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Influence of irbesartan on the pharmacodynamics and pharmacokinetics of gliclazide in rats and rabbits

T.E. Gopala Krishna Murthy[1], Candasamy Mayuren[2]

[1] *Department of Pharmaceutics, Bapatla College of Pharmacy, AndhraPradesh, India*
[2] *Department of Pharmacology, Bapatla College of Pharmacy, AndhraPradesh, India*

Abstract: The influence of irbesartan on the hypoglycemic effect of gliclazide was studied in normal/diabetic rats and normal rabbits. Gliclazide and irbesartan was studied at a dose of 1.44 mg/200 g, 5.4 mg/200 g in normal/diabetic rats and at a dose of 5.6 mg/1.5 kg, 21 mg/1.5 kg in rabbits, respectively. All the animals were fasted for 18 h prior to experimentation; during this period the animals were fed with water *ad libitum*. All the drugs used in this study were administered orally. The blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 hours and analyzed for glucose levels by GOD/POD method in normal/diabetic rats and rabbits. The blood samples were also analysed for the gliclazide concentration by HPLC in rabbits. Gliclazide exhibited a maximum reduction of blood glucose levels at the 2nd and 8th hour in normal and diabetic rats and at the 3rd hour in rabbits. Irbesartan exhibited a maximum hypoglycemic activity at the 6th hour in normal rats. Although single dose interaction did not show much enhancement of the hypoglycemic activity of gliclazide, multiple dose study exhibited significant potentiation of hypoglycemic activity of gliclazide effect on concurrent administration with irbesartan. The interaction was found to be predominantly pharmacodynamic as no significant interaction was observed pharmacokinetically. The study indicates that irbesartan pretreatment elevates the hypoglycemic effect of gliclazide by a possible rise in insulin sensitivity. The study also suggests the necessity to readjust the dose of gliclazide when used concomitantly with irbesartan.

Key words: drug interaction, hypoglycemia, dynamic studies, gliclazide, irbesartan

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, altered metabolism of lipids, carbohydrates, proteins and an increased risk of complications from vascular diseases [1-3]. Diabetes occurs due either to decreased synthesis of insulin or to defective secretion of insulin from beta cells of islets of Langerhans [4]. Literature study reveals that diabetic patients develop multiple pathology, such as fungal infection, cardiovascular disorders, nephropathy, retinopathy, neuropathy, sexual impotence, hyperacidity and respiratory tract infections [5]. For many years, pharmacological stimulation of insulin secretion by sulfonylurea drugs has been a tool in the treatment of diabetic patients [6-8]. Hypertension which coexists with diabetes mellitus is not only an indicator of increased risk of mortality but also a contributory factor to the development of diabetic complications [9]. To treat the coexisting disease, multi-drug therapy is inevitable, and there is every possibility of the occurrence of a drug interaction when drugs are used concomitantly. Drug interactions have been reported to be the 4th-6th leading cause of death among hospitalized patients in the United States [10]. Among the sulfonylureas, gliclazide is the drug of choice owing to its various haemobiological effects [11].

Corresponding author: Candasamy Mayuren, M.Pharm., PhD, Asst. Prof., Department of Pharmacology, Bapatla College of Pharmacy, Bapatla-522101, Guntur Dist, AndhraPradesh, India.
E-mail: myn_5@yahoo.com

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Irbesartan – an angiotensin-II receptor blocker – is widely used in the management of hypertension, and reportedly influences blood glucose levels and insulin secretion. Thererfore, because of the possibility of its utilization in chronic diabetes, together with with gliclazide, the present study was undertaken to find the effectiveness of a combination therapy which has clinical significance.

MATERIALS AND METHODS

Drugs and Chemicals. Gliclazide and Irbesartan were obtained from Aurobindo, Hyderabad and Sun Pharmaceuticals Ltd, Mumbai, India, respectively. Alloxan monohydrate was obtained from Otto Kemi, Mumbai, India. The glucose estimation kits were obtained from Excel diagnostics Pvt. Ltd, Hyderabad, India.

Animals. Adult wistar rats of either sex, weighing 150-260 g, and albino rabbits, weighing 1.3-1.5 kg, obtained from the animal house of Bapatla College of Pharmacy (1032/ac/07/CPCSEA), Bapatla, were maintained at a constant temperature of 26 ± 2°C and humidity 30-40% with 12 h light/dark cycle, throughout the experiments. The animals were fed with commercial rat/rabbit feed (Rayan's Biotechnologies Pvt. Ltd, Hyderabad, India) and sterile water was given *ad libitum*. The animals were housed in clean rabbit cages in an air-conditioned animal house. The experimental protocol (IAEC/I/BCOP/07-08) was approved by the Institutional Animal

Ethics Committee (IAEC) of Bapatla College of Pharmacy, in accordance with the guidelines of the Committee for the purpose of control and supervision of experimentation on animals.

Dose and Drug administration. In clinical practice, irbesartan and gliclazide in therapeutic doses are administered orally. Hence, human therapeutic doses extrapolated to rats and rabbits – based on the body surface area – were used and administered orally [12].

Pharmacodynamic interaction studies in normal rats

Single dose interaction study in normal rats. Adult wistar rats were used in the study. The animals were divided into 3 groups of 6 animals each. The animals were fasted for a period of 18 h prior to the experimentation and water was supplied *ad libitum* [10].Group I served as control and received distilled water, group II received gliclazide 1.44 mg/200 g, group III received irbesartan 5.4 mg/200 g. The blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16 h before and after drug treatment by retro orbital puncture method. The samples were centrifuged (RM 12C, Mumbai, India) for serum separation at 4,000 rpm for 10 min. The serum samples were analyzed for glucose by GOD/POD method [2, 13]. Single dose interaction studies were carried out on group II animals after a brief washout period of 1 week. The animals were fasted for 18 h prior to experimentation and water supplied *ad libitum*. The animals were administered with the interacting drug irbesartan 5.4 mg/200 g followed by gliclazide 1.44 mg/200 g after half-an-hour of interacting drug administration. The blood samples were collected before and after administration of drug at predetermined time intervals from the rats by retro orbital puncture method and subjected to analysis, as previously mentioned.

Multiple dose interaction study in normal rats. In the case of multiple dose study, the group II animals were administered with irbesartan 5.4 mg/200 g, for the following 7 consecutive days after single dose interaction. During this period, the animals had free access to food and water. On the 7th day, 6 h after the irbesartan administration, food was withdrawn but water supplied *ad libitum*. On the 8th day, half-an-hour after irbesartan administration, the animals received gliclazide 1.44 mg/200 g. Blood samples was withdrawn by retro orbital puncture, processed for serum, and analyzed for glucose by GOD/POD method [2, 13].

Pharmacodynamic interaction studies in diabetic rats

Induction of Diabetes. Experimental diabetes in rats was induced by injecting alloxan monohydrate intraperitonially at a dose of 150 mg/kg in ice-cold normal saline. After 72 h, samples were collected by retro orbital puncture from all surviving rats, and the serum analyzed for glucose levels. Rats with blood glucose levels of 200 mg/dL and above were considered as diabetic and selected for the study [2, 14, 15].

Single/Multiple dose interaction studies in diabetic rats. The diabetic animals were divided into 2 groups of 6 animals each. The animals were fasted for a period of 18 h prior to experimentation and water supplied *ad libitum*. Group I was treated with the vehicle, and group II administered with gliclazide 1.44 mg/200 g; after a brief washout period of 1 week, the animals of group II were used for the interaction study. The experimental protocol similar to that of earlier studies in normal rats was followed for single and multiple dose interaction study in diabetic rats [2, 13].

Pharmacodynamic and pharmacokinetic interaction studies in normal rabbits

Single/Multiple dose interaction study in normal rabbits. Albino rabbits of either sex weighing between 1.3-1.5 kg were included in the study. The animals were divided into 2 groups of 5 animals each. The animals were fasted for a period of 18 h prior to experimentation and water supplied *ad libitum*. Group I was treated with the vehicle and group II treated with gliclazide 5.6 mg/1.5 kg. Blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h before and after drug treatment from the marginal ear vein of the rabbits. The collected samples were centrifuged within half-an-hour at 4,000 rpm for 10 min for separation of serum. The serum samples was analyzed for glucose by GOD/POD method [5, 13], and also analyzed for gliclazide concentration using HPLC [16, 17, 18]. After a brief washout period of 1 week, the animals of group II were used for the interaction study. The single dose interaction study was performed with group II animals. The animals were fasted for 18 h prior to experimentation and water supplied *ad libitum*. The animals were administered with the interacting drug irbesartan 21 mg/1.5 kg, followed by gliclazide 5.6 mg/1.5 kg, after half-an-hour of interacting drug administration. The blood samples were collected before and after administration of drugs at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h from the marginal ear vein, and the samples were centrifuged within half-an-hour at 4,000 rpm for 10 min. The serum samples were analyzed for glucose by GOD/POD method, and also analyzed for gliclazide concentration using HPLC [16-18].

Multiple dose interaction study in normal rabbits. In case of multiple case study, the group II animals were administered with irbesartan 21 mg/1.5 kg, p.o for the following 7 consecutive days after the single dose interaction. During the experiment, the animals had free access to food and water. On the 7th day, 6 h after irbesartan 21 mg/1.5 kg administration, food was withdrawn and water was supplied *ad libitum*. On the 8th day, half-an-hour after irbesartan 21 mg/1.5 kg administration, the animals received gliclazide 5.6 mg/1.5 kg. Blood samples were withdrawn from the marginal ear vein at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 h. The serum samples was analyzed for glucose by GOD/POD method [5, 13], and also analyzed for gliclazide concentration using HPLC [16-18].

Data analysis. The hypoglycemic activity of gliclazide at anytime, 't' in rats and rabbits, was calculated as the percentage blood glucose change at that time with respect to initial blood glucose level according to the formula given below [4].

Percentage blood glucose reduction at time 't' = [(a-b)/a] ×100

a – Initial blood glucose level

b – Blood glucose level at time 't'.

The pharmacokinetic parameters of gliclazide were estimated by non-compartmental methods, with the use of PK Solutions 2.0, USA. The various pharmacokinetic parameters estimated were: K_e (1/hr), $t_{1/2}$ (hr), K_a (1/hr), $AUC_{(0-\alpha)}$ (µg-hr/ml), MRT (hr), C_{max} (µg/ml), T_{max} (hr).

Statistical significance. The data are presented as Mean ± SEM. The significance of the observed difference in the pharmacodynamic and pharmacokinetic parameter of gliclazide was assessed by one way ANOVA, followed by Dunnett's multiple comparison test. A value of $P<0.05$ was considered to be statistically significant.

RESULTS

Pharmacodynamic interaction studies in normal rats. Gliclazide at the dose of 1.44 mg/200 g was studied in normal rats. The serum blood glucose levels were calculated at various time intervals. The onset of action was observed at the 1st h and the duration was observed until the16th h. The blood glucose level at the 2nd and 8th h of treatment with gliclazide was 48.97 and 49.15 mg/dL; the percentage change in blood glucose was 35.95% and 34.83%, respectively, in normal rats. Irbesartan at a dose of 5.4 mg/200 g exhibited a blood glucose level of 66.89 mg/dL at the 6th h, and the percentage change in blood glucose level was found to be 20.12 %. The blood glucose levels were statistically analyzed and were found to be significant when compared to that of control (Table 1).

Single dose interaction study. The study was conducted in normal rats by the administration of gliclazide 1.44 mg/200 g and irbesartan 5.4 mg/200 g. Blood glucose levels were calculated at various time intervals and subjected to statistical comparison with control and that of gliclazide. The statistical treatment proved it to be significantly different. The blood glucose level of the single interaction study was found to be 69.68 and 68.56 mg/dL, and the percentage change were found to be 24.73% and 26.07% during the 2nd and 8th h of the study. Blood glucose levels exhibited by the combination of gliclazide and irbesartan were found to be significantly elevated throughout the study when compared to that of single gliclazide treatment (Table 1).

Multiple dose interaction study. The study was conducted by the administration of irbesartan daily at a dose of 5.4 mg/200 g for a period of 1 week followed by gliclazide 1.44 mg/200 g on the 8th day of study. Blood glucose levels were calculated at various time intervals, and compared with that of control and single gliclazide treatment. Blood glucose levels at the 2nd and 8th h of the multiple interaction study of gliclazide and irbesartan were found to 58.21 and 51.06 mg/dL. The percentage changes were found to be 32.09% and 40.43%, respectively. Blood glucose levels were elevated initially, but showed no significant change from the 3rd to 8th h of the multiple dose interaction when compared to that of single gliclazide treatment in normal rats (Table 1).

Pharmacodynamic interaction studies in diabetic rats. In the case of diabetic rats, gliclazide was studied at a dose of 1.44 mg/200 g. Blood glucose levels were calculated and subjected to statistical analysis. Blood glucose levels exhibited by diabetic rats on treatment with gliclazide at the 2nd and 8th h were found to be 123.85 and 125.06 mg/dL and the percent change in blood glucose were found to be 40.82% and 40.16%, respectively, in diabetic rats. The blood glucose level exhibited by gliclazide together with irbesartan at the 2nd and 8th h of single dose interaction study in diabetic rats were found to be 136.57 and 132.17 mg/dL, and the percentage changes in blood glucose were found to be 33.99% and 36.17%. The blood glucose levels in the case of single dose interaction were found to be reduced gradually from 0-8th h, but it was found to be elevated when compared to that of single gliclazide treatment. Significant elevations were observed during the 1st and 2nd h when compared to single gliclazide treatment. Blood glucose levels exhibited by gliclazide together with irbesartan at the 2nd and 8th h of multiple dose interaction study in diabetic rats were found to be 121.90 and 112.76 mg/dL, and the respective percentage changes were observed to be 41.21% and 45.70%. Blood glucose levels were found to be significantly reduced from the 3rd-8th h when compared with that of single gliclazide treatment in diabetic rats (Table 2).

Pharmacodynamic and pharmacokinetic interaction studies in normal rabbits. The effect of the 5.6 mg/1.5 kg dose of gliclazide was studied in normal rabbits. Blood glucose levels were calculated at various time intervals and subjected to

Table 1 Mean serum blood glucose levels in normal rats on various treatments.

Time (h)	Mean serum blood glucose levels in normal rats with various treatments (mg/dL)				
	Control	Gliclazide 1.44 mg/200 g	Irbesartan 5.4mg/200 g	Single dose interaction	Multiple dose interaction
0	83.00±1.08	76.59±3.30$a^{ns}b^{ns}$	84.12±3.82$a^{ns}b^{ns}$	92.65±3.79a*b**	85.55±2.74$a^{ns}b^{ns}$
1	88.94±1.01	53.80±2.82a# (29.86)	77.66±2.88a**b# (7.58)	72.65±3.83a#b* (21.75)	63.13±2.17a#b* (26.19)
2	85.71±0.79	48.97±1.82a# (35.95)	76.70±3.29a*b# (8.58)	69.68±2.75a#b* (24.73)	58.21±2.57a#b* (32.09)
3	84.93±0.85	51.37±2.65a# (33.06)	74.17±3.83a**b# (11.76)	73.57±2.84a**b# (20.87)	53.15±1.81a#b^{ns} (37.85)
4	86.23±1.35	55.93±2.67a# (26.86)	71.26±2.01a**b** (15.02)	75.62±3.89a*b# (17.33)	54.45±3.81a#b^{ns} (36.72)
6	87.80±1.39	53.52±2.63a# (30.08)	66.89±1.53a#b** (20.12)	73.25±3.58a#b# (20.64)	54.59±2.28a#b^{ns} (36.26)
8	84.36±0.87	49.15±2.57a# (34.83)	68.37±1.15a#b# (18.26)	68.56±4.19a#b# (26.07)	51.06±2.37a#b^{ns} (40.43)
10	85.53±0.86	53.47±3.37a# (27.79)	73.06±3.28a**b# (13.14)	75.25±2.76a*b# (18.59)	61.09±1.87a#b^{ns} (28.47)
12	83.84±0.93	60.20±3.04a# (21.42)	75.39±3.58a^{ns}b** (10.45)	80.35±3.46a^{ns}b# (13.74)	66.52±3.73a#b^{ns} (22.41)
16	81.24±1.38	67.49±2.20a** (11.60)	78.87±2.98a^{ns}b* (6.18)	85.60±4.22a^{ns}b** (7.67)	74.41±3.64$a^{ns}b^{ns}$ (13.20)

The values are mean±SEM of 6 observations at each time interval.
a – represents the probability of significance of gliclazide, irbesartan and single/multiple dose interaction studies when compared with blood glucose levels of control in normal rats.; b – represents the probability of significance of irbesartan and single/multiple dose interaction studies when compared with the blood glucose levels of gliclazide 1.44 mg/200g in normal rats; * – $P<0.05$; ** – $P<0.01$; # – $P<0.001$; ns – non-significant.
Values in parenthesis represent the percentage change in blood glucose when compare to initial blood glucose level.

Table 2 Mean serum blood glucose levels in diabetic rats with various treatments.

Time (h)	Mean serum blood glucose levels in diabetic rats with various treatments (mg/dL)			
	Control	Gliclazide 1.44 mg/200 g	Single dose interaction	Multiple dose interaction
0	208.90 ±2.15	209.46±2.65a^{ns}	207.05±1.89$a^{ns}b^{ns}$	207.74±1.64$a^{ns}b^{ns}$
1	231.50±1.69	133.83±3.40$a^{\#}$ (36.10)	143.72±3.62$a^{\#}b$* (30.61)	135.68±2.34$a^{\#}b^{ns}$ (37.04)
2	226.80±3.80	123.85±1.73$a^{\#}$ (40.82)	136.57±3.04$a^{\#}b$** (33.99)	121.90±3.64$a^{\#}b^{ns}$ (41.21)
3	226.10±3.95	135.74±2.93$a^{\#}$ (35.20)	141.03±3.44$a^{\#}b^{ns}$ (31.85)	118.47±3.13$a^{\#}b$** (42.93)
4	211.10±2.23	142.10±3.48$a^{\#}$ (32.13)	152.45±3.50$a^{\#}b^{ns}$ (26.30)	116.61±3.70$a^{\#}b^{\#}$ (43.84)
6	212.40±1.93	129.47±3.91$a^{\#}$ (38.19)	133.93±3.48$a^{\#}b^{ns}$ (35.23)	113.36±1.62$a^{\#}b$** (45.43)
8	197.30±2.01	125.06±3.79$a^{\#}$ (40.16)	132.17±2.86$a^{\#}b^{ns}$ (36.17)	112.76±1.46$a^{\#}b$** (45.70)
10	188.90±1.95	144.28±2.85$a^{\#}$ (31.09)	150.92±3.77$a^{\#}b^{ns}$ (27.11)	139.78±2.95$a^{\#}b^{ns}$ (34.13)
12	189.41±1.54	158.16±3.84$a^{\#}$ (24.41)	165.85±3.53$a^{\#}b^{ns}$ (19.95)	153.33±3.16$a^{\#}b^{ns}$ (26.14)
16	188.00±1.95	177.94±3.94a* (15.04)	185.41±2.57$a^{ns}b^{ns}$ (11.29)	178.50±3.57a*b^{ns} (14.02)

The values are mean±SEM of six observations at each time interval.
a – represents the probability of significance of gliclazide, and single/multiple dose interaction studies when compared with the blood glucose levels of control in diabetic rats; b – represents the probability of significance of single/multiple dose interaction studies when compared with the blood glucose levels of gliclazide 1.44 mg/200g in diabetic rats; * – P<0.05; ** – P<0.01; # – P<0.001; ns – non-significant.
Values in parenthesis represent the percentage change in blood glucose when compare to initial blood glucose level.

Table 3 Mean serum blood glucose levels in normal rabbits with various treatments.

Time (h)	Mean serum blood glucose levels in normal rabbits with various treatments (mg/dL)			
	Control	Gliclazide 5.6 mg/1.5 kg	Single dose interaction	Multiple dose interaction
0	95.21±2.01	95.14±3.48a^{ns}	94.59±2.95$a^{ns}b^{ns}$	95.59±1.96$a^{ns}b^{ns}$
1	103.20±2.90	73.59±3.09$a^{\#}$ (22.48)	75.26±1.18$a^{\#}b^{ns}$ (20.22)	71.69±2.04$a^{\#}b^{ns}$ (24.88)
2	106.50±2.79	64.78±2.02$a^{\#}$ (31.75)	65.39±1.45$a^{\#}b^{ns}$ (30.63)	62.67±1.98$a^{\#}b^{ns}$ (34.35)
3	103.80±2.03	58.82±4.09$a^{\#}$ (38.42)	59.21±1.50$a^{\#}b^{ns}$ (37.19)	57.10±2.13$a^{\#}b^{ns}$ (40.27)
4	100.70±2.35	63.44±2.02$a^{\#}$ (33.12)	65.06±1.71$a^{\#}b^{ns}$ (31.05)	58.10±0.87$a^{\#}b$* (39.12)
6	98.60±2.14	69.63±1.56$a^{\#}$ (26.58)	68.35±1.58$a^{\#}b^{ns}$ (27.57)	64.17±0.86$a^{\#}b$* (32.74)
8	97.59±2.06	75.76±2.27$a^{\#}$ (20.18)	73.81±3.37$a^{\#}b^{ns}$ (21.90)	69.57±3.22$a^{\#}b^{ns}$(27.30
10	94.28±2.10	80.88±4.19a** (15.11)	78.99±2.31a**b^{ns} (16.41)	82.61±1.32a**b^{ns} (13.45)
12	92.49±1.99	84.45±4.13a^{ns}(11.40)	84.51±3.16$a^{ns}b^{ns}$ (10.66)	85.17±1.51$a^{ns}b^{ns}$ (10.83)
16	91.04±1.73	87.74±4.36a^{ns}(7.93)	88.46±2.86$a^{ns}b^{ns}$ (6.45)	89.96±2.13$a^{ns}b^{ns}$ (5.85)
20	92.27±2.07	89.57±3.91a^{ns} (5.86)	90.58±3.53$a^{ns}b^{ns}$ (4.30)	91.58±1.59$a^{ns}b^{ns}$ (4.14)
24	93.90±1.84	93.03±3.88a^{ns} (2.30)	92.36±3.26$a^{ns}b^{ns}$ (2.39)	92.52±1.82$a^{ns}b^{ns}$ (3.19)

The values are mean±SEM of five observations at each time interval.
a – represents the probability of significance of gliclazide, and single/multiple dose interaction studies when compared with the blood glucose levels of control in normal rabbits; b – represents the probability of significance of single/multiple dose interaction studies when compared with the blood glucose levels of gliclazide 5.6 mg/ 1.5 kg in normal rabbits; * – P<0.05; ** – P<0.01; # – P<0.001; ns – non-significant.
Values in parenthesis represents the percent change in blood glucose when compare to initial blood glucose level.

Table 4 Pharmacokinetic data of gliclazide with various treatments.

Parameter	Gliclazide	Single dose interaction	Multiple dose interaction
Elimination Rate (k_e) (1/hr)	0.05+0.00	0.05+0.0010a^{ns}	0.05+0.00a^{ns}
Elimination Half-life ($t_{1/2}$) (hr)	13.16+0.24	13.45+0.28a^{ns}	13.44+0.20a^{ns}
Absorption Rate (k_a) (1/hr)	0.27+0.02	0.34+0.04a^{ns}	0.45+0.10a^{ns}
AUC (0-∞) (µg-hr/ml)	24.44+0.99	24.86+1.15a^{ns}	24.58+0.91a^{ns}
MRT	21.04+0.27	21.36+0.26a^{ns}	21.48+0.45a^{ns}
Cmax (µg/ml)	1.18+0.03	1.16+0.03a^{ns}	1.18+0.03a^{ns}
Tmax (hr)	3.00+0.00	3.00+0.00a^{ns}	3.0+0.00a^{ns}

The values are mean±SEM of five observations at each time interval.
a – represents the probability of significance of single/multiple dose interaction studies when compared with the pharmacokinetic parameter of gliclazide in normal rabbits; * – P<0.05; ** – P<0.01; # – P<0.001; ns – non-significant.

statistical analysis. The blood glucose level exhibited by single gliclazide treatment at the 3rd h was 58.82mg/dL, and the percentage change was observed to be 38.42% in rabbits. Blood glucose level exhibited at the 3rd hour by gliclazide together with irbesartan in single dose interaction study was observed to be 59.21 mg/dL, and the percentage change was observed to be 37.19%. Statistical treatment showed that interaction was insignificant when compared with single gliclazide treatment. Multiple dose interaction revealed a significant reduction in blood glucose level during the 4th-6th h when compared to single gliclazide treatment. Blood glucose level exhibited at the 3rd h by gliclazide together with irbesartan was observed to be 57.10 mg/dL, and the percentage change was 40.27% (Table 3). In the case of pharmacokinetic interaction study, the serum concentrations of gliclazide alone, and in the case of interaction studies with irbesartan, were determined

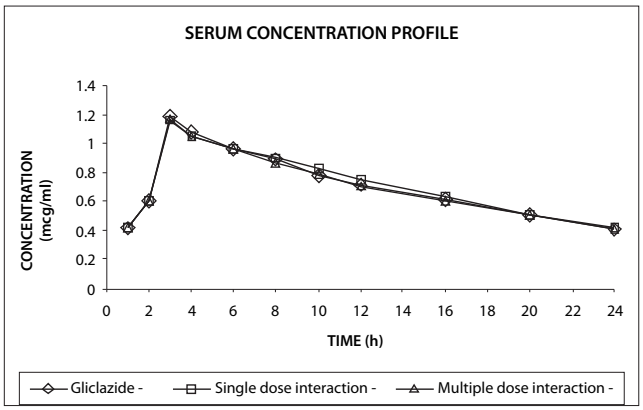

Figure 1 Serum concentration profile of gliclazide with various treatments.

(Figure 1). The various pharmacokinetic parameters were computed and subjected to statistical interference (Table 4). No significant pharmacokinetic influence of irbesartan on gliclazide was observed.

DISCUSSION

Both anti-hypertensives and oral hypoglycemic drugs are being increasingly used in many therapeutic areas. The former agents are important for controlling hypertension, heart failure and diabetic nephropathy, and are being administered increasingly at earlier stages in these conditions. The latter drugs are widely used for effecting the lowering of blood glucose. Thus, it is not unusual for patients suffering from multiple complaints to be prescribed antihypertensive drugs, together with oral hypoglycemic drugs [19]. Commonly prescribed anti-hypertensives belong to the class of angiotensin receptor blockers and angiotensin converting enzyme inhibitors. Based on the literature survey, there is a possibility of both pharmacokinetic and pharmacodynamic interactions between oral antidiabetic drug, gliclazide, and the angiotensin receptor blocker irbesartan [20, 21]. As there are no reports extant on pharmacokinetic and pharmacodynamic interactions existing between these two drugs, these studies were under taken to investigate the interactions that may be observed with these 2 drugs.

Gliclazide produced hypoglycemia in normal rats, with peak activity at the 2nd and 8th h. The maximum reduction attained at the 2nd h may be due to the simulation of initial rapid release of insulin (phase I) [22] 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). Gliclazide also increases the sensitivity of peripheral tissues to insulin, which may be the reason for the reduction at the 8th h [22]. Gliclazide is metabolized to several metabolites by hepatic cytochrome P450 3A4 and 2C9 iso enzymes, and is eliminated in urine. A part of gliclazide is eliminated through the biliary route, which involves entero hepatic circulation in rats. The reabsorption of gliclazide eliminated through the biliary route may be responsible for a second peak in its hypoglycemic effect in normal and diabetic rats. The maximum reduction in blood glucose level was observed at the 3rd h in the case of rabbits. The second peak at the 8th h was not observed in the case of rabbits, which could be due to the absence of hepatic circulation [23].

The hypoglycemic activity of irbesartan may be due to enhancement in whole body insulin sensitivity. It is reported that chronic administration of irbesartan enhanced insulin mediated glucose transport in both epitrochlearis and soleus muscle. Therefore, angiotensin II receptor antagonism either acutely or chronically improves glucose tolerance, at least in part, because of an enhancement in skeletal muscle glucose transport. It has also been stated that irbesartan potently enhances Peroxisome Proliferator-Activated Receptor γ (PPAR) activity, thereby promoting PPAR-γ dependent differentiation in adipocytes which provides a potential mechanism for the insulin sensitivity effects [24, 25]. This may be the possible reason for the pharmacodynamic potentiation of blood glucose reduction. Although the single dose interaction study did not show any potential influence of irbesartan on the blood glucose levels of gliclazide, multiple dose interaction studies revealed significant changes in blood glucose levels of gliclazide in diabetic rats and normal rabbits. This is additonal evidence of the influence of irbesartan on the blood glucose reduction potential of the anti-diabetic agent during chronic or prolonged administration. The various pharmacokinetic parameters calculated in the various treatments revealed no significant difference when treated statistically. This indicates the absence of pharmacokinetic interference of irbesartan on the blood glucose reduction potential of gliclazide.

CONCLUSION

In conclusion, on the basis of available evidence, the influence of irbesartan on the blood glucose reduction potential of gliclazide in single dose studies were not obvious, whereas a significant influence of irbesartan on the blood glucose reduction potential of gliclazide was observed during prolonged co-administration of irbesartan and gliclazide. Pharmacokinetic interference was not observed; hence, the interaction is predominately of a pharmacodynamic pattern. Although the combination was well tolerated and did not induce any hypoglycemic shock in the animals, the combination warrants careful monitoring of blood glucose levels in the case of patients on co-administration of both drugs.

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