Research Article

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PHARMACODYNAMIC DRUG INTERACTIONS OF METFORMIN AND LACIDIPINE IN ANIMAL MODELS

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ABSTRACT

The study was conducted to find the influence of lacidipine (Ca2+ channel blocker, which is widely used for hypertension) on the hypoglycemic activity of metformin (biguanide derivative), which is widely used for the type-II diabetes management in humans.Studies were conducted in normal rats,alloxan induced diabetic rats and normal rabbits with oral administration of selected doses of metformin, lacidipine and their combination with adequate washout periods in between treatments. Blood samples were collected from rats/rabbits by retro orbital/marginal ear vein puncture respectively at regular intervals of time. All the blood samples were analysed for glucose by GOD/POD method. Metformin produced hypoglycaemia / antihyperglycaemia in normal / diabetic rats with peak activity at 3 h and in rabbits at 3 h. Lacidipine produced peak hyperglycaemia at 4h in rats, whereasat 6h rabbits. Lacidipine when given alone and in combination it reduced the effect of metforminin peak action level both in rats and in normal rabbits. Similar to the theoretical expectation, the pharmacodynamic effect of metformin was significantly changed when combined with lacidipine in rats and rabbits indicating that peer research need to carry out to confirm the mechanism established.

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

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by rise in blood glucose level known as hyperglycaemia. DM is mainly of two types, type I and Type II. Type I or Insulin dependent diabetes mellitus (IDDM) is due to lack of synthesis of insulin in the β cells of islets of Langerhans of pancreas, whereas type II or noninsulin dependent diabetes mellitus (NIDDM) is due to lack of release of insulin from the β cells of islets of Langerhans of pancreas however Type II is common than type I. According to review estimations, approximately 215 million people all over the world suffer from diabetes among which 80-90% belongs to type-II diabetes [1]. A number of type II diabetic people are expected to increase because of modern life styles with high caloric diet and low energy expenditure leading to obesity and also due to medical advances that extend life span [2, 3].

Chronic diabetes mellitus precipitates other disorders in the long run leading to existence of several disorders simultaneously [4]. Such situations (existence of simultaneous multiple disorders) demand the use of more than one drug simultaneously known as polypharmacy which may precipitate drug interaction problems that will adversely affect their health (American Society of Health-System Pharmacists). Hence care should be taken to avoid the possibility for over medication/ under medication / unwanted effects of the combinations particularly used in clinical disorders. It is desirable if more information is generated on the safety of such drug combinations by conducting more studies in this area.

Patients with DM, whose blood glucose is not tightly controlled with drug treatment, are at risk of retinopathy, nephropathy and

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neuropathy (microvascular complications) and hypertension, angina pectoris, myocardial infarction and cardiac dysrrhythmias (macrovascular complications) which increase morbidity and mortality [5]. As a result, author focused on the possible drug interations between DM and Antihypertensive drugs used in the treatment of the diabetic complications of Hypertenstion (DCH).

Oral hypoglycaemic agents are used in the treatment of type-2 diabetes, among which a biguanide derivative known to be Metformin is widely prescribed and preferred in therapy because of its multiple beneficiary effects in diabetics.Metformin is known to act mainly by peripheral glucose utilisation, activation of insulin binding and enhancing insulin receptor kinase. Vital advantages of metformin over other major class of oral hypoglycaemic agents are, it does not cause hypoglycaemia,not lower blood glucose levels in non-diabetic individuals [6] and direct beneficial effect on serum lipids and lipoproteins [7-9].For hypertension treatmentCa2+ channel blockers are one group of drugs which will be used frequently. Lacidipine, a dihydropyridine derivative is widely used now a daysfor the treatment of hypertension. Since Ca2+ is necessary for the secretion of insulin, Ca2+ channel blockers are expected to interact with antidiabetic drugs. Since there is possibility for their combined use in diabetes associated with hypertension, it is planned to find out the safety of the combination in animal models. Hence in the present study the influence of Lacidipine on the pharmacodynamics of metformin was found in rats/rabbits.

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/12h 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 250-300 g were administered with 50mg/ kg body weight metformin, orally. The same group was administered with 0.36mg/ kg body weight lacidipine, orally after a wash out period of one week. The same group was also administered with 0.36mg/ kg body weight lacidipine 30 min 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 [10] using commercial glucose kits (Span diagnostics).

Study in diabetic rats:

Diabetes was induced by the administration of alloxan monohydrate in two doses i.e. 100 mg and 50 mg/kg body weight, intraperitoneally for two consecutive days [11]. A group of 6 rats with blood glucose levels above 250 mg/dL was selected for the study. The study similar to the one conducted in normal rats was repeated in diabetic group.

Study in normal rabbits:

A group of six albino rabbits weighing between 1.38 -1.70 kg were used in the study. They were administered with 15 mg/kg body weight metformin, orally. The same group was administered with 0.19 mg/kg body weight lacidipine, orally after a wash out period of one week. The same group was also administered with 0.19 mg/ kg body weight lacidipine (single dose treatment) 30 min prior to 15 mg/kg body weight metformin after a further wash out period of one week. After interaction study the animals were continued with the daily treatment of lacidipine (multiple dose treatment) for the next eight days with regular feeding. Later after 18 h fast they were again given the combined treatment on the ninth day. Blood samples were collected at 0,1,2,3,4,6,8,12,16,20 and 24h intervals by puncturing the marginal ear vein in all the experiments. Blood samples were analysed for blood glucose content by GOD/POD method[10].

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 hypoglycaemia / antihyperglycaemia in normal / diabetic rats with peak activity at 3h, hower similar activity was produced in rabbits at 3 h. Lacidipine produced peak hyperglycaemia at 4h in rats, whereas at 6h rabbits. Lacidipine when given alone and in combination it reduced the effect of metformin in peak action level both in rats and in normal rabbits. Hyperglycaemic effect produced by lacidipinewas prominent and was not significant in normal/diabetic rat and normal rabbits during SDT (Single Dose Treatment (Metformin + Lacidipine)); whereas the activity was significant during MDT (Multiple Dose Treatment (Metformin + Lacidipine)) which causes the reduction of hypoglycaemic activity of metformin in normal/diabetic and normal rabbit.

Drug interactions are usually seen in clinical practice and the mechanisms of interactions are evaluated usually in animal models. We studied the influence of lacidipine on the pharmacodynamics of metformin in normal and diabetic rats and also in normal rabbits. The normal rat model served to quickly identify the interaction. The diabetic rat model served to validate the same response in the actually used condition of the drug (in Type II diabetes). The rabbit model is another dissimilar species to validate the occurrence of interaction in another species.

It is well established that metformin acts by peripheral glucose utilisation, activation of insulin binding, enhancing insulin receptor kinase and reduce the production of glucose from liver. Literatures revealing that metformin increase glucose utilisation of peripheral tissues by 50% at high insulin infusion rate [12]. 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 [13] Calcium channels are located on a variety of tissues. A combination of electrophysiological and pharmacological criteria suggests that there are five distinct types of voltage gated Ca2+ channels L, T, N, P and R. In general L type channels are particularly important in regulating contraction of cardiac and smooth muscles [14]. L type calcium channel is believed to be important in mediating sustained insulin release at high glucose concentration and G type channels mediate pulsatile insulin secretion. All approved Ca2+ channel blockers bind to the α-subunit of the L type Ca2+ channels. The α-subunit of L type Ca2+ channels was again subdivided into three classes depending on their location. S class located on skeletal muscle, C class located on smooth/ cardiac muscle and neurons and D class located on endocrine glands. Literature reports indicate that Lacidipine antagonize L type Ca2+ channels [15, 16] and theoretically are expected to decrease release of insulin and raise blood glucose level. It is also reported that lacidipine selectively acts on vascular smooth muscle and has little effects on heart and pancreatic cells [17, 18]. That might be due to its more selectivity towards C class channels and the same may be responsible for its low level effect on blood glucose increase and antagonism to metformin induced hypoglycaemia.

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

Normal RAT								
TIME (hrs)	METFORMIN		LACIDIPINE		SDT		MDT	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	15.86	0.54	-9.01	0.85	13.59*	0.45	13.12*	0.84
2	18.74	1.18	-11.79	1.33	16.64	0.42	15.11*	0.58
3	24.09	1.21	-13.29	0.91	21.22*	0.34	19.21**	0.90
4	14.68	2.01	-17.02	1.82	10.87	0.78	8.86*	0.81
6	10.88	1.56	-9.60	1.73	9.13	0.76	7.42	0.78
8	8.44	0.82	-1.01	1.45	7.19	0.59	6.29	0.45
10	6.45	0.76	2.07	1.19	5.71	0.51	5.13	0.59
12	4.52	0.58	6.47	0.66	4.11	0.55	3.92	0.57

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 + Lacidipine)
MDT: Multiple Dose Treatment (Metformin + Lacidipine)

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

Diabetic RAT(GLUCOSE ≥250 mg/Dl)								
TIME (HRs)	METFORMIN		LACIDIPINE		SDT		MDT	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	25.48	1.38	-8.40	0.87	22.62*	1.60	19.98*	1.40
2	30.02	1.24	-9.89	0.79	27.51*	1.06	23.20**	1.66
3	39.97	2.09	-12.94	0.52	35.73*	1.98	30.32**	1.83
4	21.72	2.37	-16.33	0.86	18.95	1.58	13.44**	0.77
6	19.28	1.50	-12.84	1.54	15.30	1.16	11.34***	0.90
8	12.28	1.10	-4.11	0.76	10.89	1.29	8.43*	0.63
10	9.17	1.30	2.61	0.58	8.12	0.54	7.10	0.78
12	6.73	1.06	4.25	0.91	6.42	0.57	5.18	0.50

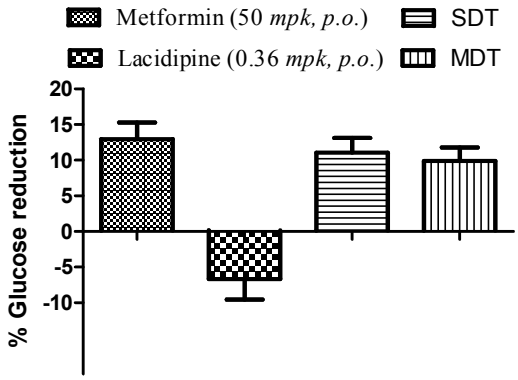
Values are expressed as Mean ± SEM; n=6 animals / group
* P<0.05, ** P<0.01 and ***P<0.001 as compared to Metformin Group by One-way ANNOVA followed by Dunnett's Test
SDT: Single Dose Treatment (Metformin + Lacidipine)
MDT: Multiple Dose Treatment (Metformin + Lacidipine)

Table 3: Summary of Mean percent of blood glucose reduction in normal Rabbits

Normal Rabbit								
TIME (HRs)	METFORMIN		LACIDIPINE		SDT		MDT	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	15.77	0.85	-5.18	1.43	13.78	0.80	12.26**	0.45
2	17.23	0.86	-7.00	0.72	15.70	0.75	13.91*	0.56
3	20.06	0.79	-9.67	0.84	16.98*	0.83	15.59**	0.59
4	12.01	0.84	-12.04	1.62	11.73	1.52	9.25	0.55
6	9.28	0.57	-12.18	1.81	8.17	0.45	7.19*	0.59
8	7.01	0.80	-8.39	1.19	5.33	0.26	4.46*	0.47
12	4.51	0.65	-6.04	1.24	3.13	0.42	2.27*	0.34
16	2.05	0.49	-1.71	0.87	1.12	0.51	0.92	0.56
20	-0.36	0.69	1.36	1.00	-1.35	0.68	-0.85	0.74
24	-2.59	0.30	2.07	0.73	-2.92	0.62	-3.01	0.70

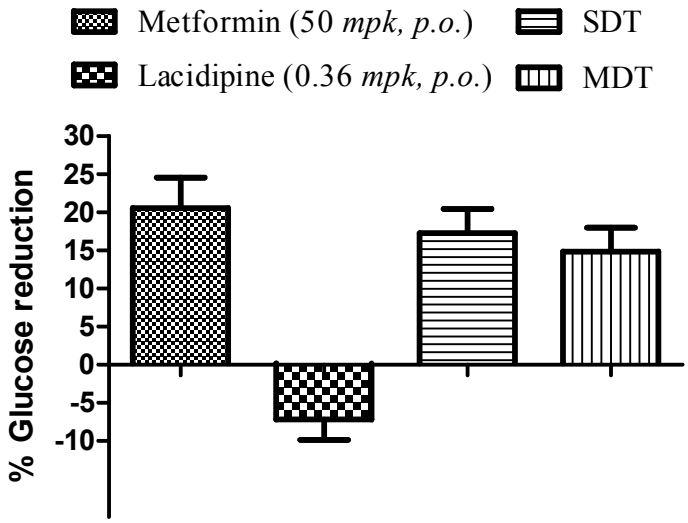
Values are expressed as Mean ± SEM; n=6 animals / group
* P<0.05, ** P<0.01 and ***P<0.001 as compared to Metformin Group by One-way ANNOVA followed by Dunnett's Test
SDT: Single Dose Treatment (Metformin + Lacidipine)
MDT: Multiple Dose Treatment (Metformin + Lacidipine)

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



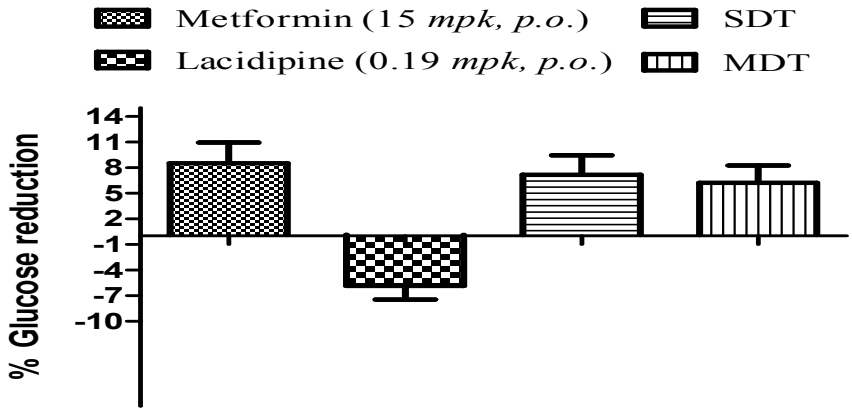
Values are expressed as Mean ± SEM; n=6 animals / group

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



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

Figure 3: Effect ofLacidipine on Mean percent of blood glucose reduction of Metformin in normal Rabbits



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

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