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# Influence of Lansoprozole on the pharmacokinetics and pharmacodynamics of Glimepiride in normal and diabetic rats

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## ABSTRACT

*Drug interactions are usually seen in clinical practice and the interactions are evaluated usually in animal models. We studied the influence of Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Glimepiride in normal and diabetic rats. In this study Pharmacokinetics of Glimepiride (2mg/kg/ p.o.) was studied in adult healthy Spargue-Dawly rats (n=6). In first phase, the Pharmacokinetics of Glimepiride (2mg/kg/p.o.) was studied. After a washout period of one week the animals were used for second phase studies and were administered with Lansoprazole (30 mg/kg/p.o.) and Glimepiride (2mg/kg/p.o.) 30 minutes later. In the third phase, the animals were administered with Lansoprazole (30 mg/kg/p.o.) for 7 consecutive days to the post second phase. On the 8th day of post second phase and 30 minutes after the Lansoprazole (30 mg/kg) administration, Glimepiride (2mg/kg/p.o.) was administered. And pharmacodynamic study was evaluated in single and multiple studies of both diabetic and normal rats. In all the blood samples were collected from the orbital sinuses at time intervals of 0, 1, 2, 4, 8, 12, 24 hours and the drug concentrations were estimated using HPLC and glucose levels estimated using GOD-POD Method and the PK-PD parameters were calculated. Increase in AUC, Cmax indicates the improved bioavailability of Glimepiride in presence of Lansoprazole. And statistically significant difference in glucose levels was observed in single and multiple studies of both diabetic and normal rats.*

**Key words:** Drug-Drug interaction, Glimepiride, Lansoprazole.

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## INTRODUCTION

Drug interactions are usually seen in clinical practice and evaluated usually in animal models. Drug interaction can be defined as “It may arise either from alteration of Pharmacological response or effect due to Pharmacodynamic or Pharmacokinetic of one drug by the other or from combination of their actions or effects” [1]. Drug-drug interactions occur when one therapeutic agent either alters the concentration (Pharmacokinetic interactions) or the biological effect of another agent (Pharmacodynamic interactions) [2]. Drug-drug interactions are mainly possible in the metabolic enzymes (CYP enzymes) and transporters [3]. The interaction mechanisms involving drug metabolizing enzymes are Inhibition or induction. Drugs that inhibit the CYP enzyme can greatly raise the plasma concentrations of certain other drugs metabolized by these enzymes and thereby they enhance the pharmacological and toxicological effects[4].

Induction of CYP enzyme can lower the plasma concentration and that leads to reduction of therapeutic effect. So number of interaction studies is required to get therapeutic benefits of patients[4]. In the present work we studied the influence of Lansoprazole on the pharmacokinetics and pharmacodynamics of Glimepiride in normal and diabetic

rats. The diabetes and peptic ulcer are diseases, which require chronic treatment. The data suggest that these two disorders may occur in a single person, treatment for both diabetes and peptic ulcer are to be given simultaneously. Lansoprazole is one of the frequently used proton pump inhibiter. In addition, sulfonylurea (Glimepiride) is antidiabetc agents which have been extensively used. Glimepiride is metabolized by the isoenzyme of CYP2C9 [5]. Lansoprazole is metabolized by CYP3A4 and CYP2C19 and also inhibitor of CYP2C19, CYP3A4 and CYP2C9 due to this interaction between Lansoprazole and Glimepiride may be possible [6].

## MATERIALS AND METHODS

Glimepiride and Gliclazide were obtained from Aurobindo Laboratories, Hyderabad, India. Lansoprazole was obtained from Dr. Reddy's Lab, Hyderabad, India. Glucose estimation kits were obtained from R.K. Diagnostics, Karimnagar, A.P, India. HPLC grade methanol, Acetonitrile (HPLC grade), Sodium di hydrogen phosphate HPLC Grade water, all the HPLC Grade and AR Grade chemicals are obtained from Merck Pvt. Limited, Mumbai, India.

### ANIMALS:

Spargue Dawley rats of either sex, 6–7 weeks of age, weighing between 180 to 220 g, were used in the study. They were procured from the Teena Bio Labs (Reg. No. 177/99/A/CPCSEA) Hyderabad, India. The animals were kept in polypropylene cages (6 in each cages) under standard laboratory condition (12-h light/12-h dark cycle) and had free access to commercial pellet diet (Hindustan lever Ltd., Bombay, India) and water *ad libitum*. Animals were housed at CPCSEA approved animal house (Reg.no.1278/ac/09 CPCSEA) of St. John College of Pharmacy, Warangal. The temperature was maintained at 25 ± 2 °C and 50 ± 15% relative humidity. The study was approved by the IAEC of St. John College of Pharmacy (002/IAEC/St.JCOP/2011).Ethical norms were strictly followed during all experiments.

### Experimental Method:

The pharmacokinetic study of Glimepiride (2mg/kg) [7] p.o. was studied in adult healthy Spargue-Dawley rats (n=6). In first phase, the pharmacokinetics of Glimepiride (2mg/kg/p.o.) was studied. After a washout period of one week the animals were used for second phase studies and were administered with Lansoprazole (30 mg/kg) [8] p.o. and Glimepiride (2mg/kg/p.o.) 30 minutes later. In the third phase, the animals were administered with Lansoprazole (30 mg/kg/p.o.) for 7 consecutive days post second phase. On the 8th day 30 minutes after the Lansoprazole (30 mg/kg/p.o.) administration, Glimepiride (2mg/kg/p.o.) was administered. The pharmacodynamic study of Glimepiride (2mg/kg/p.o.) was studied in alloxan induced [9] diabetic rats (n=6). The study was conducted in 3 groups the first group of six rats was administered with of Glimepiride (2 mg/kg/p.o.) and the second group was treated with Lansoprazole (30 mg/kg/p.o.) followed by Glimepiride (2 mg/kg/p.o.) for single dose interaction studies (SDIs). Third group was Pretreated with Lansoprazole (30 mg/kg/p.o.) and Glimepiride (2 mg/kg/p.o.) 8 days for multiple dose interaction studies (MDIs). The blood samples were collected from the orbital sinuses at time intervals of 0, 1, 2, 4, 8, 12, 24 hours and the drug concentration was estimated using HPLC and glucose levels estimated using GOD-POD Method and the PK-PD parameters were calculated.

### ESTIMATION OF GLIMEPIRIDE BY A SENSITIVE RP-HPLC METHOD:

### HPLC Description:

A Waters 2487 HPLC system used in the study consists of a pump (Model code 515)operating at flow rate of 1ml/min, a syringe loading sample injector of 20ul capacity, C-18 reverse phase column of 250 X 4.6 mm dimension and 5u particle size and a dual wave length UV-Visible detector. The data analysis is done by Autochro 3000.

### Chromatographic conditions:

Mobile phase: 10Mm Potassium dihydrogen orthophosphate (pH 3.0) and methanol in the proporation of 20:80 (v/v). Flow rate: 1ml/min. Wavelength: 230nm.Run time: 15min. Injection volume: 20µL.

### Preparation of the Standard Solutions:

### Stock and Working Standard Solutions

The stock solution of Glimepiride (1000 µg/ml) was prepared by dissolving 25 mg in 25 ml methanol and further dilutions were prepared in methanol to obtain working standards in a concentration range of 0.1 - 500 µg/ml.

**Internal Standard (IS)**
For IS stock solution 10mg of gliclazide was weighed and dissolved in 10 ml of methanol. The stock solution was again diluted with methanol to working solution of gliclazide which was at 10µg/ml. All solutions were stored at –20°C.

**Sample Preparation**
Serum samples were stored at –20°C and allowed to thaw at room temperature before processing. In brief, to 100 µL serum, 100 µL aliquot of working standard solution of Glimepiride was added in a polypropylene centrifuge tubes; 100 µL aliquot of Gliclazide solution (10 µg/ml) was added as an IS and the tube was shaken for 1 min. To this, 100 µL of methanol was added for precipitation and the tubes were vortexed each for 1min. Then all the tubes were centrifuged for 20 min at 3000 rpm. Clear supernatant was collected in another centrifuge tubes and a 20 µL aliquot was injected into the analytical column.

**Construction of calibration curve:**
The calibration curve was obtained by plotting peak area ratios of standard drug and internal standard drug (y-axis) against standard drug concentration (x-axis).

**Statistical Analysis:**
Student post t-tests using Graph pad Instant Software version and "KINETICA'' software.

## RESULTS

**Standard graph of Glimepiride in rat serum:**
A Six point calibration curve from concentrations ranging (0.1, 0.3, 0.5, 1, 10 and 30µg/ml) was plotted. The equation of the calibration curve obtained was y=0.086x+0.014.And its calibration curve was show in fig.6

**Table.1 Standard graph of Glimepiride in rat serum**

| Glime Con (µg/ml) | IS Con (µg/ml) | Glime Peak area | IS Peak area | PAR |
|---|---|---|---|---|
| 0.1 | 4.3 | 10 | 459.9 | 0.00935 |
| 0.3 | 12.8 | 10 | 459.88 | 0.027833 |
| 0.5 | 21.98 | 10 | 458 | 0.047991 |
| 1 | 43.23 | 10 | 459.78 | 0.094023 |
| 10 | 441.32 | 10 | 459.76 | 0.959892 |
| 30 | 1190.87 | 10 | 459 | 2.594488 |

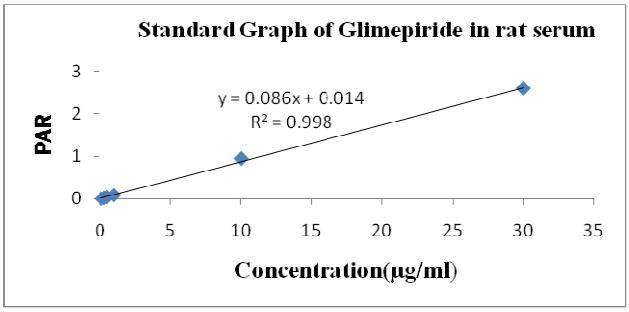


**Fig.1 Calibration curve Glimepiride in rat serum**

**Pharmacokinetic data in normal rats:**
The plasma concentrations of Glimepiride in normal rats before and after treatment with Lansoprazole and plots of time course of Mean±SD Plasma concentrations of Glimepiride following oral route of administration vs.time were shown in tables and figures respectively.

**Table 2: Comparison of Pharmcokinetic parameters of Glimepiride(2mg/kg) following pretreatment with Lansoprazole(30mg/kg) by oral administration in normal rats (n=6)**

| Time points (hrs) | Glimepiride(ng/ml) | Glime±Lanso (acute) | Glime±Lanso (chronic) |
|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 |
| 1 | 411.24±17.57 | 892.85±15.40 | 1398.78±23.18 |
| 2 | 943.00±15.32 | 1497.18±18.49 | 1844.65±131.51 |
| 4 | 1508.81±24.92 | 2105.48±37.27 | 3074.6±161.25 |
| 8 | 603.03± 15.38 | 913.10±15.46 | 1308.73±33.13 |
| 12 | 386.56±12.87 | 633.88±13.43 | 878.82±27.79 |
| 24 | 121.27±11.98 | 393.02±15.37 | 619.56±30.07 |

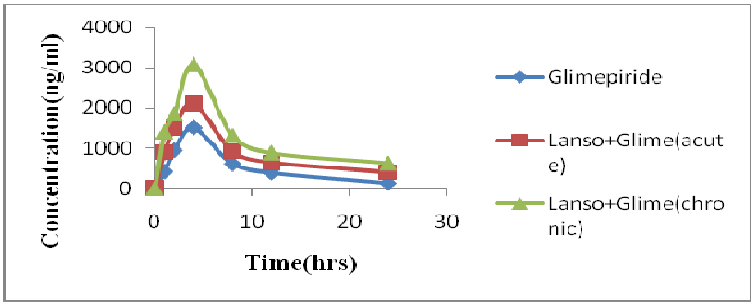


**Fig 2: Comparision of Mean serum concentration of Glimepiride (2mg/kg) following pretreatment with Lansoprazole (30mg/kg) by oral route of administration in normal rats (n=6)**

**Table 3: Comparison of Pharmcokinetic parameters of Glimepiride (2mg/kg) following pretreatment with lansoprazole (30mg/kg) by oral administration in normal rats (n=6)**

| Pk parameters | Glimepiride | Gli ± Lanso(acute) | Gli ±Lanso(chronic) |
|---|---|---|---|
| Cmax | 1508.82±24.93 | 2105.48±37.27 | 3074.6±161.25 |
| Tmax | 4±0 | 4±0 | 4±0 |
| AUC | 11970.38±346.77 | 20059.65±406.63* | 28768.5±788.58** |
| $T_{1/2}$ | 6.96±0.35 | 12.16±0.22 | 13.20±0.63 |
| MRT | 10.5±0.39 | 17.27±0.32 | 18.79±0.82 |

**- Significant at P< 0.05, **- Significant at P< 0.01, compared to glimepiride control (Compared by one way ANOVA followed by Dunnet's test).*

## PHARMACODYNAMIC DATA:

In the present study the blood glucose levels were estimated by GOD-POD method and the hypoglycemic activity of Glimepiride at any time 't' was calculated as the percentage reduction of blood glucose at that time with respect to intial blood glucose levels accordindg to following formula: Percentage reduction in blood glucose at time t = a-b/a × 100; Whare 'a' is initial blood glucose level and 'b' is blood glucose level at time't'.

## NORMAL RATS:

**Table 4: Mean percentage blood glucose reduction in normal rats after oral administration of Glimepiride, Lansoprazole, and their combinations (SDI&MDI)**

| Time(hrs) | Gli | Glime+Lanso (acute) | Glime+Lanso (Chronic) |
|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 |
| 1 | 11.73±0.94 | 21.40±1.11 | 24.98±1.09 |
| 2 | 25.21±7.28 | 33.22±2.25 | 38.28±2.68 |
| 4 | 40.14±13.21 | 46.20±2.31 | 51.90±1.49 |
| 8 | 26.88±13.54 | 33.05±0.85 | 39.24±0.69 |
| 12 | 16.54±10.71 | 20.39±3.37 | 25.85±0.91 |
| 24 | 9.53±6.81 | 18.25±1.85 | 22.30±1.25 |

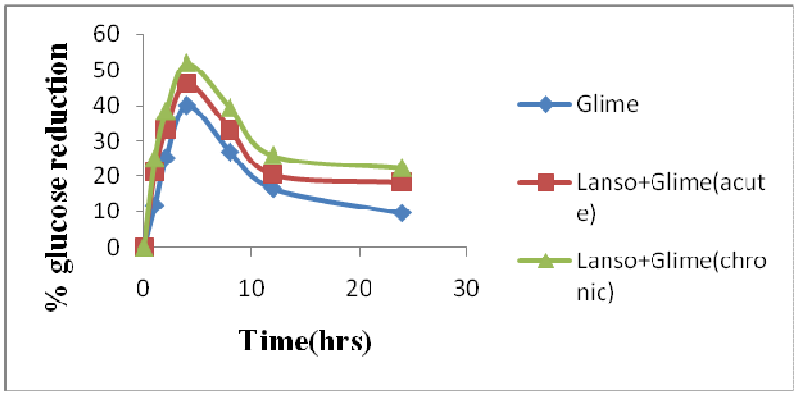


**Fig 3: Comparative % glucose reduction in normal rats**

## PHARMACODYNAMIC DATA IN DIABETIC RATS:

**Table 5: Mean percentage blood glucose reduction in diabetic rats after oral administration of Glimepiride, Lansoprazole, and their combinations (SDI&MDI)**

| Time(hrs) | Glimepiride | Glime+Lanso (acute) | Glime+Lanso (Chronic) |
|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 |
| 1 | 25.18±3.17 | 28.37±0.77 | 47.90±1.77 |
| 2 | 33.43±3.47 | 42.78±1.68 | 51.96±0.54 |
| 4 | 51.28±2.95 | 56.70±0.48 | 70.17±0.97 |
| 8 | 22.45±0.85 | 31.32±4.02 | 42.44±2.41 |
| 12 | 12.35±3.03 | 22.36±2.50 | 34.28±1.55 |
| 24 | 7.25±1.38 | 15.81±1.79 | 32.34±1.56 |

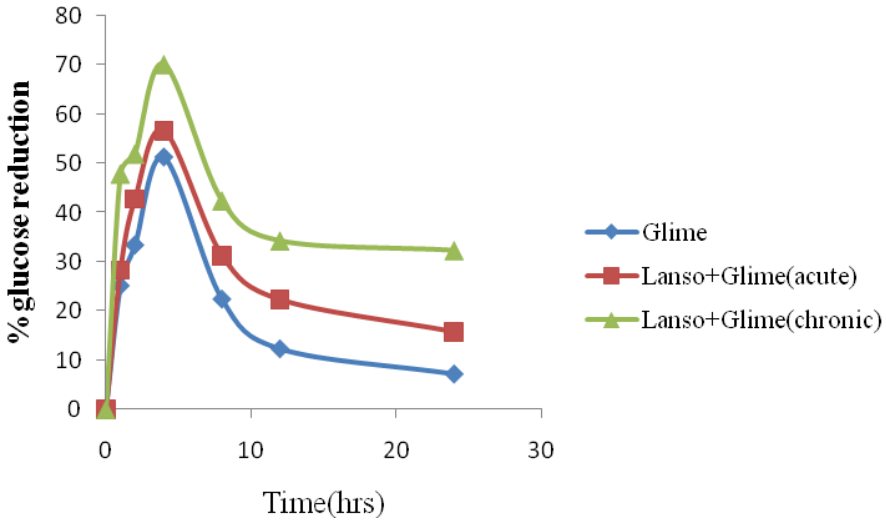


**Fig 4: Comparative % glucose reduction in diabetic rats**

## DISCUSSION

In present study, the pharmacokinetic parameters of Glimepiride like AUC, $t_{1/2}$, Cmax, and MRT were altered significantly with single and multiple dose treatment of Lansoprazole in normal rats. Increase in AUC, Cmax indicates the improved bioavailability of Glimepiride in presence of Lansoprazole. This may be due to the interaction of Lansoprazole with Glimepiride metabolism i.e. Lansoprazole reduce the hepatic metabolism by inhibiting the CYP enzyme 2C9 which leads to rise in serum levels in presence of Lansoprazole. Thus the actions of Glimepiride get

enhanced. There is a statistically significant difference in glucose levels was observed in single and multiple studies of both diabetic and normal rats. Finally Lansoprazole improved Glimepiride activity appeared to involve pharmacokinetic and pharmacodynamic mechanisms.

The present study results suggest that, intial treatment (Single dose studies in normal rats) Lansoprazole enhanced the bioavailability of Glimepiride. In multiple dose studies also Lansoprazole increased the bioavailability of Glimepiride and these results were found to be statistically significant. There is a statistically significant difference in glucose levels was observed in single and multiple studies of both diabetic and normal rats.

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