International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Effect of Acute and Chronic Administration of Nicorandil (A Potassium Channel Activator) on Blood Glucose of Albino Rabbit

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ABSTRACT

Many cells are equipped with so called potassium (K^+) channels which have an important role in maintaining transmembrane potential. Nicorandil being a K^+ channel activator (primary mechanism) causes hyperpolarization of membrane potential of vascular endothelial cells leading to vasodilation. Earlier studies suggest that besides vasodilation this drug could alter physiological blood glucose homeostasis. The purpose of the present study is to evaluate the acute and chronic effect of Nicorandil (graded doses) on fasting and postprandial blood glucose level in albino rabbits (n=30). For this study, the blood glucose levels were estimated before and after intraperitoneal (IP) administration of nicorandil to see its effect. In our study, we observed no significant changes in blood glucose level in acute administration (single dose) even at higher doses 512 mcg/kg body weight ($p > 0.1$).
Although we observed no significant changes in fasting glucose levels, there was significant rise in postprandial levels during chronic administration (for 15 days) $p < 0.05$.

Keywords: Nicorandil, blood glucose, potassium channel activator.

INTRODUCTION

Nicorandil, a potassium channel activator is already in the global market for the management and long-term prophylaxis of chronic stable angina pectoris. [1-4] This drug has potential use in the management of hypertension of various etiologies, myocardial salvage in MI, congestive cardiac failure, alopecia, bronchial asthma, urinary urge incontinence, premature labor, peripheral vascular diseases (Raynaud's, cerebrovascular) and penile erection disorders. [5] It is a novel derivative of Nicotinamide that possesses a terminal nitrate group chemically known as N (2-hydroxy ethyl) Nicotinamide Nitrate. Few studies showed that acute administration of nicorandil may reduce glucose tolerance in adrenaline induced hyperglycemia in rats. [6] However our current study primarily focuses on the possible diabetogenic effect of Nicorandil following its acute and chronic administration (graded doses) in albino rabbit. We hypothesized that acute and chronic administration of nicorandil has diabetogenic effects in albino rabbits in a dose dependent manner.

MATERIALS AND METHODS

The Institutional Ethical Committee has approved this work. For this study, we selected 30 adult albino rabbits with male/female 1:1 ratio (one to one and a half Kg body wt.). All animals were maintained

at optimum room temperature in a well-ventilated animal house under natural photoperiod conditions. These were divided into five groups each, having six in every group with male-female ratio 1:1. The administration was affected in a volume of one ml/kg body wt. and the route of administration was intraperitoneal injection. The initial study revealed that the fasting and postprandial blood sugar levels were reliable and consistent.

To observe the acute effect of Nicorandil, we collected blood samples after 30 minutes of its single administration in various groups in pre-decided doses. To observe the chronic effect, we administered identical doses of nicorandil in the respective test groups once a day for a period of 15 days. Administration of drug was made effective at 9 AM every day.

In contrary, the control group was treated with normal saline of equal volume to the testing drug doses. The time for administration of normal saline was essentially the same as drug administration i.e. 9 AM. Route of administration in all groups was intraperitoneal injection. All samples were collected by venipuncture of marginal ear vein in the rabbits. Blood glucose was estimated by readily available kit (Merck) in SELECTRA-E fully auto clinical chemistry analyzer.

Nicorandil for this study was obtained in the form of injection IKOREL (Rhone-Poulenc). The dose of nicorandil for this study was determined as per the study done by Krumenacker M et al. [7]

Statistical Analysis

All the results were expressed as mean ± SD. Student T-test was used to assess the statistical significance of results before and after administration in both control (saline treated) and drug (nicorandil) treated groups. The P value <0.05 was considered as significant, and P value >0.1 as insignificant.

RESULT

Acute administration of nicorandil (in graded dose) did not changed blood glucose levels (fasting and postprandial), p>0.1 (table-1).

Even during the chronic administration of nicorandil (in graded dose), we observed no statistically significant changes in fasting blood glucose level (p > 0.1) but significantly elevated postprandial blood glucose (p<0.05) within a dose range between 32 to 512 micro gm./kg body wt. (Table-2).

Table no. 1 Effect of Nicorandil (Acute Administration) on Fasting and Post Prandial Blood Sugar of Albino Rabbit

S. No.	Name of Drug	Dose (Unit/kg) IP	No. of Rabbits	Mean fasting blood sugar in mg/dL ± SEM*		P value	Mean post prandial blood sugar in mg/dL ± SEM		P value
				Before drug	After drug		Before drug	After drug	
1.	Nicorandil	8 mcg	6	76.0±3.22	76.0±2.68	>0.1	120.0±2.97	118.0±3.47	>0.1
2.	Nicorandil	32 mcg	6	74.0±2.92	72.0±3.02	>0.1	124.0±3.02	120±3.22	> 0.05
3.	Nicorandil	128 mcg	6	77.0±3.54	76.0±3.82	> 0.5	127.0±2.82	127.0±3.64	>0.1
4.	Nicorandil	512 mcg	6	80.0±2.44	80.0±2.65	>0.1	125.0±4.65	127.0±3.91	> 0.1
5.	Normal Saline	1 ml.	6	75.0±2.29	75.0±2.46	>0.1	130.0±4.08	129.0±4.16	> 0.5

*SEM: Standard error of the Mean

Table no. 2 Effect of Nicorandil (Chronic Administration) on Fasting and Post Prandial Blood Sugar of Albino Rabbit

S. No.	Name of Drug	Dose (Unit/kg) IP	No. of Rabbits	Mean fasting blood sugar in mg/dL ± SEM*		P value	Mean post prandial blood sugar in mg/dL ± SEM*		P value
				Before drug	After drug		Before drug	After drug	
1.	Nicorandil	8 mcg	6	74.0±2.64	72.0±2.98	> 0.1	122.0±2.22	124.0±2.69	> 0.1
2.	Nicorandil	32 mcg	6	77.0±2.51	77.0±2.62	>0.1	128.0±3.11	133.0±3.50	< 0.05
3.	Nicorandil	128 mcg	6	75.0±3.03	76.0±3.12	> 0.5	120.0±3.23	132.0±3.44	< 0.05
4.	Nicorandil	512 mcg	6	82.0±3.32	82.0±3.41	>0.1	125.0±2.66	140.0±3.61	< 0.05
5.	Normal Saline	1 ml.	6	72.0±2.99	70.0±3.01	> 0.1	120.0±3.05	122.0±3.25	> 0.1

*SEM: Standard error of the Mean

DISCUSSION

A single administration of graded doses of nicorandil did not affect the fasting and the postprandial blood glucose level (acute administration) (Table-1). Chronic administration (for 15 days) of nicorandil (in graded doses) also had no significant effect on fasting blood glucose, while the postprandial blood glucose level was significantly elevated within a dose range of 32 to 512 mcg /Kg body weight (table-2). The tested hypothesis was partially proven correct with the fact that chronic administration of nicorandil has increased postprandial blood glucose level in a dose dependent manner. On the other hand, the first component of the hypothesis pertaining to the effect of acute administration was disproven. Studies have shown that one of the dual mechanisms of action of nicorandil is Potassium channel activation (all types). [8,9] The increase in postprandial blood glucose could be due to activation of ATP-sensitive potassium channels located on the surface membrane of beta cells of islets of the Langerhans. [10] Potassium channel activation leads to hyperpolarization of beta cells that hinders the activation of voltage-gated calcium channels from insulin release. Lack of insulin in the blood leads to hyperglycemia. Such diabetogenic potential of nicorandil on chronic administration was observed in prescription–event monitoring. This finding is in conformity with the observation made by Ahmed et al, [11] who concluded that "nicorandil when added to glibenclamide (a sulfonylurea) in alloxan induced diabetic rats, worsened diabetes by antagonizing the hypoglycemic effect of glibenclamide. This is probably due to blockade of potassium channel closing action of glibenclamide by nicorandil on ATP sensitive K+ channels on the surface of beta cells of pancreas." Furthermore, Dunn N et al [12] and Biswas et al [6] reported that nicorandil is not hyperglycemic in non-diabetic volunteers. This sort of different findings could be due to species variation but further studies are required to establish this fact.

CONCLUSION

From this study, we concluded that Nicorandil may have diabetogenic potential in animals on chronic administration. Several animal & clinical studies have been conducted to explore the diabetogenic potential of nicorandil. However, many of those conflicted with each other. Hence, there is a need for further research and long-term follow up of this drug in clinical setting in order to draw a more satisfactory conclusion.

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How to cite this article: Das S, Alsalhanie KM, Nauhria S et al. Effect of acute and chronic administration of nicorandil (a potassium channel activator) on blood glucose of albino rabbit. Int J Health Sci Res. 2017; 7(5):123-126.

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