ORIGINAL RESEARCH

The Clinical Safety and Efficacy of Ketoconazole in the Prevention of Postoperative Erection: A Systematic Review

Achilles C. Sta. Cruz, MD and Genlinus D. Yusi, MD, FPUA

Department of Urology, National Kidney and Transplant Institute

Objective: To identify and assess the available literature in evaluating the efficacy and safety of ketoconazole in preventing postoperative erection among patients who underwent penile or urethral reconstructive surgery.
Methods: From the period of 1990 to September 2016, the investigators assessed Cochrane Central Register of Controlled Trials, EMBASE, HERDIN, and PubMed for studies evaluating the efficacy and safety of ketoconazole in preventing post operative erection among patients who underwent penile or urethral reconstructive surgery. Review authors selected articles for inclusion, extracted data and assessed trial quality.
Results: One randomized controlled study and 2 retrospective studies were included in the review. Three studies for a total of 83 patients ages 13-72 comprised the evidence for this review. All trials investigated the efficacy and safety of ketoconazole in the prevention of post operative erection. In both retrospective studies, ketoconazole had significant prevention of erection in however both of these studies were non-RCTs. In the randomized control study by DeCastro et.al., ketoconazole had no significant difference in the prevention of post operative erection against placebo. Sixteen out of 19 patients (84%) taking ketoconazole had episodes of erection and 15 out of 18 patients in the placebo group (83%) had episodes of erection. Common side effects include nausea (9 - 21%) and elevated liver enzymes (0 - 5.3%). Other reported adverse events include feet swelling, pruritus, frequent urination and headache, Present in only 1 out of the 31 patients (3.2%) in the study of DeCastro. All these adverse events were not statistically significant.
Conclusion: This review demonstrated that the use of Ketoconazole in the prevention of postoperative erection remains inconclusive. Further prospective randomized controlled trials with testosterone assay will help determine the appropriate dose and its efficacy in the prevention of postoperative erections. Ketoconazole is relatively safe if target testosterone levels are achieved using the 400mg/tab TID dosing.

Key words: ketoconazole, postoperative erection, systematic review

Introduction

Postoperative erections may occur in patients who underwent penile or urethral reconstructive surgery. This can impair wound healing as well as cause pain and discomfort to these postoperative patients. Various agents have been used before in the past. Amyl nitrate, benzodiazepines, narcotics, dorsal nerve blocks, cold refrigerant spray to the thigh and intercavernous injections have all shown limited effectiveness for this problem.[1] High estrogen levels have been associated with erectile dysfunction and have been shown in several animal studies and human studies.[2,3,4,5] Its

therapeutic use in the prevention of postoperative erection has not been further utilized.

Ketoconazole is an antifungal agent and a CYP17A1 inhibitor which has been used to treat metastatic prostate cancer by lowering serum testosterone levels.[6] It inhibits testicular and adrenal steroid synthesis by inhibiting 17 α-hydroxylase and 17,20-lyase. It is a safe, cheap and effective treatment to ischemic priapism.[7,8] It produces a temporary hypogonadal state to suppress sleep-related erections which often evolve into episodes of ischemic priapism in this population.[9]

The neurons of the medial preoptic area in the brain have high concentration of testosterone receptors. Alterations of testosterone levels may influence the initiation of centrally mediated erections.[10] As a result of the decreased testosterone levels, it is expected that erections will be inhibited in patients taking ketoconazole.

One of the common side effects of ketoconazole is hepatotoxity and its incidence is 3.6%-4.2% and off-label use might increase the risk of liver damage.[11] In the study of Outeiro, et al. patients undergoing treatment with ketoconazole for 6 days had 1.7% increased liver transaminase activity and in patients treated for 276 days (mean) had 5.6% elevated liver enzyme activity. In the study of Evans, et al. other side effects include nausea, headache, pruritus, frequent urination.

A systematic review is essential for this study to provide further evidence with regards to the use of ketoconazole in the prevention of postoperative erections to patients who underwent penile or urethral reconstructive surgery and its clinical safety use.

The aim of this review was to identify and assess the available literature in evaluating the efficacy and safety of ketoconazole in preventing post-operative erection among patients who underwent penile or urethral reconstructive surgery.

Materials and Methods

Search for Identification of Studies

The following databases were used to identify studies for this systematic review. Cochrane Central Register of Controlled Trials, EMBASE, PubMed, and HERDIN from 1990 to September 2016. Two reviewers independently evaluated the studies without prior consideration of the results. Search terms were ketoconazole and erection.

Type of Participants

Patients who underwent penile or urethral reconstructive surgery

Type of Intervention

Postoperative penile/ urethral reconstructive surgery patients were given ketoconazole perioperatively.

Types of Outcomes

1. Number of erections (non-painful/painful - painful enough to warrant intake of pain medications)

2. Adverse reactions and side effects

Types of Studies / Methodologies and Process of Selection

Study design criteria for inclusion in this review were published randomized control trials and retrospective studies written in English with any level of blinding and containing any number of individuals of whom at least 80% were followed up.

Data Abstraction

Standard data abstraction form was used by two reviewers independently and cross checked. No attempt was made to contact the authors in cases of insufficient data.

Study Appraisal/Assessment of the Risk of Bias

The risk of bias in eligible trials was assessed independently by two reviewers using the Cochrane risk of bias tool.

Data Collection and Analysis

The titles and abstracts of all studies identified by the search strategy were assessed independently for possible inclusion by two reviewers. The full texts of all potentially relevant studies were retrieved and assessed for inclusion into the review based on the preset criteria. Standardized data extraction form was used independently by two reviewers.

Data Synthesis

Included data were processed as described in the Cochrane Handbook. Risk ratios were determined and reported for dichotomous data and mean differences with 95% confidence intervals for continuous data. A fixed effect model was used for data analysis.

Methodology

A systematic review of relevant literature assessing safety and efficacy of ketoconazole in the prevention of postoperative erection in patients who underwent penile or urethral reconstructive surgery was conducted using electronic and manual searches. The search was done of the following databases: The Cochrane Central Register of Controlled Trials, EMBASE, PubMed, and HERDIN. The search terms included ketoconazole and erection. Reference lists were identified and hand-searching of related journals and abstracts were done. Two reviewers independently assessed the titles and abstracts identified by the search strategy. The full texts of all potentially relevant studies were retrieved and evaluated independently by two reviewers and all studies that met all inclusion criteria were included in the review.

Trials were considered eligible if they met the selection criteria set prior to this review. The criteria included randomized controlled trials and case control studies with study population consisting of postoperative penile or urethral reconstructive patients using ketoconazole to prevent postoperative erection. Studies should have used ketoconazole alone versus placebo, or no intervention pre and postoperatively.

The primary outcome measures considered for the review included the episodes of erection whether they are painful or non-panful. Secondary outcomes included the side effects, elevation and derangements in the liver enzymes.

The quality of the studies and the risk of bias were assessed independently by the authors, based on the Cochrane Handbook for Systematic Reviews of Interventions. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting were checked for each study.

Results of the Search

The initial search produced 11 possible titles. After removal of duplicates, 9 possible titles were obtained. Four of the 9 studies were assessed to be potentially eligible based on the abstract. Review of the full text reports yielded 3 eligible studies. (See figure below) One report was excluded because it was a review/comment for one of the 3 eligible studies. One study was randomized and two studies were non-randomized controlled trials.

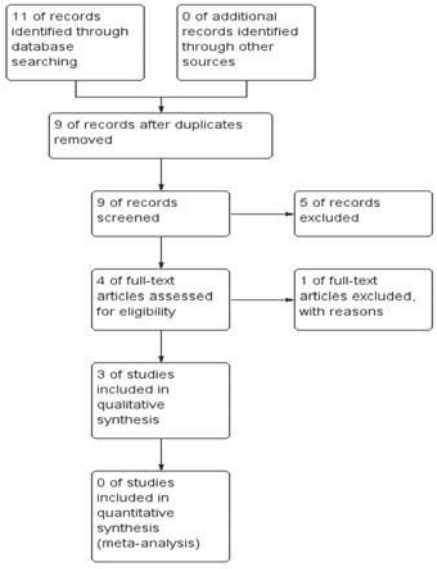

Figure 1. PRISMA flow diagram

Description of Included Studies

One randomized controlled study and 2 retrospective studies were included in the review. Three studies for a total of 83 patients comprised the evidence for this review. One study was done in 1995, the second one was in 2004, and the third one was in 2008.

Patient population in the three studies included pediatric to adult patients (13-72 years old) who underwent penile or urethral reconstructive surgery. The presence of erection was identified. One of these three studies had no medications as the control group, while one study had a placebo as control. One study had no control group.

Primary outcome of this review was to evaluate the efficacy and safety of ketoconazole in preventing postoperative erections. Efficacy was defined as the prevention of erections. Safety was defined as side effects such as elevations of liver enzymes and the presence of adverse event. Adverse event was defined as any untoward incident during the study period such as nausea, pruritus, headache, frequent urination, feet swelling.

Two of the studies were retrospective and one was randomized controlled trial. In the study of DeCastro, the consented participants were referred to a research pharmacist who randomized the patients into taking ketoconazole or placebo. The physician and patient were blinded to the medication each participant was receiving.

There were three dropouts in the study of DeCastro for failure of completing the questionnaire (1 in the ketoconazole and 2 in the placebo). During the treatment, three patients from DeCastro discontinued taking ketoconazole due to severe nausea and vomiting (4/19) but was not statistically significant.

There were no mortalities noted in all the study groups.

Table 1. Characteristics of included studies.

Study	Participants	Intervention/Comparison	Outcomes	Risk of Bias
Stock 1995	• 8 male patients from 14-42 years old undergoing hypospadias/ urethroplasty surgery. • No control group	**Group 1: (N=8)** • Ketoconozale 400mg orally three times daily starting on the operative day. Duration of treatment not specified	**Primary:** • Number of erections **Secondary:** • Liver function tests, GGT, Alkaline phosphatase, SGPT, SGOT	• Retrospective study – N/A
Evans 2004	• 38 male patients from 13-72 years old undergoing penile/urethral reconstructive surgery (urethroplasty, circumcision and revision of circumcision, corporal plication)	Group 1 (N=31) • Ketoconozale 400mg orally three times daily starting postoperatively for 10-14 days. Group 2 (N=7) • No medications	Primary • Presence of erections (non painful and painful - –warranting use of pain medications) • Postoperative pain Secondary • Side effects such as nausea, pruritus, headache, frequent urination, feet swelling • Complications	• Retrospective study – N/A
DeCastro 2008	• 37 patients undergoing penile or urethral surgery (urethroplasty, circumcision, meatoplasty) • Mean Age 29.3 for the ketoconazole group and 28.2 for the placebo group	**Group 1 (N=19)** • Ketoconozale 400mg orally three times daily starting 2 days prior to surgery and up to 7 days postoperatively. Total of 10 days **Group 2 (N=18)** • Placebo group	**Primary** • Daily erection log **Secondary** • Side effects such as nausea • Liver function test elevation.	• Randomized clinical control trial • Double-blinding was done

Discussion

There are very few studies reviewing the efficacy and safety of ketoconazole in the prevention of postoperative erection. In the previous retrospective studies made by Stock 1995 and Evans 2004, both showed that ketoconazole was effective in preventing postoperative erections in their patients.

In the study of Stock, seven out of the eight patients had no episodes of erection postoperatively due to intake of ketoconazole. One patient who had an episode of erection discontinued the drug due to unknown reasons but erection was further prevented upon resumption of ketoconazole. In the study of Evans, in patients taking ketoconazole, seven out of 31 patients (23%) had non painful erections, and 5 out of 31 patients (16%) had painful erections. Three out of 12 patients who had erection claimed that they had diminished erections. In patients who did not receive ketoconazole, 5 out of 7 patients (71%) had erections which were all painful. Thus in both studies, there was significant prevention of erection in patients taking ketoconazole however both of these studies were non-RCTs.

In the study of DeCastro 2008 which is a randomized double blinded study, it was shown that ketoconazole does not significantly prevent erection. Sixteen out of 19 patients (84%) taking ketoconazole had episodes of erection and 15 out of 18 patients in the placebo group (83%) had episodes of erection. Their study concluded that there was no significant prevention of erection in patients taking in ketoconazole. Furthermore they claimed to have discontinued using ketoconazole in their postoperative patients.

However according to the review of Levine, et al. 2008, the efficacy of ketoconazole must be further assessed by determining circulating serum testosterone and threshold level of circulating testosterone for obtaining nocturnal erections is approximately 200ng/dl. Target testosterone should be less than 200ng/dl in order to prevent erections and a serum testosterone assay will help determine the appropriate dose for treatment. Thus in the study of DeCastro, the investigators could not conclude its efficacy due to the lack of testosterone assay, which may determine if proper ketoconazole dosage is achieved. All studies used ketoconozale dosing of 400mg/tab TID for 7 to 14 days.

With regards to safety, two out of the three studies determined the elevation of liver function tests. In the study of Stock, there were no reported elevation of liver function tests. In the study of DeCastro, only 1 out of 19 patients (5.3%) had transient increase of liver function tests which returned to normal levels upon cessation of ketoconazole. Nausea is the primary adverse event noted in two of the studies. In the study of Evans, three out of the 31 patients (9%) had nausea. In the study of DeCastro, four out of 19 had nausea (21%), three of which had discontinued the medication due to severe nausea and vomiting. Other reported adverse events include feet swelling, pruritus, frequent urination and headache, which were observed in only 1 out of 31 patients (3.2%). All these adverse events were not statistically significant. Therefore, it is relatively safe to use ketoconazole in patients if 400mg/tab TID standard dose is maintained.

Conclusion

This review demonstrated that the use of ketoconazole in the prevention of postoperative erection remains inconclusive. Further prospective randomized control trials with testosterone assay will help determine the appropriate dose and its efficacy in the prevention of postoperative erections. Ketoconazole is relatively safe if target testosterone levels are achieved using the 400mg/tab three times daily dosing.

References

1. DeCastro BJ, Cosabile RA, Mcmann LP and Peterson AC. Oral ketoconazole for the prevention of postoperative penile erection: A placebo controlled, randomized, double-trial. J Urol 2008; 179: 1930-2.

2. Kataoka T, Hotta Y, Ohno M, Maeda Y, and Kimura K. Limited effect of testosterone treatment for erectile dysfunction caused by high estrogen levels in rats. Int J Impt Res 2013; 25(6): 201-5.

3. Zhou YC, Li TF, Sun ZX, Fan Q, Liu T and Jin BF. Therapeutic efficacy of Busenzhuyang Fang (Yangjinh capsule on phytoestrogen-induced erectile dysfunction: an experimental study. Zhonghua Na Ke Xue 2014; 20(12): 1103-8.

4. Vignozzi L, Filippi S, Comeglio P, Cellai I, Morelli A, Marchetta M and Maggi M. Estrogen mediates metabolic syndrome-induced erectile dysfunction: a study in the rabbit. J Sex Med 2014; 11(12): 2890-902.

5. El-Sakka Al. Impact of the association between elevated oestradiol and low testosterone levels on erectile dysfunction severity. Asian J Andol 2013; 15(4): 492-6.

6. Stock JA and Kaplan GW. Ketoconazole for prevention of post-operative penile erection. Urology 1995; 45: 308.

7. Yucel OB, Salabas E, Ermec B and Kadioglu A. The case report of priapus and a modern approach to an ancient affliction. Sex Med Rev Sept 2016.

8. Mwamukonda KB, Chi T, Shindel AW and Lue TF. Androgen blockade for the treatment of high-flow priapism. J Sex Med 2010; (7)7: 2532-7.

9. Hoeh MP and Levine LA. Prevention of recurrent ischemic priapism with ketoconazole: evolution of a treatment protocol and patient outcomes. 2014; 11: 197-204.

10. Evans KC, Peterson AC, Ruiz HE and Costabile RA. Use of oral ketoconazole to prevent postoperative erections following penile surgery. Int J Impot Res 2004; 16: 346.

11. Outerui N, Hohmann N and Mikus G. No increased Risk of ketoconazole toxicity in drug-drug interaction studies. J Clin Pharmacol 2016; 56(10): 1203-11.