Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2010, 2(2): 101-104
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Influence of Atorvastatin on the pharmacodynamics of Glipizide in normal and diabetic rats

A.Mishra*[1], R. Kumari[1], P. N. Murthy[2] and P. P. Dash[1]

[1]*Teegala Ram Reddy College of Pharmacy, Meerpet, Hyderabad, India*
[2]*Royal College of Pharmacy and Health Sciences, Berhampur, Ganjam, India*

Abstract

This work reports the evaluation of the influence of atorvastatin on glipizide in normal and diabetic rats. Glipizide produced hypoglycemia activity in a dose dependent manner in normal and diabetic condition. In the presence of atorvastatin, glipizide produced early onset of action and maintained for longer period compared to glipizide group.

Key Words: Atorvastin, Glipizide, Hypoglycemia.

INTRODUCTION

Diabetes mellitus is defined as an elevated blood glucose associated with absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action. The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories: type 1, insulin-dependent diabetes; type 2, non-insulin dependent diabetes; type 3, other; and type 4, gestational diabetes mellitus [1, 2, 6]

Diabetes itself may confer 75-90% of the excess risk of enhancing the deleterious effects of microvascular complications like diabetic retinopathy, nephropathy, neuropathy and macrovascular complications like coronary artery disease, diabetic dyslipidemia, hypertension, oxidativestress, cardiacmyopathy, hyperinsulinemia, cerebrovasculardisease, peripheral vascular disease[4-7]. Atherosclerosis and diabetic dyslipidemia is most commonly seen in chronic diabetics. In such cases it is likely that antidiabetic drugs are used along with the lipid lowering drugs used for prophylactic treatment in diabetic dyslipidemia and atherosclerosis. [8]

Atorvastatin, an antihyperlipidemic agent is widely used for prophylactic treatment in diabetic dyslipidemia and atherosclerosis. [3, 14]

Present study was conducted to find the influence of atorvastatin on the hypoglycemic and anti-hyperglycemic activities of glipizide in normal and diabetic rats.

RESULTS AND DISCUSSION

Effect in normal rats: in normal rats Atorvastatin has no effect on the blood glucose levels when administered alone, orally. The glipizide (0.18mg/200g body weight) produced 50.56% at 4 h as peak effects. In the presence of Atorvastatin (0.4mg/200g body weight), the glipizide produced antidiabetic activity at 1h and was maintained for 6h.The data was presented in Table - 1.

Table:1 percent blood glucose reduction with Atorvastatin/Glipizide/Atorvastatin+Glipizide in normal rats (n=6)

Treatment	Dose	Time (h)						
		0	0.5	1	1.5	2	4	6
Atorvastatin	0.4mg/200g bd.wt	-	0.58± 0.19	1.46± 0.28	1.84± 0.32	2.00± 0.36	3.20± 0.63	4.60± 0.40
Glipizide	0.18mg/200g bd.wt	-	27.28±1 .03	32.82±1 .01	35.77±0 .52	38.23±0 .43	50.56±1 .05	25.37±1 .21
Atorvastatin+Glipizide	0.4mg/200g bd.wt +0.18mg/200 g bd.wt	-	35.28±0 .55	43.15±0 .85	55.97±1 .02	42.62±1 .08	43.85±0 .49	14.92±0 .16

Effect in diabetic rats: in diabetic rats, oral administration of Atorvastatin at the dose of (0.4mg/200g body weight) produced no reduction in blood glucose and glipizide (0.18mg/200g body weight) produced 58.17% at 4h. In the presence of Atorvastatin (0.4mg/200g body weight), the glipizide produced antidiabetic activity at 1h.and was maintained for 6h.The data was presented in Table- 2.

Table-2: percent blood glucose reduction with torvastatin/Glipizide/Atorvastatin+Glipizide in diabetic rats (n=6)

Treatment	Dose	Time (h)						
		0	0.5	1	1.5	2	4	6
Atorvastatin	0.4mg/200g bd.wt	-	0.65±0. 59	1.20±0. 51	1.37±0. 24	2.86±0. 39	3.27±0. 56	5.23±0. 45
Glipizide	0.18mg/200g bd.wt	-	27.06±0 .16	32.59±0 .40	41.49±0 .34	44.23±0 .95	51.05±0 .26	15.39±0 .28
Atorvastatin+Glipizide	0.4mg/200g bd.wt +0.18mg/200 g bd.wt	-	33.04±0 .37	45.12±0 .65	58±0.25	42.17±0 .30	33.23±0 .25	13.93±0 .02

Drug-interaction studies are usually conducted in animal models to assess the safety of the combination, before they are conducted in humans. The normal rat model served to quickly identify the interaction and the diabetic rat model served to validate the interaction in an actual-use condition of the drugs. The rat model was used for the pharmacodynamics-interaction study, since it is the most widely used species in drug metabolism and drug interaction studies.

Atherosclerosis and diabetic dyslipidemia are the cardiac abnormalities, which were more commonly seen in chronic diabetes [12], atorvastatin an antihyperlipidemic agent is widely used for prophylactic treatment of atherosclerosis. Alloxan has been observed to cause a massive reduction of the ß-cells of the islets of Langerhans and induce hyperglycemia [11].

The present study was conducted in rats with Atorvastatin as an antihyperlipidemic agent.

The glipizide showed hypoglycemia/ antihyperglycemia in normal/ diabetic rats in dose dependent manner. Whereas Atorvastatin alone did not alterblood glucose level. Glipizide when administered in therapeutic dose produced the maximum effect at 4 h and was maintained up to 6 h in both normal and diabetic rats. In presence of Atorvastatin the onset of action of glipizide was early and maintained for long duration compared to glipizide control. Glipizide acts by stimulating insulin release [13, 15]. The early onset of action was noticed due to inhibition in metabolism of glipizide, atorvastatin inhibits hepatic CYP3A4 isoenzyme [14] and glipizide is partly metabolized by the same isoenzyme [4, 5].

MATERIALS AND METHODS

Albino rats of either sex weighing between 175-200 g were procured from Mahaveer Enterprises, Hyderabad, India, were used in the study. They were maintained under standard laboratory conditions at ambient temperature of 25 ± 2^0C and 50 ± 15% relative humidity with a 12h light/12h dark cycle. Rats were fed with commercial pellet diet (Rayans Biotechnologies Pvt.Ltd., Hyderabad) and water *ad libitum.* All experiments were e performed in accordance with the institutional animal ethics committee bearing registration number 1018/C/06/CPCSEA. The animals were divided into 3 groups of 6 each. They were fasted for 18 h prior to the experiment (allowing access to water) and during the experiment, food and water were withdrawn.

Atorvastatin was obtained from Dr Reddy's Laboratories,Hyderabad as a gift sample and it was used throughout the study. Alloxan monohydrate was purchased from LOBA Chemie, Mumbai,India. Glipizide was supplied by Macloid Pharmaceuticals, Baddi, HP. Glucose kits (Beacon diagnostics) were purchased from the local pharmacy.

Study in normal rats : Group I/II/III were treated with atorvastatin (0.4mg/200g body weight) / glipizide (0.18mg/200g body weight). Atorvastatin (0.4mg/200g body weight) given prior to the administration of glipizide (0.18mg/200g body weight), respectively.

Study in diabetic rats: albino rats of either sex (175-200g) were treated with alloxan monohydrate (100mg/Kg body weight i.p.) [9,10]. Alloxan monohydrate was dissolved in saline solution and was administered. Animals were treated with 10% dextrose orally to combat the early phase of hypoglycemia. Rats showing fasting blood glucose levels above 150 mg/dL

were selected for the study. These rats were divided in to 3 groups. Groups I/II/III were treated with atorvastatin (0.4mg/200g body weight) / glipizide (0.18mg/200g body weight). Atorvastatin (0.4mg/200g body weight) given prior to the administration of glipizide (0.18mg/200g body weight), respectively. Atorvastatin dose was fixed based on its response, which produced above 50%.

Collection of blood sample: blood samples were collected from the retro-orbital plexus of each rat at 0, 0.5, 1, 1.5,2,4 and 6 h after drug administration. Blood glucose levels were determined by using GOD-POD method [8, 9].

Statistical analysis

data were expressed as mean ± standard deviation (SD). The significance of blood glucose reduction produced by Atorvastatin with glipizide compared glipizide control was determined by applying student's unpaired t-test.

CONCLUSION

The results indicate that additive action of Atorvastatin on pharmacodynamic response of glipizide may be useful to improve the tolbutamide activity in insulin resistant cases and to postpone the occurrence of diabetic complications. However further work on human patients is required to confirm the observation in diabetic condition and usefulness of Atorvastatin as supplemental adjuvant for improved control of blood glucose levels when administered orally along with sulfonylurea.

REFERENCES

[1] M.Goldner and G.Gomori, *Endocrinology*, **1943**, 33:297.
[2]R.Vigneri,V.Pezzino and K.Y.Wang, *J.Clin.Endocrinal Metab***198,** 54:95.
[3] CD Forbes and M Maclaren, *semin.. thromb hemmort* **1999**, 55-57 .
[4] V.Chitral; *Der Pharmacia Lettre*; **2009**, 1:150-156.
[5] RE Ferner and S Chaplin, *Clin. Pharmacokinetics* **1987**, 379-401.
[6] KT Kivisto and PJ Neuvonen, *Clin. Pharmacol Ther.* **1991**, 39-43.
[7]S.Goldfarb,F.N,Ziyadeh,E.F.KernandD.ASimmons.*Diabetologia.*, **1991,**40(4),465-471.
[8] M Kristin, J Herbert, H Robert,*Clin Pharmacol. Ther* **1998**,316-323.
[9] P Trinder; *Ann.Clin.Biopharm;* **1964**;6:24DD.
[10] R Vigneri, V Pezzimo, E D Goldfine.,*J. Clin. Endocrinol* **1982**, 95-100.
[11] E Wahlin, L Amer and A Melander, *Clin Pharmacokinetic*, **1984**, 404-434.
[12] S S Ferguson, *Mol.Pharmacol* **2002**, 737-746.
[13] L Ditusa and A Luzier, *J. Clin Pharm Ther***2000**, 279-282.
[14] R R Chitral S V Surve and M K Bhat, *Toxicol.App.Pharmacol* **2005**, 268-277.
[15] T Alexander, *Int. J. Cardiology* **2003**, 16-25.