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Original Research Article

Metabolic Syndrome with Drug Olanzapine: A Comparison between Standard and Orally Disintegrating Tablets

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ABSTRACT

Objective: To compare drug emergence metabolic syndrome between patients taking standard olanzapine tablet (OST) versus orally disintegrating olanzapine (ODO) tablet.
Methods: Eighty patients receiving olanzapine were divided into two equal groups of OST and ODO formulation. They were assessed for metabolic syndrome along with parameters like body weight, body mass index (BMI), waist circumference, blood pressure, fasting serum glucose, triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) at 0, 2 and 4 months of starting the drug. All the results were compared using appropriate statistical analysis.
Results: An increase in body weight, BMI, waist circumference, blood pressure, fasting glucose, TG and a decrease in HDL-C was observed in both the groups at baseline, 2 and 4 months although the difference between the two groups was not found to be significant ($p>0.05$). The change in each parameter after 4 months between two groups was also not found to be significant ($p>0.05$). Drug emergent metabolic syndrome at 4 months of starting the therapy was 22.5% in OST group as compared to 17.5% in ODO group.
Conclusion: No significant difference was observed between oral disintegrating tablet and standard olanzapine tablet in terms of derangements in metabolic parameters and emergence of metabolic syndrome.
Key words: oral disintegrating olanzapine; standard olanzapine tablet; syndrome X; schizophrenia; metabolic syndrome.

INTRODUCTION

Olanzapine is one of the most commonly used antipsychotic drugs worldwide. Introduction of clozapine in nineties resulted in development of "atypical" or second generation antipsychotics. Olanzapine, closely resembling clozapine in structure, was developed later and was approved for clinical use in Europe in 1996. These atypical antipsychotics demonstrated an improved therapeutic efficacy as compared to the typical ones but the associated adverse effect profile of these drugs is also well known now. The clinicians are now concerned with weight gain, blood glucose imbalance and other metabolic effects associated with these atypical antipsychotics (Allison et al., 1999)

Olanzapine is a thienobenzo-diazepine with a high affinity for the serotonergic receptors 5- hydroxytrypt-amine2 (5-HT2) and 5-HT6 while low affinity for 5- HT3 receptors, high affinity for dopaminergic receptors [mainly dopaminergic-2 (DA-2), DA-3 and DA-4], muscarinic M1–5, α1 adrenergic and histaminergic H1 receptors. The drug reaches peak plasma levels in 5–8 hours. Olanzapine is metabolized through cytochrome p450 CYP1A2 and CYP2d6 in liver (Gómez et al., 2000). Treatment with olanzapine is associated with side effects like obesity, dizziness, drowsiness, confusion, postural hypotension, restlessness, amenorrhea, diabetes mellitus and dyslipidemia. The most common side-effects being somnolence and weight gain (Casey, 2005). A serious concern with olanzapine is the emergence of metabolic syndrome, also called as syndrome X, which encompasses conditions like obesity, hypertension, hypertriglyceridemia and impaired glucose tolerance (Lakka et al., 2002).

Metabolic syndrome is a cluster of risk factors that leads to increased morbidity and mortality and is considered the intermediate step towards final endpoint of type 2 diabetes and cardiovascular disease in general population (Trevisan et al., 1998). Though the etiology is multifactorial, important risk factors for its development include abdominal obesity and insulin resistance (Citrome, 2005). Olanzapine carries a greater risk of causing and exacerbating diabetes than other commonly prescribed atypical antipsychotics. It is found to be associated with increased insulin resistance and may also induce diabetic ketoacidosis (Sacher et al., 2008). The successful use of antipsychotic drug olanzapine in the treatment of psychiatric illness is hampered by the associated accompaniment of unwanted weight gain, obesity and other metabolic side effects (Holt, 2004)

Olanzapine tablets come in 2 oral formulations: standard olanzapine tablets (OST) and orally disintegrating olanzapine (ODO) tablets (Dobetti, 2004). Despite several advancements in drug delivery system, the oral route remains the preferred way because of the ease of administration. Orally disintegrating tablets are easy to administer for patients who are mentally ill, disabled and uncooperative as no water is required for their disintegration and dissolution (Dobetti, 2004). They are designed to leave minimal or no residue in the mouth after administration and lead to better adherence (Kinon et al., 2005). Some reports claim the disintegrating form of olanzapine to lead to fewer metabolic side effects like weight gain (San et al., 2008) while other researchers could not observe any significant difference in metabolic parameters among two formulations (Hoffmann and Milev, 2009). Therefore, this study is an attempt to resolve this conflict by comparing the drug emergence metabolic syndrome in patients on ODO and OST.

METHODS

Eighty patients were enrolled for the study and divided into two groups of 40 each receiving either ODO or OST after getting approval from the institutional board of studies. They were assessed according to study performa, Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10 DCR) classification of mental and behavioral disorders, Adult Treatment Panel (ATP III) diagnostic guidelines for metabolic syndrome (Ramachandran et al., 2003)

Inclusion criteria: Patients diagnosed with schizophrenia/ schizoaffective disorder/ bipolar disorder/ persistent delusional disorder/ unspecified nonorganic psychotic disorder using ICD 10 DCR criteria within the age group of 18–65 years without prior treatment with atypical antipsychotics in past 6 months and willing to give a valid consent for participation in the study were included in the study (World Health Organization, 1993).

Exclusion criteria: Patients having any of the features of metabolic syndrome, cardiovascular disorder, diabetes, other endocrinal disorder or having co-morbid chronic medical illness preventing use of olanzapine like liver failure were excluded from the study. Methodology: ATP III diagnostic guidelines for metabolic syndrome were followed. Each patient was subjected to measurements of blood pressure (mm Hg), body mass index (Kg/m^2) and waist circumference in cm (measured midway between the lowest rib and the iliac crest with the subjects standing using a tape with a spring-loaded mechanism to standardize tape tension during measurement) at the time of diagnosis and then at 2 and 4 months of respective treatment. Information regarding the socio-demographic variables was collected on the data sheet. Fasting blood samples (baseline, 2 months and 4 months) were collected in plain vacutainer and analyzed for glucose, triglycerides (TG) and high-density lipoprotein-cholesterol (HDL-C) on Randox Suzuka autoanalyzer using standard kits (Rush et al., 1970).

The results were subjected to Chi-square test and unpaired t-test for statistical analysis.

RESULTS

Out of 40 patients, 22 were males and 18 females in OST group while 30 males and 30 females in ODO group. The body weight in OST group at 0, 2 and 4 months showed no statistically significant difference ($p>0.05$) when compared with that of ODO group at the same intervals. Similarly no statistically significant differences ($p>0.05$) were observed in blood pressure, BMI and waist circumference, although the trend showed a persistent increase in all the parameters with passage of time (0, 2 and 4 months). The levels of fasting serum glucose, TG and HDL-C in OST group at 0, 2, 4 months when compared with ODO group showed no statistically significant difference ($p>0.05$). The comparison of different parameters at baseline, 2 and 4 months is shown in tables 1-3. Out of 40 patients in OST group, 9 were found fulfilling the criteria of metabolic syndrome after 4 months as per ATP-III guidelines. Three out of 18 females in OST group were fulfilling the criteria of metabolic syndrome after 4 months as per ATP-III guidelines. Out of 40 patients in ODO group, 7 were found to fulfill the criteria of metabolic syndrome after 4 months as per ATP-III guidelines. Similarly 3 out of 10 females were found to fulfill the criteria of metabolic syndrome after 4 months as per ATP-III guidelines. Odds ratio for above data was found to be 0.73 and did not imply any group specific vulnerability. The comparison of drug emergent metabolic syndrome in the two groups is shown in table 4. The comparison of change in each parameter after 4 months of drug treatment is shown in table 5 and figure 1. The graphical representation of drug emergent metabolic syndrome in the two groups is shown in figure 2.

Table 1: Comparison of different parameters (mean±SD) between two groups at baseline

Parameter	OST	ODO	t value	p value
Body Weight (Kg)	65.11±7.70	64.86±8.47	0.132	>0.05
Height (mt)	1.67±0.92	1.66±0.91	0.202	>0.05
BMI (Kg/m^2)	23.33±2.08	23.27±2.16	0.122	>0.05
Waist circumference (cm)	78.77±5.35	77.87±6.12	0.696	>0.05
SBP (mmHg)	117.75±6.51	119.35±6.06	-1.199	>0.05
DBP (mmHg)	76.95±4.48	78.00±4.29	-1.135	>0.05
Serum glucose (mg/dL)	84.71±9.31	85.99±9.89	-0.717	>0.05
Serum TG (mg/dL)	95.39±15.74	99.38±14.31	-1.246	>0.05
Serum HDL-C level (mg/dL)	52.83±6.29	52.69±6.16	0.105	>0.05

Table 2: Comparison of different parameters (mean±SD) between two groups at 2 months

Parameter	OST	ODO	t value	p value
Body Weight (Kg)	69.37±8.45	67.97±8.54	0.716	>0.05
Height (mt)	-	-	-	-
BMI (Kg/m^2)	24.89±2.38	79.60±8.98	0.404	>0.05
Waist circumference (cm)	121.45±5.68	122.80±7.61	0.810	>0.05
SBP (mmHg)	121.45±5.68	122.80±7.61	-0.949	>0.05
DBP (mmHg)	79.90 ± 4.77	80.10±4.87	-0.183	>0.05
Serum glucose (mg/dL)	97.20±10.76	95.96±10.76	0.64	>0.05
Serum TG (mg/dL)	117.46±17.90	117.17±15.86	0.092	>0.05
Serum HDL-C level (mg/dL)	45.53±6.17	46.15±5.26	-0.449	>0.05

Table 3: Comparison of different parameters (mean±SD) between two groups at 4 months

Parameter	OST	ODO	t value	p value
Body Weight (Kg)	71.71±8.74	70.15±9.17	0.763	>0.05
Height (mt)	-	-	-	-
BMI (Kg/m^2)	25.71±2.54	25.16±2.39	1.150	>0.05
Waist circumference (cm)	81.75±6.42	80.23±6.35	6.370	>0.05
SBP (mmHg)	123.25±6.35	125.15±6.35	-0.849	>0.05
DBP (mmHg)	82.20±6.15	82.70±5.35	0.373	>0.05
Serum glucose (mg/dL)	102.91±13.14	100.62±12.02	0.907	>0.05
Serum TG (mg/dL)	128.39±22.07	127.58±19.87	0.190	>0.05
Serum HDL-C level (mg/dL)	42.11±6.64	42.64±4.73	-0.378	>0.05

Table 4: Drug emergent metabolic syndrome in ODO and OST groups.

Patient group	Patients with metabolic syndrome	Patient without metabolic syndrome	Total	Percentage of patients with metabolic syndrome
ODO	9 (6M+3F)	31	40(22M+18M)	15
OST	7(4M+3F)	33	40 (30M+10F)	17.5
Total	16(10M+6F)	64	80 (52M+28F)	20

M=male; F= female

Table 5: Comparison of mean change in parameters after 4 months of treatment in both the groups

Parameter	OST	ODO	p value
Body Weight (Kg)	6.60	5.29	>0.05
BMI (Kg/m^2)	2.38	1.89	>0.05
Waist circumference (cm)	2.98	2.36	>0.05
SBP (mmHg)	5.5	5.8	>0.05
DBP (mmHg)	5.25	4.70	>0.05
Serum glucose (mg/dL)	18.2	14.63	>0.05
Serum TG (mg/dL)	33	28.2	>0.05
Serum HDL-C level (mg/dL)	10.72	10.05	>0.05

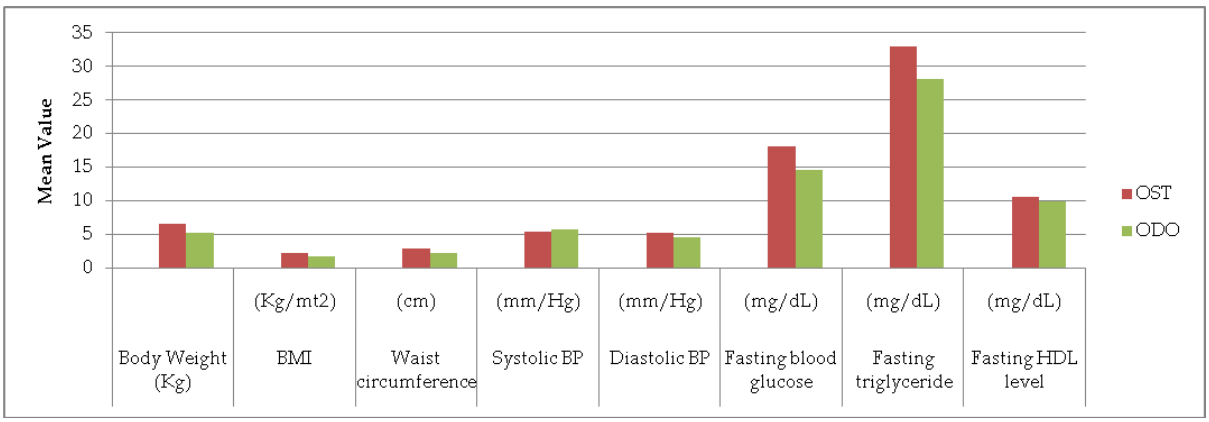

Figure 1: Comparison of mean change in metabolic parameters after 4 months in both the groups

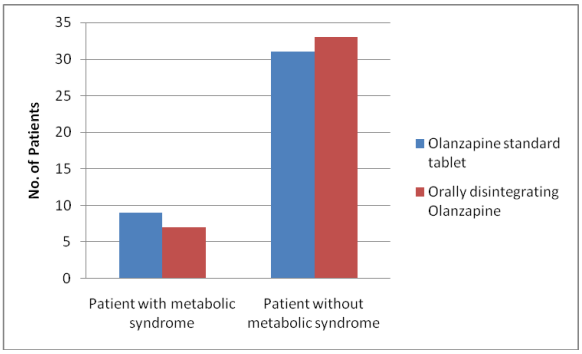

Figure 2: Patients with and without metabolic syndrome in both the groups

DISCUSSION

In the present study, patients in ODO group gained less mean body weight as compared to OST group at the end of 4 months but the difference was not statistically significant. Findings of this study are consistent with the study done by Kusumi et al, who conducted randomized trial on drug naïve schizophrenia patients, and observed no significant difference between two formulations in terms of body weight and other metabolic parameters (Kusumi et al., 2012). Another study also had similar findings i.e. mean body weight change in ODO and OST was not significant (Karagianisi et al., 2009) while few reports have shown a significant weight gain in patients on standard tablets as compared to those on orally disintegrating olanzapine (Arranz et al., 2007; Crocq et al., 2007). This contradiction might be due to the shorter treatment duration and the relatively small sample size in the studies showing no significant difference including the present one. The potential mechanism for the difference in weight gain between two formulations might be the difference in rate of gastrointestinal absorption. The sublingual administration of ODO yields a more rapid onset of absorption than oral tablet shortening the interaction of olanzapine with 5-HT2-type receptors in the pylorus. The peripheral 5-HT2-related action of 5-HT in feeding and satiation is thought to be mediated by 5-HT2-type receptors in the pylorus (Markowitz et al., 2006). If orally disintegrating tablet is completely absorbed by sublingual route, it is not able to reach pylorus and antagonize 5-HT2- like receptors leading to a lesser degree of weight gain in orally disintegrating tablet than the oral formulation. The other mechanism for less weight gain with ODO might be that olanzapine hampers insulin action via mechanistic routes other than body adiposity or physical inactivity (Vidarsdottir et al., 2010). It was proposed that H1 receptor-mediated activation of hypothalamic AMP-activated protein kinase represents an important mechanism of action for antipsychotic-induced hyperphagia (kim sf et al). Sub-chronic exposure to olanzapine upregulates the orexigenic neuropeptides neuropeptide Y and agouti-related peptide and down regulates the anorexigenic neuropeptide precursor proopiomelanocortin in the arcuate nucleus (Kim et al., 2007). Accumulating evidence also suggests that simply varying degrees of insulin resistance may be the common etiological factor for the individual components of metabolic syndrome (Lieberman, 2004).

There was increase in BMI in both the groups and the average increase in the ODO group was found to be relatively less than that of OST group though not statistically significant ($p>0.05$). This finding is in agreement with other studies (Karagianisi et al., 2009; Bobo et al., 2011). On the other hand, there are reports showing significantly greater increase in BMI in the patients treated with OST than with ODO but the inadequate sample size and non-random sampling method disfavor the generalizability of these studies (Crocq et al., 2007; Chawla and Luxton, 2008). Similarly no statistically significant difference ($p>0.05$) was observed in the waist circumference between the two groups even after 4 months of treatment, although there was slight increase in waist circumference in the OST olanzapine group. The findings are in accordance with other larger sample studies (Karagianisi et al., 2009; Bobo et al., 2011).

There was a gradual but steady increase observed in both systolic and diastolic blood pressure among both the groups. Although the ODO group showed marginally lesser increase in blood pressure, but the inter group difference was not statistically significant ($p>0.05$). These findings are in agreement with the other study assessing the blood pressure parameters in different populations, taking the two forms of olanzapine (Mitchell et al., 2011). The increase in blood pressure might be due to the associated metabolic derangements producing the loss of vascular elasticity (Saddichha et al., 2007). There was no statistically significant difference ($p>0.05$) observed in fasting glucose levels between the two study groups however there was mean increase in both groups at 4 months compared to baseline levels similar to a report (Pramyothin and Khaodhiar, 2010).

The lipid profile demonstrated a steady derangement among both the groups which was marked by the gradual reduction in serum HDL-C concentration with time as well as a gradual increase in serum TG level. The ODO group showed a marginally lower rate of derangement with respect to the OST group, although the inter group difference was not statistically significant ($p>0.05$). These findings are in consistence with other studies comparing the two modalities of olanzapine administration in various populations (Faulkner and Cohn, 2006). As the studies across various populations have shown the same trend of lipid profile derangement with different forms of olanzapine, it might imply that the local action of olanzapine on gastrointestinal hormones play a little role in the metabolic derangements (Evans et al., 2005).

It was observed that a significant number of patients developed clinically identifiable metabolic syndrome as per ATP III criteria within four months of starting of therapy with olanzapine. Though there were relatively lesser number of cases of metabolic syndrome from the ODO group (7 out of 40) compared to OST group (9 out of 40), the odds ratio does not imply any group specific vulnerability. It was found that around 19% of males as well as 21% of female patients developed clinically detectable metabolic syndrome within 4 months of treatment initiation. The incidence of metabolic syndrome varies widely in various studies across the world, depending upon the patient population, their food habit, lifestyle, time of diagnosis as well as antipsychotic drug used by them.

This is the first study, as per our knowledge, to investigate metabolic parameters in olanzapine formulations in India. Familial tendency for deranged metabolic parameters also need to be researched before commenting on the differences in both these formulations and there is further need to conduct double blind randomized study to find out whether there is any significant difference in metabolic parameters or the only advantage in the disintegrating olanzapine formulation is its ease of administration with improved compliance.

CONCLUSION

The atypical antipsychotics, especially olanzapine, quetiapine, clozapine are well known for their weight gain propensity. As the metabolic syndrome progresses gradually, the patient is exposed to significant morbidity and mortality, which is again aggravated by various co-administered drugs and sedentary lifestyle in psychotic patients under treatment. This leads to relentless search and research to protect the patients from these serious side effects of the atypical antipsychotics, and one of the approaches was to deliver the drug by bypassing gastric mucosa. Although this route has many other advantages, but it apparently lacks the metabolic advantages which was expected. In spite of the claims, no significant difference was found in metabolic side effects among two preparations of olanzapine.

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