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Research Article

EFFECT OF NICORANDIL ON BASAL GLUCOSE LEVELS AND AFTER GLUCOSE CHALLENGE IN NORMAL EUGLYCEMIC ALBINO WISTAR RATS

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ABSTRACT

Objective: To evaluate effect of Nicorandil on glucose metabolism in euglycemic albino wistar rats.

Methods: In this study 12 albino rats were divided in to 2 groups containing 6 rats each. One group constituted the control group that received tap water 5ml/kg body weight whereas the second group was treated with nicorandil 5.5mg/kg body weight for a period of 5 days. On 5th day, 2 hours after drug administration both the groups were subjected to OGTT. Blood glucose levels were checked at 0, 60, 150 minute time intervals.

Results: The basal levels of CBG at 0 minute in OGTT test were high in the Nicorandil treated group, i.e. 126.65mg%. Basal levels of CBG were almost double than that of control readings i.e. around 65.5mg%. At 60 minute CBG levels dipped when compared to the 0 minute reading with average of 116.33mg% but were significantly higher than the corresponding control values which averaged 83mg%. At 150 minute, CBG reading was 101.67mg% in the Nicorandil treated group. This CBG reading was the least amongst the three time intervals for Nicorandil treated group but was significantly higher than the corresponding control readings which was 73.67mg%.

Conclusion: Nicorandil has shown a significant rise in basal blood glucose as well as after glucose challenge in euglycemic albino wistar rats when compared to the control group at all the time intervals. It is expected to have a similar effect in human subjects also and further studies are required to confirm the same. Therefore it should be used with caution in diabetic patients.

Keywords: Nicorandil, Diabetes mellitus, OGTT.

INTRODUCTION

Diabetes mellitus is a spectrum of common metabolic disorders arising from a variety of pathogenic mechanisms, all resulting in hyperglycemia. The number of individuals with diabetes is rising rapidly throughout the world. Both genetic and environmental factors contribute to its pathogenesis, which involves insufficient insulin secretion, reduced responsiveness to endogenous or exogenous insulin, increased glucose production and/or abnormalities in fat or protein metabolism. The resulting hyperglycemia may lead to both acute symptoms and chronic abnormalities.[1] The International diabetes federation has predicted that the number of diabetics will increase from 240 million in 2007 to 380 million in 2025 and that the number of diabetic patients in India are going to be more than doubled from 19 million in 1995 to 40.9 million in 2007 and is projected to increase to 69.9 million by 2025. So India will be the diabetes capital of the world indicating the global population is approaching the midst of diabetes pandemic.[2] Insulin, a hypoglycemic hormone, is secreted by human pancreas by glucose entry into β cell through GLUT-2. It 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.[3] ATP-sensitive potassium channels are composed of K_{ir}6.x-type subunits and sulfonylurea receptor (SUR) subunits, along with additional components.[4] Type II DM is at present one of the most challenging health care problems, which requires optimum management. At present the treatment of diabetes mellitus includes insulin, sulfonylureas, biguanides, α-glucosidase inhibitors, DPP-4 inhibitors, thiazolidinediones, GLP-1 receptor agonists, amylin agonists, medical nutrition therapy and lifestyle modification.[5] Many of the drugs used for treating various diseases other than diabetes, interact with ionic channels involved in insulin secretion, causing hypoglycemia or hyperglycemia. Hence it is ideal that such drugs should be evaluated for this particular effect on beta cells of pancreas. Nicorandil is one such drug and has been selected for the study.

Nicorandil is an anti-angina medication that has the dual properties of a nitrate and K+ATP channel agonist. In humans, the nitrate action of Nicorandil dilates the large coronary arteries at low plasma concentrations.[6] Nicorandil is rapidly and almost completely absorbed from the gastrointestinal tract. Nicorandil is not metabolized significantly by the liver during passage through the portal system (lack of first-pass effect). Thus, it easily enters the systemic blood flow, resulting in almost complete bioavailability (75-100%) Steady-state plasma concentrations of Nicorandil usually are reached within approximately 96-120 h after continuous dosing (5- 20 mg b.i.d.), probably due to its distribution and metabolism patterns. After oral (and i.v.) administration of the drug, the apparent volume of distribution is approximately 1.0 L/kg body weight. Nicorandil is metabolized extensively, and the major route of elimination is the kidney: Less than 2% of the dose is excreted through the biliary route. As a consequence, the parent drug is excreted poorly in urine (very low renal clearance), whereas 2-nicotinamidoethanol, a pharmacologically inactive denitrated metabolite, is the major Nicorandil related compound excreted in urine. The nicotinamide/ nicotinic acid biotransformation pathway contributes to the accumulation of Nicorandil and 2-nicotinamidoethanol (denitrated metabolite) during repeated dosing because of the saturable merging of nicotinamide/nicotinic acid derivatives (from the Nicorandil metabolism) into the NAD/NADP endogenous pool of coenzymes. The apparent elimination half-life is short (approximately 1 hour), and total body clearance is close to 1.15 L/min, which is lower than the liver blood flow. Especially during repeated dosing, a slower elimination process appears that is related to only approximately 10% of the amount of Nicorandil found in plasma. Most of the Nicorandil metabolites are excreted during the 24-h period after dosing, with the remainder excreted more slowly as nicotinamide derivatives.[7] The OGTT is usually used to test for diabetes, insulin resistance, and sometimes reactive hypoglycemia and acromegaly, or rarer disorders of carbohydrate metabolism. In the most commonly performed version of the test, an *oral glucose tolerance test* (OGTT), a standard dose of glucose (75 gm) is ingested by mouth and blood levels are checked at 0hrs, 1hrs & at 2 hrs later.[8] This test used OGTT concept to evaluate the glycemic changes after glucose administration with some modifications to the original method.

Hypothesis

Therefore it is hypothesized that Nicorandil can exhibit a significant effect on glucose metabolism by virtue of its property to open ATP sensitive potassium channels in beta cells of pancreas involved in insulin secretion.

MATERIALS AND METHODS

The experiment has been conducted after obtaining permission from institutional animal ethics committee bearing approval no JSSMC/IAEC/2439/26/July2013.

Source of data: The experiment was done on albino wistar rats procured from central animal house facility in JSS medical college, Mysore. Rats of either sex which weighed 150-200gms aged around 3-4 months were used for the study.

Method of collection of data

In this study 12 albino rats were divided in to 2 groups containing 6 rats each.

Group-1 (**CONTROL**): tap water 10ml/kg body wt. (oral)

Group-2 (TEST): Nicorandil 5.5mg/kg body weight (oral)

Instruments used: oral feeding tube, glass beaker, syringes, glucometer, scissor, glucometer strips.

Models and methodolgy of experiment

OGTT:[9] 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 (Duvigneaud and Karr, 1925) to assess the effect of test drugs on glucose induced glycemic control alteration. All the groups of rats were subjected to OGTT.

Rats were divided into control and test groups to study the effect of glucose induced

Glycemic changes in normal rats following oral administration of tap water and Nicorandil. The rats were fasted overnight but provided water *ad libitum*.

The Control group of rats received 10ml/kg of tap water. The test group-1 received Nicorandil in the dose of 5.5mg/kg BW for 7 days. On the 7th day, 2 hours after drug administration all the groups of rats were administered oral glucose in the dose of 6gm/kg BW

The blood glucose levels were measured at 0, 60 and 150 minutes after glucose administration (slight modification in OGTT) by rat tail snipping method using ACCUCHEK glucometer.[10]

RESULTS AND DISCUSSION

Nicorandil is a potassium channel opener. It acts on KATP channels. Potassium channels are also 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, Nicorandil is a potassium channel opener which results in hyperglycaemic state by inhibiting insulin secretion either by keeping potassium channels patent or open the closed potassium channels in the beta cells of pancreas.

The basal levels of CBG at 0 minute in OGT test were very high in the Nicorandil treated group, i.e. 126.65mg%. Basal levels of CBG were almost double than that of control readings i.e. around 65.5mg%. This can be explained on the basis that Nicorandil being an ATP sensitive potassium channel opener inhibited the basal secretion of insulin in absence of glucose challenge. At 60 minute CBG levels dipped when compared to the 0 minute reading with average of 116.33mg% but were significantly higher than the corresponding control values which averaged 83mg%. This can be explained on the basis of increased basal glucose levels and partial effect of glucose challenge in releasing insulin from the beta cells. At 150 minute, CBG reading was 101.67mg% in the Nicorandil treated group. This CBG reading was the least amongst the thee time intervals for Nicorandil treated group but was significantly higher than the corresponding control readings which was 73.67mg%. Nicorandil administration leading to hyperglycemia can be explained on the fact that it is a potassium channel opener thereby inhibiting insulin secretion. Interesting phenomenon of fall in blood glucose levels was noted in subsequent time intervals in Nicorandil treated group. This can be explained on two factors. Firstly the t ½ of Nicorandil is around 1 hour. So the maximum effect off the drug was present at 0 minute of OGTT. With passing of time there was a reduction in the drug level acting at the potassium channels. At 60 minute interval only half of the drug present at 0 minute interval would be acting on the potassium channels. And almost three half life of drug would have completed at the end of 150 minute of OGTT. Secondly, glucose challenge would have resulted in fall in glucose levels by causing insulin secretion. Though the drug was acting on the potassium channels, glucose challenge would have resulted in recruitment of remaining potassium channels resulting in insulin secretion and fall in blood glucose levels. Other point which can be deduced from the results is that Nicorandil is having a predominant effect on the basal insulin secretion noted by the high CBG values at 0 minute of OGTT. Though it is having effect subsequently on 60minute and 150 minute it is less pronounced when compared to the basal levels. This can be noted by fall in the CBG levels when compared to the 0 minute CBG reading.

Table 1: Following are CBG values of test and control group expressed as mean+/-SEM

S. No.	Time since administration of glucose in minutes	Mean CBG (mg/dl) +/- SEM		T v/s C, mg/dl	% difference of CBG of T over C
		Control group (C) (n=6)	Test group (T) (n=6)		
1	0	65.50 +/-1.005	126.65 +/-0.875	T>C, 61	93.8%
2	60	83.00 +/-0.781	116.33 +/-0.976	T>C, 33	39.75%
3	150	73.67 +/-0.653	101.67 +/-0.693	T>C, 28	38.35%

Table 2: This table shows difference in CBG values between various time intervals

S. No.	Time Interval in Minutes	Difference in CBG Values mg/dl	
		Control	Test
1	0-60	17.5	-10.32
2	60-150	-9.33	-14.66
3	0-150	8.17	-24.98

Basal level of CBG was higher by 61.15mg/dl than that of corresponding CBG levels in the control i.e. at 0 minute. They were about 93.8% higher. At 60 minute CBG reading the percentage difference between the corresponding groups was 39.75%; the test

values higher by around 33.33mg/dl. At 150 minute the percentage difference between the corresponding groups was 38.35%; test CBG levels higher by around 28mg/dl.

Nicorandil treated group showed fall in glucose levels in subsequent time intervals. Whereas in control group there was rise at 60 minute and then fall in glucose levels. The fall at 150 minute in the test group was higher than that of the 0minute reading. The negative sign indicates the reduction in the CBG levels.

Table 3: This table depicts difference in CBG values between various time intervals of test & control respectively

Sl.No	Time interval between test and control respectively in minutes	Difference in CBG values (mg/dl)
1	0-0	61.15
2	0-60	43.65
3	0-150	52.98
4	60-0	50.83
5	60-60	33.33
6	60-150	42.66
7	150-0	36.17
8	150-60	18.67
9	150-150	28.00

The CBG values of test were always higher than that of control values at all the time intervals. It indicates a potent inhibition of insulin secretion at all the time intervals when compared to the control CBG values. The maximum difference between the CBG readings between test and control was at 0 minute CBG values which stood at 61.15mg/dl.

CONCLUSION

In accordance with the stated hypothesis it is proved that, Nicorandil has shown a significant rise in basal blood glucose levels & as well as after glucose challenge in euglycemic albino wistar rats when compared to the control group at all the time intervals. It is expected to have a similar effect in human subjects also and further studies are required to confirm the same. Therefore it should be used with caution in diabetic patients.

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REFERENCES

1. Alvin Powers C, David D'Alessia Endocrine pancreas, pharmacotherapy of Diabetes mellitus and hypoglycemia. In: Laurence Brunton L, Bruce Chabner A, Bjom Knollman C. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 12th edition. China: McGraw Hill; 2011. 1237
2. Juliana CN Chan, Vasanti Malik, Weipingjia, Takashi Kadowaki, Chittaranjan S Yajnik, Kun-Ho Yoon, Frank B Hu: Diabetes in Asia Epidemiology, Risk factors and pathophysiology. American Medical Association 2009; *301*(20):2129-40.
3. Tasneem Sandozi: Study of effect of Amlodipine on Blood Sugar level. Asian Journal of Medical Sciences 2010; 1:4-5.
4. Stephan D, Winkler M, Kühner P, Russ U, Quast U: "Selectivity of repaglinide and glibenclamide for the pancreatic over the cardiovascular K (ATP) channels". Diabetologia 2009; 49 (9): 2039–48.
5. Nicholson G and Hall G.M, Diabetes Mellitus: New drugs for a new epidemic. British Journal of Anaesthesia 2011; 107(1):65-73.
6. Nakae I, Matsumoto T, Horie H, Yokohama H, Omura T, Minai K, et al. Effects of Intravenous Nicorandil on Coronary Circulation in Humans: Plasma Concentration and Action Mechanism. Journal of Cardiovascular Pharmacology 2000; 35(6):919-25.
7. Frydman A: Pharmacokinetic profile of Nicorandil in humans: An overview. Journal of Cardiovascular Pharmacology 1992; 20 (3):34-44.
8. Patrick J Phillips: Oral glucose tolerance testing. Australian Family Physician- Emergency Care 2012; 41(6):391-93.
9. Vincent duVigneaud and Walter G. Karr. Carbohydrate utilization: I. rate of disappearance of *d*-glucose from the blood Journal of Biology and Chemistry 1925; 66: 281-300.
10. Sibgatullah Mohammed and Suresha R.N: Evaluation of Amiodarone for Its effect on glucose metabolism in euglycemic albino wistar rats. International Journal of Recent Trends in Science and Technology 2013; 8(3):178-181.