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PHARMACODYNAMIC STUDIES ON DRUG-DRUG INTERACTION BETWEEN VALSARTAN AND METFORMIN

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Abstract:
A drug interaction can be defined as the modification of the effects of one drug by the prior and concomitant administration of other drug. Polypharmacy and multiple drug therapy assume importance in present day clinical practice, since newer molecules are invented everyday and newer challenges face clinicians in managing either a single disease or simultaneously occurring different diseases. The present study was under taken to verify the possible drug-drug interaction if any between valsartan on hypoglycemic activity of metformin in normal and diabetic rats. The whole study is divided into four phases, clearly explained in following study. From the results obtained and concluded that Valsartan has shown hypoglycemia when administered alone in both normal and diabetic rats. Valsartan (5mg/kg) has altered peak hypoglycemia but not significantly alter onset and the duration of hypoglycemia induced by metformin in both healthy and diabetic albino rats but valsartan (10 mg/kg, 20mg/kg, 40 mg/kg) has no significant alteration in onset and the duration of hypoglycemia but altered the peak plasma levels in dose dependent manner with maximum decrease of 60% with higher dose. The maximum percentage decrease in peak plasma levels of metformin was 50%.
Key words: *polypharmacy, valsartan, metformin, hypoglycemic activity.*

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INTRODUCTION:

There are several incidences in which a patient may suffer from more than one disease simultaneously[1,2,3]. Many patients especially the elders are to be treated continuously with more than one drug for chronic diseases such as hypertension, heart failure, osteoarthritis and diabetes etc (Rang and Dale, 2003) and hence the chances for drug interactions are at high risk[4,5]. Polypharmacy and multiple drug therapy assume importance present day clinical practice, since newer molecules are invented everyday and newer challenges face clinicians in managing either a single disease or simultaneously occurring different diseases[6,7,8]. Drug interaction is the qualitative or quantitative modifications of the effect of a drug by the simultaneous administration of different drugs. The three possible effects due to drug interaction are potentiation, addition (or simulation) and antagonism respectively[9].

Hypertension in diabetes mellitus is a fascinating clinical constellation with a complex and multifactorial pathophysiology[10,11,12]. Hypertension in both type I and type II diabetes is mainly characterized by increased peripheral vascular resistance suggesting premature aging of the vasculature[13,14,15].(Hong Ding et al., 2005) 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[16,17,18]. Angiotensin receptor antagonists (ARB's) unlike diuretics and β-blockers; make up a class of antihypertensive agents not associated with metabolic abnormalities[19,20]. These agents have also been demonstrated to reduce the incidence of diabetes (J.Ostergren, 2007). ARB's also been suggested to be particularly beneficial in diabetic hypertensive patients with early diabetic nephropathy (Wenzel, 2005).

Since there are reports that angiotensin receptor blockers (ARBs) increase potassium levels in the body, increased potassium levels in diabetes mellitus increases effect of insulin on control of blood sugar[21,22]. Hence, the present study was conducted with the intention that these ARBs may also alter the pharmacokinetics of orally active hypoglycemic agents like metformin. So the present studies in planned with the following objectives.

1. To study the influence of valsartan on the hypoglycemic activity of Metformin in healthy rats[23].
2. To study the influence of valsartan on the antidiabetic activity of Metformin in the Alloxan induced diabetic rats[24].
3. To suggest the alteration in the dose and frequency of administration of Metformin, if any, when it has to be used along with valsartan[25]

MATERIALS AND METHODS:

Experimental Animals

Male and female albino a total of 36 rats (6 groups) weighing about 180- 220 gm were used in the study. The use of animals in these experiments was authorized by IAEC (institutional Animal Ethical Committee). Throughout the experiment, experimental rats were processed in accordance with CPCSEA guidelines. All the animals were fasted for 18 hours prior to the study with water ad *libitum.*

Various drugs used in the study:
1. Metformin: - Natco Pharma Limited. (Hyderabad)
2. Valsartan: - Star Tech Labs Pvt Ltd (Hyderabad)

Experimental procedure:
PHASE I:

Six albino rats (group I) of either sex weighing between (180- 220 gm) were randomly selected for the study.

On the previous day of experimentation, the food was withdrawn 18-hours advance. However water was allowed *ad libitum.* The fasting was continued till the completion of the experiment. On next day, the blood samples were withdrawn from tail vein for determination of basal glucose concentration. Then the animals were administered with plain 0.5% w/v CMC suspension (volume matched with the average volume of drugs administrated in the subsequent studies). Thereafter the blood samples (0.5 µl), each were collected at 0, 0.5, 1, 2, 4, 6, 8, 12 hours and analyzed for the determining the glucose concentration using glucometer.

Percentage reduction in blood glucose at time "t"
$$t = A\text{-}B/A \times 100$$
Where **A** is blood glucose concentration at time "0" and **B** is blood glucose concentration at time "t".

Influence of Valsartan and Metformin Individually On Blood Glucose Levels in Healthy Albino Rats:
DAY 1: GROUP: 1: 0.5%CMC
DAY 2: GROUP: 2: Metformin (100mg/kg)
DAY 3: GROUP: 3: Valsartan (5mg/kg)
DAY 4: GROUP: 4: Valsartan (10mg/kg)
DAY 5: GROUP: 5: Valsartan (20mg/kg)
DAY 6: GROUP: 6: Valsartan (40mg/kg)

Percentage reduction in blood glucose at time "t"
$$t = A\text{-}B/A \times 100$$
Where **A** is blood glucose concentration at time "0" and **B** is blood glucose concentration at time "t".

PHASE II

Effect of Valsartan on the Hypoglycaemic Activity of Metformin Healthy Albino Rats:
The animals in groups in III, IV, V, and VI are used for the study in phase 2 after the wash out period of 10 days. To study the drug interaction if any between metformin and valsartan, groups III, IV, V, VI were administered with valsartan (5, 10, 20, 40, mg/kg, p.o) and metformin (100mg/kg) respectively. Thereafter the blood samples (0.5 μl), each were collected at 0, 0.5,1, 2, 4, 6, 8, 12 hours and analyzed for the determining the glucose concentration using glucometer.
DAY1: GROUP: 3: valsartan (5mg/kg) + metformin (100 mg/kg)
DAY2: GROUP: 4: valsartan (10mg/kg) + metformin (100 mg/kg)
DAY3: GROUP: 5: valsartan (20mg/kg) + metformin (100 mg/kg)
DAY4: GROUP: 6: valsartan (40mg/kg) + metformin (100 mg/kg)

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".

Induction of Diabetes:
The 6 groups of rats were administered with 120 mg/kg of Alloxan intraperitoneally.

PHASE III:
Experimental study in diabetic rats:
Influence of Valsartan and Metformin Individually On Blood Glucose Levels in Diabetic Rats:
DAY 1: GROUP: 1:0.5% CMC
DAY 2: GROUP: 2: Metformin (100mg/kg)
DAY3: GROUP: 3: valsartan (5mg/kg)
DAY 4: GROUP: 4: valsartan (10mg/kg)
DAY 5: GROUP: 5: valsartan (20mg/kg)
DAY 6: GROUP 6: valsartan (40mg/kg)
Percentage reduction in serum glucose at time "t"
$$t = A\text{-}B/A \times 100$$

PHASE IV:
Effect of Valsartan on the Hypoglycaemic Activity of Metformin in Diabetic Rats:
DAY1: GROUP: 3: valsartan (5mg/kg) + metformin (100 mg/kg)
DAY 2: GROUP: 4: valsartan (10mg/kg) + metformin (100 mg/kg)
DAY 3: GROUP: 5: valsartan (20mg/kg) + metformin (100 mg/kg)
DAY 4: GROUP 6: valsartan (40mg/kg) + metformin (100 mg/kg)

Percentage reduction in serum glucose at time "t"
$$t = A\text{-}B/A \times 100$$

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

RESULTS:

Table 5.0. Blood :glucose levels in normal rats.

Time (hr)	Blood glucose levels (mg/dl) with 0.5% CMC						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	80.84	84.05	84.36	81.16	79.43	90.40	83.37 ±1.60
2.0	79.11	80.17	80.55	84.00	78.76	90.36	82.15 ±1.80
4.0	79.01	84.31	80.17	83.19	78.40	86.11	81.86 ±1.27
6.0	79.43	86.10	82.31	82.30	79.81	87.34	82.88 ±1.32
8.0	80.32	83.16	83.54	80.36	80.90	85.54	82.30 ±0.86
12.0	81.71	85.53	79.67	83.34	81.62	86.17	83.00 ±1.02

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	
0.5	0.94	0.83	-3.85	2.76	1.65	1.42	0.62 ±0.93
1.0	1.95	1.48	-6.59	4.14	2.61	0.13	0.62 ±1.53
2.0	4.05	6.03	-1.78	0.79	3.43	0.17	2.11 ±1.17
4.0	4.17	1.18	-1.30	1.74	3.87	4.87	2.42 ±0.94
6.0	3.66	-0.91	-4.00	2.79	2.14	3.51	1.13 ±1.22
8.0	2.58	2.53	-5.55	5.09	0.80	5.50	1.82 ±1.64
12.0	0.89	-0.24	-0.66	1.57	-0.07	4.80	1.04 ±0.82

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

Table 5.1. Blood glucose levels with metformin (100 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with metformin (100 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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**
1.0	82.94	69.16	77.14	80.13	70.45	69.21	**74.83 ±2.46**
2.0	74.38	63.16	70.20	72.16	61.15	66.40	**67.90 ±2.12**
4.0	59.11	58.17	65.12	57.18	48.10	54.18	**56.64 ±2.29**
6.0	47.14	51.24	45.29	47.17	37.29	43.13	**45.21 ±1.92**
8.0	57.42	59.14	52.10	50.12	45.16	49.12	**52.17 ±2.15**
12.0	63.12	65.26	67.19	58.69	51.13	55.19	**60.09 ±2.53**

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	**-**
0.5	2.14	6.15	3.60	3.22	3.67	3.83	**3.76 ±0.53[ns]**
1.0	8.00	11.29	10.55	10.06	8.61	6.49	**9.16 ±0.73****
2.0	17.50	18.99	18.59	19.01	20.67	18.40	**18.86 ±0.42*** **
4.0	34.43	27.95	24.48	33.58	37.60	26.80	**30.80 ±2.09*** **
6.0	47.71	51.24	47.48	47.18	51.62	41.73	**47.82 ±1.45*** **
8.0	36.31	24.15	39.58	43.74	41.41	33.63	**36.47 ±2.86*** **
12.0	29.99	16.30	22.08	34.13	33.67	25.43	**26.93 ±2.86*** **

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

Table 5.2. Blood glucose levels with single dose treatment of valsartan (5 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with valsartan(5 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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**
1.0	96.16	93.31	89.16	88.13	90.14	87.10	**90.66 ±1.40**
2.0	93.13	88.71	84.11	82.82	86.19	81.89	**86.14 ±1.71**
4.0	87.19	85.14	79.46	76.13	83.20	79.12	**81.70 ±1.70**
6.0	82.23	81.28	74.11	72.41	79.91	71.10	**76.84 ±1.98**
8.0	85.45	84.16	79.23	76.30	83.88	76.59	**80.93 ±1.66**
12.0	91.51	89.66	83.44	80.96	85.76	80.49	**85.30 ±1.85**

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	**-**
0.5	1.73	1.83	1.44	4.55	2.5	2.36	**2.40 ±0.45^{ns}**
1.0	3.09	3.99	4.83	6.70	9.98	9.43	**6.33 ±1.17****
2.0	6.14	8.72	10.22	12.32	13.93	14.80	**11.02 ±1.34*****
4.0	12.13	12.39	15.18	19.40	16.90	17.72	**15.62 ±1.19*****
6.0	17.13	16.36	20.89	23.34	20.20	26.06	**20.66 ±1.50*****
8.0	13.88	13.40	15.43	19.22	16.23	20.35	**16.41 ±1.15*****
12.0	7.77	7.74	10.94	14.29	14.35	16.30	**11.89 ±1.48*****

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

Table 5.3. Blood glucose levels with single dose treatment of Valsartan (10 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (10 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	98.89	95.25	101.35	88.70	90.62	104.95	96.62 ±2.56
0.5	94.16	93.11	97.68	84.62	86.13	99.49	92.53 ±2.46
1.0	89.19	90.23	93.94	81.57	83.74	92.27	88.49 ±1.98
2.0	85.45	87.63	88.15	77.94	79.98	87.39	84.42 ±1.78
4.0	80.65	81.13	82.63	73.66	74.47	84.96	79.59 ±1.85
6.0	74.21	76.63	74.89	68.21	69.98	78.34	73.71 ±1.58
8.0	77.89	78.41	77.96	71.18	72.81	80.71	76.49 ±1.49
12.0	81.13	82.10	79.41	75.33	78.84	86.59	80.57 ±1.53

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	4.78	2.24	3.62	4.59	4.95	5.20	4.23 +0.45[ns]
1.0	9.80	5.27	7.31	8.03	7.59	12.08	8.34 ±0.95*
2.0	13.59	8.00	13.02	12.13	11.74	16.73	12.53 ±1.15**
4.0	18.40	14.82	18.47	16.95	17.82	19.04	17.58 ±0.62***
6.0	24.95	19.54	26.10	23.10	22.77	25.35	23.63 ±0.97***
8.0	21.23	17.67	23.07	19.75	19.65	23.09	20.74 ±0.87***
12.0	17.95	13.80	21.64	15.07	12.99	17.49	16.49 ±1.30***

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

Table 5.4. Blood glucose levels of Valsartan (20 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan(20 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	90.14	94.85	88.39	101.83	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
1.0	85.52	89.69	82.44	94.96	81.78	86.95	86.89 ±2.00
2.0	77.47	82.62	75.31	88.86	77.29	79.56	80.18 ±2.00
4.0	72.94	77.10	70.43	80.37	69.11	73.49	73.90 ±1.71
6.0	60.37	62.98	58.81	66.42	58.32	62.81	61.61 ±1.24
8.0	64.33	66.13	62.39	70.94	60.49	67.36	65.27 ±1.32
12.0	71.42	73.56	69.17	80.94	67.36	73.97	72.73 ±1.94

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	3.02	3.27	4.35	5.10	2.63	3.62	3.66 ±0.37ns
1.0	5.12	5.44	6.73	6.74	5.90	6.39	6.05 ±0.27**
2.0	14.05	12.89	14.79	12.73	11.06	14.35	13.31 ±0.55***
4.0	19.08	18.71	20.31	21.07	20.48	20.88	20.08 ±0.39***
6.0	33.02	33.60	33.46	34.77	32.89	32.38	33.35 ±0.33***
8.0	28.63	30.27	29.41	30.33	30.39	27.48	29.41 ±0.47***
12.0	20.76	22.44	21.74	20.51	22.49	20.36	21.35 ±0.39***

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

Table 5.5. Blood glucose levels of Valsartan (40 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (40 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	83.19	78.66	84.31	76.91	84.40	81.12	81.43 ±1.27
2.0	79.32	71.45	77.44	69.20	79.11	75.36	75.31 ±1.70
4.0	64.61	62.10	66.26	53.78	68.26	62.80	62.96 ±2.05
6.0	52.83	56.88	54.71	39.58	54.49	56.67	52.52 ±2.66
8.0	67.48	58.98	64.32	48.61	65.79	63.88	61.51 ±2.83
12.0	73.31	67.13	68.41	53.79	69.77	69.19	66.93 ±2.76

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	3.15	2.56	2.74	5.61	3.81	2.16	3.33 ±0.50*
1.0	6.67	10.62	7.47	10.82	9.09	8.19	8.82 ±0.69***
2.0	11.01	15.66	15.01	19.76	15.55	14.71	15.28 ±1.13***
4.0	27.51	26.69	27.28	37.64	29.26	29.65	29.67 ±1.66***
6.0	40.73	32.86	39.95	54.11	41.83	35.86	40.89 ±2.98***
8.0	24.29	30.38	29.41	43.64	29.77	27.70	30.86 ±2.70***
12.0	17.75	20.76	24.92	37.63	25.52	21.69	24.71 ±2.83***

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

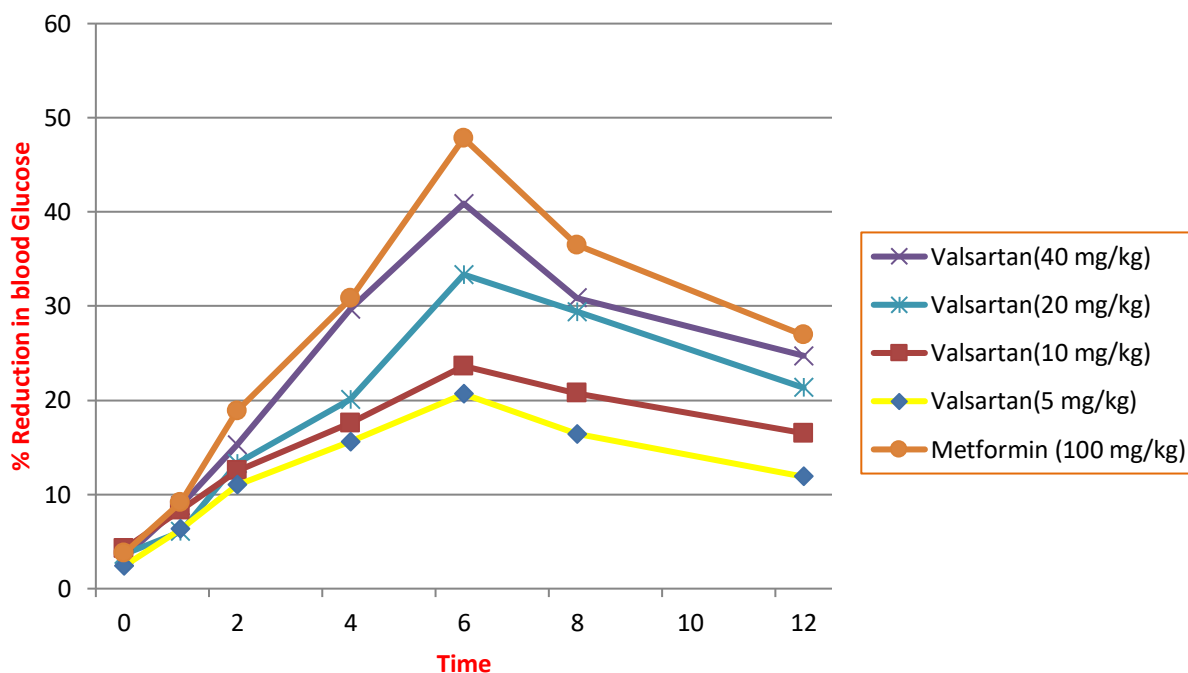**GRAPH.5.0. PERCENTAGE REDUCTION IN BLOOD GLUCOSE WITH VALSARTAN (5, 10, 20, and 40mg/kg) IN NORMAL RATS.**

Table.5.6. Effect of valsartan (5 mg/kg) on hypoglycemic activity of metformin (100 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with valsartan (5 mg/kg) + metformin (100 mg/kg)						Mean ± SEM
	R₁	R₂	R₃	R₄	R₅	R₆	
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**
1.0	74.54	77.24	79.41	72.67	75.16	82.23	**76.85 ±1.42**
2.0	60.41	64.26	62.11	58.86	64.81	71.46	**63.65 ±1.81**
4.0	58.87	63.39	59.68	55.11	60.78	65.88	**60.61 ±1.52**
6.0	36.91	33.08	38.14	35.27	39.48	48.92	**38.63 ±2.25**
8.0	46.11	41.88	46.13	43.14	49.11	55.19	**46.92 ±1.95**
12.0	58.67	56.15	60.10	43.92	58.39	60.57	**56.3 ±2.55**

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	0.64	1.82	0.38	1.28	1.12	0.29	0.92 ±0.24**
1.0	6.25	6.68	5.58	4.86	6.26	3.66	5.54 ±0.45**
2.0	24.02	22.26	26.15	22.94	19.16	16.28	21.80 +1.44ns
4.0	25.95	23.32	29.04	27.85	24.19	22.82	25.52 ±1.03**
6.0	53.57	59.98	54.65	53.82	50.76	42.68	52.57 ±2.33*
8.0	42.00	49.34	45.15	43.52	38.75	35.34	42.35 ±2.00*
12.0	26.21	32.07	28.54	42.50	27.17	29.04	30.92 ±2.45**

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

Table 5.7. Effect of valsartan (10 mg/kg) on hypoglycemic activity of metformin (100 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with valsartan(10 mg/kg) + metformin (100 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	68.14	71.91	65.38	69.39	70.95	69.27	69.17 ±0.93
2.0	54.29	65.87	57.08	61.35	60.43	56.35	59.22 ±1.70
4.0	44.56	54.62	46.54	46.26	47.08	48.95	48.00 ±1.44
6.0	34.35	41.69	33.92	34.95	31.92	33.29	35.02 ±1.39
8.0	38.96	45.13	39.41	44.76	38.50	39.20	40.99 ±1.25
12.0	58.13	60.10	52.22	58.32	54.61	55.14	56.42 ±1.19

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	3.23	3.80	2.89	3.25	2.30	3.14	3.10 +0.20^{ns}
1.0	10.49	10.32	12.66	14.68	8.65	9.55	11.05 +0.90^{ns}
2.0	28.68	17.85	23.75	24.56	22.19	26.42	23.90 +1.51*
4.0	41.46	31.88	37.83	43.12	39.38	36.08	38.29 +1.64^{ns}
6.0	54.87	48.01	54.68	57.02	58.90	56.53	55.00 ±1.13**
8.0	48.82	43.72	47.35	44.96	50.43	48.81	47.34 ±1.04**
12.0	23.64	25.05	30.24	28.29	29.68	28.00	27.48 ±1.06^{ns}

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

Table 5.8.Effect of valsartan (20 mg/kg) on hypoglycemic activity of metformin (100 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (20 mg/kg) +metformin (100 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	68.28	64.53	72.20	66.39	68.89	71.04	68.55 ±1.16
2.0	59.18	52.71	62.11	53.21	54.13	56.89	56.37 ±1.52
4.0	43.67	39.32	50.72	41.13	39.67	38.80	42.22 ±1.85
6.0	39.41	34.94	37.14	33.75	30.52	28.12	33.98 ±1.70
8.0	40.13	33.79	38.61	38.45	32.52	30.44	35.65 ±1.60
12.0	51.34	44.81	47.75	47.10	42.17	43.79	46.16 ±1.33

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	3.36	1.12	2.03	3.44	3.69	4.55	3.03 +0.50[ns]
1.0	9.76	7.98	9.12	8.56	9.82	7.85	8.84 +0.35[ns]
2.0	21.79	24.83	21.82	26.71	29.14	26.21	25.08 ±1.18*
4.0	42.28	43.93	36.09	43.35	48.07	49.67	43.89 ±1.95**
6.0	47.95	50.17	53.25	53.51	60.40	63.52	54.8 ±2.44**
8.0	41.82	51.81	51.40	47.04	57.43	60.15	51.66 ±2.76**
12.0	32.15	36.10	31.89	35.13	44.80	43.20	37.21 ±2.25**

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

Table 5.9. Effect of valsartan (40 mg/kg) on hypoglycemic activity of metformin (100 mg/kg) in normal rats.

Time (hrs)	Blood glucose levels (mg/dl) with valsartan(40 mg/kg) + Metformin (100 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	68.10	63.14	71.60	72.19	70.80	68.33	69.01 ±1.35
2.0	56.90	54.76	60.71	60.19	58.60	52.10	57.21 ±1.35
4.0	42.13	40.61	46.11	47.20	42.11	37.19	42.55 ±1.49
6.0	31.67	30.17	36.22	41.69	35.15	32.66	34.59 ±1.68
8.0	34.01	32.89	38.11	42.29	37.16	34.69	36.52 ±1.40
12.0	40.66	40.11	42.30	44.11	41.49	39.88	41.42 ±0.65

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	5.18	6.19	4.86	5.41	3.54	5.15	5.05 ± 0.35 [ns]
1.0	8.13	13.04	7.39	12.20	9.34	10.22	10.05 ± 0.91 [ns]
2.0	23.24	24.58	21.48	26.71	24.96	31.54	25.41 ± 1.41**
4.0	43.16	44.07	40.36	42.53	46.08	49.08	44.21 ± 1.23**
6.0	57.27	58.44	53.15	49.23	54.99	57.08	55.02 ± 1.39*
8.0	54.12	54.74	50.71	48.50	52.41	54.42	52.48 ± 1.00**
12.0	45.15	44.75	45.29	46.29	46.87	46.60	45.82 ± 0.35**

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

Graph.5.1. Percentage Reduction In Blood Glucose WIth Single Dose Treatment Of Valsartan (5, 10, 20, And 40mg/ Kg) + Metformin (100 Mg/Kg) In Normal Rats.
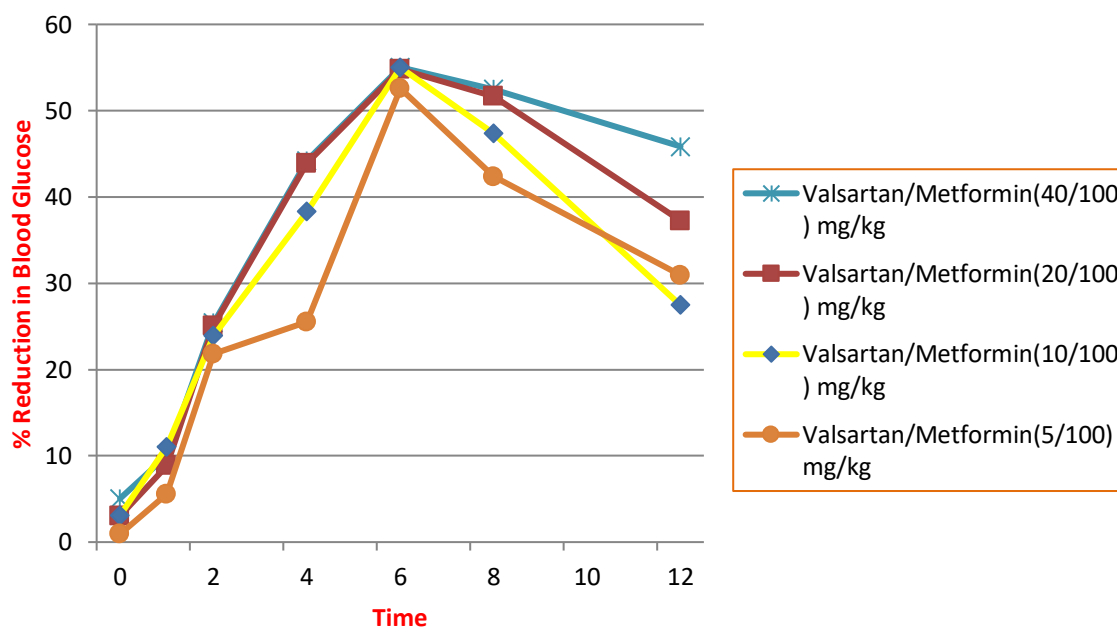
Table 5.10. Normal blood glucose levels in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with 0.5% CMC						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	434.9	487.8	488.3	477.3	392.9	430.2	451.9 ± 15.81
2.0	440.5	502.3	455.0	480.1	383.0	444.9	450.96 ± 16.59
4.0	426.1	487.1	439.1	478.3	384.8	424.9	439.95 ± 15.46
6.0	438.0	493.4	440.7	484.7	380.4	440.0	446.2 ± 16.50
8.0	436.2	490.2	432.2	479.1	383.1	434.1	442.48 ± 15.66
12.0	440.5	496.1	439.5	480.6	382.3	438.4	446.2 ± 16.22

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	-3.89	-1.31	-1.01	5.83	7.95	-5.74	0.30 ± 2.21
1.0	-1.51	-1.81	-3.69	2.25	6.38	-0.93	0.11 ± 1.48
2.0	-2.82	-4.84	3.37	1.67	8.74	-4.38	0.29 ± 2.16
4.0	0.53	-1.66	6.75	2.04	8.31	0.44	2.73 ± 1.60
6.0	-2.24	-2.98	6.41	-0.73	9.36	-3.23	1.09 ± 2.20
8.0	-1.82	-2.31	8.21	1.88	8.72	-1.85	2.13 ± 2.09
12.0	-2.82	-3.54	6.66	1.57	8.91	-2.86	1.32 ± 2.19

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

Table 5.11. Blood glucose levels with metformin (100 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels(mg/dl)with metformin (100 mg/kg)						Mean ± SEM
	R_1	R2	R_3	R_4	R_5	R_6	
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**
1.0	314.1	322.6	309.3	319.5	309.1	312.8	**314.56 ± 2.23**
2.0	268.6	277.4	270.6	275.1	276.4	273.4	**273.58 ± 1.39**
4.0	226.4	226.3	228.5	235.4	224.8	219.1	**226.75 ± 2.64**
6.0	199.1	185.9	183.3	188.0	191.1	185.6	**188.83 ± 2.31**
8.0	223.6	212.4	211.6	216.5	215.4	211.3	**215.13 ± 1.90**
12.0	291.3	286.0	281.4	286.1	285.1	276.7	**284.43 ± 2.01**

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	**-**
0.5	6.27	5.69	4.73	4.27	5.79	6.10	**5.47 ± 0.32***
1.0	20.54	17.57	19.89	17.20	20.96	18.77	**19.00 ± 0.56****
2.0	32.05	29.12	29.91	28.71	28.52	29.00	**29.55 ± 0.53****
4.0	42.72	42.18	40.81	38.99	41.86	43.10	**41.25 ± 0.68****
6.0	49.63	52.50	52.52	51.28	50.58	51.80	**51.38 ± 0.46****
8.0	43.43	45.73	45.19	43.89	44.29	45.13	**40.61 ± 0.35****
12.0	26.30	26.92	27.11	25.80	26.27	28.14	**26.75 ± 0.33****

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

Table 5.12. Blood glucose levels with single dose treatment of Valsartan (5 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with valsartan(5mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	301.1	289.4	321.3	303.6	309.1	320.3	307.46 ± 4.96
2.0	279.9	277.1	290.1	285.9	290.4	305.6	288.1 ± 4.11
4.0	263.4	257.3	249.9	278.4	279.1	280.4	271.41 ± 7.35
6.0	230.9	239.8	234.5	243.1	235.4	238.9	235.6 ± 1.34
8.0	222.8	233.4	228.7	230.6	219.7	221.9	225.95 ± 2.34
12.0	260.5	248.1	265.4	238.5	253.1	254.1	239.61 ± 3.13

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	1.33	1.47	0.92	2.50	1.81	2.57	1.61 ± 0.80[ns]
1.0	10.36	9.30	7.61	6.12	4.68	4.13	7.03 ± 1.02*
2.0	16.67	13.16	16.58	11.59	10.45	8.53	12.81 ± 1.35**
4.0	21.58	19.36	28.14	13.91	13.93	16.07	18.83 ± 2.23***
6.0	31.25	24.85	32.57	24.82	27.41	28.49	28.23 ± 1.31***
8.0	33.67	26.85	34.24	28.69	32.25	33.82	31.61 ± 1.97***
12.0	22.44	22.25	23.69	26.25	21.95	23.94	23.42 ± 0.65***

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

Table 5.13. Blood glucose levels with single dose treatment of Valsartan (10 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (10 mg/kg)						Mean ± SEM
	R_1	R2	R_3	R_4	R_5	R_6	
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
1.0	334.3	343.9	364.2	353.1	333.1	342.6	345.2 ± 4.82
2.0	322.1	318.7	332.9	336.6	320.4	321.8	321.41 ± 3.03
4.0	293.6	294.4	314.1	334.9	304.7	305.4	307.85 ± 6.24
6.0	278.4	273.8	277.8	267.5	258.1	269.9	270.91 ± 3.10
8.0	255.9	251.3	254.1	253.1	235.5	249.1	249.83 ± 3.02
12.0	282.1	285.5	291.4	299.4	305.6	299.4	293..9 ± 3.71

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	1.17	1.64	1.06	1.54	1.74	2.02	1.52 ± 0.14 ns
1.0	10.66	10.30	9.87	12.27	13.30	11.26	11.27 ± 0.52***
2.0	13.92	16.87	17.61	16.37	16.60	16.65	16.33 ± 0.51***
4.0	21.53	23.21	22.27	16.79	20.69	20.90	20.89 ± 0.90***
6.0	25.60	28.58	31.25	33.54	32.82	30.09	30.31 ± 1.19***
8.0	31.61	34.45	37.11	37.11	38.70	35.48	35.74 ± 1.02***
12.0	24.61	25.53	27.88	25.61	20.45	22.45	24.42 ± 1.06***

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

Table 5.14. Blood glucose levels with single dose treatment of Valsartan (20 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with valsartan(40 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	327.9	333.0	335.1	334.9	333.1	331.9	332.63 ± 1.07
2.0	285.1	294.1	301.4	298.3	293.4	288.4	293.45 ± 2.46
4.0	261.3	263.4	276.1	274.1	269.2	264.1	268.03 ± 2.48
6.0	235.5	241.3	250.0	245.6	252.4	250.3	243.85 ± 2.63
8.0	220.1	219.8	229.1	221.8	212.8	214.9	219.75 ± 2.33
12.0	265.4	263.5	273.8	266.4	267.1	253.7	263.98 ± 2.69

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	1.47	1.64	2.58	1.81	1.54	1.07	1.68 + 0.20 ns
1.0	7.21	5.63	5.79	4.80	3.19	3.79	5.06 ± 0.59 **
2.0	19.32	16.66	15.26	15.20	14.73	16.40	16.26 ± 0.68***
4.0	26.06	25.36	22.37	22.08	21.76	23.44	23.51 ± 0.73***
6.0	33.36	31.62	29.71	30.18	26.64	27.44	29.82 ± 1.02***
8.0	37.71	37.71	35.59	369.5	38.15	37.71	37.30 ± 0.37***
12.0	24.90	25.33	23.02	24.27	22.37	26.46	24.39 ± 0.61***

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

Table 5.15. Blood glucose levels with single dose treatment of Valsartan (40mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (40 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	353.1	342.3	346.3	354.6	351.6	338.4	347.65 ± 2.69
2.0	339.5	321.8	324.9	337.9	328.1	320.1	328.71 ± 3.35
4.0	302.9	283.4	292.3	301.1	293.4	286.6	293.28 ± 3.14
6.0	273.1	262.1	260.5	263.8	271.6	267.3	266.4 ± 2.10
8.0	238.8	230.9	227.1	236.5	234.2	233.5	233.5 ± 1.68
12.0	245.4	246.3	254.4	252.9	237.4	247.1	247.25 ± 2.47

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	1.79	1.81	3.68	2.72	1.58	1.81	2.23 + 0.33 ns
1.0	11.85	13.69	10.83	9.79	9.96	13.69	11.63 ± 0.71***
2.0	15.25	18.36	16.34	14.04	15.97	18.36	16.38 ± 0.70***
4.0	24.38	26.90	24.74	23.40	24.86	26.90	25.19 ± 0.57***
6.0	31.82	32.13	32.92	32.89	30.44	31.82	32.03 ± 0.37***
8.0	40.38	40.21	41.52	39.83	40.02	40.44	40.4 ± 0.24***
12.0	38.74	36.22	34.50	35.66	39.20	36.98	36.88 ± 0.74***

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

GRAPH.5.2. PERCENTAGE REDUCTION IN BLOOD GLUCOSE WITH VALSARTAN (5, 10, 20, and 40mg/kg) IN DIABETIC RATS.

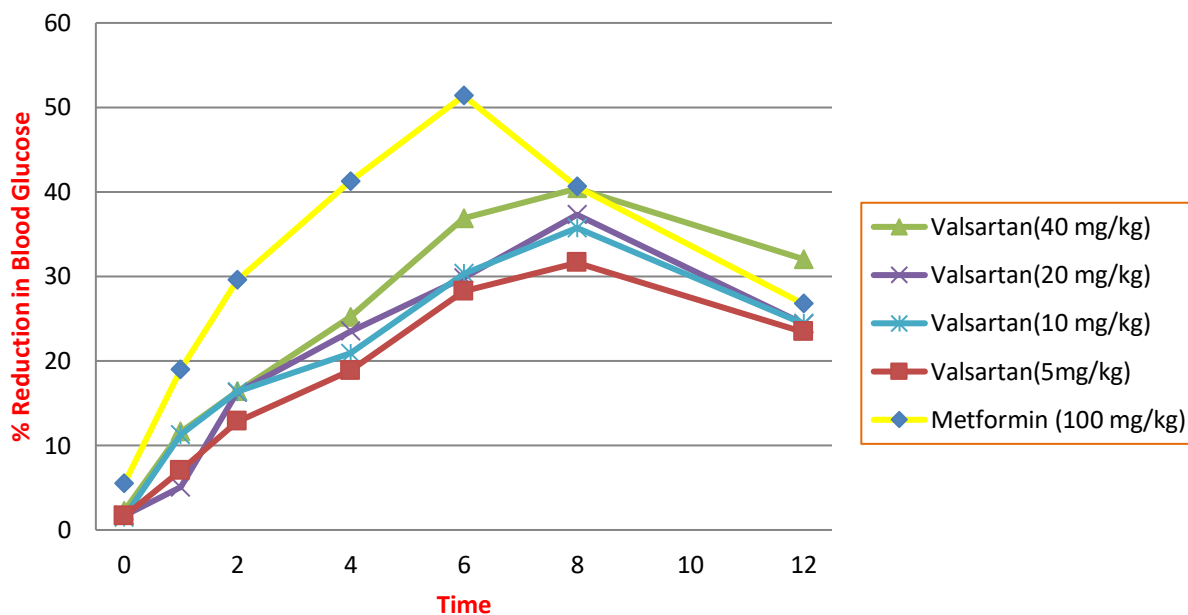

Table 5.16. Effect of Valsartan (5 mg/kg) on antidiabetic activity of Metformin (100 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (5 mg/kg) + Metformin (10 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	339.1	337.1	339.2	341.3	338.1	352.2	341.16 ± 2.27
2.0	257.4	266.9	268.4	264.7	263.4	268.4	269.86 ± 1.70
4.0	214.3	226.5	211.9	213.4	208.6	210.2	214.15 ± 2.61
6.0	201.7	181.3	172.4	194.8	192.3	194.6	189.51 ± 4.36
8.0	216.4	203.6	194.8	201.5	204.5	213.9	205.78 ± 3.28
12.0	270.8	264.3	268.5	273.1	271.4	273.6	270.28 ± 1.40

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R₁	R₂	R₃	R₄	R₅	R₆	
0.0	-	-	-	-	-	-	-
0.5	3.87	4.15	3.86	4.04	4.53	4.46	4.15 ± 0.11*
1.0	14.60	13.47	13.07	13.24	13.77	10.65	13.13 ± 0.54**
2.0	35.18	31.49	31.21	32.71	32.82	31.91	32.55 ± 0.58*
4.0	46.03	41.86	45.69	45.75	46.79	46.67	45.46 ± 0.74**
6.0	49.20	53.46	55.81	50.48	50.95	50.63	51.75 ± 0.99 ns
8.0	45.50	47.74	50.07	48.77	47.84	45.73	47.60 ± 0.71**
12.0	31.80	32.16	31.18	30.57	30.78	30.59	31.18 ± 0.27**

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

Table 5.17. Effect of valsartan (10 mg/kg) on antidiabetic activity of Metformin (100 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (10 mg/kg) + metformin (100 mg/kg)						Mean ± SEM
	R₁	R₂	R₃	R₄	R₅	R₆	
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
1.0	283.4	291.0	286.1	287.7	289.2	288.4	287.6 ± 1.07
2.0	245.9	230.1	232.6	230.1	233.6	226.0	233.05 ± 2.78
4.0	191.7	193.4	196.8	189.4	192.4	188.4	192.01 ± 1.22
6.0	162.4	161.8	145.1	150.8	161.9	157.9	156.65 ± 2.92
8.0	183.2	192.1	191.0	194.1	197.3	188.4	191.01 ± 1.98
12.0	241.7	246.3	250.4	251.7	249.1	242.9	247.01 ± 1.66

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0.0	-	-	-	-	-	-	-
0.5	6.01	5.54	6.11	4.88	7.09	5.38	5.83 ± 0.31 ns
1.0	19.92	20.07	22.23	19.72	19.17	19.91	20.17 ± 0.43 ns
2.0	30.51	36.80	36.77	35.79	34.71	37.23	35.30 ± 1.02**
4.0	45.83	46.88	46.50	47.15	46.22	47.68	46.71 ± 0.27*
6.0	54.11	55.56	60.55	57.92	54.75	56.15	56.50 ± 0.96**
8.0	48.23	47.23	48.08	45.84	44.85	47.68	46.98 ± 0.55 ns
12.0	31.70	32.35	31.93	29.77	30.38	32.54	31.44 ± 0.45**

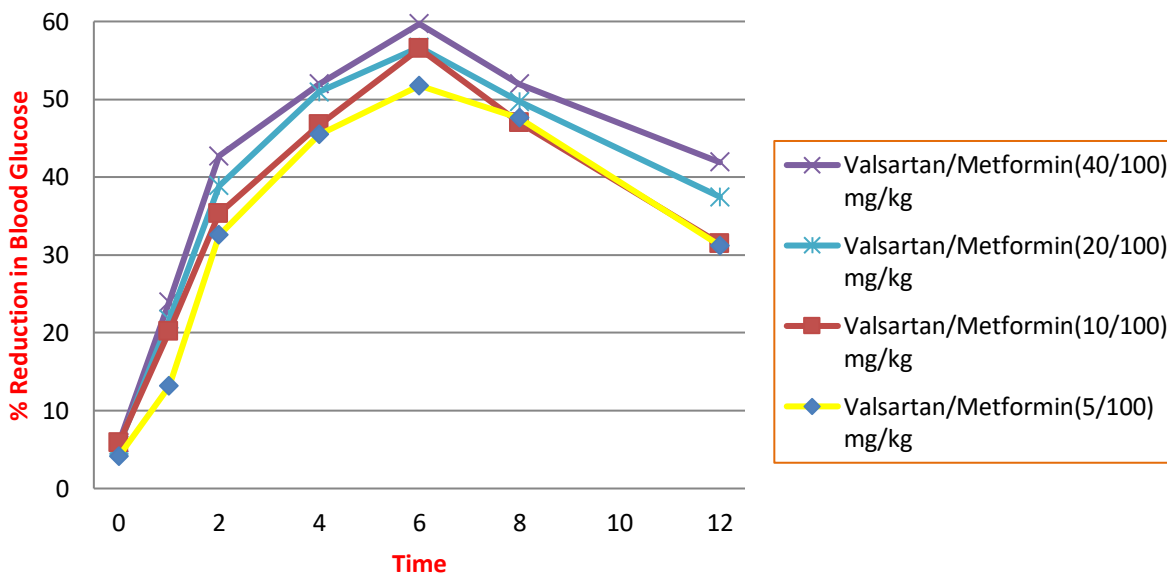n=6, Significant at $p<0.05$*, 0.01**and 0.001***, ns = not significant

Table 5.18. Effect of valsartan (20 mg/kg) on antidiabetic activity of Metformin (100 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (20 mg/kg) + Metformin (100 mg/kg)						Mean ± SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
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
1.0	311.4	323.7	320.4	314.2	318.3	319.6	317.93 ± 1.81
2.0	252.8	246.1	243.2	246.9	247.5	252.1	248.1 ± 1.50
4.0	199.5	196.3	192.0	199.7	21.8	206.3	199.26 ± 1.98
6.0	172.3	178.5	174.9	175.4	172.6	181.5	175.86 ± 1.45
8.0	202.9	206.8	200.1	203.8	205.3	207.1	204.33 ± 1.07
12.0	269.3	251.3	247.6	253.2	250.1	252.3	253.96 ± 3.16

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R₁	R₂	R₃	R₄	R₅	R₆	
0.0	-	-	-	-	-	-	-
0.5	5.88	6.29	6.63	3.47	5.25	5.54	5.51 ± 0.45 ns
1.0	22.69	20.68	21.29	21.50	22.89	21.26	21.71 ± 0.35**
2.0	37.23	39.69	40.26	38.32	40.04	37.89	38.90 ± 0.51**
4.0	50.47	51.89	52.83	50.11	51.11	49.17	50.93 ± 0.53**
6.0	57.22	56.26	57.03	56.18	58.18	55.28	56.69 ± 0.41**
8.0	49.62	49.32	50.84	49.08	50.26	48.97	49.68 ± 0.29**
12.0	33.14	38.42	39.17	36.74	39.41	37.84	37.45 ± 0.94**

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

Table 5.19. Effect of valsartan (40 mg/kg) on antidiabetic activity of metformin (100 mg/kg) in diabetic rats.

Time (hrs)	Blood glucose levels (mg/dl) with Valsartan (40 mg/kg) + Metformin (100 mg/kg)						Mean ± SEM
	R₁	R₂	R₃	R₄	R₅	R₆	
0.0	370.2	366.6	361.4	363.8	362.3	369.1	365.56 ± 1.48
0.5	351.81	341.39	339.2	338.7	342.8	350.7	344.1 ± 2.34
1.0	274.10	283.10	277.4	275.1	280.4	277.6	277.95 ± 1.36
2.0	215.3	206.7	203.9	201.4	206.8	222.4	209.41 ± 3.22
4.0	188.4	176.5	166.1	168.7	169.2	184.9	175.63 ± 3.78
6.0	150.7	145.1	144.8	142.4	149.1	152.1	147.36 ± 1.55
8.0	186.3	169.3	171.1	169.1	178.4	179.8	175.66 ± 2.84
12.0	225.4	207.8	204.7	206.4	215.1	214.3	212.28 ± 3.14

Time (hrs)	Percentage reduction in blood glucose						Mean ± SEM
	R₁	R₂	R₃	R₄	R₅	R₆	
0.0	-	-	-	-	-	-	-
0.5	4.96	6.87	6.14	6.89	5.38	4.98	5.87 ± 0.36 ns
1.0	25.95	22.77	23.24	24.38	22.60	24.79	23.95 ± 0.53**
2.0	41.84	43.61	43.58	44.63	42.92	39.74	42.72 ± 0.70**
4.0	49.10	51.85	54.03	53.62	53.29	49.90	51.96 ± 0.84**
6.0	59.29	60.42	59.93	60.85	58.84	58.79	59.68 ± 0.34**
8.0	49.67	53.81	52.65	53.51	50.75	51.28	51.94 ± 0.67**
12.0	39.11	43.31	43.35	43.26	40.62	41.93	41.93 ± 0.71**

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

GRAPH.5.3. PERCENTAGE REDUCTION IN BLOOD GLUCOSE WITH SINGLE DOSE TREATMENT OF VALSARTAN (5, 10, 20, and 40mg/kg) + METFORMIN (100mg/kg) IN DIABETIC RATS.

DISCUSSION:

In the first phase of study effect of Valsartan 5 mg/kg, p.o. (LD), 10 mg/kg, p.o. (ID), 20 mg/kg, p.o, (MD) ,40 mg/kg p.o. (HD) and metformin (100 mg/kg, p.o) individually on blood glucose levels were studied in different groups of normal rats. From the results it was observed that when compared to control group dose dependent increase in peak plasma concentrations were observed for each dose respectively with valsartan. Metformin has produced a significant hypoglycemic effect and the peak hypoglycemic effect was observed at 6th hr.

In the second phase of study effect the effect of valsartan LD, ID, MD and HD on hypoglycaemic activity of metformin was studied, From the results it was confirmed that treatment with valsartan LD has not altered the onset of action, peak plasma levels of metformin but ID, MD and HD increased peak effect with no change in onset and duration of action in normal rats. This may perhaps be due to a slight increased absorption or decreased excretion of metformin due to valsartan.

These results suggest that concomitant administration of metformin and valsartan is safe in diabetes at lower dose and the dose and frequency has to be adjusted accordingly in increased doses.

In the earlier phases of study normal animals were used to study the effect of valsartan on hypoglycemic activity of metformin. To confirm the results of the earlier study and to understand the drug-drug interaction between valsartan and metformin (i.e., effect of valsartan) on blood 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 Alloxan (120 mg/kg, i.p) and blood glucose was analyzed after 48hrs so as to confirm the stabilized blood glucose levels in the diabetic state.

In diabetic rats metformin (100 mg/kg, p.o) has reduced the blood glucose levels to the maximum extent of 52.00 % at the 6th hr. The onset of action was seen at 1 hr and a significant antidiabetic effect was seen till 12 h.Valsartan LD has showed no significant effect on metformin hypoglycaemic activity.

In fourth phase valsartan LD, ID, MD and HD treatment followed by treatment of metformin (100 mg/kg, p.o).Valsartan LD, ID reduced the blood glucose levels from 2^h hr upto 8th hr. MD, HD doses of valsartan have reduced the blood glucose levels from 2nd hr to 12th hr with a peak antidiabetic effect at 6th hr.
These results suggest that, during concomitant administration of metformin and valsartan, treatment of valsartan has not altered the onset of action but slightly increased the peak effect with no change in duration of action of metformin in normal rats. The dose and frequency of metformin need to be readjusted if necessary.

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

CONCLUSIONS:

The interaction studies of valsartan with metformin were conducted in normal and diabetic rats based on pharmacodynamic (blood glucose) response for 12 hrs. The normal rat model served to quickly identify the interaction and diabetic rat model served to validate the same response in the actual condition of drug use.

Valsartan has shown hypoglycemia when administered alone in both normal and diabetic rats. The increased hypoglycemic 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 Angiotensin receptor blockers or due to increased absorption or decrease excretion of metformin due to valsartan.

Valsartan (5mg/kg) has altered peak hypoglycemia but not significantly alter onset and the duration of hypoglycemia induced by metformin in both healthy and diabetic albino rats but valsartan (10 mg/kg, 20mg/kg, 40 mg/kg) has no significant alteration in onset and the duration of hypoglycemia but altered the peak plasma levels in dose dependent manner with maximum decrease of 60% with higher dose. The maximum percentage decrease in peak plasma levels of metformin was 50.

From the above conclusion it may be suggested that monitoring of blood glucose levels is essential during concomitant use of metformin with valsartan. Therefore it is further suggested that readjustment of dose and frequency of administration of metformin may be made with increased doses of valsartan.

I would like to place on record that the present study is carried out in healthy albino rats and diabetic rats. Therefore I suggest that similar study should be conducted in healthy volunteers and diabetic patients to confirm the obtained results. It is further required to establish the influence of valsartan pre- treatment on the pharmacokinetic parameters of metformin in human volunteers.

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