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Role of metformin on clozapine induced dyslipidaemia in Wistar rats

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Background: The clinical research in the past decade has reported that most second-generation antipsychotics (SGAs) can cause serious metabolic derangement, which substantially increases the risk for type II diabetes mellitus. Several retrospective studies have shown increased in serum triglyceride in patients treated with Clozapine. SGAs induced metabolic syndrome is characterized by weight gain, hyperglycaemia, hypertension, hyperlipidaemia, glucose intolerance and insulin resistance. Metformin is currently used to treat metabolic syndrome and type II diabetes mellitus. It is therefore important to determine whether Metformin is efficacious in treating Clozapine-induced metabolic derangement like dyslipidaemia. **Objectives:** To evaluate the effect of Metformin in minimizing Clozapine induced metabolic derangement like dyslipidaemia. **Methodology**: Wistar rats weighing 180-240g either sex were divided into 3 groups of 6 rats each. Group 1 served as the control, Group 2 Treated with Clozapine 25mg/kg body weight and Group 3 Treated with Clozapine 25mg + Metformin 100mg/kg body weight for 28 days P.O. Group 2 and group 3 were treated for 28 days. **Biochemical investigations:** Retro-orbital blood was collected for Lipid profile. **Result:** Lipid profile of group 2 rats treated with Clozapine showed dyslipidaemia (TG 103.3 ±1.7mg/dl, Tc 113.7 ±1.6mg/dl). Whereas group 3 rats treated with Clozapine 25mg + Metformin showed normal lipid levels (TG 94.7±1.7mg/dl, TC 102.8 ±0.8 mg/dl) comparable to group 1(TG 93.0 ±2.6mg/dl, TC 103.7 ±1.5mg/dl). C**onclusion:** This study exploring the use of Metformin to prevent metabolic derangement like dyslipidaemias in patients of schizophrenia treated with Clozapine.

KEYWORDS: *Clozapine; Metformin; Dyslipidaemia*

INTRODUCTION

In recent years Second generation antipsychotics (SGAs) are effective pharmacotherapeutic agents for various neuropsychiatric diseases, especially Schizophrenia, but also for bipolar disorder, autism, as a add on therapy in many major depressive disorders and are used by millions of patients in the world [1]. The major advantage of these drugs is that they are less likely to cause neurologic side effects. The neurologic side effects of first-generation antipsychotics (FGAs) are due to potent dopamine D2 receptor blockade and are important limiting factors for long term use of these agents [2]. The second-generation antipsychotics (SGAs) are currently more prescribed due to lack of these neurological side effects. SGAs act both $5HT_2$ and are weak D2 blocker. In addition, they have alpha adrenergic blocking, anticholinergic and H1 antihistaminic activity. However, the clinical research in past decade has reported that most SGAs can cause serious metabolic adverse

effects like dyslipidaemia, resulting in a metabolic syndrome that substantially increases the risk for cardio-metabolic disorders, such as type II diabetes mellitus and cardiovascular diseases [3]. Several studies have reported that there is increased loss of life in patients with Schizophrenia. Besides, they have higher risks for cerebrovascular illnesses, respiratory disorders and mortality from suicide. However, the most common reason for death suggested to be cardiovascular disorders [4]. With widespread use of these drugs, the metabolic adverse effects of antipsychotics are a major public health problem and there is a great need for a better understanding for their management. Consistent with the literature on type II diabetes mellitus, some success has been obtained through lifestyle changes, including exercise and dietary modifications [5]. However, these changes may be more challenging in the psychiatric population [6], therefore the mainstay of treatment remains the use of antidiabetic drug like Metformin to minimise or to ameliorate metabolic derangement like dyslipidaemia. Metformin is being currently used to treat metabolic syndrome and type II diabetes mellitus. Metformin acts through diverse pharmacological mechanisms. Metformin has been demonstrated to reduce the incidence of type 2 diabetes mellitus by 31% compared to control subjects who received placebo [7]. The present study proposes that reduced progression from pre-diabetes to diabetes should be a treatment goal for patients with Schizophrenia treated with SGAs. Regular use of Metformin would be expected to lower the progression rate to a considerable extent. It is therefore important to determine whether Metformin is efficacious in treating SGAs induced metabolic derangement like dyslipidaemia. Therefore, the present study is undertaken to evaluate the effects of Metformin on metabolic derangement like dyslipidaemia caused by Clozapine, a SGA drug in a rat model [8].

Study design: An Experimental animal-based study.

Ethics approval: The study was reviewed and approved by the Institutional Animal Ethics Committee (IAEC)vide letter reference number; 665/15, dated 07.12.2015. Study was carried out as per guidelines of Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA).

Locus of study: BLDEU’s Shri B.M. Patil Medical College Hospital &Research Centre, Vijayapur.

Sample size: 18 Wistar rats

Sex: Either

Drugs used: **Clozapine:** It was procured from Rajesh Chemicals co. Mumbai. The dose used was 25mg / kg/ day orally. It was dissolved in dilute acetic acid.

Metformin: It was obtained from Rajesh Chemicals co. Mumbai. The dose used was 100mg / kg/ day orally. It was dissolved in distilled water.

Methodology: Wistar rats weighing 180-240g either sex bred from a stock obtained from the Central Animal House, BLDEU’s Shri BM Patil Medical College Hospital & Research Centre, Vijayapur, were used in the study. Animals were housed in separate room 3 each in polypropylene cages for one week acclimatization before the start of the study. The cages were lined with paddy husk which was replaced every day and animals were kept under standard condition of illumination with a 12 - h light-dark cycle at room temperature of 25 ± 1° C and 45-70% relative humidity. The animals were fed with commercial pellet rat chow (manufactured by VRK Nutritional solutions, Sangli, Maharashtra) and water ad libitum.

Dose calculation: Rat dose per day is calculated using average human dose/day and converted into rat dose using following formula: Rat dose/200g = human dose x 0.18.

Grouping of animals, dose of drug and route of administration:

Animals will be divided into 3 groups of six rats each, each group having equal number of male and female rats.

Group 1: Control (n=6) was given distilled water p.o

Group 2: Received Clozapine (n=6)25mg/kg p.o[9]

Group 3: Received Clozapine25mg/kg + Metformin 100mg/kg p.o[10]

All animals had access to food and water *ad libitum*.

Dyslipidaemia: Group 2 rats treated with Clozapine for 28days to produce dyslipidaemia. Whereas group 3 rats treated with Clozapine 25mg + Metformin 100mg/kg per P.O. for 28days.

Sample collection: Retro-orbital blood was collected for Lipid profile.

Parameters studied: Triglycerides, Total Cholestrol, HDL, LDL, VLDL by auto analyser method

Statistical analysis: All the values have been expressed as the mean ± SEM and analysed by one-way analysis of variance (ANOVA) in order to test differences between groups. The level of statistical significance has been set at $p<0.05$.

RESULTS

Table 1 and Figure 1 shows that Group 2 (Clozapine treated rats) showed statistically significant increase in serum levels of Triglycerides, Total cholesterol, LDL and VLDL levels compared to those in normal control group over study period.

Administration of Clozapine along with Metformin in Group 3 (Clozapine + Metformin treated rats) there was no such statistically significant increase and was comparable to those rats in untreated control group.

Lipid profile	Days	Control	Clozapine	Clozapine + Metformin	ANOVA p value
		Mean±SEM	Mean±SEM	Mean ±SEM	
Triglyceride (mg/dl)	0 day	91.5±2.6	92.8±1.9	92.0±1.9	0.906
	28 day	93.0±2.6	103.3±1.7	94.7±1.7	0.006*
Total cholesterol (mg/dl)	0 day	101.0±1.4	101.5±0.6	101.7±0.6	0.878
	28 day	103.7±1.5	113.7±1.6	102.8±0.8	<0.001*
HDL (mg/dl)	0 day	29.8±0.7	29.3±0.3	28.8±0.5	0.427
	28 day	31.7±1.1	31.0±0.4	30.3±0.6	0.444
LDL (mg/dl)	0 day	52.9±1.7	53.6±0.6	54.4±1.0	0.648
	28 day	53.4±1.8	62.0±1.7	53.6±0.6	0.001*
VLDL (mg/dl)	0 day	18.3±0.5	18.6±0.4	18.4±0.4	0.906
	28 day	18.6±0.5	20.7±0.3	18.9±0.3	0.006*

Table 1. *Change in mean lipid profile among study groups according to time* (Note: *means significant at 5% level of significance (p<0.05))

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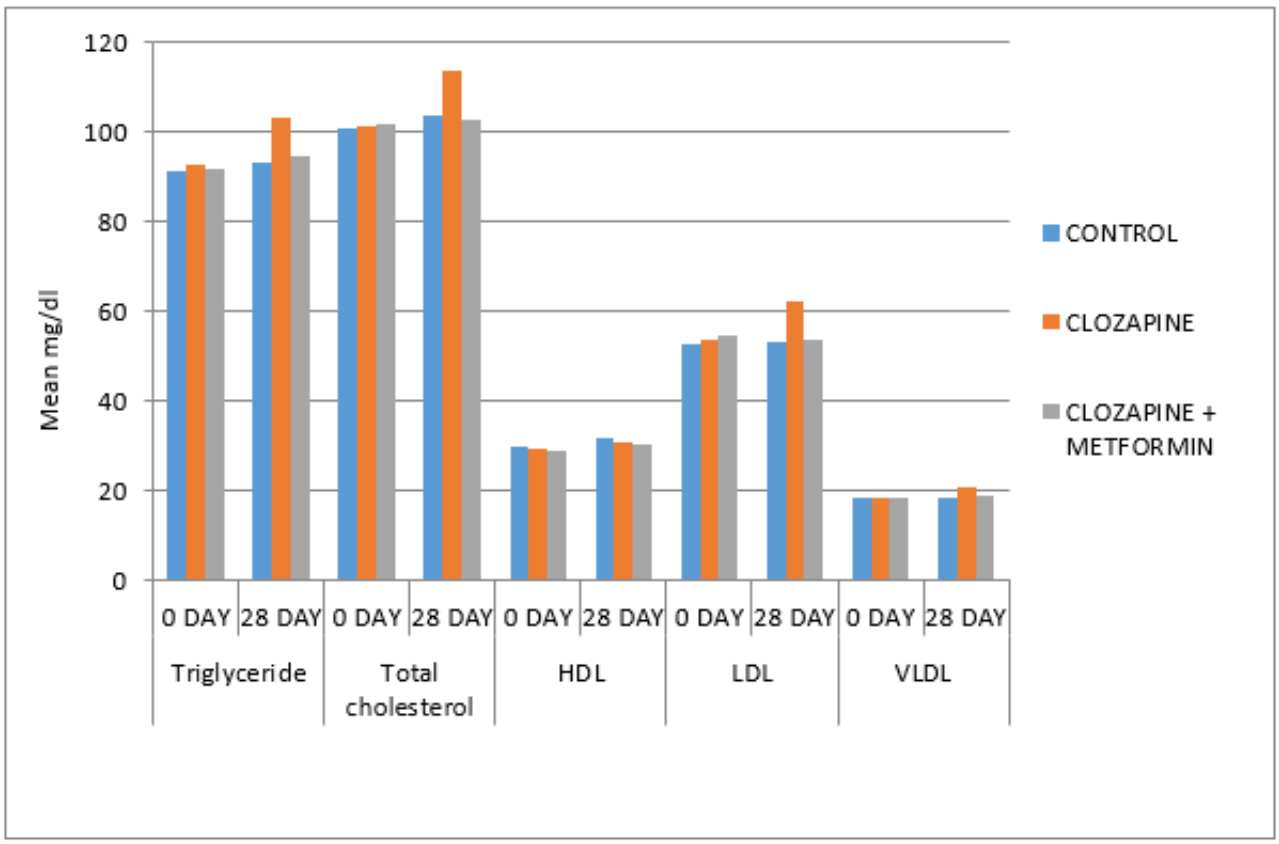

Figure 1. *Change in mean lipid profile among study groups according to time*

DISCUSSION

Major psychosis, Schizophrenia is characterised by its chronicity, disordered behavioral function and disturbed emotions and thinking. Availability of effective antipsychotic drugs has considerably improved the outcome. Older or first-generation antipsychotic drugs have been used for years. But undesirable effects like disorders of movements have been major limiting factor.

This resulted in development of newer more effective and safe drugs like Clozapine. However, they are also not completely free from adverse effects like metabolic derangement on long term use. This metabolic derangement can be reversed by simultaneous administration of drug like Metformin.

The incidence of diabetes mellitus has been shown to be increased in patients treated with SGAs in comparison with general population [11]. Several retrospective studies shown increased in serum triglyceride in patients treated SGAs like Clozapine[12].SGAs drugs induced metabolic syndrome is characterized by weight gain, hyperprolactemia, hyperlipidaemia, hyperglycaemia, glucose intolerance, hypertension cardiovascular disease and insulin resistance [13]. For the patients who are taking Clozapine, the risk of developing type 2 diabetes during the first 6 years is greatest. It has been reported that among the patients who took Second generation antipsychotic like Clozapine more than 50% become overweight [14]. Treatment with Clozapine was associated with an average weight gain of 9.8lb over 10weeks which is as high as any other antipsychotics[10]. In one of the studies the prevalence of metabolic syndrome has been found to be as high as 24.6% [15]. Metabolic syndrome is also predictive of both cardiovascular diseases and type 2 diabetes mellitus. This may lead to early death [14].These metabolic changes are seen regardless of age, sex or duration of antipsychotic therapy [16-17].

In our study there was a statistically significant increase in serum levels of TG, TC, LDL and VLDL in Group 2 compared to group 1. whereas in Group 3(treated with Clozapine + Metformin) there was no significant increase in TG, TC, LDL and VLDL similar results have been reported by Chen C et al (2013), He studied effects of adjunctive Metformin on metabolic derangement in non-diabetic schizophrenic patients treated with Clozapine and found that Metformin significantly reversed the metabolic derangement particularly due to its effect on triglycerides caused by Clozapine. Metformin also reduced body weight significantly. However, beneficial effect of Metformin on body weight in Clozapine treated patients disappeared on discontinuation of Metformin. Metformin is well tolerated by these patients. Thus, it supports the strategy for long term Metformin supplementation in Clozapine treated patients with Schizophrenia and pre-existing metabolic abnormalities [18].

In our study there was no significant change in serum HDL levels and these are also similar with study conducted by Ozenoglu et al [19] and he also did not report any significant changes in serum levels of HDL.

CONCLUSION

The results of this study suggest that Metformin reverses the metabolic derangement like dyslipidaemia caused by Clozapine in Wistar rats. This raises the possibility that Metformin supplementation can be considered to improve metabolic derangement like dyslipidaemia in treated with Clozapine. Careful monitoring of risk patients may help in the prevention of metabolic derangements as well as the management of any possible symptoms which they occur.

Limitations: Further studies are required to confirm the more beneficial effects of Metformin in the patients who are treated with Clozapine.

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