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Contentment of Diabetics with Co-Use of Sulphonylureas and Nicorandil

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ABSTRACT

Nicorandil, a K^+ channel opener is frequently used in ischaemic heart disease (IHD). Diabetes mellitus is often associated with IHD. There is a possibility of alteration of blood glucose level (BGL) by nicorandil when used with sulfonylureas by influencing insulin release as it's a K^+ channel opener. The study has been done to know the changes of BGL after administration of low-dose nicorandil with sulfonylureas in Diabetic as well as normal rabbits. The study has been done on normal and alloxan induced diabetic rabbits by keeping them 12 hrs fasting & water ad lib. Glibenclamide was given in a dose of 50µg/kg body weight &Nicorandil was administered in a dose of 10,20,40,80 and160µg/kg body weight concurrently. The drugs were given by oral route. Normal saline treated rabbits were used as control. Blood samples were collected from marginal ear vein & BGL was estimated in the process described by Hultmann. The statistical significance was calculated by employing student "t" test. Glibenclamide per se in a dose of 50 µg/kg produced significant hypoglycemia, Nicorandil in in doses of 20µg/kg abolishes the hypoglycemic effect of glibenclamide, & in dose of 40µg/kg produced significant hyperglycemia. Nicorandil, a K^+ channel opener can increase blood glucose level by its action probably on ATP sensitive K^+ channel of β cells of pancreas only at a certain dose range (20 to40 µg/kg body weight doses) for 2 to 3 hours., but no change in BGL in 80 and 160 µg/kg body weight doses which are also relatively low doses than conventional dose. The sensitivity of low dose nicorandil is more than sulfonylureas on β cells of pancreas & the response is dose dependent. In alloxan induced diabetic rabbit, the change in BGL is not so marked probably due to lack of β cells of pancreas.

Key words : Blood Glucose ,Nicorandil, Sulphonylureas,

INTRODUCTION

Epidemiological studies have shown that diabetic patients are more prone to develop post infaction complications (Davis et al. 2001). The purpose of therapy in D M is to restore metabolism to normal, avoid symptoms due to hyperglycemia and glycosuria, prevent short term complications and long term squealed-cardiovascular , retinal ,neurological , renal etc (Bertrm et al. 2010). Orally effective ant diabetic agents , sulfonylureas SU produce reduction in blood sugar level by stimulating insulin release from pancreatic β cells by binding to and blocking an ATP sensitive K^+ channels of β cells of Langerhans (Davis et al. 2001) leads to membrane depolarization ; thereby triggering the entry of Ca^{+2}& release of insulin. In pancreatic β cells KATP channels are open at low glucose concentration; their closure in response to an increase in blood glucose level (Rorsman P, 2005). In cardiac muscle, the KATP channels are believed to be closed under normal physiological conditions (Nichols et al.1991). In all these tissues, the KATP channels are believed to respond to changes in the concentrations of adenine nucleotides. Some drugs relax smooth muscle by selectively increasing the membrane permeability to K^+ by KATP channel activation. This hyperpolarizes the cells and switches off voltage

dependent Ca channels (Bertrm et al. 2010). KATP channels respond to alterations in the metabolic state. The ATP sensitive K^+channels provide a link between metabolic state of a cell and its excitability. K^+ channels are opened by K^+ channel openers, viz., Nicorandil which are of importance in several therapeutic areas, including ischemic heart disease, intermittent claudication, asthma and urinary incontinence (Edwards et al. 1995). Some K^+ channels are target of important drugs. Frequently the effect of one drug may be altered in the presence of anther drug (Rang et al. 2007). Since diabetic patient is susceptible to a series of complications affecting the eyes, kidneys and heart, hypertension, angina and silent Myocardial Infarction (Krolewski et al. 2000). K^+ channel openers are used frequently in angina and post MI in diabetic as well as non diabetic individuals. The KATP channels in various tissues including cardiac muscles are target of two important class of drugs – (1) Antidiabetic sulfonylureas (a K^+ channel blocker) and (2) K^+ channel openers _ which tend to maintain the channels in open conformation and lead to smooth muscle relaxation. The current study was therefore, undertaken to explore the possibilities of any drug interactions between SU, viz., Glibenclamide and K^+ channel openers, viz., Nicorandil on blood glucose level in rabbits.

MATERIAL AND METHODS

Animals :

Study was performed on healthy albino rabbits of either sex weighing between 1-2 Kg .The rabbit were fed on commercial pellets diet and water ad lib.

Drugs:

Nicorandil- a potassium channel opener. Solution was prepared in distilled water as 10 mgNicorandil in100 ml distilled water.

Glibenclamide – an oral hypoglycemic drug; second generation SU. The solution was prepared (100 mg of Glibenclamide dissolved in 100 ml of distilled water).

Reagents :

a. O-toludine reagent- 6%(v/v)

b. Glacial acetic acid

c. Glucose standard solution (1%)

d. Analytical reagent

Proceedure:

The blood glucose level was studied in non diabetic as well as experimentally induced diabetic rabbits. Animals were kept fasted for 24 hrs before starting the experiment and water was allowed ad lib during the period of fasting as well as during the period of study. The animals were divided into various groups comprising of 6 animals in each group. All the drugs were administered orally by intragastric tube. Group-1 served as control and treated with N. saline. Group 2-4, treated with graded doses of Nicorandil, 20, 40, 80, µg/Kg respectively. Group 5, was given Glibenclamide 50 µg/kg. Group 6 to 8, were administered with Nicorandil (20, 40, and 80 µg/kg) plus Glibenclamide(50 µg/kg). Experimental diebties was produced in rabbits within 72 hrs by injecting 1% aqueous solution of Alloxon 200 mg / Kg IV through marginal ear vein. Like non diabetic rabbits, diabetic rabbits were also divided in the same way in to various groups with 6 animals in each group. Collection of blood sample- The blood sample was collected from marginal ear vein. 0.2 ml blood was collected at 0hr & ½ hr intervals for 3hrs for estimation of blood glucose level. The blood glucose level was estimated by the method described by Hultman (Hultman, 1959). The results obtained were statistically analyzed .The fasting BGL of

each rabbit on that day served as its own control and was taken as 100. The changes in BGL after administration of drugs have been expressed as percent change in BGL. The statistical significance was calculated by employing student't' test.

Table 1 Effect of Nicorandil on Blood Glucose level in rabbits

Drug treatment(µg\kg)	Percentage change in Blood Glucose level ± SEM Time(hr)						
	0	1\2	1	1 ½	2	3	4
Saline (2ml)	100	100.98±2.15	o99.82 ±2.83	98.05± 1.64	100.16±2.68	100.80±3.43	100.01±3.83
Nicorandil (20)	100	117.32*±4.37	130.85**±4.40	136.48***±3.29	129.69*±7.81	122.86±9.12	99.99±12.04
Nicorandil (40)	100	125.40*±5.10	136.95**±8.43	139.56***±6.05	141.00**±9.12	137.32**±7.71	102.11±9.19
Nicorandil (80)	100	105.14±3.12	107.31±4.79	106.57±6.66	103.75±4.82	104.08±5.25	100.04±2.81

** p≤ 0.05, **p o.01 , ***p ≤0.001 in comparison to saline treatment*

Table 2 Effect of Nicorandil in various doses on Blood Glucose Level in Diabetic rabbits

Drug treatment (µg/kg. oral)	Percent Change in Blood Glucose Level ±SEM Time (hr)					
	0	½	1	1½	2	3
Saline (2ml)	100	106.30±1.32	110.21±4.51	107.07±3.71	105.55±2.73	102.18±4.77
Nicorandil(20)	100	102.78±5.2	108.19±3.79	108.38±3.54	106.19±6.36	102.20±4.17
Nicorandil(40)	100	110.23 ±4.06	118.61±4.01	126.27*±4.85	113.43±3.76	108.62±5.17
Nicorandil(80)	100	106.79±9.22	110.76±4.33	117.23±5.11	113.99±6.43	105.5±7.73

**p < 0.05 in comparisons to saline treatment*

Table 3 Effect of Nicorandil in various doses on Blood Glucose Level and its interaction with Glibenclamide (50 µg/kg) in Rabbits (n =6)

Drug treatment (µg/kg , oral)	Percent change in Blood Glucose level ± SEM Time (hr)					
	0	1/2	1	1½	2	3
Saline (2ml)	100	100.98±2.15	99.12±3.14	98.72±1.99	99.91±2.01	99.67±4.11
Glibenclamide (50)	100	87.70*±2.88	69.85**±3.75	59.02***±6.64	52.93***±7.01	48.9***±4.09
Nicorandil(20) + Glibenclamide(50)	100	104.17^{++}±4.17	92.79^{+++}±3.17	97.98^{+++}±5.47	85.26^{++}±6.23	86.8^{+++}±3.98
Nicorandil(40) + Glibenclamide(50)	100	112.65^{+++}±4.36	122.1^{+++}±5.43	126.32^{+++}±4.18	127.33^{+++}±5.04	115.80^{+++}±3.01
Nicorandil(80) + Glibenclamide(50)	100	102.53^{++}±3.68	95.46^{++}±5.73	86.44^{++}±4.79	83.43^{++}±3.62	74.6^{++}±4.21

**p < 0.05, **p < 0.01, ***p < 0.001 in comparison to saline treatment. +p < 0.05, ++p < 0.01, +++p < 0.001 in comparison to glibenclmide treatment*

Table 4 Effect of Nicorandil in various doses on Blood Glucose Level and its interaction with Glibenclamide (50µg/kg) in Diabetic Rabbits (n=6)

Drug treatment (µg/kg, oral)	Percentage change in Blood Glucose level ± SEM Time (hr)					
	0	1/2	1	$1^{1/2}$	2	3
Saline (2ml)	100	106.30± 13.2	110.21±4.51	107.07± 3.71	105.55±2.73	102.18±4.77
Glibenclamide(50)	100	102.12± 7.11	101.71± 6.91	100.99± 5.57	99.73±3.41	95.61±4.11
Nicorandil (20) + Glibenclamide(50)	100	104.48± 5.62	99.53± 6.13	98.82±7.2	96.94*±5.4	102.64±4.66
Nicorandil(40) + Glibenclamide(50)	100	102.37± 4.68	107.81± 4.12	110.07±3.72	103.71±6.71	100.66±7.1
Nicorandil(80) + Glibenclamide(50)	100	104.22± 6.3	105.88±4.71	108.22±5.1	103.92±3.90	111.77±6.1

**p < 0.05 in comparisons to saline treatment*

RESULTS

The BGL in the control, i.e. Saline treated rabbits fasted for 24 hrs did not change significantly throughout the experiment. The BGL was determined after oral administration of Nicorandil in doses of, 20, 40, 80 µg /Kg. A significant rise was depicted only by the 20 µg & 40 µg dose starting at ½ hr& the effect tested for 2 hrs, & 3 hrs with 40 µg /kg dose, it returned to control level at 4 hrs. The 80 µg/kg doses failed to produce any significant increase in blood sugar level (Table 1) .The peak rise in Blood sugar level was observed in 1hr to 1.5 hr with 20µg and 40µg/kg doses (Table 1). Administration of Glibenclamide 50 µg/kg orally per se produced significant decrease in blood sugar at half hour to 3 hours. On simultaneous administration of Nicorandil orally in doses of 20, 40 and 80 µg/kg and Glibenclamide 50µg/kg orally, produced significant change in blood glucose level. The hypoglycaemic effect of Glibenclamide was not observed with 20µg and 80µg/kg doses and the 40µg/kg dose instead produced hyperglycemia. In diabetic rabbits no significant change in blood sugar level after administration of nicorandil with glibenclamide (Table 1 to Table 4).

DISCUSSION

Nicorandil is the most commonly used KCO having both nitrate like and ATP sensitive K^+ channel activating properties.By virtue of this dual mechanism of action Nicorandil acts as a balanced coronary and peripheral vasodilator and reduce both prelude and after lode.Diabetes mellitus is usually found to be associated with cardiac complications (Cogolludo et al. 1999). Type – 2 Diabetes incidences is increasing worldwide (Mensah et

al. 2004). CVD account for the death of almost 70% diabetic patients and international cardiovascular management guidelines identify type- 2 diabetes as a CVD equivalent (Ashcroft et al. 1999). Cardiovascular complications are the principal cause of death in type-2 Diabetes. Improved glycemic control prevents the development and progress of microvascular and to a lesser extent macrovascular complications (Mensah et al. 2004). The importance of glycemic control in preventing cardiovascular complications has been demonstrated1 (Valensi et al. 2006). Nicorandil is now considered as an important drug in IHD and it hasantianginal efficacy similar to β blockers, nitrates and calcium channel blockers (Morrow et al. 2008). It has a dual action, operating both as a nitric oxide – generating agent and as an opener of ATP – sensitive K^+ (KATP) channels in vascular smooth muscle & cardiac muscle (Cogolludo et al., 1999) .The KATP channels in these tissues are closely related to those that regulate insulin secretion from pancreatic β cells (Aguilar-Bryan et al. 1999). Like the β cell channel, they are blocked by many of sulfonylureas that are widely used to treat type-2 diabetes (Ashcroft et al. 1999). Because type -2 diabetes increases the risk of cardiovascular disease, many diabetic patients might benefit from therapy with both sulfonylureas &nicorandil. The concomitant therapy of Nicorandil with antidiabetic agents like Glibenclamide is likely to produce some changes in regulation of blood sugar level so it was thought worthwhile to explore the effect of drug interaction between these drugs on blood sugar level in normal rabbits and Alloxan induced diabetic rabbits. In our study, nicorandil in doses of 20 & 80 µg/kg body weight significantly abolishes the hypoglycemic effect of glibenclamide&nicorandil in the dose of 40µg/kg body weight produces hyperglycemia up to 2-3 hrs. Insulin secretion from β cells of pancreas is related to inhibition of ATP sensitive K^+ channel , causing depolarization of cells of pancreatic islets which subsequently causes increase in intracellular Ca^{+2} concentration resulting release of insulin by exocytosis (Ahmed. 2006) . ATP sensitive K^+ channels that couple metabolism with membrane potential. An increase in local ATP, ADP ratio closes the channels, this reduces K^+ efflux & therefore tends to depolarize the cell membrane. The K^+ATP channel that are regulated by SUR are the Kir 6.2 channels. There are three main SUR subtypes, Kir 6.2 SUR 1 is expressed by β cells, Kir 2 SUR 2A by cardiomyocytes, and Kir 6.2 SUR 2B by arterial smooth muscle cells (Davis et al. 2001). The possible explanation of loss of effect of glibenclamide in the presence of nicorandil in 20 to 80 µg/kg body weight dose may be due to more affinity of nicorandil to Kir 6.2 SUR1 receptor than glibenclamide which causes opening of pancreatic ATP sensitive K^+ channel, membrane hyperpolarization and subsequent decrease in insulin release &hyperglycemia. The variation of response in different doses is due to dose dependent affinity of nicorandil to ATP sensitive K^+channel. The changes in blood sugar level after giving nicorandil d-were not significant in alloxon induced diabetic rabbits because there is loss of β cells in pancreas.

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