Relation between hyponatremia and alteration in gross metabolic parameters after atypical antipsychotic therapy

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ABSTRACT

Background: Weight gain and hyponatremia which is dilutional in nature, has been well known adverse effects associated with use of atypical antipsychotic medication but the plausible impact of dilutional hyponatremia on weight gain has not been explored.

Methods: One hundred and three patients more than 18 years of age of either gender who were prescribed, olanzapine or risperidone, were tested for serum electrolytes (Na⁺ and K⁺) and gross metabolic parameters (weight and waist circumference) were measured for baseline and post drug testing.

Results: Most common age group was 30-39 years of age in the patient study sample (n=103) with 38 (36.90%) patients were females while rest 63 (63.10%) were males. There was no significant association between serum sodium levels and weight gain was observed (p >0.05). It was observed that in olanzapine group 64% of the studied cases had weight gain whereas in risperidone group only 20.8% reported weight gain (p <0.001). There was significant association between olanzapine and increase in waist circumference over risperidone, irrespective to serum sodium status (χ²=0.0148, p >0.05).

Conclusions: Olanzapine was primarily responsible for weight gain and increase in waist circumference over risperidone. These gross metabolic parameters were not influenced by hyponatremia.

Keywords: Atypical antipsychotic, Hyponatremia, Weight gain, Waist circumference

INTRODUCTION

The global burden of disease (GBD) studies have derived detailed and comparable epidemiological and burden of disease estimates for all countries and concluded that although schizophrenia is a low prevalence disorder, the burden of the disease is substantial. Globally, prevalent cases rose from 13.1 (95% UI: 11.6-14.8) million in 1990 to 20.9 (95% UI: 18.5-23.4) million cases in 2016. Schizophrenia contributes 13.4 (95% UI: 9.9-16.7) million years of life lived with disability to burden of disease globally.¹ Atypical antipsychotic drugs are the cornerstone of therapy and are routinely prescribed for the treatment of these psychiatric disorders such as schizophrenia, acute psychosis, schizophreniform psychosis, delusional disorder as well as for behavioural and psychological symptoms of dementia. Commonly used atypical antipsychotics include risperidone, olanzapine and quetiapine.²³⁹

Weight gain can lead to hypertension, coronary heart disease and diabetes mellitus and also have psychological
consequences like low self-esteem and impaired social functioning. Drug-induced weight gain has long been recognized, particularly as a consequence of the use of psychotropic medication. More recently, some newer atypical antipsychotics have also been firmly associated with weight gain. Although weight gain has been a documented adverse effect of antipsychotic drugs for decades, it has received surprisingly little attention.

Numerous case reports have suggested a possible association between atypical antipsychotics and hyponatremia but is limited to only a few studies. Only one case control study has examined the association between atypical antipsychotic use and hyponatremia.

Atypical antipsychotic drugs have become the most widely used agents because of their superiority with regard to safety and tolerability profile compared to conventional typical antipsychotics.

The present study intended to evaluate the association between use of atypical antipsychotic medications and gross metabolic derangements if any, by taking into account hyponatremia and two parameters namely weight gain and increase in waist circumference as a part of metabolic monitoring.

METHODS

This prospective observational study was carried out after obtaining due approval from the institutional ethics committee at Department of Pharmacology in collaboration with the Department of Psychiatry, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur, Madhya Pradesh, India from March 2017 to March 2018.

One hundred and three patients of more than 18 years of age and either gender who presented to the psychiatry clinics and were prescribed, olanzapine or risperidone by the consultant psychiatrist were included after obtaining informed consent. Exclusion criteria were patient refusal, patients on more than one antipsychotic drugs, pregnancy, hypothyroidism, diabetes mellitus, hypovolemia, edema, ascites, patients receiving any other medication likely to affect the parameters being observed, alcoholism, any other addiction.

Detailed history was obtained, and a thorough physical examination was done. Blood sample for estimation of serum electrolytes (Na⁺ and K⁺) was drawn and sent for testing to the pathology laboratory, weight and waist circumference were measured at baseline and two weeks after drug administration.

The patient and the accompanying attendant were counselled regarding compliance with the medication regimen. The data of the present study was recorded and analysed with the help of SPSS 20 software for windows. Appropriate univariate and bivariate analysis using paired t-test was applied to check the hypothesis. All means were expressed as mean±standard deviation and proportion was expressed as percentage. The critical value for the significance of the results was considered at 0.05 level.

RESULTS

Most common age group was 30-39 years of age in the patient study sample (n=103) with observed mean of 35.04±11.539 (Mean±SD) years. Thirty eight patients (36.90%) were females while rest 63 patients (63.10%) were males.

In the present study, a higher proportion of patients (64.10%) were clinically diagnosed as schizophrenics, 33% were having schizoaffective disorder and 2.9% had a brief psychotic disorder.

In cases with a serum sodium level less than or equal to 139 mmol/L, 8 cases (36.4%) were observed to have gained weight and 14 cases (63.6%) did not show any change in weight. In cases with serum sodium level more than 139 mmol/L, the proportion of cases that gained weight was 35 (43.2%). Statistically no significant association between serum sodium levels and weight gain was observed (p >0.05) (Table 1).

Table 1: Association between weight gain and serum sodium level aftertreatment with atypical antipsychotic medications.

<table>
<thead>
<tr>
<th>Weight gain</th>
<th>Serum sodium mmol/l</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤139</td>
<td>&gt;139</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>63.60%</td>
<td>56.80%</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>36.40%</td>
<td>43.20%</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>100.00%</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

x²=0.333, p >0.05.

It was observed that in olanzapine group 64% of the studied cases had weight gain whereas in risperidone group only 20.8% reported weight gain. Statistically this was significant (p <0.001). Thus, it was observed that olanzapine has a higher probability to cause weight gain as compared to risperidone (Table 2).

Table 2: Association between weight gain and treatment with an atypical antipsychotic medication (olanzapine or risperidone).

<table>
<thead>
<tr>
<th>Weight gain</th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>32</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>64.0%</td>
<td>20.8%</td>
<td>41.7%</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>42</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>36.0%</td>
<td>79.2%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>53</td>
<td>103</td>
</tr>
</tbody>
</table>

x²=19.785; p < 0.001.
The Table 3 shows, in less than or equal to 139 serum sodium level categories, olanzapine was given in 8 cases, of which 75% were observed with increase in waist circumference whereas a total of 14 cases received risperidone, of which only 28.6% reported increase in waist circumference. Statistically this showed significant association between olanzapine and increase in waist circumference ($\chi^2= 4.43, p <0.05$). Similarly, in more than 139 serum sodium level categories, olanzapine was given in 42 cases, of which 73.8% were observed with increase in waist circumference whereas a total of 39 cases received risperidone, of which only 17.9% reported increase in waist circumference. Statistically this too showed significant association between olanzapine and increase in waist circumference ($\chi^2=25.34, p <0.05$). The results revealed that olanzapine was primarily responsible for increase in waist circumference over risperidone while there was no impact of sodium status on the same ($\chi^2=0.0148, p >0.05$).

**Table 3: Association between increase in waist circumference, serum sodium level and treatment with an atypical antipsychotic medication (olanzapine or risperidone).**

<table>
<thead>
<tr>
<th>Increase in waist circumference</th>
<th>Serum sodium ≤139 mmol/L</th>
<th>Serum sodium &gt;139 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>75.0%</td>
<td></td>
<td>28.6%</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>25.0%</td>
<td></td>
<td>71.4%</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

$x^2 = 4.43, p <0.05$  
$x^2 = 25.34, p <0.05$

**DISCUSSION**

A total of 103 patients were included in this prospective before-after observational study.

The observed mean age of the patient sample in the present study was 35.04 years (±11.539), which is somewhat similar to the mean age of the patients in the study by Meulendijks D et al.$^4$ The mean age of patients in the study by Mannesse CK et al, was 66.5 years (±18.5) and that of the patients in the study by Gandhi S et al, was 81 years (±7.7)$^2,15$

In the present study, gender distribution was (63.1%) males which is somewhat similar to the study by Meulendijks D et al, which had (57%) males, by Mannesse CK et al, had 66.5% and Gandhi S et al, had 67% males.$^2,4,15$

Fifty patients (48.5%) received atypical antipsychotic medication olanzapine and 53 patients (51.50%) received atypical antipsychotic medication risperidone.

Although hyponatremia is usually defined as serum sodium levels less than 136 mmol/l, a more conservative definition of hyponatremia (sodium levels <138 mmol/l) was suggested by Kumar S et al.$^{17}$ When considering a serum sodium level in the range ≤138 mmol/l, the incidence of hyponatremia in the present study was 16.5% before treatment, which after treatment with atypical antipsychotic medication (olanzapine or risperidone) prescribed singularly increased to 21.35%.$^{17,19}$

The present study observed that in the olanzapine group 64% of the studied patients had weight gain whereas in the risperidone group only 20.8% reported weight gain. Statistically this was significant (p <0.001). Thus, it was observed that olanzapine has a higher probability to cause weight gain as compared to risperidone. This observation is in agreement with the results of the study by Simpson MM et al, which concluded that there is a more significant association between olanzapine and weight gain as compared to clozapine or risperidone.$^{20}$

In the present study in less than 139 serum sodium level categories, olanzapine showed significant association between olanzapine and increase in waist circumference ($x^2=4.43, p <0.05$). Similarly, in more than 139 serum sodium level categories, olanzapine also showed significant association between olanzapine and increase in waist circumference ($x^2=25.34, p <0.05$). The results revealed that olanzapine was primarily responsible for increase in waist circumference over risperidone. Though there was no impact of sodium status on the same ($x^2=0.0148, p >0.05$). This finding also is in corroboration with the randomized double blind study by Ader M et al, conducted over a period of six months which confirmed increase in waist circumference after treatment with olanzapine using objective parameters (abdominal CT) to quantify visceral adiposity.$^{21}$

The limitations of the present study were that author could only study younger adults within this study sample as 88.4% patients studied were between 20-49 years.
Younger patients are often healthier and may be less susceptible to develop drug induced hyponatremia. Secondly, author’s follow up was done after two weeks at which point the study ended and long term risk of hyponatremia due to the therapeutic use of atypical antipsychotic medications could not be examined.

CONCLUSION

Based on the observations of the present study, it can be concluded that olanzapine was primarily responsible for weight gain and increase in waist circumference over risperidone. These gross metabolic parameters were not influenced by hyponatremia.

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