Research Article

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EFFECT OF NICORANDIL ON THE PHARMACODYNAMICS OF METFORMIN IN NORMAL AND HYPERGLYCAEMIC RATS

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ABSTRACT

In situation of polypharmacy one drug may interact with other drug leading to drug-drug interactions. Thus in order to provide rational therapy, study of mechanisms of drug interactions plays a vital role in selecting the drug combination. These interactions are more often with high risk disorders like diabetes, hypertension and drugs having narrow margin of safety used for prolonged period of time. Studies were conducted in normal and alloxan induced diabetic rats with oral administration of selected doses of metformin, nicorandil and their combination with adequate wash out periods between treatments. Blood samples were collected from rats at regular intervals of time and were analyzed for glucose by GOD/POD method. Metformin produced antihyperglycemia in normal/diabetic rats with peak activity at 3h. Therapeutic dose of metformin alone or in combination with nicorandil produced hypoglycemic condition in normal rats and the same phenomenon observed in diabetic rats also. There was significant change in the percentage of mean reduction glucose levels of metformin when given in alone/combination with nicorandil in normal/diabetic rats. Hence it is concluded that metformin treated along with single/multiple dose treatment with nicorandil has influence on pharmacodynamics of metformin in rats.

Keywords: Metformin, Nicorandil, Diabetes, Hypertension, Hypoglycaemia, Pharmacodynamics.

INTRODUCTION

Polypharmacy is inevitable common practice all over the world to treat single or multiple disorders which are accompanied with several other complications. Predictors for polypharmacy may include multiple prescribers, complex drug therapies and psychosocial contributions, which in turn leads to adverse drug events, drug-drug interactions, potential complications of therapy and decreased adherence to the drug regimen. In situation of polypharmacy one drug may interact with other drug leading to drug-drug interactions. Thus in order to provide rational therapy, study of mechanisms of drug interactions plays a vital role in selecting the drug combination. These interactions are more often with high risk disorders like diabetes, hypertension (HT) and drugs with narrow margin of safety used for prolonged period of time.

Diabetes is a chronic disorder, in which maintenance of normal blood glucose levels is of critical importance. Diabetes in the long run may precipitate several disorders like cardiovascular, renal, retinal and fungal infections simultaneously. Among which cardiovascular complications are more prevalent. Angina or stroke is one such complication seen in much chronic diabetes [1]. Incidence of HT is 75% attributable to risk in people with diabetes [1]. Canadian study conducted between 2007 and 2008, represented 1 in 4 Canadians with HT and 2 by 3 of those with diabetes. The mortality rate was 2.5 times higher in conditions with diagnosed HT and Diabetes than those of Canadians without either condition [2].

Oral hypoglycemic agents are used in the treatment of Type-2 diabetes, among which a biguanide derivative known to be Metformin

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is widely prescribed and preferred in therapy because of its multiple beneficiary effects in diabetics. Metformin is known to act mainly by peripheral glucose utilization, activation of insulin binding and enhancing insulin receptor kinase. Vital advantages of metformin over other major class of oral hypoglycemic agents are, it does not cause hypoglycaemia, not lower blood glucose levels in non-diabetic individuals [3] and has direct beneficial effect on serum lipids and lipoproteins [4-6]. Currently nicorandil is used for the treatment of HT, as it acts by opening K^+ channels in cardiac muscle cells and also by releasing nitric oxide. Nitric oxide is involved in the release of insulin from pancreatic-β cells [7-8]. K^+ channel openers are one group of drugs used for the treatment of hypertension and angina [9]. Nicorandil is one of the widely using drug and the drug of choice for the last few years in treatment of hypertension [10]. Since closing of K^+ is necessary for the secretion of insulin, K^+ channel openers are likely to interact with metformin used simultaneously for the treatment of diabetes, since there is possibility for their combined use in diabetes associated hypertension which may lead to drug-drug interaction. Hence it is planned to find out the safety of the combination in normal and hypoglycemic rats.

MATERIALS AND METHODS

Albino rats of either sex obtained from M/s. Mahaveer Enterprises, Hyderabad. All animals were maintained on pellet diet supplied by M/s. Provimi pellet feed for rodents, Bangalore with 12h/2h light/dark cycle and water ad libitum. Animals were fasted for 18 h before the experiment. Both water and food were withdrawn during the experiment.

Study in normal rats:

A group of six albino rats weighing between 250-300g were administered with 50mg/kg body weight metformin, orally. The same group was administered with 1.8mg/kg body weight nicorandil, orally after a wash out period of one week. The same group was also administered with 1.8mg/kg body weight nicorandil 30min prior to 50mg/kg body weight metformin, after a further wash out period of 1 week. Blood samples were withdrawn from retro orbital puncture at 0, 1, 2, 3, 4, 6, 8, 10 and 12h intervals. Blood samples were analyzed for blood glucose levels by GOD/POD method [11] using commercial glucose kits (Span diagnostics).

Study in diabetic rats:

Diabetes was induced by the administration of alloxan monohydrate in two doses i.e. 100mg and 50mg/kg body weight, intraperitoneally for two consecutive days [12]. A group of 6 rats with blood glucose levels above 250mg/dL was selected for the study. The study similar to the one conducted in normal rats was repeated in diabetic group.

Data and Statistical analysis:

Data was expressed as Mean ± Standard Error Mean (SEM). The significance was determined by applying One-way ANNOVA followed by Dunnett's Test.

RESULTS AND DISCUSSION

Metformin produced a peak response of antidiabetic activity at 3h in normal and diabetic rats. Nicorandil produced hyperglycemic effect at 6h in both normal and diabetic rat model and significantly reduced the hypoglycemic effect of metformin in both normal and diabetic rat; however the effect was effective and prominent in MDT (Multiple Dose Treatment (Metformin + Nicorandil)) than that of SDT (Single Dose Treatment (Metformin + Nicorandil)). In normal rats, there was significant decrease in hypoglycemic effect of metformin due to nicorandil was which observed at 3h, whereas in diabetic rats the effect was from 2-4h of the treatment period.

Drug interactions are usually perceived in clinical practice, whereas animal models are evaluated usually in appliances for those interactions. We studied the influence of nicorandil on the pharmacodynamics of metformin in normal/diabetic rats. The normal rat model served to quickly identify the interaction. Whereas the diabetic rat model served to validate the same response in the actually used condition of the drug (in Type II diabetes). It is well established that metformin acts by peripheral glucose utilization, activation of insulin binding, enhancing insulin receptor kinase and reduce the production of glucose

from liver. Literatures revealing that metformin increase glucose utilization of peripheral tissues by 50% at high insulin infusion rate [13]. Metformin may stimulate glucose transport by increasing GLUT-4 glucose transporters in the plasma membrane which is similar to that produced by acute administration of insulin [14]. Nicorandil is used for the treatment of HT, as it acts by opening K^+ channels in cardiac muscle cells and also by releasing nitric oxide. Nitric oxide is involved in the release of insulin from pancreatic-β cells. The dose of nicorandil is selected by human therapeutic dose extrapolated to rats basing on the body surface area. The selected dose of nicorandil produced a slight increase in the blood glucose levels which was found to be insignificant. In combination it changes the blood glucose reduction produced by metformin.

Table 1: Summary of Mean percent of blood glucose reduction in normal rats

Normal RAT								
TIME (HRs)	METFORMIN		NICOANDIL		SDT		MDT	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	20.70	0.67	-10.01	1.08	17.82	1.56	16.22*	0.70
2	25.16	1.68	-15.09	2.42	18.37*	1.37	17.80**	0.89
3	30.99	2.50	-20.62	2.63	22.63**	0.50	18.24***	0.95
4	18.05	1.56	-16.76	6.53	12.86	1.02	10.34**	1.97
6	15.46	1.00	-22.68	4.64	10.93*	1.23	9.91*	1.60
8	12.53	1.67	-7.81	5.06	9.94	1.50	7.48*	1.15
10	10.44	1.14	0.22	4.40	7.28	1.40	6.64	1.95
12	7.45	1.48	4.59	2.70	4.16	2.13	3.26	1.71

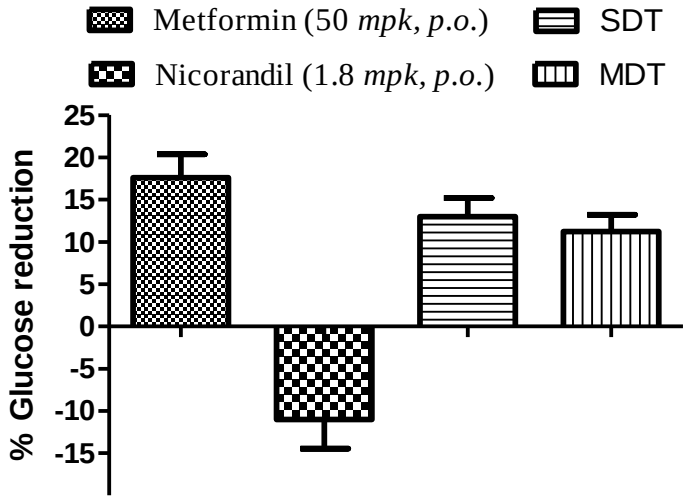
Values are expressed as Mean ± SEM; n=6 animals / group
* P≤0.05, ** P≤0.01 and ***P≤0.001 as compared to Metformin Group by One-way ANNOVA followed by Dunnett's Test
SDT: Single Dose Treatment (Metformin + Nicorandil)
MDT: Multiple Dose Treatment (Metformin + Nicorandil)

Table 2: Summary of Mean percent of blood glucose reduction in Diabetic rats

Diabetic RAT(GLUCOSE ≥250 mg/Dl)								
TIME (HRs)	METFORMIN		NICOANDIL		SDT		MDT	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	29.67	1.65	-12.47	0.52	24.10*	0.84	21.17**	1.93
2	36.63	1.77	-15.13	0.88	29.80**	0.78	26.05***	0.98
3	45.60	1.21	-19.63	1.20	30.61***	1.04	27.28***	0.41
4	27.48	1.09	-23.53	1.04	22.15**	1.29	17.79***	0.83
6	21.42	1.65	-21.77	1.49	19.50	0.78	16.35**	0.50
8	19.02	4.91	-1.68	1.59	17.35	0.72	12.41	0.96
10	13.74	2.03	3.06	1.22	12.20	0.98	10.03	0.65
12	9.04	1.75	7.26	0.88	7.41	0.64	6.61	0.65

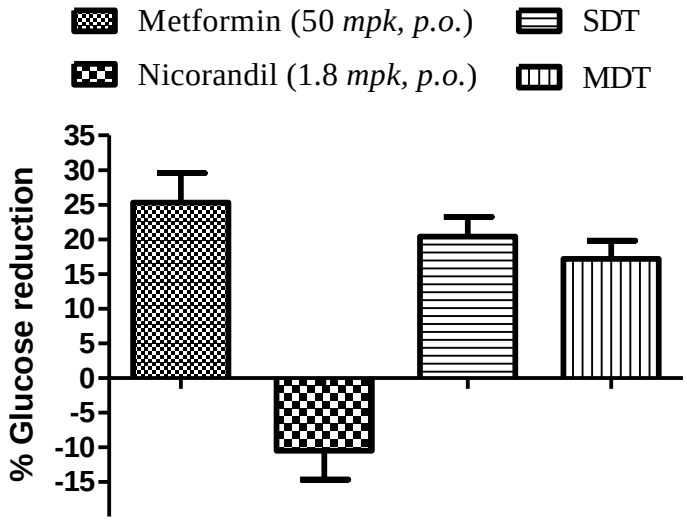
Values are expressed as Mean ± SEM; n=6 animals / group
* P≤0.05, ** P≤0.01 and ***P≤0.001 as compared to Metformin Group by One-way ANNOVA followed by Dunnett's Test
SDT: Single Dose Treatment (Metformin + Nicorandil)
MDT: Multiple Dose Treatment (Metformin + Nicorandil)

Figure 1: Effect of Nicorandil on Mean percent of blood glucose reduction of Metformin in normal rats



Values are expressed as Mean ± SEM; n=6 animals / group

Figure 2: Effect of Nicorandil on Mean percent of blood glucose reduction of Metformin in Diabetic rats



Values are expressed as Mean ± SEM; n=6 animals / group

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