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EFFECTS OF ATENOLOL AND NEBIVOLOL ALONE AND COMBINATION WITH GLIPIZIDE ON GLUCOSE LEVELS IN NORMAL AND STZ INDUCED DIABETIC RATS.

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Abstract

Drugs are used in the prevention and treatment of symptoms and diseases but the drug-drug interactions are one of the major problems in multi-drug therapy. Beta blockers are commonly used in the treatment of hypertension in diabetic patient. Literature showed that risk of retinopathy and cardiovascular disease are more in diabetic hypertensive patients, which may cause morbidity and mortality. Therefore present study was undertaken to understand the effects of atenolol and nebivolol alone and combination with glipizide in normal and diabetic rats. The study was conducted on healthy albino andstreptozotocin induced diabetic rats. Diabetes was induced by single i.p. injection of STZ (60mg/kg) administration. The hypoglycemic effects of atenolol, nebivolol and glipizidealone and in combination were tested. Results showed that atenolol and glipizide did not have any significant effect on glucose levels on alone administration. Though repeated administration of atenolol followed by glipizide enhances hypoglycemic effect of glipizide up to one hour followed reduced hypoglycemic effect of glipizidethroughout the study period in normal animals but potentiated the hypoglycemic effect of glipizide on diabetic animals. However, nebivolol does not alter antidiabetic activity of glipizide. Hence study suggested that the dose and/or frequency of atenolol administration have to be readjusted accordingly when glipizide and atenolol need to be used concomitantly. Nebivolol is safe drug in patients having diabetes and hypertension than atenolol.

Introduction

Hypertension in diabetic patient is one of the major and common health problems which are frequently difficult to treat and results significant morbidity and mortality. The frequency of hypertension in diabetic people is probably 1.5-2.0 times more than in the general people [1]. The combined presence of hypertension and diabetes affect same major target organs and responsible for left ventricular hypertrophy and coronary artery disease, decrease in renal function, the development of diabetic retinopathy and the development of cerebral diseases [2].

Beta blockers are often used as first line therapy in patients with hypertension including those with diabetes mellitus [3]. 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 β cells [4]. Beta blockers have been convincingly shown to reduce total and cardiovascular morbidity and mortality in hypertensive diabetic patients. After myocardial infarction these agents confer a twice as high protective effect when compared to non-diabetic patients [5] β-blocker use improves outcomes even more for the patient with diabetes mellitus than for the patient without diabetes with a history of acute myocardial infarction or coronary artery disease. However, most paradoxically, beta blocking agents are used less frequently in diabetes.[6] Atenolol is a second generation hydrophilic beta 1-blocker. Nebivolol is a selective third generation beta 1 lipophilic blocker and devoid of intrinsic sympathomimetic activity. It also modulates NO release and vasodilatory properties.[7,8.]Glipizide, a potent second generation sulfonyleureasbelongs to the group of oral antidiabetic drugs causes stimulation of beta cell of the islet of langerhans of pancreas to secrete insulin and reducing blood glucose.[9, 10] Both the drug metabolized in liver by cytochrome P450 enzyme system

In clinical practice as there arise several situations, where a diabetic patient

receiving either atenolol or nebivolol need to be administered with glipizide. However, the effect of atenolol and nebivolol on antidiabetic activity of glipizide has not been yet properly studied and reported. Hence, in the present study was undertaken to understand the effects of atenolol and nebivolol alone and combination with glipizide on glucose level in normal and diabetic rats.

Materials and methods

Animals

Albino rats of either sex weighing between 200-250 g were used for the study. Animals were kept relative temperature (25±2°C) and relative humidity 44–56%, light and dark cycles of 10 and 14 h, respectively during the experiments. Animals were provided with standard rodent pellet diet. Rats were fasted 18 h before the experiment though water was allowed *ad libitum*. All animal procedures have been approved and prior permission from the Institutional Animal Ethical Committee was obtained as per the prescribed guidelines.

Drugs and chemicals

Standard drugs Atenolol, nebivolol and glipizide are obtained from J.B. Chemicals, Zyduscadila and Sun Pharmaceuticals Pvt. Ltd respectively as a gift sample. Streptozotocin procured from Sigma-Aldrich, USA. Other chemicals were obtained local sources and were of analytical grade. Glucose estimation kit purchased from Span Diagnostic Ltd (India)

Induction of diabetes and treatment protocol

The animals were fasted overnight and diabetes was induced by single intraperitoneal injection of freshly prepared solution of streptozotocin (60 mg /kg body weight i.p.) in 0.1 M cold citrate buffer (PH 4.5). The animals were allowed to drink 5% Glucose solution 2 day before and 2 day after STZ injection to overcome STZ-induced hypoglycemia. Control rat were injected with citrate buffer alone. Animals were checked for the extent of blood glucose level 48h after the injection of STZ. Animals showing blood glucose level (250 mg/dl) were considered as diabetic. After the week time for development of the diabetes, the rats were moderate diabetes having hyperglycemia (250 mg/dl) were consider as a diabetic and used for the drug treatment.

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 retro orbital plexus at time intervals after drug administration and glucose levels were estimated by using glucose oxidase/peroxidase (GOD/POD) method, which is compared with fasting blood sugar level. Influence of repeated treatment of atenolol and nebivolol for seven days on the hypoglycemic effect of glipizide was studied.

Influence of repeated treatment of atenolol and nebivolol on the hypoglycemic activity of glipizide in healthy and diabetic rats

Animals were divided into two Set contain six animals each. Set A contain healthy and Set B contain diabetic animals.

Set A	**Group 1**	**Treated with vehicle**
(healthy animals)	Group 2	Treated with Atenolol
	Group 3	Treated with nebivolol
	Group 4	Treated with Glipizide
	Group 5	Treated with Atenolol + Glipizide
	Group 6	Treated with Nebivolol + Glipizide
Set B	Group 1	Diabetic animals Treated with vehicle
(Diabetic animals)	Group 2	Diabetic animals Treated with Atenolol
	Group 3	Diabetic animals Treated with nebivolol
	Group 4	Diabetic animals Treated with Glipizide
	Group 5	Diabetic animals Treated with Atenolol + Glipizide
	Group 6	Diabetic animals Treated with Nebivolol + Glipizide

Animals received atenolol and nebivolol per day orally for one week. After 18 hrs of fasting, on the 8th day, '0' hour blood samples were collected for determining fasting blood glucose levels. Atenolol and nebivolol was given first followed by the administration of glipizide (10 mg/kg) after 60 min to all the animals. Blood samples

were collected thereafter at prefixed time intervals i.e. 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 hrs and blood glucose levels were estimated by GOD/POD method in both healthy and diabetic albino rats.

Determination of percentage of blood glucose reduction

Blood glucose was analyzed using spectrophotometer and the percentage reduction in blood glucose levels at time "t" was calculated by using the following equation.

Percentage of Blood glucose reduction at time't' = [(A - B)/A] × 100

Where, A= initial blood glucose level before drug administration.

B= blood glucose levels at time "t" after the drug administration.

Statistical analysis

All the values are expressed as mean ± S.E.M for groups of six animals each and values are analyzed by one way ANOVA and compared by using Tukey- Kramer multiple comparison test. The values are statistically significant at, ***P<0.001, **P<0.01, *P<0.05.

Results and Discussion

Individual effect of atenolol and nebivolol, glipizide on blood glucose level and effect of repeated treatment of atenolol and nebivolol for seven days on the hypoglycemic effect of glipizide in normal and diabetic animals were shown in Figure 1 and 2. Result showed that administration of atenolol and nebivolol as alone did not produce any significant change in blood glucose level in normal and diabetic animals, whereas antidiabetic drug glipizide produce significant decrease in blood glucose level in normal and diabetic rats. Repeated administration of atenolol for 8 days has enhanced the hypoglycemic effect of glipizide up to one hour and afterwards it had reduced the hypoglycemic effect of glipizide throughout 30 hrs of study, but repeated administration of nebivolol significantly increased the hypoglycemic activity of glipizide in diabetic animals. Table 1 and 2 showed the percentage decrease in blood glucose level when compared with fasting blood glucose level of respective groups after the administration of atenolol and nebivolol, glipizide alone as a single dose and in combination in normal and diabetic rats. In

case of diabetic animals, atenolol potentiate the peak effect (i.e., reduction in blood glucose level is 59.55 % ± 0.89 after 6 hrs) and duration of action 24 hrsglipizide significantly. But there was no significant change in onset time.

The risk of retinopathy, stroke, and cardiovascular events like left ventricular hypertrophy, cardiovascular morbidity and mortality are doubled in diabetic hypertensive patients when compared with non-diabetic ones. Elevated BP has been identified has a major risk factor in progression of diabetic nephropathy [11]. Results suggested that atenolol, nebivolol and glipizide did not have any potential drug interaction on alone administration. However, repeated treatment of atenolol enhance hypoglycemic effect of glipizide up to one hour followed reduced hypoglycemic effect of glipizidethroughout the study period in normal animals. While in diabetic animals repeated administration of atenolol followed by glipizide potentiated the hypoglycemic activity. However, in diabetic animals repeated administration of atenolol followed by glipizide not altered the hypoglycemic activity of glipizide. Second generation beta blocker can delay the return of insulin induced low blood sugar levels to normal in healthy and diabetic animals [12]. This may be the possible reason for potentiation of glipizide activity in normal and diabetic animals. Further, β1-blockers results in increased insulin resistance HbA1C levels, β2-blocker stimulation causes liver glucogenolysis and gluconeogenisis resulting in stimulation of insulin release. Experience as indicated that non selective βblockers tend to cause a small interfere in blood sugar level and increase in the prescription of hypoglycemic agents in atenolol group [13, 14]. These effects may be one of the reasons for the diminished hypoglycemic effect of glipizide after repeated administration of atenolol in healthy albino rats after a period of one hour.

Conclusions

The present study may suggest that during simultaneous treatment of hypertension and diabetes with atenolol, nebivolol withglipizide the dose and frequency of administration of atenolol are to be readjusted accordingly in order to avoid severe hypoglycemia. Along with this it is necessary to consider individual blood glucose levels and other drug therapy.

Nebivolol is safe drug in treatment of patients with diabetes and hypertension.

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Table 1: antidiabetic effect of atenolol, nebivolol and glipizide alone and in combination in healthy albino rats

Time in hrs	Percentage reduction in blood glucose level (mean ±sem)					
	Vehicle	Atenolol	Nebivolol	Glipizide	Atenolol +glipizide	Nebivolol + glipizide
Fasting	0.00	0.00	0.00	0.00	0.00	0.00
0.5	1.18±2.41	4.14±0.15	1.67±0.5	3.13±0.22	5.26±1.54*	1.10±0.43
1.0	2.35±3.28	2.15±0.32	3.58±0.89	7.36±0.36	15.45±1.49	4.90±0.54
2.0	2.35±3.09	3.23±0.46	5.10±0.56	20.28**±1.77	19.66±1.01	7.22±0.85
3.0	1.18±3.55	0.83±0.56	6.09±0.76	36.61***±1.26	25.02±1.22**	8.43±0.32
4.0	-4.71±3.38	1.08±0.57	7.27±0.46	47.55***±1.80	31.13±1.14***	8.81±0.35
6.0	1.18±0.58	4.30±0.58	9.11±0.56	53.76***±1.61	34.26±0.93***	8.32±0.65
8.0	0.33±0.06	6.45±0.50	8.26±0.97	58.22***±1.10	39.02±1.28***	10.49±1.12
12.0	4.71±0.64	5.38±0.54	7.30±1.02	38.64***±1.27	22.68±0.84	8.08±1.10
18.0	-5.67±0.97	3.23±0.69	5.49±0.92	23.21***±0.98	17.54±0.86	6.00±0.45
24.0	-1.90±0.06	4.68±0.53	4.68±0.91	14.97**±1.15	6.34±2.14**	3.32±0.23
30.0	-3.35±0.31	5.38±0.17	4.56±0.84	12.70**±1.28	2.22±0.97**	3.92±0.18

Table 2: Antidiabetic effect of atenolol, nebivolol and glipizide alone and in combination in diabetic albino rats

Time in hrs	Percentage reduction in blood glucose level (mean ±sem)					
	Vehicle	Atenolol	Nebivolol	Glipizide	Atenolol +glipizide	Nebivolol + glipizide
Fasting	0.00	0.00	0.00	0.00	0.00	0.00
0.5	2.48±0.87	6.74±1.12	6.98±	5.72±0.52	13.64±0.13	5.53±0.65
1.0	2.93±0.24	5.62±0.12	11.63±	10.76*±0.38	26.14±0.25***	10.14±0.95
2.0	3.39±0.77	4.27±0.26	12.79±0.26	16.02**±0.55	34.77±0.64***	11.29±1.23
3	4.51±0.73	7.42±0.38	16.28±0.38	21.51***±0.68	46.36±1.59***	18.20±2.54
4	3.61±0.81	9.44±0.14	18.60±	27.92***±0.79	50.68±0.51***	21.66±3.23
6.0	2.71±0.69	4.94±0.29	19.53±	34.78***±1.09	59.55±0.89***	22.35±2.54
8.0	1.81±0.54	4.27±0.39	12.09±	43.94***±1.19	55.00±0.84	15.90±1.14
12.0	2.48±0.38	2.25±0.40	10.00±	23.11**±1.80	40.00±1.20***	11.29±2.13
18.0	3.61±1.06	4.94±0.32	7.67±	11.44**±1.78	24.09±1.48	9.22±1.98
24.0	2.48 ±0.94	6.07±0.19	1.63±	3.20±1.39	13.64±1.12	3.23±1.13
30.0	2.93±0.33	4.92±0.27	0.70±	1.14±0.82	11.36±0.95	0.92±0.12

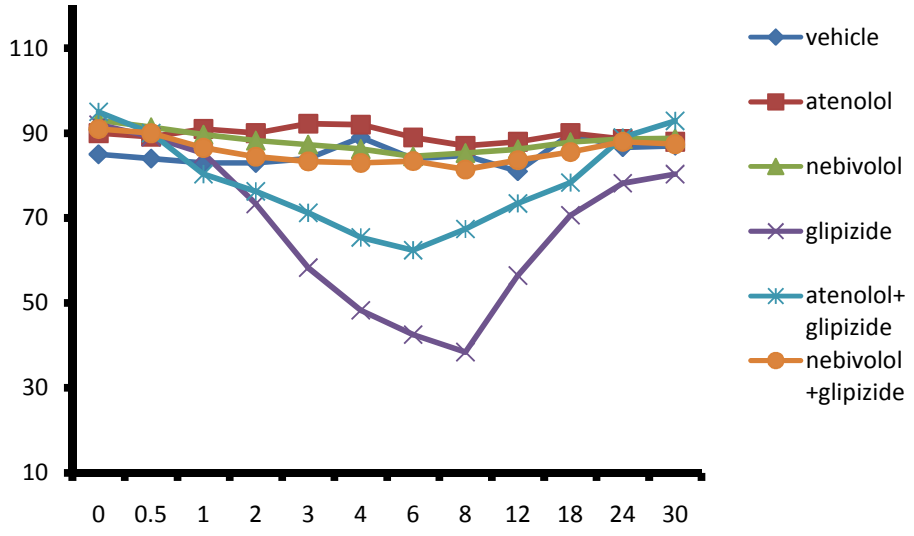

Fig: 1 Effect of atenolol, nebivolol and glipizide alone and there combination on blood glucose levels in healthy wistar albino rats

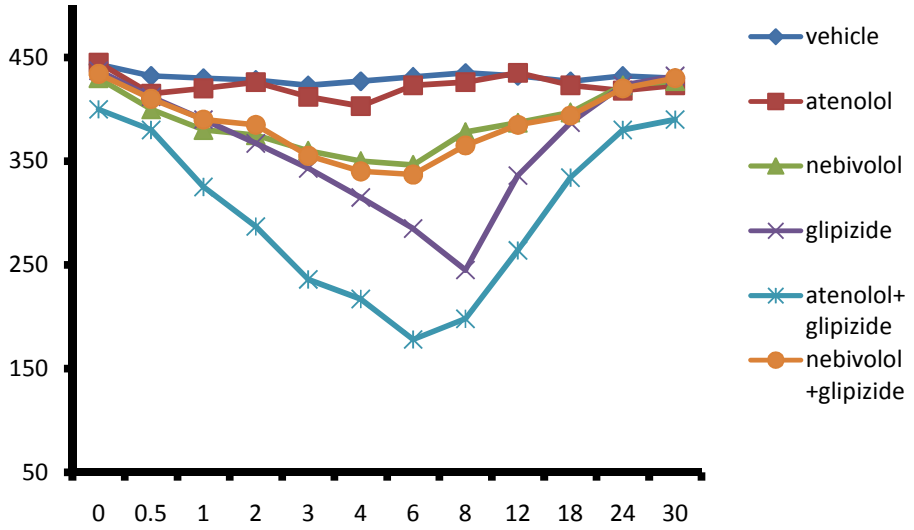

Fig: 2 Effect of atenolol, nebivolol and glipizide alone and there combination on blood glucose levels in diabetic wistar albino rats

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