0.5, 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6} and 10^{-7} μg ml^{-1} for terbinafine and 10, 7, 5, 4, 3, 2, 1, 0.5, 0.1, and 0.05 μg ml^{-1} for griseofulvin. In each set of experiments a control isolate of *T. rubrum* and *T. mentagrophytes* with a known susceptibility profile was included [11]. The distribution of MIC values for terbinafine and griseofulvin among the isolates tested is shown in Table 2.

Cause of therapy and clinical outcome

After obtaining written consent from one parent, terbinafine treatment was initiated at a dose of 125 mg a day^{-1} (half a tablet). Topical treatment was initiated in all cases with fusidic acid cream (Fucidine^{R} Cream), which was applied to the affected area twice daily for a fortnight. The duration of antimycotic therapy in each patient is shown in Table 1. Patients were seen initially after 1 week and then every second week. At each visit patients were thoroughly questioned about possible side-effects and cultures were taken for mycological investigation. None of the children, even when treated for 10 weeks (case no. 1), reported side-effects. Microbiological evaluation was repeatedly negative in all cases. At the end of the therapy there were no remaining signs of inflammation. The only remaining symptom seen in all cases was mild dryness of the infected areas, which did not require special treatment and disappeared during the following 1–3 months.

Discussion

Terbinafine, a recently introduced antimycotic drug of the allylamine group, is fungicidal against a wide spectrum of dermatophytes [12, 13]. Its mode of action is probably inhibition of ergosterol synthesis at the level of squalene epoxidase without affecting the cytochrome P450-mediated steps that are inhibited by azole antifungal drugs [14, 15].

Table 1. Relevant clinical data from the four children treated with terbinafine

Case no.	Sex (M/F); Age (years)	Duration of symptoms before first visit	Clinical findings	Blood analysis before treatment	Duration of therapy (weeks)
1	F;8	3 weeks	Demarcated elevated lesion with central lamellar desquamation and yellow pustules	Sedimentation rate ↑ (40/70)	10
2	M;8	2 months	Various red and infiltrated lesions with yellow scurf	Sedimentation rate ↑ (20/40)	5
3	M;3	4 weeks	Highly inflammatory suppurating lesions	Normal	5
4	F;9	2 months	Inflammatory infiltrated patches with pustules and marked scaling	Sedimentation rate ↑ (18/42)	4

Table 2. Isolated dermatophytes and corresponding minimal inhibitory concentrations (MICs) for terbinafine and griseofulvin

No.	Culture	Terbinafine, (MIC, $\mu g\ ml^{-1}$)	Griseofulvin, (MIC, $\mu g\ ml^{-1}$)
1	*Trichophyton quinckeanum*	0.001	7
2	*Microsporum canis*	0.005	2
3	*Trichophyton rubrum*	0.001	3
4	*Microsporum canis*	0.01	4

The MIC data presented demonstrate the known exceptionally low MIC of terbinafine, which is about 1000 times lower than that of griseofulvin (Table 2). Several clinical studies of dermatophyte infections of the skin and nails have shown the superiority of terbinafine compared with griseofulvin in terms of duration of treatment and relapse rate [16, 17]. The efficacy of terbinafine in cases of tinea capitis requires further clinical investigation. Available data include the result of a study by Alvi *et al.* [18], who proved the efficiency and tolerability of terbinafine in a randomized, double-blind study of 105 patients of all ages who weighed more than 10 kg. Therapy with terbinafine orally for 4 weeks was as effective as an 8-week course of griseofulvin. In addition, a continued antifungal effect after cessation of therapy was observed in the case of terbinafine but not with griseofulvin. In *T. violaceum* caused tinea capitis a 4-week treatment with terbinafine proved as safe and effective as an 8-week treatment with griseofulvin [19]. Nejjam *et al.* [20] recently conducted a pilot study in children suffering from tinea capitis and treated with terbinafine 125 mg once daily for 56 days. All patients were completely cured at the end of the treatment period. The clinical tolerability was good with only mild side-effects seen in four of the children, which did not lead to a discontinuation of the study medication. Our own data also prove the efficiency of terbinafine in childhood tinea capitis independent of the causative dermatophyte species.

Two crucial points concerning the use of terbinafine in tinea capitis in children need to be addressed. The first concerns the need for randomized treatment duration and dose-finding studies. The pharmacology and potential antidermatophyte activity of the drug suggest that 2 weeks treatment with terbinafine may be feasible. The second, more important issue, concerns the safety profile of the drug. After treatment of 500 000 patients only very mild side-effects were reported, consisting in minor gastrointestinal upset and skin rash with an incidence of about 10% [21]. Another annoying side-effect, loss of taste, occurs in far less than 1% of cases and is usually seen with prolonged treatment periods (average time of onset is 5 weeks after the start of treatment) and is always reversible. In our patients neither of these side-effects occurred.

However, recently severe side-effects have been reported in adults, consisting in erythema multiforme (three patients) [22, 23] and toxic epidermal necrolysis (one patient who survived) [23]. In the patient with toxic epidermal necrolysis skin eruption started as early as 5 days after beginning terbinafine treatment at the recommended dose of 250 mg once daily. Further critical observation of the frequency and severity of terbinafine-induced side-effects with increased use of the drug is necessary before terbinafine can be generally recommended for the treatment of tinea capitis in children.

It should be stated, however, that terbinafine is

not the only alternative to griseofulvin currently under consideration. In particular, itraconazole comes to mind [24].

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