Research Article **ISSN: 2347–8330**

Journal of Pharmaceutical and Biological Research
Online at ***www.pharmaresearchlibrary.com/jpbr***
JPBR, 2014, Vol.2(1): 63-68

A Study on Drug-Drug Interaction between Anti-Hypertensive Drug Combination Amlodipine and Telmisartan on Anti-Diabetic Effect of Glimepiride and Metformin in Normal and Streptozotocin Induced Diabetic Rats

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Received: 11 April 2014, Accepted: 24 May 2014, Published Online: 21 June 2014

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Manuscript ID: JPBR2075

PAPER QR-CODE

Abstract

The aims of this study was to investigate the prevalence and to describe the most frequent potential interactions between antihypertensive drug combination, Amlodipine (AMD) and Telmisartan (TLS) on anti-diabetic effect of Glimepiride (GLP) and Metformin (MTF) combination. Study was conducted in normal rats and Streptozotocin (STZ) induced diabetic rats with oral administration of selected doses of antihypertensive drug combination of AMD and TLS, and antidiabetic drug combination of GLP and MTF with adequate wash out periods in between treatments. Blood samples were collected from rats at regular intervals of time and were analyzed for blood glucose. Amlodipine 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 Amlodipine and Telmisartan.

Keywords: Amlodipine, telmisartan, anti-diabetic, glimepiride, metformin, Streptozotocin, antihypertensive.

1. 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]. For many years, pharmacological stimulation of insulin secretion by sulfonylurea drugs has been a tool in the treatment of diabetic patients [5-7].

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[8]. 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 [9].

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" [10].

Numerous studies on medication errors, including drug-drug interactions, are currently underway worldwide, analyzing the medication systems in various hospitals and systematically assessing the errors. A hospital study by Cassiani *et al.* [11] suggests that factors contributing to medication errors include lack of concern by health staff towards the treatment plan adopted by prescribers. The authors found a striking lack of drug information centers and revision of medical prescriptions by pharmacists and nurses to evaluate the treatment, excessive doses, and drug-drug interactions [11]. Wiltink [12] highlights the pharmacist's importance in controlling and evaluating the prescribed drugs, since interactions pose a permanent risk that deserves investigation.

Among the anti-diabetic drug combinations, Glimepiride (GLP) and Metformin (MTF) is the drug of choice owing to its various haemobiological effects [13-15]. A combination of Amlodipine (AMD) and Telmisartan (TLS) is widely used in the management of hypertension, and reportedly influences blood glucose levels and insulin secretion. Therefore, because of the possibility of their utilization in chronic diabetes, together with GLP and MTF, the present study was undertaken to find the effectiveness of a combination therapy on normal healthy and Streptozotocin induced diabetic rats with oral administration of selected doses which may has clinical significance.

2. Experimental

Materials and Methods:

Drugs and Chemicals

Pure drug samples of TLS, AMD 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 carboxymethyl cellulose 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 ± 20^{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 AMD+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 AMD + TLS on anti-diabetic effect of GLP+MTF were tested after administration of single dose in animals, whereas the influence of repeated treatment of AMD+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 Amlodipine+ Telmisartan was assessed. It was evident from results (Table 1) obtained that, treatment of Amlodipine + Telmisartan has no significant influence on the blood glucose levels in healthy albino rats. This indicates that Amlodipine + Telmisartan does not possess any hypoglycemic effect.

Table 1. Blood Glucose Levels after the administration of Amlodipine+Telmisartanin healthy Albino Rats

TIME (Hrs)	Mean Blood Glucose Levels (mg %)	Percentage Blood Glucose Reduction
	MEAN±SEM*	MEAN±SEM*
0	101.40±3.33	-
30	101.30±2.20	0.19±1.26
1	101.56±5.53	0.02±2.23
2	98.30±3.23	3.03±1.31
4	100.74±2.46	0.60±1.65
6	100.23±4.33	1.19±1.81
8	103.84±2.94	0.56±0.37
12	100.45±3.74	1.00±2.01
18	99.73±1.93	0.40±1.66
24	100.56±2.60	0.81±1.62

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)	Mean Blood Glucose Levels (mg %)	Percentage Blood Glucose Reduction
	MEAN±SEM*	MEAN±SEM*
0	89.45±4.30	-
30	86.49±4.19	3.31±0.16
1	83.02±4.06	7.20±0.18
2	80.59±4.59	11.15±0.21
4	77.79±3.81	13.03±0.22
6	63.73±1.40	28.22±2.46
8	73.30±3.55	18.05±0.11
12	74.03±3.57	17.22±0.18
18	75.01±2.90	16.37±0.59
24	75.72±3.61	15.31±0.21

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

The effect of repeated dose treatment of Amlodipine + Telmisartan was assessed. It is evident from the Table-3that, treatment of Amlodipine + 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 Amlodipine+Telmisartan in healthy Albino rats.

Time(h)	Percentage blood glucose reduction (mean ± SEM) with repeated Dose treatment of Amlodipine+Telmisartan in healthy rats		
	5mg/kg	10mg/kg	15mg/kg
0.0	0.00±0.00	0.00±0.00	0.00±0.00
0.5	1.37±0.26	0.97±0.25	1.14±0.40
1.0	1.94±0.29	1.84±0.23	1.96±0.52
2.0	2.31±0.24	2.98±0.37	3.42±0.54
4.0	4.11±0.27	4.17±0.47	4.78±0.31
6.0	8.92±1.04	14.12±1.82	17.59±2.95
8.0	8.90±0.66	11.21±1.30	15.50±2.33
12.0	6.44±1.11	11.04±1.99	15.46±3.19
18.0	5.58±0.98	10.97±1.34	15.20±3.14
24.0	5.17±1.09	10.29±1.99	14.27±3.34

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

The effect of repeated dose treatment of Amlodipine+Telmisartan and on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in healthy Albino rats was assessed. It is evident from the Table-4 that, treatment has influence on the blood glucose levels in healthy albino rats.

Table 4. Blood glucose levels with repeated dose treatment of Amlodipine+Telmisartan on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in healthy Albino rats.

Time(h)	Percentage blood glucose reduction (mean ± SEM) with repeated dose treatment of Amlodipine+Telmisartan in healthy rats		
	5mg/kg	10mg/kg	15mg/kg
0.0	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 ± SEM; Number of trials (n=6)

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

Table 5. Blood glucose levels with repeated dose treatment of Amlodipine+Telmisartan in diabetic rats.

Time (h)	Percentage blood glucose reduction (mean ± SEM) with treatment of Amlodipine+Telmisartan in healthy rats. Repeated dose		
	5mg/kg	10mg/kg	15mg/kg
0.0	0.00±0.00	0.00±0.00	0.00±0.00
0.5	1.10±0.26	2.03±0.33	2.02±0.61
1.0	2.41±0.48	4.04±0.62	5.00±1.37
2.0	4.89±0.88	7.02±0.52	8.49±1.74
4.0	7.51±0.52	10.95±0.29	14.23±0.96
6.0	11.87±0.25	17.81±0.15	21.03±0.38
8.0	6.45±0.93	13.74±1.09	18.52±0.53
12.0	3.52±0.76	10.72±0.94	15.71±1.26
18.0	2.96±0.58	10.01±1.06	14.38±1.35
24.0	1.72±0.59	9.20±1.16	13.58±1.55

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

The effect of repeated dose treatment of Amlodipine + Telmisartan and on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in healthy Albino rats was assessed. ItisevidentfromtheTable-6 that, treatment has influence on the blood glucose levels in diabetic albino rats.

Table 6. Effect of repeated dose treatment of Amlodipine +Telmisartan on hypoglycemic activity of Metformin + glimepiride (10 mg/kg) in diabetic rats.

Time(h)	Percentage blood glucose reduction (mean ± SEM) with treatment of Amlodipine+Telmisartan in healthy rats. repeated dose		
	5mg/kg	10mg/kg	15mg/kg
0.0	0.00±0.00	0.00±0.00	0.00±0.00
0.5	2.60±0.40	2.42±0.41	3.08±0.57
1.0	4.73±0.51	6.54±0.46	8.03±2.05
2.0	8.89±0.66	11.23±0.84	17.53±2.34
4.0	13.01±0.35	16.88±0.78	26.20±2.08
6.0	17.72±0.14	30.38±0.09	41.34±0.37
8.0	16.51±0.21	28.00±0.69	33.24±0.27
12.0	15.36±0.29	26.84±0.89	28.32±0.27
18.0	14.96±0.39	24.04±0.80	26.51±0.27
24.0	14.58±0.38	22.08±0.30	24.46±0.31

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

It was observed that single dose of Amlodipine + Telmisartan (5,10&15mg/kg) has failed to influence the blood glucose indicating Amlodipine + Telmisartan does not possess any hypoglycemic activity in rats. Indicating that the possible interactions with antihypertensive agents are 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 Amlodipine + Telmisartan.

4. Conclusion

Amlodipine + Telmisartan single dose treatment has not influenced the blood glucose levels in healthy albino rat sand diabetic rats. Whereas Amlodipine + 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 are essential during concomitant use of Amlodipine + Telmisartan with Metformin + Glimepiride.ThereforeitisfurthersuggestedthatreadjustmentofdoseandfrequencyofadministrationoforalanticdiabeticagentsmaybemadewhentheyareusedsimultaneouslywithAmlodipine+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 Amlodipine + Telmisartan pre-treatment on the pharmacokinetic parameters of oral anti-diabetic agents in human volunteers.

5. Acknowledgements

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

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