Original experimental study

TREATMENT OF MICROSPORUM CANIS INFECTED CATS WITH TERBINAFINE

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ABSTRACT

Terbinafine is a new allylamine antifungal agent with its primary characteristic of fungicidal action. Because of its excellent qualities this drug is interesting for use in veterinary medicine too. Among the diseases, which are common in humans and animals, we are dealing with the effective control of *Microsporum canis* infection. Humans are often infected by contact with cats. The most dangerous sources of infection are stray cats and asymptomatic carriers. Because an effective vaccine against the disease is still not available, it is important to detect infected cats and treat them. Due to excellent results in humans it is reasonable to use the terbinafine.

Our preliminary results using terbinafine in cats showed that cats tolerated terbinafine well in a dosage of 10-20 mg/kg daily for 5 months. Half of the cats got cured in 145 days, and all were cured in 159 days. It is too early to estimate the result of such treatment, but according to our clinical experience with the combination of drugs, we would expect shorter treatment periods from a fungicidal agent. It is highly probable that the dose 10-20 mg/kg in cats acts fungistatically and that higher doses should also be tried.

KEY WORDS

terbinafine, cats, M.canis, dermatophytes, treatment

INTRODUCTION

Microsporum canis (M. canis) infection in man was first recognized in Slovenia in 1977 (1) and in animals in 1984 (2). From 1986 we have been able to follow a constant increase in the number of cases and the spread of the disease all over the country (3). Important sources of infection for humans are considered household or stray cats (4). *M.canis* is the most common cause of dermatophytosis in cats (5). It is estimated that seventy percent of humans become infected by contact with cats (1), and half of exposed individuals become infected (6). Besides the direct infection from animals, hair shafts containing infectious arthrospores may remain infectious in the environment up to 18 months (7,8). Asymptomatic carriers of *M.canis* in cats represent a very important

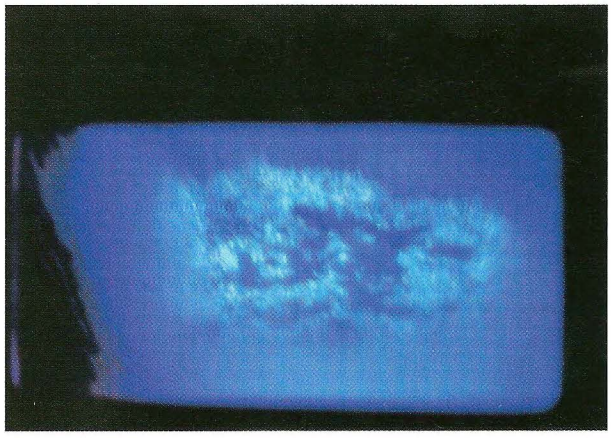

Figure 1. Positive Wood's lamp examination of the experimentally infected site. A well-expressed lesion is presented. We were able to observe the fluorescence of the hair shafts as soon as 7 days post inoculation.

and often unsuspected threat to animals and humans. Show cats, cattery cats, and those frequenting veterinary clinics, in 6.5 to 100 per cent may be asymptomatic carriers of *M. canis* (9). Approximately one half of infected cats may not show any clinical signs (2,4). The isolation of *M. canis* from a cat should be considered as a significant finding and treatment should be initiated (10).

Terbinafine is a new allylamine antifungal agent, which acts by preventing fungal ergosterol biosynthesis via specific and selective inhibition of fungal squalene epoxidase. Fungi treated with these drugs accumulate squalene while becoming deficient in ergosterol, an essential component of fungal cell membranes. It seems that the terbinafine's fungicidal action is

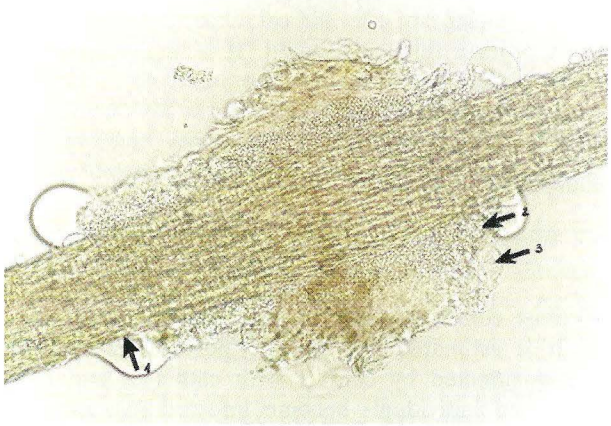

Figure 2. Infected hair at the high power magnification, 400 x, native. Changed, thick hair shaft (1) surrounded by arthrospores (2), and numerous of hyphae (3).

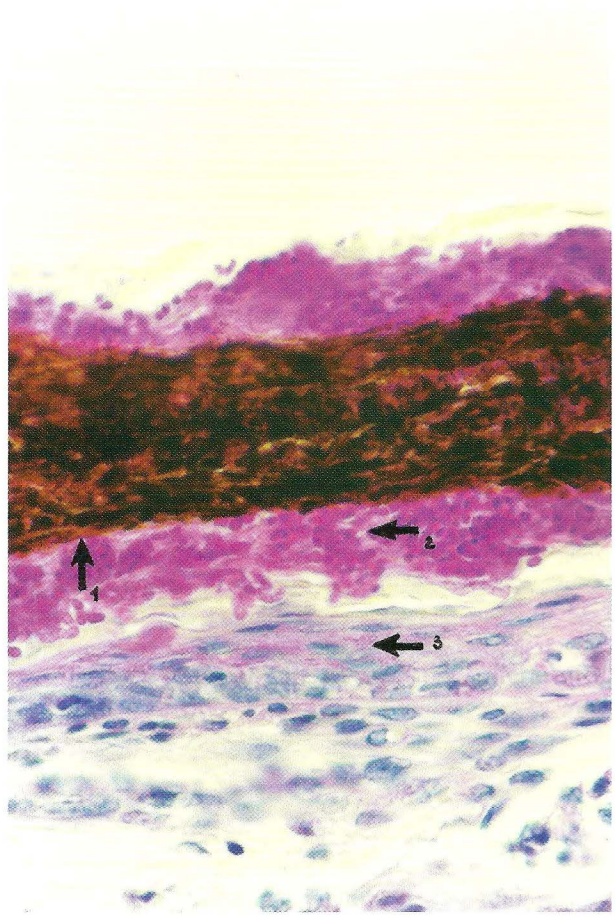

Figure 3. Infected hair; periodic acid Schiff (PAS) stain, 400 x. A changed hair shaft (1), pink arthrospores surrounding the involved hair (2) and wall of the hair follicle seems to be normal (3).

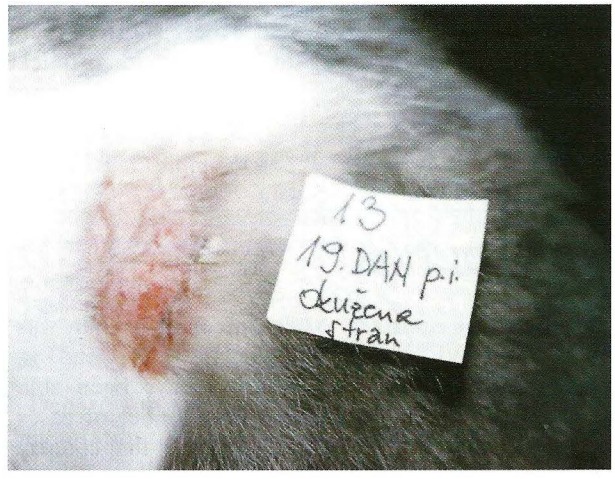

Figure 4. Infected site of a cat, day 19.

closely associated with the development of high intracellular squalene concentrations (11,12,13). The development of high intracellular squalene concentrations is not characteristic of azoles - another large group of antifungal drugs. These drugs prevent synthesis of ergosterol at a different step, by inhibition of the enzyme 14-α-demethylase. The mode of their action is fungistatic and they exhibit side effects by affecting sterol synthesis in mammals (11,13,14). Terbinafine is active in vitro against a wide range of pathogenic fungi and is exceptionally potent against dermatophytes (12,15,16). The clinical experience with terbinafine in humans is extensive: an estimated 5 million patients have already been treated with oral terbinafine (17). There have been no reports to date on acquired resistance to the drug. This may also be connected with its fungicidal action, which leaves no opportunity for resistance to develop (18,19). The drug may provoke minor side effects in humans, mostly gastrointestinal disturbances, which appear at the beginning of the treatment and are transient (20,21). Because of its excellent qualities this drug is interesting for use in veterinary medicine too. According to our knowledge there are no published data yet on clinical use of terbinafine in cats.

MATERIAL AND METHODS

ANIMALS

Six healthy cats of domestic breed, five females, and one male were included in the study. The age at the beginning of the study ranged between 3 - 4,5 months. Before entering the study they were kept inside the facilities of the Veterinary faculty of Ljubljana. They never became exposed to any pathogenic fungi. They were FIV (Feline immunodeficiency virus) and FeLV (Feline leukemia virus) negative and received antihelmintics twice. Complete blood count, fungal culture and enzyme tests (AP, AST, ALT, GLDH, LDH) were performed before the study. During the study they were housed separately in individual cages.

Table 1. The scheme of the dosage of terbinafine. It is designed in the manner that the dose per kg ranged always between 10 to 20 mg, considering the growth of the young cats.

weight (kg)	portion of 125 mg tablet daily
0,0 - 3,0 kg	1/4
3,1 - 6,0 kg	1/2
6,1 - 9,0 kg	3/4

PREPARATION OF CONTAGIOUS MATERIAL

The cats were experimentally infected with a *M.canis* isolate of feline origin (1032/97) obtained from a hair sample of a naturally infected cat at the Small animal clinic of the Veterinary faculty of Ljubljana. The strain was highly fluorescent under the Wood's lamp. We prepared the contagious material using a similar method as it is described in literature (22). The hair sample was cultured for 14 days on Sabouraud's dextrose agar. Two plates were poured with 10 ml of sterile water each and the mycelial growth was gently scraped off. We used this suspension in the next 3 consecutive days. During the infection procedure, the suspension was stored at 4°C.

INDUCTION OF INFECTION

Cats were sedated with medetomidine (Domitor^R, Orion corp. Farmos, Finland) 0,1 ml/kg i/m and placed in dextral lateral recumbency. The hair was clipped from the left caudo-lateral thorax of each cat using Aesculap^R clippers so that 1-2 mm long hair remained spared in the clipped area. A 5 x 4 cm area was marked with a water-resistant pencil. The skin was gently scarified with a scalpel blade and 1 ml of mycelial suspension was rubbed into the clipped area using a sterile cotton swab. The same procedure was repeated for the next two consecutive days but without scarification; instead we gently rubbed the suspension into the skin for at least 3 minutes each time. The animals were fitted with Elisabethan collars for the incubation period of 14 days, because licking might remove the fungi from the skin and render the infection procedure more difficult (7,23).

TREATMENT AND MONITORING

During the incubation period of 14 days cats wore Elisabethan collars so they couldn't lick the infected area. We monitored daily their general condition as well as the infected site and fluorescence with Wood's lamp (Figure 1). On days 4, 7, and 14 we sedated the animals again and took 6 mm punch skin biopsies, on days 7 and 14 we obtained blood and hairs from the infected cats.

The infection was confirmed on day 14 by culture,

microscopy, and histology.

On day 17 we started treatment with terbinafine (Lamisil^{R}, Novartis) 125 mg tablets (Table 1). The portions of a tablet as presented in Table 1 were placed individually into the mouth of each animal to make sure that every cat took the medicament. During treatment we daily monitored the general health status in order to recognize any side effects. Every week for the first 3 months and every 2nd week for the consecutive 2 months we estimated the clinical features and took body weight. We adjusted the dose of the medicament weekly when necessary. Hair samples were obtained every 2 weeks and stored for microscopy and fungal culture. Blood samples were obtained at the beginning of treatment and at week 10 of treatment. Skin biopsies were obtained at weeks 12, 14, 16, 20, and 24.

RESULTS

EXPERIMENTAL INFECTION

Experimental infection was successful in all 6 cats, as confirmed by culture, microscopy and histology at day 14 post inoculation (Figures 2 and 3).

SIDE EFFECTS

At the beginning of treatment (8th day) we noticed a softer stool in 4 animals. This was transient, and otherwise the animals were well. This appeared again a few times during treatment. One cat also vomited after taking a tablet on day 52. We then gave to give the tablets simultaneously with food and the sign disappeared. The same cat also developed lymphadenitis after the biopsy. We treated it for 9 days with amoxiclave injections and it responded to the treatment. All 6 animals completed the study.

Table 2. Days of treatment with terbinafine in cats with experimental M.canis infection (No=6).

days of treatment	number of non healed cats
14	6
28	6
42	6
56	6
70	6
84	5
102	4
114	4
133	4
145	3
159	0

DRUG DOSAGE

The animals had no problems with taking the medication. Adjustment of the dose was only necessary in one cat during treatment because of exceeded weight limit. At the beginning of treatment the dosage per kg ranged from 12.76 mg to 20.8 mg/kg, median 17.05 mg/kg. The doses at the end of the treatment ranged from 10.96 mg to 16.89 mg/kg, median 13.37 mg/kg (data not shown).

THE TIME OF CURE

For the estimation of the cure rate we considered the presence of alopecia, the presence of the Wood's lamp fluorescence, microscopy results, biopsy results and fungal culture results. Any animal which had 2 or more positive tests was considered not cured. Table 2 shows the numbers of healed animals with the days until cure.

DISCUSSION

Experimental infection was successful in all animals, we consider the method used as good and reliable. Periodically, a soft stool was noticed during treatment. This might be a side effect triggered by the drug. In humans mild gastrointestinal disturbances are one of the most common side effects with an incidence of 5%, while the incidence of all other side effects (skin rashes, loss of taste, nervous symptoms, headaches and elevated liver enzymes) accounts for 5.4% (21). Because the disturbance was mild and transient, we didn't consider it particularly important. Vomiting in one cat might show her special susceptibility to the drug or it may be only have been its reflex to bad taste. The problem was resolved with simultaneous feeding.

Recently, a study of pharmakokinetics of terbinafine in cats was done in Vienna (24). The author suggested a dose of 10 mg per kg daily to be the most appropriate. When we developed the treatment schedule, we tried to use this dose as much as possible. Among the tests for detection of the fungal skin infection the fungal culture is considered the most reliable (10), but it may also reflect a recent exposure to a contaminated environment (9). We followed the animals until fungal cultures were

negative. Because cats were caged for a long period we felt that the possibility of false positive culture results was greater. For that reason we decided to consider those animals not cured with at least 2 positive diagnostic tests at the same time. The sensitivity of microscopic examination was estimated at 70% and sensitivity of histology is around 80%, but when any of the tests is positive, it means definitive proof of infection (9). According to this we found that within 70 days of treatment no cat was healed, within 145 days of treatment one half of animals were cured and all were cured within 159 days.

It is too early to comment these preliminary results because it is necessary to wait for the data of the controls and the higher dosage groups. The occurrance of spontaneous remission must also be considered. In shorthaired cats it may occur within 4 months (9). We also have clinical experience with terbinafine used together with topically administered enilconazole in naturally *M.canis* infected cats. During the years 1995 and 1996 we used terbinafine orally in 18 cats, confirmed to be *M.canis* infected or carriers. Additionally to terbinafine, animals received enilconazol baths twice a week. Although the dosage of terbinafine ranged from 13.2 to 41.7 mg per kg daily, cats perfectly tolerated (both) drugs. Only one cat vomited. The dose used in this cat was 19.5 mg per kg daily. The time of cure ranged from 18 to 60 days with an average of 38.8 days (Orožim, unpublished data). We don't know what part either drug played in the treatment, but azoles and terbinafine may act synergistically for two reasons: they both disturb the synthesis of ergosterol on two different consecutive steps. Second: hepatic cytochrome P-450 is the crucial enzyme system in terbinafine degradation (13). As we know, azoles strongly inhibit this group of enzymes (11,13,14).

CONCLUSIONS

Our preliminary results show that cats tolerated terbinafine well in dosage of 10-20 mg/kg daily for 5 months. Half of the cats were cured in 145 days, and all were cured in 159 days. It is too early to estimate the result of such treatment, but according to our clinical experience with the combination of drugs we would expect shorter treatment periods from the fungicidal agent. It is highly possible that the dose of 10-20 mg/kg in cats only acts fungistatically and that higher doses should also be tried.

ACKNOWLEDGEMENT
We thank Novartis pharma for their kind support of this study.

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