Research Article www.pharmaresearchlibrary.com/ajmps **ISSN: 2348-0165**

Asian Journal of Medical and Pharmaceutical Sciences

Pharmacodynamic Drug Interaction of Anti-Hypertensive Drug Combination Metoprolol and Telmisartan on Combined Anti-diabetic Effect of Glimepiride and Metformin in Normal and Streptozotocin Induced Diabetic Rats

B. Kishore Kumar Reddy[1]*, K. Mohan[1], C. Hari Kumar[2], Dr. Hindustan Abdul Ahad[3], B. Mohammed Ishaq[3]

[1]PG Department of Pharmacology, College of Pharmaceutical Sciences, Sri Krishnadevaraya University, Anantapur–515001, A.P. India.
[2]Department of Pharmacology, Vasavi College of Pharmacy, Bhakarapeta, Kadapa, A.P. India.
[3]Balaji College of Pharmacy, Anantapur–515001, A.P. India.
Received: 10 March 2014, Accepted: 30 May 2014, Published Online: 19 June 2014

Abstract

Polytherapy is a useful tool for treating coexistent diseases, but drug combination may reduce efficacy and/or favor the appearance of adverse reactions with different degrees of severity. A Combination of Metoprolol [MTP] with Telmisartan [TLS] are commonly used in the treatment of hypertension in diabetic patient under the therapy of Glimepiride [GLP] and Metformin [MTF]. Literature showed that risk of retinopathy and cardiovascular disease are more in diabetic hypertensive patients, which may cause morbidity and mortality. Therefore present study is aimed to investigate the safety, reliability of Combination of Metoprolol with Telmisartan on the combined anti-diabetic effect of Glimepiride and Metformin and possible drug interaction with the later combination when they were administered as combination treatment. The study was conducted on healthy and streptozotocin induced diabetic rats. The hypoglycemic effects of Combination of Metoprolol with Telmisartan alone and in combination were tested. The results obtained shows that Metoprolol with Telmisartan combination repeated dose treatment has influence the blood glucose levels in healthy and diabetic rats. They have hypoglycemic property. Therefore it was further suggested that readjustment of dose and frequency of administration of oral anti-diabetic agents may be made when they are used simultaneously with Metoprolol and Telmisartan.

Keywords: Metoprolol, telmisartan, antidiabetic, glimepride, metformin, streptozotocin, antihypertensive.

Contents

***Corresponding author**
B. Kishore Kumar Reddy
Department of pharmacology,
College of Pharmaceutical Sciences
Sri Krishnadevaraya University
Anantapur–515001, A.P. India.
Manuscript ID: AJMPS2076

PAPER QR-CODE

1. Introduction

New drugs, new indications, and new interactions appear daily, and *drug-drug interactions* are thus an everyday issue in medical practice [1]. Irrational use of medicines is a major public health problem worldwide. According to estimates, incorrect prescription leads to costs involving 50 to 70% of government funds earmarked for drugs [2]. Meanwhile, when used correctly, medicines are the most cost-effective therapeutic resource [3].

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by rise in blood glucose level known as hyperglycemia. DM is mainly of two types, Type I and Type II. Type I or Insulin dependent diabetes mellitus (IDDM) is due to lack of synthesis of insulin in the β cells of islets of Langerhans of pancreas, whereas Type II or Non-Insulin Dependent Diabetes Mellitus (NIDDM) is due to lack of release of insulin from the β cells of islets of Langerhans of pancreas however Type II is common than Type I. According to review estimations, approximately 215 million people all over the world suffer from diabetes among which 80-90% belongs to Type-II diabetes [4]. A number of Type II diabetic people are expected to increase because of modern life styles with high caloric diet and low energy expenditure leading to obesity and also due to medical advances that extend life span [5-7]. Beta blockers are often used as first line therapy in patients with hypertension including those with diabetes mellitus.The rise in plasma adrenaline and other counter-regulatory hormones during hypoglycemia was enhanced by beta adrenoceptor blockade. Potential mechanisms by which beta blockers may contribute to the development of diabetes include weight gain, alteration of the beta-receptor mediated release of insulin from pancreatic βcells. Propranolol is a non-selective beta-adrenergic receptor blocking agent commonly used in the treatment of hypertension. [8]

Several studies in recent years have shown a strong correlation between hypertension and such clinical diseases as diabetes mellitus. Patients with diabetes showed an increased risk of not only hypertension but also with many number of other complications. And those with diabetes and hypertension appear to have a higher risk of complications, as well as more difficult blood glucose control. Evidence also indicates that the reverse may occur, namely hypertension increases the risk of diabetes. Due to the high incidence of simultaneous hypertension and diabetes, it is common to find patients that use antihypertensive and glucose lowering drugs concurrently. This Polytherapy requires increased knowledge of these drug classes, particularly in relation to drug-drug interactions. “Due to the pathophysiological characteristics of these clinical entities and the complexity and narrow therapeutic index of these drugs, severe complications can be triggered by their interactions if they are selected or managed inadequately” [9]. Therefore, because of the possibility of the utilization of the combination of Glimepride with Metformin in chronic diabetes, together with combination of Metoprolol with Telmisartan, the present study was undertaken to find the effectiveness of a combination therapy which has clinical significance.

2. Materials and Method

Drugs and Chemicals:

Pure drug samples of TLS, MTP and MTF were obtained as a gift sample from Aurobindo, Hyderabad and GLP from Sun Pharmaceuticals Ltd, Mumbai, India. Streptozotocin was purchased from Otto Kemi, Mumbai, India. The glucose estimation kits were obtained from Excel diagnostics Pvt. Ltd, Hyderabad, India. Sodium carboxy methylcellulose was purchased from SD Fine Chem., Mumbai. All the other chemicals used were analytical grade.

Animals:

Study was conducted on healthy and diabetic rats (Wistar strain) of either sex; weighing 150-200 g. All the animals were housed in polypropylene cages. Animals were housed under standard conditions (temperature of 28±2^{o}C and 45±2% relative humidity) with. Rats were fed with standard animal pellet diet and water *ad libitum*. The animals were randomly distributed into 4 groups of 6 animals each. The study was conducted with the prior permission from Institutional Animal Ethics Committee (IAEC) (Approval No. SKU/IEAC/007/14) of College of Pharmaceutical Sciences, Sri Krishnadevaraya University, Anantapur, A.P. India. Studies were performed in accordance with the CPCSEA guidelines (Regd no.516/01/A/CPCSEA).

Induction of diabetes in rats:

Diabetes was induced by single intra peritoneal injection of freshly prepared solution of STZ at the dose of 60mg/kg in normal saline (pH 5.5) to the overnight fasted rats. After 3 days of STZ induction, the animals having blood glucose levels between 250–300 mg/dl were selected for the study.

Study procedure:

Effect of MTP+TLS combination was tested anti diabetic effect of GLP+MTF on healthy and STZ induced diabetic rats. Diabetes was induced to a group of animals by injecting 60 mg/kg Streptozotocin by i.p. route in normal saline (pH 5.5). Blood glucose level was monitored periodically and hypoglycemic rats after 10-14 days used for the study. Overnight fasted normal and diabetic rat were used for the study. The changes in blood glucose level were observed during the study. Blood samples were collected from the tail vein at time intervals after drug administration and glucose levels were estimated by using Blood Glucose Meter (One touch horizon), which is compared with fasting

blood sugar level. Effect of MTP+TLS on anti-diabetic effect of GLP+MTF were tested after administration of single dose in animals, whereas the influence of repeated treatment of MTP+TLS for seven days on the anti-diabetic effect of GLP+MTF was studied.

Data and Statistical analysis:

Data was expressed as Mean ± Standard Error Mean (SEM). The significance was determined by applying One-way ANNOVA followed by Dunnett's Test.

3. Results and Discussion

In the present study the effect of Metoprolol+ Telmisartan was assessed. It was evident from results (Table 1) obtained that, treatment of Metoprolol +Telmisartan has no significant influence on the blood glucose levels in healthy albino rats. This indicates that Metoprolol +Telmisartan does not possess any hypoglycemic effect.

Table 1:BloodGlucoseLevels after the administration of Metoprolol +Telmisartan in healthy Albino Rats

	Percentage blood glucose reduction (mean ± SEM) Blood glucose levels with repeated dose treatment of Metoprolol +Telmisartan in normal rats.		
Time(h)	5mg/kg	10mg/kg	15mg/kg
Fasting	0.00±0.00	0.00±0.00	0.00±0.00
0.5	2.88±0.94	4.22±0.85	6.25±0.87
1.0	7.68±0.79	9.32±1.07	11.28±0.66
2.0	11.29±0.74	12.58±0.93	18.37±1.31
4.0	20.84±0.83	24.85±2.27	26.94±1.54
6.0	25.50±1.34	31.22±1.79	36.26±0.99
8.0	21.54±0.80	25.12±2.40	28.19±1.33
12.0	19.5±0.66	22.02±2.48	26.03±1.26
18.0	11.37±2.21	13.81±2.24	19.12±1.40
24.0	6.87±1.13	8.01±1.36	10.99±0.86

All values were expressed as mean ± S.D; Number of trials (n=6).

The effect of Metformin + glimepiride (10mg/kg) was assessed. It is evident from the Table 2 that, treatment of Metformin + glimepiride (10mg/kg) has significant influence on the blood glucose levels in healthy albino rats. This indicates that Metformin + glimepiride has shown hypoglycemic effect.

Table 2. Blood Glucose Levels after the administration of Metformin + glimepiride in healthy Albino Rats

Time(h)	**Percentage blood glucose reduction (mean ± SEM) Effect of repeated dose treatment of Amlodipine + Telmisartan on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in normal rats.**		
	5mg/kg	**10mg/kg**	**15mg/kg**
Fasting	0.00±0.00	0.00±0.00	0.00±0.00
0.5	1.42±0.15	6.39±0.37	4.96±0.85
1.0	3.24±0.23	9.79±1.00	11.17±1.27
2.0	5.56±0.52	13.52±0.74	15.37±1.24
4.0	8.42±0.62	15.84±0.87	19.51±0.91
6.0	10.80±0.57	30.85±0.27	33.51±0.26
8.0	9.67±0.74	23.41±0.18	24.45±0.36
12.0	8.31±0.73	19.39±0.20	20.73±0.22
18.0	7.91±0.73	18.49±0.20	18.73±0.22
24.0	7.01±0.88	16.47±0.23	16.24±1.17

All values were expressed as mean ± S.D , Number of trials (n=6).

The effect of repeated dose treatment of Metoprolol + Telmisartan was assessed. It is evident from the Table.3 that, treatment of Metoprolol + Telmisartan (5, 10&15mg/kg) has influence on the blood glucose levels in healthy albino rats.

Table 3. Blood glucose levels with repeated dose treatment of Metoprolol+Telmisartan in healthy Albino rats.

Time(h)	Percentage blood glucose reduction (mean ± SEM) Effect of repeated dose treatment of Metoprolol+ Telmisartan on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in normal rats.		
	5mg/kg	10mg/kg	15mg/kg
Fasting	0.00±0.00000	0.00±0.00	0.00±0.00
0.5	7.9±0.34	8.90±0.69	8.48±1.23
1.0	15.04±0.90	19.19±1.24	21.39±1.45
2.0	23.65±1.40	28.69±1.59	30.75±1.59
4.0	33.59±1.24	38.13±1.96	39.52±2.11
6.0	47.41±1.66	49.42±1.56	50.17±0.98
8.0	32.09±2.03	35.08±1.95	35.94±2.02
12.0	28.08±2.05	28.36±2.47	29.53±2.41
18.0	20.21±1.97	25.04±2.68	26.09±2.47
24.0	15.92±1.13	19.33±2.69	20.45±2.48

All values were expressed as mean ± S.D; Number of trials (n=6)

The effect of repeated dose treatment of Metoprolol + Telmisartan was assessed. It is evident from the Table 4that,treatmentofMetoprolol+Telmisartan (5, 10&15mg/kg)has influence on the blood glucose levels in diabetic albino rats.

Table 4. Blood glucose levels with repeated dose treatment of Metoprolol + Telmisartan in diabetic rats.

Time(h)	Percentage blood glucose reduction (mean ± SEM) Blood glucose levels with repeated dose treatment of Metoprolol + Telmisartanin diabetic rats.		
	5mg/kg	10mg/kg	15mg/kg
Fasting	0.00±0.00	0.00±0.00	0.00±0.00
0.5	2.43±0.20	3.09±0.45	4.24±0.88
1.0	7.24±0.73	9.89±1.49	11.44±1.40
2.0	12.04±0.56	14.91±1.46	16.23±1.09
4.0	20.57±0.38	21.39±1.96	23.70±1.20
6.0	26.94±0.69	32.05±1.15	37.38±0.62
8.0	22.92±0.51	24.40±0.40	25.34±0.91
12.0	18.37±1.07	20.06±0.57	22.02±0.67
18.0	14.15±0.63	15.39±0.70	17.17±1.51
24.0	8.65±0.90	8.82±1.32	10.27±0.89

All values were expressed as mean ± S.D; Number of trials (n=6)

The effect of repeated dose treatment of Metoprolol + Telmisartan and on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in healthy Albino rats was assessed. It is evident from the Table.5 that,
treatment has influence on the blood glucose levels in diabetic albino rats.

Table 5. Effect of repeated dose treatment of Metoprolol + Telmisartan on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in diabetic rats.

Time(h)	Percentage blood glucose reduction (mean ± SEM) Effect of repeated dose treatment of Metoprolol + Telmisartan on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in diabetic rats.		
	5mg/kg	10mg/kg	15mg/kg
Fasting	0.00±0.00	0.00±0.00	0.00±0.00
0.5	8.19±0.46	9.04±1.61	9.91±0.91
1.0	17.33±0.84	18.07±0.76	19.62±0.98
2.0	26.23±0.61	27.68±1.79	28.15±0.60
4.0	39.88±1.20	41.04±1.08	42.51±1.14
6.0	52.21±0.89	55.06±0.26	61.78±0.81

8.0	42.12±1.02	43.00±0.84	44.22±0.50
12.0	38.32±0.40	39.01±0.74	39.19±0.59
18.0	27.13±0.76	27.45±0.66	28.80±0.84
24.0	20.84±1.14	22.46±0.97	23.60±0.79

All values were expressed as mean ± S.D; Number of trials (n=6)

It was observed that single dose of Metoprolol + Telmisartan (5,10&15mg/kg) has failed to influence the blood glucose indicating Metoprolol + Telmisartan does not possess any hypoglycemic activity in rats. Indicating that the possible interactions with antihypertensive agents is not pharmacodynamics type. Influence of Metformin + Glimepiride on blood glucose levels in diabetic rats was evaluated. It was observed the dose of Metformin + Glimepiride (10mg/kg) has influence the blood glucose maximum 45mg/dl. In all the phases ripped treatment antihypertensive drugs show drug interactions. The Metformin + glimepiride (10 mg/kg) it show the redaction of blood glucose levels max 52mg/dl at 5mg dose, 55mg/dl at 10mg dose, 61mg/dl at 15mg dose of Metoprolol + Telmisartan.

4. Conclusion

Metoprolol+Telmisartan single dose treatment has not influenced the blood glucose levels in healthy albino rats and diabetic rats. Whereas Metoprolol+Telmisartan ripped dose treatment has influence the blood glucose levels in healthy albino rats and diabetic rats. This combination has hypoglycemic property. It may be concluded that monitoring of blood glucose levels is essential during concomitant use of Metoprolol + Telmisartan with Metformin + Glimepiride. Therefore it is further suggested that readjustment of dose and frequency of administration of oral anti-diabetic agents may be made when they are used simultaneously with Metoprolol+Telmisartan. We would like to place on record that the present study is carried out in healthy albino rats and diabetic rats. Therefore we suggest that similar study should be conducted in healthy volunteers and diabetic patients to confirm the obtained results. It is further required to establish the influence of Metoprolol + Telmisartan pre-treatment on the pharmacokinetic parameters of oral antidiabetic agents in human volunteers.

5. Acknowledgement

The authors are grateful to the management of SK University, Anantapur, AP for providing all facilities to conduct the experimental work.

6. References

1. Marcolin MA, Cantarelli MG, Garcia-Junior M. Drug interactions among clinical and psychiatric drugs. Rev PsiquiatrClin (São Paulo), **2004**, 31: 70-81.
2. Marin N, Luiza VL, Osório-de-Castro CGS, Machado- dos-Santos S. Assistência farmaceutica paragerent esmunicipais. Rio de Janeiro: Organizaçao Pan-Americana da Saude/Organização Mundial da Saúde; 2003.
3. McIsaac W, Naylor CD, Anderson GM, O'Brien BJ. Reflections on a month in the life of the Ontario Drug Benefit Plan. Can Med Assoc J, **1994**,150: 473-7.
4. Hussain, A., Claussen, B., Ramachandran, A. & Williams, R. Prevention of type 2 Fdiabetes: A review. Diabetes Res ClinPract (**2006**).
5. Aude, Y.W., Mego, P. & Mehta, J.L. Metabolic syndrome: dietary interventions. CurrOpinCardiol., **2004**, 19: 473-9.
6. Jacobs-van der Bruggen, M.A. et al. Lifestyle Interventions Are Cost-Effective in People with Different Levels of Diabetes Risk: Results from a modeling study. Diabetes Care, **2007**, 30:128-34.
7. Hindustan Abdul Ahad, Formulation and in vitro Evaluation Glimepiride and ParecoxibMucoadhesive Tablets for diabetics associated with pain and inflammation, Der Pharmacia Sinica, **2011**, 2 (2): 101-109
8. B. Parameshappa et.al., A study on drug-drug interaction between anti-hypertensive drug(propranolol) and anti-diabetic drug (glipizide), *Scholars Research Library, Annals of Biological Research*, **2010**, 1 (3): 35-40.
9. Sucar DD. Interaçãomedicamentosa de venlafaxine com captopril. Rev Bras Psiquiatr, **2000**, 22: 134-7.