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Research article

A COMPARATIVE STUDY OF ORAL OLANZAPINE AND ORAL HALOPERIDOL ON GLUCOSE TOLERANCE LEVELS IN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

Background: Schizophrenia is a mental disorder characterized by persistent defects in the perception, thinking or the expression of reality. The term "schizophrenia" translates roughly as "shattered mind," and comes from the Greek (schizo, "to split" or "to divide") and (phrēn, "mind"). **Material and Methods:** The study was designed to be a prospective control study. Schizophrenic patients taking Olanzapine and Haloperidol were selected and follow up at three weeks and six weeks was done. **Results**: In this prospective control study, Olanzapine and Haloperidol were associated with an increase in Blood Glucose Levels. The mean changes in Glucose remained within clinically normal range in this six week study. **Conclusion:** Antipsychotic treatmemt leads to the development of Diabetes mellitus in a significant 10.1% of patients within 6 weeks. Given the serious implications for morbidity and mortality attributable to diabetes mellitus, clinicians need to be aware of these risk factors when treating patients with chronic schizophrenia

Keywords: Schizophrenia, Olanzapine, Haloperidol, Blood Glucose levels

INTRODUCTION

Schizophrenia is often described in terms of "positive" and "negative" symptoms. Positive symptoms include delusions, auditory hallucinations and thought disorder and are typically regarded as manifestations of psychosis. Negative symptoms are so named because they are considered to be the loss or absence of normal traits or abilities, and include features such as flat, blunted or constricted affect and emotion, poverty of speech and lack of motivation. Some models of schizophrenia include formal thought disorder and planning difficulties in a third group, a "disorganization syndrome."[1]

The most commonly used criteria for diagnosing schizophrenia are from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD). The most recent versions are ICD-10. [2]

Cause: Genetic: Some researchers estimate schizophrenia to be highly heritable (some estimates are as high as70%). Environmental [3]. There is also considerable evidence indicating that stress may trigger episodes of schizophrenia psychosis.

Neurobiological influences: Role of dopamine: In adult life, particular importance has been placed upon the function (or malfunction) of dopamine [4] in the mesolimbic pathway in the brain. This theory, known as the dopamine hypothesis of schizophrenia, largely resulted from the accidental finding that a drug group which blocks dopamine function, known as the phenothiazines, reduced psychotic symptoms. These drugs have now been developed further and antipsychotic medication is commonly used as a first line treatment. Role of glutamate and the NMDA receptor: Interest has also focused on the neurotransmitter glutamate and the reduced

function of the NMDA glutamate receptor in the development of schizophrenia.

Treatment: Medication and hospitalization

The first line treatment for schizophrenia is usually the use of antipsychotic medication. Therefore, antipsychotic drugs are only thought to provide symptomatic relief from the positive symptoms of psychosis. The newer atypical antipsychotic medications [5] (such as clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole) are usually preferred over older typical antipsychotic medications (such as chlorpromazine and haloperidol) due to their favourable side-effect profile. While the atypical antipsychotics[3] are associated with less EPS and TD than the conventional antipsychotics, some of the agents in this class (especially olanzapine and clozapine) appear to be associated with metabolic side effects [6] such as weight gain, hyperglycemia and hypertriglyceridemia that must be considered when choosing appropriate pharmacotherapy.

Drugs: Haloperidol is a butyrophenone [7] with general properties similar to those of the phenothiazine, cholorpromazine. It is an antipsychotic with actions most closely resembling those of phenothiazines with a piperazine side-chain.

Olanzapine is a thienobenzodiazepine atypical antipsychotic. It has affinity for serotonin, muscarinic, histamine-H_1 and adrenergic (a_1) receptors as well as various dopamine receptors.

Olanzapine is used for the management of schizophrenia and for the treatment of moderate to severe mania associated with bipolar disorder.

Olanzapine may share some of the adverse effects seen with the classical antipsychotics, the incidence and severity of such effects may vary. The most frequent adverse effects with Olanzapine are somnolence and weight gain; hyperprolactinaemia is also common, but usually asymptomatic. More severe abnormalities of glucose homeostasis [8] occur uncommonly; severe hyperglycaemia, or exacerbation of pre-existing diabetes, sometimes leading to ketoacidosis or coma, has been reported. Clinical monitoring for hyperglycaemia [9] has been recommended, especially in patients with or at risk of developing diabetes. Olanzapine has been associated with a low incidence of extrapyramidal symptoms including tar dive dyskinesia although extrapyramidal symptoms may be more likely at high doses. Neuroleptic malignant syndrome has been reported rarely. [10]

Lambert BL [11] states that exposure to olanzapine is associated with a 34-41% increase in the developing of type 2 diabetes among recipients with schizophrenia and compared with older generation antipsychotics, exposure to olanzapine is associated with an increased risk of hyperlipidemia among people with schizophrenia. Still prospective, randomized trials are needed to confirm these retrospective, observational finding.

MATERIALS AND METHODS

A prospective study was conducted in the Psychiatry department at Institute of Mental Health, Chennai on patients admitted between October, 2005 to January, 2006. Patients who were newly started on Olanzapine and Haloperidol and those who had been antipsychotic free for the last six months formed the sample of the study. The Olanzapine group had 38 patients and Haloperidol group had 25 patients.

Inclusion Criteria: Outpatient/Inpatient in Psychiatry department, Age 20 – 60 years, Patient Sex-Male and Female Diagnosed by ICD-10 for Schizophrenia, Patients taking oral Olanzapine 5-20 mg/day or Haloperidol 5-20 mg/day., Patients who had given informed consent.

Exclusion Criteria:. Patients with other Mental illness like bipolar mood disorders, Patients on substance abuse or alcohol abuse, Pregnant or lactating patients

Procedure: The study was a naturalistic study; patients were diagnosed by the Consultant Psychiatrist as suffering from Schizophrenia according to ICD-10 [2].Informed consent was taken from all the patients. Treatment was started and monitored by a psychiatrist. The patients were either started on Haloperidol or Olanzapine based on the psychiatrist's opinion. Patients could continue taking their concomitant drugs like Benzhexol, Benzodiapines, and Multivitamins and anti hypertensives.

After taking informed consent, a semi structured proforma was used to collect information about relevant socio demographic data details about family history and previous medical history.

The duration of the study was six weeks. During the study cases took only one antipsychotic drug i.e. oral

Olanzapine and controls took oral Haloperidol along with their concomitant treatment.

After the patients fulfilled the inclusion criteria, Random Plasma Glucose was taken before the start of treatment patients who had above normal random blood glucose (Normal RBS-120-140 mg/dl.) were not taken into the study.

After the patient was started on an antipsychotic i.e. in the first week, Blood was taken for Fasting Blood Glucose and Post Prandial blood glucose. When the patient came for review after three weeks and again after six weeks fasting blood glucose and post prandial blood glucose was taken. At each visit 2ml Blood was taken under aseptic conditions. From the blood sample sent to the laboratory, serum was separated immediately after clotting.

Fasting blood glucose and post prandial blood glucose was estimated by standardized enzymatic procedure (applying glucose oxidase – peroxidase method). Enzymatic method yields maximum specificity for the procedure. From the blood sample sent to the laboratory, serum was separated immediately after clotting. Samples were used on the same day. Haemolysed or grossly contaminated samples were not used.

The following reference values were used in the Laboratory.

Random Blood Sugar = 120 – 140 mg/dl.
Fasting Blood Sugar = 60 – 90 mg/dl.
Post prandial blood sugar = 140 – 160 mg/dl.

RESULTS

Basic Description of Data: A total of seventy patients who satisfied the inclusion criteria and who signed the consent form were selected for the study. Seven patients were lost in the follow up. The remaining sixty three patients constituted the main study group. The Olanzapine study group had 38 subjects (n=38) and the Haloperidol control group had 25 subjects (n=25).

The mean age of study group was 34.5 ± 9.9 years. The mean age of Olanzapine group was 33.1 ± 9.8 and the Haloperidol group was 35.6 ± 10 years(Table I). The Olanzapine group had Male 22 (57.9%) and female 16 (42.1), Haloperidol group had male 11 (44%) and female 14 (56%). The Olanzapine group had 5 subjects (13.2%) with family history of Diabetes Mellitus and Haloperidol group had 5 subjects (20%) with family history of Diabetes Mellitus. There was no statistical difference with regard to family history of Diabetes Mellitus between the two groups. When Chi square test was done, p was 0.500 (P<0.05 it is significant). Most of the subjects belonged to low socio-economic status (83.3%) and the rest middle socio-economic status (16.7%). The most common diagnosis was Paranoid Schizophrenia; in the Olanzapine group Undifferentiated Schizophrenia (18.4%), Paranoid Schizophrenia (55.3%) and chronic schizophrenia (26.3%). In the Haloperidol group undifferentiated schizophrenia (2%), Paranoid Schizophrenia (68%) and Chronic Schizophrenia (24%).

The mean dose of Olanzapine used was 13± 4.7 mg/day and the mean dose of Haloperidol that was used in the study was 14 ± 3.2 mg/day.

Table 1: Comparison Between Olanzapine and Haloperidol Groups (Baseline Characteristics) Student Independent't' Test

	Olanzapine Mean ±SD (n=38)	Haloperidol Mean ± SD (n=25)	p Value
Age (Yrs.)	33.1±9.8	35.6±10.0	0.33
Height (cms.)	164.3 ±8.9	165.2 ±7.7	0.678
Weight (kgs.)	63.80±9.6	65.8 ±8.4	0.389
BM I	23.5 ± 1.7	24.1 ±2.1	0.234
Random Blood Glucose (mg/ml)	99.5 ±15.1	101.1± 23.0	0.74

P<0.05 – Significant

There is no statistically significant difference between the Olanzapine group and Haloperidol group in Age, Weight or Random Blood Sugar levels.

Regarding the Change in Fasting Blood Glucose and Post Prandial Blood Glucose between the Olanzapine and Haloperidol groups there was no statistically significant increase. The change in the Fasting Blood Glucose for the 1st and 3rd week was P=0.434, for the 1st and 6th week was P=0.805, for the 3rd and 6th week was P=0.68. The change in the Post Prandial Blood Glucose for the 1st week and 3rd week was P=0.429, 1st and 6th week was P=0.922, 3rd and 6the week was P=0.236 (Table 2)

Table2: Comparison between Olanzapine and Haloperidol groups Student Independent't' test

Blood Glucose	Time Point	Olanzapine Mean ± SD	Haloperidol Mean ± SD	P Valve
Fasting Blood Glucose	1st week	78.1 ± 17.	84.1 ± 19.2	0.211 (NS)
	3rd week	84.8 ± 17.0	88.8 ±17.2	0.372 (NS)
	6th week	88.3 ± 16.7	95.0 ± 17.9	0.132 (NS)
Increase in Fasting Blood Glucose	1st week & 3rd week	6.7 ± 7.7	4.7 ±12.8	0.434 (NS)
	1st week & 6th week	10.2 ± 7.6	10.9 ± 14.0	0.805 (NS)
	3rd week & 6th week	3.5 ± 5.7	6.2 ± 6.1	0.068 (NS)
Post Prandial Blood Glucose	1st week	108.7 ± 22.0	113.7 ± 31.9	0.465 (NS)
	3rd week	115.2 ±23.3	117.3 ± 23.7	0.728 (NS)
	6th week	121.3±23.6	126.8 ± 29.9	0.420 (NS)
Increase in Post Prandial Blood Glucose	1st week & 3rd week	6.5 ±9.7	3.6 ± 18.9	0.429 (NS)
	1st week & 6th week	12.6 ± 7.4	13.1 ±24.5	0.922 (NS)
	3rdt week & 6th week	6.1 ± 9.8	9.5±12.5	0.236 (NS)

P ≤ 0.05 Significant; NS-Non Significant

There is no statistically significant difference between Olanzapine and Haloperidol group for Fasting blood glucose and post prandial blood glucose between 1st and 3rd week, 1st and 6th week and 3rd and 6th week. Significant increase in Blood glucose was seen in the Olanzapine group. In Fasting Blood Glucose, the significant increase for 1st and 3rd week was P=0.001, for 1st & 6th week was P=0.001 and for 3rd and 6th week was P=0.003.In Post Prandial Blood Glucose the significant increase for 1st & 3rd week was P=0.001, 1st & 6th week was P=0.001 and 3rd & 6th week was P=0.001

Table3: Comparison of Blood Glucose within Olanzapine Group n=33 (between 1st, 3rd and 6th week) Students Paired't' Test

Blood Glucose (mg/dl)	Time Point	Change Mean±SD	P Valve
Fasting Blood Glucose	1st and 3rd week	6.7 ± 7.7	<0.001*
	1st and 6th week	10.2 ± 7.6	<0.001*
	3rd and 6th week	3.5 ± 5.7	0.003*
Post Prandial Blood Glucose	1st and 3rd week	6.5 ±9.7	<0.001*
	1st and 6th week	12.6 ± 7.4	<0.001*
	3rd and 6th week	6.1 ±9.8	<0.001*

*

P<0.05 – Significant

There is statistically significant difference for Olanzapine group for fasting blood glucose and post prandial blood glucose for 1st and 3rd week, 1st and 6th week and 3rd and 6th week (Table3). For Haloperidol group there was a significant increase in blood glucose. For fasting blood glucose there was no increase for 1st and 3rd week was P=0.237, the increase for 3rd and 6th week was P = 0.003, 3rd and 6th week P = <0.001. For Post Prandial Blood glucose there was no significant increase for the 1st and 3rd week P=1.000, there was significant increase for 1st and 6th week P=0.039, and 3rd and 6th week P=0.003.

Table 4: Comparison of Blood Glucose within Haloperidol, Group n =25 (between 1st, 3rd and 6th week) Student Paired't' Test

Blood Glucose (mg/dl)	Time Point	Change Mean±SD	P Valve
Fasting blood Glucose	1st and 3rd week	4.7 ± 12.8	0.237
	1st and 6th week	10.9±14.0	0.003*
	3rd and 6th week	6.2 ± 6.1	<0.001*
Post Prandial Blood Glucose	1st and 3rd week	3.6 ±18.9	1
	1st and 6th week	13.1±24.5	0.039*
	3rd and 6th week	9.5 ± 12.5	0.003*

* P<0.05 – Significant

There is statistically significant difference for Halperiodol group for fasting blood glucose and post prandial blood glucose between 1st and 6th week, and 3rd and 6th week. There is no statistically significant difference between 1st and 3rd week for fasting blood glucose and post prandial blood glucose within Haloperidol patients group (Table 4)

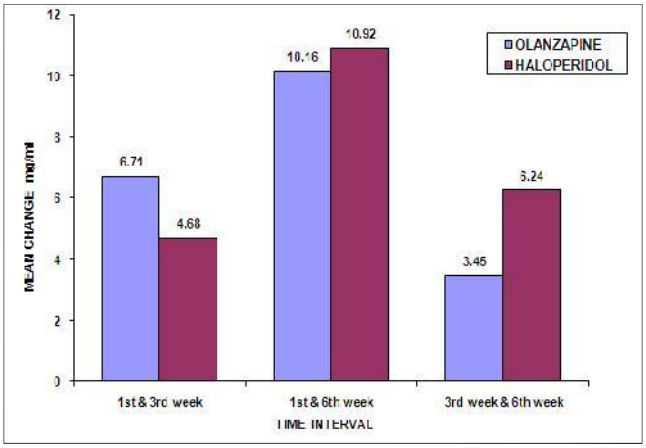

Fig1: Mean change in Fasting Blood Glucose between different time interval for Olanzapine and Haloperidol group.

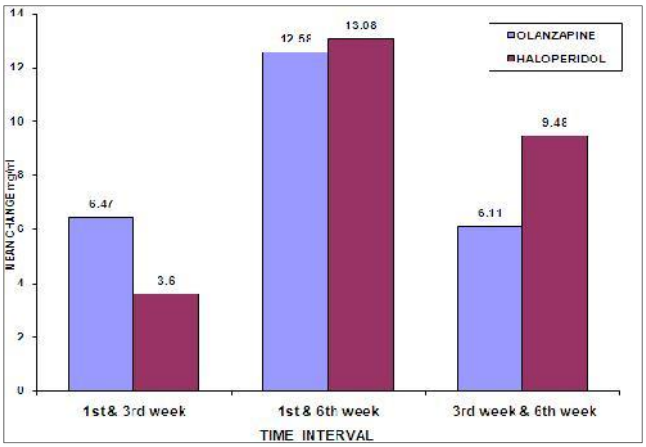

Fig2: Mean change in Post Prandial Blood Glucose between different time interval for Olanzapine and Haloperidol group.

The relevant findings of the study are

- Olanzapine produced significant increase in fasting blood glucose and Post Prandial blood glucose at 3rd week and 6th week
- Haloperidol produced significant increase in fasting blood glucose and Post Prandial blood glucose at 6th week.

When Olanzapine and Haloperidol groups were compared there was no statistically significant difference between the increase in fasting and Post Prandial blood glucose.

DISCUSSION

There is a re-emerging and controversial issue of glycaemic control in schizophrenia and its possible relationship to antipsychotic drug therapy. Obesity and physical inactivity, which are common in patients with schizophrenia, are known to increase the risk of developing diabetes. It is reported a rate of diabetes of 1.2% for persons age 18 to 44 years and 6.3% for persons age 45 to 64 years. In patients with schizophrenia, the prevalence of diabetes was 6 to 8% in patients<45 years of age, 15 to 19% in patients 45 to 64 years of age, and 19 to 21% in patients>65 years of age. [12]

Case reports have also associated atypical antipsychotic agents with exacerbation of pre-existing diabetes, new-onset diabetes and diabetic ketoacidosis (DKA). [13, 14] There are significantly more reports associated with olanzapine.

In a pharmacoepidemiological study in >58,000 patients receiving a single antipsychotic, the overall frequency of diabetes was about 3 times that found in the reference general population. This result is very similar to that found in studies to determine the rate of diabetes in patients with schizophrenia done prior to the widespread use of atypical agents.

In this report we are comparing the simultaneous effect of two antipsychotic medications on a important metabolic measure, indexing glucose in patients with schizophrenia. We found that haloperidol was associated with significantly elevated mean glucose levels after 6 week of treatment, that olanzapine was associated wtih significantly elevated glucose levels after 3 weeks of treatment. The mean increases were modest and remained within clinically normal ranges (one patient given Haloperidol developed abnormally high glucose levels >125 mg/dl during the course of study treatment). The Olanzapine-treated groups had significant elevations in post prandial glucose levels when compared with haloperidol-treated patients. Among antipschotics, Olanzapine seems to have diabetogenic potential when measured from baseline to endpoint. Haloperidol fares better. [15, 16]

In our study, the typical antipsychotic haloperidol was associated with an elevation of Blood glucose levels within a clinically normal range. Haloperidol has been reported to increase insulin resistance and to be associated with higher fasting glucose levels in obese women compared with control subjects. Haloperidol has also been reported to be associated with higher glucose levels in schizophrenia subjects. Increased insulin resistance in peripheral tissues can be caused by hyperprolactinemia and may be involved in the mechanism underlying hyperglycemia in patients treated with typical antipsychotics.

Limitations:

- Short follow up.
- Confounding variables of co-medications.
- Short duration requires 6th month or 1 year follow up study.

More specific test can be used like Hydroxylated Haemoglobin A (HbA) which will give the blood glucose level for the previous 6 weeks.

CONCLUSION

In this prospective study, Olanzapine and Haloperidol were associated with an increase in Blood Glucose Levels. The mean changes in Glucose remained within clinically normal range in this six week study.

Given the concerns regarding endocrine dysregulation in the context of treatment of schizophrenia patients with antipsychotic medication the baseline and 6th week monitoring of fasting blood glucose and post prandial blood glucose levels be obtained in routine clinical practice with both antipsychotics in order to monitor the risk for development of hyperglycaemia.

Given the serious implications for morbidity and mortality attributable to diabetes mellitus, clinicians need to be aware of these risk factors when treating patients with chronic schizophrenia.

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Conflict of interest: Nil

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