ORIGINAL ARTICLE

Comparison of Side Effects of Tolterodine and Solifenacinsucinate in Patients with Urinary Incontinence

MARYAM RANA, IRAM MOBUSHER

ABSTRACT

Background: Overactive bladder syndrome is a common symptom complex that affects millions of people worldwide, with an increasing prevalence with increased age. The ideal anti muscurinic agent should effectively relieve the symptoms of OAB, with the minimum of side effects; it should be available as a once-daily sustained release formulation.
Aim: To compare the side effects of tolterodine &solifenacin succinate in pts with urinary incontinence.
Study design: Randomized controlled trial
Setting: Department of Obstetrics and Gynecology, Lady Willington Hospital Lahore
Duration: 09th October 2013 to 8th April 2014.
Methods: An informed consent was obtained. Patients were randomly divided (using lottery method) in both study groups. In Group-A patients were treated with Tolterodine (4mg) and in Group-B patients were treated with Solifenacin Succinate (5mg). All information including side effects (as per operational definitions) were collected post treatment and follow up at 3 months by the researcher herself.
Results: Mean age of all 830 patients was 57.34±11.54 years. In Group-A there were 123(29.64%) patients who had dry mouth and in Group-B there were 101(24.34%) patients told that they had dry mouth. In Group-A there were 123(29.64%) patients who had dry mouth and in Group-B there were 101(24.34%) patients told that they had dry mouth. It was observed that more patients had dry mouth in Group-A as compared to that of in Group-B.
Conclusion: This study found that solifenacin succinate (5mg) had significantly higher occurrence of constipation as compared to Tolterodine (4mg). i.e., 9.88% vs. 5.06%. While occurrence of dry mouth was also higher but not significant in solifenacin succinate. These results showed that difference in side effects between tolterodine and solifenacin succinate in patients with urinary incontinence.
Keywords: urinary incontinence, tolterodine, solifenacine succinate

INTRODUCTION

Urinary incontinence is defined as complaint of involuntary loss of urine[1], in contrast continence is the ability to hold the urine at all the times except during micturation. Urinary incontinence has been estimated to affect 10-13 million people in united states and around 200 million people worldwide. On review of incontinence as a worldwide problem, studies from high income countries report a median prevalence of 27.6%[2] while a recent review of studies conducted in developing -countries-show-mean-prevalence of 28.7 % with a range from 5.2%-72.8%[3] and shows that prevalence of significant incontinence increases with age. Several studies have shown that the burden of urinary incontinence may vary across the racial groups. Various, cross sectional studies reported a lower prevalence of overall incontinence in Black and Asian population when compared with white women[4,5].

Department of Obstetrics & Gynaecology, King Edward Medical University/Lady willington Hospital, Lahore
Correspondence to Dr Iram Mobusher Senior Registrar, Email Add dr_iram@yahoo.com dr_iram@yahoo.com>

A very little data regarding urinary incontinence is available in Pakistan. One study was conducted in 'Sindh among 5064 participants (response rate 95.8%), the prevalence of urinary incontinence was found to be 11.56%[6].

Urinary bladder is a hollow muscular organ designed to store urine. It is composed of smooth muscles known as Detrussor muscle. Muscurinic receptors are known to mediate the Detrussor muscle contraction and in this regard important role of muscurinic receptor antagonist such as tolterodine is well recognized but tolerance and compliance to the drug is limited due to its side*effects* such as dry mouth and constipation[7].

Moreover, 59% of solifenacin treated patients who were incontinent at baseline became continent as compared to 49% of patients treated with tolterodine.(8)The incidence of side effects such as dry mouth was greatest in the solifenacin treated group 14(38%), followed by the tolterodine treated group 9(24%), $p<0.05$ (significant)[9] while another study showing the incidence of dry mouth was 17.5% in solifenacin treated and 14.8% $p>0.05$ (insignificant) in tolterodine treated group. In the same study the incidence of constipation

was (3.2%) in solifenacin treated while 1.3%, p>0.05 (insignificant)in tolterodinegroup[8]. Another study was done showing the incidence of constipation 7% in tolterodine treated group alone[10].

The rational of this study is to see the side effects of solifenacin and tolterodine as there is variability in side effects of tolterodine and solifenacin succinate in literature. In developing countries like Pakistan where basic health care is out of reach of common man a problem like urinary incontinence is largely overlook and those who seek medical help remain non complaint due to side effect if drug prescribed. Therefore, a study is required to chose a drug with lesser side effects to cope with the problem that make a woman's religious, marital and social life miserable and poses economic burden on family.

The objective of the was to compare the side effects of tolterodine and solifenacinsucinate in patients with urinary incontinence.

MATERIAL & METHODS

This randomized controlled trial was conducted in the Department of Obstetrics and Gynecology, Lady Willington Hospital Lahore over a period of six months from Jan 2014-June 2014. A sample size of 830 cases (415 in each group) was calculated with 80% power of test, 5% level of significance and taking expected percentage of constipation in both groups. i.e., 3.2% in Solifenacin group versus 7% Tolterodine group in patients with urinary incontinence. Non Probability purposive sampling technique was used.

Inclusion criteria

- Patients having complaint of urinary incontinence
- Patients having complaints of nocturia. (The complaint of having to wake at night or more times to void)
- Patients having complaints of frequency (The number of times a women voids during her waking hours. Normally it is between 4-7 voids per day)

Exclusion criteria

- Patients with UTI
- Patients with fistula (History of continuous dribbling of urine)
- Pregnant women (on history)
- Patients with history of prolapspe
- Patients with diabetes (BSF >126 mg/dl and BSR>200 mg/dl)

Data collection procedure: After approval of study from ethical committee of Lady Willingdon Hospital, patients fulfilling the inclusion and exclusion criteria were registered through OPD of Lady Willingdon Hospital. An informed consent was obtained. Demographic information like name, age address, etc was recorded. Patients were randomly divided (using lottery method) in both study groups. In Group-A patients were treated with Tolterodine (4mg) and in Group-B patients were treated with Solifenacin Succinate (5mg). All information including side effects (as per operational definitions) were collected post treatment and follow up at 3 months by the researcher herself from OPD.

Data analysis procedure: All collected information was entered and analyzed using SPSS version 18. Quantitative data like age was presented in form of mean±SD and qualitative data like side effects (Dry Mouth, Constipation). The frequency of side effects in both study groups was assessed using Chi-Square test and significance level was set as $p \leq 0.05$.

RESULTS

Mean age of all 830 patients was 57.34±11.54 years. Minimum and maximum age of patients was 35 years and 90 years respectively (Table 1). Mean age of patients in Group-A and in Group-B patients was 58.31±12.09 and 56.38±10.89 years respectively. In both treatment groups minimum and maximum age of patients was 35 and 90 years respectively (Table 2).

Table 1: Descriptive statistics for age

N	830
Mean	57.34
SD	11.54
Minimum	35
Maximum	90

Table 2: Descriptive statistics for age in relation to treatment groups

	Group-A	**Group-B**
n	**415**	**415**
Mean	58.31	56.38
SD	12.09	10.89
Minimum	35.00	35.00
Maximum	90.00	90.00

Group-A= Solifenacin Succinate Group-B=Tolterodine

Table 3: Frequency of dry mouth in treatment groups

	Group-A	**Group-B**
Yes	123(29.64%)	101(24.34%)
No	292	314
Total	415	415

Group-A= Solifenacin Succinate Group-B=Tolterodine
Chi-Square Test= 2.959 p-value=0.085

In Group-A there were 123(29.64%) patients who had dry mouth and in Group-B there were 101(24.34%) patients told that they had dry mouth. It was observed that more patients had dry mouth in Group-A as compared to that of in Group-B. This difference in both treatment groups was not

statistically significant. i.e. (p-value=0.085) (Table-3). In Group-A there were 41(9.88%) patients who had constipation and in Group-B there were 21(5.96%) patients told that they had constipation. It was observed that more patients had constipation in Group-A as compared to that of in Group-B. Thisdifference in both treatment groups regarding occurrence of constipation was statistically significant. i.e., (p-value=0.000) (Table 4).

Table 4: Frequency of constipation in treatment groups

	Group-A	Group-B
Yes	41(9.88%)	21(5.06%)
No	374	394
Total	415	415

Group-A= Solifenacin Succinate Group-B=Tolterodine
Chi-Square Test= 6.872 p-value= 0.008

DISCUSSION

Overactive bladder (OAB) syndrome is a common symptom complex that affects millions of people worldwide, occurring with an increasing prevalence with advancing age. OAB may be defined as urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia (Urgency incontinence is an evolution of the term urge incontinence and provides a more precise characterization of incontinence in OAB.) These symptoms have been shown to be bothersome to patients, to affect their well-being and have an impact on quality of life[11,12].

Accordingly, in recent years a number of therapeutic agents, all with anantimuscarinic mode of action, have been developed and have received regulatory approval; including oxybutynin, tolterodine, propiverine, trospium and recently launched drugs such as darifenacin and solifenacin. However OAB is both under-reported by patients and under-treated by clinicians despite clear evidence that antimuscarinics reduce OAB symptoms. Furthermore antimuscarinics such as solifenacin achieve a good balance of efficacy and tolerability and as a consequence is associated with good long term compliance and patient satisfaction. The therapeutic profile however may differ because antimuscarinics have differing profiles of receptor interaction on the five subtypes of muscarinic receptor that represent targets for OAB treatments[13,14,15].

It is likely that selectivity for, or tissue penetration of the drug onto, anti-muscarinic receptors in the bladder as contrasted to those present in other peripheral tissues may be useful in achieving a balance between efficacy and side-effects such as dry mouth and may result in differences in the efficacy and adverse event profiles of the different antimuscarinics.

Christopher R. Chapple in his study compared OAB symptom outcomes following initial randomized treatment with solifenacin 5 mg or tolterodine ER 4mg at the 4-week clinic-visit and again at 12 weeks for patients choosing to remain on this treatment dose from 4 weeks. He reported that Dry mouth was seen in 27.6% patients who were given Solifenacin and 24% in patients who were given Tolterodine. Incidence of constipation in Solifenacin and Tolterodine was 4% and 2.4% respectively[16].

Findings of this study showed that occurrence of dry mouth was 29.64% in Solifenacin Succinate group and 24.35% in Tolterodine. But no statistically significant difference was present for dry mouth in both treatment groups. These results are consistent with results reported by Christopher R. Chapple. However constipation was significantly higher in Solifenacin Succinate i.e., 9.88% as that Tolterodine group 5.06%. However occurrence of constipation in Solifenacin Succinate group was high as that of reported in Christopher R. Chapple study.

Chapple C in his another study evaluated the safety and tolerability of solifenacin and to compare the efficacy and safety of solifenacin with tolterodine 2 mg twice daily. Incidences of dry mouth, the most bothersome side effect, were 4.9% (placebo), 14.0% (solifenacin 5 mg), 21.3% (solifenacin 10 mg), and 18.6% (tolterodine)[17].

In this study dry mouth occurrence was higher in Solifenacin Succinate i.e., 29.64% as that of 24.35% in Tolterodine. Both these percentages were high as that of reported in Chapple C study but the trend for high dry mouth occurrence in Solifenacin Succinate group was same as that of results of this study C.R. Chapple in his study (Star trial) compared two new generation antimuscarinics at their recommended doses for treatment of over active bladder syndrome. Analysis of the adverse events data for solifenacin- and tolterodine ER treated patients showed that the most commonly reported AEs were dry mouth, constipation and blurred vision, which are expected AEs of antimuscarinic treatment. Dry mouth was seen in 30% of the patients who were given solifenacin and in tolterodine group it was observed in 24% patients only. Constipation in solifenacin- and tolterodine was seen in 6.4% and 2.5%[8].

C.R. Chapple results are also consistent with the results of this study showing high occurrence of dry mouth and constipation with solifenacin group.

Fred E Govier in his Double-Blind, Placebo-Controlled Phase III Pivotal Trial investigated the efficacy and safety of solifenacin succinate 10 mg, a once-daily (OD) oral antimuscarinic agent, in overactive bladder syndrome. In his results he reported that constipation and dry mouth occurred 38% and 19% of the patients[18].

In this study occurrence of dry mouth and constipation with solifenacin was 29.64% and 9.88% these percentages are quite low as that of reported by Fred E Govier.

Frnaklin Chu in his Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled trail investigate the efficacy, safety, and tolerability of solifenacin 10 mg QD in patients with OAB. Adverse events like constipation and dry mouth was observed in 17.1% and 26.8% of the patients[19].

Michael B. Chancellor evaluated the use of solifenacin in patients experiencing residual urgency symptoms during treatment with tolterodine extended re-lease (ER) 4 mg for overactive bladder (OAB). As per his findings occurrence of dry mouth and constipation was observed in 17.5% and 11.6% patients[20].

At the present time a range of antimuscarinic agents are available and the efficacy and tolerability of these compounds have been improved with the advent of extended release (ER) formulations. This has made antimuscarinics, such as tolterodine ER, leaders in providing OAB symptom relief. Solifenacin succinate (5 mg and 10 mg doses) once-daily (OD) is a new generation antimuscarinic agent that has demonstrated a good efficacy and tolerability profile in four large Phase III clinical trials. These improvements were maintained in a 40-week open-label extension study of two of the Phase III trials. In different studies different trend was seen for the occurrence of constipation and dry moth for both drugs. i.e., Tolterodine and solifenacin. However in this study both adverse effect (constipation and dry mouth) were observed to be high in solifenacin group but a dry mouth was significantly high in solifenacin group.

CONCLUSION

This study found that solifenacin succinate (5mg) had significantly higher occurrence of constipation as compared to Tolterodine (4mg). i.e., 9.88% vs. 5.06%. While occurrence of dry mouth was also higher but not significant in solifenacin succinate. These results showed that difference in side effects between tolterodine and solifenacin succinate in patients with urinary incontinence.

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