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Investigation of Comparative dose study of Olanzapine as chemically induced Preclinical model for Cardio Metabolic Syndrome in Rats

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ABSTRACT

The second generation antipsychotic (SGA) drugs are widely used in psychiatry due to their clinical efficacy and low incidence of neurological side-effects. However, many drugs in this class cause deleterious metabolic side-effects. Olanzapine, second generation antipsychotic mimics the clinical features in animals such as weight gain associated hyperphagia, increased feeding efficiency, adiposity and altered locomotor activity and satiety signaling in 28 days. The purpose of the present study was to evaluate a comparative dose study of Olanzapine as chemically induced preclinical model for cardio metabolic syndrome in rats. In the present study, Sprague Dawley rats were randomly allocated. Olanzapine doses were selected for: 1mg/kg i.p. (o.i.d) (OLZ-D 1mg/kg) & 15 mg/kg i.p. weekly (OLZ-W 15mg/kg). After 0th day , 2nd week , 3rd week & 4th week , following parameters were assessed - Body weight, mean blood pressure and QTc interval, while in serum sample - glucose , oral glucose tolerance test (OGTT) , total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL),. One way analysis of variance (ANOVA) followed by post-hoc Dunnett's test was performed for statistical analysis with p<0.05 set as statistical significance. In the group of animals challenged only once per week with Olanzapine OLZ-W 15mg/kg, the metabolic side-effects significantly intensified with the passage of time as compared to group of animals challenged daily with Olanzapine OLZ-D 1mg/kg.

KEYWORDS: *Cardiometabolic syndrome, Olanzapine.*

INTRODUCTION

Cardio Metabolic Syndrome, so-called "*deadly quartet*" – a clinical entity of substantial heterogeneity, represented by the co-occurrence of overweight (obesity), high blood pressure, elevated insulin level and lipid metabolism disorder [5].

Epidemiologists in India and International agencies such as the world health organization (WHO) have been sounding an alarm on the rapidly rising burden of cardio metabolic syndrome for the past 10 years. Developed countries like Australia, Europe and America with 48.2 %, 30 – 80 % and 35 % respectively are highly prevalent in hub of cardio metabolic syndrome. [1]But the data doesn't stop at developed countries.

Similar to developed countries, the prevalence is rapidly increasing in developing countries, reflecting the transition from a traditional to a western-like lifestyle : demographic transition (shift to low fertility, low mortality, and higher life expectancy), and epidemiological transition (from widely prevalent infectious diseases to a pattern of a high prevalence of lifestyle related diseases) evolved in developing countries as they become economically more resourceful, leading to significant shifts in dietary and physical activity patterns resulting in cardio metabolic syndrome [3].

In India, Cardio metabolic syndrome is responsible for 2/3rd of the total morbidity burden and about 53% of total deaths (up from 40.4% in 1990 and expected to increase to 59% by 2015) [4]. According to predictions, by 2030 cardio metabolic syndrome will account for almost three quarters of all deaths in India [4].

Estimates concerning the costs incurred yearly in the developed countries by direct expenses and indirect costs through loss of productivity by polypharmacy therapy account for 40 % of their budget-and this is increasing [2]. Whereas, India is losing more than 6% of its GDP annually due to premature deaths and preventable illnesses, according to a World Bank 2010 report [4].

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Oodles of epidemiological studies depict that cardio metabolic syndrome is not only a global burden but also an economic burden.

The widespread occurrence of metabolic syndrome in humans means that there is an urgent need to study relevant causes and progression of the signs. In light of the above facts, the objective of the present investigation is: To evaluate the effect of Olanzapine as preclinical model for inducing cardio metabolic syndrome in rats.

The second generation antipsychotic (SGA) drugs are widely used in psychiatry due to their clinical efficacy and low incidence of neurological side-effects. However, many drugs in this class cause deleterious metabolic side-effects. Olanzapine (0.2mg/kg – 15mg/kg) mimics the clinical features in animals such as weight gain associated hyperphagia, increased feeding efficiency, adiposity and altered locomotor activity and satiety signaling in 28 days [10].

Olanzapine, H_1 antagonism play key role in weight gain since it mediates the orexigenic effects of AMP kinase, an enzyme involved in regulating food intake, while reversing the actions of leptin, an anorexigenic hormone [6].

Oodles of research studies have proved that Olanzapine attenuate insulin signaling pathway, decreased protein levels of IRS2 and of the insulin signaling and glycogen synthesis, diminishing insulin-stimulated AKT and GSK3a/b phosphorylation [7].

RLP-C is an intermediate metabolite of triglycerides. Under normal conditions; RLP-C is metabolized very rapidly. Lipoprotein lipase activity, hepatic triglylipase activity, and remnant receptor activity are involved in the catabolism of RLP-C. All these enzyme and receptor activities are diminished in the presence of insulin resistance [8].

Tachycardia to Olanzapine treatment may be mediated via blockade of cardiac muscarinic M cholinergic, can block presynaptic a-adrenoceptors, thus may increase sympathetic activity and indirectly activate the ß-adrenoceptors in the heart to elevate HR. Furthermore, it has been suggested that tachycardia may be induced via the baroreceptor reflex [9].

MATERIALS AND METHODS

Material:

Drugs and preparation of solutions:

Olanzapine pure powders were obtained from pharmaceutical suppliers. Olanzapine solution was prepared freshly

everyday by suspending the drug in 1% Carboxymethyl Cellulose (CMC) suspension. All the chemicals used in this project were of analytical grade and were obtained from Astron chemicals, Ahmedabad and SD fine chemicals, Mumbai.

All the biochemical tests were performed using the standard kits purchased from Coral chemical systems, Goa. Phenobarbital ampoules were purchased from krupa medical store, Anand.

Animals:

Healthy male Sprague Dawley rats of 6-8weeks weighing 150 ± 30 were used for the study. The animals were housed in a group of 3 rats per cage under well-controlled conditions of temperature (22 ± 2°C), humidity (55 ± 5%) and 12hrs/12hrs light-dark cycle. Animals had free access to conventional laboratory diet and tap water *ad libitum*.

The protocol of the experiment was approved by Institutional Animal Ethical Committee as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. (Protocol No: APC/2013-IAEC/1320)

METHODS:

Experimental procedure:

Induction of cardio metabolic syndrome by Olanzapine:

In the present study, Animals were randomly allocated based on serum cholesterol levels in 2 groups with n=6 animals.

Olanzapine doses were selected for:

1mg/kg i.p. (o.i.d) (OLZ-D 1mg/kg) [10].

15 mg/kg i.p. weekly (OLZ-W 15mg/kg) [11].

Collection of Biological sample: Blood for various biochemical parameters: [12-15]

On 0th day, 2nd and 4th week, blood was collected retro-orbitally under anesthetic conditions and animals were sacrificed by Phenobarbital anesthesia. Serum was separated by centrifugation at 3000 rpm for 15 min and was then analyzed for various biochemical parameters.0n 0th day and 4th week, OGTT were assessed.

Blood pressure & corrected QT interval: [16, 17]

The blood pressure & corrected QT interval was measured using Biopac Student Lab (MP-36 Biopac Systems, Inc).

Statistical Analysis: [18]

Results were presented as mean ± SEM. Statistical analysis of various biochemicals parameters were carried out using the one way analysis of variance (ANOVA) followed by Dunnett's post hoc test. Data were considered statistically significant at P≤0.05.

RESULTS AND DISCUSSION

OLZ-W 15mg/kg 2nd & 4th week showed a significant (P<0.05) elevation in blood glucose, total cholesterol, total triglyceride and low density lipoprotein as compared to 2nd & 4th week of OLZ-D 1mg/kg.Whereas 4th week OLZ-W 15mg/kg animals showed significant (P<0.05) elevation in blood glucose, total cholesterol, total triglyceride and low density lipoprotein as compared to the 0th day OLZ-W 15mg/kg animals. There was no significant differences were found in high density lipoprotein of OLZ-D 1mg/kg & OLZ-W 15mg/kg animals.

A significant (P<0.05) elevation was found in blood glucose level of OGTT at 0 min, 30 min, 60 min, 90 min of OLZ-W 15mg/kg as compared to OLZ-D 1mg/kg animals & 4th week OLZ-W 15mg/kg animals exhibit increased in blood glucose level as compared to 0th day OLZ-W 15mg/kg animals.

Percentage change in weight of 2nd, 3rd & 4th week of OLZ-D 1mg/kg & OLZ-W 15mg/kg were significantly (P<0.05) higher compared to that 0th day of OLZ-D 1mg/kg & OLZ-W 15mg/kg animals. Whereas 4th week OLZ-W 15mg/kg animals showed significant elevation in Percentage change in weight as compared to the 0th day OLZ-W 15mg/kg animals.

There was a significant increase in blood pressure & QT_c at 4th week of OLZ-W 15mg/kg as compared to 4th week of OLZ-D 1mg/kg animals. OLZ-W 15mg/kg 4th week showed significant elevation in blood pressure & QT_c as compared to initial period of study of OLZ-W 15mg/kg animals.

Table No. 1: Effect of Olanzapine on Biochemical parameters

Period of Study	Glucose(mg/dl)		Cholesterol(mg/dl)		TG(mg/dl)				HDL-C(mg/dl)	
	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg
0th day	142.45 ±2.67	140.45 ±1.19	130.67 ±2.5	155.73 ±2.65	100 ±3.7	117.61 ±3.9	34.89 ±2.6	39.12 ±2.9	95.04 ±2.7	90±1.6
2nd week	156.89 ±3.89	235.17 ±7.29*	135.56 ±2.5	168.4 ±3.5*	114.89 ±3.8	140.04 ±2.8*	35.89 ±2.9	43.82 ±2.9	99±1.9	110.78 ±1.9*
4th week	170.89 ±1.78	270.45 ±5.34**§	135.67 ±2.6	185.62 ±1.61**§	120 ±3.5	170.64 ±2.9**§	38.9 ±2.6	46.7 ±2.7	107.9 ±2.8	130.9 ±2.8**§

Table No. 2: Effect of Olanzapine on OGTT

Period of Study	0 min		30 min		60 min		90 min	
	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg	OLZ-D 1mg/kg	OLZ-W 15mg/kg
0th day	120.89±3.5	143.69±1.9*	128.9±2.7	169.7±3.4*	130.9±1.7	184.03±1.5*	143.78±2.3	218.69±1.6*
4th week	138.09±3.6	167.36±1.7*§	140.78±3.2	234.14±3.8*§	145.89±2.9	214.91±1.8*§	149.65±1.7	254.88±2.7*§

Table No. 3: Effect of Olanzapine on Percentage change in weight

Percentage change in Weight (%)		
Period of Study	**OLZ-D 1mg/kg**	**OLZ-W 15mg/kg**
1st week	7±2.01	6±2.1
2nd week	14±1.4§	15±3.01§
3rd week	20±2.4§	28±2.9§
4th week	30±1.5§	46±2.7**§

Table No. 4: Effect of Olanzapine on Blood Pressure

Blood Pressure (mmHg)				
	0th day	**1st week**	**3rd week**	**4th week**
OLZ-D 1mg/kg	110.09±1.6	125.085±2.002§	144.85±1.08§	165.23±2.67**§
OLZ-W 15mg/kg	120.56±3.09	126.04±2.19	137.78±2.9	140.45±3.4§

Table No. 5: Effect of Olanzapine on QTC Interval

	QTC interval (msec)	
	OLZ-D 1mg/kg	**OLZ-W 15mg/kg**
0th dy	0.3295±1.54	0.3869±0.03
2nd week	0.3459±0.06	0.4412±0.06
4th week	0.3505±0.01	0.543±1.13*§

Values are represented as Mean ± SEM; The statistical analysis was carried out by one way ANOVA (repeated measures); § Significantly different from 0th day at p<0.05; * Significantly different from OLZ-D 1mg/kg at p<0.05

SUMMARY & CONCULSION

In the group of animals challenged only once per week with Olanzapine OLZ-W 15mg/kg, the metabolic side-effects significantly intensified with the passage of time as compared to group of animals challenged daily with Olanzapine OLZ-D 1mg/kg.

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REFERENCES:

1. Vanita P & Jhansi K. Metabolic Syndromes in Endocrine System, *J. Diabetes Metab.,* **2011**; 2: 163-165.
2. Diabetes Atlas, International Diabetes Federation, **2003**.
3. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries, J. Clin. Endocrinol. Metab., **2008**; 93: S9-30.
4. Patel V, Chatterji S, Chisholm D, Ebrahim S, Gopalakrishna G, Mathers C, et al, Chronic diseases and injuries in India, *Lancet,* **2011**; 377: 413-28.
5. Meigs JB, Am J, Manag Care. Epidemiology of the metabolic syndrome, **2002**; 8: S283-292.
6. Halise Devrimci Ozguven, Bora Baskak, Ozgur Oner and Cem Atbasoglu. Metabolic Effects of Olanzapine and Quetiapine: A Six-Week Randomized, Single Blind, Controlled Study, *The Open Neuropsychopharmacology Journal,* **2011**; *4:* 10-17.
7. V. Mondelli. Haloperidol and Olanzapine mediate metabolic abnormalities through different molecular pathways, *Transl. Psychiatry*, **2013**; 3: e208.
8. Takahiko Nagamine. Effects of risperidone and Olanzapine on remnant-like lipoprotein particle cholesterol (RLP-C) in schizophrenic patients, *Neuropsychiatric Disease and Treatment,* **2008**; 4(2): 481–486.
9. Joanne Y.T. Leung. Cardiovascular side-effects of antipsychotic drugs: The role of the autonomic nervous system, *Pharmacology & Therapeutics*, **2012**; 135: 113–122.
10. Petchi, *et al*., Effects of Curcumin and Telmisartan on Olanzapine and high fructose diet induced Metabolic Syndrome in Sprague Dawley Rats, *Pharmacognosy Journal,* **2012**; 4(30): 26-29.
11. Boyda HN, et al., Intermittent treatment with Olanzapine causes sensitization of the metabolic side-effects in rats, Neuropharmacology, **2012**; 62(3): 1391-400.
12. Parasuraman S, Raveendran R, Kesavan R. Blood sample collection in small laboratory animals, *J. Pharmacol. Pharmacother.,* **2010**; 1: 87-93.
13. P. Trinder. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor, Ann. Clin. Biochem., **1969**; 6: 24-7.
14. Trinder P, Webster D. Determination of HDL-cholesterol using 2, 4, 6- tribromo-3-hydroxybenzoic acid with a commercial CHOD-PAP reagent, *Ann. Clin. Biochem.,* **1984**; 21: 430.
15. Sullivan D, Kruijswijk Z, West C, Kohlmeier M, *et al.*, Determination of serum triglycerides by an accurate enzymatic method not affected by free glycerol, *Clin. Chem., **1985***; 31: 1227-1228.
16. Gupta S. Dietary Curcuma longa protects myocardium against isoproterenol induced hemodynamic, biochemical and histopathological alternations in rats, *International J. Applied Research in Natural Products*, **2008**; 1(4): 19-28.
17. S. Hwang, H. Hoaug, B. B. Hoffman and G. M. Reaven. Fructose-induced insulin resistance and hypertension in rats, *Hypertension*, **1987**; 10: 512-6.
18. Lang J, Bolton S. A comprehensive method validation strategy for bioanalytical applications in the pharmaceutical industry-2 Statistical analyses, *J. Pharma. Biomed. Analy.*, **1991**; 9(6): 435-42.

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