

## Antifungal activity of potassium iodide: insight in the XXI century

### Review Article

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### Introduction

Potassium iodide is an important anti-fungal drug listed in the World Health Organization [WHO] essential drug list, Category D in pregnancy widely used off-label in cutaneous sporotrichosis [including fixed and lymphocutaneous types], basidiobolomycosis, subcutaneous granulomas due to *Pythium insidiosum*, erythema nodosum, and erythema induratum of Bazin in developing countries with more and more reports published, although the currently available evidence is insufficient to determine potassium iodide as first-line treatment for these infections [1,2].

It's presented as white crystals, water-soluble, with a molecular weight of 166, it contains 76% of iodine and 23% of potassium, this solution is neutral or slightly alkaline [3,4].

### Usage

In 1898 Benjamin Schenk described the first case of sporotrichosis in Johns Hopkins Hospital, and 5 years later in 1903 Raymond Sabouraud suggested to De Beurmann and Gougerot the use of potassium iodine for the treatment of sporotrichosis in France [5,6].

Although it has been used for the last century, the mechanism of action it's still totally unclear to this day, but it is thought to work on the immune response as the immunomodulatory or anti-inflammatory drug, especially acting toward neutrophil chemotaxis, destructing granulomas, or on phagocytosis of *Sporothrix* cells [7].

In 1991 a study conducted in Atlanta; Georgia demonstrated that a saturated solution of potassium iodide had no activity *in vitro* against *Sporothrix schenckii* [8].

So later on, in 2001 it was proposed that macrophages are stimulated by potassium iodide to inhibit fungus growth [1].

### Sporotrichosis

It's a subacute or chronic disease caused by a dimorphic fungus *Sporothrix schenckii* complex. characterized by nodules or gummas causing mainly fixed verrucous or lymphangitic lesions. This infection has a variety of forms and is localized in the skin and subcutaneous tissue when acquired through penetration of the skin with materials contaminated with this fungus.

The Systemic form is rare, and inhalation of the spores could be the mechanism of transmission [9].



Figure 1: Lymphangitic sporotrichosis.



**Figure 2:** After 3-month treatment with KI.

As mentioned before, De Beurmann in the early XX century treated this infection with good results and, fewer reported side effects, that later on, were communicated and established [10].

Although treatment of choice in most international guidelines for limited forms [skin and subcutaneous tissue] is itraconazole, other therapeutic modalities like potassium iodide [KI] is still considered a first-line treatment in many third-world countries and it is used in cutaneous forms, especially fixed or lymphangitic cases, but not in systemic or cutaneous disseminated cases [11].

There is no scientific evidence for its use, but effectiveness has been supported by the experience of many Latin-American dermatologists and mycologists and have shown the same level of scientific evidence as itraconazole in response when treating this infection [A-II] [12,13].

Potassium iodide solution can be prepared in two galenic formulations, a KI solution and a saturated solution [SSKI] [7].

## Preparation

### KI solution

- A spoon contains 1 g
- Potassium iodide 20g
- Distilled water 300 ml

### Saturated solution of KI [SSKI]

- Each ml [20 drops] contain 1g.

Potassium iodide 20g

Distilled water 20 ml

When using KI solution, recommended dose is 2 to 6 g daily, usually 3 g a day, during 6 to 12 weeks [12].

In treatment with SSKI some practitioners initiate at a dosage of 5 drops [using a standard eye-dropper] 3 times daily and increasing, as tolerated, to 40–50 drops 3 times daily [evidence level A-II].

In children 1 drop 3 times a day, increasing gradually up to a maximum of 10 drops [1 drop per kg of body weight], or 40–50 drops 3 times daily, whichever is lowest [evidence level B-III] it can be administered with milk or fruit juice, after meals [13].

A Brazilian study has demonstrated that doses of 1-2g/day for children, and 2-4g/day for adults, administered t.i.d with milk, juice or yogurt are effective to cure most patients [14].

Previous starting medication with KI it is important to check the TSH and T4 serum levels, although during treatment a slight increase in TSH serum levels is considered to be physiological, it is also important check if the patient has hypertension and is taking diuretics and potassium savers, check thyroid disorders, and administration is prohibited in nursing women, during pregnancy because can develop goiter and hypothyroidism in fetus [Congenital hypothyroidism, Category D in pregnancy] [4].

## Basidiobolomycosis

Entomophthoromycosis include conidiobolomycosis and basidiobolomycosis. The last one is an unusual infection caused by *Basidiobolus* spp, a fungus which belongs to the zygomycetes class and entomophthorales order [15].

It is an environmental saprophyte, found in soil, decaying vegetation, and inside the gastrointestinal tract of amphibians, causing disease after traumatic inoculation of the skin [16].

Basidiobolomycosis is endemic in rural areas of the subtropical and tropical zone, mainly Indonesia, India and sub-Saharan Africa, affecting immunocompetent children and young adults [17,18].

The infection caused by *Basidiobolus ranarum*, known as the most relevant pathogenic species to humans, is generally associated with a chronic and slowly progressive

subcutaneous lesion, which often presents as a single, painless, hard and circumscribed plaque [16,19].

This disease predominantly affects the perineum, buttocks, trunk and thighs, although visceral involvement has also been reported [17].

Diagnosis of basidiobolomycosis requires culture and specific histopathological findings that include suppurative and granulomatous inflammation, broad, thin-walled hyphae surrounded by eosinophilic material [Splendore-Hoepli phenomenon], and multinucleated giant cells. The severity and progression of the infection determines the treatment, requiring in some cases both surgical and antifungal therapy [15].

Recent guidelines recommend the use of itraconazole as a first line treatment in several subcutaneous infections including entomophthoromycosis [20].

Nevertheless, in limited settings such as endemic areas, potassium iodide [KI] turns out to be a better option due to its affordability and efficacy in both subcutaneous and systemic basidiobolomycosis [16].

In India it has been used in adults and children. A 47-year-old male with subcutaneous entomophthoromycosis, initially treated with itraconazole but it has been changed to a SSKI showing a dramatic reduction a 9-week [19]. Also, in three children: a 6-month-old infant healed after 8 weeks of SSKI treatment [18]; a 9-month-old baby improved combining itraconazole and SSKI [21]. A 20-month-old infant started with KI and cotrimoxazole, showing complete clinical resolution at 3 months follow-up [22]. Also, a 2.5-year-old boy from Iran with visceral involvement, management was with several surgical procedures, amphotericin B and itraconazole without clinical response, but evident improvement when KI was added to the therapy.

All patients achieved complete resolution of the dermatoses when KI was prescribed either alone or in combination with another antifungal, which clearly demonstrates the efficacy of the therapy for this particular mycosis

### Other uses

Potassium iodide therapy has a history of over 150 years. Iodine was discovered in seaweed in early 1800's and first used in thyroid diseases, and a century later in 1980 it began its use for dermatology in affections like erythema

nodosum, nodular vasculitis erythema multiforme and sweet's syndrome [16,23,24].

There have been novel, communications regarding treatment for this infection. Combining drugs for better outcomes, specifically targeting biofilms *in vitro*. Resulting in reduction of over 70% of the biofilm metabolic activity in filamentous forms and over 50% for yeast forms [25].

### Side effects

The most common are gastrointestinal [nausea, vomiting], coryza, sneezing, parotid and eyelids swelling, edema, iodism [headache, sore, metallic taste, increasing salivation and burning mouth] and an acneiform eruption with numerous follicular pustules involving the face, trunk and upper extremities [26]

Less common are erythema nodosum, vegetant iododerma, chronic iodine intoxication, leukocytoclastic vasculitis, intraepidermal spongiform pustules, and suppurative folliculitis. Wolff-Chaikoff effect: Hypothyroidism or thyroid suppression. In patients with chronic high-dose treatment with pre existing thyroid disease, thyrotoxicosis [Jod-Basedow phenomenon]. Exacerbation of Dühring's disease as well as psoriasis, acne and rosacea, also depression can be observed. It is contraindicated in kidney failure, iodine allergy and autoimmune diseases [1,2,27].

Side effects can be controlled stopping the drug for a few days, and then beginning again with a reduced dose. Severe side effects respond to prednisone, but forced diuresis with furosemide and sodium chloride can be used to wash out the iodide.

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