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A Comparative Study of the Effects of Clozapine and Risperidone Monotherapy on Lipid Profile in Nigerian Patients with Schizophrenia

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Abstract: Although antipsychotic drugs are known to have an array of adverse effects, they also exhibit significant differences in causing these effects. The atherogenic effects of clozapine and risperidone have not been fully investigated among schizophrenics in Nigeria hence this research work. This study therefore investigated the extent to which monotherapy with clozapine and risperidone (atypical antipsychotic drugs) influence lipid profile in patients with schizophrenia. The study population comprised 29 Schizophrenic patients from Psychiatric Hospital, Uselu, Benin city, Nigeria. They were placed on typical antipsychotics for six weeks: 10 patients were on risperidone (1-4 mg day^{-1} in divided doses) and 19 patients were on clozapine (25-300 mg day^{-1} in divided doses). The control group comprised 30 apparently healthy volunteers. Blood samples were collected from all subjects on the first day before the commencement of treatment with antipsychotic drug and 24 h after the last administration of antipsychotics at the end of week 6 for analyses of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and very low density Lipoprotein cholesterol (VLDL) using standard methods. Comparing with the control, the basal serum TC, TG, LDL and VLDL of the clozapine treated group were not significantly different except for HDL which was significantly reduced and the atherogenic indices (TC/HDL and LDL/HDL) which were significantly increased. However the risperidone treatment group showed significantly higher TC, TG, LDL and VLDL levels while HDL was significantly reduced. At the end of week 6, there was significant increase in serum TC, TG, HDL and VLDL and a significant decrease in HDL in both treatment groups compared to the control except VLDL that was not significantly different in the clozapine group. Comparing the two treatment groups, risperidone caused a more significant increase on lipid profile and atherogenic indeces than clozapine. This effect was about two times or greater with risperidone than clozapine. Conclusively, additional prospective clinical trials are required to support a specific therapeutic approach for managing dyslipidaemia that are present in clozapine and risperidone treated schizophrenic patients in an attempt to avoid its consequent adverse effects.

Key words: Atypical antipsychotics, clozapine, risperidone, dyslipidaemia, schizophrenia, lipid profile

INTRODUCTION

The prevalence of the metabolic syndrome and individual cardiovascular risk factors including obesity, dyslipidaemia, diabetes mellitus, cigarette smoking and hypercortisolemia are greater in individuals with major mental illness compared with the general population (Muck-Seler et al., 1999; Grant et al., 2004; McEvoy et al., 2005; Saari et al., 2005; Hagg et al., 2006; Van Winkel et al., 2008). While unhealthy lifestyle

(Brown et al., 1999; Grant et al., 2004; Compton et al., 2006) and apparent genetic predisposition (Bellivier, 2005; Gough and O'Donovan, 2005; Tsang et al., 2006) contribute to this, there is growing evidence that treatment with antipsychotic medications may be a factor in the increased prevalence of the cardio-metabolic problems among patients with major mental illness (Newcomer and Haupt, 2006; Yumru et al., 2007; Newcomer, 2007; Le Noury et al., 2008) especially in the presence of reduced levels of antioxidant trace metals as

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seen in schizophrenia (Ariola and Idonije, 2009; Gariyu *et al.*, 2010). Antipsychotics have been implicated in causing a variety of cardiovascular, metabolic, hepatic, haematologic and endocrine diseases (Golebiewski and Kim, 2006). In schizophrenia this is partly due to increase oxidative stress (Ariola and Idonije, 2009) and immune exhaustion as shown by decrease levels of immunoglobulin G in schizophrenia (Idonije *et al.*, 2009).

Atypical antipsychotic agents (second generation antipsychotics), first introduced in the 1990s, have several major advantages over their predecessors the conventional (first generation) or typical antipsychotics (Perkins, 2004) with mild or no complication when combined with Electroconvulsive Therapy (ECT) (Masoudzadeh and Khalilian, 2007). Although, studies of schizophrenic patients before the use of second-generation antipsychotics suggested elevated rates of overweight and diabetes, substantial evidence from case reports, clinical trials, case registries, insurance databases and government surveillance programs implicates some or all second-generation antipsychotics in causing or worsening weight gain, dyslipidaemia and diabetes (Newcomer, 2005). Although categorized as a single class of drugs, atypical antipsychotic agents vary widely in their mechanism of action and their adverse effect profiles. For example, a growing body of clinical evidence indicates that in some patients, they are associated with a particular constellation of adverse effects, namely, cancer, osteoporosis, metabolic and endocrine dysfunction (Perkins, 2004), diabetes and diabetic ketoacidosis, hyperglycaemia (Cohen, 2004; Koller *et al.*, 2004), metabolic side effects including weight gain, diabetes mellitus and an atherogenic lipid profile (American Diabetes Association, 2004; Newcomer, 2005; Tschoner *et al.*, 2007), these effects are reduced if used in combination with ECT (Masoudzadeh and Khalilian, 2007). It is important to include here that not all drugs are equally implicated and differences are bound to be seen among them in the extent to which they cause these adverse effects. This study therefore investigated the extent to which monotherapy of clozapine and risperidone (atypical antipsychotic agents) affect lipid profile in patients with schizophrenia.

MATERIALS AND METHODS

Subjects: This 6 week study, took place between November 2006 and January 2007 at the Psychiatric Hospital, Uselu, Benin City, Nigeria. Subjects enrolled for the study were schizophrenic patients of Psychiatric Hospital, Uselu, Benin City, Nigeria. They comprised of 29 schizophrenic patients on atypical antipsychotics: 19 on

clozapine (25 mg that was gradually increased to 300 mg per day in divided doses) and 10 on risperidone (1 mg daily that was gradually increased to 4 mg per day in divided doses). Treatment lasted 6 weeks. The control included 30 apparently healthy non psychiatric patient volunteers.

Ethical approval was obtained from the Ethic Committee of Psychiatric Hospital, Uselu and informed consent was obtained from all the subjects and/or their close relative as the case might be before they were enrolled for the study. Eligibility was determined by an interview and a medical record review of history and recent laboratory findings. Before inclusion into the study, a urine pregnancy test was performed for female patients of childbearing age and the diagnosis of schizophrenia was established by a consultant psychiatrist according to axis 1 of DSM-IV (the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders). Psychological evaluation of each subject was done using Positive and Negative Syndrome Scale PANSS). None of the patients had significant psychiatric or somatic comorbidity.

Test subjects were both out and in-patients of Psychiatric Hospital, Uselu. Only patients who had a normal blood pressure and glucose level were recruited. Patients were excluded on the basis of current substance abuse, hypertension, pregnancy, diabetes mellitus, thyroid disease, significant medical illness, hepatic or renal disease and unstable and other psychiatric illnesses. Patients treated with medications known to affect glucose tolerance were also excluded. Patients treated with oral contraceptives containing norgestrel, steroids and β-blockers and anti-inflammatory drugs such as aspirin and ibuprofen, thiazide diuretics and agents that induce weight loss were excluded.

Sample collection and analysis: Before the study, blood samples were collected from all subjects. Twenty-four hours after the last administration of atypical antipsychotic drugs, 5 mL of venous blood was collected from the antecubital vein of each subject under aseptic condition into EDTA anticoagulant bottles.

Serum was obtained by centrifugation at 2500 rpm for 5 min and serum Triglyceride (TG) and Total Cholesterol (TC) concentrations were determined as described by Erickson *et al.* (1990), while high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were determined according to the method of Nicholls *et al.* (1986). Very Low Density Lipoprotein cholesterol (VLDL-C) were calculated using the Friedewald (1972) formula.

Data analysis: Data were presented in Mean±standard deviation. One-way analysis of variance (ANOVA) was performed using SPSS version 17 soft ware to test for significance with the significance level set at $p<0.05$.

RESULTS

Table 1 shows the demographic characteristic of the study population. For the entire treatment sample (N = 29), the Mean±SD age was 39.62±11.41 years for the clozapine treated group while that of the risperidone treated group was 43.74±9.61 years, values not significantly different. Also, in the clozapine treatment group, 8 (42.11%) were males and 11 (57.89%) were females while 5 (50%) were male and 5 (50%) were females for the risperidone treatment group. The control group did not differ in age and sex with the treatment groups as the Mean±SD of age was 40.27±3.56 years and 15 (50.00%) were males and 15 (50.00%) were females (Table 1).

Tables 2 and 3 present serum lipid changes in the control and treatment groups. Comparing with the control, the basal (week 0) serum lipid values of the clozapine treatment group were not significantly different except for HDL that was significant reduced and the atherogenic

indeces (TC/HDL and LDL/HDL) which were significantly increased. At the end of week six, there was significant increase in serum lipids except in VLDL and a significant decrease in HDL compared to the control. The changes in serum lipids values at week six were only significant with serum TG, HDL and atherogenic index (Table 2). Comparing with the control, the basal (week 0) serum lipid values of the risperidone treatment group were significantly higher except for HDL which was significantly lower. The week 6 values also showed an even higher serum lipid values and atherogenic index which were significantly different from the control and the basal values. HDL reduces even more at the end of the six weeks period and was significantly different from the control but not from the basal value (Table 3).

Comparing the two drugs, treatment with risperidone caused a greater increase in lipid profile and worse atherogenic indeces than clozapine. This was shown by the percentage changes in serum lipid profile between the basal and week six values which were higher with risperidone. In the entire serum lipid values, the dyslipidaemia and atherogenic index effect where about two times or greater with risperidone than clozapine (Table 2, 3).

Table 1: Demographic characteristic of the control subjects and atypical antipsychotic treatment groups

Characteristic	Control	Clozapine treatment group	Risperidone treatment group
Age (year)	40.27±3.56	39.62±11.41	43.74±9.61
No. of patients	30	19	10
Gender			
Male	15 (50%)	8 (42.11%)	5 (50%)
Female	15 (50%)	11 (57.89%)	5 (50%)

Table 2: Changes in serum lipid profile in control and clozapine treatment schizophrenia patients

Plasma lipids (mg dL^{-1})	Control	Clozapine treatment group		Percent increase (%)
		Basal value (week 0)	Week 6 value	
TG	119.73±9.63[a]	113.90±24.73[a]	135.73±31.40[b]	19.17
TC	121.83±14.31[a]	133.55±32.93[ab]	142.22±31.61[b]	6.49
HDL	43.53±5.99[a]	34.54±14.60[b]	30.96±14.66[b]	-10.36
LDL	72.19±17.68[a]	76.23±22.55[ab]	84.12±24.14[b]	10.35
VLDL	25.76±3.22[a]	22.79±4.93[a]	27.13±6.28[a]	19.04
TC/HDL	3.26±0.50[a]	4.18±1.34[b]	5.27±2.06[c]	26.08
LDL/HDL	1.79±0.49[a]	2.46±1.08[b]	3.25±1.76[c]	32.11

Values are Mean±SD, Values in a row having different super scripts are significantly different ($p<0.05$)

Table 3: Changes in serum lipid profile in control and risperidone treated schizophrenia Patients

Plasma lipids (mg dL^{-1})	Control	Risperidone treatment group		Percent increase (%)
		Basal value (week 0)	Week 6 value	
TG	119.73±9.63[a]	139.23±35.60[b]	193.08±26.49[c]	38.68
TC	121.83±14.31[a]	150.65±46.23[b]	202.08±10.09[c]	34.14
HDL	43.53±5.99[a]	31.05±9.71[b]	25.99±7.00[b]	-16.30
LDL	72.19±17.68[a]	91.75±40.43[b]	137.46±14.11[c]	49.82
VLDL	25.76±3.22[a]	27.85±7.12[b]	38.63±5.29[c]	38.71
TC/HDL	3.26±0.50[a]	5.14±1.74[b]	8.39±2.76[c]	60.23
LDL/HDL	1.79±0.49[a]	3.18±1.53[b]	5.78±2.22[c]	81.76

Values are Mean±SD, Values in a row having different super scripts are significantly different ($p<0.05$)

DISCUSSION

Dyslipidaemia is characterized by increased Free Fatty Acids (FFAs), elevated triglycerides, low High-Density Lipoprotein (HDL) cholesterol, increased small, dense Low-density Lipoprotein (LDL) cholesterol and increased apolipoprotein B (Ginsberg and Huang, 2000). The results of this study confirmed schizophrenia to be associated with dyslipidaemia and a high atherogenic indeces. Supporting this fact are past studies which demonstrated that psychiatric patients have combined dyslipidaemia in acute phases (Huang and Wu, 2000; Huang, 2001; Huang and Chen, 2005) and are at high risk of developing coronary heart disease (Manninen *et al.*, 1992; Assman and Schulte, 1992; Sheu *et al.*, 1993; National Cholesterol Education Program, 2001). Also, the study of Davidson *et al.* (2001) reported that patients with schizophrenia are prone to obesity due to positive and negative symptoms as well as overall sedentary lifestyle. It is known that obesity and sedentary lifestyle are predictors of dyslipidaemia and cardiovascular disorder such as atherosclerosis. Interestingly, some studies have shown that weight gain is generally associated with increases in lipids (Osser *et al.*, 1999; Mokdad *et al.*, 1999; Must *et al.*, 1999; Henderson *et al.*, 2000).

Atypical antipsychotics are currently the most frequently prescribed class of drugs for schizophrenia (Harrington *et al.*, 2000). Published evidence indicates that these agents provide antipsychotic efficacy with a lower risk of Extrapyramidal Symptoms (EPS) than typical antipsychotics (Haro and Salvador-Carulla, 2006). Although the use of atypical antipsychotics offers many benefits and may reduce some of the factors related to the morbidity and mortality of schizophrenia. Clozapine and risperidone atypical antipsychotic drugs appear to be associated with hyperlipidaemia that may increase the risk of atherosclerosis. The finding that atypical antipsychotics drugs such as clozapine and risperidone contribute to the development of hyperlipidaemia is supported by numerous studies (Meyer and Koro, 2004; Chrzanowski *et al.*, 2006; Kinon *et al.*, 2006; Perez-Iglesias *et al.*, 2007; Rettenbacher *et al.*, 2006; Spurling *et al.*, 2007; Su *et al.*, 2005; Wu *et al.*, 2006; De Leon *et al.*, 2007; Hasnain *et al.*, 2009). They reported that treatment with atypical antipsychotic drugs resulted in dyslipidaemia including reduced HDL-C, elevated TC, TGs and LDL-C. Also, treatment with antipsychotic medications has been shown to increase the prevalence of cardio-metabolic problems among patients with major mental illness (Newcomer and Haupt, 2006; Yumru *et al.*, 2007; Le Noury *et al.*, 2008; Newcomer, 2007). Moreover, a number of epidemiological studies of patients with schizophrenia have documented a higher incidence of cardiovascular disease than in the general population and patients with schizophrenia may be at an elevated risk for cardiovascular disease even in the absence of antipsychotic treatment (Casey *et al.*, 2004; Goff *et al.*, 2005; Newcomer, 2006). According to the literature, this may likely be due to higher rates of unhealthy lifestyle, obesity, lipid abnormalities, diabetes mellitus, hypertension, physical inactivity, poor compliance, smoking (Casey *et al.*, 2004; Brown *et al.*, 2000; Meyer, 2003) and micronutrient deficiency especially selenium with associated immune deficiency in this population (Ariola and Idonije, 2009; Idonije *et al.*, 2009; Ganiyu *et al.*, 2010). Compared with the General population, life expectancy in patients with schizophrenia is shorter by as much as 20%, attributable to higher rates of suicide, accidental deaths and natural causes such as cardiovascular disease, infectious disease and endocrine disorders (Harris and Barraclough, 1998; Newman and Bland, 1991). The life expectancy can also be further threatened by lipid disorders and increased atherogenic indeces as reported in this study. Weight gain associated with atypical antipsychotic drug treatment may explain dyslipidaemia, but this lipid disturbance may occur independent of weight gain (De Leon *et al.*, 2007; Birkenaes *et al.*, 2008).

The occurrence of dyslipidaemia and increased atherogenic indeces reported in this study are observed to be worse with risperidone than clozapine. The risk of dyslipidaemia in many other studies however appears to be higher with clozapine than with risperidone (Casey *et al.*, 2004; Taylor *et al.*, 2005; Henderson *et al.*, 2005; Newcomer *et al.*, 2002; Scheen and De Hert, 2007; Hasnain *et al.*, 2009). In a comparative study, treatment with various antipsychotics resulted in significantly elevated TG levels in 56% of clozapine, 39% of olanzapine and 21% of risperidone-treated patients compared to none of haloperidol and 8% of fluphenazine treated patients (Wirshing *et al.*, 2002). The same study showed a reduction of HDL-C during treatment with clozapine and olanzapine, whereas total cholesterol levels were significantly lower in risperidone and fluphenazine treated patients. Although some workers reported risperidone-induced increases in TG levels of 20% (Khalili *et al.*, 2007), surprisingly, the study of Weinbrenner *et al.* (2009) reported an elevation of 600%. According to them, they were unable to detect excessive eating behavior or abnormal leptin levels or glucose metabolism. The general explanations of second-generation antipsychotic-induced metabolic disturbances implicate the antiserotonergic and antihistaminergic effects of drugs such as clozapine and olanzapine (Meyer and Koro, 2004). However, risperidone

interacts particularly with serotonin 5-HT$_{2A}$ receptors and only to a lower extent with 5-HT$_{2C}$ receptors and the drug has very low affinity to histamine H$_1$-receptors, rendering observations in the patient somewhat unexplained (Weinbrenner *et al.*, 2009).

Conclusively, dyslipidaemia may occur in schizophrenic patients even without antipsychotic treatment as shown by the basal (week 0) values in this study. Also, antipsychotic treatments may worsen the hyperlipidaemia that is associated with psychotic patients. Additional work is required to fashion out a better therapeutic approach for managing schizophrenic patients treated with atypical antipsychotics such as clozapine and risperidone because of the metabolic problems associated with these drugs.

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