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posology = science of dosage
up to 6.3 gm/day KI (= 4.7 gm I-) divided for adults

Table 1: Dosing A and B

ORIGINAL ARTICLE

New posology of potassium iodide for the treatment of cutaneous sporotrichosis: study of efficacy and safety in 102 patients

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Abstract

Background The first therapeutic choice for the treatment of cutaneous sporotrichosis is oral itraconazole; however, the increase in cases of zoonotic transmission outbreak necessitates a search for effective and safe treatment alternatives.

Objective To evaluate a new potassium iodide (KI) posology as an alternative for the treatment of limited cutaneous forms of sporotrichosis.

Methods One hundred and two patients with sporotrichosis diagnosed by isolation of *Sporothrix* sp. were included and were divided into 2 groups that received different doses of KI: group A received the conventional dose, and group B received the reduced dose. The cure criteria were based on clinical and serological data.

Results Seventy-nine patients (77.4%) reached clinical cure: 70.6% and 84.3% of groups A and B respectively. Sixteen patients (15.6%) were lost during follow-up, and seven changed drug therapy: five in group A and two in group B. The incidence of adverse events was similar for both groups (64.7%): predominantly metallic taste (44%), followed by mild gastrointestinal intolerance and acneiform eruption (10.7% each). No serious adverse events occurred, and there were no recurrences. Analysis of the results showed no statistically significant difference between groups ($P = 0.9255$). The improvement in serologic titres was significant in both treatment groups.

Conclusion Through statistical analysis, the usual posology was not shown to be superior to the one proposed in this study. Serology for sporotrichosis may be used as a valuable tool in the clinical monitoring of these patients.

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Conflict of interest

None reported.

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Introduction

Sporotrichosis is the most common subcutaneous mycosis in most countries of Americas.[1] This disease is acquired through the insertion into the skin of materials contaminated with *S. schenckii* complex fungi, although it is recognised that inhalation of the fungus is also a route of infection, especially for systemic forms.[2,3] Despite the variety of species currently described, *Sporothrix brasiliensis* is considered the responsible agent for the endemic sporotrichosis in the city of Rio de Janeiro, Brazil.[4] Approximately, 80% of the patients are present with limited forms of this disease. The identification of a fungal complex including different species encouraged new studies on their potential virulence and resistance to anti-fungal agents, as well as seeking wider options for therapeutic possibilities.[5–9] It is also important to examine disease geographical mapping and population characteristics. According to Kauffman *et al.*, the treatment of choice for limited forms of the disease is itraconazole.[10] However, other therapeutic modalities such as potassium iodide (KI) and terbinafine show the same level of scientific evidence (A-II).[10] The sporotrichosis epidemics of zoonotic transmission has become a serious public health problem in Brazil. *Sporothrix* sp. has been shown resistance to itraconazole, thus there is a need to find therapeutic possibilities that are well tolerated and cost-effective to face the epidemics such as that observed in Brazil and other countries.

The aim of this study was to evaluate the effectiveness and safety of KI in doses and frequency of administration smaller than the values usually recommended.

Materials and methods

Study design

Intervention study, ambidirectional, non-randomised, approved by the Pedro Ernesto University Hospital/Rio de Janeiro State University (Hospital Universitário Pedro Ernesto/Universidade do Estado do Rio de Janeiro - HUPE/UERJ) Research Ethics Committee.

Inclusion/exclusion criteria

Patients of both sexes and all ages presenting a clinical picture compatible with fixed cutaneous, lymph-cutaneous or mucosal sporotrichosis, in addition to isolation and identification of the *Sporothrix* sp., were included. All participants or the legal responsible person needed to be able to understand and sign the informed consent form and to return for the scheduled appointments. Pregnant women, lactating women, patients with thyroid dysfunction, immunosuppressive conditions, severe sporotrichosis or any type of known reaction to the studied medication were excluded. Patients already treated for sporotrichosis were also excluded.

Patients

One hundred and two patients were divided into two groups according to the dose and frequency of KI administration. Group A included 51 patients who entered the research in reverse temporal order, between July 2009 and July 2003, while in Group B, 51 patients were enrolled between September 2009 and January 2013. All patients who met the inclusion/exclusion criteria within both period times entered the study.

Laboratory tests

The skin secretion or fragment from the suspected cases was subjected to a direct mycology examination and culture, as previously described, considered the gold standard for the sporotrichosis diagnosis.[11] The patients underwent tests for routine biochemistry and haematology (complete blood count; fasting blood glucose; and renal, liver and thyroid function tests) before treatment, after 1 month, and whenever there was a need in the opinion of the investigators. Serology for sporotrichosis was performed from blood samples taken before treatment and then monthly until clinical cure, employing the indirect ELISA test with the antigenic fraction *Ss*CBF.[12] After clinical cure, the test was repeated every three months until serological cure or up to one year, whichever occurred first.

Treatment

KI was formulated as a saturated solution of potassium iodide (SSKI) in 50 or 100 mL flasks with a standard dropper according to specific physicochemical references of KI saturation in water (1 g KI in 0.7 mL water).[13] For a final solution volume of 100 mL, 100 g of KI P.A. was added to 70 mL of distilled water.[14] These bottles were standardised and freely provided to the patients. Considering a standard dropper, in which the drop has a volume of 0.05 mL, each drop of the saturated solution used in the study held 0.07 g of KI.[14] To be more precise, concerning the dose, in this study, the dose in grams (instead of drops) was adopted as a reference. In both groups, the treatment began with an intake of five drops (0.35 g) b.i.d. (0.7 g/day) or t.i.d. (1.05 g/day), depending on the study group. One drop (0.07 g) was added to the drug intake every day until the desired total daily dose was reached. Patients in group A received KI 3×/day with the daily dose ranging from 4.2 to 6.3 g and from 2.1 to 4.2 g for adults and children respectively. In group B, the drug was administered 2×/day, and the prescribed adult daily dose was 2.8 to 3.5 g, while the paediatric dose was 1.4 to 2.1 g, approximately half of the dose prescribed for group A. In both groups, children less than 20 kg of weight received the lowest paediatrics dose while those weighing 21–40 kg received the highest. Those with more than 40 kg were given adult dose. The total daily dose could be lowered if not well tolerated (usually nausea or bad taste).

= 70 mg/ drop

started at 5 drops = 350 mg KI either 2x/day or 3x/ day for a total of 700 or 1050 mg/day of KI.

does not say if it was mixed with water or orange juice

Criteria for cure

Clinical and serological cure were established when patients had no recurrence for 12 months and the serologic titres were negative or close to the established cut-off values (6400). This follow-up period could be reduced if the serological cure occurred before 12 months. Clinical cure was defined as patients with healed lesions and no sign of clinical activity after treatment withdrawal. Recurrence was defined as clinical activity after clinical cure, at the same previously injured sites, observed at any follow-up appointment. Treatment failure was considered when the patient did not show any improvement or if the skin lesion had worsened after one month.

Statistical analysis

The Excel™, Microsoft Informática Ltda. São Paulo, Brazil, R-Project version 3.0.1 (16/05/2013), The R Foundation for Statistical Computing, Vienna, Austria, and SPSS Statistics 22 (17/04/2014), IBM Corporation, Armonk, NY, USA, software were employed. All statistical tests were performed assuming a significance level of 5% (0.05). To analyse the outcomes, the Kaplan–Meier survival curve was used, applying the log rank and Breslow tests for comparison between groups. Parametric and non-parametric variables were evaluated using the Mann–Whitney and chi-square tests respectively. Serological

pre-treatment and final follow-up titres were analysed using the sign test and compared within each group to correlate the titre level with therapeutic response.

Results

Population analysis

Most patients in both groups were female, 33 (64.7%) and 31 (60.8%), with a mean age of 33 and 32 years old respectively, for groups A and B, and the median was 31 years old for both groups. Twenty children aged 4 to 11 years old and 9 teenagers entered the study. Students and housewives predominated in both groups, making up 15 (29.4%) and 10 (19.6%) of the patients, respectively, in group A and 17 (33.3%) and 11 (21.5%) of the patients in group B. There were no patients with a history of alcoholism, according to WHO criteria, in either of the studied groups. Comorbidities were present in 10 (19.6%) and 15 (29.4%) patients from groups A and B, respectively, divided into cardiovascular (blood pressure, coronary vascular disease and heart failure), metabolic (diabetes mellitus and dyslipidemia), neuro-psychiatric and other comorbidities. No diabetic patient was insulin-dependent. The patients' use of drugs in this research was related directly to the comorbidity, such as anti-hypertensive, oral hypoglycaemic and anti-lypaemic. There was no significant difference between groups as to comorbidities ($P = 1.0$) or the use of drugs ($P = 0.1542$) as variables.

Clinical aspects and transmission forms

Lymph-cutaneous sporotrichosis prevailed in both groups: 82.3% and 84.3% in groups A and B ($P = 1.0$) respectively. Skin lesions were located more frequently in the upper limbs in both groups, in 36 patients (70.6%) in group A and 28 (55%) in group B. The involvement of the face was more frequent in children and adolescents, and most acquired the disease by contact with cats in similar proportions: 40 patients per group (78.4%) ($P = 1.0$).

KI is 76.5% Iodide; 2.5 gm KI contains 1.9 grams of iodide

Treatment

The mean dose of KI was 4.8 and 2.5 g, respectively, for groups A and B, while the mean and median of days of treatment were 55 and 60 days for group A and 58 and 54 days for group B, with no significant difference ($P = 0.9368$). (Figs. 1–2) Adverse events occurred in 64.7% of the patients in each group, mostly a metallic taste (39.2% in A and 49% in B) and gastrointestinal intolerance (11.7% in A and 9.8% in B), although there was no significant difference ($P = 1.0$). No serious adverse events occurred. Elevation in serum TSH was the only laboratory abnormality related to drug intake, and it was detected in four patients (one in group A and three in group B) approximately 1 month after the start of the treatment. The abnormality was transient, and there was no consequence for thyroid function, as shown by later measurements, which returned to pre-drug levels.

Outcomes

In the group receiving conventional treatment, out of the 51 evaluated patients, 36 (70.6%) achieved clinical cure, with 19 (37.2%) regarded as achieving both clinical and serological cure. In the group receiving the new posology, 43 (84.3%) out of the 51 evaluated patients achieved clinical cure, and 25 (49.0%) achieved both clinical and serological cure. Ten patients (19.6%) in group A and six (11.7%) in Group B dropped out of the study after starting the treatment. At different times throughout the research, 17 patients (33.3%) in group A and 18 (35.3%) in group B were lost to clinical-serological follow-up after achieving clinical cure. In group A, five (9.8%) patients had to change drug treatment, two because of gastrointestinal intolerance, one due to allergy, and two as a consequence of treatment failure, while in group B only two patients (3.9%) had to use other treatment (one on account of iodism and the other due to treatment failure). No statistically significant difference in outcomes was observed between the two groups ($P = 0.9255$). The survival curves for each group, considering the time of treatment in days, showed no significant difference between the two groups (Fig. 3). The decrease in serologic titres between the pre-treatment appointment and discharge (Fig. 4) was statistically significant: $P = 0.011$ for the conventional dose group and $P = 0.001$ for the new therapeutic group (Fig. 5).

Discussion

The identification of new species by molecular techniques was an important step towards better knowledge of the clinical and epidemiological aspects of sporotrichosis.[5,15,16] Some colonies that were genotyped revealed that *Sporothrix brasiliensis*, the species isolated from some of the patients of this study, is the same as the one isolated from the outbreak among patients in a referral hospital.[4] The affected population lives mostly in the regions of the state with low socio-economic and poor sanitary

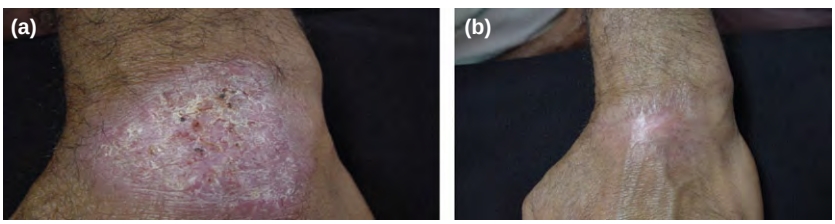

Figure 1 (a) Infiltrated, erythematous, squamous, crust, exulcerated plaque, located on the dorsum of the left hand before treatment; (b) Skin scar 3 months after 53 days of treatment with potassium iodide (KI), t.i.d., daily dose of 5.25 g.

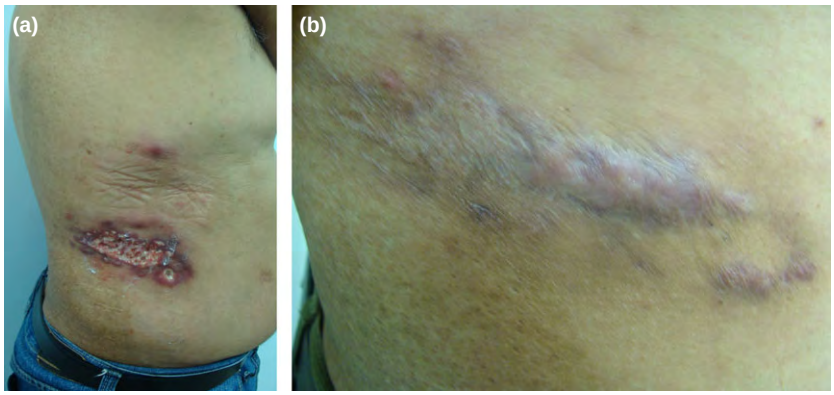

Figure 2 (a) Ulcerated purulent lesion on the side of the trunk and regional lymph nodes before treatment; (b) clinical appearance of the scar tissue 9 months after 64 days of treatment with KI, b.i.d., daily dose of 2.1 g.

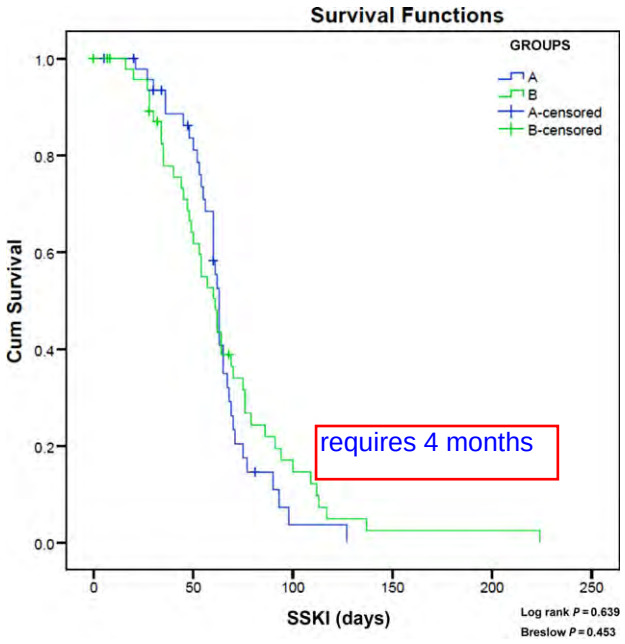

Figure 3 Survival curves (Kaplan–Meier method) demonstrating the upshot experiences of group A including patients who received potassium iodide t.i.d in conventional doses and group B including patients who received potassium iodide b.i.d in reduced dose.

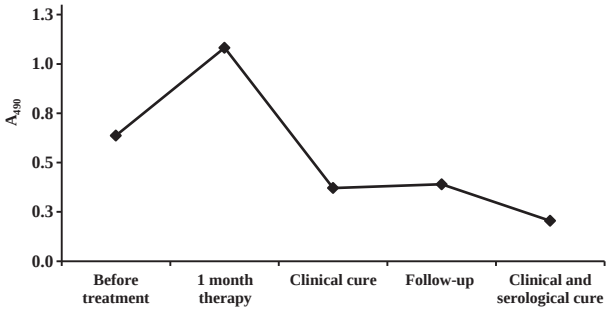

Figure 4 Serological analysis by *Ss*CBF fraction ELISA of the patient showed in Fig 2. Decrease in serologic titres between the pre-treatment appointment and patient discharge.

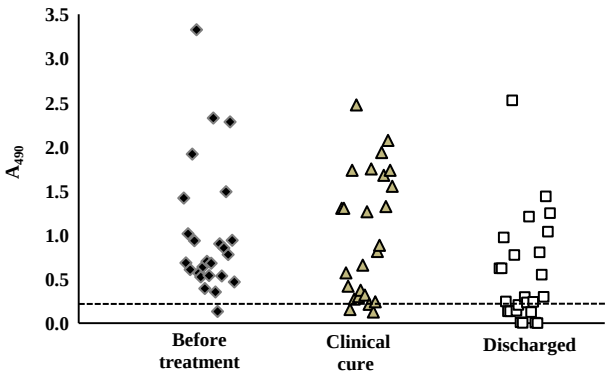

Figure 5 Reactivity determined by *Ss*CBF fraction ELISA of 25 serum samples in 1:6400 dilution. Patients treated b.i.d with reduced dose of potassium iodide. The dotted line represents the set cut-off point (0.23).

conditions, and therefore all forms of treatment need to be properly evaluated, as cost-effectiveness is an important factor for controlling the impact on the Public Health budget.[17] Approximately, 90% of cases treated in our hospital presented the localised form of the disease, the most frequent being lymph-cutaneous (80%). The drug of choice for the treatment of the mucosal and cutaneous forms of sporotrichosis is itraconazole;[10] however, there are frequent contraindications to its use, either due to drug interactions and the risk of serious adverse events, especially in the elderly, or to the pharmaceutical form as a capsule, which does not allow dose fractioning. Furthermore, although it is an effective and safe drug for the treatment of cutaneous sporotrichosis, *Sporothrix* sp. resistance to itraconazole has been reported.[7,8,18] Another therapeutic option is terbinafine, a fungicidal drug already tested for

Table 1 Comparison between the conventional dose of potassium iodide and the dose used in the groups in this study

	Standard treatment Concentrated Solution 1 g/mL–t.i.d	Group A Saturated Solution 1.42 g/mL–t.i.d	Group B Saturated Solution 1.42 g/mL–b.i.d
Concentration/standard drop (0.05 mL)	0.05 g/drop	0.07 g/drop	0.07 g/drop
Adult dose	40–50 drops 6.0–7.5 g/day	20–30 drops 4.2–6.3 g/day	20–25 drops 2.8–3.5 g/day
Paediatric dose	25–40 drops 3.75–6.0 g/day	10–20 drops 2.1–4.2 g/day	10–15 drops 1.4–2.1 g/day

Adapted from Orofino-Costa *et al.*, 2013.

Table 2 Main features of larger studies involving itraconazole, terbinafine and potassium iodide for the treatment of cutaneous sporotrichosis

	Itraconazole* (*n* = 645)	Terbinafine† (*n* = 50)	Potassium Iodide‡ (*n* = 102)
Cure (%)	94.6	86.0	77.4
Abandonment (%)	4.0	2.0	15.7
Mean treatment period (weeks)	14	2–42 not specified	8
Side-effects (%)	40.0	1.0	64.7
Main side-effects (%)	Gastrointestinal (27.7)	Gastrointestinal (6.3)	Metallic taste (44.0) Gastrointestinal (10.7)
Other treatment (n)	9	1	7
Recurrence/Therapeutic failure (%)	12.4	None	2.9
Laboratory adverse events (%)	24.1	4.2	3.9

*Barros *et al.*, 2011.
†Francesconi *et al.*, 2009.
‡This study.

higher recurrence/failure argues against "cure"

sporotrichosis that shows results similar to itraconazole.[19] KI was the first drug used in the treatment of sporotrichosis at the beginning of the last century, and its safety and effectiveness are well known.[20] However, there are no randomised controlled trials using this drug in the literature, and the casuistic is usually small. Although that KI occupies the A-II level of scientific evidence[10] (as does itraconazole), its intake in three daily doses and the high recommended doses, in addition to gastrointestinal intolerance, eventually leads to its disuse. It is noteworthy that the pharmaceutical industry has no interest in producing a low-cost drug with restricted use. In Brazil, the cost in U.S. dollars for 30 capsules of 100 mg itraconazole varies from $54.00 to $130.00; for 28 tablets of 250 mg terbinafine, it ranges from $38.00 to $100.00, while 100 mL of KI costs approximately $13.00 to $15.00. It is possible to reduce the dose due to the differentiated KI immune-mediated mechanism of action, which also disrupts granuloma, suppresses the production of toxic oxygen intermediates by polymorphonuclear leucocytes, inhibits neutrophil chemotaxis and reduces the halogen reaction of myeloperoxidase.[20,21] For this reason, KI is used in immune-mediated inflammatory dermatitis such as erythema nodosum and in neutrophilic diseases such as Sweet's syndrome and pyoderma gangrenosum, as well as in infectious granulomatous dermatitis. There is the possibility that KI induces cell lysis in the yeast form of *S. schenckii* through the release of lysosomal enzymes, when applied at high concentrations.[22] The main indication for the use of KI in sporotrichosis is the limited forms of the disease, when the immune system of the host is fully capable of responding to the agent. The pharmaceutical form of KI as a liquid facilitates its acceptance by children and also by the elderly. Both doses of the studied drug were shown to be safe. The frequency of adverse events found in both groups was similar (64.7%), and complaining about the bad taste of the drug was the most limiting factor (44.1%), followed by mild gastrointestinal intolerance and acne-like eruption, 10.7% each. Other less frequently reported side-effects were mild headache (9.8% in each group), mild allergic reactions (3.9% in group A and 1.9% in group B) and asthenia (1.9% in group A). There was no record of any serious adverse event. Transient elevations in TSH levels are physiological, occurring usually at the beginning of the treatment, and they were observed in four (3.9%) out of 102 patients in this study. The human organism has an escape mechanism that controls the increased supply of iodine, maintaining normal thyroid function.[23] When compensatory mechanisms are impaired in individuals with underlying thyroid dysfunction, the Wolf-Chaikoff and Jod-Basedow phenomena may occur,[20,23,24] which are complications not registered among our patients. The solution recommended in the pharmacological literature and international guidelines for the treatment of limited forms of sporotrichosis is actually a concentrated solution (CSKI) because it is formulated with 1 g of KI in 1 mL of distilled water,[10,13] whereas the saturated solution should contain 1.42 g of KI in

pure form (P.A.) per mL of water (Table 1).[14] Through statistical analysis of the outcomes, it was possible to observe that the clinical response to KI in the classic dose (group A) was not better than the response to the new dose, and the therapeutic regimen proposed in this study (group B) is approximately one-third of what is recommended in the literature and half of what was previously used by our team. Two studies of the treatment of cutaneous sporotrichosis with large samples have been published: one with 645 patients, which used itraconazole, and one with 50 patients treated with terbinafine (Table 2).[25,26] The clinical response of cutaneous sporotrichosis to itraconazole is the best with a minimal dose of 100 mg/day, and the most frequent adverse event was gastrointestinal intolerance (27.7%), but cases of hypercholesterolemia and hypertriglyceridemia were also recorded.[25] When it needed to be replaced due to side-effects or treatment failure, the chosen drugs were terbinafine or KI.[25] The study cases treated with terbinafine also showed that this drug can be used safely and effectively in the treatment of this mycosis, especially in the group at risk for drug interactions and serious cardiopathy.[26] The analysis of the largest series of patients treated with SSKI (n = 102) in this study demonstrated its effectiveness and safety in both treatment groups. Although we could not find statistical difference in safe and effectiveness actually a reduced dose of KI is given b.i.d to the patients, and the final treatment cost is certainly reduced. The improvement in serologic titres was significant in both treatment groups and has been used as a valuable tool in the clinical monitoring of these patients. This study was not a controlled or randomised trial and this is a limitation.

No randomized controlled trial for the treatment of cutaneous sporotrichosis with KI has been conducted until now. Authors suggest that new studies could be directed comparing KI to itraconazole, the standard treatment of sporotrichosis; and also with terbinafine, a fungicidal drug known to be effective in the limited forms of this disease.

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