ORIGINAL ARTICLE

An open-label prospective study to assess metabolic side effects with atypical and typical antipsychotic drugs in patients with schizophrenia

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ABSTRACT

Background: Schizophrenia is a major psychiatric illness comprising thought, perception, emotion, movement, and behaviour. Pharmacotherapy plays an important role in managing this disorder, comprising mostly typical and atypical antipsychotics. Treatment with antipsychotics can cause metabolic side effects leading to medical disorders among the patients suffering from schizophrenia.

Aims: To study the effects on glucose and lipid metabolism with the use of atypical and typical antipsychotics in the treatment of schizophrenia.

Methods: The present study is a 12 weeks open label prospective study of antipsychotic drugs olanzapine, risperidone and haloperidol in patients with schizophrenia. 80 patients having diagnosis of schizophrenia according to ICD-10 are assigned to treatment with olanzapine (N=20), risperidone (N=20) and haloperidol (N=40). Assessment for analysis include weight, body mass index(BMI), fasting blood glucose (FBS), postprandial blood glucose (PPBS) at baseline and at 4th week, 8th week and 12th week. Lipid profile is assessed at baseline and 12th week.

Results: Out of 80 subjects, only 65 patients completed the study; there are 15 dropouts. At the end of 12 weeks in haloperidol group, there is a mean increase of 3.2 mg/dl in FBS and 2.71 mg/dl PPBS and mean decrease of 2.76 mg/dl in serum cholesterol levels. In olanzapine group there is a mean increase of 6.3 mg/dl in FBS and 3.7 mg/dl in PPBS and mean increase of 7.8 mg/dl in serum cholesterol. In risperidone group, there is mean increase of 2.3 mg/dl in FBS and 2.8 mg/dl in PPBS and mean increase of 0.98 mg/dl in serum cholesterol.

Conclusion: Metabolic side effects are more with atypical antipsychotics. Regular blood monitoring of metabolic parameters should be strictly implemented. Consideration should be given for prescribing drugs like metformin for antipsychotic induced weight gain along with dietary management and lifestyle change if deemed necessary.

Keywords: Antipsychotics; metabolic side effects; weight gain

Date of first submission: 9/12/14 Date of initial decision: 12/12/14 Date of acceptance: 29/12/14

INTRODUCTION

The patients suffering from schizophrenia are at increased risk for Type II diabetes, [1] because of poor overall physical health, poor health care, less healthy lifestyles, and side effects of antipsychotic medication. The rates of diagnosed diabetes exceeded general population well before the widespread use of the new antipsychotic drugs. [2, 3] The risk of cardio metabolic problems can be due to genetic predisposition, environmental stressors and developmental stressors. [4] Even the first-episode, drug-naive patients with schizophrenia[5,6] have impaired fasting glucose tolerance and are more insulin resistant and have higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects. [7] This leads to metabolic syndrome highly prevalent in schizophrenic patients. [8-10]

The advent of atypical drugs became an important milestone in pharmacotherapy of schizophrenia. This is largely due to reduced propensity for extrapyramidal symptoms leading to more tolerability and thereby improving patient compliance. Apart from these drugs are reported to be effective over negative symptoms in schizophrenia. This made atypical antipsychotics effective first line agents for treatment of schizophrenia and other psychosis for mental health professionals. Atypical antipsychotics reported to cause changes in the metabolic parameters, chances of developing metabolic syndrome and associated disorders like diabetes mellitus type-II and cerebrovascular accidents. [11] The younger patients may be sensitive to weight gain, especially with olanzapine, as well as extrapyramidal side effects and metabolic changes. [12] The use of these drugs is associated with metabolic effects, these include, increased weight gain, glucose intolerance, hyperglycemia, insulin resistance, diabetic ketoacidosis, increased risk for diabetes and heart diseases, hypertriglyceridemias and hypercholesteremia. Aripiprazole, ziprasidone, risperidone and quetiapine were not associated with increased, but, olanzapine and clozapine were associated with an increased risk. [13]

Hence, the present study aims at assessing the metabolic effects on glucose and lipids with atypical antipsychotics like olanzapine, risperidone and typical antipsychotic haloperidol.
Aims and objectives
To study the effects on glucose and lipid metabolism with use of atypical and typical antipsychotics in the treatment of schizophrenia

MATERIALS AND METHODS
Subjects are inpatients from Government hospital for mental care, Visakhapatnam, Andhra Pradesh, India. Required permissions are taken from the authorities for conducting the study. The present study is 12 week open label prospective study of olanzapine, risperidone and haloperidol in schizophrenia. For olanzapine dose ranges from 5mg/day to 30 mg/day (mean dose of 20 mg), for risperidone 2 to 8mg/day(mean dose of  6 mg/day) and for haloperidol (HPL) dose ranges from 10-25 mg/day(mean dose of 20 mg) is used.

Concomitant medication allowed
Trihexyphenidyl at dose of 2-4 mg/day is given prophylactically to all patients receiving haloperidol. In case of olanzapine and risperidone if the treating psychiatrists recommends trihexiphenidyl then these patients are allowed to take trihexiphenidyl. Propranolol is allowed for treatment of akathasia. Lorazepam and nitrazepam are allowed for treatment of agitation and insomnia.

80 patients who are having diagnosis of schizophrenia according to ICD-10 are assigned to treatment with olanzapine (N=20), risperidone (N=20) and haloperidol (N=40)

Inclusion criteria
Subjects of 18-60 year age of both genders, able to give written informed consent, participated in the study. Patients with a diagnosis of schizophrenia and not taking antipsychotic medication within the previous 3 months, with BMI less than 30 kg/m², FBS less than 110mg/dl, PPBS less than 170mg/dl, serum cholesterol less than 200 mg/dl, serum triglyceride less than 150 mg/dl are eligible for this study.

Exclusion Criteria
Substance abuse (including nicotine abuse) within the previous 3 months and women expecting to have pregnancy are excluded. Those with glaucoma, tardive dyskinesia, having family history of diabetes mellitus, taking depot preparations for more than 1 month, taking medication to control cholesterol from past 180 days, taking more than one antipsychotic medication are excluded.

Those with a history of endocrine disorders, type 1 or 2 diabetes mellitus, anemia, acute intermittent porphyria, anorexia nervosa, obesity, malnutrition, gaucher’s disease, lipodystrophy, multiple myeloma, autoimmune disorders, monoclonal gammapathy, and orchidectomy, prolactin tumours, pheochromocytoma, hyperlipedemias, dehydration, acute infection ,significant medical illness including severe cardiovascular, hepatic, or renal disease are excluded. Patients receiving medication with antihistamines, tricyclic antidepressants, bupropion, clonidine, pemoline, atomoxetine, mood stabilizers ,selective serotonin reuptake inhibitors(SSRI’s,) testosterone,recombinant human growth hormone, oral glucocorticoids, birth control pills containing norgestrel, anti-inflammatory drugs (including aspirin and ibuprofen),thiazide diuretics are excluded from this study. Patients having BMI more than 30 kg/m²,FBS more than 110mg/dl,PPBS more than 170mg/dl, serum cholesterol more than 200mg ,triglycerides more than150 mg/dl in the blood stream are excluded.

Assessments:
Patient’s height is measured at the enrolment of the study weight is assessed at baseline, 4th week, 8th week and 12th week. Body mass index was computed as body weight (kg) divided by the square of height (m²). BMI is calculated at baseline, 4th week, 8th week and 12th week. Assessment for analysis includes fasting blood glucose, postprandial blood glucose at baseline and at 4th week, 8th week and 12th week.

Lipid profile including serum cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and triglycerides are assessed at baseline and at12 weeks. Drug compliance is assessed by asking the patient and informant whether patient is taking medication correctly and continuously. Patients who had stopped medication for more than one week during the study is removed from the study and considered as drop out.

RESULTS:
The study consists of 80 patients in 3 groups. Haloperidol group consists of 40 patients, olanzapine group consists of 20 patients, and risperidone group consists of 20 patients. The results are interpreted with descriptive statistics (Table 1) and analysed by t test and change in mean.

Haloperidol group:
In this group the baseline mean body weight is 49.25kgs. there is decrease in the mean body weight from 49.25 to 49.18 at the end of 4 weeks and increased to 49.49 at 12th week and 50.26kgs at 12th week.16 males and 13 males had increase in bodyweight compared to baseline.BMI  is also increased from 19.02 kg/m2 at baseline to 19.42kg/m2 at 12th week (p=0.28).

Table 1 Sociodemographic and other parameters

<table>
<thead>
<tr>
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<th>Haloperidol</th>
<th>Olanzepine</th>
<th>Risperidone</th>
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<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean age(years)</td>
<td>30.2</td>
<td>33.9</td>
<td>26.4</td>
</tr>
<tr>
<td>Mean Height</td>
<td>1.61</td>
<td>1.54</td>
<td>1.63</td>
</tr>
<tr>
<td>Number of males</td>
<td>23</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Number of females</td>
<td>17</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Dropouts</td>
<td>8</td>
<td>4</td>
<td>3</td>
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The mean fasting blood sugar levels decreased from 82.95 mg/dl at baseline to 82.79 mg/dl at the 4th week but increased to 85.10 mg/dl at the 8th week and to 86.15 mg/dl at the 12th week. The mean postprandial blood sugar levels decreased from 125.5 mg/dl at baseline to 126.69 mg/dl at the 4th week and increased to 127.83 mg/dl at the 8th week and further increased to 128.21 mg/dl at the 12th week (p=0.06).

There is a decrease in the mean serum cholesterol levels from 144.6 mg at baseline to 141.84 mg at the 12th week (p=0.29). The mean LDL levels increased from 93.49 mg/dl at baseline to 92.73 mg/dl at the 12th week (p=0.43). The mean VLDL levels increased from 22.51 mg/dl at baseline to 24.3 mg/dl at the 12th week (p=0.06). The mean HDL levels decreased from 38.8 mg/dl at baseline to 37.7 mg/dl at the end of the 12th week (p=0.26). There is an increase in the mean triglycerides from 102.42 mg/dl at baseline to 110.9 mg/dl at the 12th week (p=0.04).

The maximum dose reached is 30 mg in 1 patient, 25 mg in 3 patients, 20 mg in 22 patients, and 15 mg in 6 patients at the end of the 12th week. One patient discontinued the study at the 4th week and 2 patients at the 8th week, and 5 patients at the 12th week. The total dropouts in the haloperidol group are 8 patients.

Olanzapine group:

In this group, the mean body weight increased from baseline to 50.40 kg at the 4th week and further increased to 51.69 kg at the 8th week and to 52.54 kg at the 12th week (p=0.14). 10 males and 6 females showed weight gain. The mean BMI increased from 18.24 kg/m² at baseline to 18.74 kg/m² at the 4th week and to 19.49 kg/m² at the 8th week. There are no significant changes in the BMI from the 8th week to the 12th week. The mean fasting blood sugar increased from 85.2 mg/dl at baseline to 85.45 mg/dl at the 4th week and further increased to 88.11 mg/dl at the 8th week and significant increase to 91.5 mg/dl at the 12th week (p=0.04). The mean postprandial sugar increased from 122.9 mg/dl at baseline to 124.7 mg/dl at the 4th week and decreased to 124.4 mg/dl at the 8th week and increased to 125.7 mg/dl at the 12th week (p=0.06).

The mean serum cholesterol increased from 155.8 mg at baseline to 169.58 mg at the end of the 12th week (p=0.04). The mean LDL levels decreased from 103.26 mg/dl at baseline to 102.39 mg/dl at the end of the 12th week (p=0.43). The mean VLDL levels increased from 28.46 mg/dl at baseline to 29.56 mg/dl at the 12th week (p=0.43). The mean triglycerides increased from 146.3 mg/dl at baseline to 157.88 mg/dl at the end of the 12th week (p=0.05). The mean HDL levels were decreased. There is a decrease in the mean HDL levels from 39.55 mg/dl at baseline to 38.70 mg/dl at the end of the 12th week (p=0.33).

The maximum dose reached for risperidone is 12 mg in 3 patients and 10 mg in 4 patients and 8 mg in 7 patients, and 6 mg for 3 patients. Two patients discontinued at the 8th week from this study group. One patient discontinued at the 12th week. The total dropouts in the risperidone group are 3.

DISCUSSION

This is a prospective open label study. Schizophrenia itself is a risk factor for the development of metabolic abnormalities and diabetes. Hence, we excluded the basal metabolic disturbances in our subjects. Patients who are at risk of metabolic disturbances are excluded in the present study. Previous studies done are mostly cross...
sectional and retrospective studies, but in this study we have followed for 12 weeks for recording metabolic disturbances in glucose and lipid metabolism. We have included postprandial glucose levels apart from the fasting blood glucose levels to have more information regarding the glucose levels. In our study apart from serum cholesterol we have included the lipid profile where the data is less in the previous studies.

The study sample has more males compared to females and most of the patients are in age groups of 20-50. This could be due to the importance given to the male patients as they are the breadwinners of the family and their occupational impairment due to disorder needs early medical attention.

In our study olanzapine patients had significant increase in mean weight gain, but the weight gain is less compared to previous studies. [16] The weight gain is more in males compared to females. Gupta et al., [17] reported patients undergoing treatment with olanzapine to be prone to metabolic syndrome as the drug induces weight gain after 16 weeks of treatment. Our study found that there is weight gain in 1st week but not associated with significant change in fasting blood sugar and post prandial blood sugar. This is similar to the study reported by Meyer et al., [18] The reason for differences of weight gain between different drugs could be due to the relative receptor affinities of the atypical antipsychotics for histamine H1 receptors as well as the ratio of their affinity for serotonin 5-HT2 and dopamine D2 receptors.

The induction of leptin secretion may also have important impact on bodyweight gain in patients treated with atypical antipsychotics. [19] The molecular mechanisms responsible for antipsychotic drug-induced weight gain have been hypothesized to be due to interactions of antipsychotic drugs with several neurotransmitter receptors, including 5-HT(2A) and 5-HT(2C) serotonin receptors, H(1)-histamine receptors, alpha(1)- and alpha(2)-adrenergic receptors, and m3-muscarinic receptors.

Genetic association could be the reason for some patients to gain more weight. This can be due to the genes in pathway encompassing appetite peptides and peripheral lipid homeostasis thereby differentiation of olanzapine and risperidone side effect profile. A certain series of single nucleotide polymorphisms (SNPs) in cholesterol metabolism-related genes coding for apolipoproteins E and A4 were significantly associated with the weight profile in the olanzapine-treated group but not in the risperidone group. [20] Polymorphism in the resistin gene (-420 C/G rs1862513) can also contribute to weight gain to antipsychotic use. [21]

This study has found more change in means of fasting and postprandial blood glucose levels in olanzapine groups. Decreased sensitivity, increased insulin resistance to the insulin action as well as decreased insulin secretion can be the other causes. Insulin resistance during antipsychotic treatment can be due to increased abdominal adiposity which in turn causes weight gain. Antipsychotic drugs may affect glucose transporter function. structure-function relationship in which similar drugs that achieve relatively higher intracellular concentrations may similarly bind to, and interfere with the function of, the glucose transporter proteins. This affinity for glucose transporters can be hypothesized to underlie clinical observations of decreased sensitivity to insulin action. Ardizzona et al studies suggest that the drugs may block glucose accumulation directly at the level of the glucose transporter (GLUT) protein in cells derived from both peripheral and brain tissue. [22] Margaret et al study on Hyperglycaemic Clamp Assessment of Insulin secretory response found that olanzapine or risperidone directly not impair pancreatic beta cell function. [23] However, Beting et al, [24] hypothesized that serotonin (5-HT1A) antagonism may decrease the responsiveness of the pancreatic beta-cells. This would then result in inappropriately low insulin secretion and, therefore, hyperglycemia. The dysregulated blood glucose could be due to central blood glucose regulation by the hypothalamus and the hypothalamic dopamine antagonism by some antipsychotics. [25] Even though fasting and postprandial blood glucose levels are increased in the present study the increase is less compared to the previous studies. The reason could be in the present study the patients are mostly from rural and low socioeconomic status. Their life style, food habits may differ from the patients of the previous studies.

This study also found that there is raise in serum cholesterol and triglycerides but not statistically significant in all the groups. The LDL, HDL, VLDL did not show any statistical changes in the levels in haloperidol and olanzapine. There is increase in the triglycerides along with the change in weight in first week. There is no case diagnosed as diabetes mellitus or hyperlipidemia during the course of the study. This can be due to exclusion of patients who are having basal metabolic disturbances thereby eliminating patients who are in borderline glucose levels to develop diabetes.

Hence, selection of drugs is very important in the treatment of schizophrenia. Even though we did have increase in glucose and lipid levels in olanzapine group other newer drugs which do not have affect on metabolic profiles like ziprasidone and aripiprazole, amisulpride (low weight gain), [26] can be used for the patients who are at risk of metabolic abnormalities. Aseanipine can be considered as it is reported to have a lower risk of metabolic adverse effects than olanzapine, [27] and the effects on weight and metabolic variables appear modest, [28] but with iloperidone weight gain and related lipid and glucose parameters may pose an increased risk with higher doses and longer-term exposure. [29]

Apart from regular monitoring of glucose and lipid profiles life style modification, exercises play pivotal role for the patients taking antipsychotic treatment. For pharmacological treatment for controlling weight gain drugs like subutramine,
Strength of the study

1. Only fasting blood glucose, postprandial blood glucose, body weight are done for assessing glucose metabolism

Strength of the study:

Ours is a prospective study with sample of 80, eliminating baseline metabolic discrepancies, assessing all components of lipids

CONCLUSIONS:

Atypical antipsychotics can cause metabolic side effects. Regular monitoring of metabolic parameters should be strictly followed. Life style management, drugs for controlling weight gain can be considered. There is a need for double blind studies, of long duration ,with oral glucose tolerance test ,other advanced tests and also to include children as group as there are reports to have a high liability for children to experience antipsychotic induced weight gain and associated metabolic disturbances.[37]

Acknowledgments: The authors are grateful to Dr Padma V, Professor of psychiatry, Andhra Medical College, Vishakhapatnam, India for her valuable suggestions.

References:


Conflict of interest: None declared  Source(s) of support: Nil