INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
Earthjournals Publisher
E-ISSN:2320-3137
www.earthjournals.org

Research Article

EFFECTS OF QUETIAPINE AND OLANZAPINE ON SERUM PROLACTIN LEVELS IN SCHIZOPHRENIA

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Abstract

Objective: This double-blind randomized, comparative study evaluated the efficacy and the effects of quetiapine and olanzapine on serum prolactin in female patients with schizophrenia. Method: Eligible sixty adult female patients meeting DSM-IV-TR criteria for schizophrenia were randomly assigned to quetiapine 200-800 mg/day (N=30) or olanzapine 5-20mg/day (N=30) for six weeks. The efficacy measure, change from baseline on the PANSS total and subscale scores was obtained. Serum prolactin estimation was done at baseline and at six weeks and the method used was microplate immunoenzymometric assay. Results: Quetiapine was equieffective to olanzapine at endpoint in reducing PANSS total score. In quetiapine group, baseline mean (s.d.) serum prolactin level decreased from 33.84 ng/ml (34.70) to 18.78 (13.69) ng/ml which was statistically significant ($p<0.05$). In olanzapine treatment group, mean (s.d.) serum prolactin levels increased from baseline level of 42.68 ng/ml (36.67) to 45.78 ng/ml (33.96) which was statistically not significant ($p>0.05$). Conclusion: Quetiapine was equally effective to olanzapine in the treatment of schizophrenia and was well tolerated by the female patients. The mean change in serum prolactin levels after treatment with olanzapine was higher than at the baseline and the mean changes in serum prolactin levels in the quetiapine group at endpoint were significantly reduced than that at the baseline.

Key-words: quetiapine, olanzapine, serum prolactin, female patients, schizophrenia

INTRODUCTION

Atypical antipsychotics have revolutionized the treatment of schizophrenia. Quetiapine and olanzapine, among other atypical antipsychotic drugs are the first line atypical antipsychotics for the comprehensive management of schizophrenia. These newer molecules are necessary for many patients but they can contribute to the burden of a newer spectrum of side effects as well. Affected population needs safe and sustainable possibly lifelong treatments. Prolactin elevation and consequent galactorrhoea is a well known side effect of antipsychotics.[1] All conventional antipsychotic drugs block dopamine D_2 receptors on lactotrope cells in the pituitary gland and thus remove the main inhibitory influence on prolactin secretion. Elevation of prolactin levels occurs within a few hours of treatment initiation.[2] Previously some studies with an open or double-blind design have shown that short-term treatment with antipsychotics increases mean baseline prolactin levels.[3-8] Among atypical antipsychotics,

quetiapine and olanzapine are reported either to cause no increase in prolactin secretion at all or to increase it only transiently and mildly. There are inconsistent reports available in literature about this side effect.[3, 9, 10-22]

Till date studies comparing the effects of quetiapine and olanzapine on serum prolactin levels are scanty in our country and there is paucity of Indian data, particularly in northern region of India. Thus, this study was conducted with the aims and objectives: a) to compare the efficacy of quetiapine versus olanzapine in female patients with schizophrenia and b) to compare the effects of quetiapine and olanzapine on serum prolactin levels in such patients.

MATERIALS AND METHODS

A total of sixty consecutive female patients with a diagnosis of schizophrenia who gave *written* informed consent for the study were enrolled. The study was approved by the Institutional Ethics Committee. Confidentiality of the information provided by the patients was ensured. The inclusion criteria were: female patients with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual-IV Text revision *(DSM - IV - TR)*, age range 18 – 65 years, non-pregnant females and females not planning conception. The exclusion criteria were: comorbid medical/ gynecological /psychiatric disorder, history of seizure disorder, substance abuse/ dependence, mental retardation. Patients were also excluded if they had received any pharmacological treatment or electroconvulsive therapy (ECT) within 1 month prior to the study.

Procedure:

Patients were screened for inclusion in the study at the initial visit. After complete description of the study protocol to the subjects and their family members, written informed consent was obtained. The diagnostic interview included the following: psychiatric evaluation (DSM-IV-TR diagnosis of schizophrenia)[25], history of the disease, a general clinical evaluation (including medical history, gynecological and obstetrics history, physical examination) and medication history during past month, demographics, as well as vital signs, body weight, electrocardiogram (ECG) and laboratory tests, Positive and Negative syndrome scale (PANSS**)** scores, UKU side effect rating scale[26] scores. The laboratory tests (complete haemogram, electrocardiogram (ECG), lipid profile, liver and renal function tests) were conducted at baseline and after 1-week intervals until 6 weeks of treatment. These patients were randomly allocated to quetiapine (group1) or olanzapine group (group 2) 30 patients each. Quetiapine and olanzapine were used as similar pink colored capsules of 100mg and 2.5 mg respectively. The initial starting dose was two capsules a day which was gradually increased maximum up to 8 capsules a day. Patients in group 1 received quetiapine (200-800mg/day) and in group 2 received olanzapine (5 – 20 mg/day). Concomitant use of lorazepam (1-4 mg/day) was given in case of agitation and insomnia. The medication trihexyphenydyl up to maximum dose of 6mg/day was permitted as per study protocol if extrapyramidal symptoms emerged in any patient.Patients were assessed with Positive and Negative syndrome scale for clinical symptoms and UKU scale for side effect. The assessment was done at baseline and at the end of the study i.e. at 6th week. The primary measure of efficacy was the percentage of patients showing clinical improvement defined as 40% reduction in the PANSS total score as compared to baseline between two groups. Serum prolactin concentrations were measured by microplate immunoenzymometric assay.

RESULTS

Total twenty-seven patients in the olanzapine treatment group and twenty six patients in the quetiapine group completed the study protocol. Efficacy and adverse effects data were analyzed for those patients who remained compliant with treatment protocol for six weeks. There were 4 dropouts (13.3%) in the quetiapine group and 3 dropouts (10%) in the olanzapine group. These seven patients (4 in quetiapine group and 3 in olanzapine group) were excluded from the analysis. The four patients discontinued due to adverse effects and three patients did not follow-up after one week of admission. The telephonic reminders were employed to ensure patient retention in the study. The drop out rate was less than 15% and none of the participant had received prior antipsychotic drugs treatment.Regarding socio-demographic variables, both groups were almost equally represented. The two groups were comparable in age distribution parameters (x^2 = 3.946; df = 3; p = 0.267). 30.8% (n=8) of the patients in the quetiapine group were in the age group 18-25 years while 55.6% (n=15) in the olanzapine group were in the age group 18-25 years. There were no significant difference found on detailed analysis in both the groups regarding various parameter, namely religion [x^2 = 0.29 ; df =1 3; p = 0.865] , occupation [x^2 = 1.887 ; df = 2; p = .389] , education [x^2 = 5.566, df=4; P=0.234] , marital status [x^2= 2.540, df=1; p =0.111] and residential status [x^2= 3.172, df=1; P=.075] .

The results of comparison between clinical variable in the two groups indicated no significant difference in the duration of illness [x^2= 1.017,df=4; p=0.907] and family history of psychiatric disorder [x^2 =0.167, df=1; p=0.682]. Duration of illness in majority of the patients from both the groups was found in the range of 1-5 year (50% in quetiapine group and 56.67% in olanzapine group). In quetiapine group, 33.33% of the patients and in olanzapine group, 20% of the patients reported to have suffered from illness for more than five years. Further it was found that only 16.67% of patients in the quetiapine group had family history of psychiatric illness and 23.33% of patients in olanzapine group had family history of psychiatric illness. Mean (s.d.) dose requirement of quetiapine was 433.33 (151.3) mg with range of 100-800 mg while mean (s.d.) dose requirement of olanzapine was 12.91 ± 5.8 mg with range of 2.5-20 mg. Concomitant medication like lorazepam was used more in quetiapine group than in olanzapine group. More patients in quetiapine group (n=19; 73.08%) required lorazepam than in olanzapine group (n=16; 59.26%). Statistically, there was no significant difference between two groups regarding requirement of lorazepam (x2 = 1.128; p>0.05). The requirement of anti-parkinsonian medication varied in both groups. One patient in quetiapine group received trihexyphenydyl for extrapyramidal symptoms i.e. akathisia and tremors and two patients in olanzapine received trihexyphenydyl for extrapyramidal symptoms. . Statistically, there was no significant difference between two groups regarding trihexyphenidyl requirement. (X^2 = 0.315; p>0.05).

The various efficacy PANSS scale scores of the quetiapine and olanzapine groups after the treatment were significantly lower than those at baseline, all differences being statistically significant (p<0.001)(Table 1). Quetiapine reduced the mean (s.d.) PANSS total score from 105.04 point (15.50) to end point 62.19 (±11.24) with the change of 42.85 point (±13.22) which is statistically highly significant (t= 16.529, df = 25; p<0.001). While in case of olanzapine the effect was that it reduced PANSS total score (s.d.) from baseline 95.96 point (±11.59) to end point 56 (±8.63) with a change of 39.96 point (±8.59) which is statistically highly significant ('t' =24.18, df = 26; p<0.001). However, mean (s.d.) percent change

observed in case of quetiapine group was 40.38 (±8.60) which was less than olanzapine change 41.24 (7.04), statistically this difference was not significant (t= 0.399; p>0.05).

In our study, the mean (s.d.) percentage changes from baseline to endpoint in the quetiapine group on PANSS Total scores, PANSS Positive scores, PANSS Negative scores, PANSS General Psychopathology scores were 40.38(8.60) percent change, 42.98 (11.77) percent change, 40.57 (8.07) percent change, 38.79 (9.35) percent change respectively, which were highly statistically significant (p<0.01). In our study, the mean(s.d.) percentage changes from baseline to endpoint in the olanzapine group on PANSS Total score, PANSS Positive score, PANSS Negative score, PANSS General Psychopathology scores were 41.24 (7.04) percent change, 42.39 (9.67) percent change , 38.95 (8.60) percent change , 42.42 (10.57) percent change respectively, which were statistically highly significant (p<0.01).

Most common side effect on UKU side effect rating scale in quetiapine group was weight gain (range 1-5kg; 26.92%), increased duration of sleep in (11.54%). Orthostatic hypotension was seen in 7.69% of patients, asthenia, tremor, nausea and headache were seen in 3.85% of patients. In olanzapine group most common side effects were weight gain (range 1-5kg) in 66.67% of patients, sedation (25.92%), tremor, nausea, amenorrhea & headache (7.41%). Only one patient complained of akathisia and constipation. On comparison between two groups on tolerability profile, statistically there was significant difference between the groups on weight gain adverse effects. (x^2=8.396, df=1, p=0.003).

In our study, change in mean serum prolactin level from baseline to endpoint of study was different in both the groups. The mean change in serum prolactin levels after treatment with olanzapine was higher than at the baseline(Table 2). The mean changes in serum prolactin levels in the quetiapine group after treatments were lower than that at the baseline. In quetiapine group, baseline mean (s.d.) serum prolactin level decreased from 33.84 ng/ml (34.70) to 18.78(13.69) ng/ml which is statistically significant (p<0.05). In olanzapine treatment group, mean (s.d.) serum prolactin levels increased from baseline level of 42.68 ng/ml (36.67) to 45.78 ng/ml (33.96) which is statistically not significant (p>0.05). When both the groups were compared in regard to mean change in serum prolactin level, the difference was found to be statistically not significant (‘t= 1.641; p>0.05). On Pearson’s product moment correlation serum prolactin levels showed no significant correlation with age and duration of illness in both the treatment groups (p>0.05).

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Earthjournals Publisher
E-ISSN:2320-3137
www.earthjournals.org

Table 1 Comparison of PANSS scores before and after treatment

Variable	Quetiapine group (n=26)					Olanzapine group (n=27)				
	Baseline	**After Treatment**	**t**	**df**	**p**	**Baseline**	**After treatment**	**t**	**df**	**P**
PANSS total Mean (s.d.)	**105 (15.4)**	**62.1 (11.2)**	**16.5**	**25**	**0.001***	**95.96 (11.59)**	**56 (8.63)**	**24.18**	**26**	**0.001***
PANSS Positive Mean (s.d.)	27.19 (5.492)	15.46 (4.675)	13.5	25	**0.001***	29.48 (5.584)	16.93 (4.196)	16.14	26	**0.001***
PANSS negative Mean (s.d.)	29.38 (4.989)	17.38 (3.073)	17.321	25	**0.001***	26.30 (4.53)	16.11 (3.816)	19.999	26	**0.001***
PANSS General psychopathology Mean (s.d.)	48.46 (7.426)	29.35 (4.923)	14.268	25	**0.001***	40.19 (5.077)	22.96 (4.174)	16.677	26	**0.001***

P< 0.001* S=Significant; s.d.- standard deviation

Table 2 Changes in mean serum prolactin levels (ng/ml)

	Baseline Mean (s.d.)	**After treatment Mean (s.d.)**	**Mean change (s.d.)**	**t**	**df**	**p value**
Quetiapine (N=26)	33.8 (34.7)	18.7 (13.6)	-15.1 (35.1)	2.184	25	**0.039***
Olanzapine (N=27)	42.6 (36.6)	45.7 (33.9)	+3.10 (13.81)	-1.167	26	0.254

***significant; s.d.- standard deviation**

DISCUSSION:

This study aimed to compare the efficacy and the effects of quetiapine and olanzapine on serum prolactin levels among female patients with schizophrenia. Comparisons between quetiapine and olanzapine treatment group matched on sociodemographic and clinical parameters. The result of the present study suggests that quetiapine and olanzapine are equieffective in the treatment of schizophrenia. On the analysis of data, it was observed that the both quetiapine and olanzapine drug groups had a highly significant improvement in primary efficacy measure score of PANSS positive symptoms, negative symptoms, general psychopathology symptoms and total symptoms.

Our results corroborate the finding of other workers. Pewkens et al[12] found that quetiapine treatment was not associated with increase in serum prolactin levels. Similar to this finding, in our study quetiapine treatment group revealed no increase in serum prolactin levels. Nakajima et al[16] found that serum prolactin levels were significantly decreased after switching to quetiapine from conventional antipsychotic drugs. Svestka et al [18] evaluated the effect of quetiapine and olanzapine on prolactinaemia during 6 week therapy in female patients with mainly schizophrenic disorders. Our findings matched with the results documented by Svestka et al[18], the previous authors conducted a prospective and open label study. In the current study quetiapine decreased serum prolactin levels (the baseline mean 33.84 ng/ml vs. Endpoint mean 18.78 ng/ml). Serum prolactin levels were elevated to a smaller extent by olanzapine (the baseline mean 42.68 ng/ml vs. Endpoint mean 45.78 ng/ml). The difference of our study from study conducted by Svestka et al [18] was in the research design. Svestka et al [18] conducted an open label study which is in contrast to our study design (double blind). Svestka et al [18] reported that quetiapine decreased serum prolactin levels (the baseline mean 828 mIU/l vs. endpoint mean prolactinaemia 304 mIU/l; $p<0.002$). Prolactinaemia was elevated to a smaller or greater extent by olanzapine (1095 vs. 1247 mIU/l; $p<0.05$). The authors found that quetiapine relatively reduced prolactinemia significantly, as early as from week 1 of the treatment. In our study we estimated the serum prolactin levels at the baseline and at the end of the study, thus we could not document the earlier onset of this action of quetiapine on serum prolactin hormone. Kapur and colleagues reported that quetiapine differentially occupied striatal and pituitary D2 receptors.[12] Kapoor et al proposed that prolactin raising potency of antipsychotic is dependent on the ratio of striatal and pituitary effective dose. This ratio is higher for olanzapine and quetiapine This explained the less frequent association of quetiapine with prolactin elevation. Quetiapine is deemed to be the least galactogenic of all atypical antipsychotics. Our study supports this finding.

In contrast to our findings of hypoprolactinaemia with quetiapine, Hammer et al[11] found that quetiapine didn't differ from placebo in their observations in the degree of decline of plasma prolactin levels. Kelly and Conley[17] reported that quetiapine was associated with a normalization of prolactin levels. Alexiadis et al reported elevation of prolactin due to quetiapine. Pae et al reported galactorrohoea due to quetiapine which subsided on stopping quetiapine. From an Indian setting, Sethi et al reported dose dependent galactorrohoea with quetiapine. However it must be realized that majority of these were case reports, both male and female patient population and these patients were not drug naive and were taking many medications.

In our study, the increase in serum prolactin level among patient on olanzapine treatment group as a whole is in keeping with as found by Melkersson[15] in a cross-sectional study.

Melkersson[15] reported hyperprolactinemic symptoms in 3% of the olanzapine treated patients. Arvanitis et al have reported that 70% patients on olanzapine had higher level of serum prolactin. In literature some contradicting results have also been reported. Goodnick et al[13] reported that serum prolactin levels has been found to be decreased among patients on olanzapine. Volavka[14] found that olanzapine was associated with decreases in plasma prolactin. Kim et al[14] reported that olanzapine reversed prolactinemia in risperidone-treated female schizophrenic patients. Chen et al in 2009 conducted a study designed to investigate the serum prolactin level in schizophrenia and the predictors of response for olanzapine treatment. None of the patients were drug-naïve, and they were given olanzapine in a flexible dose of 10-30 mg/day. Serum prolactin levels were measured at baseline and at months 1, 2, and 3 during olanzapine treatment. Results showed serum prolactin level decreased in schizophrenic patients with olanzapine treatment, although the difference was not statistically significant. There was a close relationship between the improvement in positive symptoms and the change in serum prolactin levels before and after olanzapine treatment. Moreover, the serum prolactin level also had a positive association with female gender ($p = 0.008$). The findings of our study are in contrast to study by Chen et al as this study included both males and females and was of longer duration i.e. 3 months. Our study was of six weeks and comprised of female patients. In our study the serum prolactin levels increased after treatment with olanzapine. The differences from our study may be that we have strong methodological design of the study and estimation of serum prolactin was undertaken on fasting blood sample. As well defined studies have not been carried out in India previously and our study is in line with the attempt to examine the effects of treatment on serum prolactin levels in inhabitants of Punjab, an Indian population. The ethnic variations are known to affect serum prolactin activity. Our study is first in India in this field.

Women show increased sensitivity of the lactotrophs to prolactin stimulation compared with men Some authors documented that women have significantly greater prolactin elevations than men during antipsychotic treatment with equivalent doses.[18] Serum prolactin level had a positive association with female gender. Svestka et al [18] and Chen et al suggested that the serum prolactin level may be a useful biological marker to predict the effectiveness of antipsychotics in schizophrenia.[20-22]

The adverse effect of weight gain was found to be a significant difference between two treatment groups. In the current study, the patient in the quetiapine group showed weight gain (26.92%), increased duration of sleep (11.54%), orthostatic hypotension (7.69%) and asthenia, nausea, headache and tremor were seen in 3.85% of patients. In olanzapine group most common side effects were weight gain in 66.67% of patients, sedation (25.92%), headache, nausea/vomiting, tremor and amenorrhoea (7.41%). Constipation, reduced salivation and akathisia were complained by 3.70% of patients in the olanzapine treatment group.

Our study has significant clinical implications in current era of psychopharmacology. Regular monitoring of serum prolactin in female patients on olanzapine treatment is suggested. Mental health professionals and women patients should be made aware of the endocrinological effects of medications like gonadal function and estimation of prolactin hormone. There is a need to spread this awareness and understanding of the impact of drug induced hyperprolactinaemia on physical health in female patients in India. This clinical practice may have bearing on the outcome of pharmacotherapy in patients. It requires to be seen in future studies if the finding of the current study holds true or not. Long term studies

studies from various regions of India are suggested for replication of the findings of the present study.

CONCLUSION

The results of the current study indicate that quetiapine and olanzapine are equi-effective in the improvement of overall psychopathology including positive and negative symptoms of schizophrenic patients. Quetiapine is safe in female schizophrenic patients and is well tolerated in dosages between 200-800mg/day. Overall, quetiapine has an excellent risk/benefit profile and is a suitable first-line option for the treatment of schizophrenia. Quetiapine decreased serum prolactin levels and olanzapine increased the serum prolactin levels in female patients with schizophrenia.

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