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Effect of Candesartan cilexetil on the Blood Glucose Levels of Glimepiride in Normal and Diabetic Albino Rats

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Research Article

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Abstract

Background: Co administration of two or more medications to a patient is called polypharmacy. Hence, much attention is required to study the possible drug interaction in the prescription, to reduce the influence of one drug action on the another. Accordingly, the effect of candesartan cilexetil was studied on the blood glucose levels of glimepiride treated normal and diabetic rats. **Method:** Effect of blood glucose levels were studied by using Candesartan cilexetil and Glimepiride in normal and diabetic albino male rats at a dose of 1.44 mg/kg and 0.09 mg/kg, respectively. The blood samples were collected during the study at the time intervals of 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours. The samples were subjected to estimation of blood glucose levels using glucometer. **Results:** The present study was conducted in both normal and diabetic rats. Glimepiride showed its hypoglycemic effect at the 4th hour, whereas candesartan cilexetil doesn't show any changes in blood glucose levels in both normal and diabetic rats. In normal rats, candesartan cilexetil doesn't affect on the blood glucose levels of glimepiride in both single and multiple dose studies. In diabetic rats, the candesartan cilexetil showed significant action on blood glucose levels of glimepiride in multiple dose interaction study but the insignificant effect of candesartan cilexetil in single dose interaction on glimepiride. Hence, the interaction was carefully monitored in type-2 diabetes mellitus patients. **Conclusion:** The study suggested that candesartan cilexetil has a profound effect on blood glucose levels of glimepiride on long term use; the possible mechanism for the cause is either angiotensin converting enzyme inhibitors improve insulin sensitivity or inhibition of CYP2C9. The study also recommended that caution must be taken while prescribing with the combination of candesartan cilexetil and glimepiride or its analogs.

Keywords: Diabetes, Polypharmacy, blood glucose levels, Candesartan cilexetil, Glimepiride, albino male rats.

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1. INTRODUCTION

In India, several physicians prescribing medication unnecessarily to the patient for him or her self- advantages within the hospitals. Simultaneous coadministration of two or more medications by the patient, usually adults aged over sixty- five years called as Polypharmacy. Polypharmacy is commonest within the aged, affecting about four-hundredth of older adults living in their own homes. Polypharmacy isn't forever unhealthy, however, it's unhealthy in several instances, usually being additional harmful than useful or presenting an excessive amount of risk for too little benefit. Therefore, health professionals think about it a scenario that needs observation and review to validate whether or not all of the medications are still necessary.[1] Hence, the patients have many disease conditions like hypertension with diabetes or diabetes with hyperlipidemia or hyperlipidemia with hypertension etc., for those doctors was prescribing many medications to them. When two or more drugs are given in combination the response may be greater or smaller than the sum of the effects of the two drugs given separately. This one drug may antagonize or potentiate the effects of another and in some cases, there may be qualitative differences in response.[2]

Diabetes is a metabolic disorder manifested by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage dysfunction and failure of different organs especially the eye, kidneys, nerves, heart, and blood vessels.[3] The pressure exerted by the blood against the walls of the blood vessels, especially the arteries called as blood pressure.[4] The literature reveals that hypertension in the diabetic individual markedly increases the risk and accelerates the course of the cardiac disease, peripheral vascular disease, stroke, retinopathy, and nephropathy.[5-7] Patients relating to such condition, they are treated by prescribing many medications. Therefore, there is a possibility of drug interaction among it. Hence, monitoring and dose adjustment are necessary for the treatment. So that the present study was assumed to assess the possible drug interaction between candesartan cilexetil and glimepiride. Candesartan cilexetil, an oral nonpeptide angiotensin receptor II antagonist used for treating hypertension, whereas glimepiride is a sulfonyl urea derivatives for treating diabetes mellitus and both drugs are metabolized by cytochrome P-450 (CYP-450). The CYP2C9 is an isoform of CYP-450 and play a major role in a phase-I reaction like oxidation of both exogenous and endogenous compounds.[8] candesartan cilexetil is metabolized through CYP2C9 and glimepiride also metabolized through CYP2C9.[9,10] Therefore, it is hypothesized that whether the candesartan cilexetil interfere with glimepiride metabolism by either increasing or decreasing blood glucose levels. Hence, Hence, the effect of candesartan cilexetil was studied on the blood glucose levels of glimepiride in normal and diabetic rats.

2. MATERIALS AND METHODS

2.1 Drugs and chemicals

Glimepiride and Candesartan cilexetil were procured from Mylan labs, Bengaluru, India. Alloxan mono hydrate procured from Chemists laboratories, Hyderabad, India. Glucometer [Freestyle optimum H (Abbot)] was procured from the local market, Guntur, Andhra Pradesh, India.

2.2 Animals

Albino wistar rats weighing 250-300gm were procured from M/s Mahaveera enterprises, Hyderabad, India. Experimental animals were acclimatized to laboratory condition at Animal house, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur. Animals were maintained at room temperature 22±4°C and humidity 60-70% with 12h light/dark cycles throughout the study. The animals were supplied with commercial rat feed, procured from rayans biotechnologies Pvt Ltd, Hyderabad, India. Supplied with sterile water *ad libitum*. The protocol was approved by the institutional animal ethics committee (IAEC5/PRO-9/2016-17), in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA).

2.3 Preparation of suspension

Weighed accurately the prescribed dose of candesartan cilexetil and glimepiride and transferred into the separeted motor and added 3-4 drops of tween 80 to each motor and triturated well. Then added 0.5% Hydroxy Propyl Methyl Cellulose (HPMC) drop by drop and finally made up the volume up to 10ml.

2.4 Dosage and Dose administration

In clinical practice, Candesartan cilexetil and Glimepiride used to administer orally. Hence, their human therapeutic

Table 1. The blood glucose levels and mean reduction levels of different groups in normal treated animals.

Time (hr)	Control	Glimepiride	Candesartan cilexetil	Single-dose study	Multiple-dose study
0	(112.16 ± 2.18)	(120.5 ± 0.76)	(122 ± 0.63)	(118 ± 0.85)	(120.16 ± 1.53)
0.5	-0.33 ± 0.21 (111.83 ± 2.25)	-9.83 ± 0.87 (110.66 ± 0.49)	-2 ± 1.09 (120 ± 0.85)	-13 ± 1.86 (105 ± 1.63)	-19.33 ± 1.14 (100.83 ± 1.85)
1	0.166 ± 0.60 (112.33 ±1.99)	-22.5 ± 0.71 (98 ± 0.36)	-3.5 ± 0.99 (118.5 ± 0.84)	-20.66 ± 0.80 (97.33 ± 0.88)	-28.5 ± 1.54 (91.66 ± 1.25)
2	-0.16 ± 0.79 (112 ± 2.30)	-33.66 ± 0.71 (86.83 ± 0.30)	-4.66 ± 1.02 (117.33 ± 0.95)	-33.83 ± 0.98 (84.16 ± 0.60)	-37.33 ± 1.49 (82.83 ± 1.47)
3	0.33 ± 0.55 (112.5 ± 2.04)	-43.5 ± 0.80 (77 ± 0.77)	-5.5 ± 1.08 (116.5 ± 1.05)	-39.83 ± 1.01 (78.16 ± 0.79)	-46.5 ± 2.04 (73.66 ± 1.80)
4	0.16 ± 0.65 (112.33 ± 1.96)	-47.5 ± 0.61 (73 ± 0.57)	-6.66 ± 1.33 (115.33 ± 1.38)	-44.5 ± 1.08 (73.5 ± 0.56)	-52.16 ± 2.68 (68 ± 2.54)
6	0 ± 0.77 (112.16 ± 1.88)	-43.16 ± 1.04 (77.33 ± 0.49)	-8.33 ± 1.54 (113.66 ± 1.42)	-35 ± 2.04 (83 ± 1.77)	-37.83 ± 2.10 (82.33 ± 0.84)
8	0.16 ± 0.79 (112.33 ± 1.94)	-34.33 ± 0.80 (86.16 ± 0.47)	-10 ± 0.89 (112 ± 0.96)	-25.66 ± 1.49 (92.33 ± 0.88)	-30 ± 1.61 (90.16 ± 0.60)
10	0 ± 0.77 (112.16 ± 1.88)	-25.16 ± 1.22 (95.33 ± 0.71)	-6 ± 1.06 (116 ± 1.29)	-17.33 ± 1.62 (100.66 ± 1.56)	-20 ± 1.29 (100.16 ± 0.54)
12	-0.16 ± 0.90 (112 ± 1.82)	-12 ± 0.96 (108.5 ± 0.84)	-2.33 ± 1.25 (119.66 ± 1.45)	-10 ± 1.34 (108 ± 1.46)	-13.16 ± 1.30 (107 ± 1.12)
24	-0.16 ± 0.90 (112 ± 1.82)	-3.83 ± 0.65 (116.66 ± 0.80)	-0.83 ± 0.83 (121.16 ± 0.60)	0.33 ± 1.17 (117.33 ± 1.96)	-4.83 ± 2.24 (115.33 ±2.17)

The results were expressed as Mean ± SEM. (n=6); $p<0.05$.

doses were extrapolated to rats based on the body weight by using an animal conversion factor.[11] Throughout the study; experimental animals were administered with Candesartan cilexetil and Glimepiride at a dose of 1.44mg/kg and 0.09mg/kg respectively.

2.5 Collection of blood as per time intervals

The blood samples were collected from the tail vein method at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after drug treatment.

2.6 Estimation of blood glucose in rats

The blood glucose levels (BGL's) were estimated by using glucometer [Freestyle optimum H (Abbot)]

2.7 Estimation of Percentage of blood glucose reduction

The BGL's of glimepiride at any time't' in rats was calculated according to the formula given below. Percent blood glucose reduction at time't' = [(a/b)/b) × 100]. Where a=initial blood glucose level, b=blood glucose level at time't'.

2.8 Pharmacodynamic drug interaction studies in normal and diabetic rats

2.8.1 Normal rats

Effect of candesartan cilexetil and glimepiride on blood glucose levels in normal rats

Male adult Wistar rats were divided into five groups of six animals each. The animals fasted for a period of 18 hrs before the experimentation and water was supplied *ad libitum*. The animals were grouped as follows; Group I served as the control and received 0.5% HPMC, group II received Glimepiride 0.09mg/kg, group III received Candesartan cilexetil 1.44mg/kg, group IV received Glimepiride 0.09mg/kg and Candesartan cilexetil 1.44mg/kg (single dose interaction study) and group V received Glimepiride and Candesartan cilexetil (Multiple dose interaction study).

Table 2. The blood glucose levels and mean reduction levels of different groups in diabetic treated animals

Time (hr)	Control	Glimepiride	Candesartan cilexetil	Single-dose study	Multiple-dose study
0	(187.66 ± 1.97)	(198 ± 0.77)	(199.33 ± 1.74)	(203.33 ± 0.66)	(200.16 ± 1.24)
0.5	0.51 ± 0.21 (187.33 ± 2.07)	-23.16 ± 1.77 (174.83 ± 1.62)	-12.33 ± 1.96 (187 ± 0.73)	-15.83 ± 1.72 (187.5 ± 1.60)	-31.33 ± 1.68 (168.83 ± 1.90)
1	1.86 ± 0.76 (187.33 ± 1.83)	-42.66 ± 1.22 (155.33 ± 0.91)	-17.83 ± 1.92 (181.5 ± 0.99)	-38.33 ± 1.92 (165 ± 1.46)	-49.33 ± 1.22 (150.83 ± 0.94)
2	0.63 ± 0.25 (187 ± 1.96)	-54.33 ± 1.66 (143.66 ± 1.68)	-23.33 ± 1.78 (176 ± 1.73)	-45.16 ± 1.74 (158.16 ± 1.30)	-61.66 ± 1.52 (138.5 ± 0.88)
3	1.76 ± 0.71 (187.5 ± 1.87)	-64.33 ± 1.49 (133.66 ± 1.62)	-29.16 ± 1.44 (170.16 ± 1.57)	-64.33 ± 1.49 (139 ± 1.59)	-73 ± 1.21 (127.16 ± 1.40)
4	1.96 ± 0.80 (187.33 ± 1.78)	-84.16 ± 1.62 (113.83 ± 1.32)	-36.16 ± 2.56 (163.16 ± 1.74)	-89.33 ± 1.38 (114 ± 1.59)	-98.33 ± 1.78 (101.83 ± 1.77)
6	2.22 ± 0.90 (187.16 ± 1.70)	-63.5 ± 2.20 (134.5 ± 1.87)	-41.83 ± 2.86 (157.5 ± 1.87)	-63.5 ± 1.05 (139.83 ± 0.79)	-72.33 ± 2.29 (127.83 ± 1.62)
8	2.31 ± 0.94 (187.16 ± 1.81)	-49 ± 2.28 (149 ± 2.22)	-47.33 ± 2.56 (152 ± 1.54)	-53.33 ± 0.84 (150 ± 0.68)	-46.83 ± 2.48 (153.33 ± 1.89)
10	2.22 ± 0.90 (187.16 ± 1.70)	-28 ± 1.36 (170 ± 1.31)	-28.66 ± 3.70 (170.66 ± 2.09)	-34.5 ± 1.78 (168.83 ± 1.74)	-33.83 ± 1.24 (166.33 ± 0.76)
12	2.56 ± 1.04 (186.83 ± 1.68)	-18.16 ± 0.98 (179.83 ± 0.87)	-19 ± 3.85 (180.33 ± 2.20)	-23.33 ± 1.62 (180 ± 1.73)	-17.83 ± 1.64 (182.33 ± 1.22)
24	2.52 ± 1.03 (187 ± 1.63)	-5 ± 1.57 (193 ± 1.77)	-0.16 ± 1.13 (199.16 ± 1.07)	-6 ± 0.81 (197.33 ± 1.20	-5.16 ± 1.30 (195 ± 1.84)

The results were expressed as Mean ± SEM. (n=6); $p<0.05$.

2.8.2 Single-dose interaction study in normal Rats

Single dose interaction study was carried out on group IV animals to evaluate the effects of a single dose of candesartan cilexetil on the BGL's of Glimepiride. The animals were priorly administered with Candesartan cilexetil 1.44mg/kg followed by Glimepiride 0.09mg/kg after 30mins. The blood samples were collected before and after administration of the drug at the pre set time intervals and subjected to glucose estimation.

2.8.3 Multiple Dose Interaction Study in Normal Rats

Group V animals were administered with candesartan cilexetil 1.44mg/kg for 7 consecutive days. During this period the animals had free access to food and water. On the 7th day of study, the food was withdrawn 6hrs after the candesartan cilexetil administration, but the water was supplied *ad limited.* On the 8th day, Glimepiride 0.09mg/kg was given 30 minutes after candesartan administration and the blood samples were collected at the pre set intervals and analyzed for glucose levels using the glucometer.

2.9 Diabetic Rats

2.9.1 Alloxan monohydrate induced diabetes in rats

After a washout period of two weeks, the animals were reused for induction of diabetes. Experimental diabetes in rats was elicited by injecting Alloxan monohydrate, intraperitoneal route at a dose of 150mg/kg in ice cold normal saline. After 72hrs, samples were collected from tail vein and analyzed for glucose levels. Rats with BGL's of 200 mg/dl and higher than were thought of diabetic and chosen for the study. The diabetic animals were grouped as follows; Group, I served as the control and received 0.5% HPMC, group II received Glimepiride 0.09mg/kg, group III received Candesartan cilexetil 1.44mg/kg, group IV received Glimepiride 0.09mg/kg and Candesartan cilexetil 1.44mg/kg (single dose interaction study) and

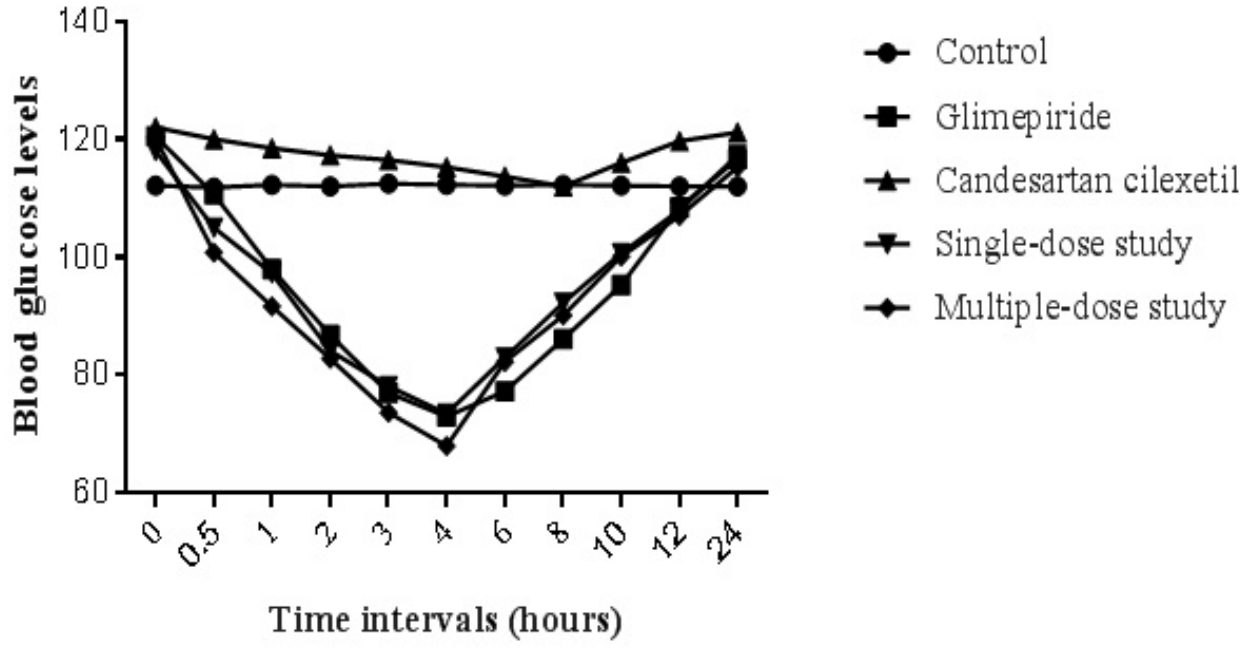

Figure 1. The effect of candesartan cilexetil on blood glucose levels of glimepiride in normal rats.

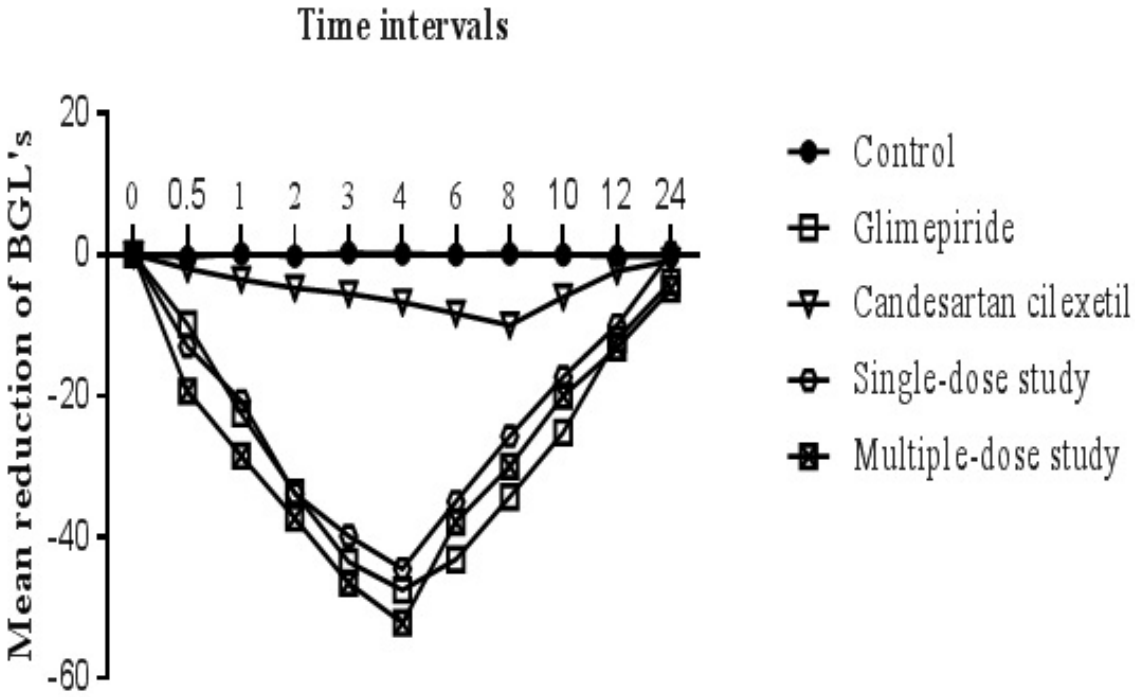

Figure 2. The mean reduction levels of blood glucose levels on different normal rat groups.

group V received Glimepiride and Candesartan cilexetil (Multiple dose interaction study).[12-14]

2.9.2 Single Dose Interaction Study in Diabetic Rats

Single dose interaction study was carried out on group IV animals to evaluate the effects of a single dose of candesartan cilexetil on the BGL's of glimepiride. The diabetic animals were administered with Candesartan cilexetil 1.44mg/kg followed by Glimepiride 0.09mg/kg after 30mins. The blood samples were collected before (i.e. 0hr) and after administration of the Candesartan cilexetil and Glimepiride at the pre set time intervals and subjected to glucose estimation.

2.9.3 Multiple Dose Interaction Study in Diabetic Rats

The study was extended to include a multiple dose interaction studies to evaluate the effect of chronic use of candesartan cilexetil on the BGL's after Glimepiride. Group V animals were administered with candesartan cilexetil 1.44mg/kg for 7 consecutive days. During this period the animals had free access to food and water. On the 7th day of study, the food was withdrawn 6hrs after the candesartan cilexetil administration, but the water was supplied *ad limited.* On the 8th day, glimepiride 0.09mg/kg was given 30 minutes after candesartan cilexetil administration and the blood samples were collected at the pre set intervals and were analyzed for glucose levels using a glucometer.

2.9.4 Statistical Analysis

The significance of the observed difference in the Pharmacodynamic parameters of glimepiride was assessed by one-way analysis of variance (ANOVA), followed by Dunnett's multiple comparison tests. A value of $p < 0.05$ was considered to be statistically significant by using graphpad prism, version 6.

3. RESULTS

3.1 Pharmacodynamic interaction studies in normal rats

The study was conducted in normal rats of group II & III, were received Glimepiride and Candesartan cilexetil at a dose of 0.09 mg/kg and 1.44 mg/kg respectively. After Glimepiride administration, a peak hypoglycemic activity i.e. 73 ± 0.57 of BGL was observed at 4th hour and mean reduction of BGL was found to be 47.5±0.61. Whereas candesartan cilexetil treated group shown its peak activity i.e. 112±0.96 at the 8th hour and mean reduction of BGL were found to be 10±*0.89*. The results were tabulated as Table 1and represented in Figure 1 and 2.

3.2 Single dose interaction study

The single dose interaction study was conducted in group IV, was administered with Candesartan cilexetil followed by glimepiride after 30 minutes. This combination produced peak hypoglycemic effect i.e. 73.5±0.56 at the 4th hour and mean reduction of BGL as 44.5±1.08. Results of BGL obtained in this group were compared with BGL of Glimepiride treated group. The results were tabulated as Table 1and represented in Figure 1 and 2.

3.3 Multiple Dose Interaction Study

Animals mentioned in this group (Group V) were administered with Candesartan cilexetil for 8 consecutive days. On 8th day, Glimepiride was administered after 30 minutes of Candesartan cilexetil. This combination produced peak hypoglycemic effect i.e. be 68 ± 2.54 at the 4th hour and mean reduction of BGL as 52.16 ± 2.68. The results were tabulated as Table 1and represented in Figure 1 and 2.

3.4 Pharmacodynamic Interaction Studies in Diabetic Rats

The study was repeated on same animals after 2 weeks of washout period, induced diabetes mellitus and segregated into different groups. The group II and III were received glimepiride and candesartan cilexetil at the dose of 0.09 mg/kg and 1.44 mg/kg respectively. The group II treated animals showed peak activity i.e. 113.83 ± 1.32 at the 4th hour and mean reduction of BGL as 84.16 ± 1.62. Whereas group III treated animals showed peak activity i.e. 152 ± 1.54 at the 8th hour, and mean reduction of BGL as 47.33±2.56. The results were tabulated as Table 2and represented in Figure 3 and 4.

3.5 Single Dose Interaction Study

The single dose interaction study was conducted in group IV, administered with Candesartan cilexetil followed by glimepiride after 30 minutes. The group IV treated group

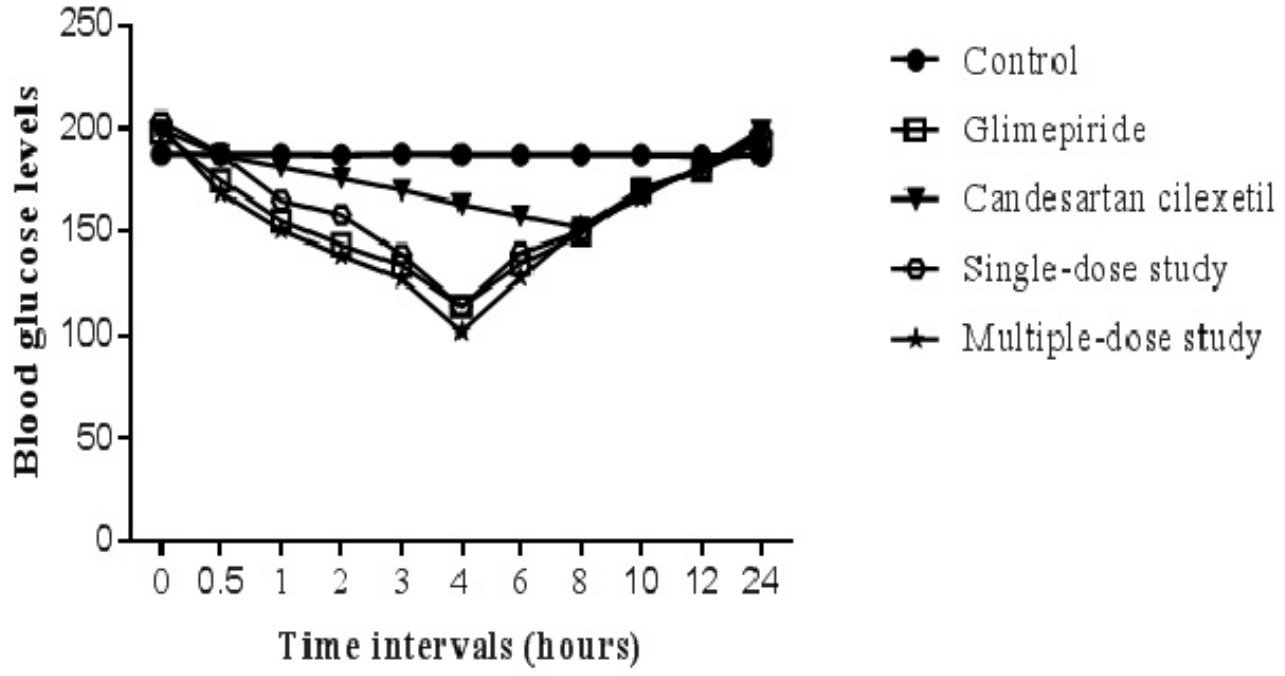

Figure 3. The effect of candesartan cilexetil on blood glucose levels of glimepiride in diabetic rats

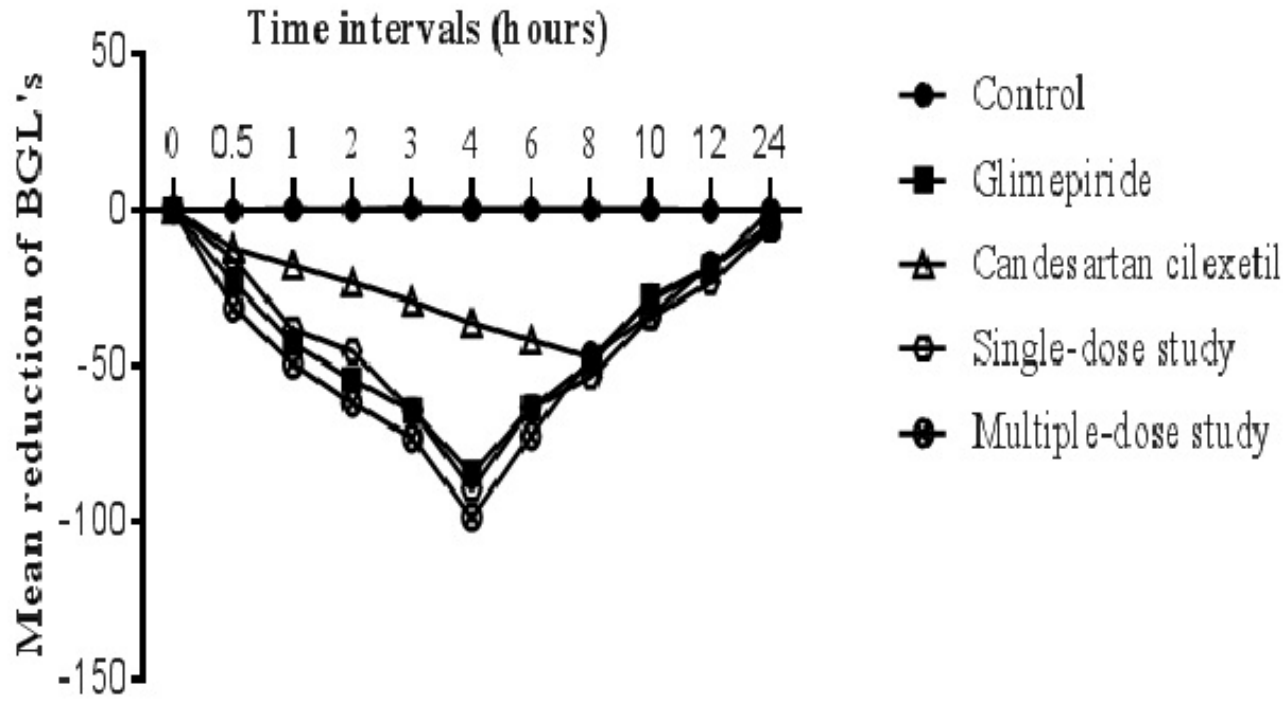

Figure 4. The mean reduction levels of blood glucose levels on different diabetic rats.

showed peak activity i.e. 114 ± 1.59 at 4th hour and mean reduction as 89.33±1.38. The results were tabulated as Table 2and represented in Figure 3 and 4.

3.5 Multiple Dose Interaction Study

Animals mentioned in this group (Group V) were administered with Candesartan cilexetil for 8 consecutive days. On 8th day, Glimepiride was administered after 30 minutes of Candesartan cilexetil. This combination was produced peak activity i.e. 101.83± 1.77 at the 4th hour and mean reduction of BGL as 98.33±1.78. The results were tabulated as Table 2and represented in Figure 3 and 4.

4. DISCUSSION

Drug interaction study in normal rats, Glimepiride treated group produced hypoglycemic effect due to rapid release of insulin and increases the sensitivity of pancreatic β-cell to glucose.[15, 16] A little change was observed with Candesartan cilexetil treated group. Single dose interaction studies, the BGL's are significantly changed but when compared with Glimepiride treated group, the results were insignificant. Multiple dose interaction studies, BGL's are significantly changed when compared with single dose interaction study but insignificant results when compared with Glimepiride treated group. The possible mechanism of significant changes in BGL's in both single and multiple dose interaction studies was due to improve insulin sensitivity by Angiotensin Converting Enzyme (ACE) inhibitors [i.e. Candesartan cilexetil]. The molecular mechanism of ACE was due to increased glucose uptake in skeletal muscle via enhanced synthesis and translocation of glucose transporter 4 proteins to the cell surface.[17-19] This might explain the association of insulin resistance with endothelial dysfunction[20] and hypertension [or] due to inhibition of hepatic glucose output.[21] Candesartan cilexetil is used to treat hypertension and prevent the early kidneys from damage due to diabetes at a low dose. [22, 23] The Candesartan cilexetil was helpful in treating diabetic retinopathy due to its angiotensin I receptor antagonist activity.[24-26] Candesartan cilexetil mediated improvement in insulin sensitivity is mainly due to an increase in nonoxidative glucose metabolism and blood flow in insulin-resistant hypertensive patients.[27]

Drug interaction study in diabetic animals; as in single dose interaction studies, the BGL's are insignificant when compared with Glimepiride treated group. Multiple dose interaction studies the BGLs were significant when compared with single dose interaction studies but insignificant with Glimepiride treated group. The role of Angiotensin generating system in pancreatic islets was explained by exogenous administration of angiotensin II, thereby which inhibit insulin release associated with decreased blood flow to islet and pro-insulin biosynthesis.[28] Improved islets morphology after blockade of RAS, that reveals that angiotensin blockers improve the pancreatic cell sensitivity and helpful for the diabetic patient.[29-31] Previous studies reveal rennin angiotensin system inhibition prevents type 2 diabetes mellitus through increases sensitivity and enhances β-cell responsiveness to glucose and enhances glucose homeostasis. [32-35]

5. CONCLUSION

The interaction study of candesartan cilexetil with glimepiride was conducted in normal and diabetic rats based on the pharmacodynamic response for 24hrs. In normal study after administration of both candesartan and glimepiride, there were significant changes in BGL's was observed in multiple dose study as compared with that of glimepiride alone and single dose study. Where as in diabetic study there was no change in BGL's in single dose interaction study, but in multiple dose interaction study only a minute change can be observed which indicates that there was no interaction with this combination of drugs even these two drugs undergo metabolism through CYP2C9 enzyme. This study clearly revealed that this was the best combination for both diabetic as well as hypertension with chronic kidney diseases. An even minute change in BGL's does not affect in animals behavioral actions was not observed. Hence these co administrations of both candesartan and glimepiride can be tolerable and did not induce any severe hypoglycemic shock in diabetic rats.

6. ACKNOWLEDGEMENT

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7. CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

8. ABBREVIATION USED

BGL's: Blood Glucose Levels; RAS: Renin Angiotensin System; CYP-450: Cytochrome P 450; HPMC: Hydroxy Propyl Methyl Cellulose; ACE: Angiotensin Converting Enzyme; NO: Nitric Oxide; IRS-1: Insulin Receptor Substrate 1.

9. REFERENCES

1. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. The American journal of geriatric pharmacotherapy. 2007 Dec 1; 5(4):345-51.
2. Prescott LF. Clinically important drug interactions. Drugs. 1973 Mar 1; 5(3):161-86.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care. 2014 Jan 1; 37 (Supplement 1):S81-90.
4. Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Annals of internal medicine. 2003 Nov 4; 139 (9):761-76.
5. Epstein M, Sowers JR. Diabetes mellitus and hypertension. Hypertension. 1992 May 1; 19(5):403-18.
6. Sowers JR, Epstein M. Diabetes mellitus and hypertension, emerging therapeutic perspectives. Cardiovascular Therapeutics. 1995 Jun 1;13 (2):149-210.
7. Solini A, DeFronzo RA. Hypertension, cardiovascular disease, diabetes mellitus, and diabetic nephropathy: role of insulin resistance. InThe Kidney and Hypertension in Diabetes Mellitus 1996 (pp. 61-74). Springer US.
8. Van Booven D, Marsh S, McLeod H, Carrillo MW, Sangkuhl K, Klein TE, Altman RB. Cytochrome P450 2C9-CYP2C9. Pharmacogenetics and genomics. 2010 Apr;20(4):277.
9. Murakami H, Yabusaki Y, Ohkawa H. Expression of rat NADPH-cytochrome P-450 reductase cDNA in Saccharomyces cerevisiae. DNA. 1986 Feb;5(1):1-0.
10. Holstein A, Beil W, Kovacs P. CYP2C metabolism of oral antidiabetic drugs-impact on pharmacokinetics, drug interactions and pharmacogenetic aspects. Expert opinion on drug metabolism & toxicology. 2012 Dec 1;8 (12):1549-63.
11. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. Journal of basic and clinical pharmacy. 2016 Mar;7(2):27.
12. Rees DA, Alcolado JC. Animal models of diabetes mellitus. Diabetic medicine. 2005 Apr 1; 22(4):359-70.
13. Etuk EU. Animals models for studying diabetes mellitus. Agric Biol JN Am. 2010;1(2):130-4.
14. Ghosh M. Fundamentals of Experimental Pharmacology Hilton and Company. Kolkata, India. 2005.
15. Korytkowski M, Thomas A, Reid L, Tedesco MB, Gooding WE, Gerich J. Glimepiride improves both first and second phases of insulin secretion in type 2 diabetes. Diabetes Care. 2002 Sep 1;25 (9):1607-11.
16. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes. Diabetes care. 2005 Dec 1;28(12):2948-61.
17. Prasad A, Quyyumi AA. Renin-angiotensin system and angiotensin receptor blockers in the metabolic syndrome. Circulation. 2004 Sep 14;110 (11):1507-12.
18. Kurtz TW, Pravenec M. Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the renin–angiotensin system. Journal of hypertension. 2004 Dec 1;22(12):2253-61.
19. Higashiura K, Ura N, Takada T, Li Y, Torii T, Togashi N, Takada M, Takizawa H, Shimamoto K. The effects of an angiotensin-converting enzyme inhibitor and an angiotensin II receptor antagonist on insulin resistance in fructose-fed rats.
20. Onuchin SG, Elsukova OS, Onuchina EL. Potential of combined hypoglycemic, antihypertensive, and hypolipidemic therapy in patients with diabetes mellitus and diabetic foot syndrome. Klinicheskaia meditsina. 2007 Dec;86 (8):61-6.
21. Srivastava RA. Fenofibrate ameliorates diabetic and dyslipidemic profiles in KKAy mice partly via down-regulation of 11β-HSD1, PEPCK and DGAT2: Comparison of PPARα, PPARγ, and liver x receptor agonists. European journal of pharmacology. 2009 Apr 1;607(1):258-63.
22. Murayama S, Hirano T, Sakaue T, Okada K, Ikejiri R, Adachi M. Low-dose candesartan cilexetil prevents early kidney damage in type 2 diabetic patients with mildly elevated blood pressure. Hypertension Research. 2003;26(6):453-8.
23. Rosei EA, Rizzoni D, Muiesan ML, Sleiman I, Salvetti M, Monteduro C, Porteri E, CENTRO (CandEsartaN on aTherosclerotic Risk factors) Study Investigators. Effects of candesartan cilexetil and enalapril on inflammatory markers of atherosclerosis in hypertensive patients with non-insulin-dependent diabetes mellitus. Journal of hypertension. 2005 Feb 1; 23(2):435-44.
24. Sjølie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, Bilous R, Chaturvedi N, DIRECT Programme Study Group. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. The Lancet. 2008 Oct 24; 372 (9647):1385-93.
25. DIRECT Programme Study Group, Chaturvedi N. The Diabetic Retinopathy Candesartan Trials (DIRECT) programme, rationale and study design. Journal of the Renin-Angiotensin-Aldosterone System. 2002 Dec; 3(4):255-61.
26. DIRECT Programme Study Group. The DIabetic REtinopathy Candesartan Trials (DIRECT) Programme:

baseline characteristics. Journal of the Renin-Angiotensin-Aldosterone System. 2005 Mar; 6(1):25-32.

27. Grassi G, Seravalle G, Dell'Oro R, Trevano FQ, Bombelli M, Scopelliti F, Facchini A, Mancia G. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. Journal of hypertension. 2003 Sep 1; 21 (9):1761-9.
28. Chu KY, Lau T, Carlsson PO, Leung PS. Angiotensin II type 1 receptor blockade improves β-cell function and glucose tolerance in a mouse model of type 2 diabetes. Diabetes. 2006 Feb 1; 55 (2):367-74.
29. Ramracheya RD, Muller DS, Wu Y, Whitehouse BJ, Huang GC, Amiel SA, Karalliedde J, Viberti G, Jones PM, Persaud SJ. Direct regulation of insulin secretion by angiotensin II in human islets of Langerhans. Diabetologia. 2006 Feb 1; 49(2):321-31.
30. Lau T, Carlsson PO, Leung PS. Evidence for a local angiotensin-generating system and dose-dependent inhibition of glucose-stimulated insulin release by angiotensin II in isolated pancreatic islets. Diabetologia. 2004 Feb 1; 47(2):240-8.
31. Tikellis C, Wookey PJ, Candido R, Andrikopoulos S, Thomas MC, Cooper ME. Improved islet morphology after blockade of the renin-angiotensin system in the ZDF rat. Diabetes. 2004 Apr 1;53(4):989-97.
32. Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus: part 1. A meta-analysis of randomised clinical trials. Diabetes & metabolism. 2004 Dec 1; 30(6):487-96.
33. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin–angiotensin system reduces the incidence of new-onset diabetes. Journal of hypertension. 2005 Mar 1; 23(3):463-73.
34. Putnam K, Shoemaker R, Yiannikouris F, Cassis LA. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. American Journal of Physiology-Heart and Circulatory Physiology. 2012 Mar 15; 302 (6):H1219-30.
35. Scheen AJ. Prevention of type 2 diabetes mellitus through inhibition of the Renin-Angiotensin system. Drugs. 2004 Nov 1; 64 (22):2537-65.