CHRONIC ADMINISTRATION OF OLANZAPINE (AN ANTIDEPRESSANT DRUG) LEADS TO IMPAIRED GLUCOSE TOLERANCE IN MICE

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ABSTRACT

Background. Olanzapine is a prescription drug used for treatment of psychotic mental disorders. Some reports have indicated diabetes risk following chronic administration of olanzapine. It was of interest to see whether chronic olanzapine treatment leads to impaired glucose tolerance in mice. Methods. Impairment of glucose tolerance was determined through oral glucose tolerance tests (OGTT) in mice. Results. Oral administration of olanzapine to mice at a dose level of 100 mg olanzapine per kg body weight led to statistically significant elevations in blood glucose levels compared to control animals (without olanzapine) following OGTT. After 1, 2 and 4 weeks of olanzapine administration, in oral glucose tolerance tests, the elevations in blood glucose in glucose-challenged mice were, respectively, 119.8, 161.1, and 166.4% compared to control mice (100.0%). Conclusion. Chronic administration of olanzapine can cause impaired glucose tolerance, which can serve as a model to explore other medications to alleviate the problem.

KEYWORDS: Olanzapine, Bangladesh, glucose, OGTT.

BACKGROUND

Olanzapine is a second generation antipsychotic drug used for treatment of various psychotic disorders. Administration of the drug has been reported to cause glucose intolerance in rats.1]
In human beings, the reports have been more mixed. One study observed that there is no increased risk of diabetes with intake of olanzapine.\(^2\) However, other studies have shown increased risks of type 2 diabetes and dyslipidemia and other diabetes related complications with use of olanzapine.\(^3-7\) As a result, it was of interest to determine whether chronic administration of olanzapine causes impaired glucose tolerance in mice as measured through oral glucose tolerance test (OGTT).

**METHODS**

*Chemicals and Drugs*

Olanzapine was obtained from Sigma Chemical Co., USA and glucose was obtained from Square Pharmaceuticals Ltd., Bangladesh. All other chemicals were of analytical grade. Olanzapine was dissolved in DMSO prior to oral gavaging in mice.

*ANIMALS*

Swiss albino mice, which weighed between 15-19g were used in the present study. The animals were obtained from International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). The animals were acclimatized for three days prior to actual experiments, the actual experiments being conducted over a period of four weeks where the mice were supplied with normal mice chow (obtained from ICDDR, B) and water *ad libitum*. Experimental mice received olanzapine dissolved in DMSO by gavaging every day during this time period (4 weeks). The study was conducted following approval by the Institutional Animal Ethical Committee of University of Development Alternative, Dhaka, Bangladesh.

*Oral glucose tolerance tests*

Oral glucose tolerance tests were carried out as per the procedure previously described by Joy and Kuttan (1999)\(^8\) with minor modifications. Briefly, mice were grouped into four groups of five mice each (control groups without olanzapine administration) and four groups of fifteen mice each (experimental groups receiving olanzapine). The various groups received different treatments like Groups 1-4 received vehicle (DMSO) for 0, 1, 2 and 4 weeks and served as control, Groups 5-8 received olanzapine solution at concentrations such that each mice received olanzapine at a dose of 100 mg per kg body weight, respectively, for 0, 1, 2, and 4 weeks. All substances were orally administered. At the end of 0 (Groups 1 and 5), 1 (Groups 2 and 6), 2 (Groups 3 and 7) or 4 weeks (Groups 4 and 8), all mice were fasted overnight for 12 hours. After 12 hours fasting, mice were orally administered 2g glucose/kg
of body weight. Blood samples were collected 120 minutes after the glucose administration through puncturing heart. Blood glucose levels were measured by glucose oxidase method.\textsuperscript{[9]}

\textit{Statistical analysis}

Experimental values are expressed as mean ± SEM. Independent Sample t-test was carried out for statistical comparison. Statistical significance was considered to be indicated by a p value < 0.05 in all cases.\textsuperscript{[10]}

\textbf{RESULTS}

Experimental mice receiving olanzapine demonstrated increased glucose intolerance with time in oral glucose tolerance tests. Thus mice fed olanzapine for 0, 1, 2 and 4 weeks showed increasingly elevated and statistically significant increases in blood glucose levels. The mean blood glucose concentrations at the afore-mentioned four time periods were, respectively, in mmol/l, 4.35, 5.21, 7.01 and 7.24, which translate to rises of 19.8, 61.1 and 66.4\% above values on Day 0. There were no significant differences in mean blood glucose values between control (Group 1) and experimental mice (Group 5) on Day 0, the values being 4.72 and 4.35 mmol/l respectively. Control groups of animals that is Groups 1-4 showed a tendency to rise in blood glucose levels between Day 0 and Day 28, but the results were not statistically significantly different between the Groups. The results are shown in Figure 1 and strongly suggest that olanzapine administration at a dose of 100 mg per kg body weight for even one week can lead to increased glucose intolerance and so is indicative of impaired glucose metabolism.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Elevated blood glucose levels in glucose-challenged mice following chronic olanzapine administration.}
\end{figure}
DISCUSSION

Along with advances in technology, the modern era has seen a number of other changes. Change in food habits and adopting a more sedentary lifestyle is leading to increased incidences of diabetes and cardiovascular disorders. Rise in stress and tension is leading to depression with an increased use of antidepressant drugs. A number of such antidepressant drugs including olanzapine appear to cause impairment in glucose homeostasis and resulting ultimately in type 2 diabetes and diabetes-induced complications.\textsuperscript{[6,7]} The present results suggest that such antidepressant drugs should be used with caution for even though these drugs may be beneficial in alleviating depression, they can cause a complicated metabolic disorder like diabetes.

Diabetes cannot be cured with allopathic medicine. However, elevated blood glucose levels – a characteristic feature of diabetes can be treated with both allopathic and traditional medicines, including medicinal plants and formulations. We had been experimenting with various antihyperglycemic or antidiabetic plants and formulations for a number of years.\textsuperscript{[11-31]} It would be of interest to examine whether such medicinal plants and formulations are able to alleviate olanzapine-induced hyperglycemia. It is noteworthy in this regard that metformin-glyburide and rosiglitazone-glyburide administered adult female rats showed significantly greater reductions in glucose levels following acute administration of olanzapine.\textsuperscript{[1]} Thus medicinal plants and traditional antidiabetic medicines can open up new routes for controlling olanzapine-induced glucose intolerance for they are more available and affordable to particularly rural people than modern allopathic drugs.

CONCLUSION

The results suggest that chronic administration of olanzapine can induce glucose intolerance in mice.

Conflicts of interest

The author(s) declare that they have no competing interests.

REFERENCES


