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Research Article

Pharmacokinetic and Pharmacodynamic Interactions between Concomitantly used Gliclazide with Pravastatin

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ABSTRACT

Diabetic hyperlipidemia is associated with increased lipoproteins in the blood hence, the introduction of a lipid lowering drugs aids in controlling the same. This comedication may lead to drug–drug interactions between anti-diabetic and anti-hyperlipidemic drugs. The current research is aimed at evaluating the pharmacodynamic and pharmacokinetic interactions of gliclazide (anti-diabetic) therapy by pravastatin (anti-hyperlipidemic) when administrated in combination. The studies conducted on rats dosed with gliclazide, pravastatin individually and in combination. Statistical comparisons of plasma concentration – response study in groups with gliclazide alone, pravastatin alone and in combination was carried out. The response study among concentrations and time were calculated employing student's paired T-Test. The results indicate that gliclazide is completely absorbed with peak plasma concentration of 6.82 ± 0.12 ng/mL and 7.82 ± 0.12 ng/mL when administrated alone and 7.22 ± 0.12 ng/mL and 7.22 ± 0.12 when administrated in combination in diabetic rats on first day (day 1) and eighth day (day8) respectively. Similarly, peak plasma concentration of pravastatin is 3.92 ± 0.03 ng/mL and 4.80 ± 0.04 ng/mL when administrated alone and 3.683 ± 0.02 ng/mL and 4.657 ± 0.04 ng/mL when administrated in combination in diabetic rats on first day (day 1) and eighth day (day 8) respectively. There was no statistically noteworthy variation observed in peak plasma concentration ($p > 0.05$). Similarly, no variations observed in values of t_{max} , AUC and $T_{1/2}$. The fasting serum glucose concentrations in normal and STZ-induced diabetic group on first day (day 1) and eighth day (day 8) were analyzed. The reduction of blood glucose levels at different time intervals on administration of gliclazide and pravastatin alone and in combination analyzed and results indicate no significant change in pharmacodynamic parameters.

Hence the results conclude that combinational therapy of gliclazide and pravastatin were found safe and highly potential in treating hyperlipidemia patients.

INTRODUCTION

The potential Drug-Drug Interaction (DDI) refers to the prospect of drug to modify the effects of another drug, being administered, simultaneously.^[1] It is a common medical practice to use drug combinations with the potential to interact. Not all DDIs are potential in nature, hence their detection is significant as they may increase the risk of adverse drug reactions (ADRs), loss of drug efficacy, which also causes adverse consequences for patients in increasing duration of hospital stay and cost.^[2,3]

In recent days the number of patients suffering from atherosclerosis and other cardiac disorders is rising. Diabetes mellitus, also known as “hyperglycemia”, is marked by increase in blood glucose. Type I and Type II are two types of diabetes with 5 and 95% prevalence, respectively. Type II diabetics lead to obesity in 60% of the cases according to World Health Organization (WHO) which is 1.5 times higher in patients with dyslipidemia. This leads to the need of lipid lowering drugs for treatment of dyslipidemia. This may lead to -drug interactions between anti-diabetic and anti-hyper lipidemic drugs.

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Sulfonylureas are used for type II diabetic treatment. Gliclazide, which belongs to second generation sulfonylureas, is used widely due to its selective inhibition towards pancreatic K⁺ATP channels,^[4] fewer prevalence of causing severe hypoglycemia^[5] and related haemobiological effects.^[6]

Pravastatin is used for treatment of hypertriglyceridemia, and dysbetalipoproteinemia^[7] also known for preventing cardiovascular events.^[8] Pravastatin is metabolized by P 450 CYP 3A4 & CYP 3A5 isozymes in the liver.^[9-11]

The objective of current research is to understand the pharmacokinetic and pharmacodynamic drug interaction amongst gliclazide and pravastatin, when used in combination.

MATERIALS AND METHODS

Material

Gliclazide and pravastatin were obtained from Aurabindo laboratories.

Analytical grade Methanol was obtained from Finar chemicals Ltd. Ahmadabad.

Other analytical grade solvents were used.

Animal Preparation

Twenty-four male Wistar rats (weigh 200–220 g) were segregated into five different groups of six animals, each. The animals were maintained at 50% RH, fed with *ad libitum* and water. The protocol was approved by institutional animal ethics committee.

Induction of Experimental Diabetes

The animals were fasted for about 16 hours prior induction of diabetes using Streptozotocin (STZ), for induction of Type-1 diabetes mellitus.

Six animals were injected intraperitoneally with 0.23–0.25 ml of freshly prepared STZ solutions (60 ng/mL in 0.01 M citrate buffer of pH 4.5) at a final dosage of 60 mg/kg body weight. The diabetic state analyzed STZ-treated animals by measuring glucose concentration in non-fasting serum post 48 hours. Only animals with serum glucose levels > 300 mg/dL were chosen for experiment.

Study Design^[12]

Animals were categorized into five groups of six each

Group I : Control group

Group II : Diabetic control group

Group III : Gliclazide administrated as single dosage/day in diabetic rats

Group IV : Pravastatin administrated as single dosage/day in diabetic rats

Group V : Gliclazide and pravastatin concomitant administrated as a single dosage/ day in diabetic rats

Preparation of Drug Solutions

Preparation of Gliclazide

A total of 80 mg of pure gliclazide dissolved in 0.5% of carboxy methyl cellulose. This makes a solution of 8 mg/mL concentration.

Preparation of Pravastatin

A total of 40 mg of pure pravastatin suspended into 10 mL of carboxy methyl cellulose (0.5%) to obtain final solution of 4mg/mL concentration for immediately use.

Blood samples collection procedure

A total of 0.5 mL blood sample drawn from each anesthetized rat. The samples collected using capillary tube from retro-orbital plexus with 20µL of 10% disodium ethylene diamine tetracetate salt.

The blood samples collected at specified intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 16 and 24 hours. Each blood withdrawal is followed by administration of saline. The blood samples centrifuged for 5 minutes at 2500–3000 rpm. The plasma obtained is stored in pre labeled centrifuge tubes at –30°C.

The same procedure was followed on first day and eighth day. The data analyzed using Win Nonlin® 5.1 software.^[13,14]

Plasma Sample Preparation for HPLC Analysis

A total of 0.5 mL of plasma sample was precipitated for protein by adding 2.5 mL cold ethanol. The contents were centrifuged and precipitate was resuspended by adding 1mL acetonitrile followed by vortexing for 60 seconds. The contents were centrifuged for 10 minutes at 5000–6000 rpm, organic layer separate and dried over nitrogen. The samples added to 200 mL of ACN and water in 70:30 ratio for reconstitution. Those samples were used for HPLC injection.

Pharmacokinetic (PK) analysis

The concentration time data used to obtain C_{max} and t_{max} values. The AUC_{0-t} measured from 0–24 hours and $AUC_{0-\infty}$ measured from 0–∞ hours, are obtained from linear trapezoidal rule. The $AUC_{0-\infty}$ is calculated using the formula

$$AUC_{0-t} + [C_{last}/K]$$

C_{last} – concentration at last time point (ng/mL)

K -elimination rate constant

The parameters including volume of distribution (V/f), AUC, elimination half-life [$t_{1/2}$], total clearance (Cl/f) and mean residence time.

Statistical Analysis

Statistical comparisons of gliclazide, pravastatin alone and in combination groups plasma concentration–response study among various concentrations and time carried out using student's paired t-test a value of $P < 0.05$ was considered to be statistically significant.

RESULTS

Study of Plasma Level Concentrations of Gliclazide and Pravastatin

Plasma level (ng/mL) of gliclazide alone and in combination with pravastatin on first day (day 1) were found at various time intervals till 24 hours and the plasma concentrations of gliclazide alone on first day (day 1) are 0 ± 0 , 0.77 ± 0.39 , 2.88 ± 0.24 , 4.34 ± 0.14 , 6.82 ± 0.12 , 4.22 ± 0.37 , 3.62 ± 0.95 , 2.25 ± 0.23 , 1.82 ± 0.34 , 0.12 ± 0.43 , 0 ± 0 respectively and gliclazide combined with pravastatin 0 ± 0 , 1.77 ± 0.39 , 3.28 ± 0.24 , 4.64 ± 0.14 , 7.22 ± 0.12 , 5.22 ± 0.37 , 4.62 ± 0.95 , 2.75 ± 0.23 , 1.62 ± 0.34 , 0.52 ± 0.43 , 0 ± 0 respectively.

The plasma levels (ng/mL) of gliclazide alone and in combination with pravastatin on eighth day (day 8) were found the concentrations are various time intervals till 24 h and the plasma concentrations of gliclazide alone 0.77 ± 0.39 , 2.37 ± 0.39 , 3.88 ± 0.24 , 5.34 ± 0.14 , 7.82 ± 0.12 , 5.22 ± 0.37 , 4.62 ± 0.95 , 3.25 ± 0.23 , 2.82 ± 0.34 , 1.12 ± 0.43 , 0.11 ± 0.01 respectively and gliclazide in combination with pravastatin 0.97 ± 0.39 , 1.77 ± 0.39 , 3.28 ± 0.24 , 4.64 ± 0.14 , 7.22 ± 0.12 , 5.22 ± 0.37 , 4.62 ± 0.95 , 2.75 ± 0.23 , 1.62 ± 0.34 , 0.52 ± 0.43 , 0.32 ± 0.02 respectively.

The plasma level (ng/mL) of pravastatin alone and in combination with gliclazide on first day (day 1) was found the concentrations at various time intervals till 24 hours and the plasma concentrations of pravastatin alone on first day (day 1) are 0 ± 0 , 0.71 ± 0.03 , 3.92 ± 0.03 , 2.95 ± 0.01 , 1.54 ± 0.06 , 1.16 ± 0.01 , 0.92 ± 0.02 , 0.74 ± 0.01 , 0.56 ± 0.01 , 0 ± 0 , 0 ± 0 respectively, pravastatin in combination with gliclazide on first day (day 1) 0 ± 0 , 0.885 ± 0.04 , 3.683 ± 0.02 , 2.836 ± 0.03 , 1.416 ± 0.04 , 1.233 ± 0.01 , 0.78 ± 0.02 , 0.32 ± 0.02 , 0.12 ± 0.01 , 0 ± 0 , 0 ± 0 respectively.

Plasma levels (ng/mL) of pravastatin alone and in combination with gliclazide on eighth day (day 8) were found the concentrations at various time intervals till 24 hours and the plasma concentrations of pravastatin alone

on eighth day (day 8) are 0.54 ± 0.09 , 0.94 ± 0.01 , 4.80 ± 0.04 , 3.61 ± 0.13 , 2.34 ± 0.03 , 1.71 ± 0.04 , 1.23 ± 0.02 , 0.93 ± 0.01 , 0.56 ± 0.02 , 0 ± 0 , 0 ± 0 respectively, pravastatin in combination with gliclazide on eighth day (day 8) are 0.505 ± 0.02 , 0.848 ± 0.01 , 4.165 ± 0.04 , 3.568 ± 0.08 , 2.261 ± 0.03 , 1.538 ± 0.07 , 1.32 ± 0.02 , 1.02 ± 0.03 , 0.66 ± 0.04 , 0 ± 0 , 0 ± 0 respectively.

The mean \pm standard error mean (S.E.M) of plasma concentration of gliclazide alone on first day (day 1) at different time points compared with combination treatment of pravastatin and pravastatin on first day (day 1) is shown in Fig. 1 and Table 1. Similarly eighth day (day 8) plasma concentrations were shown in Fig. 2 and Table 2.

The mean \pm standard error mean (S.E.M) of plasma concentration of pravastatin alone on first day (day 1) at different time points compared with combination treatment of pravastatin and gliclazide on first day (day 1) is shown in Fig. 3 and Table 3. Similarly eighth day (day 8) plasma concentrations were shown in Fig. 4 and Table 4.

In the present study, complete absorption of gliclazide observed orally with peak plasma concentrations of 6.82 ± 0.12 ng/mL post 4 hours on first day (day 1) when administrated alone and 7.22 ± 0.12 ng/mL occurred 4 hours after dosing when administrated in combination

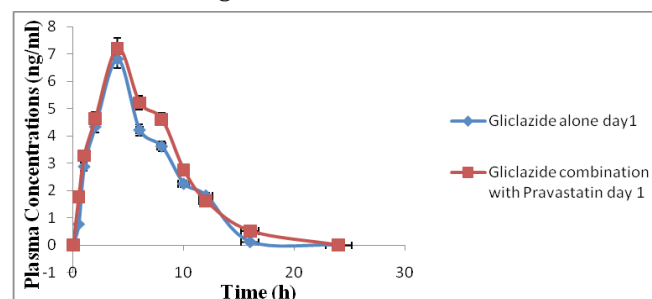


Fig. 1: Plasma levels of gliclazide (ng/mL) its combination with pravastatin on first day (day 1)

Table 1: Peak plasma concentrations of gliclazide (ng/mL) and its combination with pravastatin on first day (Day 1)

Time (h)	Gliclazide alone	Gliclazide combination with Pravastatin
0	0 ± 0	0 ± 0
0.5	0.77 ± 0.39	1.77 ± 0.39
1	2.88 ± 0.24	3.28 ± 0.24
2	4.34 ± 0.14	4.64 ± 0.14
4	6.82 ± 0.12	7.22 ± 0.12
6	4.22 ± 0.37	5.22 ± 0.37
8	3.62 ± 0.95	4.62 ± 0.95
10	2.25 ± 0.23	2.75 ± 0.23
12	1.82 ± 0.34	1.62 ± 0.34
16	0.12 ± 0.43	0.52 ± 0.43
24	0 ± 0	0 ± 0

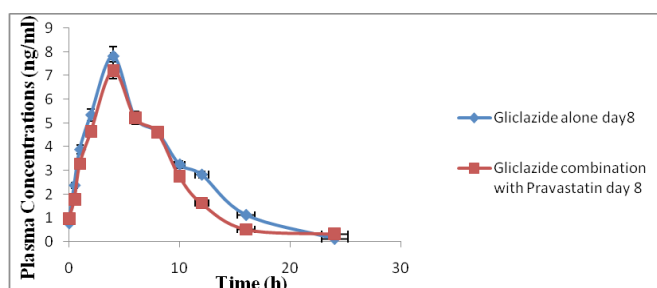
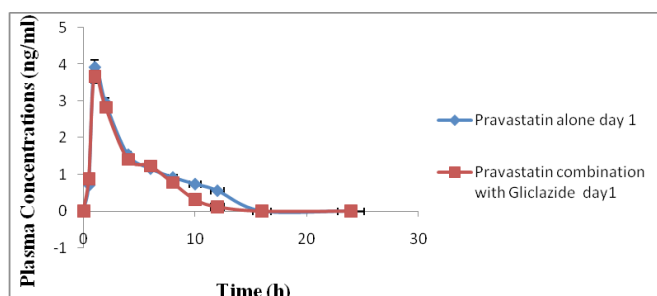
Table 2: Peak plasma concentration of gliclazide (ng/mL) and combined with pravastatin on eighth day (Day 8)

Time (h)	Gliclazide alone	Gliclazide combination with Pravastatin
0	0.77 ± 0.39	0.97 ± 0.39
0.5	2.37 ± 0.39	1.77 ± 0.39
1	3.88 ± 0.24	3.28 ± 0.24
2	5.34 ± 0.14	4.64 ± 0.14
4	7.82 ± 0.12	7.22 ± 0.12
6	5.22 ± 0.37	5.22 ± 0.37
8	4.62 ± 0.95	4.62 ± 0.95
10	3.25 ± 0.23	2.75 ± 0.23
12	2.82 ± 0.34	1.62 ± 0.34
16	1.12 ± 0.43	0.52 ± 0.43
24	0.11 ± 0.01	0.32 ± 0.02

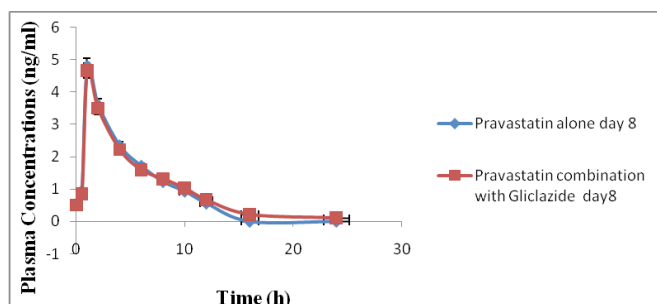


Table 3: Peak plasma concentration of pravastatin (ng/mL) and combined with glliclazide on first day (Day 1)

Time (h)	Pravastatin alone	Pravastatin combination with glliclazide
0	0 ± 0	0 ± 0
0.5	0.71 ± 0.03	0.885 ± 0.04
1	3.92 ± 0.03	3.683 ± 0.02
2	2.95 ± 0.01	2.836 ± 0.03
4	1.54 ± 0.06	1.416 ± 0.04
6	1.16 ± 0.01	1.233 ± 0.01
8	0.92 ± 0.02	0.78 ± 0.02
10	0.74 ± 0.01	0.32 ± 0.02
12	0.56 ± 0.01	0.12 ± 0.01
16	0 ± 0	0 ± 0
24	0 ± 0	0 ± 0

**Fig.2:** Plasma levels of glliclazide (ng/mL) and combined with pravastatin on eighth day (day 8)**Fig. 3:** Plasma level of pravastatin (ng/mL) and combined with glliclazide on first day (day 1)

Day 1 can be separated either in bracket like (Day 1) or with hyphen; in all figures

**Fig. 4:** Plasma level (ng/mL) of pravastatin alone and in combination with glliclazide on eighth day (day 8)

with pravastatin indicating no significant difference. Complete absorption of pravastatin observed orally with

Table 4: Peak plasma concentration (ng/mL) of pravastatin alone and in combination with glliclazide on eighth day (Day 8)

Time (h)	Pravastatin alone	Pravastatin with glliclazide
0	0.54 ± 0.09	0.505 ± 0.02
0.5	0.94 ± 0.01	0.848 ± 0.01
1	4.80 ± 0.04	4.657 ± 0.04
2	3.61 ± 0.13	3.487 ± 0.08
4	2.34 ± 0.03	2.212 ± 0.03
6	1.71 ± 0.04	1.583 ± 0.07
8	1.23 ± 0.02	1.312 ± 0.02
10	0.93 ± 0.01	1.02 ± 0.03
12	0.56 ± 0.02	0.66 ± 0.04
16	0 ± 0	0.21 ± 0.02
24	0 ± 0	0.10 ± 0.01

peak plasma concentrations of 3.92 ± 0.03 ng/mL observed 1 hour post dosage on first day (day 1) when administrated alone and 3.783 ± 0.02 ng/mL occurred 1 hours after dosing when administrated in combination with glliclazide indicating no major difference in values.

The peak plasma concentration of glliclazide on eighth day (day 8) is 7.82 ± 0.12 and combination of glliclazide with pravastatin is 7.22 ± 0.12 ng/mL. The values for pravastatin on eighth day (day 8) and combination with glliclazide concentration are 4.80 ± 0.04 ng/mL and 4.615 ± 0.04 ng/mL respectively. No noteworthy variation in peak plasma concentration on eighth day (day 8) observed ($P > 0.05$). No noteworthy variation observed t_{max} , AUC, and $T_{1/2}$ for single drugs and combination. And there is no significant difference in pharmacodynamic parameters also.

Study of Pharmacokinetic Parameters (PK) of Glliclazide and Pravastatin

Different PK parameters of glliclazide, pravastatin alone and combined treated parameters were studies in this study. Pharmacokinetic parameters were studied.

The PK parameters of glliclazide alone and in combination with pravastatin on first day (day 1), glliclazide alone parameters are C_{max} 6.82 ± 0.12 ng/mL, t_{max} 4 ± 0 h, AUC_{0-t} 72.45 ± 0.74 ng/mL/h, AUC_{0-inf} 96.82 ± 2.50 ng/mL/h, $T_{1/2}$ 9.56 ± 0.28 h. Glliclazide in combination with Pravastatin the parameters are C_{max} 7.22 ± 0.12 ng/mL, t_{max} 4 ± 0 h, AUC_{0-t} 81.37 ± 0.52 ng/mL/h, AUC_{0-inf} 99.15 ± 1.85 ng/mL/h and $T_{1/2}$ 9.64 ± 0.09 h. (Table 5).

The PK parameters of glliclazide alone and in combination with pravastatin on eighth day (day 8), glliclazide alone parameters are C_{max} 7.82 ± 0.12 ng/mL, t_{max} 4 ± 0 h, AUC_{0-t} 87.36 ± 2.38 ng/mL/h, AUC_{0-inf} 98.36 ± 2.63 ng/mL/h, $T_{1/2}$ 9.496 ± 0.024 h. Glliclazide in combination with pravastatin the parameters are C_{max} 7.22 ± 0.12 ng/mL, t_{max} 4 ± 0 h, AUC_{0-t} 89.38 ± 2.49 ng/mL/h, AUC_{0-inf} 113.49 ± 2.74 ng/mL/h, $T_{1/2}$ 9.08 ± 0.018 h. The results were showed in Table 6.

Table 5: The pharmacokinetic parameters of gliclazide and combined with pravastatin on first day (Day 1)

Parameters	Gliclazide	Gliclazide and pravastatin
C _{max} (ng/mL)	6.82 ± 0.12	7.22 ± 0.12
t _{max} (h)	4 ± 0	4 ± 0
AUC _{0-t} (ng/mL/h)	72.45 ± 0.74	81.37 ± 0.52
AUC _{0-inf} (ng/mL/h)	96.82 ± 2.50	99.15 ± 1.85
T _{1/2} (h)	9.56 ± 0.28	9.64 ± 0.09

Table 7: Pharmacokinetic parameters of pravastatin and combined with gliclazide on first day (Day 1)

Parameters	Pravastatin	Pravastatin and Gliclazide
C _{max} (ng/mL)	3.92 ± 0.03	3.683 ± 0.02
t _{max} (h)	1 ± 0	1 ± 0
AUC _{0-t} (ng/mL/h)	33.49 ± 0.016	31.62 ± 0.20
AUC _{0-inf} (ng/mL/h)	52.33 ± 1.37	42.16 ± 0.52
T _{1/2} (h)	2.50 ± 0.49	2.50 ± 0.27

Table 6: Pharmacokinetic parameters of gliclazide alone and combined with pravastatin on eighth day (Day 8)

Parameters	Gliclazide	Gliclazide and pravastatin
C _{max} (ng/mL)	7.82 ± 0.12	7.22 ± 0.12
t _{max} (h)	4 ± 0	4 ± 0
AUC _{0-t} (ng/mL/h)	87.36 ± 2.38	89.38 ± 2.49
AUC _{0-inf} (ng/mL/h)	98.36 ± 2.63	113.49 ± 2.74
T _{1/2} (h)	9.496 ± 0.024	9.08 ± 0.018

Table 8: Pharmacokinetic parameters of pravastatin alone and combined with gliclazide on eighth day (Day 8) (N=6)

Parameters	Pravastatin alone	Pravastatin in combination with Gliclazide
C _{max} (ng/mL)	4.80 ± 0.04	4.657 ± 0.04
t _{max} (h)	1 ± 0	1 ± 0
AUC _{0-t} (ng/mL/h)	33.5 ± 0.22	45.6 ± 1.25
AUC _{0-inf} (ng/mL/h)	52.6 ± 0.43	61.76 ± 1.88
T _{1/2} (h)	2.50 ± 0.18	2.50 ± 0.29

Table 9: Fasting serum glucose concentrations in control and stz-induced diabetic animals on first day (DAY 1)

Group	Serum glucose mg/dl						
	0 h	1 h	2 h	4 h	8 h	12 h	24 h
Normal	95.76 ± 0.24	96.2 ± 0.21	96.86 ± 0.47	97.3 ± 0.26	97.96 ± 0.29	98.65 ± 0.15	97.68 ± 0.44
Diabetic Control	262.16 ± 7.96 b	266.5 ± 7.39 b	275.5 ± 7.2 b	285 ± 7.42 b	296.16 ± 6.84 b	316.5 ± 4.61 b	326.16 ± 4.76 b
Gliclazide alone	243 ± 3.36	164.83 ± 5.36** a	86 ± 4.09** a	89.5 ± 3.48** a	94.00 ± 2.06** a	96.35 ± 1.75** a	140 ± 4.09** a
Gliclazide with Pravastatin	243 ± 3.36	163.83 ± 5.36** a	84 ± 4.09** a	87.5 ± 3.48** a	89.00 ± 2.06** a	90.35 ± 1.75** a	137 ± 4.09** a

n = 6; Values are expressed as mean ± S.E.M

^ap < 0.001; ^cp < 0.05 Vs Normal

^bp < 0.001 vs Diabetic Control

The PK parameters of pravastatin alone and in combination with gliclazide on first day (day 1), pravastatin alone parameters are C_{max} 3.92 ± 0.03 ng/mL, t_{max} 1 ± 0 h, AUC_{0-t} 33.49 ± 0.016 ng/mL/h, AUC_{0-inf} 52.33 ± 1.37 ng/mL/h, T_{1/2} 2.50 ± 0.49 h. Pravastatin in combination with gliclazide the parameters are C_{max} 3.783 ± 0.02 ng/mL, t_{max} 1 ± 0 h, AUC_{0-t} 31.62 ± 0.20 ng/mL/h, AUC_{0-inf} 42.16 ± 0.52 ng/mL/h, T_{1/2} 2.50 ± 0.27 h. The results were showed in Table 7.

The PK parameters of pravastatin alone and in combination with gliclazide on eighth day (day 8), pravastatin alone parameters are C_{max} 4.80 ± 0.04 ng/mL, t_{max} 1 ± 0 h, AUC_{0-t} 33.5 ± 0.22 ng/mL/h, AUC_{0-inf} 52.6 ± 0.43 ng/mL/h, T_{1/2} 2.50 ± 0.18 h. Pravastatin in combination with gliclazide the parameters are C_{max} 4.615 ± 0.04 ng/mL, t_{max} 1 ± 0 h, AUC_{0-t} 41.6 ± 0.25 ng/mL/h, AUC_{0-inf} 59.76 ± 0.88 ng/mL/h, T_{1/2} 2.50 ± 0.29 h. The results were showed in Table 8.

Based on pharmacokinetic parameters obtained from the results gliclazide alone and gliclazide in combination with pravastatin, no noteworthy variation in gliclazide PK

parameters observed. Similarly, no significant difference in pharmacokinetic parameters of pravastatin alone and combined with gliclazide observed.

Pharmacodynamic Studies of Gliclazide and Pravastatin

Pharmacodynamic results of gliclazide alone and combined with pravastatin on first day (day 1) and eighth day (day 8) was showed in Tables 9 and 10. The glucose levels in blood samples are analyzed at 0, 1, 2, 4, 8, 12 and 24 h for gliclazide alone are found to be 243 ± 3.36, 164.83 ± 5.36, 86 ± 4.09, 89.5 ± 3.48, 94.00 ± 2.06, 96.35 ± 1.75, 140 ± 4.09 mg/dl and gliclazide with pravastatin 221 ± 4.26, 130.83 ± 3.36, 61 ± 4.19, 62.5 ± 2.48, 80.00 ± 1.16, 92.32 ± 1.25, 112 ± 4.19 mg/dL. No significant difference observed in the values of gliclazide and pravastatin.

Similarly on eighth day (day 8) gliclazide alone the reduction blood glucose levels are 223 ± 4.16, 138.83 ± 4.36, 63 ± 4.29, 65.5 ± 2.48, 81.00 ± 1.06, 94.33 ± 1.55, 113 ± 4.17 mg/dl, gliclazide with pravastatin 221 ± 4.26, 130.83 ± 3.36, 61 ± 4.19, 62.5 ± 2.48, 80.00 ± 1.16, 92.32 ±



Table 10: Fasting serum glucose concentrations in control and stz-induced diabetic animals on eighth day (DAY 8)

Group	Serum glucose mg/dl						
	0 h	1 h	2 h	4 h	8 h	12 h	24 h
Normal	95.76 ± 0.24	96.2 ± 0.21	96.86 ± 0.47	97.3 ± 0.26	97.96 ± 0.29	98.65 ± 0.15	97.68 ± 0.44
Diabetic Control	262.16 ± 7.96 b	266.5 ± 7.39 b	275.5 ± 7.2 b	285 ± 7.42 b	296.16 ± 6.84 b	316.5 ± 4.61 b	326.16 ± 4.76b
Gliclazide alone	223 ± 4.16	138.83 ± 4.36** a	63 ± 4.29** a	65.5 ± 2.48** a	81.00 ± 1.06** a	94.33 ± 1.55** a	113 ± 4.17** a
Gliclazide with Pravastatin	221 ± 4.26	130.83 ± 3.36** a	61 ± 4.19** a	62.5 ± 2.48** a	80.00 ± 1.16** a	92.32 ± 1.25** a	112 ± 4.19** a

n = 6; Values are expressed as mean ± S.E.M

^ap < 0.001; ^cp < 0.05 Vs Normal

^bp < 0.001 vs Diabetic Control

1.25, 112 ± 4.19 mg/dL. Here also there is no significant difference for alone and combined treatment. From the above results there is no significant difference for pharmacodynamics of alone and combined treatment of gliclazide and pravastatin.

DISCUSSION

The safety of gliclazide (anti-diabetic) therapy by pravastatin (anti-hyperlipidemic) in rats is evaluated in present research. Studies conducted on rats dosed with gliclazide, pravastatin, and combination of both. The pharmacokinetic pharmacodynamics study among gliclazide, pravastatin and the combination carried out. The plasma concentration-responses was obtained from student's paired t-test with p < 0.05 considered as statistically significant. The results reveal no significant difference in the values of peak plasma concentration, t_{max} , AUC, and $T_{1/2}$ for both drugs alone and combination treatment. No significant difference in pharmacodynamics parameters observed.

The present study states that administration of gliclazide with pravastatin is highly efficient in treatment of diabetes and hyperlipidemia. The pharmacokinetic and pharmacodynamics interactions of combined drug administration are found safe and advantageous.

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