Shivraj N. *et al*. / *International Journal of Phytopharmacology*. 4(3), 2013, 174-178.

e- ISSN 0975 – 9328
Print ISSN 2229 – 7472

International Journal of Phytopharmacology

Journal homepage: www.onlineijp.com

IJP

PHARMACODYNAMIC AND PHARMACOKINETIC DRUG INTERACTION OF GLIMEPIRIDE AND IRBESARTAN IN ANIMAL MODELS

Shivraj N*, Chandrashekhar M Sultanpur

Department of Pharmacology, Government college of Pharmacy, Bangalore, Karnataka, India.

ABSTRACT

The study was conducted to find out the influence of irbesartan on the pharmacodynamics and pharmacokinetics of glimepiride, which is widely used drug for type II diabetes. Studies were conducted in normal rats; streptozotocin induced diabetic rats and normal rabbits with oral administration of selected doses of glimepiride, irbesartan and their combination. Blood samples were collected from rats/diabetic rats by retro orbital method and marginal ear vein puncture from rabbits at regular intervals of time. All the blood samples were analyzed for glucose by GOD/POD method and serum concentration of glimepiride estimated by HPLC. Glimepiride produced significant hypoglycemia and antihyperglycemia in normal/diabetic rats and in normal rabbits. Therapeutic doses of irbesartan and in combination with glimepiride did not alter the blood glucose levels and the hypoglycemic response in normal rats/ diabetic rats and normal rabbits. There was no significant change in the pharmacokinetic parameters of glimepiride like, AUC, $T_{1/2}$, Clearance, Vdss, Vdarea, MRT, C_{max} and T_{max} when given in combination with irbesartan in normal rabbits, the studies indicates there is no pharmacokinetic and pharmacodynamic interaction. The glimepiride is metabolized by CYP 2C9 and irbesartan being metabolized by two CYP isoenzymes primarily CYP2C9 and to minor extent CYP3A4 there was no significant changes in the absorption and elimination of glimepiride by irbesartan was produced in the single dose treatment. Hence the therapy was found to be safe when given in combination and its use can be encouraged in clinical situation after assessing safety profile in chronic animal studies, healthy volunteers and diabetic patients with hypertension.

Key words: Drug interactions, Glimepiride, Irbesartan, Pharmacodynamics, Pharmacokinetics.

INTRODUCTION

The primary requirements of any individual are food, shelter, clothing and health. Several quotations indicate the importance of health, the best being "Health is wealth". Health can be defined as homeostatic condition of physical, mental and social behavior. Any change in the physiology of an individual without the involvement of infecting organism is known as disorder and with the involvement of infecting organism is known as a disease. Hence the panorama of a disorder /disease is as old as the origin of human beings and requires remedial measures in the form of medical treatment (Chandrashekhar CS, 2007).

Hyperglycemia is a chronic condition with high blood glucose levels referred to as Diabetes mellitus, is mainly due to body producing insufficient insulin and/or an inability of tissues to respond properly to insulin. The prevalence of diabetes in India is alarmingly high, World Health Organization (WHO) estimated that in 2010 there were 50.8 million people with diabetes in India and by 2030 number is expected to rise to 87 million (Wandell PE, 2005). The highest number of deaths attributable in 2010 to diabetes is expected to occur in countries with large populations 1,008,000 deaths in India, 575,000 in China, 231,000 in United States of America and 182,000 in Russian Federation and there is higher proportion of deaths in women than in men (Shaw J *et al*., 2010).

Corresponding Author

Shivraj N
Email: shivrj10@gmail.ocm

Management of diabetes mellitus involves lifestyle modification & antihyperglycemic therapy. Antihyperglycemic therapy in patients without co-morbidities involve insulin secretagogues (sulfonylureas & rapid-acting post-prandial insulin releasers), insulin sensitizers (biguanides & thiazolidinediones), glucosidase inhibitors and other new modalities like enzyme-resistant GLP-1 analogues (exendin-4), albumin-bound GLP-1 derivatives (liraglutide) and DPP-IV enzyme inhibitors (vildagliptin & sitagliptin) (Roglic G *et al*., 2005).

Hypertension is defined as a sustained increase in systolic blood pressure (SBP) of 140 mmHg or greater and/or diastolic blood pressure (DBP) of 90 mmHg or greater. The prevalence of hypertension in the adult population was estimated to be 26.4% in 2000 and is projected to be 29.2% by 2025 (De Micheli A, 2008). Hypertension significantly increases the risk of developing disorders such as coronary artery disease, stroke, arrhythmia, heart failure, abnormal renal function and many other complications associated with structural damage to the cardiovascular system. Hence the management of hypertension is very essential and it involves different approaches like life style modification and antihypertensive therapy. Antihypertensive therapy in patients without co-morbidities involves administration of different classes of drugs like diuretics, angiotensin convertase enzyme (ACE) inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, and aldosterone antagonist and rennin inhibitors to achieve desired blood pressure. Initiating treatment with two drug combination may allow blood pressure targets to be reached earlier than monotherapy (Cadman PE *et al*., 2003).

Almost 70% of adult (type 2) diabetes patients have clinical hypertension, it is estimated that prevalence of diabetes is 221 million in 2010 and it is projected to be 300 million in 2025. The reported death rate from hypertension and diabetes was 3.94 and 1.85 per 100,000 people, respectively (Chobanian A, 2003). A study carried out in 12,550 adults, it was observed that development of type 2 diabetes was almost 2.5 times more likely in persons with hypertension than in their normotensive counterparts (Sookaneknun P *et al*., 2010).

To manage BP and glucose level in hypertensive diabetics, more than two drugs are usually required. Treatment of type 2 diabetes and Renin-Angiotensin-Aldestrone System (RAAS) blockade seems to offer survival benefits to diabetics with hypertension (Gress TW *et al*., 2000). There is every possibility of concomitant administration of glimepiride and Irbesartan for the management of diabetes associated with hypertension.

Glimepiride is a second generation sulfonylureas, which is metabolized by CYP2C9 (Niemi M *et al*., 2002). It is bound to serum albumin to an extent of 99% (Balant L, 1981).

Irbesartan is an angiotensin receptor-II blocker, which is metabolized by primarily by CYP2C9 (Retone KW, 1985) and to minor extent by CYP3A4 (Husain A *et al*., 2011) it is bound to serum albumin to an extent of 90% to plasma (Zafar H, 2000).

Glimepiride & Irbesartan are metabolised by the same enzyme and are bound to same plasma proteins; hence concomitant administration of these drugs in treatment of diabetes associated with cardiovascular disorders, there is every possibility of drug-drug interaction. The information with respect to blood glucose level of above said combination of drug is scanty.

Hence the study is planned to evaluate pharmacodynamic parameters in normal rats, streptozotocin induced diabetic rats (rodent model) and pharmacodynamic & pharmacokinetic parameters in rabbits (non-rodent model). This type of studies in two dissimilar species help in predicting the mechanism of drug interactions and the results can be extrapolated to humans, which will provide information regarding rational usage of this combination in a clinical situation.

MATERIALS AND METHODS

Albino rats and rabbits of either sex obtained from Drug Testing Laboratory, Bangalore were used in the study. All animals were maintained on pellet diet supplied by venkateshwara stores, Bangalore. With 12h/12h light/dark cycle and water *ad libitium.* Animals were fasted for 18h before the experiment.

Study in normal rats

A group of six albino rats weighing between 180-250 g were administered with 2.7mg/200gm body weight of irbesartan and to another group of six albino rats glimepiride of 40µg/200gm body weight was administered orally. The same group was administered with 2.7mg/200gm body weight of irbesartan and glimepiride of 40µg/200gm body weight after the washout period of one week. Blood samples were withdrawn from retro orbital puncture at 0, 1, 2, 4, 6, 8, 12 and 24hr intervals. Blood samples were analyzed for blood glucose levels by GOD/POD method (Rani TS *et al*., 2012) using commercial kit method (span diagnostics).

Study in diabetic rats

Diabetes was induced by administration with 50mg/kg of streptozotocin intraperitonially. After 24 hours, the blood samples were collected and analyzed for blood glucose level. Rats with blood glucose levels more than200mg/dl were selected for the study. The study similar to the one conducted in normal rats was repeated in diabetic group.

Study in normal rabbits

A group of four albino rabbits weighing between 1.5 -2.5 kg were used in the study. They were administered with 10.5mg/1.5 kg body weight of irbesartan and to another group of four albino rabbits glimepiride of 560µg/1.5 kg body weight was administered orally. The same group was administered with 10.5mg/1.5 kg body weight of irbesartan and glimepiride of 560µg/1.5 kg body weight after the washout period of one week. Blood samples were withdrawn from marginal ear vein puncture at 0, 1, 2, 4, 6, 8, 12, 18 and 24hr intervals. Blood samples were analyzed for blood glucose levels by GOD/POD method using commercial kit method (span diagnostics). And estimation of serum glimepiride concentration by HPLC method. (Rani TS *et al*., 2012)

The animal experiments were approved by our institutional Animal Ethics Committee with Ref. no.DCD/GCP/IAEC/02/2011-2012 dated 17.03.2012.

Data and Statistical Analysis

Data obtained were expressed as mean ± standard error of mean (SEM). The significance was determined by student's t test using prism graphpad software. The statistical differences in the sample means were considered significant at $p<0.05$.

RESULTS

When blood samples withdrawn at 1hr interval upto 24hr were analysed, glimepiride produced peak hypoglycemic activity at 6hr in normal/diabetic rats and in normal rabbits. Therapeutic dose of irbesartan alone did not alter the normal blood glucose level and it did not alter the hypoglycemic response produced by glimepiride in combination. The same phenomenon observed in diabetic rats and normal rabbits.

In pharmacokinetic parameters, there was no change in absorption parameters of glimepiride like AUC, C_{max}, t_{max} and clearance and elimination parameters of glimepiride like $t_{1/2,}$ Vdss, Vdarea and MRT in the presence of irbesartan in normal rabbits. This indicates there is no change in the pattern of absorption and elimination of glimepiride in the presence of irbesartan which is not affecting the pharmacodynamic and pharmacokinetic effect of glimepiride.

Table 1. Mean percent blood glucose reduction before and after treatment with Irbesartan in normal rats (n=6)
Mean percent blood glucose reduction (Mean ± SEM)

Time (hr)	Irbesartan	Glimepiride	Combination
0	0	0	0
1	-0.67±0.43	7.97±0.92	7.61±1.36
2	-2.50±1.28	15.94±1.55	22.12±0.82*
4	-5.53±0.95	36.98±2.65	30.98±1.31
6	-4.11±0.80	50.06±2.27	47.92±1.08
8	-2.89±0.89	39.66±2.31	34.99±1.23*
12	-1.15±0.87	22.20±2.13	19.82±1.30
24	0.38±1.03	8.34±1.65	6.98±1.45

*Mean ± SEM; *Significant at p< 0.05, ** significant at p<0.01 & *** significant at p<0.001compared to glimepiride control*

Table 2. Mean percent blood glucose reduction before and after treatment with Irbesartan in diabetic rats (n=6)
Mean percent blood glucose reduction (Mean ± SEM)

Time (hr)	Irbesartan	Glimepiride	Combination
0	0	0	0
1	-0.54±0.18	6.76±1.05	7.00±1.64
2	-0.97±0.39	16.70±0.46	13.67±2.79
4	-1.71±0.23	34.84±0.91	27.86±2.12
6	-1.36±0.24	49.30±0.69	46.09±2.54
8	-1.02±0.32	40.50±2.61	40.76±1.34
12	-0.70±0.31	25.93±1.64	27.21±1.62
24	-0.79±0.22	15.28±1.53	15.98±1.32

*Mean±SEM; *Significant at p< 0.05, ** significant at p<0.01 & *** significant at p<0.001compared to glimepiride control*

Table 3. Mean percent blood glucose reduction before and after treatment with Irbesartan in normal rabbits (n=4)
Mean percent blood glucose reduction (Mean ± SEM)

Time (hr)	Irbesartan	Glimepiride	Combination
0	0	0	0
1	0.03±1.08	11.35±2.34	10.70±2.86
2	0.83±1.12	15.44±2.55	13.99±2.14
4	1.98±0.19	20.79±2.51	19.85±2.42
6	2.81±0.15	28.85±2.14	28.61±2.57
8	2.48±0.86	22.26±2.44	18.04±2.13
12	2.73±0.77	19.23±2.54	14.72±1.96
18	2.18±0.87	12.89±2.74	9.99±2.38
24	3.51±0.87	7.84±2.60	6.65±1.73

*Mean±SEM; *Significant at p< 0.05, ** significant at p<0.01 & *** significant at p<0.001compared to glimepiride control*

Table 4. Mean serum glimepiride levels before and after treatment with Irbesartan in normal rabbits (n=4).
Mean percent blood glucose reduction (Mean ±SEM)

Time (hr)	Glimepiride	Glimepiride + Irbesartan
0	0	0
1	685.0±50.40	639.0±90.32
2	1546.0±135.1	1473±174.5
4	2597±223.8	2260±208.4
6	4194±305.9	3749±294.8
8	2187±145.9	2070±228.4
12	1173±68.81	1192±169.6
18	526.8±76.26	477.5±124.6
24	240.8±24.23	243.5±60.99

*Mean ± SEM; *Significant at p< 0.05, ** significant at p<0.01 & *** significant at p<0.001compared to glimepiride control*

Table 5. Mean pharmacokinetic parameter of Glimepiride before and after Irbesartan administration in rabbits. (n=4)

Parameter	Glimepiride	Glimepiride + Irbesartan
AUC (0-24) (ng/ml/hr)	30628±37	32884±25
AUC (0-α) (ng/ml/hr)	32564±41	34717±28
$T_{1/2}$ (hr)	5.14±0.56	5.23±0.15
Clearance (ml/hr/kg)	0.006±0.0009	0.005±0.0004
Vdss(ml/kg)	44.35±4.47	41.93±2.511
Vdarea (ml/kg)	44.25±4.43	41.90±2.49
MRT (hr)	8.34±0.28	8.30±0.05
C_{max}(ng/ml)	3749±294.8	4194±305.9
T_{max}(hr)	6.0±0.0	6.0±0.0

*Mean ± SEM; *Significant at p< 0.05, ** significant at p<0.01 & *** significant at p<0.001compared to glimepiride contro.*

DISCUSSION

Drug interactions are usually seen in clinical practice and the mechanism of interaction are evaluated usually in animal models. We studied the influence of irbesartan on the pharmacodynamics of glimepiride in normal and diabetic rats and also in normal rabbits. Additionally pharmacokinetics of glimepiride was studied in normal rabbits. The normal rat model served to validate the same response in the actually used condition of the drug (in type II diabetes) the rabbit model is another species. It is well established that glimepiride acts by both pancreatic and extra pancreatic mechanism. The target for sulphonylureas activity is ATP sensitive K+ channels. The sulphonylureas and related drugs used in type II diabetes stimulate insulin release by closing K^+ channels, in pancreatic β-cells. They target SUR (Sulphonylureas receptor) subunit of K^+ATP channels, which exist in several isoforms expressed in different tissues, SUR1 in pancreatic β-cells, SUR 2A in cardiac muscle and SUR2B in vascular smooth muscle. the pancreatic β-cell ATP

increases when plasma glucose level rises resulting in the closure of K^+ ATP channels in the plasma membrane, allows the cells to depolarize, triggering Ca^{2+} entry and insulin release.(Kamat V *et al*., 2012)

Irbesartan is an antihypertensive drug widely used for the treatment of hypertension. The dose of irbesartan is selected by human therapeutic dose extrapolated to rats basing on the body surface area. Single dose treatment of irbesartan alone and in combination with glimepiride did not alter the blood glucose level in normal rats indicating the absence of interaction. The same pattern was observed in streptozotocin induced diabetic rats and normal rabbits. In pharmacokinetic parameters, there was no change in absorption parameters of glimepiride like AUC, C_{max}, t_{max} and clearance and also elimination parameters of glimepiride like $t_{1/2,}$ Vdss, Vdarea and MRT in the presence of irbesartan in normal rabbits. This indicates there is no change in the pattern of absorption and elimination of glimepiride in the presence of irbesartan which is not affecting the pharmacodynamics and pharmacokinetics of glimepiride. The glimepiride is metabolized by CYP 2C9 and irbesartan being metabolized by two CYP isoenzymes primarily CYP2C9 and to minor extent CYP3A4 there was no significant changes in the absorption and elimination of glimepiride by irbesartan was produced in the single dose treatment. Hence the therapy with the combination was found to be safe.

CONCLUSION

Since the combination of single dose treatment of irbesartan and glimepiride did not result in interaction in two dissimilar species, the combination may be safe in humans. Therefore, this suggests its use can be encouraged in clinical situation after assessing safety profile in chronic animal studies, healthy volunteers and diabetic patients with hypertension.

REFERENCES

Balant L. Clinical pharmacokinetics of sulphonylureas hypoglycemic drugs. *Clinical pharmacokinetics,* 6, 1961, 215-4.

Cadman PE, O'Connor DT. Pharmacogenomics of hypertension. *Current opinion in nephrology and hypertension*.12(1), 2003, 61.

Chandrashekhar CS. Studies on the influence of selected antihyperlipidemic drugs on the pharmacodynamics and pharmacokinetics of gliclazide in rats and rabbits. Ph.D. Thesis submitted to Andhra University, Visakhapatnam. 2007, 01.

Chobanian A, Bakris G, Black H, Cushman W, Green L, Izzo Jr J *et al*., National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*, 289(19), 2003, 2560–72.

De Micheli A. Italian standards for diabetes mellitus 2007: executive summary. *Acta Diabetologica,* 45(2), 2008, 107-27.

Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *New England Journal of Medicine*, 342(13), 2003, 905-12.

Husain A, Azim SM, Mitra M, Bhasin SP. A Review of pharmacological and pharmaceutical profile of irbesartan. *Pharmacophore*, 2(6), 2011, 276-286.

Kamat V, Neelam R, Pramod N, Rajendra SV. Possible occurance of interaction between fluoxetine and glimepiride in two dissimilar species. *International Journal of PhytoPharmacology,* 3(3), 2012, 304-307.

Niemi M, Cascorbi I, Timm R. Glyburide and glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. *Clin Pharmacol Ther,* 72(3), 2002, 326-32.

Rani TS, Sujatha S, Veeresham C. Pharmacokinetic and pharmacodynamic interaction of curcumin with glimepiride in normal and diabetic rats. *Pharmacog commun*, 2, 2012, 14-21.

Rentone KW. Inhibition of hepatic microsomal drug metabolism by the calcium channel blockers diltiazem and verapamil. *Biochem Pharmacol*, 34, 1985, 549-53

Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S *et al*., The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes care*, 28(9), 2005, 2130-5.

Shaw J, Sicree R, Zimmet P. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes research and clinical practice,* 87(1), 2010, 4-14.

Sookaneknun P, Saramunee K, Rattarom R, Kongsri S, Senanok R, Pinitkit P *et al*., Economic analysis of the diabetes and hypertension screening collaboration between community pharmacies and a Thai government primary care unit. *Primary Care Diabetes*, 4(3), 2010, 155-64.

Wandell PE. Quality of life of patients with diabetes mellitus. An overview of research in primary health care in the Nordic countries. *Scand J Prim Health Care*, 23, 2005, 68-74.