Research Article

Available online at www.JGTPS.com

ISSN: 2230-7346
Journal of Global Trends in Pharmaceutical Sciences
Volume- 5, Issue -2, pp - 1547 – 1552- April –June (2014)

# PHARMACODYNAMIC DRUG INTERACTIONS OF METFORMIN AND LACIDIPINE IN ANIMAL MODELS

**Suresh Goli[1]***
**K. Eswar Kumar[2]**

[1*] *Research Scholar, Jawaharlal Nehru Technological University (JNTUK), Kakinada- 533 003, (A.P), INDIA.*

[2] *Pharmacology Division, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530 003, (A.P), INDIA.*

***Journal of Global Trends in Pharmaceutical Sciences***

## 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, 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 hypoglycemia / antihyperglycemia in normal / diabetic rats with peak activity at 3h and in rabbits at 3h. Lacidipine produced peak hyperglycemia at 4h in rats, whereas at 6h rabbits. Lacidipine when given in combination it reduced the effect of metformin peak action level in both rats and 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, Hypoglycemia, Pharmacodynamics.

## INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by rise in blood glucose level known as hyperglycemia. 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 Non-Insulin 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

**Address for correspondence**
***Suresh Goli**
Mob: 9966374700
E-mail: sureshgoli@hotmail.com

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 interactions between DM and Antihypertensive drugs used in the treatment of the diabetic complications of hypertension (DCH).

Oral hypoglycemic 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 hypoglycemic agents are, it does not cause hypoglycemia, not lower blood glucose levels in non-diabetic individuals [6] and direct beneficial effect on serum lipids and lipoproteins [7-9]. For hypertension treatment $Ca^{2+}$ channel blockers are one group of drugs which will be used frequently. Lacidipine, a dihydropyridine derivative is widely used now a day for the treatment of hypertension. Since $Ca^{2+}$ is necessary for the secretion of insulin, $Ca^{2+}$ 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 18h 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 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 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 [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. 100mg/kg and 50mg/kg body weight, intraperitoneally for two consecutive days [11]. 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.

**Study in normal rabbits:**

A group of six albino rabbits weighing between 1.38 - 1.70kg were used in the study. They were administered with 15mg/kg body weight metformin, orally. The same group was administered with 0.19mg/kg body weight lacidipine, orally after a wash out period of one week. The same group was also administered with 0.19mg/kg body weight lacidipine (single dose treatment) 30min prior to 15mg/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 18h 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 hypoglycemia / antihyperglycemia in normal / diabetic rats with peak activity at 3h, however similar activity was produced in rabbits at 3h. Lacidipine produced peak hyperglycemia 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. Hyperglycemic effect produced by Lacidipine was 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 hypoglycemic 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 $Ca^{2+}$ 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 $Ca^{2+}$ channel blockers bind to the α-subunit of the L type $Ca^{2+}$ channels. The α-subunit of L type $Ca^{2+}$ 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 $Ca^{2+}$ 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 hypoglycemia.

**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 ≥250mg/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 |

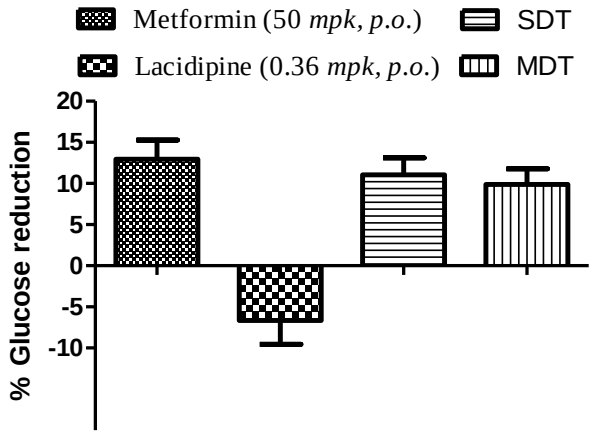
Values are expressed as Mean ± SEM; n=6 animals / group
* P≤0.05, ** P≤0.01 and ***P≤0.001 as compared to Metformin Group by One-way ANNOVA followed by Dunnett's Test
SDT: Single Dose Treatment (Metformin + Lacidipine)
MDT: Multiple Dose Treatment (Metformin + Lacidipine)

**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 |

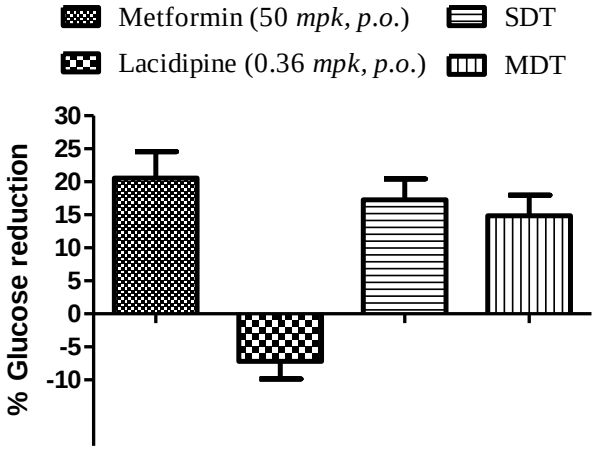
Values are expressed as Mean ± SEM; n=6 animals / group
* P≤0.05, ** P≤0.01 and ***P≤0.001 as compared to Metformin Group by One-way ANNOVA followed by Dunnett's Test
SDT: Single Dose Treatment (Metformin + Lacidipine)
MDT: Multiple Dose Treatment (Metformin + Lacidipine)

**Figure 1:** Effect of Lacidipine on Mean percent of blood glucose reduction of Metformin in Normal rats



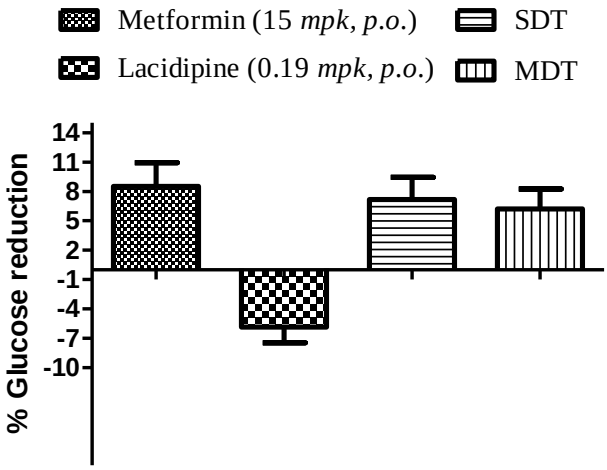

Values are expressed as Mean ± SEM; n=6 animals / group

**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 of Lacidipine on Mean percent of blood glucose reduction of Metformin in Normal Rabbits




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

## REFERENCES


1. Hussain, A., Claussen, B., Ramachandran, A. & Williams, R. Prevention of type 2 Fdiabetes: A review. Diabetes Res ClinPract (2006).
2. Aude, Y.W., Mego, P. & Mehta, J.L. Metabolic syndrome: dietary interventions. Curr Opin Cardiol 19, 473-9 (2004).
3. Jacobs-van der Bruggen, M.A. et al. Lifestyle Interventions Are Cost-Effective in People with Different Levels of Diabetes Risk: Results from a modeling study. Diabetes Care 30, 128-34 (2007).
4. Brady PA, TerzicA. The sulfonylurea controversy: more questions from the heart. J Am CollCardiol. 1998; 31(5): 950-956.
5. Cerveny JD, Leder RD &Weart CW: Issues surrounding tight glycemic control in people with type 2 diabetes mellitus. Ann Pharmacother 1998; 32(9):869-905.
6. Hermann LS: Metformin: a review of its pharmacological properties and therapeutic use. DiabeteMetab 5:233-45, 1979.
7. Rains SGH, Wilson GA, Richmond W, Elkeles RS: The effect of glibeclamide and metformin on serum lipoproteins in type 2 diabetes. Diabetic Med 5:653-58, 1988
8. Sirtori CR, Tremoli E, Sirtoli M, Conti F, Paoletti R: Treatment of hypertriglyceridemia with metformin: effectiveness and analysis of results. Atherosclerosis 26:583-92,1977.
9. Descovich G, Montaguti U, Ceredi C, Cocuzzsa E, Sirtori CR: Long-term treatment with metformin
10. P. Trinder, Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chemogen, J ClinPathol, 22, 1969, 158-61.
11. R.E. Heikkila, The prevention of alloxan-induced diabetes in mice by dimethyl sulfoxide, Eur J Pharmacol, 44(2), 1988, 191-93.
12. Nosadini R, Avogaro A, Trevisan R, Valerio A, Tessari P, Duner E, Tiengo A, Velussi M, Del Prato S, De Kreutzenberg S, Muggeo M, Crepaldi G: Effect of metformin on insulin-stimulated glucose turnover and insulin binding to receptors in type II diabetes. Diabetes Care 10:62-67,1987.
13. Amlal T, Rastogi S, Vranic M, Klip A: Decrease in glucose transporter number in skeletal muscle of mild diabetic (streptozotocin-treated) rats. Endocrinology 125:890- 97, 1989.
14. Rang HP, Dale MM, Ritter JM. Pharmacology 2003; 5th ed. Edinburgh: Churchill Livingstone; 52 53.
15. Leonetti G & The Northern Italian Study Group of Lacidipine in Hypertension: Comparative study of lacidipine and nifedipine SR in the treatment of hypertension: an Italian multicenter study. J CardiovascPharmacol. 1991; 17(suppl 4):S31-S34.
16. Hall ST, Harding SM, Evans GL et al. Clinical pharmacology of lacidipine. J CardiovascPharmacol 1991; 17(4): S9-S13.
17. Galeone F, Giuntoli F, Fiore G, Brunelleschi G, Saba P. Antihypertensive and metabolic effects of lacidipine in patients with NIDDM and/or hypertension. J CardiovascPharmacol 1994; 23 Supl5 : S 105-7.
18. Spieker C, Zidek W. The impact of lacidipine, a novel dihydropyridine calcium antagonist, on carbohydrate and lipid metabolism. J Cardiovascular Pharmacol 1995; 25 suppl 3: S23-6.