International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

To Study the Influence of Amantadine On Pharmacodynamics of Sitagliptin in Rats.

[1]P.Lakshmi,
M.Pharm student, Department of pharmacology, Sri k.v college of pharmacy, chickballapura, Karnataka, India.

Submitted: 15-08-2022 Accepted: 23-08-2022

ABSTRACT:
Diabetes mellitus (DM) is a condition of increased blood glucose levels in body. The increasing prevalence of type-2 diabetes itself may confer 75-90% of the excess risk of enhancing micro vascular complications like diabetic retinopathy, nephropathy, neuropathy and macro vascular complications like coronary diseases, hypertension, cardiac myopathy, cerebrovascular diseases and peripheral vascular diseases[1.] Sitagliptin, a novel therapeutic agent for treatment of type 2 DM is a selective inhibitor of enzyme dipeptidyl peptidase 4 which metabolises the incretin hormones in control of blood glucose levels. Amantadine used to treat Parkinson's disease. Clinically Sitagliptin is given as a oral antidiabetic drug to treat DM. Amantadine may be coprescribed along with Sitagliptin to treat diabetes and Parkinson's disease respectively[2]. As such, no information is available regarding the interaction taking place between Sitagliptin / Amantadine. Hence the present work has been undertaken to find out the interaction taking place between the above said drugs in rodent model, since such studies cannot be performed in humans.
Key words: Diabetes mellitus, Sitagliptin, Amantadine, drug interactions.

I. INTRODUCTION:

Diabetes mellitus is one such disorder, which requires careful management of its therapy with respect to blood glucose level since hyperglycaemia and hypoglycaemia are unwanted. Sitagliptin is a new class of oral drug and novel therapeutic agent for treatment of type 2 diabetes[3]. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4) which metabolizes the naturally occurring endogenous incretin hormones like glucagon–like peptide-1(GLP-1) and glucose- dependent insulinotropic polypeptide (GIP). Sitagliptin exists its activity in patients with type 2 DM by protecting the endogenous incretin hormones, GLP-1 and GIP resulting in enhanced glucose-dependent insulin secretion from the pancreas & decreased hepatic glucose production to maintain glucose homeostasis[4]. GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways. A few epidemiological studies have investigated the association between diabetes and Parkinson's disease. Systemic chronic inflammation, which increases the risk of diabetes, was also found to be associated with higher risk of Parkinson's disease[5,6]. Further more oxidative stress and mitochondria abnormalities have been implicated in both diseases[7,8,9]. Patients with type 2 diabetes is 83% more likely to be diagonised with Parkinson's disease later in life.

Amantadine, an antiviral and anti-parkinsonian agent, shown to act as a non-competitive NMDA antagonist[10,11]. Activation of NMDA receptors increases intracellular calcium influx in to the cell in SN and activates protein kinases and phosphorylating enzymes which initiates a series of central sensitization. This sensitization may be blocked with NMDA receptor antagonist (Amantadine) which increases dopamine release and blocks dopamine reuptake.

The information on the safety of such classes of drugs in combination with Sitagliptin is scanty. The safety of the above drug combinations with respect to blood glucose is not known and needs to be established by preclinical and clinical studies.

For pre-clinical evaluation of drug interactions, Hence in the present study albino wistar rats (rodent model) were selected for study of pharmacodynamic drug interactions and to identify the mechanisms of drug interactions. Such interactions are likely to occur in humans also, if it occurs in the above said animal species. Such studies in animal model may help in predicting the mechanism of interaction and the results can be extrapolated to humans to provide safe combinations in clinical situation.

II. RESEARCH METHODOLOGY:

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

Materials and Procurements: The drugs and chemicals used in the study were obtained as gift samples and purchased from various sources as detailed below.

Instrument for glucose estimation: Semi Auto analyzer

Glucose Kits: Glucose kits used for the estimation of serum glucose were purchased from Span Diagnostic Ltd. India.

Sitagliptin: Gifted fromActis Pharmaceuticals Pvt. Ltd., Hyderabad.

Nifedipine: Gifted fromKumar organic Pvt. Ltd., Bangalore.

Amantadine: Purchased fromRajesh chemicals Ltd, Mumbai.

Alloxan Monohydrate: Purchased from Rolex chemical industries, Mumbai

Animals:

Normal albino wistar rats (Rattus norvegicus) of either sex weighing between 175-250 g were procured from registered breeders (Sri Raghavendra Enterprises, Bangalore). The animals were housed under standard conditions of temperature (25 ± 2^{o} C) and relative humidity (30-70%) with a 12:12 hr light dark cycle. The animals were fed with standard pellet diet and water ad libitum. The protocol was approved by the Institutional Animal Ethical Committee (IAEC) (Ref. No. IAEC/SKVCP/PGCOL/11-12/04) of Sri K.V College of Pharmacy, Karnataka (117/1999/CPCSEA) was undertaken for conducting drug interaction studies.

Preparation of drug solutions:

Sitagliptin Phosphate (STP) solution: 9 mg of Sitagliptin was weighed accurately and dissolved in 2 ml of normal saline.

Amantadine: 2.7 mg of drug was weighed accurately and dissolved in 20 ml of normal saline. The doses of all interacting drugs were calculated by extrapolating the human therapeutic dose to animals (rats) based on body surface area and were found to be 9 mg/kg B.W of Sitagliptin and 2.7mg/kg B.W Amantadine[12].

Studies on the influence of Amantadine on the pharmacodynamics of Sitagliptin in normal healthy rats

Normal albino rats (Rattus norvegicus) of either sex weighing between 175-250 g were divided into two groups given below. The experiment was conducted in following stages in overnight fasted animals to study the pharmacodynamic interactions in normal healthy rats.

Two groups of rats for pharmacodynamic interaction studies in healthy rats.

GROUPS	TREATMENT	NUMBER OF ANIMALS
Group-I	Normal Control	6
Group-II	Sitagliptin (9 mg/Kg) + Amantadine (2.7 mg/kg B.W) (p.o)	6
	Total	12

Route of administration: Per oral (p.o)

Dose: Sitagliptin (9 mg/kg), Amantadine (2.7 mg/kg B.W)

Stage-I: All groups of rats which were fasted for overnight were administered with vehicle control and blood samples were collected at different time intervals and were estimated for blood glucose levels.

Stage-II: After a washout period of six days test groups of rats (Group II) which were fasted for overnight and administered with the TD of Sitagliptin and blood samples were collected at different time intervals and were estimated for blood glucose levels.

Stage-III: After a washout period of six days, the same groups of animals rats which were fasted for overnight were administered with the interacting drugs in following order,

Group-II: **Amantadine (2.7 mg/kg B.W)**

Blood samples were collected at different time intervals and were estimated for blood glucose levels.

Stage-IV: After a washout period of six days, the same groups of rats which were fasted for overnight were administered with combination of interacting drugs and the TD of Sitagliptin as follows.

Group-II: Amantadine (2.7 mg/kg B.W) followed by Sitagliptin after 30 minutes.

Blood samples were collected at different time intervals and were estimated for blood glucose levels.

Collection of blood samples:

Blood was collected from the retro orbital plexus of rats; a fine capillary was inserted gently in the inner angle of the eye then the capillary slides under the eye ball at 45^{o} angle and over the bony socket to rupture the fragile venous capillary of the

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

ophthalmic venous plexus. Thepassage was about 10 mm. The tip ofthe capillary was slightly retracted and the blood collected in the orbital cavity flows out from the capillary, which was collected in a microcentrifuge tube. Capillary tube should be held gently, merely resting on fingers while blood was flowing. After collecting the desired volume, capillary was removed with simultaneous release of pressure by fore finger and thumb. Any residual blood droplet around eye ball was wiped off by sterilized wet cotton wool.
The blood samples were collected in to the Tarson centrifuge tubes (1.5ml). The blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 10 and12h intervals from all groups of rats after drug administration. Every time about 0.2ml of blood was collected. The serum was separated by centrifuging the samples and the serum were analyzed immediately for blood glucose by GOD/POD method as described earlier.

Studies on the influence of amantadine on the pharmacodynamics of Sitagliptin in diabetic rats

The above topic describes the influence of amantadine on the pharmacodynamic of Sitagliptin in healthy normal rats. In those studies the treatment with Sitagliptin/ Amantadine combination were given to different groups of rats for obtaining information regarding the dose response relationship and drug interaction. But the antidiabetic drugs are used only in diabetic but not in normal condition. So to check the validity of the interactions seen earlier in normal rats, the studies were repeated on diabetic rats. The interaction is considered to be significant if it exists in diabetic condition also. Diabetes was induced with alloxan whose details are given below.The study was intended to find out the effect of above drugs on Sitagliptin induced response in diabetic condition. The studies in diabetic rats can be considered as the one representing the actual use condition of the drugs in disease state.
The experimental conditions and protocols were same for all groups.

Experimental diabetic animal models:
Alloxan induced diabetes: Alloxan is the next most commonly used chemical for induction of diabetes mellitus. It is a well- known diabetogenic agent widely used to induce Type 2 diabetes in animals[13.] The most frequently used intravenous dose of alloxan in rats is 65 mg/kg, but when it is administered intraperitoneally, subcutaneously its effective dose must be higher[14]. So, s.c or i.p route of administration is preferred. Albino rats (175-250g) of either sex were used for the induction of diabetes. These animals were allowed to fast for 18h and were injected with freshly prepared aqueous solution alloxan monohydrate at a dose of 100mg/kg through intraperitoneal route[15].

Three groups of rats for pharmacodynamic interaction studies in diabetic rats.

GROUPS	TREATMENT	No. of ANIMALS
Group-I	Normal Control	6
Group-II	Diabetic control	6
Group-III	Amantadine (2.7 mg/kg B.W)+Sitagliptin(9mg/Kg) (P.O)	6
	Total	18

Route of administration: p.o.
Dose: Sitagliptin (9 mg/kg), Amantadine (2.7 mg/kg B.W).
Stage-I: All groups of rats which were fasted overnight were administered with vehicle control and blood samples were collected at different time intervals and were estimated for blood glucose levels.
Stage-II: After a washout period of six days test groups of rats (Group II) which were fasted for overnight and administered with the TD of Sitagliptin (9 mg/kg body weight) and blood samples were collected at different time intervals and estimated for blood glucose levels.
Stage-III: After a washout period of six days, the same groups of animals were fasted overnight were administered with the interacting drugs in following order,
Group-II: Amantadine (2.7 mg/kg B.W)
Blood samples were collected at different time intervals and were estimated for blood glucose levels.
Stage-IV: After a washout period of six days, the same groups of rats which were fasted for overnight were administered with combination of

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

interacting drugs and the TD of Sitagliptin as follows. **Group-II: Amantadine (2.7 mg/kg B.W)**followed by Sitagliptin after 30 minutes.
Blood samples were collected at different time intervals and were estimated for blood glucose levels.

Analytical methods used in the Study:
Estimation of blood Glucose by GOD / POD methods.
Blood serum Sitagliptin concentration estimation by UV-Spectrophotometry
Serum insulin by chemiluminescence assay.They were mixed well and incubated at 37^{o} C for 10 minutes and absorbance was read at 505 nm against a reagent blank.
Calculation: Glucose conc. = $\frac{\textbf{Absorbance of Test (T)}}{\textbf{Absorbance of Standard(S)}} \times \mathbf{100}$
Note: Unused working glucose reagent was refrigerated immediately.
Estimationofserum Sitagliptin concentration by UV-Spectrophotometry[16]:Procedure for estimation of Sitagliptin in serum:
Absorbance of 1ml of serum were measured at 265nm against blank. The obtained absorbance values were subjected to calculate the amount of Sitagliptin present in the serum by calculating molar absorptivity of each serum sample.
$C = A/EB$,
C=Concentration, A=Absorbance, E=Molar absorptivity, B=path length.
Procedure for estimation of Amantadine and Sitagliptin in serum:
Absorbance of collected serum were measured at 267nm and 281.5 nm against serum blank. The obtained absorbance values were substituted in the following equations to get the concentration of each drug.
For Sitagliptin

$$\mathbf{C_x = \frac{A_2 a y_1 - A_1 a y_2}{a x_2 a y_1 - a x_1 a y_2}}$$

A1=Absorbanceof Sitagliptin at 267nm. $A_{2=}$Absorbance of Sitagliptin at 281.5nm. $ax_{1=}$molar absorptivity of A_1, $ax_{2=}$molar absorptivity of A_2
For Amantadine

$$Cy = \frac{A1ax2 - A2ax1}{ax2ay1 - ax1ay2}$$

A1=Absorbanceof Amantadine at 267nm. $A_{2=}$Absorbance of Amantdine at 281.5nm. $ax_{1=}$molar absorptivity of A_1, $ax_{2=}$molar absorptivity of A_2
Procedure for estimation of Amantadine and Sitagliptin in serum:
Sitagliptin, Nifedipine and Amantadine shows maximum absorbance at 238, & 281.5nm respectively.
EstimationofseruminsulinlevelsbyChemiluminescenceAssay:
Instrumentdescription: The ADVIA Centaur CP Insulin assay.
IntendedUse: Forin-vitro, the diagnosticuseinthedeterminationofinsulinin serum usingthe ADVIA Centaur CP Insulin Chemiluminescenceassay Systems.Thisassaycanbe usedtoaidinthediagnosisofdiabetesmellitusandhypoglycaemia.

III. RESULTS:

PHASE-I: Pharmacodynamic interactions in normal rats
STAGE-I: Effect of vehicle on blood glucose level in rats (Group I, II):
The results of the blood glucose levels and the percent blood glucose reduction treated with vehicle were tabulated in the tables 1 and 1 (a) and were presented graphically in the fig-1 and 1(a). Reduction on blood glucose levels may be due to fasting of animals which deprived of both food and water.
STAGE-II: Effect of Sitagliptin (9 mg/kg B.W) on blood glucose level in rats (Group II):
Sitagliptin, a novel therapeutic agent for diabetes which inhibits DPP-4 enzyme was used in the present study of drug interactions. Sitagliptin induced hypoglycaemia was studied by administering the TD to Groups - IIin the actual laboratory conditions. TD of Sitagliptin produced percent blood glucose change at 6 hr in (Groups-II) -59.81±1.076 respectively. The results of effect of Sitagliptin on blood glucose level in rats (Groups - II) were given in the tables 1 and 1 (a) and were presented graphically in the fig-1.
STAGE-III: Effect of Amantadine (2.7 mg/kg B.W) on blood glucose level in rats (Groups II):
The results of the blood glucose levels and the percent blood glucose reduction with Amantadine alone and combination were tabulated in the tables 1 and 1 (a) and were presented graphically in the fig1.TD of Amantadine shows percent blood glucose change of -49.97±1.605 % was observed at 4 hr which was hypoglycaemic in group-II.

STAGE-IV: Effect of Amantadine (2.7 mg/kg B.W) followed by Sitagliptin after 30 min on blood glucose level in rats (Groups II) :

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

The results of the blood glucose levels and the percent blood glucose Amantadine followed by Sitagliptin after 30 min, were tabulated in the tables 1and 1(a) and were presented graphically in the fig.1.It was observed that administration of Amantadine followed by Sitagliptin after 30 min produced response with a peak response of percent blood glucose change of -49.95±1.339% at 6 hr. Hypoglycaemia produced after administration combination of Amantadine and Sitagliptin was high when compared to individual administration of Amantadine and Sitagliptin.

TABLE-1.PHASE-I: Pharmacodynamic interactions in normal rats
Effect of Sitagliptin (9mg/kg B.W.), amantadine(2.7mg/kg B.W) on blood glucose level in rats (Group II) (Mean ± SEM)

Time(h)	Blood Glucose levels (mg / dl) in rats (Mean ± SEM)			
	Group-I(vehicle)	Group-II(sitagliptin)	Group-II(amantadine) After wash out period	Group-II(amantadine followed by sitagliptin afterwashout period
0	67.43±0.392	77.94±1.417	69.63±0.581	70.46±0.415
1	66.41±0.688	64.13±1.295	66.58±0.671	67.53±0.752
2	64.24±0.911	53.16±0.629	57.98±1.75	63.05±5.415
3	62.75±0.243	48.97±0.433	43.84±1.357	56.03±1.578
4	60.41±0.323	40.30±0.917	34.31±1.119	47.17±0.497
6	62.96±0.683	31.32±0.806	42.24±2.085	34.31±1.119
8	61.32±0.298	39.03±1.135	54.29±2.193	42.24±2.085
10	60.94±0.905	48.16±1.247	65.78±1.182	54.29±2.193
12	60.12±0.713	55.46±1.383	69.96±1.841	65.76±1.181

TABLE-1(a)
Percent blood glucose change

Time(h)	Percent Blood Glucose change in rats (Mean±SEM)			
	Group-I(vehicle)	Group-II(sitagliptin)	Group-II(amantadine)	Group-II(amantadine followed by sitagliptin)
0	-	-	-	-
1	-1.512±0.564	-17.71±1.632	-4.38±0.964	-4.15±1.067
2	-4.73±0.415	-31.22±0.843	-16.72±2.513	-10.51±7.686
3	-6.94±0.628	-37.16±0.513	-37.03±1.949	-20.46±2.239
4	-10.41±0.543	-48.29±1.624	-50.72±1.607	-33.05±0.706
6	-6.62±0.521	-59.81±1.076	-39.33±2.995	-51.3±1.588
8	-9.06±0.455	-49.92±1.274	-22.02±3.15	-40.04±2.96
10	-9.62±0.342	-38.20±1.617	-5.52±1.697	-22.94±3.113
12	-10.84±0.462	-28.84±1.742	0.47±2.644	-6.66±1.676

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

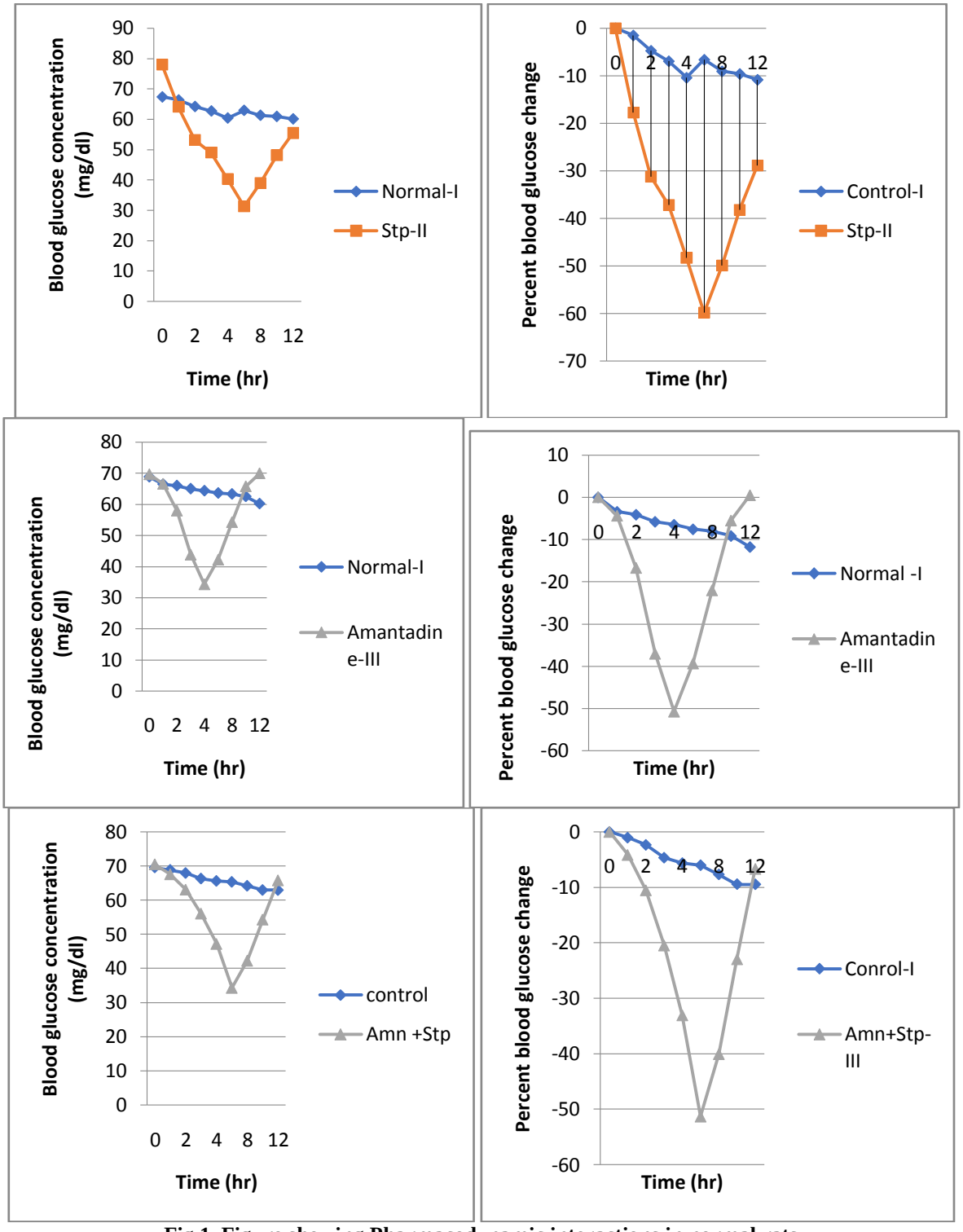

Fig 1. Figure showing Pharmacodynamic interactions in normal rats
Effect of Sitagliptin (9mg/kg B.W.) , amantadine(2.7mg/kg B.W) on blood glucose level in rats (Group II) (Mean ± SEM) and percentage change in blood glucose values.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

Time (h)	Blood Glucose levels (mg / dl) in rats (Mean±SEM)				
	Group-I(vehicle control)	Group-II(diabetic control)	Group-III(sitagliptin)	Group-III(amantadine afterwash out period)	Group-III(amantadine followed by sitagliptin after wash out period)
0	67.00±0.666	169.89±0.143	173.74±2.302	187.31±2.907	188.33±3.45
1	66.89±0.921	168.23±0.664	152.86±1.625	152.55±1.468	150.23±1.355
2	65.56±0.553	167.06±0.589	127.94±2.899	114.83±3.95	114.81±4.492
3	64.32±0.446	166.03±0.876	102.35±2.106	98.78±5.09	70.46±0.415
4	64.01±0.356	165.38±0.352	94.51±2.363	74.65±4.209	52.27±0.912
6	63.78±0.786	164.67±0.621	71.79±3.141	89.28±4.843	63.13±1.777
8	63.22±0.632	164.34±0.512	98.50±1.999	121.55±4.93	122.34±4.982
10	63.09±0.785	163.55±0.233	123.16±2.095	145.17±1.707	151.9±2.118
12	63.00±0.668	162.42±0.446	149.35±3.130	168.91±1.571	174.23±0.905

TABLE-2. PHASE-II Pharmacodynamic interactions in Diabetic rats

Effect of Sitagliptin (9mg/kgB.W), amantadine(2.7mg/kg B.W)and amantadine followed by sitagliptin on blood glucose level in ratsin (Groups III)

Time (h)	Percent blood glucose change in rats (Mean±SEM)				
	Group-I	Group-II	Group-III	Group-III	Group-III
0	-	-	-	-	-
1	-0.16±0.764	-0.97±0.789	-12.01±4.245	-18.55±0.783	-20.22±0.719
2	-2.14±0.325	-1.66±0.167	-26.36±1.528	-38.69±2.109	-39.03±2.385
3	-4.00±0.678	-2.27±0.301	-41.09±1.818	-47.26±2.717	-62.58±0.22
4	-4.46±0.542	-2.65±0.589	-45.60±2.136	-60.14±2.247	-72.24±0.484
6	-4.80±0.443	-3.07±0.745	-58.56±1.582	-52.33±2.585	-66.47±0.943
8	-5.64±0.765	-3.26±0.986	-43.30±3.037	-35.1±2.632	-35.03±2.645
10	-5.83±0.342	-3.73±0.332	-29.11±1.625	-22.49±0.911	-19.34±1.124
12	-5.97±0.56	-4.39±0.456	-14.03±1.264	-9.82±0.838	-7.48±0.48

TABLE-2(a). Percent blood glucose change

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

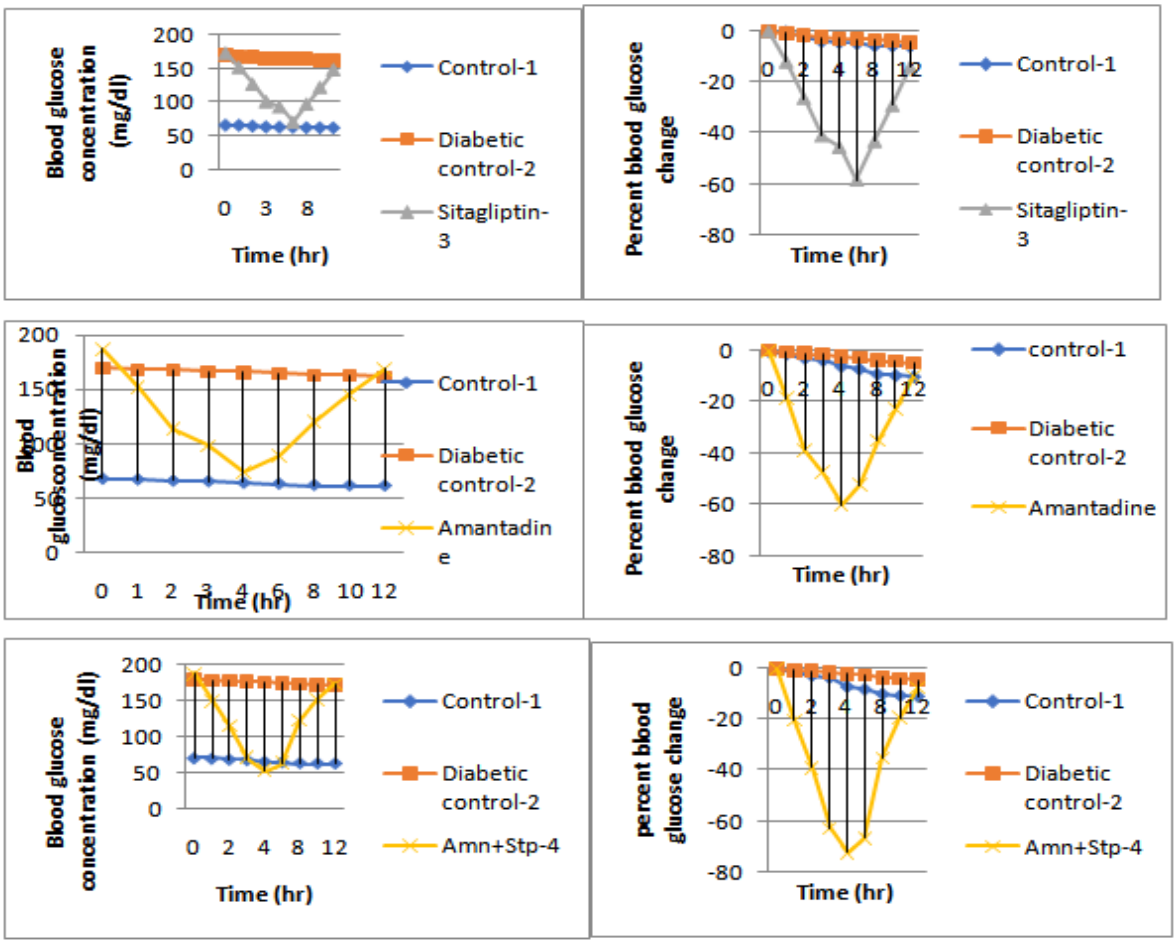

FIG-2. PHASE-II Pharmacodynamic interactions in Diabetic rats

Figure showing the Effect of Sitagliptin (9mg/kgB.W), Amantadine on blood glucose level in rats and percentage change in blood glucose levels (Groups III)

IV. DISCUSSION

Studies on the influence of Amantadine on the pharmacodynamics of Sitagliptin in normal healthy rats

The work was conducted to findout the effect of amantadine on the pharmacodynamic effect (blood glucose levels) of Sitagliptin in normal rats. This study was done to find out the safety of the above co-administered drugs with Sitagliptin since such drugs are used in diabetes associated with Parkinson disease**.** STP, produced hypoglycaemia with about 60% reduction in blood glucose levels in rats. It was observed that sitagliptin produces its peak effect (hypoglycaemic effects) at 6 hr after the oral administration which might be due to the peak plasma concentration which elicit the maximum activity and decrease in blood glucose levels was observed upto 12hr.Amantadine significantly relieved the symptoms of Parkinson's disease. Amantadine is a weak NMDA receptor antagonist[17]. It was observed that Amantadine produces hypoglycaemia and it showed its response with peak effect at 3-4 hr after oral administration and blood glucose level decreases upto 50% and blood glucose levels comes to normal after 10 hr. The cellular and molecular mechanism of neuroprotection by Amantadine remains unclear. It was reported by FaudLechinet al that Amantadine reduces glucagon secretion and enhances the insulin secretion, our results are in agreement with the above findings and might be responsible for the hypoglycemic effect of Amantadine.

Studies on the influence of Amantadine on the pharmacodynamics of Sitagliptin in diabetic rats

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1736-1744 www.ijprajournal.com ISSN: 2456-4494

The effect of Sitagliptin / amantadine on blood glucose levels in diabetic rats was found to be similar to that of observed in normal rats and diabetic rats. However, slight variation (quantitative) in percent blood glucose reduction was observed when treated with Sitagliptin and amantadine.

V. CONCLUSION

TD of Sitagliptin produced hypoglycaemic effect in normal and diabetic rats. Administration of Amantadine followed by Sitagliptin after 30 min potentiates the action of Sitagliptin and leading to produce enhanced hypoglycaemia when compared to individual administration of Sitagliptin and Amantadine. It was observed that combination of both drugs shows peak action (hypoglycaemic effect) at 6 hr and blood glucose level decreased up to 70% and also showed action up to10 hr. Amantadine potentiating the action of Sitagliptin might be due to its ability to release insulin and suppression of glucagon as reported earlier. Amantadine produced significant reduction in blood glucose levels when administered alone and also significantly potentiated the hypoglycaemic effect of Sitagliptin when administered in combination. Hence the therapy with Sitagliptin should be monitored closely when Amantadine is co-administered to maintain the normal blood glucose levels.Since the interaction was observed in rodent model. In future, studies can be extended to non-rodent models and also in clinical studies.

REFERENCES

[1]. Aaron Vinik& Mark Flemmern. Diabetes and macrovascular disease. Journal of Diabetes and Its Complications. 2002; 16: 235–45.
[2]. Sandyk R. The relationship between diabetes mellitus and parkinson's disease. Int JNeurosci 1993: 69:125-130.
[3]. Gallwitz B. Sitagliptin: Profile of a novel DPP-4 inhibitors for the treatment of type 2 diabetes.Drugs today 2007;43: 13-25.
[4]. J.Girard. The Incretins: From the concept to their use in treatment of type 2 diabetes. Part A: Incretins: Concept & Physiological functions. Diabetes & Metabolism 2008; 34: 550-59.
[5]. Pradhan A. Obesity, metabolic syndrome, and type 2 diabetes: inflammatory basis of glucose metabolic disorders. Nutr Rev 2007; 65: S125-S156.
[6]. Chen H, O' Reilly EJ, S chwarzarzschild MA, A scherio A. Peripheral inflammatory biomarkers and risk of PD. AM J Epidemiol 2008; 167:90-95.Gallwitz B.
[7]. Sandyk R. The relationship between diabetes mellitus and parkinson's disease. Int JNeurosci 1993: 69:125-130.
[8]. Friederich M, Hansell P, Palm F. Diabetes, oxidative stress, nitric oxide and mitochondria function. Curr Diabetes Rev 2009; 5: 120-144.
[9]. Henchcliffe C, Beal MF. Mitochondrial biology and oxidative stress in PD pathogenesis. Nat clin practNeuorl 2008; 4: 600-609.
[10]. Maugh, T.H (1976). Amantadine: an alternative for the prevention of influenza. Science 192(4235) : 130-131. Doi : 10. 1126 / science. 192. 4235. 130. PMID 17792438.
[11]. Blanpied TA, Clarke RJ, Johnson JW (2005). Amantadine inhibits NMDA receptors by accelerating channel closures during channel block. Journal of Neurosciences 25(13): 3312-3322.
[12]. Laurence DR, Bacharach AL. Evaluation of drug activities and pharmacometrics . London and New York: Academic press ;1964.
[13]. Sandyk R. The relationship between diabetes mellitus and parkinson's disease. Int JNeurosci 1993: 69:125-130.
[14]. Friederich M, Hansell P, Palm F. Diabetes, oxidative stress, nitric oxide and mitochondria function. Curr Diabetes Rev 2009; 5: 120-144.
[15]. Henchcliffe C, Beal MF. Mitochondrial biology and oxidative stress in PD pathogenesis. Nat clin practNeuorl 2008; 4: 600-609.
[16]. Gallwitz B. Sitagliptin: Profile of a novel DPP-4 inhibitors for the treatment of type 2 diabetes.Drugs today 2007;43: 13-25.
[17]. Kornhuber J, Bormann J, Hubers M, Rusche K, RiederelP(1991). Effects of the 1-aminoadamantanes at the MK-801 biniding site of the NMDA receptor gated ion channel: a human postmartum brain study. Eur J. Pharmacol. Mol. Pharmacol. Sect 206:297-300.