Original Article

Influence of Telmisartan on Pharmacodynamic and Pharmacokinetic Properties of Glimepiride-metformin Combination Using Rodent and Non-Rodent Models

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ABSTRACT

Aim: The present study was planned to evaluate the pharmacodynamic and pharmacokinetic interactions between telmisartan and glimepiride + metformin in single and multiple dose studies using rats and rabbits. **Materials and Methods:** The blood samples were collected from the rats/ rabbits from retro orbital/ marginal ear vein respectively. The serum glucose, plasma insulin and serum glimepiride were estimated at respective time intervals in all treatment groups. **Results:** The single and multiple dose treatments of telmisartan alone and combined treatment with glimiperide + metformin does not showed any significant reduction of glucose and elevated insulin levels in normal and diabetic rats and showed synergistic hypoglycemic activity by enhancing blood glucose reduction and peak insulin levels in normal rabbits. The serum glimepiride levels were found to be enhanced with telmisartan single and multiple dose treatments. There is significant increase in the pharmacokinetic parameters of glimepiride like $AUC_{0-\infty}$, $AUMC_{0-t}$, $AUMC_{0-\infty}$, $t_{1/2}$, C_{max} and MRT and there is a decrease in clearance (Cl) with single and multiple dose treatments of telmisartan. **Conclusion:** The interactions observed in rabbits (a non rodent model) but not in rats (a rodent model). Hence care must be taken while prescribing telmisartan in combination with glimipiride-metformin.

Key words: Telmisartan, Glimepiride, Metformin, Pharmacokinetics, Pharmacodynamics.

INTRODUCTION

The emerged risk factor for the mortality and morbidity of diabetes is raised in blood pressure. According to the Global Burden of Disease (GBD) 2017, higher levels of systolic blood pressure was observed globally as risk factor with mortality rate of 10.2 million and 208 million people are suffering with disabilities.[1] The age dependent hypertension was observed more in men (24.5%) than women (20%). The persistent hypertension cause increase in severity up to 7.2 fold and 37 fold increase in chances of mortality in diabetic patients.[2] The reduced systolic blood pressure upto 10 mm of Hg may control the occurrence of diabetes and related complications upto 27%, 11% myocardial infarction and 13% of microvascular complications.[3]

In general, hypertension is not associated with DM1, but the DM2 is associated with hypertension even at time of diagnosis.[4] The incidence of essential hypertension is associated with degree of obesity, elderly age and cardiovascular risk.[5] The mechanism of renin angiotensin aldosterone system and vascular sensitivity are also played a key role in essential hypertension.[6] The hyperinsulinemia and insulin sensitivity are the leading cause of diabetes associated hypertension, because insulin promotes the sodium retention and activity of sympathetic system.[7] Such conditions were controlled with recommended combined

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drug therapies. The standard care of type 2 diabetes includes aspirin, antihypertensive agent and anticholesteremic agents according to the American Diabetes Association (ADS) 2015.[8] An increasing number of simultaneous medications increase the risk of a patient experiencing adverse drug reactions or drug interactions with diabetics.[9]

Polypharmacy is a place of concern for the elderly for a number of reasons. Older people are at greater risk of developing harmful effects due to the physical changes and weight loss associated with aging; this risk is greatly increased due to the repeated drug administration of multiple medications for the concomitant disease.[10] The chances of drug-drug interactions are found to be more in the practice of polypharmacy. Hence, it needs to identify the potential drug-drug interaction studies in patients in multidrug use.[11] Several epidemiological studies indicating that the use of renin angiotensin system blockers (ARB's) was found to more and efficient in type 2 diabetics.[12] Based on the need, the current study was designed to evaluate the influence of widely prescribing ARB, telmisartan on pharmacodynamic and pharmacokinetic aspects of commonly prescribed combination of Glimepiride (Glim) with Metformin (Met) using rodent and non rodent models.

MATERIALS AND METHODS

Drugs and Chemicals

APIs were provided as gift samples by Apotex Research Pvt Ltd., Bangalore for the purpose of evaluation in our research work. All chemicals used were of analytical grade.

Experimental Animals

Albino rats and rabbits procured from Sri. Venkateswara Enterprises, Bangalore, India were used in the study. They were maintained under standard laboratory conditions at ambient temperature of 25±2°C and 50±15% relative humidity with 12 h light/12 h dark cycle. They were provided with a standard pellet diet (Hindustan Lever Ltd., Bangalore, India) and water *ad libitum*. All animal procedures have been approved by the Institutional Animal Ethical Committee (No: VIPS/1442/15-16, Dated: 14.01.2016) in accordance with animal experimentation and care guidelines provided by IAEC/CPCSEA.

Study in normal rats[13,14]

A group of six albino rats weighing between 250–300 g were injected with glimepiride (0.09 mg / kg) + metformin (45 mg / kg) orally. The same group was given 1.8 mg / kg body weight of oral telmisartan after a one-week washing period. The same group was also given 1.8 mg / kg body weight telmisartan 30 min before glimepiride (0.09 mg / kg) + metformin (45 mg / kg), after a continuous wash period of 1 week. Blood samples were withdrawn from retro orbital plexus at 0, 1, 2, 4, 6, 8, 10, 12, 14 and 16 h intervals.

Study in diabetic rats[15-17]

Diabetes is caused by administration of alloxan monohydrate in two doses 100 mg and 50mg / kg intraperitoneal body weight for two days in a row. A group of 6 rats with a blood glucose level above 250 mg / dL was selected from the study. The study was similar to that of normal rats repeated in a diabetic group.[13,14]

Study in normal rabbits[14]

A group of albino rabbits weighing between 1.38 to 1.7kg was given Glimepiride + Metformin (0.07mg + 35 mg / 1.5 kg) orally. The same group was given 1.4mg / 1.5 kg of telmisartan in a single treatment and in multiple doses. In addition to all medical procedures blood samples are collected through marginal ear vein. Blood samples were collected at 0 (predose), 1, 2, 3, 4, 6, 8, 12, 18 and 24 h after drug administration. Blood samples are collected in clean centrifuge tubes.

Blood samples were analyzed for blood glucose by using GOD/POD method,[18] Insulin by using Chemiluminescence assay[19] and estimation of serum Glimepiride by using HPLC method.[20,21]

Data and Statistical Analysis

Results were represented using mean and standard error mean. Two way ANOVA, Bonferroni post test was used to give significance.

RESULTS AND DISCUSSION

Since high blood pressure is often associated with insulin resistance and glucose tolerance disorders, the metabolic effect of anti-hypertensive agents is considered an important consideration for first-line treatment options. The chances of combining antidiabetic and antihypertensive treatments are metformin and glimiperide with ARBs because, in diabetic hypertensives, ACEIs are the first line drugs in high blood pressure management, and can be replaced by ARBs if patients are intolerant. Recent research suggests that ARBs should be equal to ACEI in reducing both complex hypertension and diabetic complications.[11]

The commonly prescribed ARBs in diabetic hypertension are losartan, candesartan, irbesartan, olmesartan and telmisartan. Among these ARBs, Telmisartan shown to

have normoglycemic activity by reducing fasting glucose and insulin levels and improvement in homeostatic model assessment.[23,24] It is reported that there is a possibility of pharmacodynamic drug interaction between telmisartan with antidiabetic agents such as metformin and glimiperide.[25]

Hence, the study was to evaluate the pharmacodynamic and pharmacokinetic influence of telmisartan on combination of glimepiride + metformin using rodent and non rodent models to represent healthy and diabetic status.

In normal rats, glimepiride (0.09 mg/ kg) + metformin (45 mg/ kg) alone showed 36.89% blood glucose reduction at 4 h. Telmisartan at a dose of 1.8 mg/ kg body weight found to have 12.82% reduction in blood glucose levels at 2 h. In combination, telmisartan does not influence the hypoglycemic activity produced by glimepiride + metformin with single dose 36.03% and multiple dose 36.67% treatments (Figure 1). The insulin levels at peak reduction in blood glucose levels were also found to be not altered with single and multiple dose treatments at 4 h significantly (Table 1). During single drug administration of Telmisartan did not produce hypoglycemia and even in not influence the blood levels of glimepiride + metformin both in single and multiple dose treatments indicates there is no existence of interaction.

In diabetic rats, glimepiride (0.09 mg/ kg) + metformin (45 mg/ kg) showed 41.96% blood glucose reduction at 4 h and telmisartan at 1.8 mg/ kg does showed 17.44% blood glucose reduction at 2 h. In combination, the selected dose of telmisartan does not influence the antihyperglycemic activity produced by glimepiride + metformin with single dose 41.69% and multiple dose 43.26% treatments (Figure 2). The insulin levels were not found to be enhanced at peak reduction of blood glucose with glimepiride + metformin at 4 h compared to 0 h (Table 2). This indicates there is no existence of

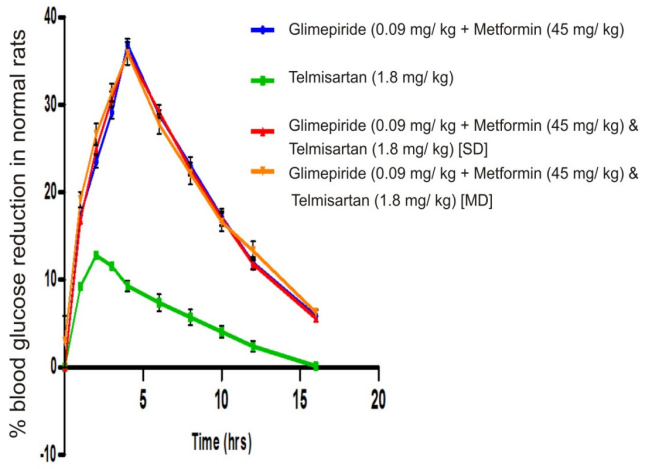

Figure 1: Average percent blood glucose reduction after administration of glimepiride + metformin, telmisartan and in combination in single and multiple dose treatement in normal rats.

Table 1: Mean Serum insulin (µIU/mL) with mean serum glucose level (mg/dL) in Glim+Met, Telmisartan and single and multiple dose treatment Glim +Met+Telmisartan in normal rats.

Groups	Time (hrs)	Mean serum glucose levels (mg/dL)	Serum Insulin (µIU/mL)
Glimepiride	0.00	79.50±0.84	9.97±0.28
	4.00	50.17±0.66	10.45±0.17
Telmisartan	2.00	69.83±2.07	9.91±0.30
Glimepiride + Telmisartan (SD)	4.00	55.00±0.69	10.06±0.14
Glimepiride + Telmisartan (MD)	4.00	55.17±1.68	10.12±0.18

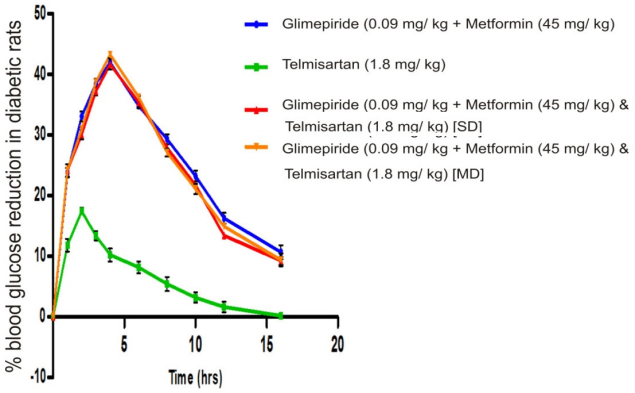

Figure 2: Average percent blood glucose reduction after administration of glimepiride + metformin, telmisartan and in combination in single and multiple dose treatement in diabetic rats.

Table 2: Mean Serum insulin (µIU/mL) with mean serum glucose level (mg/dL) in Glim+Met, Telmisartan and single and multiple dose treatment Glim +Met+Telmisartan in diabetic rats.

Groups	Time (hrs)	Mean serum glucose levels (mg/dL)	Serum Insulin (µIU/mL)
Glimepiride	0.00	259.50±5.58	8.03±0.18
	4.00	150.50±2.62	10.41±0.31
Telmisartan	2.00	208.50±7.25	9.02±0.17
Glimepiride+ Telmisartan (SD)	4.00	152.50±4.65	10.17±0.17
Glimepiride + Telmisartan (MD)	4.00	146.50±3.38	10.53±0.22

pharmacodynamic interaction between telmisartan and glimepiride + metformin in diabetic rats.

In normal rabbits, glimepiride (0.07 mg/ 1.5kg) + metformin (35 mg/ 1.5 kg) showed 35.51% blood glucose reduction at 4 h. The selected dose of telmisartan at 1.4mg/ 1.5 kg showed 42.30% blood glucose reduction at 4 h. Telmisartan found to produce significant enhancement of hypoglycemic activity of glimepiride + metformin with single 42.30% and multiple dose 43.25% treatments (Figure 3). The insulin levels of glimepiride + metformin were found to be elevated at 4 h compared to that of 0 h (Table 3). The telmisartan in single and multiple dose treatments enhanced the hypoglycemic activity in rabbits. The serum insulin levels were found to be enhanced with single dose and multiple dose treatments of telmisartan respective to the blood glucose levels. The serum glimepiride levels were found to be enhanced significantly with single and multiple dose treatments of telmisartan from 1 h to 24 h at peak level at 4 h (Figure 4). There is significant increase in the pharmacokinetic parameters of glimepiride like $AUMC_{0-t}$, $AUMC_{0-\infty}$, and MRT and there is decrease in clearance (Cl) with single and multiple dose treatment of telmisartan. The enhancement in the serum glimepiride levels and pharmacokinetic parameters indicate that there is a pharmacokinetic interaction between telmisartan and glimepiride.

Table 3: Mean serum glucose level (mg/dL) and mean Serum insulin (µIU/mL) in Glimepiride + Metformin, Telmisartan alone and single and multiple dose treatments of Telmisartan with Glimepiride + Metformin in normal rabbits.

Groups	Time (h)	Mean serum glucose levels (mg/dL)	Serum Insulin (µIU/mL)
Glim+Met	0.00	94.60±1.94	9.02±0.05
	4.00	61.00±1.26	10.11±0.20
Telmisartan	2.00	82.20±2.96	8.82±0.15
Glim+Met+ Telmisartan (SD)	4.00	57.40±1.63	10.19±0.26
Glim + Met+ Telmisartan (MD)	4.00	52.80±1.80	10.37±0.20

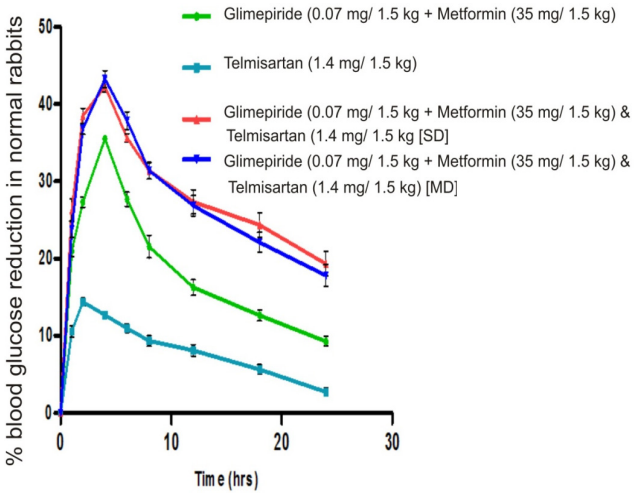

Figure 3: Average percent blood glucose reduction after administration of glimepiride + metformin, telmisartan and in combination in single and multiple dose treatement in normal rabbits.

Table 4: Pharmacokinetic profile of Glimepiride alone and Glimepiride with single and multiple doses of Telmisartan in normal rabbits.

Pharmacokinetic parameter	Mean Pharmacokinetic Parameters (Mean±SEM)		
	Glimepiride alone	Glimepiride + Telmisartan (SD)	Glimepiride + Telmisartan (MD)
AUC $_{0-24}$ (µg/ml/h)	133.62±4.19	151.46±1.65*	152.65±4.66*
AUC $_{0-\alpha}$ (µg/ml/h)	143.56±5.63	165.92±2.65*	168.63±6.87*
AUMC $_{0-24}$ (µg/ml/h*h)	1094.19±84.75	1351.27±68.25*	1421.82±79.76*
AUMC $_{0-\alpha}$ (µg/ml/h*h)	1423.25±138.59	1844.93±156.08*	1971.36±171.35*
Ka (h^{-1})	1.15±0.00	1.15±0.00 ^{ns}	1.15±0.00 ^{ns}
$T_{1/2}$ (h)	6.14±0.27	6.78±0.38 ^{ns}	7.02±0.29 ^{ns}
Vd_{SS} (ml/kg)	1451.49±43.66	1432.68±97.59 ^{ns}	1486.23±46.02 ^{ns}
Cl (ml/h/kg)	163.52±6.31	140.77±2.23*	139.27±5.50*
Tmax(h)	4.00±0.00	4.00±0.00 ^{ns}	4.00±0.00 ^{ns}
Cmax (µg/ml)	12.29±0.25	13.08±0.35 ^{ns}	12.63±0.22 ^{ns}
MRT (h)	9.83±0.58	11.08±0.80 *	11.61±0.58*

$p>0.05$ ^{ns}, $p<0.05$* Significance followed by unpaired t-test

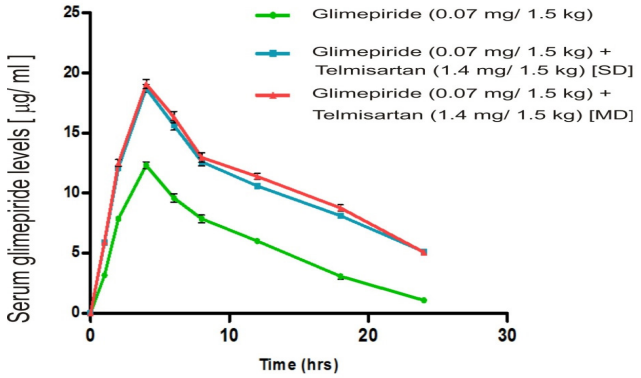

Figure 4: Serum glimepride levels (µg/ ml) alone and glimepiride with telmisartan in single and multiple dose treatment in normal rabbits.

The observed pharmacokinetic interactions in rabbits might be due to displacement of glimepiride from the protein binding sites by telmisartan as both the drugs are highly protein bound in nature.[26] Such interactions are not observed in rats. The present study concludes that the interactions observed in rabbits (a non rodent model) but not in rats (a rodent model). Hence care must be taken while prescribing telmisartan in combination with glimepiride-metformin.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

$AUC_{0-\infty}$: Area under the concentration time-curves from time zero to infinity; **$AUMC_{0-t}$:** Area under the concentration-time curve from time zero to the last measurable concentration using linear-log. trapezoidal rule; **$AUMC_{0-\infty}$:** Area under first moment curve; **$t_{1/2}$:** Pharmacokinetic term half-life; **C_{max}:** Maximum (or peak) of serum concentration; **MRT:** Mean residence time; **Cl:** Clearance; **DM1:** Diabetes Mellitus Type 1; **DM2:** Diabetes Mellitus Type 2; **APIs:** Active Pharmaceutical Ingredients; **VIPS:** Visveswarapura Institute of Pharmaceutical Sciences; **IAEC:** Institutional Animal Ethics Committee; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **Mg:** Milligram; **Kg:** Kilogram; **H:** Hour; **dL:** Decilitre; **GOD/POD:** Glucose oxidase-peroxidase; **ELISA:** Enzyme-linked immunosorbent assay; **HPLC:** High performance liquid chromatography; **ANOVA:** Analysis of variance; **ACEIs:** Angiotensin-converting enzyme inhibitors; **SD:** Single dose; **MD:** Multiple dose; **ml:** Milli litre; **µIU:** Milli-international units; **SEM:** Standard error of measurement; **°C:** Degree Centigrade; **µg:** Microgram; **µm:** Micrometer; **Ka:** Absorption rate constant; **Vdss:** volumes of distribution are commonly calculated by the steady-state; **C_{max}:** Maximum concentration; **T_{max}:** Time at which the Cmax.

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PICTORIAL ABSTRACT

About Authors

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SUMMARY

The objective of the present study is to evaluate the pharmacodynamic and pharmacokinetic interactions between telmisartan and glimepiride + metformin in single and multiple dose studies using normal and alloxan induced diabetic rats and normal rabbits. Blood samples were analyzed for blood glucose by GOD/POD method, insulin by ELISA, serum glimepiride levels by HPLC method at pre-determined time intervals. The single and multiple dose treatments of telmisartan alone and combined treatment with glimiperide + metformin does not showed any significant reduction of glucose and elevated insulin levels in normal and diabetic rats and showed synergistic hypoglycemic activity by enhancing blood glucose reduction and peak insulin levels in normal rabbits. The serum glimepiride levels were found to be enhanced with telmisartan single and multiple dose treatments. There is significant increase in the pharmacokinetic parameters of glimepiride like $AUC_{0-\infty}$, $AUMC_{0-t}$, $AUMC_{0-\infty}$, $t_{1/2}$, C_{max} and MRT and there is a decrease in clearance (Cl) with single and multiple dose treatments of telmisartan. The interactions observed in rabbits, but not in rats. Hence, care must be taken by physicians while prescribing telmisartan with glimipiride-metformin combination.

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