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A STUDY ON DRUG-DRUG INTERACTION BETWEEN PERINDOPRIL AND GLIMEPIRIDE IN RATS

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Abstract:

Background and Objectives: *The risk of hypoglycemia was reported with ACE inhibitors in patients who are taking insulin or other hypoglycemic agents. But there are no reports available about the drug-drug interaction between perindopril and glimepiride. Hence, the present study was planned to study the influence of single and repeated dose treatment of perindopril on the hypoglycemic and antidiabetic effect of glimepiride in normal and streptozotocin induced diabetic albino rats.*

Methods: *14 groups of normal albino rats (Group I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII and XIV) (n=6) were selected. At "0" hour blood samples were collected from tail vein then groups I, II, III, IV, V and VI were administered with vehicle, glimepiride 10 mg/kg, perindopril 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg p.o respectively. After drug treatment at 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 h blood samples were collected and analyzed for serum glucose by GOD/POD method. Similarly blood samples were collected from groups VII, VIII, IX and X and were administered with single doses of perindopril 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg, p.o respectively followed by single dose of glimepiride 10 mg/kg, p.o 30 min later. Groups XI, XII, XIII and XIV were administered with different doses of perindopril 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg p.o for 7 days and on 8th day 30 min after administration of last dose of perindopril a single dose of glimepiride 10 mg/kg was administered orally. After drug treatment at 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 h blood samples were collected and analyzed for serum glucose levels as mentioned above. Similarly the experiments were conducted in diabetic rats following the above procedure and serum glucose levels were analyzed as mentioned earlier.*

Results: *Perindopril significantly altered the peak effect and enhanced the duration of hypoglycemic activity but not altered onset of action of glimepiride in both normal and diabetic rats.*

Interpretation and Conclusion: *The study suggests that, the dose and frequency of glimepiride must be readjusted when it is to be administered concomitantly with antihypertensive drug perindopril in hypertension and diabetic conditions to avoid severe hypoglycemia due to perindopril.*

Key words*: Glimepiride, Perindopril, hypoglycemic, antidiabetic, drug- drug interaction.*

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1. INTRODUCTION:

A drug interaction can be defined as the modification of the effects of one drug (i.e. the object drug) by the prior and concomitant administration of other drug (i.e. the precipitant drug).[1]

Drug interaction is the qualitative or quantitative modifications of the effect of a drug by the simultaneous administration of different drugs. If two drugs are given together their combined effects may be greater, same or lesser than the effects of the individual drugs or no effect at all. The three possible effects due to drug interaction are potentiation, addition (or simulation) and antagonism respectively. There are several incidences in which a patient may suffer from more than one disease simultaneously. Many a patients especially the elders are to be treated continuously with more than one drug for chronic diseases such as hypertension, heart failure and osteoarthritis etc.[2] and hence the chances for drug interactions are at high risk.

A study which was conducted on drug-drug interactions in selected community pharmacies over a span of 3 months in which out of 1368 prescriptions evaluated, 613 interactions were found in 516 prescriptions, out of which 16.15% interactions were severe, 3.75% interactions were found where patient was receiving more than 8 drugs and 11.58% had a significant level of interactions. Hence a concerted effort is required to minimize the problem of drug-drug interactions.

Ever since the discovery of insulin and sulfonylureas as clinically useful antidiabetic agents, control of blood sugar level with drug(s) has been the primary objective in diabetic patients. Simultaneous use of other drugs is the usual event in the life of these patients. So, drug interactions between antidiabetic agents and other classes of drugs, affecting the safety and/or efficacy of these drugs, are likely to occur. The severity of the situation is clearly reflected by data collected from the literature by Seltzer' who recorded 473 cases of drug induced hypoglycemia of which 60 were fatal. The survey included 220 cases of hypoglycemia induced by sulfonylurea only of which 25 were fatal.[3]

Hypertension in diabetes mellitus is a fascinating clinical constellation with a complex and multifactorial pathophysiology. Hypertension in both type I and type II diabetes is mainly characterized by increased peripheral vascular resistance suggesting premature aging of the vasculature. Studies have suggested that exaggerated smooth muscle contractility may be secondary to cellular insulin deficiency and resultant abnormalities in cellular cation transport. The major role of insulin in the regulation of two important membrane pumps, i.e. the Ca^{+2}-ATPase and the Na^{+}-K^{+} ATP ase has been well documented. Accordingly, insulin deficiency or insulin resistance could result in decreased activity of these pumps, which in turn lead to increase in the intracellular Ca^{++} concentration. ACE inhibitors unlike diuretics and β-blockers; make up a class of antihypertensive agents not associated with metabolic abnormalities. These agents have also been demonstrated to improve insulin sensitivity when used in diabetes. ACE inhibitors have also been suggested to be particularly beneficial in diabetic hypertensive patients with early diabetic nephropathy.[4]

2. OBJECTIVE OF THE STUDY

Since there are reports that ACE inhibitors increase potassium levels in the body, increased potassium levels in diabetes mellitus increases effect of insulin on control of blood sugar. Hence, the present study was conducted with the intention that these ACE inhibitors may also alter the pharmacokinetics of orally active hypoglycemic sulfonylurea like Glimepiride. So the present study in planned with the following objectives.

1. To study the influence of single and repeated administration of perindopril on the hypoglycemic activity of Glimepiride in healthy rats.
2. To study the influence of single and repeated administration of perindopril on the antidiabetic activity of Glimepiride in the streptozotocin induced diabetic rats.
3. To suggest the alteration in the dose and frequency of administration of Glimepiride, if any, when it has to be used along with perindopril.

3. METHODOLOGY:

The whole study was divided into 3 phases. In the I phase the effect of single dose treatment of perindopril (2.5,5,10 and 20 mg/kg p.o) and glimepiride (10 mg/kg, p.o) on the serum glucose levels in normal rats were established. In the II phase effect of single dose treatment of perindopril (2.5,5,10 and 20 mg/kg p.o) and repeated treatment of perindopril (2.5,5,10 and 20 mg/kg p.o) for one week on the hypoglycemic effect of glimepiride (10 mg/kg, p.o) in normal rats were studied. In the third phase, the studies conducted in the first and second phase were repeated similarly in diabetic rats to find out the drug-drug interaction between perindopril and glimepiride in diabetic conditions.

Estimation of Serum Glucose

There are several methods used in practice for estimating serum glucose levels. Few of them are mentioned below [5-10]

1. GOD/POD method
2. End point 0-Toludine method
3. Nelson Somogyi method

The older methods were based on reducing property of glucose. But these methods do not measure true glucose because of interferences. Subsequently other chemical and enzymatic methods were involved to overcome this problem. The GOD/POD method is one such evolved method which is simple, single stepped, rapid, reliable, safe and precise. Hence, in the present study we have adopted this method. This method utilizes two enzymes Glucose Oxidase (GOD) & Peroxidase (POD) along with chromogen 4- amino antipyrine and phenol. This method is intended for *in-vitro* quantitative determination of glucose in serum, plasma and CSF. There is no interference due to the creatinine, fructose, galactose, reduced glutathione, ascorbic acid and xylose. Haemoglobin or bilirubin upto 10mg% does not affect the test.

Principle

Glucose is oxidised by the enzyme glucose oxidase (GOD) to give D-gluconic acid and hydrogen peroxide. Hydrogen peroxide in presence of enzyme peroxidase (POD) oxidizes phenol, which combines with 4-amino–antipyrine to produce red colored quinoneimine dye which is measured at 505nm and the intensity of the colour produced is proportional to glucose concentration in the sample.

Reagent No.	Reagent	Reagent Code no.	Pack size	Composition	Concentration
1	Glucose reagent	LG0711	5 ×100mL	Phosphate buffer (7.5) Glucose Oxidase 4 aminoantipyrine Phenol Peroxidase	200mmol/L >15KU/L 0.3mmol/L 5mmol/L >3KU/L
2	Glucose standard	LG0712	1 x 5 mL	Dextrose Preservative	100 mg/dL q.s.
3	Glucose standard	LG0713	1x 2.5 mL	Dextrose Preservative	400 mg/dL q.s.

Preparation of working reagent

The mono reagent is ready for use.

Reagent storage and stability

Reagents were stored at 2-8°C and protected from light. Reagent bottle were closed immediately after use to avoid contamination of the reagents. The reagents are stable at 2-8°C until the expiry date printed on the container label and if contamination is avoided.

Reagent performance

Maximum allowable of glucose mono reagents, measured at 505nm is 0.2.

Equipment

Liquid Cold glucose reagents for glucose estimation are suitable for use on all fully automated, semi automated analyzers, spectrophotometers, and colorimeters having 490-550 nm filter.

Procedure:

Pipette into clean dry micro-centrifuge tubes labeled as blank, standard and test.

Addition sequence	Blank(ml)	Standard (ml)	Test (ml)
Glucose reagent	1.0	1.0	1.0
Standard	-	0.02	-
Sample	-	-	0.02

Mix well; incubate at 37°C for 10 minutes. Measure the absorbance of standard and sample against reagent blank within 60 minutes on an auto analyzer at 505nm.

Preparation of working reagent

The reagent is ready for use.

Reagent storage and stability

All reagents are stable at room temperature till the expiry date mentioned.

Method for oral administration of drug

An 18 –gauge needle was suitably covered with flexible polythene tubing, where the edge was made blunt; the needle was fixed to 1ml tuberculin syringe. The rat was held firmly in left hand, the tubing was moistened with glycerine and inserted right into the

esophagus and gently pressing plunger for drug administration, and this was followed by 0.2ml of distilled water to ensure administration of correct dose of the drug.

Method for collection of blood sample [11]

The rat was placed into the rat holder, such that the tail was pulled out and was deplitated for collection of blood sample. Tail vein was dilated by focusing a low voltage electric lamp. The tip of the tail was thin sliced (0.05 mm) using a sharp scissors. The blood drops were collected though the walls of 0.5 ml of centrifuge tube (to avoid haemolysis of the blood sample). The tail was gently pressed with fingers to enhance the blood flow and allowed to clot in centrifuge tube. Later dry cotton was applied for few minutes to stop the blood flow and the tail was sterilized by spirit.

Method of collection of Serum

The serum was obtained by centrifuging the blood samples for 20 minutes (3000 rpm), supernatant fluid was decanted into the clean dry test tube.

Experimental Study in normal rats

Materials and methods

1. 0.1 N NaOH
2. Glimepiride: A solution was prepared in 0.1 N NaOH.
3. Perindopril: The solution of Perindopril was prepared in distilled water.
4. Albino Rats: Obtained from Bangalore.
5. Glucose kit (Liquid glucose)
6. Spirit, low voltage table lamp, 1ml pipettes, micropipette, 10ml centrifuge tubes, 10ml test tubes, thin aluminium foil, incubator, distilled water etc.
7. Autoanalyser (ERBA mannheim, CHEM- 5 plus v2).

Experimental procedure

XIV groups of albino rats of either sex weighing between 180- 220 gm,marked suitably were selected for the study and were kept in colony cages at ambient temperature of 28±2°C and relative humidity 45 to 55% with a 12 h light/dark cycle. The animals were fasted for 18 h before commencing the experiment. During this period, the rats were allowed to take water ad libitum. The fasting was continued till completion of the experiment.

The '0' h blood samples were collected for the estimation of fasting serum glucose level. To study the hypoglycemic effect of vehicle, glimepiride and perindopril, groups I, II, III, IV, V and VI were administered with 0.1 N NaOH, glimepiride (10 mg/kg p.o), perindopril (2.5, 5, 10 and 20 mg/kg, p.o) respectively. To study the hypoglycemic effect of single dose treatment of perindopril on glimepiride groups VII, VIII, IX and X were administered with single doses of perindopril (2.5, 5, 10 and 20 mg/kg, p.o) respectively and 30 min later all the groups were administered with glimepiride (10mg/kg, p.o). To study the influence of repeated treatment of perindopril on hypoglycemic effect of glimepiride groups XI, XII, XIII and XIV were administered with repeated doses of perindopril (2.5, 5, 10 and 20 mg/kg, p.o), respectively, daily once for 7 days. On 8 th day 30 min later the last dose of perindopril glimepiride (10mg/kg, p.o) was administered in the above groups.

The blood samples were collected at prefixed time intervals 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 h and were analysed for glucose levels by the above mentioned methods. The percentage reduction in serum glucose levels at time "t" was calculated by using the following equation.

Percentage reduction in serum glucose at time "t"

$$t = A\text{-}B/A \times 100$$

Where **A** is serum glucose concentration at time "0" and

B is serum glucose concentration at time "t".

The results are tabulated in tables 4.9-5.12, 5.13-5.26 and graphically depicted in fig: 4.9-5.1, 5.2-5.4.

Induction of Diabetes

Rats of either sex weighing between 175-200 gms were selected and fasted for 18 hrs prior to experiment and water supplied ad-libitum. The animals were kept in colony cages at ambient temperature of 28± 2°C and relative humidity 45 to 55% with a 12 h light/ dark cycle. The rats were administered with 50 mg/kg of Streptozotocin intraperitoneally.

STZ solution: STZ solution (65 mg/kg/ml) was prepared freshly at the time of administration in citrate buffer. It was used within 10 minutes of its preparation.

Citrate buffer (P^H4.4, 0.1M): citric acid monohydrate 0.6306 gm was dissolved in 50ml of distilled water. Trisodium citrate 0.7352 gm was dissolved in 25 ml of distilled water.28 ml of citric acid monohydrate and 22 ml trisodium citrate solutions were taken and mixed. It is made upto a volume of 1000 ml with distilled water. The pH of the solution was adjusted to pH 4.4. After one week, the serum samples were collected and analysed for serum glucose levels. Rats with serum glucose levels more than 200 mg/dl were included in the experiment. In our experiment diabetes was

characterized by weight loss and hyperglycemia.[12] and these animals were used for antidiabetic study.

Experimental Study in diabetic rats

Materials and methods:

1. 0.1 N NaOH
2. Glimepiride: A solution was prepared in 0.1 N NaOH.
3. Perindopril: The solution of Perindopril was prepared in distilled water.
4. Albino Rats: Obtained from Bangalore.
5. Glucose kit (Liquid glucose)
6. Spirit, low voltage table lamp, 1ml pipettes, micropipette, 10ml centrifuge tubes, 10ml test tubes, thin aluminium foil, incubator, distilled water etc.
7. Autoanalyser (ERBA mannheim, CHEM- 5 plus v2).

Experimental procedure:

XIV groups of albino rats of either sex weighing between 180- 220 gm, marked suitably were selected for the study and were kept in colony cages at ambient temperature of 28±2°C and relative humidity 45 to 55% with a 12 h light/dark cycle. The animals were fasted for 18 h before commencing the experiment. During this period, the rats were allowed to take water ad libitum. The fasting was continued till completion of the experiment.

The '0' h blood samples were collected for the estimation of fasting serum glucose levels estimation. To study the antidiabetic effect of vehicle, glimepiride and perindopril groups I, II, III, IV, V and VI were administered with 0.1 N NaOH, glimepiride (10 mg/kg p.o), perindopril (2.5, 5, 10 and 20 mg/kg, p.o) respectively. To study the hypoglycemic effect of single dose treatment of perindopril on glimepiride groups VII, VIII, IX and X were administered with single doses of perindopril (2.5, 5, 10 and 20 mg/kg, p.o) respectively and 30 min later all the groups were administered with glimepiride (10mg/kg, p.o). To study the influence of repeated treatment of perindopril on antidiabetic effect of glimepiride groups XI, XII, XIII and XIV were administered with repeated doses of perindopril (2.5, 5, 10 and 20 mg/kg, p.o), respectively, daily once for 7 days. On 8 th day 30 min later the last dose of perindopril glimepiride (10mg/kg, p.o) was administered in the above groups.

The blood samples were collected at prefixed time intervals 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 h and were analysed for glucose levels by the above mentioned methods. The percentage reduction in serum glucose levels at time "t" was calculated by using the following equation.

Percentage reduction in serum glucose at time "t"

$$t = A\text{-}B/A \times 100$$

Where **A** is serum glucose concentration at time "0" and

B is serum glucose concentration at time "t".

Statistical Analysis:

The results are expressed as the mean ± SEM and were analyzed by one-way ANOVA followed by Dunnett's multiple comparison "t" test. Data was computed for statistical analysis by using Graph Pad PRISM Software.

4. RESULTS:

When compared to normal control group glimepiride (10 mg/kg, p.o) administered has significantly reduced serum glucose levels at 1, 2, 4, 6, 8, 12, 18 and 24 th h of the experimental study and the peak hypoglycemic effect was observed at 6 th h.

Perindopril 2.5 mg/kg, p.o. (LD), 5 mg/kg, p.o. (ID) when administered as single doses to normal rats it has significantly reduced serum glucose levels at 2, 4, 6, 8 12 and 18 th h of the experimental study. Perindopril with MD and HD i.e.10 mg/kg, p.o. and 20 mg/kg HD, p.o when administered as single doses have significantly reduced the serum glucose levels throughout the experimental study except at 0.5 h.

In diabetic rats, glimepiride as a single dose exhibited significant serum glucose reduction from 0.5 to 18 h of experimental study and the peak antidiabetic effect was observed at 6 th hour.

Single dose of trearment of Perindopril (LD) in diabetic rats has produced significant decrease in serum glucose levels from 2 to 12 th h, ID from 1 to 12 th h, MD from 2 to 12 th h and HD produced significant decrease in serum glucose levels from 1 to 18 th h of experimental study.

In normal rats treatment with single doses of Perindopril i.e. LD, ID, MD and HD followed by single dose of glimepiride in all the groups have shown significant and dose dependent increase in the hypoglycemic activity of Glimepiride throughout the study period.

Repeated treatment of Perindopril LD and ID administered for 7 days followed by single dose of glimepiride has not altered the hypoglycemic activity of glimepiride upto 1hour but later there was a significant decrease in the serum glucose levels at 2, 6, 8, 12 th h. Similarly, repeated Perindopril MD treated group had shown significant serum glucose reduction from 2 to 18 th h and also at 24 th h of the

study period and HD had shown its significant hypoglycemic effect on glimepiride from 2nd h till the end of the experimental period.
In case of diabetic rats, single dose treatment of Perindopril LD followed by single dose of glimepiride has shown significant increase in the antidiabetic effect of glimepiride at 2, 4, 12, 24 and 30 th h. Perindopril ID single dose followed by single dose of glimepiride had produced significant increase in antidiabetic activity of glimepiride from 2 nd hour to the end of the study period except at 8 h. Perindopril MD and HD as single doses followed by single dose of Glimepiride has shown significant antidiabetic activity of glimepiride from 1st h of administration of glimepiride to the end of the study period.

Effect of Perindopril administration daily once for 7 days followed by single dose of glimepiride was studied in streptozotocin induced diabetic rats. Perindopril LD has shown significant increase in antidiabetic activity of glimepiride throughout the study period except at 1 and 30 th h. Perindopril ID repeated administration for 7 days has significantly increased the antidiabetic effect of glimepiride throughout the study period except at 18 th h. Similarly, Perindopril MD and HD in repeated treatment for 7 days have significantly altered antidiabetic effect of single dose of glimepiride throughout the study period.
Glimepiride when administered as a single dose to normal rats produced significant hypoglycemic activity. Onset of hypoglycemic action was observed between 0.5 and 1 h and the action continued beyond 18 hrs. Thus glimepiride has an onset of action of 1.5 h and duration of action more than 16 h.
When compared to control group single dose treatment of Perindopril LD, ID, MD and HD in different groups of normal rats have significantly reduced serum glucose levels at different time intervals but the percentage reduction of serum glucose level is very low in Perindopril LD and ID and not in case of MD and HD. In single dose treatment of Perindopril LD, ID, MD and HD followed by single dose treatment of glimepiride there was no alteration in onset of action and t_{max} of glimepiride.

Repeated treatment of Perindopril (LD, ID, MD, HD) administered daily once as single doses for a period of 7 days in different groups of animals followed by single dose of glimepiride 30 min later on 8 th day it was observed that there was a dose related increase in the hypoglycemic activity of the glimepiride and also an increase in duration of action of glimepiride. After repeated administration of Perindopril LD and ID there was no alteration in t_{max} but in MD and HD treated groups the t_{max} was shifted to 8 th h from 6 th.
Single doses treatment of Perindopril LD, ID, MD and HD has shown peak antidiabetic effect at 8 th h.
In single dose treatment of Perindopril LD, ID, MD and HD followed by single dose treatment of glimepiride in diabetic rats there was no alteration in onset of action and t_{max} of glimepiride.

Repeated treatment of Perindopril (LD, ID, MD, HD) administered daily once as single doses for a period of 7 days in different groups of diabetic animals followed by single dose of glimepiride 30 min later on 8 th day it was observed that there was a dose dependent increase in the antidiabetic activity of the glimepiride and also an increase in duration of action of glimepiride without an alteration in t_{max} was observed with any of the dose.

Table 1. Serum glucose levels in normal rats.

Time (h)	Serum glucose levels (mg/dl) with 0.1 N NaOH						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	82.45	85.32	79.14	84.67	81.56	90.52	**83.94 ±1.59**	-	-	-	-	-	-	
0.5	81.67	84.61	82.19	82.33	80.21	89.23	**83.37 ±1.30**	0.94	0.83	-3.85	2.76	1.65	1.42	**0.62 ±0.93**
1	80.84	84.05	84.36	81.16	79.43	90.40	**83.37 ±1.60**	1.95	1.48	-6.59	4.14	2.61	0.13	**0.62 ±1.53**
2	79.11	80.17	80.55	84.00	78.76	90.36	**82.15 ±1.80**	4.05	6.03	-1.78	0.79	3.43	0.17	**2.11 ±1.17**
4	79.01	84.31	80.17	83.19	78.40	86.11	**81.86 ±1.27**	4.17	1.18	-1.30	1.74	3.87	4.87	**2.42 ±0.94**
6	79.43	86.10	82.31	82.30	79.81	87.34	**82.88 ±1.32**	3.66	-0.91	-4.00	2.79	2.14	3.51	**1.13 ±1.22**
8	80.32	83.16	83.54	80.36	80.90	85.54	**82.30 ±0.86**	2.58	2.53	-5.55	5.09	0.80	5.50	**1.82 ±1.64**
12	81.71	85.53	79.67	83.34	81.62	86.17	**83.00 ±1.02**	0.89	-0.24	-0.66	1.57	-0.07	4.80	**1.04 ±0.82**
18	84.33	82.15	77.54	81.16	82.03	88.32	**82.58 ±1.46**	-2.28	3.71	2.02	4.14	-0.59	2.43	**1.57 ±1.02**
24	82.95	82.66	74.00	84.14	82.54	90.48	**82.79 ±2.14**	-0.60	3.11	6.49	0.62	-0.57	0.04	**1.51 ±1.14**
30	84.56	86.29	78.19	84.32	84.11	91.13	**84.76 ±1.70**	-2.55	-1.13	1.20	0.41	-3.12	-0.67	**-97 ±0.67**

Table 2. Serum glucose levels with Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	90.16	77.97	86.24	89.10	77.09	74.02	**82.43**	-	-	-	-	-	-	-
0.5	88.23	73.17	83.13	86.23	74.26	71.18	**79.36 ±3.00**	2.14	6.15	3.60	3.22	3.67	3.83	**3.76 ±0.53^{ns}**
1	82.94	69.16	77.14	80.13	70.45	69.21	**74.83 ±2.46**	8.00	11.29	10.55	10.06	8.61	6.49	**9.16 ±0.73****
2	74.38	63.16	70.20	72.16	61.15	66.40	**67.90 ±2.12**	17.50	18.99	18.59	19.01	20.67	18.40	**18.86 ±0.42*****
4	59.11	58.17	65.12	57.18	48.10	54.18	**56.64 ±2.29**	34.43	27.95	24.48	33.58	37.60	26.80	**30.80 ±2.09*****
6	47.14	51.24	45.29	47.17	37.29	43.13	**45.21 ±1.92**	47.71	51.24	47.48	47.18	51.62	41.73	**47.82 ±1.45*****
8	57.42	59.14	52.10	50.12	45.16	49.12	**52.17 ±2.15**	36.31	24.15	39.58	43.74	41.41	33.63	**36.47 ±2.86*****
12	63.12	65.26	67.19	58.69	51.13	55.19	**60.09 ±2.53**	29.99	16.30	22.08	34.13	33.67	25.43	**26.93 ±2.86*****
18	70.39	69.16	67.39	64.52	59.19	63.10	**65.62 ±1.70**	21.92	11.29	13.83	27.58	23.21	14.75	**18.76 ±2.60*****
24	77.15	72.13	76.01	70.45	65.17	69.33	**71.70 ±1.81**	14.42	7.49	11.86	20.93	15.46	6.33	**12.74 ±2.21*****
30	85.12	73.46	81.10	81.49	70.13	71.19	**77.08 ±2.55**	5.59	5.78	5.96	8.54	9.02	3.82	**6.45 ±0.80****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant

Table 3. Serum glucose levels with single dose treatment of Perindopril (2.5 mg/kg) in normal rats

Time (h)	Serum glucose levels (mg/dl) with Perindopril (2.5 mg/kg)						Mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	99.23	97.19	93.69	94.46	100.14	96.17	**96.81**	-	-	-	-	-	-	-
0.5	97.51	95.41	92.34	90.16	97.62	93.90	**94.49 ±1.20**	1.73	1.83	1.44	4.55	2.5	2.36	**2.40 ±0.45^{ns}**
1	96.16	93.31	89.16	88.13	90.14	87.10	**90.66 ±1.40**	3.09	3.99	4.83	6.70	9.98	9.43	**6.33 ±1.17****
2	93.13	88.71	84.11	82.82	86.19	81.89	**86.14 ±1.71**	6.14	8.72	10.22	12.32	13.93	14.80	**11.02 ±1.34*****
4	87.19	85.14	79.46	76.13	83.20	79.12	**81.70 ±1.70**	12.13	12.39	15.18	19.40	16.90	17.72	**15.62 ±1.19*****
6	82.23	81.28	74.11	72.41	79.91	71.10	**76.84 ±1.98**	17.13	16.36	20.89	23.34	20.20	26.06	**20.66 ±1.50*****
8	85.45	84.16	79.23	76.30	83.88	76.59	**80.93 ±1.66**	13.88	13.40	15.43	19.22	16.23	20.35	**16.41 ±1.15*****
12	91.51	89.66	83.44	80.96	85.76	80.49	**85.30 ±1.85**	7.77	7.74	10.94	14.29	14.35	16.30	**11.89 ±1.48*****
18	93.69	92.58	88.49	86.14	89.45	86.92	**89.54 ±1.23**	5.58	4.74	5.55	8.80	10.67	9.61	**7.49 ±1.02****
24	95.13	94.50	90.60	90.88	94.19	91.41	**92.78 ±0.83**	4.13	2.76	3.29	3.78	5.94	4.94	**4.14 ±0.47^{ns}**
30	97.89	96.18	92.47	92.11	98.65	94.78	**95.34 ±1.11**	1.35	1.03	1.30	1.48	1.44	2.41	**1.50 ±0.19^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 4. Serum glucose levels with single dose treatment of Perindopril (5 mg/kg) in normal rats.

time (h)	Serum glucose levels (mg/dl) with Perindopril (5 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	98.89	95.25	101.3	88.70	90.62	104.9	**96.62 ±2.56**	-	-	-	-	-	-	-
0.5	94.16	93.11	97.68	84.62	86.13	99.49	**92.53 ±2.46**	4.78	2.24	3.62	4.59	4.95	5.20	**4.23 ±0.45^{ns}**
1	89.19	90.23	93.94	81.57	83.74	92.27	**88.49 ±1.98**	9.80	5.27	7.31	8.03	7.59	12.08	**8.34 ±0.95***
2	85.45	87.63	88.15	77.94	79.98	87.39	**84.42 ±1.78**	13.59	8.00	13.02	12.13	11.74	16.73	**12.53 ±1.15****
4	80.65	81.13	82.63	73.66	74.47	84.96	**79.59 ±1.85**	18.40	14.82	18.47	16.95	17.82	19.04	**17.58 ±0.62*****
6	74.21	76.63	74.89	68.21	69.98	78.34	**73.71 ±1.58**	24.95	19.54	26.10	23.10	22.77	25.35	**23.63 ±0.97*****
8	77.89	78.41	77.96	71.18	72.81	80.71	**76.49 ±1.49**	21.23	17.67	23.07	19.75	19.65	23.09	**20.74 ±0.87*****
12	81.13	82.10	79.41	75.33	78.84	86.59	**80.57 ±1.53**	17.95	13.80	21.64	15.07	12.99	17.49	**16.49 ±1.30*****
18	89.16	84.18	88.19	79.30	84.52	95.74	**86.84 ±2.27**	9.83	11.67	12.98	10.59	6.73	8.77	**10.08 ±0.89***
24	93.56	91.49	94.43	82.14	86.74	98.89	**91.20 ±2.43**	5.38	3.94	6.82	7.39	4.28	5.77	**7.26 ±1.40^{ns}**
30	95.10	93.97	97.63	86.79	88.91	101.8	**94.04 ±2.26**	3.83	1.34	3.67	2.15	1.88	2.96	**2.63 ±0.41^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 5. Serum glucose levels with single dose treatment of Perindopril (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	90.14	94.85	88.39	101.8	86.91	92.89	**92.50 ±2.20**	-	-	-	-	-	-	-
0.5	87.41	91.74	84.54	96.63	84.62	89.52	**89.07 ±1.89**	3.02	3.27	4.35	5.10	2.63	3.62	**3.66 ±0.37^{ns}**
1	85.52	89.69	82.44	94.96	81.78	86.95	**86.89 ±2.00**	5.12	5.44	6.73	6.74	5.90	6.39	**6.05 ±0.27****
2	77.47	82.62	75.31	88.86	77.29	79.56	**80.18 ±2.00**	14.05	12.89	14.79	12.73	11.06	14.35	**13.31 ±0.55*****
4	72.94	77.10	70.43	80.37	69.11	73.49	**73.90 ±1.71**	19.08	18.71	20.31	21.07	20.48	20.88	**20.08 ±0.39*****
6	60.37	62.98	58.81	66.42	58.32	62.81	**61.61 ±1.24**	33.02	33.60	33.46	34.77	32.89	32.38	**33.35 ±0.33*****
8	64.33	66.13	62.39	70.94	60.49	67.36	**65.27 ±1.32**	28.63	30.27	29.41	30.33	30.39	27.48	**29.41 ±0.47*****
12	71.42	73.56	69.17	80.94	67.36	73.97	**72.73 ±1.94**	20.76	22.44	21.74	20.51	22.49	20.36	**21.35 ±0.39*****
18	77.48	79.45	74.51	86.71	71.12	80.38	**78.27 ±2.18**	14.04	16.23	15.70	14.84	18.16	13.46	**15.40 ±0.69*****
24	81.66	83.57	78.39	92.76	78.44	82.29	**82.85 ±2.15**	9.40	11.80	11.39	8.90	9.74	11.41	**10.45 ±0.51****
30	88.52	91.71	86.91	99.77	85.11	88.19	**90.03 ±2.13**	1.79	3.31	1.67	2.02	2.07	5.05	**2.65 ±0.53^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 6. Serum glucose levels with single dose treatment of Perindopril (20 mg/kg) in normal rats

Time (h)	Serum glucose levels (mg/dl) with Perindopril (20 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	89.14	84.72	91.12	86.25	93.68	88.36	**88.87 ±1.32**	-	-	-	-	-	-	-
0.5	86.33	82.55	88.62	81.41	90.11	85.91	**85.82 ±1.37**	3.15	2.56	2.74	5.61	3.81	2.16	**3.33 ±0.50***
1	83.19	78.66	84.31	76.91	84.40	81.12	**81.43 ±1.27**	6.67	10.62	7.47	10.82	9.09	8.19	**8.82 ±0.69*****
2	79.32	71.45	77.44	69.20	79.11	75.36	**75.31 ±1.70**	11.01	15.66	15.01	19.76	15.55	14.71	**15.28 ±1.13*****
4	64.61	62.10	66.26	53.78	68.26	62.80	**62.96 ±2.05**	27.51	26.69	27.28	37.64	29.26	29.65	**29.67 ±1.66*****
6	52.83	56.88	54.71	39.58	54.49	56.67	**52.52 ±2.66**	40.73	32.86	39.95	54.11	41.83	35.86	**40.89 ±2.98*****
8	67.48	58.98	64.32	48.61	65.79	63.88	**61.51 ±2.83**	24.29	30.38	29.41	43.64	29.77	27.70	**30.86 ±2.70*****
12	73.31	67.13	68.41	53.79	69.77	69.19	**66.93 ±2.76**	17.75	20.76	24.92	37.63	25.52	21.69	**24.71 ±2.83*****
18	76.67	72.69	72.71	64.67	76.33	73.67	**72.78 ±1.77**	13.98	14.19	20.20	25.02	18.52	16.62	**18.08 ±1.70*****
24	82.72	80.78	82.69	76.66	82.41	79.89	**80.85 ±0.96**	7.20	8.32	9.25	11.11	12.03	9.58	**9.58 ±0.72****
30	84.77	82.24	88.31	82.19	88.65	86.91	**85.51 ±1.18**	4.90	2.92	3.08	4.70	5.36	1.64	**3.76 ±0.58^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant

Fig.1; PERCENTAGE REDUCTION IN SERUM GLUCOSE WITH PERINDOPRIL (2.5,5,10 and 20mg/kg) IN NORMAL RATS.

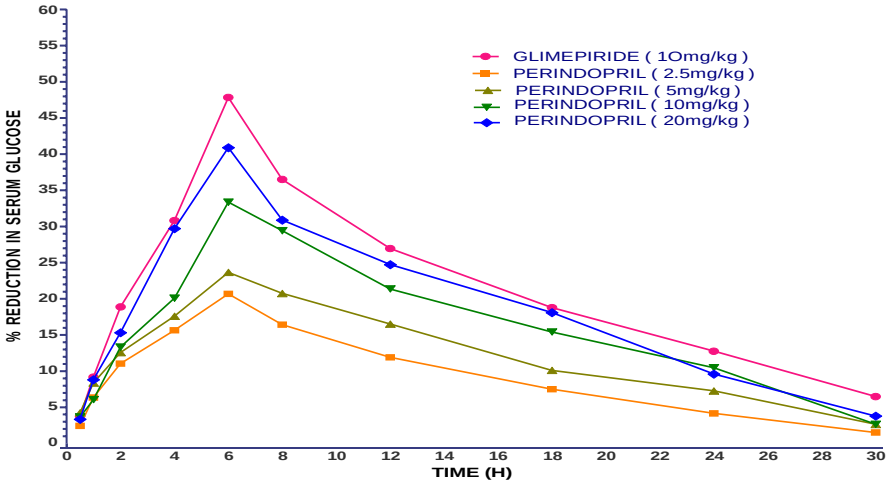

Table 7. Effect of single dose treatment of Perindopril (2.5 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (2.5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	79.51	82.67	84.11	76.39	80.18	85.36	**81.37 ±1.35**	-	-	-	-	-	-	-
0.5	79.00	81.16	83.79	75.41	79.28	85.11	**80.62 ±1.43**	0.64	1.82	0.38	1.28	1.12	0.29	**0.92 ±0.24****
1	74.54	77.24	79.41	72.67	75.16	82.23	**76.85 ±1.42**	6.25	6.68	5.58	4.86	6.26	3.66	**5.54 ±0.45****
2	60.41	64.26	62.11	58.86	64.81	71.46	**63.65 ±1.81**	24.02	22.26	26.15	22.94	19.16	16.28	**21.80 ±1.44^{ns}**
4	58.87	63.39	59.68	55.11	60.78	65.88	**60.61 ±1.52**	25.95	23.32	29.04	27.85	24.19	22.82	**25.52 ±1.03****
6	36.91	33.08	38.14	35.27	39.48	48.92	**38.63 ±2.25**	53.57	59.98	54.65	53.82	50.76	42.68	**52.57 ±2.33***
8	46.11	41.88	46.13	43.14	49.11	55.19	**46.92 ±1.95**	42.00	49.34	45.15	43.52	38.75	35.34	**42.35 ±2.00***
12	58.67	56.15	60.10	43.92	58.39	60.57	**56.3 ±2.55**	26.21	32.07	28.54	42.50	27.17	29.04	**30.92 ±2.45****
18	64.13	71.33	67.58	61.76	65.14	67.40	**66.22 ±1.35**	19.34	13.71	19.65	19.15	18.75	21.04	**18.60 ±1.03^{ns}**
24	72.41	75.67	73.16	68.14	70.67	74.12	**72.36 ±1.80**	8.92	8.46	13.01	10.79	11.86	13.16	**11.03 ±0.82^{ns}**
30	75.18	79.11	80.39	72.19	76.13	82.31	**77.55 ±1.52**	5.46	4.30	4.42	5.49	5.05	3.57	**4.71 ±0.30^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 8. Effect of single dose treatment of Perindopril (5 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	76.13	80.19	74.86	81.33	77.67	76.59	**77.79 ±1.01**	-	-	-	-	-	-	-
0.5	73.67	77.14	72.69	79.68	75.88	74.18	**75.54 ±1.05**	3.23	3.80	2.89	3.25	2.30	3.14	**3.10 ±0.20^{ns}**
1	68.14	71.91	65.38	69.39	70.95	69.27	**69.17 ±0.93**	10.49	10.32	12.66	14.68	8.65	9.55	**11.05 ±0.90^{ns}**
2	54.29	65.87	57.08	61.35	60.43	56.35	**59.22 ±1.70**	28.68	17.85	23.75	24.56	22.19	26.42	**23.90 ±1.51***
4	44.56	54.62	46.54	46.26	47.08	48.95	**48.00 ±1.44**	41.46	31.88	37.83	43.12	39.38	36.08	**38.29 ±1.64^{ns}**
6	34.35	41.69	33.92	34.95	31.92	33.29	**35.02 ±1.39**	54.87	48.01	54.68	57.02	58.90	56.53	**55.00 ±1.13****
8	38.96	45.13	39.41	44.76	38.50	39.20	**40.99 ±1.25**	48.82	43.72	47.35	44.96	50.43	48.81	**47.34 ±1.04****
12	58.13	60.10	52.22	58.32	54.61	55.14	**56.42 ±1.19**	23.64	25.05	30.24	28.29	29.68	28.00	**27.48 ±1.06^{ns}**
18	63.19	65.11	56.16	64.40	59.12	62.94	**61.82 ±1.41**	16.99	18.80	24.97	20.81	23.88	17.82	**20.54 ±1.34^{ns}**
24	67.91	75.67	65.30	71.68	70.77	74.22	**70.92 ±1.37**	10.79	5.63	12.77	11.86	8.88	3.09	**8.83 ±1.54^{ns}**
30	73.40	78.29	71.16	78.23	74.98	74.35	**75.06 ±1.14**	3.58	2.36	4.94	3.81	3.46	2.92	**3.51 ±0.35^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 9. Effect of single dose treatment of Perindopril (10 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (10 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	75.67	70.13	79.45	72.61	76.40	77.10	**75.22 ±1.36**	-	-	-	-	-	-	-
0.5	73.12	69.34	77.83	70.11	73.58	73.59	**72.92 ±1.23**	3.36	1.12	2.03	3.44	3.69	4.55	**3.03 ±0.50^{ns}**
1	68.28	64.53	72.20	66.39	68.89	71.04	**68.55 ±1.16**	9.76	7.98	9.12	8.56	9.82	7.85	**8.84 ±0.35^{ns}**
2	59.18	52.71	62.11	53.21	54.13	56.89	**56.37 ±1.52**	21.79	24.83	21.82	26.71	29.14	26.21	**25.08 ±1.18***
4	43.67	39.32	50.72	41.13	39.67	38.80	**42.22 ±1.85**	42.28	43.93	36.09	43.35	48.07	49.67	**43.89 ±1.95****
6	39.41	34.94	37.14	33.75	30.52	28.12	**33.98 ±1.70**	47.95	50.17	53.25	53.51	60.40	63.52	**54.8 ±2.44****
8	40.13	33.79	38.61	38.45	32.52	30.44	**35.65 ±1.60**	41.82	51.81	51.40	47.04	57.43	60.15	**51.66 ±2.76****
12	51.34	44.81	47.75	47.10	42.17	43.79	**46.16 ±1.33**	32.15	36.10	31.89	35.13	44.80	43.20	**37.21 ±2.25****
18	58.41	56.61	62.77	60.32	56.29	61.39	**59.29 ±1.07**	22.80	19.27	20.99	16.92	26.32	20.37	**21.11 ±1.31^{ns}**
24	62.98	64.18	67.13	64.11	65.15	67.30	**65.14 ±0.71**	16.77	8.48	15.50	11.70	14.78	12.71	**13.32 ±1.22^{ns}**
30	67.05	65.13	70.50	69.30	71.33	70.14	**69.07 ±1.05**	11.39	7.12	11.26	4.55	6.63	9.02	**8.32 ±1.11^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 10. Effect of single dose treatment of Perindopril (20 mg/kg) on hypoglycemic activity of Glimepiride (10mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (20 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						Mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	74.13	72.61	77.32	82.13	78.10	76.11	**76.73 ±1.36**	-	-	-	-	-	-	-
0.5	70.29	68.11	73.56	77.68	75.33	72.19	**72.86 ±1.40**	5.18	6.19	4.86	5.41	3.54	5.15	**5.05 ± 0.35** ^{ns}
1	68.10	63.14	71.60	72.19	70.80	68.33	**69.01 ±1.35**	8.13	13.04	7.39	12.20	9.34	10.22	**10.05 ± 0.91** ^{ns}
2	56.90	54.76	60.71	60.19	58.60	52.10	**57.21 ±1.35**	23.24	24.58	21.48	26.71	24.96	31.54	**25.41 ± 1.41****
4	42.13	40.61	46.11	47.20	42.11	37.19	**42.55 ±1.49**	43.16	44.07	40.36	42.53	46.08	49.08	**44.21 ± 1.23****
6	31.67	30.17	36.22	41.69	35.15	32.66	**34.59 ±1.68**	57.27	58.44	53.15	49.23	54.99	57.08	**55.02 ± 1.39***
8	34.01	32.89	38.11	42.29	37.16	34.69	**36.52 ±1.40**	54.12	54.74	50.71	48.50	52.41	54.42	**52.48 ± 1.00****
12	40.66	40.11	42.30	44.11	41.49	39.88	**41.42 ±0.65**	45.15	44.75	45.29	46.29	46.87	46.60	**45.82 ± 0.35****
18	47.81	46.23	47.62	50.67	48.71	44.11	**47.52 ±0.90**	35.50	36.33	38.41	38.30	37.63	42.04	**38.03 ± 0.92****
24	55.18	50.11	53.88	57.13	54.41	52.72	**54.03 ±1.01**	24.48	30.98	30.31	27.72	30.33	30.73	**29.09 ± 1.03****
30	59.30	55.39	57.01	65.33	61.24	60.29	**59.76 ±1.41**	20.00	23.83	26.26	20.45	21.58	20.78	**22.15 ± 0.99****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Fig.2: PERCENTAGE REDUCTION IN SERUM GLUCOSE WITH SINGLE DOSE TREATMENT OF PERINDOPRIL (2.5,5,10 and 20mg/kg) + GLIMEPIRIDE (10mg/kg) IN NORMAL RATS.

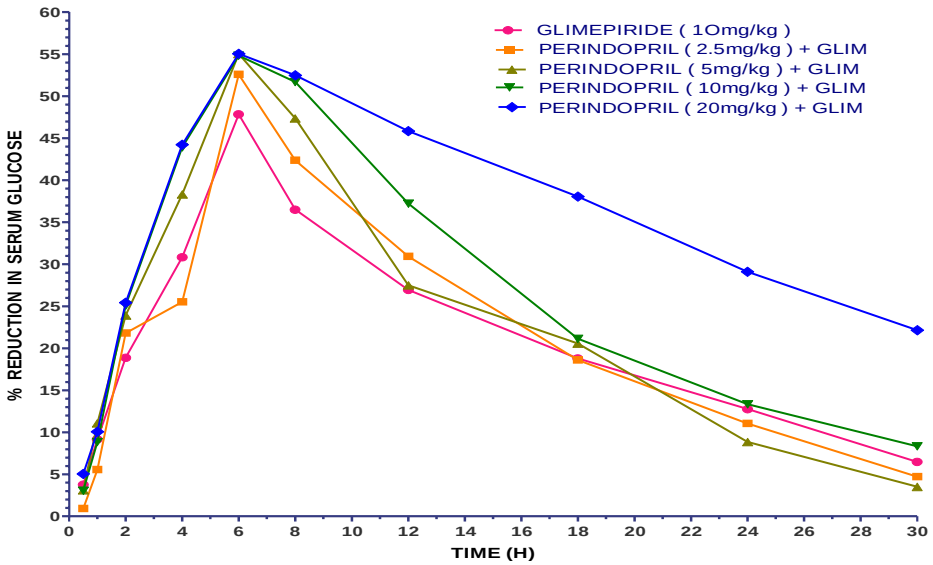

Table 11. Effect of repeated dose treatment of Perindopril (2.5 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (2.5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	84.39	80.15	78.36	80.17	85.67	75.19	**80.65 ± 1.57**	-	-	-	-	-	-	-
0.5	81.31	79.14	73.36	75.13	80.11	71.14	**76.74 ± 1.66**	3.64	1.26	5.99	6.28	6.49	5.38	**4.84 ± 0.83** ^{ns}
1	76.63	70.47	71.32	71.67	74.92	68.67	**72.28 ± 1.20**	9.19	12.07	8.98	10.60	12.54	8.67	**10.34 ± 0.67** ^{ns}
2	63.24	58.31	55.77	57.14	66.18	56.11	**59.45 ± 1.74**	25.06	27.24	28.82	28.72	22.72	25.37	**26.32 ± 0.97****
4	52.17	49.15	51.18	55.11	57.11	49.68	**52.4 ± 1.27**	38.17	38.67	34.68	31.25	33.33	33.92	**35.00 ± 1.17** ^{ns}
6	39.46	36.61	36.30	38.17	36.39	31.95	**36.48 ± 1.03**	53.24	54.32	53.67	52.38	57.52	57.50	**54.77 ± 0.90***
8	40.51	34.32	34.14	38.78	41.15	32.71	**36.93 ± 1.48**	51.99	57.18	56.43	51.62	51.96	56.49	**54.27 ± 1.09****
12	49.73	47.16	49.32	51.21	53.78	44.89	**49.34 ± 1.26**	41.07	41.16	37.05	36.12	37.22	40.29	**38.81 ± 0.92****
18	66.29	68.91	63.11	62.44	71.84	63.86	**66.07 ± 1.50**	21.44	14.02	19.46	22.11	16.14	15.06	**18.03 ± 1.40** ^{ns}
24	74.86	75.31	69.14	70.31	80.32	69.14	**73.18 ± 1.81**	11.29	6.03	11.76	12.29	6.24	8.04	**9.27 ± 1.16** ^{ns}
30	77.41	78.67	71.18	74.81	77.62	72.33	**75.33 ± 1.25**	8.27	1.84	9.16	6.68	9.39	3.80	**6.52 ± 1.26** ^{ns}

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 12. Effect of repeated dose treatment of Perindopril (5 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	81.42	77.31	79.93	81.75	78.67	83.48	**80.42 ± 0.91**	-	-	-	-	-	-	-
0.5	77.63	74.11	76.45	78.47	74.88	79.42	**77.32 ± 0.75**	4.65	4.13	4.35	4.01	4.81	4.86	**4.46 ± 0.14** ^{ns}
1	69.08	70.52	71.67	72.32	66.11	77.83	**71.25 ± 1.59**	15.15	8.78	10.33	11.53	15.96	6.76	**11.41 ± 1.46** ^{ns}
2	59.15	57.13	59.43	58.37	51.77	60.65	**57.75 ± 1.28**	27.35	26.10	25.64	28.59	34.19	27.34	**28.20 ± 1.27****
4	48.13	51.55	51.81	49.18	48.66	49.56	**49.81 ± 0.62**	40.88	33.32	35.18	39.84	38.14	40.63	**37.99 ± 1.27** **
6	35.67	38.17	36.48	34.81	30.13	38.39	**35.60 ± 1.23**	56.19	50.71	54.36	57.41	61.70	54.01	**55.73 ± 0.51***
8	33.71	39.12	39.69	35.67	31.81	36.11	**36.01 ± 1.24**	58.59	49.39	50.34	56.36	59.56	56.74	**55.16 ± 1.74****
12	47.32	43.47	41.12	47.32	44.67	43.77	**44.61 ± 0.98**	41.88	43.77	48.55	42.11	43.21	47.56	**44.49 ± 1.16****
18	68.14	63.96	61.57	66.69	65.95	69.92	**66.03 ± 1.21**	16.31	17.26	22.97	18.42	16.16	16.24	**17.89 ± 1.07** ^{ns}
24	75.45	75.81	74.11	75.11	76.13	75.17	**75.29 ± 0.28**	7.33	4.52	7.28	8.12	3.22	9.95	**6.73 ± 1.00** ^{ns}
30.0	79.31	74.99	77.27	79.38	77.81	79.43	**78.03 ± 0.71**	2.59	3.00	3.32	2.89	1.09	4.85	**2.95 ± 0.49** ^{ns}

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 13. Effect of repeated dose treatment of Perindopril (10 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (10 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	78.43	73.67	71.86	75.11	69.24	74.18	**73.74 ± 1.26**	-	-	-	-	-	-	-
0.5	73.65	70.23	68.35	71.95	65.38	71.83	**70.23 ± 1.21**	6.09	4.66	4.88	4.20	5.57	3.16	**4.74 ± 0.42** ^{ns}
1	67.32	64.92	66.78	66.17	58.11	65.14	**64.74 ± 1.37**	14.16	11.87	7.06	11.90	16.07	12.18	**12.20 ± 1.23** ^{ns}
2	58.44	53.41	51.13	55.90	48.71	53.38	**53.49 ± 1.39**	25.48	27.50	28.84	25.57	29.65	28.03	**27.51 ± 0.69****
4	47.15	43.77	41.38	42.04	39.93	42.67	**42.82 ± 1.01**	39.88	40.58	42.41	44.02	42.33	42.47	**41.94 ± 0.60****
6	35.03	29.16	30.91	35.12	31.05	35.11	**32.73 ± 1.08**	55.33	60.41	56.98	53.52	55.15	52.66	**55.67 ± 1.12****
8	33.14	32.93	32.15	32.67	31.62	32.44	**32.49 ± 0.22**	57.74	55.30	55.26	56.50	54.33	56.26	**55.89 ± 0.48****
12	40.69	41.33	37.98	40.78	38.93	40.05	**39.96 ± 0.51**	48.11	43.89	47.14	45.70	43.77	46.00	**45.76 ± 0.70****
18	53.11	55.48	54.19	51.70	58.03	50.13	**53.77 ± 1.14**	32.28	24.69	24.58	31.16	16.19	32.42	**26.88 ± 2.59***
24	60.78	62.15	60.15	59.11	66.11	59.05	**61.22 ± 1.08**	22.50	15.63	16.29	21.30	4.52	2.39	**16.77 ± 2.69** ^{ns}
30	64.86	64.17	66.33	69.56	68.32	68.77	**67.00 ± 0.90**	17.30	12.89	7.69	7.38	1.32	7.29	**8.97 ± 2.23** ^{ns}

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 14. Effect of repeated dose treatment of Perindopril (20 mg/kg) on hypoglycemic activity of Glimepiride (10 mg/kg) in normal rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (20 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	105.33	99.86	95.11	101.67	98.43	92.77	**98.86 ± 1.84**	-	-	-	-	-	-	-
0.5	101.67	94.13	89.47	97.21	93.49	86.44	**93.73 ± 2.21**	3.47	5.73	5.92	4.38	5.01	6.82	**5.22 ± 0.48 ns**
1	91.56	90.67	81.30	85.43	90.54	86.17	**87.61 ± 1.63**	13.07	9.20	14.52	15.97	8.01	7.11	**11.31 ± 1.50 ns**
2	75.11	72.86	68.81	72.55	71.35	65.39	**71.01 ± 1.40**	29.82	27.03	27.65	28.64	27.51	29.51	**28.36 ± 0.46****
4	62.86	59.43	58.21	61.27	59.22	54.08	**59.17 ± 1.22**	40.32	40.48	38.79	39.73	39.83	41.70	**40.14 ± 0.39****
6	44.17	39.19	45.39	44.13	38.91	34.14	**40.98 ± 1.76**	58.06	60.75	52.27	56.59	60.46	63.19	**58.55 ± 1.56****
8	36.19	34.05	37.81	39.08	34.11	36.93	**36.36 ± 0.82**	65.64	65.90	60.24	61.56	65.43	60.19	**63.16 ± 1.13****
12	49.13	52.67	49.94	51.59	51.78	51.48	**51.09 ± 0.53**	53.35	47.25	47.49	49.25	47.39	44.50	**48.20 ± 1.20****
18	70.42	63.11	61.27	69.86	63.19	66.95	**65.8 ± 1.56**	33.14	36.80	35.57	31.28	35.80	27.83	**33.40 ± 1.38****
24	81.59	75.16	73.14	82.43	74.55	70.04	**76.15 ± 1.99**	22.53	24.73	23.09	18.92	24.26	24.50	**23.00 ± 0.88****
30	90.88	81.49	80.67	86.77	80.16	79.11	**83.18 ± 1.88**	13.71	18.39	15.18	14.65	18.56	14.72	**15.86 ± 0.84****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Fig.3: PERCENTAGE REDUCTION IN SERUM GLUCOSE WITH REPEATED TREATMENT OF PERINDOPRIL (2.5,5,10 and 20mg/kg) + SINGLE DOSE OF GLIMEPIRIDE (10mg/kg) IN NORMAL RATS.

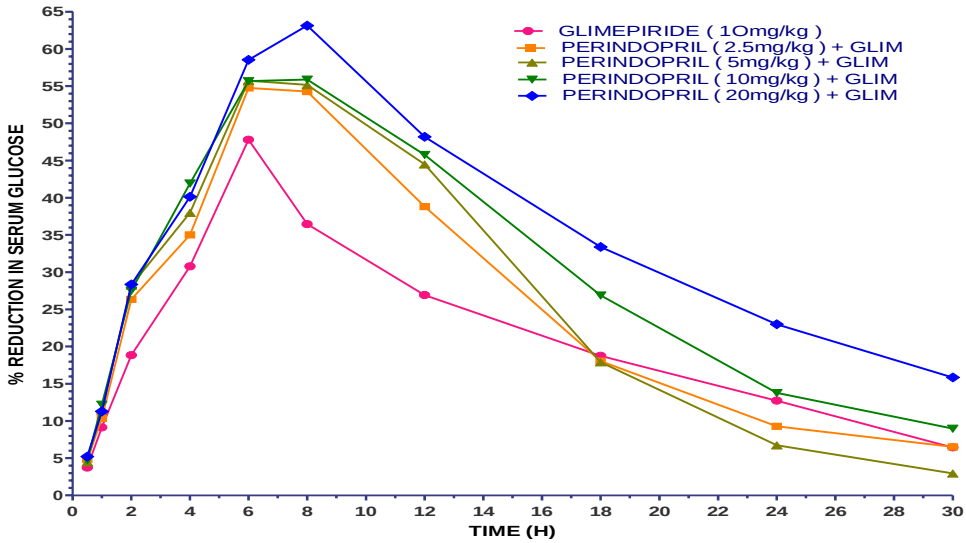

Table 15. Normal serum glucose levels in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with 0.1 N NaOH						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	428.4	479.1	470.9	488.3	419.7	426.2	**452.1 ± 12.48**	-	-	-	-	-	-	-
0.5	445.1	485.4	475.7	451.8	386.3	450.7	**449.6 ± 14.24**	-3.89	-1.31	-1.01	5.83	7.95	-5.74	**0.30 ± 2.21**
1	434.9	487.8	488.3	477.3	392.9	430.2	**451.9 ± 15.81**	-1.51	-1.81	-3.69	2.25	6.38	-0.93	**0.11 ± 1.48**
2	440.5	502.3	455.0	480.1	383.0	444.9	**450.96 ± 16.59**	-2.82	-4.84	3.37	1.67	8.74	-4.38	**0.29 ± 2.16**
4	426.1	487.1	439.1	478.3	384.8	424.9	**439.95 ± 15.46**	0.53	-1.66	6.75	2.04	8.31	0.44	**2.73 ± 1.60**
6	438.0	493.4	440.7	484.7	380.4	440.0	**446.2 ± 16.50**	-2.24	-2.98	6.41	-0.7	9.36	-3.23	**1.09 ± 2.20**
8	436.2	490.2	432.2	479.1	383.1	434.1	**442.48 ± 15.66**	-1.82	-2.31	8.21	1.88	8.72	-1.85	**2.13 ± 2.09**
12	440.5	496.1	439.5	480.6	382.3	438.4	**446.2 ± 16.22**	-2.82	-3.54	6.66	1.57	8.91	-2.86	**1.32 ± 2.19**
18	432.8	501.7	424.2	477.2	369.6	430.9	**439.4 ± 18.73**	-1.02	-4.71	9.91	2.27	11.93	-1.10	**2.88 ± 2.71**
24	446.0	488.3	439.7	490.4	386.4	444.2	**449.16 ± 15.59**	-4.10	-1.92	6.62	-0.4	7.93	-4.22	**0.64 ± 2.18**
30	413.1	452.1	405.9	467.3	362.2	411.4	**418.66 ± 15.18**	3.57	5.63	13.80	4.30	13.70	-3.47	**7.41 ± 2.02**

n=6, Significant at $p<0.05$*, 0.01**and 0.001***, ns = not significant.

Table 16. Serum glucose levels with Glimepiride (10 mg/kg) in diabetic rats

Time (h)	Serum glucose levels(mg/dl)with Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	395.3	391.4	386.1	385.9	386.7	385.1	**388.41 ± 1.65**	-	-	-	-	-	-	-
0.5	370.5	369.1	367.8	366.4	364.3	361.6	**366.61 ± 1.33**	6.27	5.69	4.73	4.27	5.79	6.10	**5.47 ± 0.32***
1	314.1	322.6	309.3	319.5	309.1	312.8	**314.56 ± 2.23**	20.54	17.5	19.89	17.2	20.9	18.77	**19.00 ± 0.56*****
2	268.6	277.4	270.6	275.1	276.4	273.4	**273.58 ± 1.39**	32.05	29.1	29.91	28.7	28.5	29.00	**29.55 ± 0.53*****
4	226.4	226.3	228.5	235.4	224.8	219.1	**226.75 ± 2.64**	42.72	42.1	40.81	38.9	41.8	43.10	**41.25 ± 0.68*****
6	199.1	185.9	183.3	188.0	191.1	185.6	**188.83 ± 2.31**	49.63	52.5	52.52	51.2	50.5	51.80	**51.38 ± 0.46*****
8	223.6	212.4	211.6	216.5	215.4	211.3	**215.13 ± 1.90**	43.43	45.7	45.19	43.8	44.2	45.13	**40.61 ± 0.35*****
12	291.3	286.0	281.4	286.1	285.1	276.7	**284.43 ± 2.01**	26.30	26.9	27.11	25.8	26.2	28.14	**26.75 ± 0.33*****
18	336.7	328.4	321.7	330.4	323.6	329.1	**328.4 ± 2.17**	14.28	16.09	16.67	14.3	16.3	14.54	**15.37 ± 0.44****
24	366.9	373.1	354.1	374.7	373.1	358.4	**366.71 ± 3.52**	7.33	4.67	8.28	2.9	3.51	6.93	**5.60 ± 0.90** ns
30	376.4	377.8	368.4	383.1	380.7	375.4	**376.96 ± 2.06**	4.78	3.47	4.58	0.72	1.55	2.51	**2.93 ± 0.66** ns

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 17. Serum glucose levels with single dose treatment of Perindopril (2.5 mg/kg) in diabetic rats

Time (h)	Serum glucose levels (mg/dl) with Perindopril (2.5 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	335.9	319.1	347.8	323.4	324.3	334.1	**330.7 ± 4.32**	-	-	-	-	-	-	-
0.5	331.4	323.8	344.6	315.3	318.4	325.5	**326.5 ± 4.28**	1.33	1.47	0.92	2.50	1.81	2.57	**1.61 ± 0.80^{ns}**
1	301.1	289.4	321.3	303.6	309.1	320.3	**307.46 ± 4.96**	10.36	9.30	7.61	6.12	4.68	4.13	**7.03 ± 1.02***
2	279.9	277.1	290.1	285.9	290.4	305.6	**288.1 ± 4.11**	16.67	13.1	16.58	11.5	10.4	8.53	**12.81 ± 1.35****
4	263.4	257.3	249.9	278.4	279.1	280.4	**271.41 ± 7.35**	21.58	19.3	28.14	13.9	13.9	16.07	**18.83 ± 2.23*****
6	230.9	239.8	234.5	243.1	235.4	238.9	**235.6 ± 1.34**	31.25	24.8	32.57	24.8	27.4	28.49	**28.23 ± 1.31*****
8	222.8	233.4	228.7	230.6	219.7	221.9	**225.95 ± 2.34**	33.67	26.8	34.24	28.6	32.2	33.82	**31.61 ± 1.97*****
12	260.5	248.1	265.4	238.5	253.1	254.1	**239.61 ± 3.13**	22.44	22.2	23.69	26.2	21.9	23.94	**23.42 ± 0.65*****
18	305.1	297.4	313.8	283.8	295.4	295.9	**315.23 ± 4.21**	9.16	6.80	9.77	12.2	8.91	11.43	**9.71 ± 0.79***
24	321.3	305.1	336.1	314.1	313.1	319.4	**318.18 ± 4.26**	4.28	4.38	3.36	2.87	3.45	4.39	**3.77 ± 0.25 ^{ns}**
30	334.1	317.6	344.6	319.0	321.6	330.6	**327.91 ± 4.28**	0.23	0.47	0.92	1.36	0.83	1.04	**0.85 ± 0.13***

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 18. Serum glucose levels with single dose treatment of Perindopril (5 mg/kg) in diabetic rats

Time (h)	Serum glucose levels (mg/dl) with Perindopril (5 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	374.2	383.4	404.1	402.5	384.2	386.1	**389.08 ± 4.80**	-	-	-	-	-	-	-
0.5	369.8	377.1	399.8	396.3	377.5	378.3	**383.13 ± 4.90**	1.17	1.64	1.06	1.54	1.74	2.02	**1.52 ± 0.14 ns**
1	334.3	343.9	364.2	353.1	333.1	342.6	**345.2 ± 4.82**	10.66	10.3	9.87	12.2	13.3	11.26	**11.27 ± 0.52*** **
2	322.1	318.7	332.9	336.6	320.4	321.8	**321.41 ± 3.03**	13.92	16.8	17.61	16.3	16.6	16.65	**16.33 ± 0.51*** **
4	293.6	294.4	314.1	334.9	304.7	305.4	**307.85 ± 6.24**	21.53	23.2	22.27	16.7	20.6	20.90	**20.89 ± 0.90*** **
6	278.4	273.8	277.8	267.5	258.1	269.9	**270.91 ± 3.10**	25.60	28.5	31.25	33.5	32.8	30.09	**30.31 ± 1.19*** **
8	255.9	251.3	254.1	253.1	235.5	249.1	**249.83 ± 3.02**	31.61	34.4	37.11	37.1	38.7	35.48	**35.74 ± 1.02*** **
12	282.1	285.5	291.4	299.4	305.6	299.4	**293..9 ± 3.71**	24.61	25.5	27.88	25.6	20.4	22.45	**24.42 ± 1.06*** **
18	355.4	360.1	347.9	329.3	330.1	345.1	**344.65 ± 5.20**	5.02	6.07	13.90	18.1	14.0	10.61	**11.31 ± 2.07***
24	355.1	364.3	386.5	385.1	367.9	372.5	**371.9 ± 4.97**	5.10	4.98	4.35	4.82	4.24	3.52	**4.41 ± 0.23 ns**
30	372.8	374.2	399.1	401.3	379.3	381.0	**384.61 ± 5.09**	0.37	2.39	1.23	0.29	1.27	1.32	**1.14 ± 0.31***

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 19. Serum glucose levels with single dose treatment of Perindopril (10 mg/kg) in diabetic rats

Time (h)	Serum glucose levels (mg/dl) with Perindopril (10mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	353.4	352.9	355.7	351.8	344.1	345.0	**350.48 ± 1.95**	-	-	-	-	-	-	-
0.5	348.2	347.1	346.5	345.4	338.8	341.3	**344.55 ± 1.50**	1.47	1.64	2.58	1.81	1.54	1.07	**1.68 ± 0.20 ns**
1	327.9	333.0	335.1	334.9	333.1	331.9	**332.63 ± 1.07**	7.21	5.63	5.79	4.80	3.19	3.79	**5.06 ± 0.59 ** **
2	285.1	294.1	301.4	298.3	293.4	288.4	**293.45 ± 2.46**	19.32	16.6	15.26	15.2	14.7	16.40	**16.26 ± 0.68*** **
4	261.3	263.4	276.1	274.1	269.2	264.1	**268.03 ± 2.48**	26.06	25.3	22.37	22.0	21.7	23.44	**23.51 ± 0.73*** **
6	235.5	241.3	250.0	245.6	252.4	250.3	**243.85 ± 2.63**	33.36	31.6	29.71	30.1	26.6	27.44	**29.82 ± 1.02*** **
8	220.1	219.8	229.1	221.8	212.8	214.9	**219.75 ± 2.33**	37.71	37.7	35.59	369.	38.1	37.71	**37.30 ± 0.37*** **
12	265.4	263.5	273.8	266.4	267.1	253.7	**263.98 ± 2.69**	24.90	25.3	23.02	24.2	22.3	26.46	**24.39 ± 0.61*** **
18	318.3	305.1	316.3	319.7	317.4	303.1	**331.31 ± 2.96**	9.93	13.5	11.07	9.12	7.75	12.14	**10.59 ± 0.85***
24	332.1	326.4	342.9	329.1	321.8	320.0	**328.71 ± 3.37**	6.02	7.50	3.59	6.45	6.48	7.24	**6.21 ±0.57***
30	346.9	345.6	351.8	346.4	340.0	339.6	**345.08 ±1.88**	1.83	2.06	1.09	1.53	1.19	1.56	**1.54 ± 0.15***

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 20. Serum glucose levels with single dose treatment of Perindopril (20 mg/kg) in diabetic rats

Time (h)	Serum glucose levels (mg/dl) with Perindopril (20mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	400.6	386.2	388.42	393.1	390.5	392.1	**391.81 ± 2.03**	-	-	-	-	-	-	-
0.5	393.4	379.1	374.1	382.4	384.3	385.0	**383.05 ± 2.63**	1.79	1.81	3.68	2.72	1.58	1.81	**2.23 ± 0.33 ns**
1	353.1	342.3	346.3	354.6	351.6	338.4	**347.65 ± 2.69**	11.85	13.69	10.83	9.79	9.96	13.69	**11.63 ± 0.71*** **
2	339.5	321.8	324.9	337.9	328.1	320.1	**328.71 ± 3.35**	15.25	18.36	16.34	14.04	15.97	18.36	**16.38 ± 0.70*** **
4	302.9	283.4	292.3	301.1	293.4	286.6	**293.28 ± 3.14**	24.38	26.90	24.74	23.40	24.86	26.90	**25.19 ± 0.57*** **
6	273.1	262.1	260.5	263.8	271.6	267.3	**266.4 ± 2.10**	31.82	32.13	32.92	32.89	30.44	31.82	**32.03 ± 0.37*** **
8	238.8	230.9	227.1	236.5	234.2	233.5	**233.5 ± 1.68**	40.38	40.21	41.52	39.83	40.02	40.44	**40.4 ± 0.24*** **
12	245.4	246.3	254.4	252.9	237.4	247.1	**247.25 ± 2.47**	38.74	36.22	34.50	35.66	39.20	36.98	**36.88 ± 0.74*** **
18	353.1	330.7	331.1	328.1	327.1	321.9	**332.11 ± 4.42**	11.85	14.37	14.75	16.53	16.23	17.90	**15.27 ± 0.86** **
24	372.3	362.1	362.8	363.4	368.7	362.5	**365.3 ± 1.71**	7.06	6.24	6.59	7.55	5.58	7.54	**6.76 ± 0.31***
30	388.5	378.3	382.9	374.6	386.2	385.3	**375.00 ± 2.99**	3.02	2.04	1.41	4.07	1.10	1.73	**2.22 ± 0.45 ns**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Fig.4: PERCENTAGE REDUCTION IN SERUM GLUCOSE WITHPERINDOPRIL (2.5,5,10 and 20mg/kg) IN DIABETIC RATS.

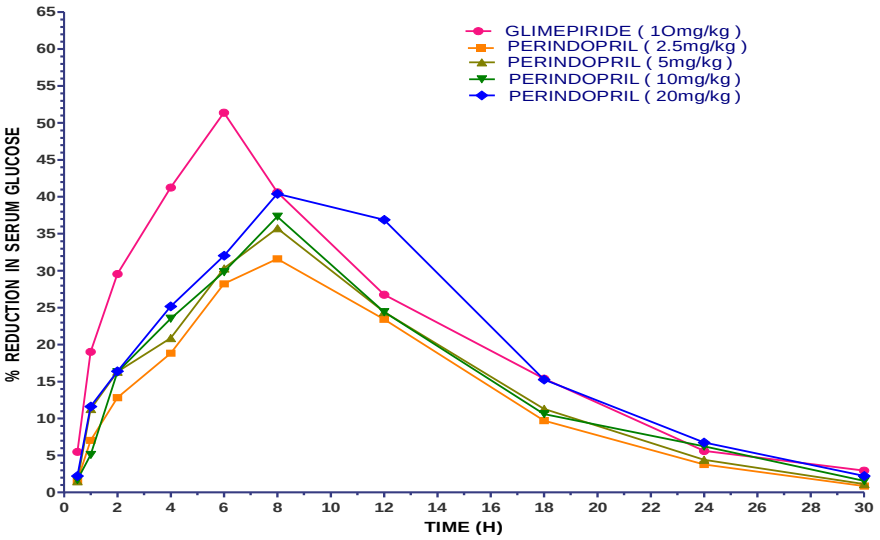

Table 21. Effect of single dose treatment of Perindopril (2.5 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (2.5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	397.1	389.6	390.2	393.4	392.1	394.2	**392.76 ± 1.13**	-	-	-	-	-	-	-
0.5	381.7	373.4	375.1	377.5	374.3	376.6	**379.76 ± 2.92**	3.87	4.15	3.86	4.04	4.53	4.46	**4.15 ± 0.11***
1	339.1	337.1	339.2	341.3	338.1	352.2	**341.16 ± 2.27**	14.60	13.4	13.07	13.2	13.7	10.65	**13.13 ± 0.54****
2	257.4	266.9	268.4	264.7	263.4	268.4	**269.86 ± 1.70**	35.18	31.4	31.21	32.7	32.8	31.91	**32.55 ± 0.58***
4	214.3	226.5	211.9	213.4	208.6	210.2	**214.15 ± 2.61**	46.03	41.8	45.69	45.7	46.7	46.67	**45.46 ± 0.74** **
6	201.7	181.3	172.4	194.8	192.3	194.6	**189.51 ± 4.36**	49.20	53.4	55.81	50.4	50.9	50.63	**51.75 ± 0.99** ns
8	216.4	203.6	194.8	201.5	204.5	213.9	**205.78 ± 3.28**	45.50	47.7	50.07	48.7	47.8	45.73	**47.60 ± 0.71****
12	270.8	264.3	268.5	273.1	271.4	273.6	**270.28 ± 1.40**	31.80	32.1	31.18	30.5	30.7	30.59	**31.18 ± 0.27****
18	315.1	322.9	318.3	311.4	321.1	323.4	**318.7 ± 1.93**	20.64	17.1	18.42	20.8	18.1	17.96	**18.84 ± 0.62** **
24	348.4	351.1	349.1	352.1	348.3	353.1	**350.35 ± 0.83**	12.26	9.88	10.53	10.4	11.1	10.42	**10.79 ± 0.33****
30	379.1	368.4	367.4	374.2	364.5	377.9	**371.91 ± 2.45**	4.53	5.44	5.84	4.88	7.03	4.13	**5.30 ± 0.42***

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant

Table 22. Effect of single dose treatment of Perindopril (5 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	353.9	364.1	367.9	358.4	357.8	360.1	**360.36 ± 2.27**	-	-	-	-	-	-	-
0.5	322.6	343.9	345.4	340.9	332.4	340.7	**339.31 ± 2.27**	6.01	5.54	6.11	4.88	7.09	5.38	**5.83 ± 0.31** ns
1	283.4	291.0	286.1	287.7	289.2	288.4	**287.6 ± 1.07**	19.92	20.0	22.23	19.7	19.1	19.91	**20.17 ± 0.43** ns
2	245.9	230.1	232.6	230.1	233.6	226.0	**233.05 ± 2.78**	30.51	36.8	36.77	35.7	34.7	37.23	**35.30 ± 1.02****
4	191.7	193.4	196.8	189.4	192.4	188.4	**192.01 ± 1.22**	45.83	46.8	46.50	47.1	46.2	47.68	**46.71 ± 0.27***
6	162.4	161.8	145.1	150.8	161.9	157.9	**156.65 ± 2.92**	54.11	55.5	60.55	57.9	54.7	56.15	**56.50 ± 0.96****
8	183.2	192.1	191.0	194.1	197.3	188.4	**191.01 ± 1.98**	48.23	47.2	48.08	45.8	44.8	47.68	**46.98 ± 0.55** ns
12	241.7	246.3	250.4	251.7	249.1	242.9	**247.01 ± 1.66**	31.70	32.3	31.93	29.7	30.3	32.54	**31.44 ± 0.45****
18	281.9	285.7	281.2	282.3	286.4	281.6	**283.18 ± 0.92**	20.34	21.5	23.56	21.2	19.9	21.79	**21.39 ± 0.51****
24	318.1	320.1	312.7	314.1	311.2	316.1	**315.38 ± 1.37**	10.11	12.0	15.00	12.3	13.0	12.21	**12.46 ± 0.64****
30	323.7	328.4	329.1	327.5	323.9	324.5	**326.18 ± 0.98**	8.53	9.80	10.54	8.62	9.47	9.88	**9.47 ± 0.31****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 23. Effect of single dose treatment of Perindopril (10 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (10mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	402.8	408.1	407.1	400.3	412.8	405.9	**406.16 ± 1.77**	-	-	-	-	-	-	-
0.5	379.1	382.4	380.1	386.4	391.1	383.4	**383.75 ± 1.80**	5.88	6.29	6.63	3.47	5.25	5.54	**5.51 ± 0.45 ns**
1	311.4	323.7	320.4	314.2	318.3	319.6	**317.93 ± 1.81**	22.69	20.6	21.29	21.5	22.8	21.26	**21.71 ± 0.35 ****
2	252.8	246.1	243.2	246.9	247.5	252.1	**248.1 ± 1.50**	37.23	39.6	40.26	38.3	40.0	37.89	**38.90 ± 0.51****
4	199.5	196.3	192.0	199.7	21.8	206.3	**199.26 ± 1.98**	50.47	51.8	52.83	50.1	51.1	49.17	**50.93 ± 0.53****
6	172.3	178.5	174.9	175.4	172.6	181.5	**175.86 ± 1.45**	57.22	56.2	57.03	56.1	58.1	55.28	**56.69 ± 0.41****
8	202.9	206.8	200.1	203.8	205.3	207.1	**204.33 ± 1.07**	49.62	49.3	50.84	49.0	50.2	48.97	**49.68 ± 0.29****
12	269.3	251.3	247.6	253.2	250.1	252.3	**253.96 ± 3.16**	33.14	38.4	39.17	36.7	39.4	37.84	**37.45 ± 0.94****
18	321.1	311.5	306.4	304.1	308.4	309.8	**310.21 ± 2.41**	20.28	23.6	24.73	24.0	25.2	23.67	**23.61 ± 0.71****
24	367.4	351.8	347.1	349.3	352.2	354.1	**353.65 ± 2.92**	8.78	13.7	14.73	12.7	14.6	12.76	**12.91 ± 0.90****
30	384.1	386.7	381.9	378.9	383.6	381.7	**382.81 ± 1.07**	4.64	5.24	6.19	5.34	7.07	5.96	**5.74 ± 0.34***

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 24. Effect of single dose treatment of Perindopril (20 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (20mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	370.2	366.6	361.4	363.8	362.3	369.1	**365.56 ± 1.48**	-	-	-	-	-	-	-
0.5	351.8	341.39	339.2	338.7	342.8	350.7	**344.1 ± 2.34**	4.96	6.87	6.14	6.89	5.38	4.98	**5.87 ± 0.36 ns**
1	274.1	283.1	277.4	275.1	280.4	277.6	**277.95 ± 1.36**	25.95	22.7	23.24	24.3	22.6	24.79	**23.95 ± 0.53****
2	215.3	206.7	203.9	201.4	206.8	222.4	**209.41 ± 3.22**	41.84	43.6	43.58	44.6	42.9	39.74	**42.72 ± 0.70****
4	188.4	176.5	166.1	168.7	169.2	184.9	**175.63 ± 3.78**	49.10	51.8	54.03	53.6	53.29	49.90	**51.96 ± 0.84****
6	150.7	145.1	144.8	142.4	149.1	152.1	**147.36 ± 1.55**	59.29	60.4	59.93	60.8	58.8	58.79	**59.68 ± 0.34****
8	186.3	169.3	171.1	169.1	178.4	179.8	**175.66 ± 2.84**	49.67	53.8	52.65	53.5	50.7	51.28	**51.94 ± 0.67****
12	225.4	207.8	204.7	206.4	215.1	214.3	**212.28 ± 3.14**	39.11	43.3	43.35	43.2	40.6	41.93	**41.93 ± 0.71****
18	273.1	253.2	251.0	253.9	250.8	263.1	**257.41 ± 3.62**	26.22	30.9	30.54	30.2	30.7	28.71	**29.56 ± 0.74****
24	325.9	316.7	313.4	316.5	318.5	322.4	**318.9 ± 1.84**	11.96	13.6	13.28	13.0	12.0	12.65	**12.76 ± 0.26****
30	357.0	346.8	348.1	350.1	347.1	360.0	**351.51 ± 2.29**	3.56	5.40	3.68	3.76	4.19	2.46	**3.84 ± 0.31 ns**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Fig.5: PERCENTAGE REDUCTION IN SERUM GLUCOSE WITH SINGLE DOSE TREATMENT OF PERINDOPRIL (2.5,5,10 and 20mg/kg) + GLIMEPIRIDE (10mg/kg) IN DIABETIC RATS.

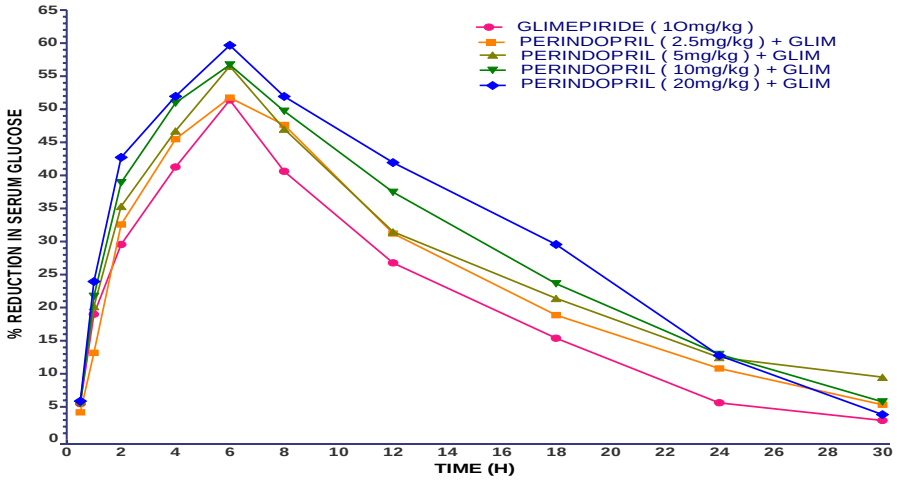

Table 25. Effect of repeated dose treatment of Perindopril (2.5 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (2.5 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	417.8	412.1	422.3	420.9	414.7	409.3	**416.18 ± 2.07**	-	-	-	-	-	-	-
0.5	388.2	386.9	401.4	399.2	387.9	386.1	**391.61 ± 2.77**	7.08	6.11	4.94	5.15	6.46	5.66	**5.9 ± 0.33^{ns}**
1	322.5	327.1	332.8	331.5	324.1	317.4	**325.9 ± 2.36**	22.80	20.62	21.19	21.24	21.84	22.45	**21.69 ± 0.33 ^{ns}**
2	263.9	268.7	271.1	270.9	268.5	264.2	**267.88 ± 1.29**	36.83	34.79	35.80	35.63	35.25	35.45	**35.62 ± 0.27****
4	206.3	209.0	213.0	213.7	203.2	208.1	**208.88 ± 1.63**	50.62	49.28	49.56	49.22	51.00	49.15	**49.80 ± 0.32****
6	155.1	154.5	164.3	159.4	157.1	146.6	**156.1 ± 2.40**	62.87	62.50	61.09	62.12	62.11	64.18	**62.47 ± 0.41****
8	167.8	199.3	203.8	199.1	191.8	190.3	**192.01 ± 5.26**	59.83	51.63	51.74	52.69	53.74	53.50	**53.85 ± 1.24****
12	243.6	251.8	252.1	249.0	241.3	239.7	**246.25 ± 2.21**	41.69	38.89	40.30	40.84	41.81	41.43	**40.82 ± 0.45****
18	294.9	292.2	301.8	297.3	288.5	295.4	**295.01 ± 1.84**	29.41	29.09	28.53	29.36	30.43	27.82	**29.10 ± 0.36****
24	345.1	353.7	355.4	354.1	348.7	346.7	**350.61 ± 1.77**	17.40	14.17	15.84	15.87	15.91	15.29	**15.74 ± 0.42****
30	403.7	401.9	405.1	400.5	399.7	395.2	**401.01 ± 1.42**	3.37	2.47	4.07	4.84	3.61	3.44	**3.63 ± 0.32 ^{ns}**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 26. . Effect of repeated dose treatment of Perindopril (5 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (5 mg/kg) + Glimepiride (10mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	391.7	386.3	380.2	383.4	389.1	378.6	**384.88 ± 2.08**	-	-	-	-	-	-	-
0.5	357.4	350.9	342.6	353.1	353.8	344.2	**350.33 ± 2.36**	8.75	9.16	9.88	7.90	9.07	9.08	**8.97 ± 0.26****
1	290.1	271.6	278.4	281.9	288.1	270.8	**280.15 ± 3.31**	25.93	29.69	26.77	26.47	25.95	28.47	**27.21 ± 0.62****
2	244.6	239.4	233.9	236.3	239.4	231.1	**237.45 ± 1.94**	37.55	38.02	38.47	38.36	38.47	38.95	**38.30 ± 0.19****
4	191.3	177.9	170.2	174.1	190.1	164.32	**177.98 ± 4.42**	51.16	53.94	55.23	54.59	51.14	56.59	**53.77 ± 0.90****
6	138.5	134.2	127.4	135.7	137.6	124.11	**132.91 ± 2.38**	64.64	65.26	66.49	64.60	64.63	67.21	**65.47 ± 0.45****
8	186.9	173.7	168.1	171.4	180.3	174.3	**175.78 ± 2.76**	52.28	55.03	55.29	53.66	52.63	53.96	**53.80 ± 0.49****
12	260.4	251.5	241.6	242.1	259.8	244.0	**249.9 ± 3.53**	33.52	34.89	36.45	36.85	33.23	35.55	**35.08 ± 0.60****
18	321.7	309.2	306.2	299.3	319.4	309.1	**310.81 ± 3.42**	17.87	19.95	19.46	21.93	17.91	18.35	**19.24 ± 0.63 ns**
24	344.1	322.4	320.7	322.8	343.9	324.8	**329.78 ± 4.52**	12.15	16.54	15.64	15.80	11.61	14.21	**14.32 ± 0.83****
30	353.8	351.3	344.9	356.9	348.4	355.1	**351.73 ± 1.82**	9.67	9.06	9.28	6.91	10.46	6.20	**8.59 ± 0.68****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 27. Effect of repeated dose treatment of Perindopril (10 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (10 mg/kg) + Glimepiride (10 mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	363.19	357.3	361.7	359.4	349.1	351.7	**357.06 ± 2.28**	-	-	-	-	-	-	-
0.5	335.4	329.6	335.2	330.1	321.1	318.1	**328.26 ± 2.93**	7.65	7.75	7.32	8.15	7.99	9.55	**8.06 ± 0.31***
1	277.1	258.2	276.9	268.4	248.3	247.8	**262.79 ± 5.44**	23.70	27.7	23.4	25.3	28.8	29.54	**26.43 ± 1.07****
2	241.8	247.9	241.6	231.2	223.1	219.4	**234.16 ± 4.65**	33.42	30.6	33.2	35.6	36.0	37.61	**34.43 ± 1.02****
4	169.5	183.6	170.4	166.9	160.6	154.9	**167.66 ± 3.98**	53.33	48.6	52.8	53.5	53.9	55.95	**53.05 ± 0.98****
6	111.7	104.3	113.1	114.7	109.0	105.1	**109.66 ± 1.74**	69.24	70.8	68.7	68.0	68.7	70.11	**69.28 ± 0.40****
8	148.2	136.1	149.7	140.3	136.1	134.3	**140.79 ± 2.70**	59.19	61.9	58.6	60.9	60.9	61.81	**60.57 ± 0.55****
12	193.9	175.8	194.0	194.1	176.3	171.9	**184.35 ± 4.35**	46.61	50.7	46.3	45.9	49.4	51.10	**48.39 ± 0.95****
18	238.4	212.0	237.1	229.7	217.6	215.3	**225.01 ± 4.71**	34.35	40.6	34.4	36.0	37.6	38.78	**37.00 ± 1.02****
24	272.6	237.1	271.5	248.0	243.1	241.7	**252.33 ± 6.39**	24.94	33.6	24.9	30.9	30.3	31.27	**29.35 ± 1.47****
30	297.4	261.9	299.2	266.3	271.3	263.5	**276.61 ± 6.99**	18.10	26.7	17.2	25.9	22.2	25.07	**22.55 ± 1.65****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 28. Effect of repeated dose treatment of Perindopril (20 mg/kg) on antidiabetic activity of Glimepiride (10 mg/kg) in diabetic rats.

Time (h)	Serum glucose levels (mg/dl) with Perindopril (20mg/kg) + Glimepiride (10mg/kg)						mean ± SEM	Percentage reduction in serum glucose						mean ± SEM
	H	B	T	HB	BT	HT		H	B	T	HB	BT	HT	
0.0	362.9	367.11	372.3	365.3	375.1	360.6	**367.21 ± 2.26**	-	-	-	-	-	-	-
0.5	326.6	304.4	334.6	330.4	340.0	324.3	**326.71 ± 5.02**	10.00	17.0	10.12	9.55	9.35	10.06	**11.02 ± 1.21****
1	259.4	273.0	257.1	265.9	263.4	253.7	**262.08 ± 2.81**	28.52	25.6	30.94	27.2	29.7	29.64	**28.61 ± 0.78****
2	223.1	213.6	220.3	221.5	225.1	221.9	**220.91 ± 1.60**	38.52	41.8	40.82	39.3	39.9	38.46	**39.82 ± 0.53****
4	158.0	144.8	141.6	165.6	148.3	149.2	**151.25 ± 3.64**	56.46	60.5	61.96	54.6	60.4	58.62	**58.78 ± 1.13****
6	97.6	91.3	98.34	97.19	101.3	92.10	**96.31 ± 1.57**	73.10	75.1	73.58	73.3	72.9	74.45	**73.77 ± 0.34****
8	122.3	121.6	127.01	120.3	133.2	117.4	**123.65 ± 2.30**	66.29	66.8	65.88	67.0	64.4	67.44	**66.33 ± 0.43****
12	169.7	167.4	177.4	169.0	184.4	157.3	**170.87 ± 3.77**	53.23	54.3	52.35	53.7	50.8	56.37	**53.48 ± 0.76****
18	232.3	229.1	247.1	227.3	255.1	223.1	**235.67 ± 5.13**	35.18	37.5	33.62	37.7	31.9	38.13	**35.84 ± 1.02****
24	271.5	265.3	286.4	265.4	293.4	260.9	**273.82 ± 5.34**	25.18	27.7	23.07	27.3	21.7	27.64	**25.45 ± 1.04****
30	319.1	317.4	321.3	314.9	327.1	312.0	**318.63 ± 2.14**	12.06	13.5	13.69	13.7	12.7	13.47	**13.22 ± 0.27****

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant

Fig.6: PERCENTAGE REDUCTION IN SERUM GLUCOSE WITH REPEATED TREATMENT OF PERINDOPRIL (2.5,5,10 and 20mg/kg) + SINGLE DOSE OF GLIMEPIRIDE (10mg/kg) IN DIABETIC RATS.

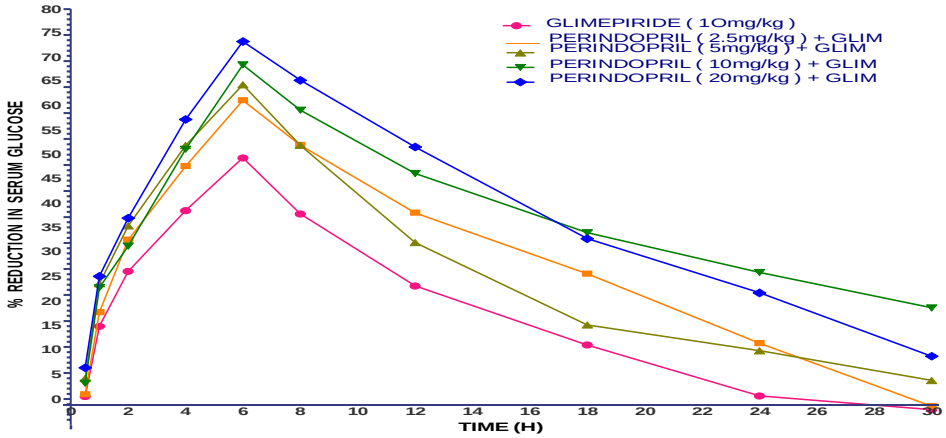

Table 29. Effect of Perindopril (2.5mg/kg) treatment on serum glucose level in normal rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (2.5mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	3.76±0.53**	2.40±0.45^{ns}	0.92±0.24**	4.84±0.83^{ns}
1.0	9.16±0.73***	6.33±1.17***	5.54±0.45**	10.34±0.67^{ns}
2.0	18.86±0.42***	11.02±1.34***	21.80±1.44^{ns}	26.32±0.97**
4.0	30.80±2.09***	15.62±1.19***	25.52±1.03^{ns}	35.00±1.17^{ns}
6.0	47.82±1.45***	20.66±1.50***	52.57±2.33*	54.77±0.90**
8.0	36.47±2.86***	16.41±1.15***	42.35±2.00*	54.27±1.09**
12.0	26.93±2.86***	11.89±1.48***	30.92±2.45**	38.81±0.92**
18.0	18.76±2.60***	7.49±1.02**	18.60±1.03^{ns}	18.03±1.40^{ns}
24.0	12.74±2.21***	4.14±0.47^{ns}	11.03±0.82^{ns}	9.27±1.16^{ns}
30.0	6.45±0.80**	1.50±0.19^{ns}	4.71±0.30^{ns}	6.52±1.26^{ns}

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 30. Effect of Perindopril (5mg/kg) treatment on serum glucose level in normal rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (5mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	3.76±0.53^{ns}	4.23±0.45^{ns}	3.10±0.20^{ns}	4.46±0.14^{ns}
1.0	9.16±0.73***	8.34±0.95**	11.05±0.90^{ns}	11.41±1.46^{ns}
2.0	18.86±0.42***	12.53±1.15**	23.90±1.51^{ns}	28.20±1.27**
4.0	30.80±2.09***	17.58±0.62***	38.29±1.64*	37.99±1.24**
6.0	47.82±1.45***	23.63±0.97***	55.00±1.13**	55.73±0.51**
8.0	36.47±2.86***	20.70±0.87***	47.34±1.04**	55.16±1.74**
12.0	26.93±2.86***	16.49±1.30***	27.48±1.06^{ns}	44.49±1.16**
18.0	18.76±2.60***	10.08±0.89*	20.54±1.34^{ns}	17.89±1.07^{ns}
24.0	12.74±2.21***	7.26±1.40^{ns}	8.83±1.54^{ns}	6.73±1.00^{ns}
30.0	6.45±0.80**	2.63±0.41^{ns}	3.51±0.35^{ns}	2.95±0.49^{ns}

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 31. Effect of Perindopril (10mg/kg) treatment on serum glucose level in normal rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (10mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	3.76±0.53^{ns}	3.66±0.37^{ns}	3.03±0.50^{ns}	4.74±0.42^{ns}
1.0	9.16±0.73***	6.05±0.27**	8.84±0.35^{ns}	12.20±1.23^{ns}
2.0	18.86±0.42***	13.31±0.55***	25.08±1.18**	27.51±0.69**
4.0	30.80±2.09***	20.08±0.39***	43.89±1.95**	41.94±0.60**
6.0	47.82±1.45***	33.35±0.33***	54.8±2.44**	55.67±1.12**
8.0	36.47±2.86***	29.41±0.47***	51.66±2.76**	55.89±0.48**
12.0	26.93±2.86***	21.30±0.39***	37.21±2.25**	45.76±0.70**
18.0	18.76±2.60***	15.40±0.69***	21.11±1.31^{ns}	26.88±2.59**
24.0	12.74±2.21***	10.45±0.51**	13.32±1.22^{ns}	16.77±2.69^{ns}
30.0	6.45±0.80**	2.65±0.53^{ns}	8.32±1.11^{ns}	8.97±2.23**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 32. Effect of Perindopril (20mg/kg) treatment on serum glucose level in normal rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (20mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	3.76±0.53^{ns}	3.33±0.50**	5.05±0.35^{ns}	5.22±0.48^{ns}
1.0	9.16±0.73***	8.81±0.68**	10.05±0.91^{ns}	11.31±1.50^{ns}
2.0	18.86±0.42***	15.28±1.13***	25.41±1.41**	28.36±0.46**
4.0	30.80±2.09***	29.67±1.66***	44.21±1.23**	40.14±0.39**
6.0	47.82±1.45***	40.89±2.98***	55.02±1.39**	58.55±1.56**
8.0	36.47±2.86***	30.86±2.70***	52.48±1.00**	63.16±1.13**
12.0	26.93±2.86***	24.71±2.83***	45.82±0.35**	48.20±1.20**
18.0	18.76±2.60***	18.08±1.70***	38.03±0.92**	33.40±1.38**
24.0	12.74±2.21***	9.58±0.72**	29.09±1.03**	23.00±0.88**
30.0	6.45±0.80**	3.76±0.58^{ns}	22.15±0.99**	15.86±0.84**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 33. Effect of Perindopril (2.5mg/kg) treatment on serum glucose level in diabetic rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (2.5mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	5.47±0.32**	1.61±0.80^{ns}	4.15±0.11*	5.9±0.33^{ns}
1.0	19.00±0.56***	7.03±1.02*	13.13±0.54**	21.69±0.33^{ns}
2.0	29.55±0.53***	12.81±1.35**	32.55±0.58*	35.62±0.27**
4.0	41.25±0.68***	18.83±2.23***	45.46±0.74^{ns}	49.80±0.32**
6.0	51.38±0.46***	28.23±1.31***	51.75±0.99^{ns}	62.47±0.41**
8.0	40.61±0.35***	31.61±1.97***	47.60±0.71**	53.85±1.24**
12.0	26.75±0.33***	23.42±0.65***	31.18±0.27**	40.82±0.45**
18.0	15.37±0.44**	9.71±0.79*	18.84±0.62^{ns}	29.10±0.36**
24.0	5.60±0.90^{ns}	3.77±0.25^{ns}	10.79±0.33**	15.74±0.42**
30.0	2.93±0.66^{ns}	0.85±0.13*	5.30±0.42**	3.63±0.32^{ns}

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 34. Effect of Perindopril (5mg/kg) treatment on serum glucose level in diabetic rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (5mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	5.47±0.32**	1.52±0.14^{ns}	5.83±0.31^{ns}	8.97±0.26**
1.0	19.00±0.56***	11.27±0.52***	20.17±0.43^{ns}	27.21±0.62**
2.0	29.55±0.53***	16.33±0.51***	35.30±1.02**	38.30±0.19**
4.0	41.25±0.68***	20.89±0.90***	46.71±0.27*	53.77±0.90**
6.0	51.38±0.46***	30.31±1.19***	56.50±0.96**	65.47±0.45**
8.0	40.61±0.35***	35.74±1.02***	46.98±0.55^{ns}	53.80±0.49**
12.0	26.75±0.33***	24.42±1.06***	31.44±0.45**	35.08±0.60**
18.0	15.37±0.44**	11.31±2.07*	21.39±0.51**	19.24±0.63^{ns}
24.0	5.60±0.90^{ns}	4.41±0.23^{ns}	12.46±0.64**	14.32±0.83**
30.0	2.93±0.66^{ns}	1.14±0.31*	9.47±0.31**	8.59±0.68**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 35. Effect of Perindopril (10mg/kg) treatment on serum glucose level in diabetic rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (10mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	5.47±0.32**	1.68±0.20^{ns}	5.51±0.45^{ns}	8.06±0.31**
1.0	19.00±0.56***	5.06±0.59^{ns}	21.71±0.35^{ns}	26.43±1.07**
2.0	29.55±0.53***	16.26±0.68***	38.90±0.51**	34.43±1.02*
4.0	41.25±0.68***	23.51±0.73***	50.93±0.53**	53.05±0.98**
6.0	51.38±0.46***	29.82±1.02***	56.69±0.41**	69.28±0.40**
8.0	40.61±0.35***	37.30±0.37***	49.68±0.29**	60.57±0.55**
12.0	26.75±0.33***	24.39±0.61***	37.45±0.94**	48.39±0.95**
18.0	15.37±0.44**	10.59±0.85**	23.61±0.71**	37.00±1.02**
24.0	5.60±0.90^{ns}	6.21±0.57*	12.91±0.90**	29.35±1.47**
30.0	2.93±0.66^{ns}	1.54±0.15**	5.74±0.34*	22.55±1.65**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

Table 36. Effect of Perindopril (20mg/kg) treatment on serum glucose level in diabetic rats (mean ±SEM).

Time (h)	Glimepiride (10mg/kg,p.o)	Perindopril (20mg/kg,p.o)	Single dose of Perindopril +single dose of glimepiride	Repeated treatment of perindopril + single dose of glimepiride
	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose	% reduction in serum glucose
	Mean ±SEM	Mean ±SEM	Mean ±SEM	Mean ±SEM
0.5	5.47±0.32**	2.23±0.33^{ns}	5.87±0.36^{ns}	11.02±1.21**
1.0	19.00±0.56***	11.63±0.71***	23.95±0.53**	28.61±0.78**
2.0	29.55±0.53***	16.38±0.70***	42.72±0.70**	39.82±0.53**
4.0	41.25±0.68***	25.19±0.57***	51.96±0.84**	58.78±1.13**
6.0	51.38±0.46***	32.03±0.37***	59.68±0.34**	73.77±0.34**
8.0	40.61±0.35***	40.4±0.24***	51.94±0.67**	66.33±0.43**
12.0	26.75±0.33***	36.88±0.74***	41.93±0.71**	53.48±0.76**
18.0	15.37±0.44**	15.27±0.86**	29.56±0.74**	35.84±1.02**
24.0	5.60±0.90^{ns}	6.76±0.31*	12.76±0.26**	25.45±1.04**
30.0	2.93±0.66^{ns}	2.22±0.45^{ns}	3.84±0.31^{ns}	13.22±0.27**

n=6, Significant at p<0.05*, 0.01**and 0.001***, ns = not significant.

5. DISCUSSION:

The present study was under taken to verify the possible drug-drug interaction if any between single and repeated dose treatment of perindopril on hypoglycemic and antidiabetic activity of glimepiride in normal and diabetic rats.

In the present study in normal animals the effect of perindopril on the hypoglycemic activity of glimepiride was studied and parameter considered for the study were onset and duration of hypoglycemic action of glimepiride. After repeated dose treatment of perindopril followed by single dose treatment of glimepiride, it has shown significant hypoglycemia in all the animals, exhibited by reduced activity (movement), confined to a single place with signs of depression which was further confirmed by significant increase in duration of hypoglycemic activity of glimepiride and slight alteration in peak effect after perindopril pre treatment.

In the first phase of the study in different groups of normal rats the effect of single dose treatment of perindopril LD, ID, MD and HD and glimepiride (10 mg/kg, p.o) on serum glucose levels were studied. From the results it was observed that when compared to control group perindopril LD has significantly altered the serum glucose levels at 0.5 h. Glimepiride has produced a significant hypoglycemic effect and the peak hypoglycemic effect was observed at 6 th h. From the results it was confirmed that single dose treatment of perindopril LD, ID, MD and HD has not altered the onset of action of glimepiride, but slightly increased peak effect with no change in duration of glimepiride in normal rats. After repeated treatment with perindopril LD, ID, MD and HD for 7 days it has not altered the onset of hypoglycemic action of glimepiride but with a positive influence on the peak hypoglycemic effect and a significant enhancement in the duration of action. This may perhaps due to increased absorption or decreased excretion of glimepiride due to perindopril. These results suggest that, during concomitant administration of glimepiride and perindopril, the dose and frequency of glimepiride need to be readjusted accordingly. In addition, monitoring of regular serum glucose levels during this period is essential to avoid the unwanted complications like severe hypoglycemia and convulsions.

These results have indicated that perindopril has influenced the absorption phase of glimepiride. Since the peak effect and duration of hypoglycemia induced by glimepiride were enhanced, so it can be concluded that perindopril appears primarily to interfere with the absorption, protein binding or metabolism, excretion, increase in micro and macro vascular circulation to pancreas and decreased insulin resistance.

In the earlier phases of study normal animals were used to study the effect of perindopril on hypoglycemic activity of glimepiride. To confirm the results of the earlier study and to understand the drug-drug interaction between perindopril and glimepiride (i.e., effect of perindopril) on serum glucose levels even in pathophysiological conditions like diabetic states, in the III phase of the study diabetic rats were used. Diabetes was induced in rats by injecting streptozotocin (50 mg/kg, i.p) and serum glucose was analyzed after every 24 h for few days so as to confirm the stabilized serum glucose levels in the diabetic state.

In diabetic rats Glimepiride (10 mg/kg, p.o) has reduced the serum glucose levels to the maximum extent of 52.00 % at the 6th h. The onset of action was seen at 1 h and a significant antidiabetic effect was seen beyond 12 h. Single dose of perindopril LD, ID have not significantly reduced the serum glucose levels initially but reduced significantly from 6th h upto 12th h. But MD, HD doses of perindopril have significantly reduced the serum glucose levels from 4th h to 12th h with a peak antidiabetic effect at 8th h. perindopril LD, ID, MD and HD single doses treatment followed by single dose treatment of glimepiride (10 mg/kg, p.o) was studied, a significant alteration in hypoglycemic activity of glimepiride which was observed from1st h to 24th h of the experimental study. After repeated treatment with perindopril LD, ID, MD and HD once daily for 7 days in individual groups followed by single dose of glimepiride (10 mg/kg) in all the four groups it was observed that perindopril LD, ID, MD and HD doses exhibited dose dependent and time dependent antidiabetic activity of glimepiride with a significant alteration in peak effect and enhanced duration of action of glimepiride.

From the results obtained, it can be concluded that not only in normal state but also in pathophysiological conditions like diabetes repeated treatment of perindopril has exerted a definite inhibitory effect on metabolism of glimepiride, confirmed by enhanced duration of antidiabetic action of glimepiride.

From these results it was confirmed that single dose treatment of perindopril has not altered the onset of action but slightly increased the peak effect with no change in duration of action of glimepiride in normal rats. But after repeated treatment with perindopril

LD, ID, MD and HD daily once for 7 days, it has enhanced the peak effect and duration of glimepiride both in normal and diabetic albino rats.

Literature review revealed that hypertension and diabetes mellitus are two common chronic conditions which frequently coexist and can significantly affect individual health care needs. The prevalence of hypertension increases with age and is common in both cases of insulin-dependent diabetes mellitus (IDDM) and non insulin-dependent diabetes mellitus (NIDDM) conditions. Hypertension appears to be critically important in diabetes mellitus, not only because of its increased prevalence, but also it accelerates both the micro vascular and macro vascular complications of diabetes. Combination of hypertension and diabetes mellitus produces greater myocardial dysfunction and is associated with significant mortality rates. Hence controlling blood pressure in diabetics is positively more beneficial as far as progressions of diabetic complications are concerned. ACE inhibitors can help people with diabetes by reducing their risk of heart attack, stroke and premature deaths and also delay the onset and progression of kidney disease. In addition, ACE inhibitors can help to reduce other complications of diabetes such as foot ulcers and eye damage (retinopathy), as retinopathy is the leading cause of blindness for people with diabetes. They can also prevent diabetic complications in people who do not have high blood pressure. People who take ACE inhibitors run a slightly increased risk of low blood sugar. Therefore, people with diabetes, should closely monitor blood sugar levels for the first few weeks after starting with ACE inhibitor, or during an increase in the dosage of ACE inhibitor. ACE inhibitor therapy appears to improve insulin sensitivity and glucose metabolism. There is evidence that pharmacologic treatment that interrupts the renin– angiotensin system (RAS) affords special benefits, not only in patients after myocardial infarction and in congestive heart failure, but also in persons with hypertension accompanied with the cardio metabolic syndrome and type 2 diabetes mellitus.

Overcoming insulin resistance (by weight reduction/increased aerobic activity or with drugs that interrupt the RAS) may prevent the development of diabetes, which is extraordinarily important in epidemic of type 2 diabetes. Thus, interruption of the RAS system may be a mechanism for improving insulin sensitivity. Angiotensin II not only increases vascular resistance but also increases hepatic glucose production and decreases insulin sensitivity. Several investigative groups had shown that ACE inhibitors have the ability to improve glycemic control and promote hypoglycemia in type 2 diabetic patients treated with sulfonylurea agents.
Improvement in insulin sensitivity was achieved by addition of an ACE inhibitor to a tissue culture system, suggesting effects independent of the microcirculation. This improvement in insulin sensitivity at a cellular level is indicated by an increase in glucose transporter–4 protein and activity of hexokinase, a key enzyme in glucose metabolism in the skeletal muscle of obese rats treated with an ACE inhibitor. Several studies have shown that ACE inhibitors and ARBs (angiotensin receptor blockers) decrease the incidence of new-onset type 2 diabetes. A possible protective effect of ARBs and ACE inhibitors on the pancreatic β-cell through inhibiting the vasoconstrictive effect of angiotensin II in the pancreas and increasing islet blood flow, which could improve insulin release by β-cells.

ACE inhibitors increases potassium levels in the body and the same in diabetes mellitus increases effect of insulin on control of blood sugar. Concurrent use of ACE inhibitors and hypoglycemic agents usually appears to be uneventful but hypoglycemia, marked in some instances and has occurred in small number of diabetic patients taking insulin or sulfonylurea when treated with ACE inhibitors. This has been attributed, but not proved, to be due to an interaction. The problem was solved in some cases by reducing the dosage of hypoglycemic agent. Clinically ACE inhibitors are one of the drugs of choice in patients who are diabetic with mild to severe hypertension. Concomitant administration of ACE inhibitors with oral hypoglycemic agents or insulin therapy has been reported. At the same time the risk of hypoglycemia was increased 3.5-flod in patients taking insulin or hypoglycemic agent with ACE inhibitors. ACE inhibitors could improve the blood circulation in skeletal muscles, thus favoring peripheral insulin action, but also in the pancreas, thus promoting insulin secretion.

6. CONCLUSION:

- In both normal and diabetic rats repeated treatment of perindopril followed by single dose of glimepiride has shown increased hypoglycemic and antidiabetic activity.
- It was concluded that repeated treatment of perindopril facilitated and increased concentration of glimepiride in normal/ diabetic rats and it may be due to increased absorption or decreased excretion or decreased protein binding due to perindopril.
- A positive drug-interaction was observed between these drugs and for long treatment

of both drugs readjustment of dose of glimepiride must be considered to avoid severe hypoglycemia.

- Co-administration of single and repeated doses of perindopril in normal and diabetic rats has shown increased AUC, peak effect and t_{max}.
- From the literature it was noted that CYP2C9 enzyme was reported for the metabolism of glimepiride and no information was reported for the effect of perindopril on cytochrome P450 enzymes.
- It can be assumed that perindopril may be interfering with action of CYP2C9 enzyme as peak effect of glimepiride was improved after perindopril and glimepiride combination.
- The increased hypoglycemic and antidiabetic activity may be due to improved micro vascular and macro vascular circulation to pancreas and increased secretion of insulin from β-cells as these are reported with ACE inhibitor drugs.
- Facilitated absorption, prevention of glimepiride from protein binding sites, decreased excretion and increased availability of free drug all these factors can be accounted for the observed effect or may be due to inhibition of CYP2C9 enzyme which is responsible for metabolism of glimepiride, this is to be confirmed.

7. SUMMARY:

Multi-drug therapy is essential for the treatment of single disease (infectious) or multiple diseases in a single patient. Since the drugs are chemical moieties they interact not only with their specific receptors but also with other biochemicals which have a potential to influence the effect of concomitantly administered drugs, leading to the drug-drug interactions. According to the reports, the incidence of interaction ranges from 1- 20% in patients receiving more than 10 drugs and is the 4 th to 6 th leading cause for death in United States. The drug interactions are two types.

1. Pharmacokinetic interactions.
2. Pharmacodynamic interactions.

Pharmacokinetic interactions result in interfering with absorption, distribution, metabolism and excretion and pharmacodynamic interactions may result in the enhanced or inhibited effects of drug and may be useful or harmful.

In case of diabetes, the influence of associated diseases like fungal infections, cardiovascular disorders, nephropathy, retinopathy, neuropathy, sexual impotence, hyperacidity and respiratory tract infections are quite high. In such conditions, there is a need for the use of other drugs or antihypertensive drugs like perindopril with antidiabetic drugs like glimepiride..

1. To study the effect of single doses treatment of perindopril 2.5 mg/kg, (LD), 5 mg/kg (ID), 10 mg/kg (MD) and 20 mg/kg, (HD), p.o and glimepiride 10 mg/kg, p.o on the serum glucose levels in normal rats.
2. To study the effect of single dose and repeated dose treatment of perindopril LD, ID, MD and HD p.o for 7 days on the hypoglycemic effect of single dose of glimepiride 10 mg/kg, p.o in four different groups of normal albino rats.
3. To study the effect of single dose treatment of perindopril LD, ID, MD and HD p.o and glimepiride (10 mg/kg, p.o) on the serum glucose levels in diabetic rats.
4. To study the effect of single dose and repeated dose treatment of perindopril LD, ID, MD and HD p.o for 7 days on antidiabetic effect of single dose of glimepiride (10 mg/kg, p.o) in diabetic albino rats to find out the drug- drug interactions if any between perindopril and glimepiride in diabetic conditions.

From the study it is evident that single dose treatment of perindopril LD, ID, MD and HD followed by single dose treatment of glimepiride (10 mg/kg, p.o) has significantly altered the onset and duration of hypoglycemic activity of glimepiride with no change in the duration of action in both cases. After repeated treatment with perindopril LD, ID, MD and HD once daily for 7 days followed by single dose of glimepiride (10 mg/kg, p.o) a dose and time dependent effect on hypoglycemic activity of glimepiride with significant alteration in peak effect and enhanced duration of action of glimepiride was observed.

It is evident in diabetic rats that single doses treatment of perindopril LD, ID, MD and HD followed by single dose treatment of glimepiride (10 mg/kg, p.o) has significantly altered duration of action of glimepiride. After repeated treatment with perindopril LD, ID, MD and HD once daily for 7 days followed by single dose of glimepiride (10 mg/kg, p.o) a dose dependent and time dependent effect on antidiabetic activity of glimepiride was observed with a significant alteration in peak effect and enhanced duration of action of glimepiride.

This study suggests that, during concomitant administration of glimepiride and perindopril the dose and frequency of glimepiride has to be readjusted. In streptozotocin induced diabetic rats it was found that perindopril pretreatment has shown change in peak effect and duration of action of

glimepiride. Therefore, we can say that even in pathophysiological conditions like diabetes, prior treatment with perindopril has enhanced the antidiabetic activity of glimepiride.

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