Journal of Cosmetics, Dermatological Sciences and Applications, 2018, 8, 264-271
http://www.scirp.org/journal/jcdsa
ISSN Online: 2161-4512
ISSN Print: 2161-4105

The Safety of Oral Ketoconazole in the Treatment of Skin Diseases (Single Blinded, Therapeutic, Comparative Study)

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How to cite this paper: Sharquie, K.E., Noaimi, A.A. and Al-Salam, W.S. (2018) The Safety of Oral Ketoconazole in the Treatment of Skin Diseases (Single Blinded, Therapeutic, Comparative Study). *Journal of Cosmetics, Dermatological Sciences and Applications*, **8**, 264-271.
https://doi.org/10.4236/jcdsa.2018.84028

Received: July 11, 2018
Accepted: December 18, 2018
Published: December 21, 2018

Abstract

Background: Ketoconazole was introduced in 1981 as the first in a series of antifungal agents that are characterized by nitrogen-containing ring. Ketoconazole acts against many different kinds of fungi such as candida, dermatophytes and as pergillus. Also oral ketoconazole had proved its effectiveness in the treatment of cutaneous Leishmaniasis. **Objective:** To evaluate the safety of oral ketoconazole in the treatment of different skin diseases like cutaneous Leishmaniasis (CL), tineacapitis, tineacorporis and tineaversicolor. **Patients and Methods:** This is a single, blinded, therapeutic, controlled study that was carried out in the Department of Dermatology, Baghdad Teaching Hospital, Baghdad, Iraq, during the time, January 2015 to July 2016. In total, 951 patients with acute cutaneous leishmaniasis, tineacapitis, tineacorporis and tineaversicolor were enrolled in this study. The diagnosis was confirmed by smear and histopathology. Patients were divided into two groups: 51 patients in Group 1; 24 of them were treated with oral ketoconazole tablets 200 mg twice daily for 6 weeks and 27 of them were treated orally with a combination of zinc sulfate 10 mg/kg/day and ketoconazole for 6 weeks. All patients were seen regularly every 2 weeks for 6 weeks of treatment period, then monthly for the next three months as follow up period. Liver enzymes monitoring was done for every patient in this study every two weeks. Elevated liver enzymes were considered as features of hepatotoxicity in the examined patients. While group 2 included 900 patients and was divided into 3 subgroups: A: 600 patients with tineacapitis and tineacorporis, B: 100 patients with tineaversicolor, and C: 200 patients with CL. All patients in group 2 were treated with oral KC tablets 200 mg twice daily for 6 weeks. The dose of oral KC in children is 3.3 - 6.6 mg/Kg/day. All patients in group 2 were not investigated for ketoconazole

biochemical side effects but watched for any clinical symptoms and signs of any side effects. **Results:** After six weeks, 951 patients had completed the treatment. In the first group (51 patients), only two out 27 patients (7.4%) from the combined group showed elevated liver enzymes while the ketoconazole treated group showed no increase in liver enzymes, hence only 3.9% showed elevated liver enzymes that went to normal during follow up. In the second group (900 patients) there were no clinical symptoms and signs in favor of hepatic toxicity or other related organs. **Conclusion:** Ketoconazole has been used tremendously in treating of different skin diseases including fungal and Leishmania infection but without side effects, accordingly this drug seems safe to be used in treatment of different skin diseases whether adults or children.

Keywords

Cutaneous Leishmaniasis, Ketoconazole, Drug Safety

1. Introduction

Ketoconazole (KC) was introduced in 1981 as the first in a series of antifungal agents that are characterized by nitrogen-containing ring [1]. Oral KC acts by inhibiting the enzyme cytochrome P450 14α-demethylase which leads to the inhibition of the conversion of lanosterol to ergosterol and this will change cell membrane permeability. In addition, ketoconazole inhibits biosynthesis of triglycerides and phospholipids by fungi as well as inhibition of several oxidative and peroxidative enzymes involved in detoxification process in fungi. All these will lead to cellular necrosis [2].

KC is an antifungal, with activity against many kinds of fungi such as candida, histoplasma, coccidioides, blastomyces and as pergillus [3]. KC is also used a potent inhibitor of human drug metabolism especially with cyclosporine [4]. KC is also used in the treatment of prostate carcinoma and Cushing disease because of its ability to inhibit adrenal steroidogenesis [5].

KC was the first broad spectrum antifungal drug approved by the Food & drugs agency (FDA) in 1981, however; posts marketing there were reports of drug-related hepatotoxicity resulting in US market withdrawal of the drug [6].

The most common reported side effects are the reversible gastrointestinal disturbances, which occur in 3% - 10% of patients [7]. In addition, gynecomastia, irregular menstrual cycle, decrease libido and impotency were recorded following oral KC due to its anti-androgenic effect [7].

In 1984, cases of KC associated hepatotoxicity, rarely fatal, were reported [8]. A number of reviews, case survey, and registry reports from around the world have been published since 2002, dealing with the general topic of drug induced hepatitis, liver injury, liver failure, in all of these publications KC was mentioned not at all, or only minimally as a potential cause of liver injury [9] [10]. Toxicity

produced by KC and N-desacetyl-ketoconazole (bio-transformer of KC) evident as cellular leakage of alanine transaminase (ALT) or lactic dehydrogenase (LDH) was dose and concentration dependent, and associated with covalent binding to hepatic protein as well as glutathione depletion [11]. In 2013, after more than three decades of clinical usage of KC, FDA and European medicines agency (EMA) concurrently issued the warning about the dangers of oral KC [12] [13]. On the other hand its usage was limited only when other effective antifungal drugs were not available or not tolerated and potential benefit of ketoconazole outweighs its potential risks [14].

Cutaneous Leishmaniasis (CL) is an endemic disease in many countries including Iraq and many drugs were used in treatment of CL and KC is one of them. In Sharquieetal study, we used KC singly and in combination with oral zinc sulphate, and the results were very encouraging [15].

So the aim of the present work is to record the side effect of systemic KC during therapy and follow up of different skin diseases.

2. Patients and Methods

This is a single, blinded, the rapeutic, controlled study that was carried out in the Department of Dermatology and Venereology, Baghdad Teaching Hospital, Medical City, Baghdad, Iraq from January 2015 to July 2016. A total of 951 patients were enrolled in this study. The cases were divided accordingly into two groups, the first group included 51 patients with CL which were tested with liver enzymes assays at pre and during treatment with KC. The second group included 900 patients treated with KC but without liver enzymes assays and patients were watched for clinical symptoms and signs of any side effects related to ketoconazole use.

A history was taken from each patient regarding the followings: age, gender, address, duration of the lesions and their number, recurrence of the lesion, history of previous therapy. Also family history, past medical history, obstetric history regarding the female in reproductive period and past drug history. Formal consent was taken from each patient before starting the therapy. Also, the ethical approval for this study was given by the scientific committee of the Scientific Council of Dermatology and Venereology-Iraqi Board for Medical Specializations.

Therapeutic groups

Patients were divided into two groups:

The **first group** included 51 patients with CL treated with KC with liver enzymes assessment and were divided into two subgroups:

A. Ketoconazole group: where 24 patients were enrolled in this group. Patients with lesions of leishmaniasis were treated with oralketoconazole tablet 200 mg twice daily for 6 weeks. Patients were seen regularly every 2 weeks for 6 weeks of therapy time, after then monthly for the next three months as follow up period. Ketoconazole was supplied from Pharma International Company, Jor-

dan. We dida baseline, laboratory tests including serum gamma-glutamyl transferase (SGGT), alkaline phosphatase, ALT, AST, total bilirubin (TBL), prothrombin time (PT), international normalization ratio (INR), and viral hepatitis serology. While the dose in children was 3 mg/kg and with similar regeme.

B. Combination group: 27 patients were enrolled in this study group. The patients lesions were received a combination of oral zinc sulfate capsule in a dose of 10 mg/kg and ketoconazole tablet 200 mg twice daily for 6 weeks. And treated patients were monitored regularly every 2 weeks for 6 weeks of therapy, and then after monthly for the next three months as follow up time. Also, SGGT, alkaline phosphatase, ALT, AST, TBL, PT, INR, and viral hepatitis serology were carried out.

The **second group** included 900 patients treated with KC without liver enzymes assessment and divided accordingly into 3 subgroups

1) A total of 600 patients with tineacapitis and tineacorporis

2) A total of 100 patients with tineaversicolor

3) A total 200 patients with CL (Cutaneous Leishmaniasis).

All patients with liver problems including alcoholic were excluded from the present study. Pregnant and lactating women were not included in the present work.

3. Results

A total 0f 951 patients were enrolled in this study.

The first group included 51 patients with acute CL. The gender distribution was almost equal with 27 (53%) males and 24 (47%) females and their ages range from 1 to 80 years with a mean ± SD of 33.7 ± 1.82 years. All patients in this study had multiple lesions with overall total number of 248.

The second group included 900 patients dived into two groups;

1) In total 600 patients were affected with tineacapitis and tineacorporis, the gender distribution was almost equal with 306 (51%) males and 294 (49%) females and their ages range from 5 to 30 years with a mean ± SD of 18.6 ± 1.43 years.

2) In total 100 patients were affected with tineaversicolor, 69 (69%) males and 31 (31%) females and their ages range from 5 to 30 years with a mean ± SD of 19.2 ± 1.64 years.

3) In total 200 patients were affected with CL, the gender distribution was almost equal with 108 (54%) males and 92 (46%) females and their ages range from 5 to 30 years with a mean ± SD of 17.4 ± 1.49 years .

Group 1:

A. CL group treated with oral Ketoconazole and assessed by liver enzymes

A total of 24 patients with 105 lesions were included in this group. The mean duration of lesions of CL was 6.5 ± 0.8 weeks with a range of 4 - 12 weeks and the cure rate was 50%

Liver Enzymes study

Liver enzymes assays were performed every 2 weeks and did not show any remarkable changes.

B. CL treated with oral zinc sulphate and Ketoconazole and assessed by liver enzymes

A total of 27 patients with 143 lesions were included in this group. The mean duration of lesions of CL was 7.00 ± 0.75 weeks with a range of 4 - 12 weeks and the cure rate was 96%.

Liver Enzymes study

Liver enzymes assays were performed every 2 weeks. There was elevation of liver enzymes in two patients (7.4%) in this group after 4 week of treatment with oral ketoconazole (Table 1). The oral ketoconazole was stopped immediately and the patients continued on oral zinc sulphate. Liver enzymes went to normal after 8 weeks of the start of the treatment. So only 3.9% of total cases of Leishmaniasis showed elevated liver enzymes.

Group 2:

1) A total of 600 patients with tineacapitis and tineacorporis were treated with oral ketoconazole for 6 weeks. The mean duration of lesions was 8.24 ± 0.735 weeks with a range of 5 - 14 weeks. All patients have excellent response to KC. There was no clinical evidence of liver injury or other organ related clinical side effects.

2) A total of 100 patients with tineaversi color were treated with oral KC for 6 weeks. The mean duration of lesions of was 11.33 ± 0.92 weeks with a range of 7 - 16 weeks. All patients had excellent response to KC. There was no clinical evidence of liver or other organs injury in all treated group.

3) A total of 200 patients with CL were treated with oral KC for 6 weeks. The mean duration of lesions of was 7.35 ± 0.86 weeks with a range of 4 - 12 weeks. All patients had satisfactory response to KC. There was no clinical evidence of liver or other organ injury in all treated group.

4. Discussion

Oral ketoconazole is a potent antifungal drug [1] [3] and this was confirmed by the present study as it had been used successfully for the treatment of tineacapitis, tineacorporis and tineaversicolor.

Table 1. Showing elevated liver enzymes in two patients in Group 1B.

Patients	Weeks after staring	ALT (U/L)	AST (U/L)	ALKP (U/L)	Bilirubin mg/100ml
First	0	37	30	120	0.4
	4	250	162	250	0.3
	8	30	20	120	0.4
Second	0	26	22	110	0.2
	4	100	120	320	0.2
	8	22	25	120	0.2
Normal values		<50	<50	<279	<1.2

Oral ketoconazole was used by *Alsaleh et al.* study [16], from Kuwaitas a therapy for leishmaniasis who used a higher oral dose 600 mg/day ketoconazole with cure 60% and oral 800 mg/day ketoconazole with cure rate 66.7% at the end of six weeks of treatment [16]. This diversity of cure rate could be explained by the higher dose of ketoconazole and the different scoring system and no side effects were reported. While Sharquie *et al.* (15) used ketoconazole as a single therapy for leishmaniasis and gave 50% cure rate, and in a combination of oral ketoconazole and zinc sulfate gave a cure rate of 96%, and by using Tuckey HSD test suggests that this combination has synergistic effect.

In the present study we identified transient elevation of liver enzymes in 3.9% from the first group with leishmaniasis without apparent clinical hepatotoxicity started at the fourth week of the initiation of treatment and resolved spontaneously after 4 weeks of stopping ketoconazole treatment. In addition, all patients in the second group with different types of fungal infection did not show any clinical features of hepatic toxicity or other organ toxicity following 6 weeks of treatment with oral KC.

These results are compatible with Salmanpour *et al.* who used oral KC (600 mg/day for adults and 10 mg/kg per day for children for 30 days) in the treatment of 64 patients with CL and found a very good response to oral ketoconazole with minimal side effects, none necessitating discontinuation of the medication [17]. Also Kubba *et al.* confirmed ketoconazole as effective and safe use of oral KC in the treatment CL [18].

In addition, Peterson *et al.* [19], who performed a case-control trial of six months course of oral ketoconazole versus placebo in twelve patients with chronic mucocutaneous candidiasis with subsequent cross-over, shows marked beneficial effects in all patients except one patient (8%) developed elevation of ALT and ALP without jaundice that improved with lowering the dose. Also another study [20] showed similar results done by Macnair *et al.* The study, which included 988 patients treated with oral ketoconazole and monitored with liver enzymes assay, found little evidence of hepatic injury as they only identified 3 cases (0.3%) of hepatitis during therapy all resolved with stopping therapy [20].

Moreover, another population based study of drug induced liver injury was conducted in Iceland identified 96 patients over a two year period, none of which was attributed to ketoconazole [21].

On the other hand, there are studies that oppose these results. In a study performed on liver transplant patients due to hepatic failure, they found 6 (4%) out of 137 were related to induced acute liver failure by ketoconazole [22].

In addition, the European medicines agency committee in 2013 recommended that a ban be imposed on the use of oral ketoconazole in humans throughout the European Union after concluding that the risk of serious liver injury outweighs its benefits [12]. In the United States of America, FDA issued a warning that oral ketoconazole can cause severe liver injury [13].

Furthermore, oral ketoconazole was discontinued in Australia in 2013 [23],

and in China in 2015 [24] for similar reasons.

It is interesting that in the present study, the elevated liver enzymes was identified in the combined treated group only using oral ketoconazole and zinc sulfate, while the other group who are using ketoconazole alone did not show any elevation of hepatic enzymes suggesting drug-drug interaction might play a role in this elevation of liver enzymes.

5. Conclusion

In conclusion, KC had been used in treating different skin diseases including fungal and Leishmania infections but without clinical features of liver toxicity. Liver enzymes were elevated in 3.9% of Leishmania treated cases but went to normal levels after stopping therapy.

Disclosure

This study was an independent study and not funded by any drug companies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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