Clinical and laboratory study

TERBINAFINE LEVELS IN HAIR-SAMPLES OF CHILDREN WITH MICROSPORUM CANIS SCALP INFECTION

V. Dragoš and L. Zaletel-Kragelj

ABSTRACT

Eighteen children, aged 2-11 years, with *Microsporum canis* scalp infection were treated with terbinafine orally for 6-16 weeks according to body weight. We studied the levels of terbinafine in the hair samples with HPLC (high-pressure liquid chromatography) at the end of treatment and again 1 and 2 weeks later. Hair samples were obtained by shaving the same area of the scalp. The cultures were made simultaneously. The concentration of terbinafine expressed in ng/10mg of hair weight was correlated with the result of culture (positive-negative). Eleven of 18 children had all cultures negative and the treatment was successful. The median value of terbinafine concentrations were 337ng/10mg of hair, at the end of the therapy, 378ng/10mg hair one week later, and 56ng/10mg hair two weeks later. Seven of 18 children had all cultures positive and treatment was not successful. The median values of terbinafine concentrations were 15ng/10mg of hair at the end of treatment, 5ng/10mg of hair one week later and, 7ng/10mg of hairs 2 weeks later. The concentrations of terbinafine were much higher in the group of patients, in whom the therapy was successful, although there were no differences in the age, dosage of the drug and duration of the treatment. The reasons for differences are not known and may have appeared due to lower sebum output in some patients. *Microsporum canis* may need much higher levels of the systemic antifugals at the site of infection for complete cure. The determination of drug levels in the target tissue and its correlation with cultures may be a useful method of evaluating the in vivo effect of systemically administered antifungals.

KEY WORDS

terbinafine level, Microsporum canis, tinea capitis, children

INTRODUCTION

Microsporum canis (M.canis) has been the most frequent dermatophyte isolated in Slovenia since 1989 (1). The majority of patients with microsporosis are children and scalp infection appears in 7% of these patients (2). *Microsporum canis* causes scalp lesions with slight erythema, scaling and broken-off hairs. Typical inflammatory lesions occur rarely.

Topical treatment of tinea capitis is usually ineffective; years ago oral griseofulvin was the only systemic antifungal agent available for tinea capitis. In the treatment of *M. canis* tinea capitis griseofulvin in the dosage of 10 mg/ kg/day usually for 23 weeks

was needed (2). Complete cure was achieved after 6-8 weeks of treatment when higher doses of 15-30 mg/kg/ day were given (3).

During the last few years we treated children with *M. canis* scalp infection with oral terbinafine. The drug inhibits the synthesis of ergosterol and has primarily fungicidal action (4). It was found effective in the treatment of various dermatophyte skin and scalp infections in childhood (5,6). Tinea capitis caused by *Trichophyton spp.* was effectively treated after a period of 4 weeks (7,8). However, in scalp infection due to *M. canis* longer treatment or higher dosis of oral terbinafine were required for a complete cure (5,9).

Orally given terbinafine is delivered to different skin compartments by direct diffusion through dermis and epidermis and persist there for several weeks after the last day of medication (10). The concentration of orally given antifungal agent at the site of infection is most important for the curative effect of the drug.

In order to evaluate the distribution of orally given terbinafine in childrens' hair we studied the levels of terbinafine in hair samples of children who were treated orally with terbinafine due to *M. canis* scalp infection.

MATERIALS AND METHODS

Eighteen children, 13 boys and 5 girls, whose age ranged from 2-11 years, with non-inflammatory tinea capitis due to *M. canis*, were treated with oral terbinafine according to body weight for 6-16 weeks. Terbinafine was given once daily, and the dosage was as follows: 62,5 mg/day for children weighing less than 20 kg; 125 mg/day for those weighing 20-40 kg; and 250 mg/day for those weighing more than 40 kg. Hair samples were obtained by shaving the same area of app. 5 cm^2, first at the end of the therapy and again one and two weeks later. The hair samples were stored in tarred tubes and were deeply frozen (-20°C). The levels of terbinafine in the hair samples were analyzed by HPLC in CEPHAC-EUROPE, 90 Avenue des Hautes de la Chaume, BP 28 86281, Saint-Benoit Cedex, France. The cultures for dermatophytes were made simultaneously. The concentrations of terbinafine were correlated with the results of culture analyses (positive-negative).

The aim of the study was to determine whether there is any difference in the concentration of terbinafine in hair samples between the children who responded to therapy and those who did not. We also wanted to know if terbinafine is present in newly grown hair, one and two weeks after the discontinuation of the drug.

RESULTS

The concentrations of terbinafine in hair samples at the end of treatment, at one and two weeks follow-up and the statistical evaluation (Mann-Whitney U test) are presented in table 1. (See Table 1)

In the group A, 11 out of 18 patients had all cultures negative and treatment was successful. The median value of terbinafine concentration was 337 ng/10mg hair at the end of therapy, one week later it was 378ng/10mg hair, two weeks later it fell to 56 ng/10mg of hair. The mean rank of drug concentrations was 11.32 at the end of therapy, 11.05 after one week and 10.41 after two weeks.

In group B, 7 out of 18 patients, the cultures were positive and treatment was not successful. The median value of terbinafine concentration at the end of the treatment was 15 ng/10mg of hair; one week later it fell to 5 ng/10mg of hair and two weeks later it was 7 ng/10mg of hair. The mean ranks of the drug concentrations were 6.64 at the end of treatment, 7.07 after one week and 8.07 after two weeks.

The concentration of terbinafine was more than 20 times higher at the end of treatment in the group A compared to group B. Significant differences (Mann-Whitney U test) were present at the end of treatment. One and two weeks later mean rank of terbinafine concentrations were lower in the group of patients in whom the treatment was not successful.

There were no differences in the age, dosage, and the duration of the treatment between the two groups of patients. Table 2.

DISCUSSION

Terbinafine is a fungicidal drug of the allylamine group. It has high in vitro activity against various dermatophytes with MIC of 0,002-0,008 mg/ml (4). In vivo studies are necessary to determine whether in vitro susceptibility profiles correlate with clinical efficacy (11).

Terbinafine reaches the stratum corneum and hair follicles by passive diffusions from the blood stream as well as via sebum (12). It may be incorporated into the basal keratinocytes and transported to the

Table 1. Distribution of terbinafine concentrations in ng/10mg of hair in children with M. canis scalp infection at the end of the treatment (week 0), one week (week 1) and two weeks (week 2) afterwards; significance of differences (Mann-Whitney U test). In group A the treatment was successful in group B it was not.

	group A (n=11)				**group B (n = 7)**				**p**
week	*quartile 1* ng/10 mg hairs	***median*** ng/10 mg hairs	*quartile 3* ng/10 mg hairs	***mean rank***	*quartile 1* ng/10 mg hairs	***median*** ng/10 mg hairs	*quartile 3* ng/10 mg hairs	***mean rank***	
0	11	**337**	1198	**11.32**	5	**15**	20	**6.64**	0.070
1	9	**378**	1504	**11.05**	5	**5**	17	**7.07**	0.122
2	5	**56**	241	**10.41**	5	**7**	12	**8.07**	0.356

stratum corneum during normal cell turnover. High levels of terbinafine were found in sebum and it may be beneficial in the treatment of mycotic infection of the hair follicles. Terbinafine strongly adheres to keratin (12). In the study performed by Faergemann, healthy adult volunteers, who had been receiving 250 mg of terbinafine for 7 days, had a drug concentration exceeding the MIC for most dermatophytes by a factor of 10-100 in various compartments of the skin, 54 days after the last day of medication (10).

Orally administered terbinafine was distributed in the childrens' hair. In children in whom the therapy was successful, twenty times higher drug levels were present in the hairs at the end of treatment compared to the group of patients in whom the therapy was not successful.

Table 2. Significance of differences (Mann-Whitney U test for numerical data and Fisher exact test for count data) for age, dosis of terbinafine and duration of treatment in children with M. canis scalp infection which could influence the results of treatment: in group A the treatment was successful in group B it was not.

	Group A (n =11)				**group B (n = 7)**				**p**
factor	*quartile1*	***median***	*quartile3*	***mean rank***	*quartile1*	***median***	*quartile3*	***mean rank***	
age (years)	3	**5**	7	**9.41**	2	**5**	11	**9.64**	0.927
dosis of terbinafine mg/kg b.w.	4.1	**4.3**	5.4	**9.09**	3.2	**5.0**	8.9	**10.14**	0.683
duration of treatment (weeks)	6.0	**12.0**	15.0	**9.55**	8.0	**12.0**	14.0	**9.43**	0.964

Nearly the same concentrations persisted one week after the discontinuation of the drug, which demonstrates that the drug is present in newly grown hairs. In some patients very high levels of the drug were found. The reason for this might be shaving the hair instead of clipping, the later being easier to perform in children. In studies performed in adult volunteers, the hair was clipped close to the skin (10,12). Some of the most superficial cells from the stratum corneum were probably present in our samples. In tinea capitis it is important to treat not only the hair shafts but also the skin between them; high levels of the drug in the most superficial parts of the skin are necessary for cure.

The phenomenon of terbinafine exerting its therapeutic effect after cessation of therapy has already been observed in clinical studies (5,8). In some recent studies, even shorter oral terbinafine treatments of 1-2 weeks have been successful (7). It can be explained by the persistence of high levels of the drug in the target tissue. Our observation in children was similar.

More interesting was the finding that the children in whom the treatment was not successful had lower levels of the drug in hair at the end of treatment although there were no differences in age, dosage and duration of the treatment compared to the group in whom the treatment was successful. The reasons for this observation are not known as yet. Terbinafine is a highly lipophilic drug; lower levels of the drug may be due to lower sebum output in those children. *M. canis* scalp infection is one of the most difficult dermatophytosis to treat and much higher concentrations of the antifungals are probably needed at the site of infection for a complete cure. In the future more studies should be performed in larger groups of children. The assessment of drug levels in the target tissue and its correlation with culture analyses may be a useful method of evaluating the in vivo effect of systemic treatment with antimycotics.

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