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Original Article

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Association of itraconazole and potassium iodide in the treatment of feline sporotrichosis: a prospective study

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Abstract

Feline sporotrichosis is an endemic disease in Rio de Janeiro, Brazil, where zoonotic transmission of *Sporothrix* spp. has been reported since 1998. Itraconazole (ITZ) remains the first choice for treating this disease in cats. However, there have been reports of therapeutic failure and a long-term endeavor. Potassium iodide (KI), considered in the past as a drug with variable effectiveness in cats with sporotrichosis, arises as an important option in the treatment of cats from the endemic area of Rio de Janeiro. In order to evaluate the effectiveness of the association of ITZ and KI in naive cats with sporotrichosis, a prospective cohort study was conducted on 30 cats receiving ITZ 100 mg/day and KI 2.5 mg-20 mg/kg/day. Clinical and laboratory adverse effects were assessed once a month according to the standard care protocol. The cure rate was 96.15% within a median of 14 weeks of treatment. Adverse effects were observed in 50% of cats and were managed with a temporary drug suspension and/or a hepatoprotective therapy. The association of ITZ and KI emerges as an effective option for the treatment of feline sporotrichosis.

Key words: *Sporothrix*, cats, therapy, potassium iodide, itraconazole.

Introduction

Sporotrichosis is a mycosis caused by species of the *Sporothrix schenckii* complex.[1] The disease in cats has been reported in several countries, but nowhere else has had an outbreak of animal sporotrichosis as the one seen in the state of Rio de Janeiro, Brazil,[2] where more than 4000 cases were described between 1998 and 2012.[3] In this country,

the most prevalent etiological agent of feline sporotrichosis is *S. brasiliensis*.[4]

In the past years, zoonotic transmission of *Sporothrix* spp. from scratches, bites or contact with sick cats has been reported in Brazil, emphasizing the importance of this mycosis as a public health problem.[5]

The clinical manifestations of the disease in cats may range from an isolated skin lesion, which can progress to multiple lesions, and even to a fatal disseminated form.[6] Nodules and ulcers are the most common types of cutaneous lesions. Extracutaneous signs such as lymphadenitis[3], respiratory signs and mucosal involvement are frequent.[7]

The multifactorial difficulties of treating cats such as length of treatment, lack of conditions to keep the animal confined during treatment and noncompliance by the owners have been an obstacle for the control of this epidemic infection.[3]

Currently, itraconazole (ITZ) and potassium iodide (KI) are the most used drugs for the treatment of feline sporotrichosis and their effectiveness as a monotherapy has already been reported.[3,7] In cases refractory to ITZ, authors had already shown the effectiveness and safety of the combined therapy of ITZ and KI capsules.[3]

Thus, the aim of this study was to evaluate the effectiveness and safety of the association of ITZ and KI in treatment-naïve cats as a new therapeutic option for feline sporotrichosis.

Material and methods

The study was an observational cohort conducted in cats assisted at the Laboratory of Clinical Research on Dermatozoonosis in Domestic Animals (Lapclin-Dermzoo), Evandro Chagas National Institute of Infectious Diseases (INI)/Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil, during the period of 2013–2014. The cats considered eligible for this study were those with sporotrichosis confirmed by isolation of *Sporothrix* spp. in culture, no previous systemic antifungal therapy, and weight >3 kg.

The cats underwent a clinical examination and laboratory tests. Regarding the distribution of skin lesions, the cats were divided into three groups: L1 (cutaneous lesions in one location), L2 (cutaneous lesions in two noncontiguous locations), and L3 (cutaneous lesions in three or more nonadjacent locations).[6]

Exudate from the ulcerated lesion or secretion from the nasal cavities were collected by sterile swab and seeded on to Sabouraud dextrose agar and Mycobiotic agar (Difco), incubated at 25 °C and observed during 4 weeks for fungal growth. Suspected isolates were subcultivated on potato dextrose agar medium (Difco) at 25 °C for macroscopic and microscopic morphological studies, and dimorphism was demonstrated by conversion to the yeast-like form on brain heart infusion agar medium (Difco) at 37 °C. Blood samples were collected for biochemistry analysis (urea, creatinine, alanine transaminase [ALT], aspartate aminotransferase [AST]) before and during the treatment. All cats were tested serologically for the feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) with an immunoenzymatic test (Snap Combo FeLV/FIV; Idexx Laboratories).

The procedures of the study were approved by the Animal Ethics Committee (CEUA-Fiocruz); number LW 37/12, and informed consent was obtained from all owners.

Treatment

A regimen of oral ITZ 100 mg and KI 2.5 mg/kg in two different capsules was administered once a day with food by the owners. At the first appointment, the dose of KI was established at 2.5 mg/kg. The cats were observed monthly for clinical examination and laboratory tests.

At the follow-up visits in cases of persistence of the initial skin/mucosal lesion, persistence of respiratory signs or worsening of the lesion(s)—which was characterized by an enlargement and/or appearance of new lesion—the dose of KI was increased with a daily increment of 2.5 mg/kg at every 30-day period until a clinical response was achieved or until the dose reached 20 mg/kg maximum.

The criteria for clinical cure were complete healing of the skin/mucosal lesions and remission of clinical signs initially presented. After clinical cure, the therapy was maintained for an additional period of four weeks, which corresponded to the discharge assessment. All procedures and drugs were supplied free-of-charge for the cats' owners.

Management of adverse effects

Cats presenting hyporexia or anorexia combined with loss of >10% of body weight, or the association of clinical adverse effects (CAE) and laboratory alterations had a temporary suspension of the drugs (minimum seven days [ITZ] and ten days [KI]). The reintroduction of each drug happened in alternated and different times in the attempt to discover which drug was causing the unwanted effect. Furthermore, cats with a mild elevation in transaminases levels[8] received a hepatoprotective therapy with oral silymarin 30 mg/kg, once a day.[9]

Statistical analysis

Data were stored at Epidata (v. 3.1) and analyzed with R-software for Windows (v. 3.2.2). For descriptive analysis, we calculated the frequencies and proportion of the categorical variables and measures of central tendency for quantitative variables (median and interquartile range). The

Mann–Whitney U-test was used to verify the statistical differences in medians of two groups. To detect differences in three groups, the Kruskal–Wallis test was performed. The Fisher exact test of independence was used to compare proportions between nominal variables. In all specified analyses, a P-value $<.05$ was considered significant.

Results

Clinical and epidemiological characteristics

Thirty owned-cats of both sexes from the Rio de Janeiro metropolitan region were included in the study. Of these, 24 were males (80%), 27 had no defined breed (90%), 16 were sexually intact (53.33%), and 14 belonged to L3 group (46.67%). The median age and time of illness before treatment was 21 months (8–72 months) and 8 weeks (1–24 weeks), respectively. All cats presented skin lesions, mostly on the head (53.33%), especially on the nasal region (30%). Ulcer was the prevalent skin lesion (76.66%) ranging in number from one to 39 (median = 5). Eight cats also had nasal mucosa involvement (17%) and conjunctivitis (10%). Respiratory signs were observed in 20% of the cats, and rhinorrhea was the most common one followed by sneezing and dyspnea. Two cats tested positive for FeLV, but no association with negative outcome was detected ($P = 1.00$). Table 1 shows the clinical and epidemiological characteristics of interesting and therapeutic outcome.

Table 1. Descriptive for clinical and epidemiological characteristics of 30 cats with sporotrichosis treated with ITZ+KI, length of treatment and outcome.

Variables	n (%)
Sex	
Male	24 (80%)
Female	6 (20%)
Overall condition	
Good	25 (83.33%)
Fair	3 (10%)
Poor	2 (6.63%)
Access to outdoors	23 (76.67%)
Age, months*	21 (15–24)
Weight, kg*	3.8 (3.3–4.3)
Clinical form	
Cutaneous	22 (73%)
Cutaneous/Mucosal	8 (27%)
Distribution of skin lesions	
L1	7 (23.33%)
L2	9 (30%)
L3	14 (46.67%)
Lymphadenitis	25 (83.33%)
Lymphangitis	3 (10%)
Cats with KI increases	5 (16.67%)
Clinical cure**	25 (96.15%)
Time until remission of clinical signs, weeks*	9 (8–17)
Time until discharge, weeks*	14 (11.5–21.5)

*Continuous variables expressed as median and interquartile range (IQR 25–75%).
**Clinical cure calculated according to 26 cats.

Evaluation of treatment

Twenty-five cats achieved clinical cure (96.15%) and were discharged from the therapeutic protocol (Figure 1). One cat died (3.85%) during treatment and four cats were lost during follow-up.

The median dose of ITZ during the study was 26.3 mg/kg (19.6–33.3 mg/kg), while KI was 3.1 mg/kg (2.5–5.4 mg/kg). Five cats needed an increase of KI dose due to a poor improvement of skin lesions (n = 1), nasal mucosa lesions (n = 2) (Figure 2) and both (n = 2).

The median time of treatment until discharge was 14 weeks (8–30 weeks). Nevertheless, cats with mucosal involvement presented a longer median time (23 weeks) when compared to cats with skin lesion only ($P < .001$). The distribution of period of time until discharge for L1 (15 weeks), L2 (13 weeks), and L3 (15 weeks) was not statistically significant ($P = .6$).

Adverse effects

Adverse effects occurred in 50% of the cats under the study protocol. Of which, 20% showed only CAE, 16.67% presented just a mild elevation in transaminase levels and 13.33% presented both CAE and mild elevation in transaminases levels. The most frequent CAE were hyporexia and weight loss. Six cats had the therapy temporarily suspended due to clinical signs of hepatotoxicity or these signs combined with a mild elevation in transaminases levels. The type and frequency of the effects that drove to an interruption are shown in Table 2. All adverse effects that required suspension of the drugs were reversible within 7 to 20 days (median = 7 days) of drug suspension or hepatoprotective therapy. The abnormalities in biochemistry panel were transient, as shown by later measurements, which returned to predrug levels.

Discussion

This is the first report to evaluate the association of ITZ and KI in cats with sporotrichosis regarding clinical signs, clinical cure, and adverse effects. Sporotrichosis persists as a neglected disease in Rio de Janeiro, Brazil. The treatment of cats is difficult and the monotherapy with ITZ has variable cure rate. The association of ITZ and KI has been

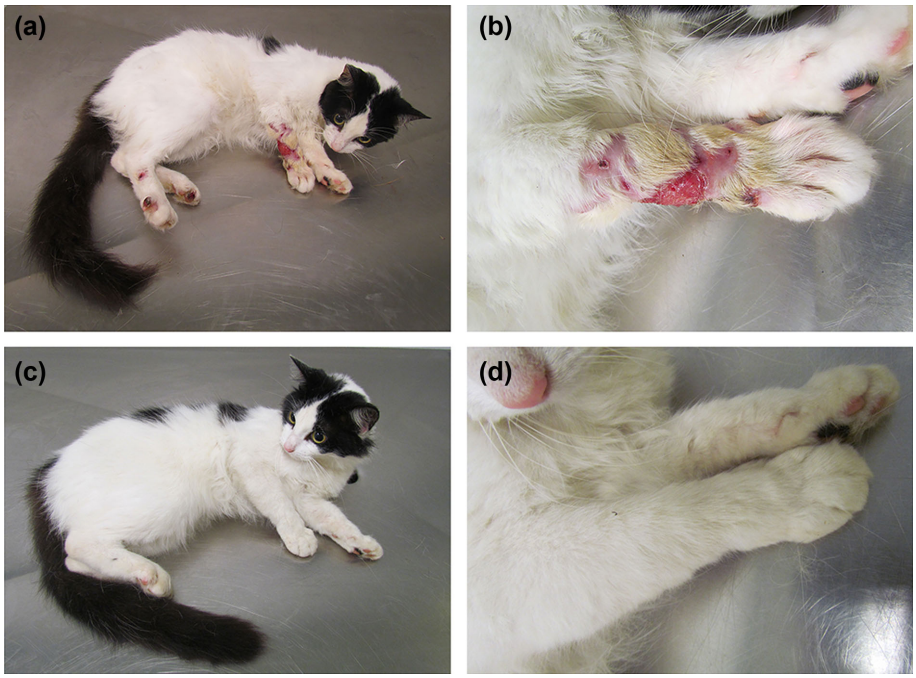

Figure 1. (a) Cat with sporotrichosis presenting multiple ulcers before antifungal treatment. (b) Close up picture of the extensive skin lesion on the right forelimb. (c, d) The skin lesions have resolved after ITZ and KI treatment. This Figure is reproduced in color in the online version of *Medical Mycology*.

Figure 2. (a) Cat with sporotrichosis presenting an ulcer on the nose before antifungal treatment. (b) Close up picture of the lesions on the nose and nasal mucosa. (c, d) The skin and mucosal lesions have resolved after ITZ and KI treatment. This Figure is reproduced in color in the online version of *Medical Mycology*.

successfully used in fungal infections with difficult resolution. This inspired us to conduct a study in cats.

The prevalence of male cats, young adults, sexually intact from the metropolitan area of Rio de Janeiro corroborates with the findings of previous studies.[2,6,7,10,11] The unneutered male cat with unrestricted access to outdoors is the most affected and involved in the agent dispersal in the environment.[12,13] The clinical aspect, location, and

Table 2. Distribution of adverse effects and drug interruption observed in cats with sporotrichosis under ITZ+KI treatment.

Cat	Type of adverse effect	Temporary drug interruption (length)
1	↑ALT	N/A
2	↑ALT	N/A
3	↑ALT	N/A
4	↑ALT +↑AST; Hyporexia + weight loss	Twice (7 days each)
5	↑ALT + ↑AST; Anorexia + weight loss	Once (20 days)
6	↑ALT + ↑AST; Hyporexia + weight loss	Once (7 days)
7	↑ALT; Hyporexia + weight loss	Twice (10 days; 7 days)
8	↑ALT + ↑AST	N/A
9	↑ALT	N/A
10	Hyporexia + weight loss	Once (7 days)
11	Anorexia + weight loss	Once (7 days)
12	Vomiting + weight loss	N/A
13	Hyporexia + vomiting	N/A
14	Weight loss	N/A
15	Hyporexia	N/A

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; N/A: Not applicable; ↑: High.

distribution of cutaneous lesions, and time of illness before treatment were similar to other studies of the same area.[3,6,14]

Lymphadenitis (83.33%) was the most frequent extracutaneous sign followed by mucosal involvement (27%) and respiratory signs (20%). In feline sporotrichosis, mucosal involvement is quite common, especially the nasal mucosa, combined with nasal discharge and sneezing[6,7,10] as noted in this series. The conjunctival mucosa was also affected as reported previously.[15]

The cats that tested positive for FeLV achieved complete resolution of clinical signs following treatment. These results corroborate with other authors[6,7,10] which could not find an association between feline retrovirus coinfection and a negative outcome in feline sporotrichosis treatment.

Despite the increasing number of cases of sporotrichosis and the high zoonotic potential of cats, few studies have presented alternatives for the treatment of feline sporotrichosis so far. ITZ remains the drug of choice even with failure reports and longtime treatment.[10,14] Besides ITZ, ketoconazole,[10] amphotericin B,[14] and KI[7] have been described for treating this disease in cats. Terbinafine and posaconazole have shown good activity *in vitro* against *S. brasiliensis* isolates[16]; however, there are no studies that evaluated the effectiveness and safety of these drugs in feline sporotrichosis. KI capsules as a monotherapy has been successfully used both in treating naïve cats[7] and in refractory to ITZ.[17] The association of ITZ and KI was described for the treatment of sporotrichosis[18] and other fungal infections in humans[19,20] as well as for sporotrichosis in cats' refractory to ITZ.[21] The combination of ITZ and KI is referred as providing better outcome when compared to each drug alone.[19,20]

Although most of the studies in cats with sporotrichosis have been reported by our research group, the comparison between these results and others previously reported must be carefully considered due to differences in study design.

The cure rate described in this study was higher than in previous reports from the same endemic region using ITZ and KI as monotherapy.[7,10] Unusually, in a retrospective study, authors reported clinical cure in 17 cats (100%) treated with ITZ 10 mg/kg,[22] although it has been mentioned capsules of ITZ 100 mg. Since it was impossible to confirm the dose of ITZ used and the clinical monitoring that was performed, these results have not been considered for comparison with our findings. Regarding the effectiveness of ITZ and KI in cats, the results of this study showed better cure rates compared to those cats' refractory to ITZ 100 mg/day[21] (96.15% vs 63.2%, respectively). These findings may confirm that treatment of cats' refractory to ITZ is more difficult and requires greater adherence of the cats' owners to the proposed therapeutic protocol.

A higher dose of ITZ has been used in this series since the one usually reported in literature (5–10 mg/kg/24 h) has previously shown to be inefficient in achieving clinical cure in cats from Rio de Janeiro.[10] The dose of KI used was lower than reported by Reis et al.[7] and could be explained by the combined therapy of ITZ and KI enhancing the antifungal activity and a small number of cats presenting mucosal involvement and respiratory signs, which are known to be a hindrance to clinical cure.

The time until discharge in this study was markedly lower (median = 14 weeks) than in previous reports with ITZ monotherapy (median = 26).[10] Nonetheless, it is consistent with the period heretofore described with KI monotherapy.[7] Although length of treatment in this series

was 14 weeks, the median time until complete remission of clinical signs was 9 weeks, which corresponds to the first evidence of clinical cure.

The occurrence of adverse effects during treatment with azoles and KI monotherapy is frequent and it has been completely established. Anorexia and increased ALT are considered to be dose dependent of ITZ[23] and also had been reported in cats with sporotrichosis under KI therapy.[7] The adverse effects are managed with a temporary drug suspension and an accurate clinical follow-up. The CAE of ITZ and KI were similar to those observed in ITZ alone[10] (8.3–27.7 mg/kg) and lower than those reported on KI monotherapy (2.5–20 mg/kg).[7] The latter fact may be explained by a lower KI dosage used here.

The mechanism of action of iodides remains poorly understood and the antifungal activity *in vitro* of this agent has never been confirmed. The immune-modulating role may be the key for the satisfactory response to treatment,[24,25] and thus, the use of drugs that may boost the immune system such as KI, should be explored for association with ITZ for treating feline sporotrichosis.

Therefore, ITZ combined with KI emerge as an effective treatment with a faster onset of action and a moderate percentual of adverse effects. To be considered as a first-line treatment of feline sporotrichosis, a clinical trial should be carried out comparing ITZ and the association of ITZ and KI in treatment naive cats. Nevertheless, the high costs of controlled clinical trials combined to the lower adherence of the owners are some of the obstacles for novel therapeutic protocols in cats with sporotrichosis.

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Declaration of interest

The authors do not have any potential conflicts of interest to declare.

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