




Potassium iodide capsule treatment of feline sporotrichosis

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Abstract

Sporotrichosis is a mycosis caused by *Sporothrix schenckii*. The most affected animal is the cat; it has played an important role in the zoonotic transmission of this disease, especially in Rio de Janeiro, Brazil, since 1998. In order to evaluate the treatment of feline sporotrichosis with potassium iodide, an observational cohort was conducted in 48 cats with sporotrichosis at Instituto de Pesquisa Clínica Evandro Chagas, Fiocruz. All cats received potassium iodide capsules, 2.5 mg/kg to 20 mg/kg q24h. The cure rate was 47.9%, treatment failure was 37.5%, treatment abandonment was 10.4% and death was 4.2%. Clinical adverse effects were observed in 52.1% of the cases. Thirteen cats had a mild increase in hepatic transaminase levels during the treatment, six of them presented clinical signs suggestive of hepatotoxicity. Compared to previous studies with itraconazole and iodide in saturated solution, potassium iodide capsules are an alternative for feline sporotrichosis treatment.

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Introduction

Sporotrichosis is a mycosis caused by the dimorphic fungus *Sporothrix schenckii*, which infects humans, as well as other mammals, especially domestic cats. Classic infection is associated with traumatic, cutaneous inoculation of the fungus.^{1,2}

Sporotrichosis occurs worldwide but is endemic in Latin America, India, South Africa and Japan. In the state of Rio de Janeiro, Brazil, a zoonotic form of this disease has been emerging over the last 12 years in a region with socioeconomic and environmental difficulties.³ In this epidemic, the domestic cat is involved in zoonotic transmission through scratches, bites and contact with lesion secretions. The potential of transmission is related to the high parasite burden in skin lesions in comparison to other animal species.^{3,4}

Infections of *S schenckii* in cats range from a subclinical form that can progress to multiple skin lesions and fatal systemic involvement with or without extracutaneous signs, particularly respiratory signs. Subcutaneous nodules and ulcers are the most frequent skin lesions in sick cats and can be found at three or more non-contiguous anatomical sites.^{5–7}

Treatment of feline sporotrichosis presents a challenge as there is a limited number of oral antifungal agents, in

addition to the adverse effects and high cost.⁶ The azoles, ketoconazole and itraconazole, are the most common drugs for the treatment of feline sporotrichosis.⁸ Itraconazole is considered the drug of choice,^{9,10} especially when cost is not an issue.¹¹ Although treatment with itraconazole has proved to be effective in cats, the clinical response is unsatisfactory in some cases, especially in those with respiratory signs and nasal mucosa lesions.^{6,12} In refractory cases to oral itraconazole, intralésional (IL) administration of amphotericin B^{6,13} or oral potassium iodide (KI) might be an alternative.¹⁴

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KI, the first successful drug for the treatment of human sporotrichosis, continues to be used for fixed cutaneous and lymphocutaneous disease because of its low cost (compared to itraconazole) and its effectiveness.¹⁵ The mechanism of iodide action still remains poorly understood, but it seems that its therapeutic effect is mediated through modulation of the inflammatory response or enhancement of the immune defense mechanism.^{15,16} In vitro studies have suggested yeast cell damage through the conversion of KI to iodine. This conversion path for some unknown and appropriate concentrations could damage the yeast cell form in vivo.¹⁶

In feline sporotrichosis, there are few reports of cases having been treated with KI and the results are inconclusive.⁸ The lack of studies on KI in cats points to the need for systematic approaches to describe the efficacy of the drug for treating the disease. For public health purposes, a favorable response to KI in feline sporotrichosis could contribute to therapeutic regimen options, as well as reduce the risks of zoonotic transmission related to diseased cats, shorten the treatment period and diminish relapses. Thus, the purpose of this study was to evaluate the effectiveness of KI capsules in feline sporotrichosis treatment.

Materials and methods

Between April 2010 and July 2011 an observational cohort was conducted with a sample of cats with sporotrichosis at the Laboratório de Pesquisa Clínica em Dermatozoonoses em Animais Domésticos (LAPCLIN-DERMZOO), Instituto de Pesquisa Clínica Evandro Chagas (IPEC)/(Fiocruz), Rio de Janeiro, Brazil. The study was approved by the Ethics Committee on the Use of Animals (CEUA-Fiocruz), number: LW 50/10. All procedures undertaken during the study were signed by the owners in terms of informed consent.

Forty-eight cats, of both sexes, with no previous history of oral antifungal therapy, were included according to the following criteria: weight >2 kg; sporotrichosis diagnosis confirmed by isolation of *S schenckii* in culture. The exclusion criteria were age <6 months and >9 years, pregnancy and lactation. Cats that did not improve within 1 month of KI treatment, or had worsening of the lesions regardless of the time of treatment, were excluded from the study and oral itraconazole monotherapy (50–100 mg/cat q24h) was initiated.

The cats underwent a clinical and dermatologic examination. Regarding the distribution of skin lesions,¹⁷ the cats were allocated into groups: L1 (cutaneous lesions in only one site), L2 (cutaneous lesions in two non-adjacent sites) and L3 (cutaneous lesions in three or more non-adjacent sites).

Samples were collected from the ulcerated lesion and nasal cavities by sterile swab for mycological culture as follows: seeding on to Sabourad-dextrose agar and

Table 1 Sociodemographic characteristics, respiratory signs occurrence, adverse clinical effects, frequency of clinical cure and time to achieve cure in the observational cohort of cats with sporotrichosis treated with KI

Variables	Cats treated with KI
Number of cats	48
Male (%)	72.9
Mongrel (%)	85.4
Age in months (median)	24
Weight in kg (median)	3.8
Frequency of respiratory signs (%)	66.7
Frequency of ACE (%)	52.1
Frequency of FeLV antigen (%)	16.6
Frequency of FIV antibodies (%)	8.3
Frequency of clinical cure (%)	47.9
Median time to achieve clinical cure (weeks)	19

ACE = adverse clinical effects

mycotic 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.¹⁷ Blood samples were collected for complete blood count and biochemistry (urea, creatinine, alanine transaminase, aspartate aminotransferase, alkaline phosphatase albumin) before and during the study, as well as for serological diagnosis for the feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) with an immunoenzymatic test (Snap Combo FeLV/FIV; Idexx Laboratories).

The therapeutic prescription for all cats was KI capsules supplied free-of-charge by the Clinical Pharmacy Service of IPEC/Fiocruz and was administered by the owners at home with food. A 5-day scaling period of the drug was initially established with 2.5 mg/kg q24h. Then, doses were progressively increased at each 5-day period until a clinical response was achieved or signs of toxicity appeared as follows: 5 mg/kg, 10 mg/kg, 15 mg/kg and 20 mg/kg q24h. Cats with mild adverse clinical effects had therapy suspended for 7 days and resumed 2.5 mg/kg dose increments until the that the highest dose that did not induce toxicity was attained. The cats were followed monthly by clinical examination and laboratory tests (hematology and biochemistry), and the owners were contacted weekly by telephone.

The criteria for cure were complete healing of the skin and mucosal lesions and remission of the extracutaneous clinical signs (ie, dyspnea, sneezing, nasal discharge,



Figure 1 (A,C) Cats with ulcerated cutaneous lesions caused by *Sporotrix schenckii* before treatment. (B,D) The cats after KI treatment — the lesions have resolved

lymphangitis and regional lymphadenitis) presented initially. KI therapy was maintained for 2 months after clinical cure. A follow-up was carried out 3 months after the clinical cure.

The data collected from each animal were stored with the software Epidata 3.1. The simple frequencies of categorical variables [sex, general health, respiratory signs, presence, location and distribution of skin lesions, adverse clinical effects (ACE), laboratorial adverse effects and outcome] and measures of central tendency for quantitative variables (age, weight, monthly time to achieve cure and dose) were recorded with the software Statistical Package for the Social Sciences (SPSS 16.0).

The frequency of clinical characteristics of the cohort animals was described by univariate statistical analysis. The medians for time of treatment (in weeks) was used owing to non-parametric distribution in the Kolmogorov-Smirnov test. Fisher's exact test was used to associate respiratory signs and treatment failure. A value of $P < 0.05$ was considered significant.

Results

Forty-eight cats from the Rio de Janeiro metropolitan region were included in the study (Table 1). Thirty-five cats (72.9%) exhibited good general health. Nasal

Table 2 Frequency of outcomes and length of treatment in weeks to achieve clinical cure according to the distribution of skin lesions in the observational cohort of cats with sporotrichosis treated with KI

Variables	Distribution of skin lesions		
	L1 (n = 15)	L2 (n = 17)	L3 (n = 16)
Clinical cure	11	7	5
Failure	3	9	6
Other outcomes	1	1	5
Median time to achieve clinical cure (weeks)	19	18	19

Others outcomes = death or abandonment

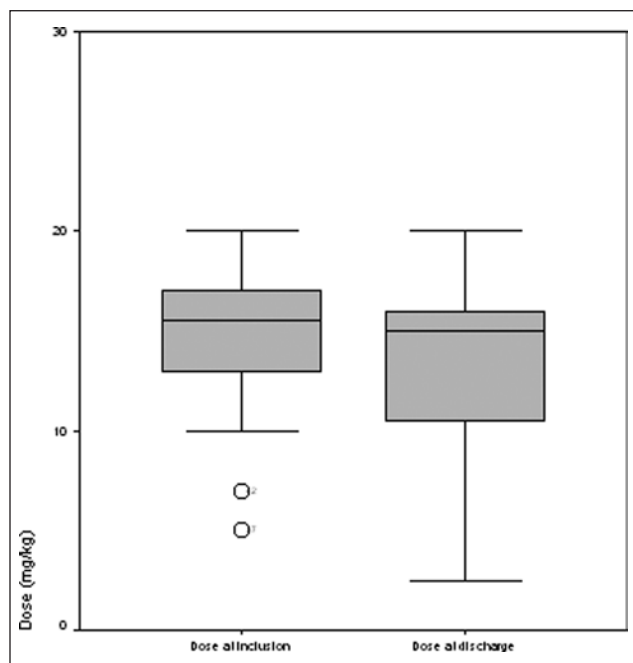


Figure 2 Median doses used at inclusion and discharge in 48 cats with sporotrichosis treated with KI capsules

discharge (40.3%) was the most frequent respiratory sign and was not associated with treatment failure according to Fisher's exact test ($P = 1000$).

Most lesions were located on the nasal mucosal ($n = 26$), right fore limb ($n = 23$), nasal bridge ($n = 20$) and head ($n = 15$). Cutaneous ulcers were observed in 34 (72.3%) animals, ulcers and nodules in 11 cats (23.4%) and nodules in two cats (4.3%).

Twenty-three (47.9%) of the 48 cats achieved clinical cure (Figure 1) and 11 belonged to L1 group (Table 2). Treatment failure was observed in 18 animals: in 17 cats because of lack of clinical response and because of severe

adverse clinical effects in one cat. Five cats (10.4%) were lost during follow-up and two cats died (4.2%) with no association to sporotrichosis. Cats that tested positive for FeLV/FIV (Table 1) did not exhibit significant clinical or laboratory differences when compared with the FeLV/FIV-negative cats.

Hyporexia was the most frequent ACE (52%) sign related to treatment, followed by lethargy, weight loss, anorexia, vomiting and diarrhea. Thirteen cats (27.1%) had a mild increase in liver enzyme levels during the study,¹⁸ six of which displayed clinical signs suggestive of hepatotoxicity, such as hyporexia, lethargy and weight loss. No further relevant alterations were identified with respect to hematology or biochemistry.

The maximum dose at the beginning of treatment (median = 15.5 mg/kg) was similar to the discharge dose (median = 15.0 mg/kg). Only two cats had lower doses upon initiation and discharge — 5 mg/kg and 7 mg/kg, respectively. The variability of the dose of outcome (2.5–20 mg/kg) was higher than the initial dose (5–20 mg/kg), as five cats had a significant reduction in dose (Figure 2).

Fifteen cats out of 23 were followed-up 3 months after clinical cure. No relevant alterations were identified in the routine hematology or biochemistry panel. One cat presented reactivation of the disease in the nasal mucosal 3 months after discharge, and eight were lost during follow-up.

Discussion

This is the first report to evaluate KI capsules in cases of feline sporotrichosis in relation to clinical cure, adverse effects and reactivation. The treatment of feline sporotrichosis remains a challenging and long-term endeavor.¹² Cats usually reject oral medication, especially in solution. This inspired us to manipulate KI in capsules, as it is convenient and easy to administer when compared with iodide in saturated solution (SSKI).

In this study, most animals had lesions in the nasal region. According to Malik et al,¹⁹ the nasal region of cats does not have a rich supply of blood nor does it possess easily-accessible mobile skin, which would facilitate reconstructive surgical procedures. Thus, cure of infections in this specific area may be problematic.

Some authors have reported that the severity of feline sporotrichosis may be related to immunosuppression caused by co-infection with FIV/FeLV.^{12,17} The small number of cats that tested positive in this study does not allow an association between the infection and outcome.

Respiratory signs were observed in most cats, mainly nasal discharge with no apparent link to treatment failure. However, the occurrence of respiratory signs is associated with treatment failure, according to previous

studies.^{12,17} KI may represent a better alternative than itraconazole in cases with nasal mucosal involvement, although further clinical trials should be carried out to determine this hypothesis.

Previous studies have reported clinical cure in feline sporotrichosis with SSKI,^{20–22} even though others have claimed treatment to be unsuccessful.^{23,24} This study describes a large and well-characterized case series of cats treated with KI capsules, including a larger sample size, a different pharmaceutical form (capsules) and dose. Therefore, it was not possible to compare the cure rate with the veterinary literature, which was based only on isolated case reports. The treatment period ranged from 4 to 5 months, which is consistent with the period heretofore reported in literature.^{21,22,24} In addition, the animals belonging to the L1 group had a higher rate of clinical cure, as noted in previous studies.^{12,17}

Regardless of the initial clinical condition, most of the cats in the failure group presented a worsening of the lesions after 1 month of therapy. KI therapy was discontinued and oral itraconazole was adopted for this group. Treatment abandonment was a result of non-compliance by owners.

Felines are susceptible to iodides and should be carefully monitored for adverse clinical signs, such as lethargy, anorexia, vomiting, diarrhea, spasms, hypothermia and cardiomyopathy.⁸ The clinical adversities evidenced in our study were consistent with the findings of other studies^{20,22} and hyporexia occurred in the majority of the cases. The increase in hepatic transaminase levels might be attributed to the use of KI being symptomatic in six cases.

Although the adverse clinical effects are common in cats treated with iodide, it does not preclude its application, as the toxic effects are reversible when the drug is suspended or administered in lower doses.²⁴ Clinical and biochemical monitoring is strongly recommended, as well as the dose-scaling period.

Continuous KI therapy could lead to interruption of the endogenous production of thyroid hormones and may also cause thyroiditis and/or hypo- or hyperthyroidism, as observed in human patients. Thyroid stimulating hormone screening is prudent to ensure that thyroid function remains normal after 1 month of treatment.²⁵

The dose of SSKI for feline sporotrichosis treatment according to the literature is 20 mg/kg q24h or q12h.^{21,24} Nevertheless, the median dose used to achieve cure with KI in capsules in our study was lower (15 mg/kg) than that established in the literature.

The clinical cure rate was similar to previous studies with itraconazole,¹² which suggests that KI should be an alternative treatment for feline sporotrichosis. Further clinical trials should be carried out to compare the efficacy and safety of KI therapy and oral itraconazole.

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

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