SAFETY AND EFFICACY OF TERBINAFINE IN A PEDIATRIC IRANIAN COHORT OF PATIENTS WITH TINEA CAPITIS

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BACKGROUND AND OBJECTIVES: Tinea capitis is a common infection of the scalp and hair shaft caused by dermatophyte fungi that mainly affects prepubescent children. Systemic therapy is required for treatment and to prevent spread. The aim of present study was to assess the effect of terbinafine for tinea capitis treatment in children.

METHODS: 30 Iranian pediatric patients with a clinical diagnosis of tinea capitis, were enrolled in the study. The Study was conducted in a general and referral teaching hospital (Imam Medical Centre – Tehran, Iran) from 2006 to 2007. Eligible patients with less than 20 kg of body weight were given 62.5 mg terbinafine and for patients between 20 to 40 kg, the dose was 125 mg, on the first visit. After two weeks, all patients had a second visit that second sample for microscopic study was taken. For each patient, direct mycology test (KOH test) and mycological culture were carried out before the study is being started and after 2nd, 4th, 5th, 6th and 8th weeks. Drug’s probable adverse effects were also recorded.

RESULTS: Based on the results of mycological culture of patients’ lesions, Microsporum canis and Trichophyton sheonlini were considered as major causes of Tinea capitis in these children. Out of 30 study patients, KOH test of 93% in the fifth and 100% in the sixth week, was negative. All patients healed completely from signs of infection, after six weeks. Also, no severe side effects were seen in any patients.

CONCLUSION: According to the results of this study, Terbinafine is an effective therapy in Iranian cases of Tinea capitis in children without having severe side effects.

Key words: Terbinafine, Tinea capitis, clinical trial.

Introduction

Skin dryness can discourages colonization by microorganisms, and the shedding of epidermal cells may inhibit many microbes from permanent residence. Occlusion of the skin with nonporous materials can interfere with the skin’s barrier function by increasing local temperature and hydration. When the protective mechanisms of the skin, fails or be inhibited, cutaneous infection may occur (1). Dermatophytes require keratin for growth, so they are restricted to hair, nails, and superficial skin and these fungi do not infect mucosal surfaces. Dermatophytoses are referred to as “tinea” infections. They are also named for the body site involved.

Tinea capitis (ringworm) is widespread throughout the world, above all in Africa, Asia, South-eastern Europe and even in UK where it is one of the most frequent forms of dermatomycosis (2). A community point prevalence study from London suggested a disease prevalence of about 2.5% with a carriage rate of between 12% and 47% among schoolchildren (3). The disease rarely affects mature
patients (but in post-menopausal women) (4) and is mostly found in children almost irrespective of age or sex (5). Scalp and hair shaft are the most common sites of infection. Transmission is fostered by poor hygiene and overcrowding, may have role in transmission of disease through contaminated hats, brushes, pillowcases, and other inanimate objects. After being shed, it should be noted that affected hairs can harbor viable organisms for more than one year after shedding (1). Irregular or well-demarcated alopecia and scaling are common clinical features of ringworm. When swollen hairs fracture a few millimeters from the scalp, “black dot” alopecia is produced. Boggy, sterile, inflammatory scalp mass due a cell-mediated immune response (kerion) and also occipital lymphadenopathy may be seen in Tinea scalp infection as well (1). In some cases, patients have symptoms and clinical signs of minimal ringworm infection but they are still mycologically positive and presumed capable of transmitting infection.

Tinea capitis requires systemic treatment because generally, topical antifungals are unable to penetrate the hair shaft sufficiently to clear the infection and systemic therapy is usually indicated. Furthermore, the use of topical antifungal treatment alone may contribute to the creation of carriers (6). The only licensed treatment is oral Griseofulvin is the most common approved drug for oral therapy. It is usually given at a dose of 10 mg/kg for six to eight weeks and in resistant cases, longer treatment may be required at doses of up to 20-25 mg/kg (5). Due to long time course of therapy, it is highly recommended to have a positive mycology result before starting (7) and in patients more complicated cases of this disease (patients with pustular tinea capitis and kerion), use of antifungal creams or shampoos while waiting for the mycology results (to reduce the risk of progression) is indicated (8). Regarding to the prevalence of ringworm in pediatric patients, unfortunately the compliance with such a lengthy treatment regimen is poor and lack of a suitable pediatric formulation of griseofulvin (e.g. suspension) for this subpopulation in many countries including Iran makes the efficacy of griseofulvine therapy much more complicated. Furthermore, some patients do not respond to standard therapy and may require higher doses or prolonged durations. In a recent survey of griseofulvin treatment of tinea capitis in a practice setting, approximately 40% of patients did not respond to the drug and required additional treatment (9). So, if an antifungal drug with sufficient efficacy on ringworm, needs a shorter course of therapy and also has a more convenient dosage regimen with an acceptable safety, it could be considered as a real therapeutic rival for griseofulvin.

Terbinafine which has an allylamine chemical structure, have been developed as a new class of ergosterol biosynthetic inhibitors that are functionally as well as chemically distinct from the other major classes of ergosterol-inhibiting antifungal agents (10). The drug is highly effective against dermatophytes in vivo and in vitro (11). In one review research, out of 21 studies with 1812 participants, terbinafine for four weeks and griseofulvin for eight weeks showed similar efficacy in 3 studies involving 382 participants. So, newer treatments including terbinafine, may be similir to griseofulvin in children with tinea capitis caused by Trichophyton species. Also, because of its fungicidal action, it requires shorter treatment period than griseofulvin (12). Allylamines act by inhibiting early steps of ergosterol biosynthesis. This inhibition coincides with accumulation of the sterol precursor squalene and the absence of any other sterol intermediate, suggesting that allylamine inhibition of sterol synthesis occurs at the point of squalene epoxidation, a reaction catalyzed by squalene epoxidase (10). Studies with isolated squalene epoxidase indicate that it is the target for allylamine activity (11). Terbinafine has a considerable hepatic metabolism which may rise concern about the pharmacogenetic differences of drug metabolism in different populations and the safety of standard dosing regimen in genetically different populations (11). The drug may also cause hepatotoxic effects on the liver which increases the above mentioned concern (13).

Many studies have evaluated the efficacy of terbinafine in white Caucasian populations (which some of them are sponsored by the manufacturer of the original brand product of drug) (8, 14-19) but up to knowledge of authors, there is not enough reliable data on both safety and efficacy of drug in Iranian pediatric patients with ringworm. The aim of present study is to evaluate the safety and efficacy of terbinafine in a pediatric Iranian cohort of patients with Tinea capitis.
and patients were asked for a third visit. The course of therapy was extended only for one week in the negative results of mycological studies, the only clinical signs were not completely cured despite 14 day treatment with terbinafine was tried and if anxiety. If therapy was not complete, another course of upset, skin rash, itching, headache, fatigue or any adverse effects like gastrointestinal drug’s probable adverse effects (gastrointestinal upset, skin rash, itching, headache, fatigue or anxiety) was completed before the start of therapy, and after 2nd, 4th, 5th, 6th and 8th weeks. Eligible patients with less than 20 kg of body weight were given 62.5mg (¼ of Lamisil® 250mg tablet) and if the patients, total body weight were between 20 to 40 kg, the dose was 125mg (½ of Lamisil® 250mg tablet) on the first visit. After two weeks, all patients had a second clinical visit and a second sample for microscopic study was taken. Patients were advised to take the prescribed dose of terbinafine tablet before meal and contact the attending physician if they felt any unexpected effect like gastrointestinal upset, skin rash, itching, headache, fatigue or anxiety. If therapy was not complete, another course of 14 day treatment with terbinafine was tried and if only clinical signs were not completely cured despite the negative results of mycological studies, the course of therapy was extended only for one week and patients were asked for a third visit.

Methods

The study design was open label clinical trial which was conducted in a general and referral teaching hospital affiliated with Tehran University of Medical Sciences (Imam medical centre, Tehran, Iran) from 2006 to 2007. All pediatric patients (up to 12 years old) with clinical signs and symptoms of erythema, scaling, hair loss and scalp itching whom were diagnosed for tinea capitis by a registered dermatologist (PM) and laboratory confirmation of primary diagnosis with a positive test of potassium hydroxide (KOH) were considered eligible for the study. During the study, patients with chronic or active liver disease or any undiagnosed rise of hepatic marker enzymes (e.g. ALT & AST), complicated gastrointestinal disease, concurrent seborrheic dermatitis, or other scalp conditions such as scabies, psoriasis, head lice, or atopic dermatitis or use of any oral/topical treatment for tinea capitis in the past 2 weeks of therapy and also patients with signs and symptoms of hypersensitivity to terbinafine after the start of therapy, were excluded. Sampling was randomly using convenient sampling method based on patients visits. For all patients who met inclusion criteria a research profile including demographic data (e.g. name, age, sex, and weight), location of infection on scalp, duration of disease, previous therapy, baseline hepatic enzymes (ALT/AST), result of KOH test and mycologic culture result and drug’s probable adverse effects (gastrointestinal upset, skin rash, itching, headache, fatigue or anxiety) was completed before the start of therapy, and after 2nd, 4th, 5th, 6th and 8th weeks. Eligible patients with less than 20 kg of body weight were given 62.5mg (¼ of Lamisil® 250mg tablet) and if the patients, total body weight were between 20 to 40 kg, the dose was 125mg (½ of Lamisil® 250mg tablet) on the first visit. After two weeks, all patients had a second clinical visit and a second sample for microscopic study was taken. Patients were advised to take the prescribed dose of terbinafine tablet before meal and contact the attending physician if they felt any unexpected effect like gastrointestinal upset, skin rash, itching, headache, fatigue or anxiety. If therapy was not complete, another course of 14 day treatment with terbinafine was tried and if only clinical signs were not completely cured despite the negative results of mycological studies, the course of therapy was extended only for one week and patients were asked for a third visit.

All eligible patients and their parents or guardians as well were interviewed by one of the investigators for explaining the whole study and also were completely free to let their child be included in the study or not. All the included subjects had also a written informed consent form which was signed freely after the interview by their guardians and they could ask for exclusion their child from the study without any fear of loosing their routine medical care. The study was performed in accordance with guidelines laid down by the Declaration of Helsinki II and also Tehran declaration for ethics in human researches. The study protocol was approved by the board of human studies in deputy of research at Tehran university of medical sciences. It should be mentioned that despite the fulfillment of all ethical issues in this study, here in Middle East, due to some cultural reasons, taking a signed informed consent form like what is taken in the same routine clinical trials in west, is so difficult.

Using NCSS-PASS (Jerry Hintze, Utah, 2004) the minimum patient number for at least an 80% of total cure 4 weeks of therapy (α=0.05) and for a power of 80%, was calculated as 30 patients. Providing an about 100% of dropping out patients (as they may meet the exclusion criteria or may not follow the long course of therapy) the total patients number needed for the study was at least 60. χ², Mann-Whitney U test, t Student and t-paired test was performed for statistical analysis using SPSS 11 statistical software.

Results

During 14 month of study, 60 patients (met the inclusion criteria from which 30 patients (17 male and 13 female) has completed the full course of study (8 weeks). One patient was infant (<2 years), 8 were between 2 and 6 and most of them (21) were more than 6 and less than 12 years old. 46.6% (14) patient had ringworm lesion in upper area of scalp, 20% (6) in the back, 26.6% (8) in right up and left up, and 6.6% (2) in the frontal part. Regarding the traditional classification of tinea capitis based on KOH test, 70% (21) of patients had endotrix form and the rest of them had favus lesions. 22 patients had no previous medical treatment before the study, while 4 had 6 weeks course of griseofulvin, 2 on oral tablet of ketokonazole and 2 on topical clotrimazole at least 14 days before the inclusion. The result of mycologic culture of study patients lesions were as
follow: Microsporum canis (46.7%), Trichophyton sheonlini (30%), Trichophyton verrucosum (10%), Microsporum gypsium (6.7%) and Trichophyton tonsurans (6.7%). No case of hepatotoxicity (rise of ALT/AST to more than 5 times of baseline) was reported (Table 1).

Table 1: Reported side effects of Terbinafine in study patients

<table>
<thead>
<tr>
<th>Side effect</th>
<th>% (number of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gastrointestinal upset</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Itching</td>
<td>16.7 (5)</td>
</tr>
<tr>
<td>skin rash</td>
<td>6.7 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>6.7 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.3 (1)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3.3 (1)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Fig. 1. Response rate of study patients to terbinafine.

Discussion

Terbinafine is a member of a new family of antifungal drugs, Allylamines. In spite of Azoles which are fungi growth inhibitors, Terbinafine is a real fungicide. Terbinafine not only by inhibiting ergosterol synthesize but also by accumulating squalene as well, leads to fungi destruction (9). Concerning therapy rate and high healing percentage even until 3 weeks after quitting drug intake, active drug concentration is high in stratum corneum and remains there for a long time after finishing therapy period (20). 30 patients which were about 7 years old, have been participated in this study. Most of the patients suffered from itching, scaling and hair loss while the affected site was on the top and frontal part of the scalp. The infection history was from one week to 2 years.

Out of 30 study patients, the direct mycology examination (KOH test) of 13.3% in the second week, 90% in the fourth, 93.3% in the fifth and 100% in the sixth week, was negative. Also, 0% of the patients in the second week, 60% in the fourth, 65% in the fifth, 80% in the sixth and 100% in the eighth week, revealed clinical healing (Fig. 1). All patients, healed completely from scaling, itching and hair loss, after six weeks. Only scar, partial inflammation and bleeding continued in 4 patients after 2 weeks, which were healed until the end of therapy period. Concerning complete therapy (clinical healing and negative culture), none of the patients healed until the fifth week but 80% in the sixth, 92% in the eighth and 100% in the twelfth week, healed completely.

In one review research, out of 21 studies with 1812 participants, terbinafine for four weeks and griseofulvin for eight weeks showed similar efficacy in 3 studies involving 382 participants. So, newer treatments including terbinafine, may be similar to griseofulvin in children with tinea capitis caused by Trichophyton species. Also, because of its fungicidal action, it requires shorter treatment period than griseofulvin.

In a same study which evaluated the effectiveness and tolerability of terbinafine treatment for a period of 12 weeks in tinea capitis caused by Microsporum canis, out of 26 patients, clinical and mycological healing was achieved in 22 patients (84.6%). Tolerability was excellent and in no cases were side effects (21). So, concerning terbinafine efficacy, the results of this study is the same as present study. In other study on 176 patients with a clinical diagnosis of tinea capitis treated with oral terbinafine for 1, 2 and 4 weeks, effective treatment was achieved in 56%, 69% and 65% of patients, respectively. According to these results, 2 weeks of terbinafine therapy appears to be the optimal treatment duration for patients with tinea capitis (22).
Although the results of current study indicates that two weeks therapy with terbinafine is not sufficient for tinea capitis treatment and complete healing is achieved after 12 weeks.

In present study referred to questions asked from patients in special data forms, no severe lifethreatening side effect were seen in patients. According to previous studies about side effects of Terbinafine, 5% of the patients suffered from gastrointestinal complications such as nausea and vomiting and 3% suffered from urticaria. Non-specific side effects such as headache and taste disorder are also reported suffered from urticaria. No severe side effects have not been seen in patients, which is the same as current study (24-26).

According to the results of this study, terbinafine is an effective therapy in cases of Tinea capitis in children without having severe side effects.

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References

ملخص البحث

(الخليفيه والأهداف: إن سعفة الرأس (Tinea capitis) هي عودة عامة للفروه الرأس وحيدة الشعر بسببها فطر جلدي يصيب الأطفال قبل سن البلوغ. ويتطلب الأمر علاجاً مجموعياً (جهنياً) لمعالجة ومنع انتشار المرض.

الطريقة: أدخل إلى الدراسة 30 مريضاً إيرانياً من الأطفال الذين نشأت مشاكلهم إيبتيكياً بسعفة الرأس. وأجريت الدراسة في مستشفى حالة تعليمي وعام (مركز الإمام الطبي، طهران، إيران) من 2006 إلى 2007. وقد أعطي المرضى الموثوقين الذين بلغ وزنهم عن 20 كغم 62.5 كغم من مادة تيربينافين، وكذلك المرضى بين 20 إلى 40 كغم 125 مع من الدواء في زياراتهم الأولى. وبعد أسبوعين، تم أخذ عينة ثانوية للدراسة المجهرية أثناء زياراتهم الثانية. وقد أجري لكل مريض الاختبار المباشر للطفيات (اختبار هيدروكسيد البيوتاميس) ومزرعة فطرية قبل بدء الدراسة وبعد الأسابيع الثانية والرابعة والسادسة والسادس الثامن. ثم أيضاً تسجيل الآثار الحادة المحتملة للدواء.

النتائج: استماعاً على نتائج المزرعة الفطرية لأفات المرضي فقد أعتر أن هو المسبب الرئيسي لسعفة الرأس في هؤلاء الأطفال. ومن بين 30 مريضاً تم دراستهم، بين أن نتائج 93% منهم في الأسبوع الخامس 100% في الأسبوع السادس كانت سلبية. وقد شغل جميع المرضى تماماً من إعلانات الموعد بعد ستة أسابيع. ولم يكن هناك أيضا أي أثار جانبية لدواء.

الاستنتاج: حسب نتائج الدراسة، فإن دواء تيربينافين هو علاج فعال في الحالات الإيرانية لسعفة الرأس دون التسبب في آثار جانبية حادة.

البحث

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