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EFFECT OF NICORANDIL ON BLOOD GLUCOSE LEVEL IN NORMAL RATS

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ABSTRACT: Nicorandil is occasionally given for cardiovascular disorders in patients also suffering from diabetes mellitus. Simultaneous use of nicorandil and sulfonylureas may interfere with the euglycemia. The study was done to find the effect of nicorandil on glucose tolerance in normal male Wistar albino rats, under oral glucose load, adrenaline injection and in receiving oral hypoglycemic drugs. Male albino rats 100-120g was divided into control and treatment groups. The control group of rats received either oral 2% gum acacia or normal saline subcutaneously. The treated groups received either glucose (1g/100g), glipizide (0.045mg/100g) or nicorandil (0.18mg/100g) orally alone or in combination. Blood samples were collected from lateral tail vein at 0, 1, 2 and 4hrs interval. Blood glucose estimation revealed that nicorandil significantly reduced glucose tolerance in normal rats and in rats made hyperglycemic by oral glucose load or adrenaline injection. It antagonized the hypoglycemic effect of glipizide and reduces glucose tolerance in rats at human therapeutic dose.

INTRODUCTION: Cardiovascular disorders like angina pectoris, hypertension are often treated with potassium channel openers like nicorandil. They act primarily on the vascular smooth muscle and mediate vasodilatation and fall of blood pressure. In a previous study it was observed that calcium channel blockers though act primarily on cardiovascular system, produced hyperglycemia in normal rats [1] and normal human volunteers and increased insulin requirement in diabetic individuals [2].

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It was presumed that potassium channel openers may cause hyperpolarization of pancreatic beta cells, reduce entry of Ca^{2+} through the voltage operated Ca^{2+} channel, inhibit insulin secretion by exocytosis and produce hyperglycemia.

It has been reported that treatment with potassium channel openers like diazoxide, pinacidil and cromakalim reduce insulin release and glucose tolerance in diabetic and normal persons [3]. Based on these previous studies it was presumed that simultaneous use of nicorandil and others along with antidiabetic agents may interfere with the maintenance of euglycemia. However nicorandil, though potassium channel opener has been claimed to have least effect on blood glucose level [4, 5]. It has also been reported that nicorandil improves outcome in patients with acute myocardial infarction when given before reperfusion [6].

On the contrary, it has been reported that nicorandil improved diabetes in rat beta cell damage induced by streptozotocin *in vivo* and *in vitro* probably by a free radical scavenging effect [7]. The available evidences suggest that the effect of nicorandil on glucose tolerance is inconclusive. Hence, the present work was undertaken to study the effect of nicorandil on blood glucose level in normal fasting rats as well as in rats made hyperglycemic by glucose load and adrenaline injection. The effect of the drug on the hypoglycemic effect of glipizide was studied to test the hypothesis of decreased insulin release by the potassium channel openers.

MATERIALS AND METHODS:

Animals: Male Wister albino rats (100-120g) were housed six per cage under standard laboratorial conditions at a room temperature of 22 ±2 °C with 12 hour light/ dark cycle. The animals were provided with pellet chow and water *ad-libitum.* The study protocol was approved by Institutional Animal Ethics Committee.

Chemicals: Nicorandil (Tab NIKORAN 5 mg, Torrent Pharmaceuticals) and Glipizide (Tab Glynase 5mg USV Pharmaceuticals) were purchased and Adrenaline (Inj. Adrenaline hydrochloride 1: 1000), 5% gum acacia, distilled water were procured from the departmental laboratory.

Experimental Procedure: After an overnight fasting rats were divided into 9 groups, each group comprising of 6 rats. The control groups of rats received either 2% gum acacia (control-A) by oral route (p.o) or normal saline by subcutaneous injection (s.c) injection (control-B). The treated groups received either of the following: nicorandil (0.18 mg/100g/day) or glucose (1g/100g/day) or nicorandil (0.18mg/100g/day) plus glucose (1g/100g/day) or glipizide (0.045 mg/100g/day) or nicorandil (0.18 mg/100g) plus glipizide (0.045mg/100g) with 2% gum acacia as vehicle orally by a feeding canula.

The other treated groups received inj. adrenaline (50mcg/100g/day s.c.), nicorandil (0.18mg/100g/ day p.o.) plus adrenaline (3mcg/100g/day s.c.). In combined oral treatment, nicorandil was administered almost simultaneously with glucose or glipizide.

But in nicorandil plus adrenaline group, nicorandil was administered per oral half an hour before the subcutaneous administration of adrenaline. The dose of the drugs was selected on the basis of human therapeutic dose [8]. All the experiments were conducted between 10:00 to 16:00 hours. The blood was collected from lateral tail vein of the restrained rats with the help of a fine tip needle with all aseptic measures at 0, 1, 2 and 4 hr interval.

The blood glucose level was estimated by the help of a glucostrip soaked with blood collected from lateral tail vein of the rat and was inserted inside the glucometer [9, 10, 11]. An automatic device generated data was displayed on the digital display board which was recorded in a tabular form in the data sheet.

Statistical analysis: The results were statistically analyzed by Student‘t’ test and one way ANOVA with post hoc test on GraphPad Instat version 3.06.

RESULTS:

Effect of Nicorandil on fasting blood sugar level: Nicorandil administered orally in dose of 0.18mg/100g significantly increased the blood glucose level in fasting rats at 1hr ($p< 0.01$) and 2hr ($p< 0.05$) when compared to their baseline value at 0hr. The blood glucose level in the nicorandil treated group almost came back to their baseline value at 4 hr.

The values of blood sugar level in the nicorandil treated group at 1h ($p<0.001$), 2h ($p<0.01$) and 4h ($p< 0.01$) were significantly higher than their corresponding values in the control group (control-A) (**Table 1).**

Effect of nicorandil on blood sugar level under glucose load: Oral administration of glucose in fasting rats caused an increase in blood sugar level at 1h ($p<0.001$) and 2h ($p<0.01$) intervals and the level got back almost to their base line values at 4h.

Simultaneous administration of nicorandil significantly augmented the hyperglycemic effect of oral glucose in fasting rats at 1h ($p<0.001$), 2h ($p<0.001$) and 4h ($p<0.001$) intervals (**Table 1).**

TABLE 1: EFFECT OF NICORANDIL ON BASELINE AS WELL AS INDUCED HYPERGLYCEMIC AND HYPOGLYCEMIC EFFECTS IN NORMAL RATS

Groups (n = 6 in each)	Treatment	Blood Sugar Level (mg %)			
		0hr (Mean ± SEM)	1hr (Mean ± SEM)	2hr (Mean ± SEM)	4hr (Mean ± SEM)
Control-A	2% Gum acacia	54.5 ± 3.12	48.6 ± 3.06	46.66 ± 3.68	42.33 ± 2.07
Nicorandil	Nicorandil in 2% Gum acacia	54.7 ± 1.80	70.1 ± 1.61^{c,**}	63.25 ± 2.56^{b,*}	55.75 ± 3.61^{b}
Glucose	Glucose	60.4 ± 5.75	100.4 ± 3.27^{c,***}	86.6 ± 4.20^{c,**}	76.2 ± 4.61^{c}
Glucose + Nicorandil	2% Gum acacia in Glucose + Nicorandil	58.2 ± 1.85	145.6 ± 4.77^{c,}***	97.6 ± 2.22^{a,}***	84.2 ± 2.77***
Control-B	Inj. Normal saline (s.c)	55 ± 4.10	45.2 ± 3.90	42.6 ± 4.05	41.2 ± 1.65
Adrenaline	Adrenaline	49.6 ± 3.04	78 ± 2.91^{c,***}	58.6 ± 2.48^{b,*}	43 ± 1.64
Nicorandil + Adrenaline	Adrenaline + Nicorandil	50.5 ± 2.70	120.33 ± 8.13^{c},***	92.33 ± 7.11^{c,}***	82.33 ± 1.95^{c,}***
Glipizide	Glipizide	53.6 ± 3.00	39.4 ± 3.42***	34 ± 3.35***	35.6 ± 3.31***
Nicorandil + Glipizide	Nicorandil + Glipizide	59.8 ± 3.77	52.66 ± 2.35^{b}	42.33 ± 1.87^{a,}**	34.8 ± 2.86***

* = p < 0.05, ** = p < 0.01, *** = p < 0.001 when compared to their baseline values, a = p < 0.05, b = p < 0.01, c = p < 0.001 when compared to their respective control values

Effect of nicorandil on adrenaline induced hyperglycemia: Subcutaneous administration of adrenaline caused a significant rise in blood sugar level in fasting rats at 1h (p<0.001) and 2h (p<0.05) intervals which came back almost to the baseline value within 4h. Oral pretreatment with nicorandil half an hour before the subcutaneous administration of adrenaline augmented the hyperglycemic effect of adrenaline at 1h (p<0.001) and 2h (p<0.001) intervals. The blood sugar level was persistently high even at 4h (p<0.01) **(Table1).**

Effect of nicorandil on glipizide induced hypoglycemia: Oral glipizide in fasting rats reduced the blood sugar level and caused persistent hypoglycemia at 1h (p<0.001), 2h (p<0.001) and 4h (P>0.001) intervals. Nicorandil when administered along with glipizide, prevented the hypoglycemic effect of the later drug at1h (p<0.01) and 2h (p<0.05) intervals **(Table 1).**

DISCUSSION: Potassium channel openers like minoxidil and diazoxide were used in the treatment of hypertension. Their clinical use has declined because of their hyperglycemic side effect and availability of better drugs in the treatment of hypertension. But nicorandil also a K^+ channel opener has been claimed to have minimum effect on blood glucose level and is frequently used in ishaemic heart diseases [6].

Results of the present study however suggest that nicorandil, though essentially a cardiovascular drug can increase blood sugar level and reduce glucose tolerance within the human therapeutic dose range in even overnight fasting rats probably by opening the potassium channels in the islets cells of pancreas leading to hyperpolarization and reduction in insulin secretion. This finding contradicts the earlier thought that Nicorandil has specificity for the K_{ATP} channels in the blood vessels and not for the K_{ATP} channels present in the pancreas.

A comparative similar result was found earlier when nicorandil was studied with gliclazide on normal rabbits and rats [9]. Nicorandil increases blood sugar level itself, augments hyperglycemic effects of oral glucose load and adrenaline injection (s.c.) in rats.

It is difficult to delineate the exact mechanism of this hyperglycemic side effect of Nicorandil. Glipizide, a well-known oral hypoglycemic drug, prevents the hyperglycemic effect of nicorandil. It is known that glipizide blocks the potassium channels of pancreatic beta cells, causes depolarization of cell membrane, increases entry of calcium inside the cells and releases insulin by exocytosis. As nicorandil prevents the hypoglycemic effect of glipizide, it can be presumed that nicorandil acts by a reverse mechanism.

Nicorandil, being a potassium channel opener, is expected to cause hyperpolarisation of the pancreatic beta cells, reduction of calcium entry inside the cells and attenuation of insulin release by exocytosis. Though the blood glucose level of rats at 4hr interval of nicorandil group as well as adrenaline group were near to normal value but the peculiar persistent high level of blood glucose in the nicorandil plus adrenaline group at similar time interval couldn't be explained though the $t_{1/2}$ of both drugs are different.

CONCLUSION: If the findings of animal experiments are extrapolated on human beings, it is expected that the patients treated with nicorandil may develop hyperglycemia and latent or potentially diabetic individuals may develop clinical diabetes mellitus.

It may also interfere with the maintenance of euglycemia in patients of cardiovascular disorders simultaneously suffering from diabetes mellitus receiving oral hypoglycemic drugs and may cause an increase in dose requirement of the later. But extensive studies on diabetic model of animals and subsequently in human beings are required to substantiate the present work.

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