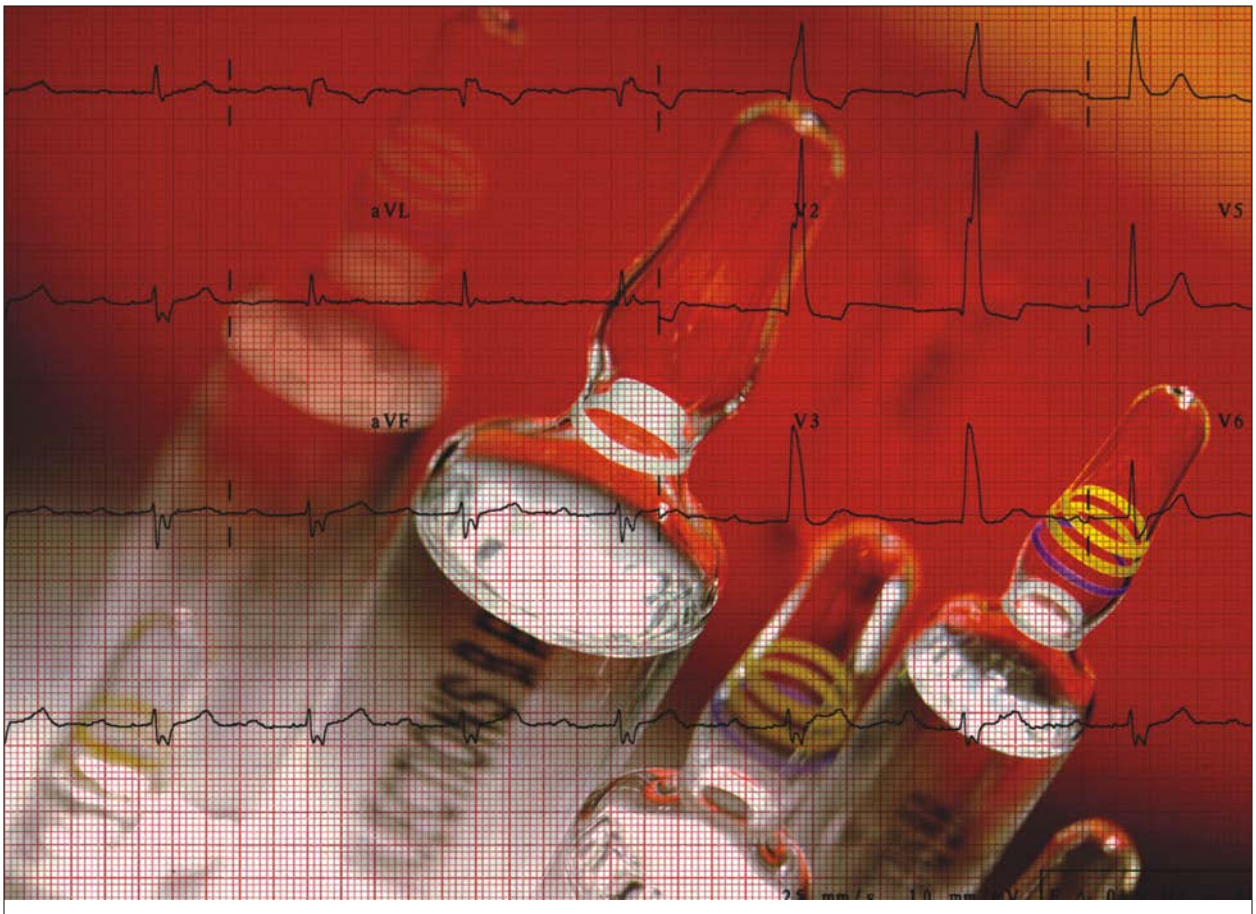


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# Research Article
# Effect of Valsartan on Pharmacokinetics and Pharmacodynamics of Gliclazide in Diabetic Rats

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## Abstract

**Background:** Diabetes mellitus and hypertension are the most common coexisting complications across the world. For the effective treatment of these types of patients, the treatment regimen should contain antidiabetic agent like gliclazide and antihypertensive agents like valsartan. In view of this combination, in the present study, we have evaluated the effect of valsartan on pharmacokinetics and pharmacodynamics of gliclazide in rats with diabetes. **Materials and Methods:** Alloxan with a dose of 120 mg $kg^{-1}$ was used to induce the diabetes in rats, then the rats were treated with test drugs i.e., gliclazide (7.2 mg $kg^{-1}$) and valsartan (37 mg $kg^{-1}$) at single and multiple doses, by grouping rats as diabetic control, gliclazide alone, gliclazide+valsartan in combination and half therapeutic dose of gliclazide+full dose of valsartan. The blood samples were collected at different intervals and evaluated for pharmacokinetic and pharmacodynamic parameters using blood plasma samples. **Results:** The pharmacodynamic results from combination of gliclazide+valsartan showed significant difference in blood glucose reduction when compared to gliclazide alone. However, half therapeutic dose of gliclazide+full valsartan dose showed blood glucose reduction as almost equal to gliclazide alone. The pharmacokinetic results showed increased gliclazide plasma concentrations when used in combination with valsartan, when compared to gliclazide+valsaratn with gliclazide alone. Drug interaction was observed between the said drugs. The half dosed gliclazide with valsartan can have significant application for diabetic patients having hypertension, when compared to gliclazide+valsartan. **Conclusion:** It is showed that combination of gliclazide and valsartan treatment has shown influence on the pharmacokinetics of gliclazide like metabolism/distribution/excretion and shown significant difference in controlling blood glucose. The dosage adjustment of gliclazide is suggestable in patients receiving gliclazide and valsartan.

Key words: Gliclazide, valsartan, hypertention, diabetes, pharmacodynamics, pharmacokinetics, drug interaction

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Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Diabetes is one of the chronic metabolic disorders characterized by chronic hyperglycemia often accompanied by glycosuria, polydipsia and polyuria. Diabetes occurs due to either decreased synthesis of insulin from β-cells of islets of pancreas or insulin resistance[1]. As per the recent evidences, cardiovascular diseases are the major complications of diabetes and the one of the leading cause of early death among people. Various complications like diabetic retinopathy, neuropathy were developed as a consequence of the metabolic derangements in diabetic population. Many of these are the result of disease of blood vessels, either large (Macrovascular disease) or small (Microangiopathy)[2]. Macrovascular disease, due to chronic hyperglycemia, consists of accelerated atheroma leads to thrombotic complications, which are more common and more severe in diabetic patients. Usually hypertension coexists with diabetes mellitus, is not only an indicator of added risk of mortality but also a causative factor to the development of diabetic complications[3]. To treat these coexisting diseases, multi-drug therapy is inevitable and there is every possibility of the occurrence of a drug interaction when drugs are used concomitantly. Both anti-hypertensive's and oral hypoglycemic drugs are being increasingly used in many clinical areas. The former agents are important for controlling hypertension, heart failure and diabetic nephropathy and the latter drugs are extensively used for effecting the lowering of blood glucose. Thus, it is usual for patients suffering from multiple complaints to be prescribed antihypertensive drugs like valsartan, together with oral hypoglycemic drugs like gliclazide[4]. In view of above, there is a possibility of both pharmacokinetic and pharmacodynamic interactions between antidiabetic drug (Gliclazide) and the angiotensin receptor blocker (Valsartan) when these two drugs are co-administered to the patients suffering with hypertension and diabetes. In view of lack of reports, we have undertaken the present study to investigate the effect of valsartan on pharmacokinetics and pharmacodynamics of gliclazide in diabetic rats.

## MATERIALS AND METHODS

**Chemicals:** Gliclazide and valsartan were gifted by Aurobindo Pharma, Hyderabad. Alloxan Monohydrate was purchased from Sigma-Aldrich, India.

**Experimental animals:** Male adult albino rats were procured from Mahaveer enterprises, Hyderabad, India with a weight of 150-200 g and were maintained as per the standard conditions with 12 h light and dark cycles. The animals are allowed for 1 week to acclimatize to the environment and supplied with a standard pellet diet and water *ad libitum*.

**Induction of diabetes mellitus:** Alloxan monohydrate in saline (120 mg $kg^{-1}$, i.p.) was used to induce diabetes or hyperglycemia in 12 h fasted rats[5]. The blood samples were collected after 48 h of alloxan treatment and blood glucose levels were estimated and rats which have more than 200 mg $dL^{-1}$ blood glucose levels were considered as diabetic and were used for the present study[6].

**Experimental design:** To evaluate the effect of valsartan on pharmacokinetics and pharmacodynamics of gliclazide in alloxan monohydrate induced diabetic rats, we have chosen single and multiple dose interaction between gliclazide and valsartan. The rats were randomly divided into 5 groups of six each. In the present study, the doses of gliclazide[7] as 7.2 mg $kg^{-1}$ and valsartan as 37 mg $kg^{-1}$ were used and were calculated from human dose by using rat dose conversion formula.

**Group 1** : Normal control (Normal rats received vehicle)
**Group 2** : Diabetic control (diabetic rats received 1% CMC)
**Group 3** : Diabetic rats treated with gliclazide (7.2 mg $kg^{-1}$, p.o.)
**Group 4** : Diabetic rats treated with gliclazide (7.2 mg $kg^{-1}$, p.o.)+valsartan (37 mg $kg^{-1}$, p.o.)
**Group 5** : Diabetic rats treated with gliclazide (½ TD*) (3.6 mg $kg^{-1}$, p.o.)+valsartan (37 mg $kg^{-1}$, p.o.). *½ therapeutic dose of gliclazide was selected based on the literature review to assess the dosage adjustment of gliclazide, if any drug interaction observed between gliclazide and valsartan

The treatment was given to all groups for 7 days, to assess the single and multiple doses pharmacokinetic and pharmacodynamic interaction between gliclazide and valsartan in rats.

**Collection of blood samples:** Blood samples in single and multiple dose interaction studies were collected from all the groups of fasting animals under mild anesthesia at different intervals on 1st and 7th days using retro-orbital puncture method[7]. The plasma was separated immediately by centrifugation of blood samples at 10,000 rpm for 10 min and was stored at -20°C until analysis.

**Analysis of blood samples:** All the plasma samples were analyzed for fasting glucose levels using GOD-POD method and plasma gliclazide concentrations by using HPLC method.

**Estimation of gliclazide concentration in plasma by HPLC:** The plasma concentration of gliclazide in all the groups of rats was estimated using High Performance Liquid Chromatography (HPLC). The following conditions were maintained.

**Preparation of gliclazide stock solution:** Ten milligrams of gliclazide pure drug was dissolved in ethanol and the further dilutions of stock solution by mobile phase were done to get different standard drug concentrations to plot the standard graph of gliclazide.

**Preparation of mobile phase:** The mobile phase was a mixture of acetonitrile and water at the ratio of 53:47% v/v and the pH was adjusted to 3 with 5% phosphoric acid by adding to the mobile phase. Then the solution was passed through 0.45 µm membrane filter and sonicated for 30 min. The flow rate maintained at 1.0 mL $min^{-1}$ and the eluents monitored at 229 nm. The column maintained at room temperature.

**Extraction of gliclazide from plasma:** Plasma samples of gliclazide were mixed with equal quantity of acetonitrile in eppendorff tubes followed by centrifugation for 10 min at 10,000 rpm which resulted in deproteinization. The supernatant layer was transferred to the other eppendorff tubes and filtered the supernatant using syringe filters. Twenty microliters sample was injected into the HPLC system and the concentrations of gliclazide in plasma samples were estimated.

**Chromatographic conditions:** All the plasma samples were analyzed for gliclazide using a sensitive High Performance liquid chromatography method with UV-detection. Chromatography was performed on a C18 MG column, 5 µm, 250×4.6 mm ID. The mobile phase is a mixture of acetonitrile and water at the ratio of 53:47% v/v. The pH 3 adjusted with 5% phosphoric acid by adding to the mobile phase.

Retention time : Observed at 11.54 min
Flow rate : Flow rate maintained at 1.0 mL $min^{-1}$

The plasma gliclazide concentration in rats at different time intervals was evaluated by using HPLC. The concentration of gliclazide was calculated by the area of the chromatogram.

**Pharmacokinetic analysis:** The peak plasma gliclazide concentration ($C_{max}$) and its time of occurrence ($T_{max}$) will directly read from the concentration-time data. The AUC, AUMC, CL, $t_{½}$, Vd, MRT were calculated using software.

**Statistical analysis:** All the results of the study were expressed as Mean±SD and the blood glucose levels compared with diabetic control value at each time point. One-way analysis of variance (ANOVA) with Dunnet's test was used to compare means. The $p<0.05$ is considered as statistical significance in the present study.

## RESULTS

**Pharmacodynamic interaction studies in diabetic rats:** In the present study we have evaluated the effect of valsartan on pharmacokinetics and pharmacodynamics of gliclazide in diabetic rats and the observed results are described.

**Single dose pharmacodynamic interaction studies in diabetic rats:** Average values of plasma glucose levels in diabetic rats after single dose treatment of gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan (mg $dL^{-1}$) were showed in Table 1. The plasma blood glucose levels were calculated at various time intervals in all the group of rats and found significant reduction ($p<0.05$) in the glucose levels (Table 1). The maximum reduction of blood glucose levels were noted at 2 and 8 h and was found to be

Table 1: Mean±SD plasma glucose values in all the group of rats

| | Time (h) | | | | | | |
|---|---|---|---|---|---|---|---|
| Groups | 0 | 1 | 2 | 3 | 6 | 8 | 10 |
| I | 97.06±2.01 | 95.12±1.08 | 96.80±3.41 | 96.20±1.79 | 95.88±2.42 | 94.98±0.96 | 95.10±3.57 |
| II | 204.68±37.7 | 203.43±36.3 | 203.40±36.6 | 201.50±34.3 | 200.96±51.3 | 202.20±35.4 | 202.60±34.9 |
| III | 205.86±3.63 | 164.00±10.62* | 123.48±6.40** | 131.40±5.91** | 139.57±35.8* | 134.62±14.2** | 144.79±27.8* |
| IV | 209.92±38.3 | 163.86±20.0* | 114.01±11.3** | 121.45±6.46 ** | 133.30±11.8 ** | 124.91±30.2** | 134.54±28.7** |
| V | 202.56±59.1 | 164.69±48.7* | 124.38±35.5*** | 129.80±32.5** | 141.51±26.9* | 134.30±44.0** | 138.96±32.4* |

*$p<0.05$ vs diabetic control, **$p<0.01$ vs diabetic control, n = 6

Table 2: Mean±SD plasma glucose values in all the group of rats

| | Time (h) | | | | | | |
|---|---|---|---|---|---|---|---|
| Groups | 0 | 1 | 2 | 3 | 6 | 8 | 10 |
| I | 93.88±2.0 | 93.56±1.6 | 92.87±0.40 | 93.5±3.3 | 92.39±1.70 | 94.84±1.51 | 94.03±3.46 |
| II | 168.40±37.0 | 171.13±42.7 | 166.96±30.4 | 170.2±33.5 | 167.26±52.5 | 166.30±51.6 | 166.80±65.8 |
| III | 137.26±74.5 | 118.67±51.6* | 93.73±19.1** | 96.5±15.5** | 99.89±53.6** | 94.26±42.2** | 98.79±41.5** |
| IV | 165.20±26.0 | 125.70±19.6** | 89.03±9.71** | 90.8±17.3** | 94.70±4.9** | 90.94±4.75** | 92.08±17.2** |
| V | 147.30±84.4 | 127.04±39.9* | 98.00±10.0** | 102.5±15.7** | 103.47±14.1** | 100.28±16.1** | 104.80±14.5* |

*p<0.05 vs diabetic control, **p<0.01 vs diabetic control, n = 6

Table 3: Mean±SD plasma gliclazide concentrations (μg mL$^{-1}$)

| Time (h) | Gliclazide | Gliclazide+valsartan | (½) gliclazide+valsartan |
|---|---|---|---|
| 0 | 0.00 | 0 | 0 |
| 1 | 6.45±0.85 | 8.27±1.13* | 5.25±1.28 |
| 2 | 10.20±0.7 | 14.81±0.42** | 8.80±0.36* |
| 3 | 7.72±1.04 | 9.60±1.15 | 5.89±0.89* |
| 6 | 3.93±0.99 | 5.42±21.42 | 2.21±0.37* |
| 8 | 5.72±0.68 | 7.06±0.6 | 4.12±0.33* |
| 24 | 2.05±0.13 | 3.61±0.55** | 1.82±0.28 |

*p<0.05 vs gliclazide, **p<0.01 vs gliclazide, n = 6

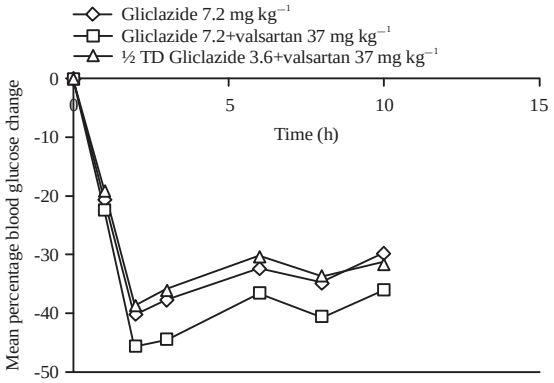


Fig. 1: Percentage of blood glucose reduction in all the groups of rats in single dose study

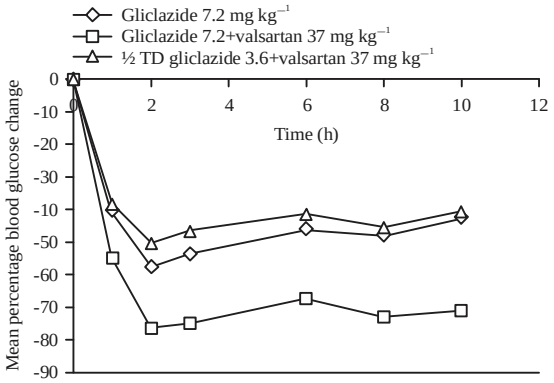


Fig. 2: Percentage of blood glucose reduction in all the groups of rats in multiple dose study

123.48 and 134.62 mg dL$^{-1}$ in gliclazide alone group, 14.01 and 124.91 mg dL$^{-1}$ were in in group of valsartan and gliclazide and 124.38 and 134.3 mg dL$^{-1}$ in (½ TD) gliclazide

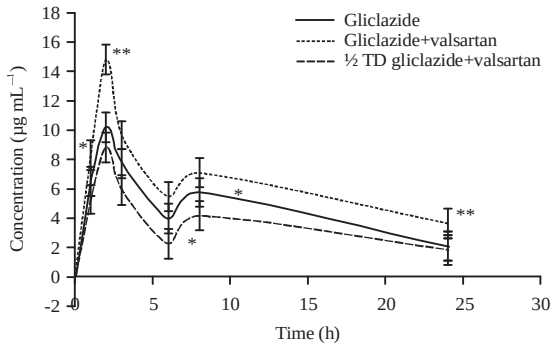


Fig. 3: Mean plasma gliclazide concentrations in all the groups of rats in single dose study. *p<0.05 vs gliclazide, **p<0.01 vs gliclazide

and valsartan group, respectively. The mean percentage blood glucose reduction in diabetic rats (Table 2) after single dose treatment of gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan were represented in Fig. 1.

**Multiple dose pharmacodynamic interaction studies in diabetic rats:** Average values of plasma glucose levels in diabetic rats after multiple dose treatment of gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan (mg dL$^{-1}$) were showed in Table 2. Similar to the single dose study, the multiple dose interaction studies also significantly reduced the blood glucose levels in all the treated rats. The mean percentage blood glucose reduction in diabetic rats after multiple dose treatment of gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan were represented in Fig. 2.

**Pharmacokinetic interaction studies**

**Single dose pharmacokinetic interaction studies in diabetic rat:** Gliclazide plasma concentrations in diabetic rats after single dose treatment of gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan were showed in Table 3. The plasma concentrations of gliclazide were found to be maximum at 2 and 8 h samples. The mean plasma gliclazide concentrations after single dose treatment with gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan were represented in Fig. 3.

**Multiple dose pharmacokinetic interaction studies in diabetic rats:** Gliclazide plasma concentrations in diabetic rats after multiple dose treatment of gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan were showed in Table 4. The mean plasma gliclazide concentrations after multiple dose treatment with gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan were represented in Fig. 4. Based on the above plasma drug concentration-time profiles, the pharmacokinetic parameters were estimated and were represented in Table 5 and 6.

Table 4: Mean±SD plasma gliclazide concentrations (μg $mL^{-1}$)

| Time (h) | Gliclazide | Gliclazide+valsartan | (½) gliclazide+valsartan |
|---|---|---|---|
| 0 | 7.43±0.54 | 9.03±0.4** | 5.89±1.76 |
| 1 | 13.93±2.81 | 16.87±2.76 | 11.85±2.37 |
| 2 | 17.38±0.85 | 22.51±3.04* | 15.90±1.1* |
| 3 | 12.82±0.53 | 16.33±1.93* | 11.15±1.78 |
| 6 | 7.44±1.16 | 11.12±2.82* | 6.26±2.32 |
| 8 | 11.59±0.93 | 14.69±1.79* | 10.37±1.88 |
| 24 | 8.67±0.46 | 9.45±2.42 | 6.51±1.39* |

*p<0.05 vs gliclazide, **p<0.01 vs gliclazide, n = 6

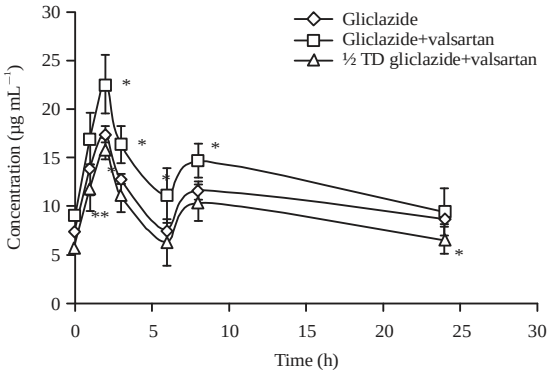


Fig. 4: Mean plasma gliclazide concentrations in all the groups of rats in multiple dose study. *p<0.05 vs gliclazide, **p<0.01 vs. gliclazide

Table 5: Different pharmacokinetic parameters (Mean±SD) after single oral administration of gliclazide alone, glaclazide+valsartan and ½ TD glicazide+valsartan in diabetic rats

| Pk parameter | Gliclazide | Gliclazide+valsartan | (½ TD) gliclazide+valsartan |
|---|---|---|---|
| $AUC_{0-t}$ (μg h $mL^{-1}$) | 109.79±4.79 | 148.250±1.08** | 82.990±1.01** |
| $AUMC_{0-t}$ | 1288.42±7.61 | 1867.135±0.90*** | 1013.550±1.38** |
| $AUC_{0-\alpha}$ (μg h $mL^{-1}$) | 141.99±1.37 | 219.140±1.02** | 115.318±0.95** |
| $AUMC_{0-\alpha}$ | 2566.87±5.41 | 4961.190±2.32*** | 2363.390±6.31** |
| $t_{½}$ (h) | 10.88±0.17 | 13.610±0.34** | 12.310±1.10 |
| CL (mL $h^{-1}$) | 10.14±0.46 | 6.570±0.39*** | 6.243±1.40** |
| CL (mL $h^{-1}$ $kg^{-1}$) | 50.70±1.12 | 32.850±0.21*** | 31.210±0.95** |
| Vdss (mL) | 183.33±2.28 | 148.750±1.14** | 127.900±1.55*** |
| Vdss (mL $kg^{-1}$) | 916.65±1.92 | 743.760±1.32*** | 639.790±3.30*** |
| Vd A (mL) | 159.28±2.59 | 129.050±1.00*** | 110.887±1.60*** |
| Vd A (mL $kg^{-1}$) | 796.41±1.45 | 695.251±3.08*** | 554.430±5.03*** |
| MRT (h) | 18.07±1.00 | 22.638±0.32** | 20.490±1.56* |
| $C_{max}$ (μg $mL^{-1}$) | 10.20±1.19 | 14.810±1.73 | 8.800±1.53 |
| $t_{max}$ (h) | 2.00 | 2.00 | 2.00 |

*p<0.05, **p<0.01, ***p<0.001 vs gliclazide

Table 6: Different pharmacokinetic parameters (Mean±SD) after multiple oral administration of gliclazide alone, gliclazide+valsartan and ½ TD glaclazide+valsartan in diabetic rats

| Pk parameter | Gliclazide | Gliclazide+valsartan | (½ TD) gliclazide+valsartan |
|---|---|---|---|
| $AUC_{0-t}$ (μg h $mL^{-1}$) | 252.93±4.68 | 312.14±3.06* | 214.05±3.35** |
| $AUMC_{0-t}$ | 3758.34±5.96 | 4377.21±5.67*** | 3043.69±4.19*** |
| $AUC_{0-\alpha}$ | 675.01±5.85 | 630.37±2.71** | 442.79±3.94*** |
| $AUMC_{0-\alpha}$(μg h $mL^{-1}$) | 34436.43±8.79 | 22729.43±3.70*** | 16570.51±7.88*** |
| $t_{½}$ (h) | 33.73±0.46 | 23.33±3.05* | 24.34±3.32* |
| CL (mL $h^{-1}$) | 2.13±0.32 | 2.28±0.71 | 1.62±0.41 |
| CL (mL $h^{-1}$ $kg^{-1}$) | 10.66±1.00 | 11.42±1.80 | 8.13±0.88** |
| Vdss (mL) | 108.83±1.55 | 82.36±3.63** | 60.85±2.81*** |
| Vdss (mL $kg^{-1}$) | 544.15±4.6 | 411.83±2.72*** | 304.25±4.07*** |
| Vd A (mL) | 103.85±3.16 | 76.92±4.06*** | 57.13±4.18*** |
| Vd A (mL $kg^{-1}$) | 519.27±3.99 | 384.60±3.81*** | 285.66±2.83*** |
| MRT (h) | 51.01±3.21 | 36.05±3.45** | 37.42±4.36* |
| $C_{max}$ (μg $mL^{-1}$) | 17.38±0.97 | 22.51±2.10* | 15.90±0.39* |
| $t_{max}$ (h) | 2.00 | 2.00 | 2.00 |

*p<0.05, **p<0.01, ***p<0.001 vs gliclazide

## DISCUSSION

Drug interactions are usually seen in clinical practice and the mechanisms of interaction are evaluated usually in animal models. The use of several different drugs concurrently, alias polypharmacy, also increases the risk of interactions. One group of patients prone to polypharmacy is patients with type 2 diabetes mellitus. In addition to antidiabetic medicine, patients with type 2 diabetes mellitus also have for example antihyperlipidemic, antihypertensive and antiplatelet medications. Drug interactions are of great importance not only for the individuals concerned, but also for the entire community. Drug interactions cause significant costs through unnecessary medications and increased number of hospitalizations. For example McDonnell and Jacobs[8] reported that 26% of the studied 437 hospitalizations were due to drug-drug interactions. The probability of drug interactions increases with the growing number of drugs used per person and the number is the single most important risk factor for interactions[9].

Potential interactions can occur between different antidiabetic drugs and between antidiabetic drugs and other widely co-administered pharmacological agents (antihypertensive, lipid-lowering and antiplatelet agents). In addition to these, especially agents with a narrow safety index (digoxin, warfarin) and those that are known to induce or inhibit the CYP enzymes are also in a great risk of causing interactions. The ACE inhibitors and sulphonylureas have been documented to have an interaction, which produces a greater decrease in blood glucose concentrations in human patients than a sulphonylurea alone[10-12]. Gliclazide and fosinopril were shown to decrease blood glucose concentration in rats more when administered concurrently than when gliclazide was administered alone[4].

The present study was conducted to assess the single and multiple dose drug interaction between the gliclazide and valsartan in alloxan monohydrate induced diabeic rats. The present study was aimed at evaluating the effect of valsartan on pharmacokinetics and pharmacodynamics of gliclazide in alloxan induced diabeic rats.

In diabetic rats, the maximum percentage of blood glucose reduction is occurred at 2 h of administration of gliclazide. After single dose treatment with gliclazide, gliclazide+valsartan and ½ TD gliclazide+valsartan in rats, the maximum percentage of blood glucose reduction at 2 h was 40.03, 45.69 and 38.6%, respectively. There is a statistically significant ($p<0.05$) change in the percentage reduction of blood glucose levels. The glucose levels were more reduced with gliclazide when it combines with valsartan indicating pharmacodynamic interaction between the drugs. The efficiency of gliclazide in ½ TD gliclazide+valsartan group to reduce the glucose levels was similar with full TD of gliclazide alone. This reflects the dosage adjustment of gliclazide when it combined with valsartan. Similar results were observed in multiple dose interaction studies.

In diabetic rats the plasma concentration of gliclazide levels were observed maximum at 2 h. Single dose administration of gliclazide, gliclazide+valsartan, ½ TD gliclazide+valsartan, at 2 h, the plasma concentration of Gliclazide levels were found to be 10.2, 14.81, 8.8 μg $mL^{-1}$, respectively. The plasma concentration of gliclazide levels, ½ TD gliclaizde+valsartan were almost equal to the gliclaizde alone treated rats. In combination of full and half therapeutic dose of gliclazide treatment with valsartan, the pharmacokinetic parameters were significantly ($p<0.05$) increased in $C_{max}$, AUC, AUMC. The significant ($p<0.05$) decrease in Vd, indicated that there is an increase in plasma concentration of gliclazide in the body. Similar results were observed in multiple dose interaction studies.

The peak hypoglycemia produced with gliclazide in normal rats was at 2 and 8 h of its post-administration. The rapid release of insulin (phase I) from the pancreas may attained at 2 h may causes the maximum reduction of glucose levels, by gliclazide and to the ability of gliclazide to increase the sensitivity of pancreatic β-cell to glucose. Gliclazide does not have any effect on prolonged insulin release (phase II), whereas, it increases the sensitivity of peripheral tissues to insulin, which may results in the reduction of glucose levels[7] at the 8th. Hepatic cytochrome P450 3A4 and 2C9 isoenzymes are responsible for gliclazide metabolites and were eliminated in urine. Part of gliclazide is eliminated via biliary route, which involves enterohepatic circulation in rats. The reabsorption of gliclazide eliminated via biliary route may be responsible for a second peak in its hypoglycemic effect in diabetic rats[7]. Valsartan pretreatment elevates the hypoglycemic effect of gliclazide by a possible rise in insulin sensitivity and secretion.

The present study results suggest the necessity to readjust the dose of gliclazide when used concomitantly with valsartan. In support of these results, Khan and Gupta[13] also reported that Angiotensin Receptor Blockers (ARB) may also induce the anti-hyperglycemic effect of oral anti diabetic drugs in experimental animals. As ARBs are the drug of choice of diabetic nephropathy and diabetic patient with hypertension in combination with oral anti diabetic drugs. It is therefore, advisable to prescribe ARBs with anti-diabetic drugs like gliclazide carefully with necessary dose adjustment to avoid adverse hypoglycemic episodes in diabetic individuals as hypoglycemic episodes may cause grievous hurt and may lead to death[13].

## CONCLUSION

In the present study, the pharmacodynamic and pharmacokinetic interaction was observed after single and multiple dose treatment between gliclazide and valsartan in diabetic rats. The combination of gliclazide+valsartan treatment has shown influence on the pharmacokinetics of gliclazide like metabolism/distribution/excretion and shown significant difference in controlling blood glucose. The dosage adjustment of gliclazide is necessary in patients receiving gliclazide and valsartan.

The antidiabetic activity of the gliclazide was found to increase in presence of the valsartan. As the pharmacokinetics and pharmacodynamics of the gliclazide is modified in presence of valsartan in diabetic rats was the main rationale behind the potentiation of gliclazide activity by valsartan. In order to minimize the hypoglycemia induced by the combination of these drugs, it is advisable to modify the dosage of the gliclazide. In the present study, it is preliminarily found that half therapeutic dose of gliclazide in presence of valsartan produces almost similar activity with that of gliclazide (full therapeutic dose) in absence of valsartan. This further suggests the dosage adjustment of gliclazide.

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