

2015

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Ashley B. Pachutski

Philadelphia College of Osteopathic Medicine, Ashleypac@pcom.edu

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Recommended Citation

Pachutski, Ashley B., "Is the Use of Itraconazole Effective in the Treatment of Patients Diagnosed With Tinea Versicolor and If So, What Is the Optimal Dosage?" (2015). *PCOM Physician Assistant Studies Student Scholarship*. 244.
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Is The Use Of Itraconazole Effective In The Treatment Of Patients Diagnosed With Tinea Versicolor And If So, What Is The Optimal Dosage?

Ashley B. Pachutski, PA-C

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 19, 2014

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not itraconazole is effective in the treatment of patients diagnosed with tinea versicolor and if so, what is the optimal dosage.

STUDY DESIGN: Review of three peer-reviewed, randomized control trials (RCTs), two of which were published in 2002 and one in 2010.

DATA SOURCES: Studies were researched through PubMed and selected based on the type of study (RCT), their relevance to the clinical question, and if they were POEMS (patient oriented evidence that matters).

OUTCOME(S) MEASURED: Patient's subjective measurement of the severity of pruritis, erythema, scaling, and pigment changes after treatment. Outcomes were also measured by a Wood's lamp examination and a KOH preparation.

RESULTS: Itraconazole was shown to be effective in treating tinea versicolor both clinically and mycologically. Patients reported a decrease in scaling, pigment changes, and pruritis, and their Wood's lamp examination and KOH preparation were also negative. Of the two studies that reported p-values, one showed that the results were statistically significant ($p < 0.001$) and the other showed the opposite ($p > 0.05$).

CONCLUSIONS: All three studies showed that itraconazole produced favorable results in the treatment of tinea versicolor and a single dose was an effective alternative to a seven day regimen. A single dose is also more advantageous because of decreased cost and increased compliance. Itraconazole is also effective as prophylaxis for tinea versicolor when taken one day each month.

KEY WORDS: itraconazole, tinea versicolor

INTRODUCTION

Tinea versicolor, also known as pityriasis versicolor, is a chronic superficial fungal infection of the skin, most commonly occurring on the upper trunk. It is caused by *Malassezia* which is a normal colonizer of human skin. When *Malassezia* grows in excess on the skin, it can lead to this infection.¹ Risk factors for the overgrowth of *Malassezia* include warm, humid environments, immunosuppression, malnutrition, corticosteroid usage, and possibly a genetic predisposition.² Although tinea versicolor is considered a chronic infection with high rates of reoccurrence, there are both topical and systemic treatments available to either eradicate the current infection or serve as prophylaxis. This paper evaluates three randomized control trials (RCTs) comparing either two doses of itraconazole or itraconazole versus a placebo to determine which is more efficacious in the treatment of tinea versicolor.

Tinea versicolor affects people worldwide, and it is most common in the tropical climates, due to warm, humid environments being a risk factor for the overgrowth of *Malassezi*. In the US the prevalence of tinea versicolor is estimated to be 2-8%. The precise number is unknown because most people do not seek medical attention when this infection occurs.² The annual health care cost of tinea versicolor is unavailable. Due to the broad spectrum of fungal infections that itraconazole is used to treat, there is no data regarding the annual cost of itraconazole in the treatment of tinea versicolor. The most recent data published regarding the amount of health care visits per year for tinea versicolor infections was in 2004, in which there were approximately 2.9 million visits in the US alone.³

Tinea versicolor affects all races, although it is more apparent in darker skinned individuals and it is most common in the age range of 15-24 years old due to increased activity

of sebaceous glands.² The infection may be asymptomatic but in some patients, the symptoms that capture their attention include tan, pink, or white colored macules that do not tan in the summertime and pruritis. The macules have scales and may be located anywhere on the body but they are most commonly seen on the trunk. Tinea versicolor is not contagious because it is a normal pathogen of human skin. This infection is considered benign; therefore there is no significant morbidity and mortality.² Most patients will experience reoccurrences of this infection, with rates reaching as high as 60% within one year and 80% within two years.⁴

There are many treatments available to treat tinea versicolor including both topical and systemic agents. Some of the topical agents include selenium sulfide shampoo, ketoconazole shampoo, zinc pyrithione shampoo, miconazole, clotrimazole, terbinafine, salicylic acid, and benzyl peroxide. Systemic agents include ketoconazole, fluconazole, and itraconazole.^{1, 2, 5}

Although itraconazole is already being used to treat tinea versicolor, the researchers wanted to compare the effectiveness of a single dose versus a seven day treatment because it would allow for a decreased cost and increased compliance. Also the researchers wanted to look at itraconazole as a prophylactic agent for tinea versicolor due to the high rates of reoccurrence.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not itraconazole is effective in the treatment of patients diagnosed with tinea versicolor and if so, what is the optimal dosage.

METHODS

Certain criteria were used to select appropriate studies on this topic. This criteria included a population of patients who were clinically diagnosed with tinea versicolor by a Wood's lamp examination or by KOH preparation, and the majority of patients were over 18 years old, non-pregnant, and had not been using an antifungal treatment. The interventions in these studies included the use of itraconazole 400mg for one day or itraconazole 200mg BID one day per month for six months. In two of the articles, comparisons were made between the treatment group which received itraconazole 400mg for one day versus the control group who received itraconazole 200mg for seven days. In the last article, itraconazole 200mg BID one day per month for six months was given to the treatment group and compared to the control group which received placebo pills BID one day per month for six months. Outcomes measured the efficacy of itraconazole in the curative treatment of tinea versicolor which was based off of decreased pruritis, scaling, and hypopigmentation.

All three of the studies were RCTs that were published in peer-reviewed journals and in the English language, with one of the studies being double blinded. Key words utilized to search for these RCTs included "itraconazole" and "tinea versicolor". The articles were researched through PubMed and selected based on the type of study (RCT), their relevance to the clinical question, and if they were POEMS (patient oriented evidence that matters). The inclusion criteria included RCTs published after 1996 and patients who were clinically diagnosed with tinea versicolor by a Wood's lamp examination or KOH preparation. Exclusion criteria varied among the studies but included criteria such as age <18 years old, pregnant women, and the use of antifungals prior to the study. The full exclusion criteria can be seen in Table 1. A summary of the statistics reported or used in the trials include RBI, ABI, NNT, and p-values.

Table 1: Demographics & characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Kose (2002) ⁴	RCT	50	For experimental group: 20 ± 41 For control group: 21 ± 38	Diagnosis of tinea versicolor based off of a positive KOH solution and Wood's lamp exam	Age <18yrs; women of childbearing age; no systemic antifungal intake prior to the study	0	Use of itraconazole 400mg x1day compared to control group using itraconazole 200mg x7d
Wahab (2010) ⁵	RCT	60	Group A: 32 ± 9 Group B: 33 ± 8	Diagnosis of tinea versicolor based off of a Wood's lamp exam and KOH solution	Age <18 yrs; pregnancy and topical and systemic antifungal agents; localized lesions, serious systemic illness	0	Use of itraconazole 400mg x1day compared to control group using itraconazole 200mg x7d
Faergemann (2002) ⁶	Double blind RCT	209	Group A (itraconazole): 12-62, avg 30 Group B (placebo): 12-65, avg 30	12-70 yrs old with a diagnosis of tinea versicolor confirmed by mycological exam	Pts with: known sensitivity to itraconazole, chronic mucocutaneous candidiasis or systemic fungal infection, immunosuppression, any other disease in the investigators' opinion should exclude the pt, participated in drug trial within 30 days, pregnant or breastfeeding, women of childbearing potential without adequate contraception	4	Prophylactic treatment: Itraconazole 200mg OR Placebo BID 1 day per month x6 months

OUTCOMES

The outcomes measured in these studies were POEMS, which included the patient's subjective measurement of the severity of pruritis, erythema, scaling, and pigment changes. They were also measured by the investigator which was based off of a negative Wood's lamp examination and a negative KOH preparation.^{4, 5, 6}

RESULTS

Study 1. In the Kose study 50 patients with recurrent and/or extensive tinea versicolor were enrolled, and all 50 completed the treatment. They all had a positive KOH preparation and Wood's lamp examination. They had not received any topical antifungal treatment for two weeks prior and no systemic antifungal treatment prior to this study. They were broken down randomly into two groups: the treatment group which received itraconazole 400mg one dose and the comparison group which received itraconazole 200mg/d for seven days. The patients were evaluated clinically and mycologically before treatment began, at three weeks, and at six weeks which was the end of the study. Clinically they received a grade based on the scaling, hyper/hypopigmentation, and pruritis. They were scored 0=absent, 1= mild, 2= moderate, 3= severe. The mycological evaluation included KOH preparation and Wood's lamp examination, and these were performed at each visit as well. At the end of the six weeks it was found that there was no difference between the two regimens both clinically and mycologically in clearing the tinea versicolor. The group that received one day of itraconazole had an 82% clinical cure rate while the group receiving seven days of itraconazole had an 84% clinical cure rate.⁶ Table 2 summarizes the results for the Kose study, including a p-value of >0.05 indicating that the study may not be statistically significant. NNT shows a value of -50 which can be interpreted as having

to treat 50 people in order for one less beneficial outcome to occur compared to the control group.

Table 2: Kose Study: Itraconazole 400mg x 1 dose vs. Itraconazole 200mg/d x 7 days

CER (7 days)	EER (1 day)	RBI	ABI	NNT	p-value
0.84	0.82	-0.02	-0.02	-50	>0.05

Study 2. The Wahab study evaluated the same dosages of itraconazole as was done in the Kose study, and it was published eight years later. They had 60 patients who were all clinically diagnosed with tinea versicolor by KOH preparation and Wood's lamp examination. They were broken down randomly into two groups: the treatment group which received itraconazole 400mg for one dose and the comparison group which received itraconazole 200mg/d for seven days. The patients were evaluated four weeks and eight weeks after the start of treatment. There were three levels of clinical response: a cure was defined as complete clearing of the lesions, with negative Wood's lamp and KOH preparation, improvement was defined as maximum clearing of lesions with or without negative Wood's lamp and KOH preparation, and failure was defined as slight improvement, unchanged or deteriorating without negative Wood's lamp and KOH preparation. This study had similar results to the prior study performed by Kose. At the end of the treatment there was not a large difference between the two treatment groups in clearing the tinea versicolor. In the group that received one day of itraconazole, 73% were cured and 17% were improved. In the group that received seven days of itraconazole, 80% were cured and 13% were improved.⁵ Table 3 summarizes the results for the Wahab study. A value of -15 for NNT means that 15 people would need to be treated in order to achieve one less beneficial outcome.

Table 3: Wahab study: Itraconazole 400mg x 1 dose vs. Itraconazole 200mg/d x 7 days

CER (7 days)	EER (1 day)	RBI	ABI	NNT	p-value
0.80	0.733	-0.084	-0.067	-15	Not reported

Study 3. The final study by Faergemann was a double blind RCT which included 238 patients with tinea versicolor who received an open treatment of itraconazole 200mg/d for seven days. The following four weeks they did not receive any treatment. After the four weeks were over, they returned to move onto the prophylactic treatment. Twenty-nine patients did not return for the second phase. The remaining patients were tested with light microscopy to make sure they were mycologically negative for tinea versicolor before continuing on with treatment. The patients were randomly assigned to two groups for the double blind prophylactic treatment. Group 1 received itraconazole 200mg BID one day per month for six months, and group 2 received placebo pills BID one day per month for six months. Findings were scored as either cured, marked improvement, moderate improvement, unchanged, or deteriorated. When patients subjectively scored the variables at the end of the treatment, including hypopigmentation, pruritis, and erythema, they were significantly higher in the itraconazole group compared to the placebo group. At the end of the prophylactic phase, 88% of patients in the itraconazole group were still mycologically negative and 57% of patients in the placebo group were still mycologically negative.⁴ Table 4 summarizes the results for the Faergemann study, including a p-value of <0.001 indicating that the study was statistically significant. NNT in this study is 4, meaning that 4 people need to be treated with the regimen in the study to have one more beneficial outcome.

Table 4: Faergemann study: Itraconazole 200mg vs placebo BID 1d/month x 6 months

CER (placebo)	EER (itraconazole)	RBI	ABI	NNT	p-value
0.566	0.88	0.555	0.314	4	<0.001

Safety and adverse events. In the Kose and Wahab studies, a complete blood count, liver function tests, and renal function tests were checked for each patient before they started the treatment. At week three of treatment, the patients in the Kose study were retested and had no abnormalities in their blood work. All three studies reported adverse events in some of the patients. In the Kose study five patients had adverse effects including fatigue, nausea, and abdominal pain.⁶ In the Wahab study five patients complained of dyspepsia, nausea, and flatulence.⁵ In the Faergemann study 26 patients reported adverse effects during open treatment and 31 patients during the prophylactic phase. One patient experienced urticaria during the open phase and was withdrawn from the study. Other patients experienced mild adverse effects including gastrointestinal complaints in the open phase, while during the prophylactic phase some patients encountered upper respiratory tract infections and influenza like symptoms.⁴

DISCUSSION

The goal of this systematic review was to determine whether or not itraconazole was effective in treating tinea versicolor and if so, what the optimal dosage is. All three of the studies demonstrated the effectiveness of itraconazole in treating tinea versicolor both clinically and mycologically. There were some limitations of the studies due to the fact that only one of them was double blinded. Also the studies did not mention if the patients were required to report to the

hospital each time they received a dose of medication, therefore treatment adherence may have been a complication and skewed the results. Patients that were required to take the medication for seven days may have not been compliant with the regimen compared to the patients that only had to take a single dose of itraconazole.

There were restrictions in these three studies due to the fact that the majority of patients were men. In the Kose study, 37 patients were male and 13 were female.⁶ In the Wahab study, 53 patients were male and 7 were female.⁵ In the Faergemann study, 116 patients were male and 93 were female.⁴ The studies excluded pregnant females and females of child bearing age who did not have access to contraception. This may be because itraconazole is a pregnancy category C drug meaning that animal studies have shown an adverse effect on the fetus but there are no adequate, well-controlled studies in humans.⁷ These three studies also were limited based on age because they did not include children less than 18 years old in two of the studies and less than 12 years old in the third study, therefore the results may not be applicable to children. In the Kose and Wahab studies, the mean duration that the patients had the tinea versicolor infection was approximately 2-3 months, therefore the results may not be applicable to patients that have had a tinea versicolor infection for a longer period of time. Lastly, race was not mentioned in the Kose and Wahab studies, but in the Faergemann study it showed that the majority of patients were Caucasian, with Asians being the next predominant race. Thus, the results may not be relevant for patients of other races.

Itraconazole is similar in price as other antifungals and is available as a generic prescription, so price should not be a concern for patients. It is also used to treat various fungal infections such as aspergillosis, histoplasmosis, candidiasis, onychomycosis in both HIV infected and non-HIV infected patients. The most common adverse effect of itraconazole is nausea.

Patients may also experience diarrhea, vomiting, headache, rash, elevated liver function tests, pruritis, dizziness, fatigue, hypertension, hypokalemia, etc. There is also a black box warning for the use of itraconazole in a patient with congestive heart failure or any ventricular dysfunction.⁷

CONCLUSION

In conclusion, all of the studies showed that itraconazole is effective in treating tinea versicolor. In the Kose and Wahab studies, it was demonstrated that a single dose of itraconazole 400mg is an effective alternative therapy to itraconazole 200mg for seven days. Using a single dose treatment would be more advantageous because it would be less expensive and there would not be problems with compliance as there may be with a seven day regimen. In the Faergemann study it was shown that itraconazole is also effective as prophylaxis for tinea versicolor. Further studies are warranted to prove the effectiveness of itraconazole as prophylaxis for a time period longer than six months, as was done in the Faergemann study. Also further studies should include double blinding, larger research groups, more female patients, various races, and a wider age distribution to include children and geriatric patients. Based on the information obtained from these three studies and the potential for future explorations, itraconazole has the potential to become a first line medication for both the treatment of and prophylaxis for tinea versicolor.

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