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"EVALUATION OF CILNIDIPINE FOR ITS EFFECT ON GLUCOSE METABOLISM IN NORMAL EUGLYCEMIC ALBINO WISTAR RATS"

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ABSTRACT

Objective: To evaluate the effect of cilnidipine on glucose metabolism in normal euglycemic albino wistar rats. **Methods**: Two groups of 6 animals each was evaluated in the study. The test group was given test drug for a period of five days. On fifth day OGTT (oral glucose tolerance test) was performed on both sets of the rats. The glucose levels were measured by rat tail snipping method using a glucometer at 0, 60 and 150 minutes. **Results**: The glucose level in test group was compared with that of control. There was significant difference in mean glucose levels at all the time intervals between control and test groups of rats. Cilnidipine caused significant hyperglycemia at all the time intervals in test groups of rats. **Conclusion**: Cilnidipine tends to cause hyperglycemia by virtue of its property of blocking the calcium channels in beta cells thereby inhibiting the release of insulin.

KE WORDS: Cilnidipine, Hyperglycemia, OGTT, Albino wistar rats.

INTRODUCTION

A changing lifestyle in developing countries like India has enormously increased the statistical figures of chronic diseases like diabetes mellitus. A survey depicts that 4% of the adults in India suffered from diabetes in the year 2000 and it is expected to increase to 6% by the year 2025.[1] Type 2 diabetes is estimated to affect >550 million people worldwide by the year 2030.[2]

Voltage dependent calcium channels are a group of voltage gated ion channels found in the excitable cells with a permeability to the ion calcium.[3]

At physiologic or resting membrane potentials these channels are generally closed. They are activated at depolarized membrane potentials and this is the source of voltage dependent epithet. Activation of particular VDCCs allows ca2+ entry into the cell,which, depending on the cell type, results in muscular contraction, excitation of neurons, up regulation of gene expression, or release of hormones or neurotransmitters.[4]

Insulin is secreted from human pancreas by glucose entry into β cell through GLUT-2 which results in inhibition of ATP-sensitive K+ channel resulting in depolarisation of β cells which increases Ca++ entry through voltage sensitive L type calcium channels into the β cells and also releasing Ca++ from intracellular binding sites, such as the internal surface of the cell membrane, sarcoplasmic reticulum and mitochondria of the β-cell resulting in release of insulin by degranulation of stored vesicles.[5]

The calcium channel blockers block voltage dependant Ca++ channels and inhibit the influx of calcium ions through the cell membrane not only directly decreasing the concentration of cytoplasmic calcium but also decrease calcium release from intracellular stores.[6]

Hypothesis: Cilnidipine may have a hyperglycemic effect by virtue of its activity of blocking calcium channels in beta cells of pancreas, thereby inhibiting release of insulin in response to glucose challenge.

MATERIAL AND METHODS

The experiment has been conducted after obtaining permission from institutional animal ethics committee bearing approval no JSSMC/IAEC/2439/4/December2013.

Albino rats of either sex of weight 150-200gms, aged 3-4 months which were bred in central animal house of J.S.S. Medical College, Mysore were used for the study. Pregnant and diseased rats were excluded from the study.

Rats were divided into control and test groups to study the effect of glucose induced glycemic changes in normal albino wistar rats following oral administration of distilled water and cilnidipine respectively. The rats were fasted overnight but provided water *ad libitum*. The control group of rats received 10ml/kg of tap water. The test group-1mg/kg body weight of

cilnidipine for 5 days. On the fifth day, 2 hours after drug administration all rats were administered oral glucose in the dose of 0.6 gm per rat. The blood glucose levels were measured at 0, 60 and 150minutes after glucose administration (slightmodification in OGTT) by rat tail snipping method using ACCUCHEK glucometer.[7]

OGTT:[8] The oral glucose tolerance test is a measure of the glucose induced Glycemic Changes which is related to changes in insulin secretion due to glucose challenge. study used OGTT for normal rats with some modifications to the standard method to assess the effect of test drugs on glucose induced glycemic control alteration. All the groups of rats were subjected to OGTT.

RESULTS AND DISCUSSION

Cilnidipine is a Calcium channel blocker. It acts on L-type of calcium channels which are present on beta cells as well as N-type of calcium channels. Calcium channels are present in beta cells of islets of pancreas where they regulate glucose metabolism by taking part in release of insulin. In presence of glucose, that enters in to the beta cells through the GLUT-2 transporters, these ATP sensitive potassium channels close, with subsequent opening of calcium channels resulting in insulin secretion. But the test drug, Cilnidipine is a calcium channel blocker which results in hyperglycaemic state by inhibiting insulin secretion by blocking the calcium channels present in beta cells of pancreas.

Table 1: Average CBG values in test and control groups at different time intervals and the percentage difference between test and control groups

Time	Avg CBG-control	Avg CBG- test	T vs C	% change
0 min	64.83 +/- 2.85	70.66 +/-2.16	T>C	8.25
60 min	83.67+/- 2.58	98+/-3.16	T>C	14.62
150 min	72.83 +/-2.31	86.5+/-1.87	T>C	15.8

The test drug cilnidipine has shown significant amount of hyperglycemic state when compared to the control group of rats at all the time intervals. The basal glucose levels, i.e glucose levels are higher at 0 minute by inhibiting the basal insulin secretion even before glucose challenge. The average CBG value in the control rats was 64.83mg% whereas in the test group it was 70.66mg%. At 60 min there the CBG levels were significantly higher when compared to the conrol group which was 83.67mg% whereas in the test group the average CBG levels were 98mg% at 60 min.

The persisting action of the drug cilnidipine by blocking the calcium channels resulted in suboptimal release of insulin in presence of glucose challenge. Hence the test values were significantly higher when compared to the test group. At 150 min there was a fall in glucose levels in both the groups when compared to the 60 min CBG values. Though there was a fall in test group, the CBG value was still significantly higher when compared to the control groups.

Table 2: Difference in CBG levels at different time intervals in control and test group respectively

S. No.	Time intervals	Control	test
1	0-60	19.34	27.33
2	60-150	-10.84	-11.5
3	0-150	8.5	15.83

Table 3: difference in CBG levels at different time intervals between control and test

S. No.	Time values of control and test respectively	Difference between test and control values
1	0-0	6.34
2	0-60	33.67
3	0-150	22.17
4	60-0	-13
5	60-60	14.33
6	60-150	2.83
7	150-0	-2.16
8	150-60	25.17
9	150-150	13.67

The average CBG value in the test group was 86.5 mg% whereas in control group it was 72.83mg%. The fall in CBG values in the test group can be attributed to various factors. Firstly, there could have been recruitment of remaining of remaining calcium channels which would have taken part in insulin secretion. Secondly the half life of cilnidipine is around 2-3 hours, hence large amount of drug would have been eliminated by the time 150 min readings were done. Hence the drug mediated inhibition of insulin secretion would have waned off by then. Hence there was a fall in CBG levels.

CONCLUSION

The test group showed increase in glucose levels at all the time intervals of OGTT when compared to the control group. Hence experimental animal models suggest that cilnidipine interferes with glucose metabolism causing hyperglycemia by virtue of its action of blocking calcium channels in beta cells of pancreas thereby inhibiting release of insulin.

Cilnidipine may be suspected to have similar effect in human subjects who are on this drug. Further studies are required to prove the derangement in glucose levels in humans if any.

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