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Research Article

Drug-Drug Interaction between Pravastatin and Gliclazide in Animal Models

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The present study is planned to evaluate the safety of gliclazide (antidiabetic) therapy in the presence of pravastatin (antihyperlipidemic) in rats and rabbits. Studies in normal and alloxan-induced diabetic rats were conducted with oral doses of gliclazide, pravastatin, and their combination. Similarly, studies in normal rabbits were conducted with oral doses of gliclazide, pravastatin, and their combination with adequate washout periods in between the treatments. Blood samples were collected from rats and rabbits at different time intervals and were analyzed for blood serum gliclazide levels. Gliclazide produced hypoglycaemic/antihyperglycaemic activity in normal and diabetic rats with peak activity after 2 hours and 8 hours and hypoglycaemic activity in normal rabbits with peak activity after 3 hours. Pravastatin alone produced minor reduction in blood glucose levels in normal rats/diabetic rats/normal rabbits. Pravastatin increased the hypoglycaemic effect of gliclazide in normal rats/diabetic rats/normal rabbits when administered together. The serum insulin levels were increased with pravastatin treatment in rabbits. The serum gliclazide levels and pharmacokinetic parameters of gliclazide were altered significantly in presence of pravastatin in rabbits. The interaction observed appears to be pharmacokinetic interaction at metabolic and excretion levels.

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1. Introduction

In the present days, the number of patients suffering from disorders like diabetes and its associated comorbidities, that is, atherosclerosis, dyslipidemia, and other cardiac disorders is increasing worldwide. Diabetes mellitusis a chronic metabolic disorder characterized by rise in blood glucose level known as "hyperglycaemia." It is of two types, type I accounting for 5% prevalence and type II for 95% prevalence among diabetics. According to WHO 40–60% type-2 diabetics are obese patients. Incidence rates of diabetes were 10 fold higher in obese individuals, 1.5 fold higher in individual with dyslipidemia. Hence, with oral hypoglycaemic drugs, the addition of lipid lowering drug is necessary for the control of dyslipidemia. In such a situation, there may be chances for drug-drug interaction between antidiabetic and antihyperlipidemic drugs.

Sulfonylureas are the drugs of choice in the treatment of type II diabetes. Currently gliclazide, a second generation sulfonylurea, was preferred in therapy because of its selective inhibitory activity toward pancreatic K^+ATP channels [1], low incidence of producing severe hypoglycaemia [2], and other haemobiological effects [3]. It is well established that sulfonylureas produce insulin secretion and improve tissue utilization of glucose at cellular level which was responsible for lowering of blood glucose level. The sulfonylureas and related drugs used in type II diabetes stimulate insulin by closing K^+ATP channels in pancreatic β cells.

Antihyperlipidemic drugs like statins and fibratesare widely used for prophylactic treatment in dyslipidemia and atherosclerosis. Among statins, HMG CoA reductase inhibitor, pravastatin is widely used because it is indicated for primary hypercholesterolemia, mixed dyslipidemia, atherosclerosis, hypertriglyceridemia, and dysbetalipoproteinemia [4]. It has also gained approval for primary prevention of coronary events and secondary prevention of cardiovascular events [5]. Pravastatin is metabolized by P 450 CYP 3A4 & CYP 3A5 isozymes in the liver [6, 7], and it also has moderate inhibition on metabolizing enzymes P 450 CYP 2C9, CYP 2D6, and CYP 3A4 [8]. Hence, there is

more possibility of pravastatin for inhibition of metabolism of gliclazide, which is also metabolized by both CYP 2C9 and CYP 3A4.

The concomitant administration of gliclazide with pravastatin in diabetes associated with atherosclerosis may result in drug-drug interaction with enhanced/decreased gliclazide activity, which is unwanted. The study is planned to establish the safety of the drug combination in animal models with respect to blood glucose level and find out the mechanisms responsible for the interaction if any.

2. Materials and Methods

2.1. Drugs and Chemicals. Gliclazide and Pravastatin are the gift samples from Micro labs (Bangalore, India) and Biocon Ltd. (Bangalore, India), respectively. Alloxan monohydrate was purchased from Sigma Aldrich (Bommasandra, Jigani, Bangalore 560100, India), Bangalore. Glucose kits of Span diagnostics were procured from local suppliers. The HPLC grade methanol and acetonitrile of Qualigens fine chemicals, Mumbai were procured from local chemical suppliers. All other chemicals used were of analytical grade.

2.2. Animals. Albino rats of either sex, weighing between 160–280 g procured from Drugs Testing Lab (Bangalore, India), were used in the study. They were maintained under standard laboratory conditions at ambient temp of 25 ± 2°C with 12-hour light/12-hour dark cycle. They were fed with standard pellet diet (Venkateshwar enterprises Pvt. Ltd, Bangalore, India) and water ad libitum. Animals were fasted for 18 hours before experiment and during the experiment they were withdrawn from food and water. Normal albino rabbits of either sex, weighing between 1.35–1.72 kg were procured from Drugs Testing Lab, Bangalore, India, were used in the study. They were maintained under standard laboratory conditions at ambient temp of 25 ± 2°C with 12-hour light/12-hour dark cycle. They were fed with standard pellet diet (Venkateshwar enterprises Pvt. Ltd, Bangalore, India) and water ad libitum. Animals were fasted for 18 hours before experiment and during the experiment they were withdrawn from food and water. The prior approval for conducting the experiments in rats and rabbits was obtained from our Institutional Animal Ethics Committee and our lab is approved by CPCSEA, Government of India (Regd. No. GCP/CPCSEA/04/2005-06).

3. Methods

3.1. Pharmacodynamic Study in Normal/Diabetic Rats. A group of six rats were administered with 0.72 mg/200 g of bd wt of gliclazide, orally. The same group was administered with pravastatin 0.72 mg/200 g bd wt orally and combination of pravastatin and gliclazide. One-week washout period was maintained between treatments. The same treatment was repeated in a group of six alloxan-induced diabetic rats. Blood samples were withdrawn by retro orbital puncture [9] at 0, 1, 2, 3, 4, 6, 8, 10, and 12 hours and were analyzed for blood glucose by GOD/POD method [10] using commercial glucose kits (Span diagnostics).

Table 1: Mean percent blood glucose changes after oral administration of gliclazide, Pravastatin, and their combination in normal rats ($n = 6$).

Time (h)	Gliclazide	Pravastatatin	Gliclazide + pravastatatin
0	0	0	0
1	−31.14 ± 4.22	−05.24 ± 1.60	−35.45 ± 4.15
2	−38.34 ± 4.63	−09.10 ± 1.29	−48.44 ± 2.50
3	−22.65 ± 3.70	−10.85 ± 1.46	−39.29 ± 3.14†
4	−13.21 ± 3.80	−09.66 ± 1.50	−41.51 ± 2.64*
6	−32.52 ± 2.85	−07.78 ± 1.58	−41.14 ± 6.45
8	−36.34 ± 2.97	−08.33 ± 1.54	−47.26 ± 6.25†
10	−28.06 ± 3.31	−07.88 ± 1.54	−34.18 ± 2.32
12	−19.61 ± 2.90	−06.69 ± 2.16	−28.48 ± 1.87

* Significant at $P < .01$: † Significant at $P < .05$ compared to gliclazide control.

3.1.1. Induction of Diabetes. Diabetes was induced in rats by the administration of alloxan monohydrate in two doses, that is, 100 mg and 50 mg/kg bd wt intraperitoneally for two consecutive days [11].

3.2. Pharmacokinetic and Pharmacodynamic Study in Rabbits. A group of five rabbits were administered with 2.8 mg/1.5 kg bd wt of gliclazide, orally. The same group was administered with 2.8 mg/1.5 kg bd wt of pravastatin, orally after a washout period of one week. After a further washout period the same group was administered with the combination of pravastatin and gliclazide. After interaction study the same group was continued with the daily treatment of interacting drug (pravastatin) for the next eight days with regular feeding. Later after 18-hour fasting, they were again given the combined treatment on the ninth day. Blood samples were withdrawn from the marginal ear vein of each rabbit at 0, 1, 2, 3, 4, 6, 8, 12, 18, and 24 hours. They were analyzed for glucose by GOD/POD [10] and for gliclazide by HPLC [12].

3.2.1. Data and Statistical Analysis. Data was expressed as mean ± standard error of mean (SEM). The significance was determined by applying Student's paired t-test.

4. Results

Gliclazide produced biphasic hypoglycaemic activity with maximum reduction of 38.34 ± 4.63% & 36.34 ± 2.97% after 2 hours and 8 hours in normal rats (Table 1 and Figure 1) and antihyperglycaemic activity with maximum reduction of 36.7 ± 1.27% & 37.04 ± 0.64% after 2 hours and 8 hours in diabetic rats, respectively (Table 2 and Figure 2). It produced peak activity of 33.1 ± 3.23% reductions after 3 hours in normal rabbits (Table 3 and Figure 3). Pravastatin alone produced 9.10 ± 1.29% & 8.33 ± 1.54% and 18.92 ± 1.04 & 8.71 ± 0.67% decrease in the blood glucose in normal

Table 2: Mean percent blood glucose changes after oral administration of gliclazide, Pravastatin, and their combination in diabetic rats ($n = 6$).

Time (h)	Gliclazide	Pravastatatin	Gliclazide + pravastatatin
0	0	0	0
1	−29.25 ± 0.60	−14.68 ± 1.10	−32.23 ± 1.71‡
2	−36.70 ± 1.27	−18.92 ± 1.04	−48.99 ± 0.72*
3	−32.57 ± 0.51	−17.64 ± 0.74	−41.39 ± 0.57*
4	−30.28 ± 0.52	−14.21 ± 0.64	−37.25 ± 0.69‡
6	−34.29 ± 0.61	−11.60 ± 0.95	−39.21 ± 0.54†
8	−37.04 ± 0.64	−08.71 ± 0.67	−48.25 ± 0.56*
10	−31.54 ± 0.81	−04.35 ± 0.82	−31.47 ± 1.19
12	−27.30 ± 0.91	−03.17 ± 0.55	−28.20 ± 0.73

* Significant at $P < .001$; † Significant at $P < .01$; ‡ Significant at $P < .05$ compared to gliclazide control.

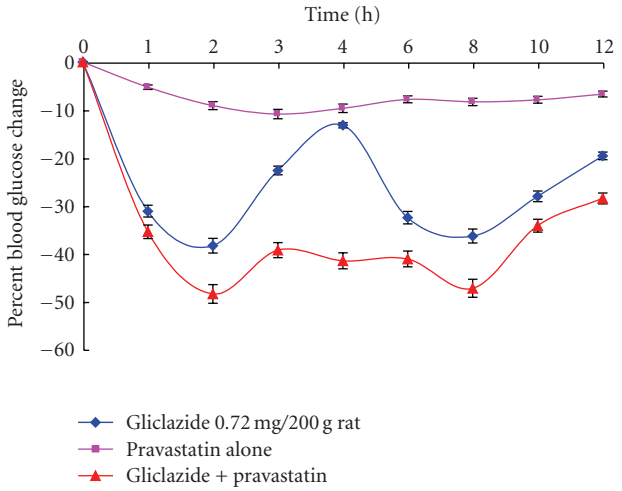

Figure 1: The mean percent blood glucose change with gliclazide alone, pravastatin alone, and in combination in normal rats ($n = 6$).

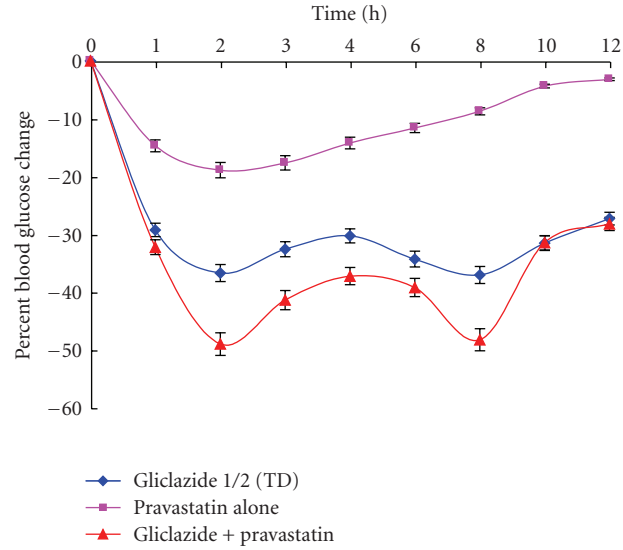

Figure 2: The mean percent blood glucose change with gliclazide alone, pravastatin alone, and in combination in diabetic rats ($n = 6$).

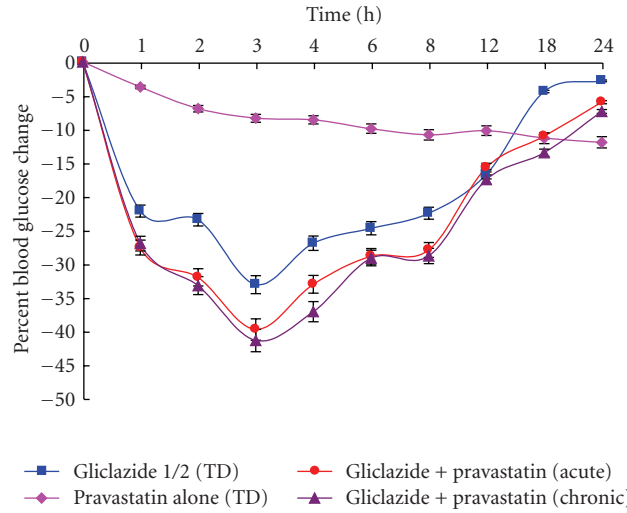

Figure 3: Effect of acute and chronic administration of pravastatin on the percent blood glucose change with gliclazide in normal rabbits ($n = 5$).

and diabetic rats after 2 hours and 8 hours, respectively and 8.35 ± 1.83% in normal rabbits after 3 hours. When gliclazide given in combination with pravastatin produced enhanced hypoglycaemic effect with maximum reduction of 48.44 ± 2.50% & 47.26 ± 6.25% and 48.99 ± 0.72% & 48.25 ± 0.56% in the blood glucose in normal and diabetic rats after 2 hours and 8 hours, and 39.77 ± 2.66% in normal rabbits after 3 hours, respectively (Tables 1, 2, 3 and Figures 1, 2, 3). The serum gliclazide levels and pharmacokinetic parameters of gliclazide like AUC, AUMC, T1/2, clearance, Vdss, Vdarea, Cmax, and Tmax were altered significantly with single- and multiple-dose treatments of pravastatin in normal rabbits (Tables 4, 5 and Figure 4). The serum insulin levels were increased with pravastatin treatment in normal rabbits.

5. Discussion

Drug interactions are usually seen in clinical practice and the mechanisms of interactions are evaluated usually in animal models. We studied the influence of pravastatin on the pharmcodynamics and pharmacokinetics of gliclazide in normal and diabetic rats and in normal rabbits. The normal rat model served to quickly identify the interaction and diabetic rat model served to validate the same response in the actually used condition of the drug. The rabbit model is another dissimilar species to validate the occurrence of the interaction.

The gliclazide produced biphasic response in rat model may be due to its enterohepatic circulation in rats [13, 14] and in humans [15]. Such effect is not seen in rabbit model. Gliclazide is known to produce hypoglycaemic activity by pancreatic [16] (stimulating insulin secretion by blocking

Table 3: Mean percent blood glucose changes after oral administration of gliclazide, pravastatin, and their combination in normal rabbits ($n = 5$).

Time (h)	Gliclazide	Pravastatatin	Gliclazide + pravastatatin (acute)	Gliclazide + pravastatatin (chronic)
0	0	0	0	0
1	−22.17 ± 2.21	−03.71 ± 1.82	−27.60 ± 3.21†	−26.99 ± 2.48‡
2	−23.44 ± 3.88	−06.93 ± 1.87	−32.02 ± 1.87‡	−33.25 ± 4.83‡
3	−33.10 ± 3.23	−08.35 ± 1.84	−39.77 ± 2.66†	−41.41 ± 2.52†
4	−26.94 ± 3.55	−08.60 ± 1.93	−33.04 ± 2.03	−37.12 ± 3.15‡
6	−24.72 ± 2.63	−09.90 ± 2.00	−28.89 ± 2.48‡	−29.14 ± 2.34
8	−22.49 ± 2.91	−10.83 ± 2.06	−27.94 ± 2.06†	−28.83 ± 0.78‡
12	−16.71 ± 3.60	−10.21 ± 1.54	−15.70 ± 2.18	−17.48 ± 2.10
18	−04.38 ± 1.62	−11.33 ± 1.70	−11.01 ± 1.71‡	−13.50 ± 3.60‡
24	−02.79 ± 2.45	−11.95 ± 1.98	−05.97 ± 1.87	−07.36 ± 1.61‡

* Significant at $P < .001$; † Significant at $P < .01$; ‡ Significant at $P < .05$ compared to gliclazide control.

Table 4: Mean serum gliclazide concentration (ng/ml) before and after oral administration of pravastatin in normal rabbits ($n = 5$).

Time (h)	Gliclazide	Gliclazide + pravastatatin (acute)	Gliclazide + pravastatatin (chronic)
0	0	0	0
1	98.54 ± 06.29	116.4 ± 03.43†	121.9 ± 08.60‡
2	246.6 ± 10.54	168.7 ± 03.58†	178.3 ± 06.60†
3	343.4 ± 11.54	393.7 ± 07.31†	396.1 ± 17.57‡
4	294.8 ± 12.19	294.6 ± 06.55	301.8 ± 07.39
6	261.2 ± 09.03	312.8 ± 04.56*	316.7 ± 09.81*
8	222.3 ± 07.33	342.3 ± 15.80*	343.8 ± 08.12*
12	151.1 ± 09.34	264.5 ± 06.02*	259.7 ± 07.58*
18	105.1 ± 06.59	108.1 ± 02.76	112.5 ± 06.24
24	74.09 ± 02.22	96.43 ± 01.74*	98.46 ± 06.27‡

* Significant at $P < .001$; † Significant at $P < .01$; ‡ Significant at $P < .05$ compared to gliclazide control.

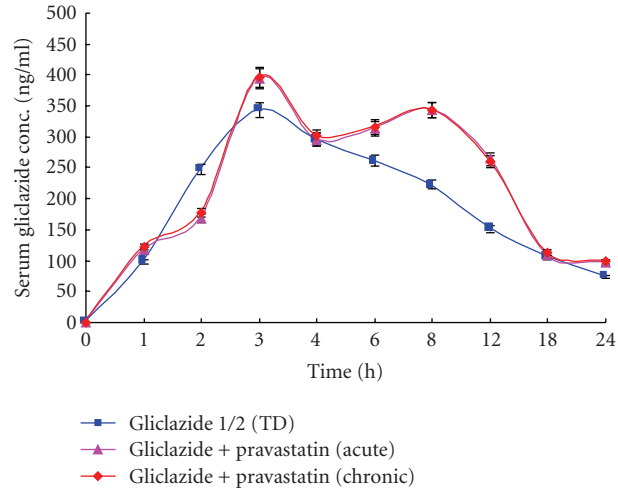

Figure 4: Serum gliclazide concentration versus time in normal rabbits treated with pravastatin ($n = 5$).

K^{+}channels in the pancreatic β cells) and extra pancreatic [17] (increasing tissue uptake of glucose) mechanisms. Pravastatin had minor effect on blood glucose levels and enhanced hypoglycaemic effect of gliclazide when administered in combination in rats and rabbits.

There was significant rise in serum gliclazide levels and pharmacokinetic parameters like AUC, AUMC, T1/2, clearance, Vdss, Vdarea, Cmax, and Tmax of gliclazide with single- and multiple-dose treatments of pravastatin. The increase in AUC, AUMC indicates improved availability of gliclazide in presence of pravastatin. The increased bioavailability cannot be due to improved absorption, since absorption rate and absorption half-life of gliclazide were not altered. There might not be interaction at absorption level since oral absorption of pravastatin is poor. Gliclazide is highly protein bound drug (85–99%) [16], whereas pravastatin is bound to proteins to the extent of 43–55% [4, 18]. Hence, the possibility of displacing gliclazide from protein bound sites by pravastatin was low. Hence, the rise of gliclazide blood levels in the presence of pravastatin might be other than improved absorption and altered distribution.

Pravastatin is metabolized by hepatic P450 CYP 3A4, CYP 2C9 isozymes [6, 8], and there is more possibility of pravastatin for inhibition of metabolism of gliclazide, which is also metabolized by both CYP 2C9 and CYP 3A4 [19]. Further gliclazide is eliminated through renal (80%) and biliary (20%) routes [16, 20]. Pravastatin is also eliminated by both the routes 20% being in urine and 71% in feacal matter [18]. Hence, there is possibility for interaction between pravastatin and gliclazide at biliary excretion also. However, the drug pravastatin did not change the pattern of biphasic response of gliclazide indicating that it did not interfere with the reabsorption of gliclazide in its enterohepatic circulation in rats. Hence, the interaction at hepatic metabolism with reduced gliclazide metabolism by pravastatin leading to raised serum levels is possible.

Alternatively, since pravastatin is acidic drug, it might promote reabsorption of gliclazide (which is also acidic) by

Table 5: Mean pharmacokinetic parameters of gliclazide before and after oral administration of pravastatin in normal rabbits ($n = 5$).

Kinetic parameters	Gliclazide	Gliclazide + pravastatin (acute)	Gliclazide + pravastatin (chronic)
AUC_{0-24} (ng/mL/h)	3905 ± 66.66	5034 ± 95.01*	5083 ± 117.10*
$AUMC_{0-24}$ (ng/mL/h*h)	47503 ± 1653	57651 ± 911.50*	59091 ± 2941.00
Kel (h^{-1})	0.07 ± 0.01	0.08 ± 0.01‡	0.07 ± 0.0063
$AUC_{0-\infty}$ (ng/mL/h)	4963 ± 98.56	6182 ± 106.60*	6342 ± 262.20‡
$AUMC_{0-\infty}$ (ng/mL/h*h)	88101 ± 4529	98882 ± 1565‡	105736 ± 10157
T1/2 (h)	9.86 ± 0.39	8.23 ± 0.11‡	8.70 ± 0.63
Ka (h^{-1})	1.15 ± 0.00	1.15 ± 0.00	1.15 ± 0.00
Clearance (mL/h)	637.80 ± 24.05	513.10 ± 21.50‡	490.30 ± 19.07‡
Clearance (mL/h/kg)	375.50 ± 8.34	301.40 ± 5.44*	296.00 ± 11.81
Vdss (mL)	10704 ± 328.30	7765 ± 346.90†	7664 ± 479.10‡
Vdss (mL/kg)	6314 ± 181.50	4562 ± 110.00†	4598 ± 144.30†
Vdarea (mL)	9037 ± 202.50	6109 ± 273.80†	6145 ± 453.60‡
Vdarea (mL/kg)	5335 ± 155.00	3589 ± 90.08†	3682 ± 157.70†
MRT (h)	17.71 ± 0.64	15.99 ± 0.14	16.53 ± 0.94
C_{max} (ng/mL)	325.80 ± 12.47	393.70 ± 7.37†	396.10 ± 17.57‡
T_{max} (h)	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00

* Significant at $P < .0001$; † Significant at $P < .001$; ‡ Significant at $P < .05$ compared to gliclazide control.

tubular reabsorption process, and hence raises the blood gliclazide levels. Hence, there is possibility for interaction at urinary excretion. So, the rise in serum levels of gliclazide in the presence of pravastatin may be because of the combined influence of its metabolism and urinary excretion.

6. Conclusions

The interaction observed appears to be pharmacokinetic interaction at metabolic and excretion levels. Since the interaction was observed in two dissimilar species, it is likely to occur in humans also. Hence, the combination of gliclazide and pravastatin should be contraindicated or used with caution in a clinical situation.

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