Effects of Olanazapine and Haloperidol on Serum Malondialdehyde, Prolactin Level, Blood Glucose and Lipid Profile in Schizophrenic Patients

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ABSTRACT

Background and Objectives: The association of the atypical antipsychotics with hyperglycemia, elevated lipids, and weight gain was recognized soon after the introduction of clozapine and has become of increased concern as the use and uses of atypical antipsychotics have been expanded. The aim of the present study was to investigate the prevalence of diabetes, dyslipidaemia, lipid peroxidation and hyperprolactinemia in Olanzepine treated patients in comparison with patients treated with haloperidol.

Methods: Fifty patients were selected randomly from psychiatric inpatient clinic in Erbil city in Iraqi Kurdistan Region between November 2007 and June 2008.

All patients were diagnosed as schizophrenia, and none of them were in acute severe state. Thirty Schizophrenic patients received Haloperidol orally as typical antipsychotic and 20 patients received Olanazapine orally as atypical antipsychotic for a minimum of one month. Fasting blood samples for the assessment of serum malondialdehyde (MDA), lipid profile, fasting blood glucose (FBG) and prolactin levels were obtained after one month of the drug prescribing time. From those fifty patients, 16 patients were selected to follow them prospectively over a mean period of time of 112 days for olanzapine and 75 days for haloperidol. The prospective study includes FBG, lipid profile, BMI and serum MDA.

Results: The prevalence of hyperprolactinaemia and lipid peroxidation was higher in Haloperidol treated patients. Whereas, the prevalence of diabetes and dyslipidaemia were higher in Olanazapine treated patients, The mean level of BMI of the Olanazapine group was significantly higher than BMI of the Haloperidol group. There was 6.66 % prevalence of DM in Olanazapine treated patients, but there was no prevalence of DM in Haloperidol treated patients. There was no incidence of diabetes mellitus in the prospective study for both Haloperidol and Olanazapine treated patients.

Conclusions: No absolute evidence indicates that the atypical antipsychotic Olanazapine is the cause of diabetes, since the glucose levels of all patients were within normal range and there was no incidence of diabetes in the prospective study in spite of their higher weight and body mass index.

Key words: Haloperidol, Olanazapine, Diabetes, Dyslipidaemia, Lipid peroxidation and Hyperprolactinaemia .

INTRODUCTION:

Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly an over activity of the mesolimbic dopaminergic neurons [1]. The antipsychotic action involves blockade of CNS dopamine receptors in mesolimbic pathways. Blockade of the D2 family of receptors is common to all effective neuroleptics. The D4 receptor shows polymorphic expression; hopes that this subtype may be the key to schizophrenia have not been fulfilled, although clozapine, a selective D4 receptor

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antagonist, is a valuable antipsychotic drug [2]. Antipsychotic drugs have traditionally been classified as "first" or "second" generation. First generation Antipsychotic drugs are with higher D2 antagonism and lower 5-HT2A antagonism while "second" generation Antipsychotic drugs are with moderate to high D2 antagonism and high 5-HT2A antagonism. The typical neuroleptics used to treat schizophrenia are effective, but some of them are associated with severe extrapyramidal side effects (EPS). The most predominant among these symptoms are dystonia, akathesia, parkinsonian-like syndrome and tardive dyskinesia. Haloperidol is the most widely used typical antipsychotic in treating the positive and relatively negative symptoms of schizophrenia. Atypical drugs seem to have similar clinical efficiency as the typical antipsychotics, but with minimal or no extrapyramidal symptoms Clozapine was the first atypical antipsychotic drug introduced, but its use was restricted because of the fatal agranulocytosis associated with it [3]. A few of the new ones to join the group are olanzapine, risperidone and quietapine which are equally potent as clozapine without apparent agranulocytosis or any other major adverse effects [4]. Schizophrenics have a higher prevalence of type 2 diabetes than non-schizophrenics, regardless of antipsychotic use. In addition there is a trend toward an increase in prevalence of diabetes mellitus in the general population. Antipsychotics may adversely affect glucose levels in diabetic patients. New onset diabetes has been reported with use of the SGAs [5]. Some SGAs and phenothiazines cause elevations in serum triglycerides and cholesterol, and the extent to which this effect differs among antipsychotics is unclear. The risk of this effect may be less with risperidone, ziprasidone, or aripiprazole. However, the true incidence of hyperglycemia and hypercholesterolemia induced by different typical or atypical medications is not well known at this time. This randomized, controlled, prospective study aims to investigate the association between Olanazapine (OLZ) and diabetes in comparison with Haloperidol (HL). Moreover to investigate the association between Haloperidol and lipid peroxidation in comparison with Olanazapine in schizophrenic patients.

MATERIALS AND METHODS:

The measurement of malondialdehyde (MDA) as one of the main products of lipid peroxidation by using the thiobarbituric acid method [6]. The level of fasting glucose, triglycerides, total cholesterol, LDL, HDL and prolactin were measured using commercial kits. Elisa method for the determination of prolactin in serum was used.

Study Designs: Cross-sectional study comparing the pharmacological effect of "atypical" antipsychotics monotherapy (in particular Olanazapine) with the pharmacological effect of typical antipsychotics monotherapy (in particular Haloperidol) in the treatment of ***schizophrenic Patients*****.** The main data involves in this study is the level of prolactin , MDA fasting glucose, triglycerides, total cholesterol, LDL, HDL , and weight (kg) as body mass index (BMI). Also a cohort prospective study was done on 16 patients.

Subjects /Sample Size: Fifty male schizophrenic patients had participated in cross-sectional study; all of them have been selected periodically from Asuda center for inpatient psychiatric disease in Erbil city.

The patient was taking prescribed Haloperidol as typical or Olanazapine as atypical antipsychotic monotherapy for a minimum of 1 month. From those fifty patients, we have selected 16 patients to follow them prospectively.

Statistical Analysis: Results are presented as mean±SD. Group differences were ascertained by unpaired t-test. The student paired t-test was used to compare differences during patients-follow up. Correlation analysis was performed by Pearson's method using Excel program. *P* value<0.05 was considered as significant.

RESULT:

Effects of Olanazapine and Haloperidol on serum prolactin :

Olanzapine users had significantly lower mean level of serum prolactin than haloperidol users (Table 1 & (Figure 1),

Effects of Olanazapine and Haloperidol on serum malondialdehyde

:The oxidative stress associated with Haloperidol treatment is higher than that of Olanazapine see Table1.

Effects of Olanazapine and Haloperidol on BMI:

The mean level of BMI of the Olanazapine group was significantly higher than BMI of the Haloperidol group (*P-value* < *0.05*) (Figure 2).

Effects of Olanazapine and Haloperidol on blood glucose :

There was no case of impaired fasting glucose or hyperglycemia in Olanazapine-treated patients. The prevalence of diabetes mellitus (6.66%) was less than other studies (10-14%). No significant correlation (R= 0.12) was found between the duration of treatment and the level of glucose see Table 1.

Effects of Olanazapine and Haloperidol on lipid profile:

The prevalence of hypercholesterolemia, high LDL-cholesterol, low HDL-cholesterol and hypertriglyceridemia were none significantly higher in patients using Olanazapine compared to patients with Haloperidol treatment (table 1).

The prevalence of abnormal BMI, diabetes, dyslipidemia and hyperprolactinaemia:

The differences between haloperidol and olanzapine with regard to the risk for weight gain, dyslipidemia , disoders in glucose level and prolactin level are illustrated in Figure 3.

Prospective study:

In this prospective study 16 male patients were selected from 50 patients who were included in the cross-sectional study. The patients were selected to follow them prospectively from the first estimation time till the second estimation time over a mean period of time of 112 days for olanzapine and 75 days for haloperidol. The prospective study includes serum MDA FBG, lipid profile and BMI (Table 2).

Statistical significant increase of serum MDA of haloperidol group during second estimation was observed, while there was an increase of serum MDA in the olanzapine group but statistically was non significant. Olanzapine caused an increase in BMI but statistically was non significant. Whereas haloperidol had no detectable effects on BMI. There was a statistically non significant reduction in the FBG level in both groups. No significant correlation (R= 0.12) was found between the duration of treatment and the level of glucose. There was a statistical significant decrease of serum cholesterol in olanzapine treated patients, while there was a decrease of serum cholesterol in haloperidol treated patients but it was statistically non significant. Haloperidol had no detectable effect on the level of HDL, whereas olanzapine induced non significant reduction in the level of HDL. Statistical significant decrease of serum LDL was seen in the olanzapine group, while there was a decrease of serum LDL in the haloperidol group but it was statistically non significant.

Table 1: Clinical Comparisons between the haloperidol and olanzapine treated groups.

Parameters	Typical antipsychotic HL (n=20) mean±SD	Atypical antipsychotic OLZ (n=30) mean±SD	Normal range
BMI (kg/m2)	24.038 ± 3.384	26.853 ± 3.974*	18.5 - 24.9
FBG (mg/dl)	85.727 ± 6.543	91.448 ± 33.889	75- 115
Total cholesterol (mg/dl)	167.272 ±31.588	183.344± 48.434	<200
Triglyceride (mg/dl)	134.454 ±40.596	166.931± 86.811	<200
HDL (mg/dl)	45.454 ± 8.477	48.137 ± 10.350	>35
LDL (mg/dl)	86.363 ± 25.184	103.862 ±40.809	<160
Prolactin (ng/ml)	90.727± 65.106	42.620± 50.639*	1.8- 17.0
MDA (µmol/L)	0.641± 0.421	0.510± 0.447	0.12- 1.71

*(*P-value* < *0.05*) - HL = Haloperidol - OLZ = Olanzapine.

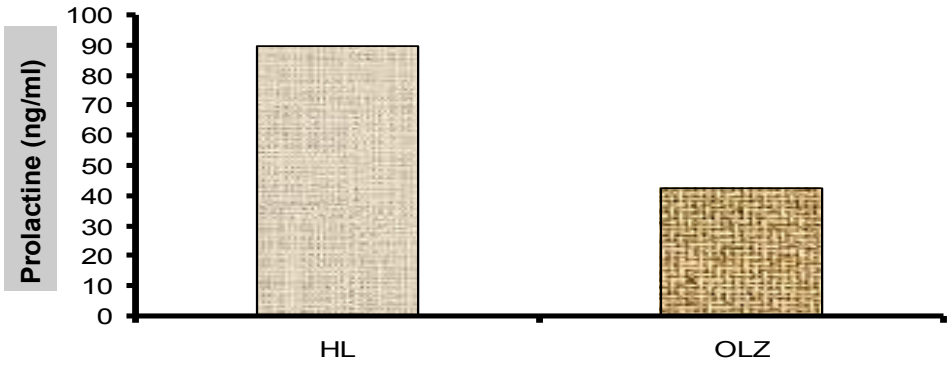

Figure 1: Mean level of prolactin in (ng /ml)) among antipsychotic patients treated with OLZ and HL .

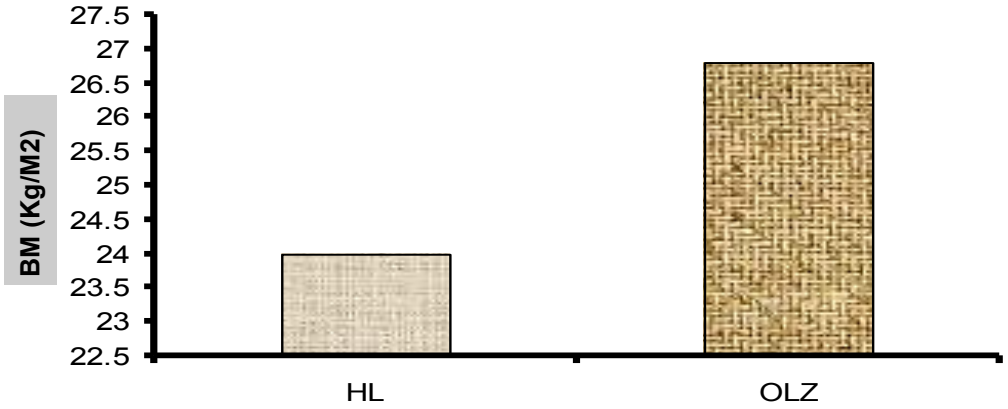

Figure 2: Mean level of BMI in (kg/m2) among antipsychotic patients treated with OLZ and HL.

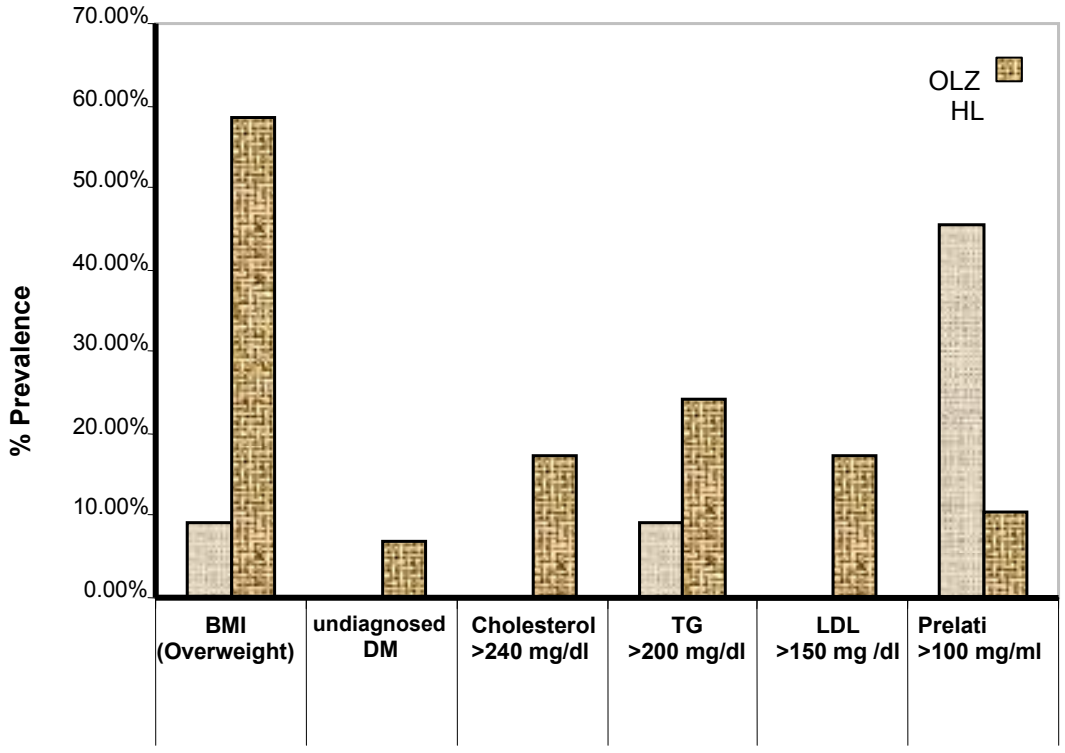

Figure 3: Result outline of prevalence study of abnormal BMI, diabetes, dyslipidemia and hyperprolactinaemia in Haloperidol and Olanazapine treated patients.

DISCUSSION:

Effect of Olanazapine versus Haloperidol on prolactin level:

In this study, Olanazapine-treated patients had 62.07% prevalence of hyperprolactinaemia (>17 ng/ml) while Haloperidol had 81.07%. Moreover, Olanazapine-treated patients had 10.34% prevalence of hyperprolactinaemia (>100 ng/ml) while Haloperidol had 45.45%. The results of this study was consistent with results of most studies which have shown that conventional antipsychotics are associated with a two-to tenfold increase in prolactin levels [7]. In two double-blind, randomized studies, Haloperidol produced a significantly ($p < 0.001$) larger increase in prolactin levels in schizophrenia patients than either placebo (72 vs. 8% increase) [8] or Olanazapine (17 vs. 4 ng) [9]. All antipsychotics block dopamine D_2 receptors which is the cause of elevation in prolactin level, but some dissociate from the receptors more quickly than others and this may explain the lower level of prolactin in Olanazapine-treated patients than Haloperidol-treated patients[10]. The increase in prolactin that occurs through the use of conventional antipsychotics develops over the first week of treatment and remains elevated throughout the period of use. Once treatment stops, prolactin levels return to normal within 2-3 weeks [11].

Effect of Olanazapine versus Haloperidol on serum MDA :

It is well established that oxidative stress within the CNS is reflected in plasma [12]. There is also evidence that psychotic disorders might impair antioxidant defense and increase lipid peroxidation, as antipsychotic treatment itself increases oxidative stress and induces irreversible neuropathological changes in animal models [13.] The most important finding from this prospective study is that the mean serum MDA level was found to be elevated significantly in patients treated with Haloperidol, compared to Olanazapine , also, in the prevalence study the mean level of serum MDA is higher in the Haloperidol group than that of the Olanazapine group but the statistics was non significant. These results indicated that the membrane lipid peroxidation was more in Haloperidol-treated patients. This comparative study is in agreement with Kropps S *et al.* study which was done in Germany. Kropps S *et al.* demonstrated that samples of patients with Olanazapine had lower serum level of MDA (mean 0.80 µmol/L) than typical antipsychotics and missed significant differences compared to typical antipsychotics. An animal study with a similar hypothesis but different markers was published, of which the main results substantiate our conclusions [14] .Therefore the results of this study on serum MDA might explain the different incidence of EPS between typical antipsychotics and atypical antipsychotics [15.] Oxidative stress induced by antipsychotic treatment is a hypothesis that should be taken into account concerning EPS and TD [16]. Effect of Olanazapine versus Haloperidol on body weight. In the present prevalence study, the mean value of BMI of the Olanazapine group is significantly higher than that of the Haloperidol group. The prevalence of overweight and obesity is higher in the Olanazapine group. These results are consistent with results of a meta-analysis [17]. The prospective study has shown that 75% of Olanazapine-treated patients gain weight. Despite a small prospective study group, we could demonstrate that there is a slight increase in the BMI of the Olanazapine group after a long period of time while there is a slight reduction in BMI of the haloperidol group over time , i.e. the cumulative weight gain will be at a slower rate with time than that at the first initial treatment time , that is consistent with previous studies which have shown that most weight gain occurs during the first four to five months of treatment, but with Olanazapine it continues for up to a year, and with clozapine even longer [18]. Antipsychotic-associated weight gain has been correlated with H1 receptors antagonism [19].

Effect of Olanazapine versus Haloperidol on blood glucose and lipid profile: Of all the metabolic effects of some of the atypical second-generation antipsychotics, their potential to induce glucose dysregulation especially Olanazapine has induced a great controversy over the past several years. The numerous published epidemiologic studies are difficult to interpret due to the high background rate of type 2 diabetes mellitus in this population, the inherent problems with analysis of observational data, and the short duration of the available studies. The associations between psychosis, antipsychotic drugs and diabetes mellitus have not been precisely defined but it has been repeatedly suggested that atypical antipsychotics are more likely to give rise to diabetes than are conventional drugs [20]. From investigation of 50 hospitalized patients (30 patients with Olanazapine and 20 patients with Haloperidol) were receiving atypical and typical antipsychotic treatment, an apparent prevalence of undiagnosed diabetes was found in 6.66 % in the Olanazapine group whereas there was no prevalence of diabetes in the Haloperidol group . In the present study none of the Olanazapine group or Haloperidol group had impaired fasting glucose between 6.1 mmol/l (110 mg/dL) and 7.0 mmol/l (126 mg/dl). From this sample of patients, 16 patients were prospectively investigated; they were not known to have any disorder of glucose homeostasis. From this prospective study, no cases of impaired fasting glucose and diabetes mellitus were detected. The results of the present study was in controversy to Lindenmayer study [21] who investigated the change in glucose level of 26 inpatients on Olanazapine over 14 weeks of treatment in four hospitals in USA. In Lindenmayer study , the Olanazapine group showed a significant increase of glucose levels at the end of the 14 weeks (105.5 ±30.4) and four of the 26 patients developed abnormal glucose levels (>125 mg/dl) during the trial, the ethnicity of them is African American.

Results of the present study about the glucose level and DM are inconsistent with the results of Lindenmayer study. The difference between the prevalence of DM in the present prevalence study and the incidence of DM in Lindenmayer study (6.66 % vs. 15.4 %) might be due to the difference in the ethnicity , also, the difference in glucose levels might be due to the difference in the estimation time , since the estimation in the Lindenmayer study was done in the initial period of treatment while in the present study the estimation was done after a longer period of time i.e. that there is an initial increase in the glucose level followed by a reduction after a longer time. A follow-up experiment shows that glucose levels in animals treated with different concentrations of Olanazapine were not different from that of control animals in week 4 [22] i.e. that there is an initial increase in glucose levels followed by a reduction. A similar result also showed that Olanazapine did not induce hyperglycemia in male Sprague -Dawley rats [23]. The results of these two experiments on animals could be translated with the results of the present clinical study. Using the National Cholesterol Education Program's definition [24], the prevalence of hypercholesterolemia, high LDL-cholesterol, low HDL-cholesterol and hypertriglyceridemia in this study were higher in persons using Olanazapine compared to persons with Haloperidol. Meyer [25] postulated that antipsychotics with a dibenzodiazepine-derived structure (e.g., clozapine, Olanazapine) may be associated with significant elevating effects on fasting triglyceride levels and with lesser effects on cholesterol levels, so the present study is in agreement with Meyer postulation since in this prevalence study, there is 24.14% hyertriglyceridemia while there is 17.24% hypercholesterolemia, also, in the prospective study there is a non significant increase in TG level. Also, Olanazapine has been associated with significant hypertriglyceridemia in other studies [26]. In the present prospective study, Olanazapine exhibited some effects on the triglyceride levels, but not on the blood glucose level.

These results are inconsistent to the clinical data, since different clinical reports showed that after 14 weeks to 25months treatment with Olanazapine; around 11% to 44% of patients were hyperglycemic[27,] while around 39% to 62% of patients were hypertriglyceridemic[28]. Aretrospective analysis showed that the mean time to peak triglyceride levels in treated patients was 10.0 months [29]. In this study, Olanazapine-treated patients had prevalence of abnormal total cholesterol, high LDL cholesterol, low HDL cholesterol and high triglyceride levels that represented approximately 17.24%, 17.24%, 13.79% and 24.14%, respectively. After a longer period prospective study, a significant reduction in the mean levels of cholesterol and LDL and a non significant reduction in the mean level of HDL was found in the study, this reduction may be associated with a lesser weight gain at that period of time, since most weight gain occurs during the first four to five months of treatment [30]. Therefore, the effect of Olanazapine on blood glucose and triglyceride levels may be influenced by the period of treatment. The small number of patients in the present prospective study may also limit the power of analyses. It is possible that the apparent discrepancy may be due to ethnic and genetic differences, period of the study and sample size. It is unclear as to how much of the increased risk of metabolic syndrome in the sample was due to unhealthy lifestyle issues, e.g. poor diet, lack of exercise and cigarette smoking, which are known to have higher prevalence in schizophrenics than in the general population. Schizophrenia and high blood glucose may also be linked independently of medication [31]. Clinicians should pay attention to the selection of antipsychotic medication, because different antipsychotics seem to have different effects on glucose and lipid levels [20].

CONCLUSION

No clear evidence indicates that Olanazapine is the cause of diabetes. The lipid peroxidation was higher in haloperidol treated patients. Olanazapine associated with higher weight gain and dyslipidemia. The mean level of prolactin in Haloperidol treated patients was two times that of Olanazapine treated patients.

RECOMMENDATION

Further larger sample size and randomized controlled trial are needed to determine how the findings of this study are relevant to treatment with other antipsychotic medication.

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