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A study on drug-drug interaction between anti-hypertensive drug (propranolol) and anti-diabetic drug (glipizide)

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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 is aimed to investigate the safety, reliability of glipizide (antidiabetic drug) and possible drug interaction with propranolol when they were administered as combination treatment. The study was conducted on healthy albino and streptozotocin induced diabetic rats. The hypoglycemic effects of propranolol, glipizide alone and in combination were tested. Results showed that propranolol and glipizide did not have any potential drug interaction on single administration. Though repeated administration of propranolol followed by glipizide enhances hypoglycemic effect of glipizide up to one hour followed reduced hypoglycemic effect of glipizide through out the study period in normal animals but potentiated the hypoglycemic effect of glipizide on diabetic animals. Hence study suggested that the dose and/or frequency of glipizide administration have to be readjusted accordingly when glipizide and propranolol need to be used concomitantly.

Keywords: Drug interaction, Propranolol, Glipizide, Hypoglycemic effect.

INTRODUCTION

Drug interactions are an important and wide source of medication errors. It is estimated that drug interaction results 6-30% of all adverse drug reactions. Adverse drug interactions in hospitalized patients have been estimated to be between 2.2 and 30.0% and for ambulatory patients it is

between 9.2 and 70.3% [1]. Drug-drug interaction can be defined as the modification of the effects of one drug (i.e., the object drug) by the prior or concomitant administration of another drug [2]. Drug-drug interactions are of wide concern in patients those receiving multi-drug therapy, these types of interactions cause an increased risk of health problem including hospitalization [3]. Drug interactions can results alteration of the therapeutic efficacy of one drug, toxicity or unexpected increase in pharmacologic activity. The extent of the drug interactions is a global problem increases extensively with increase in population of patient and as the number of medications increases [4]. Hypertension in diabetic patient is one of the major and common health problem which is 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 [5]. 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 [6].

Beta blockers are often used as first line therapy in patients with hypertension including those with diabetes mellitus [7]. The rise in plasma adrenaline and other counter-regulatory hormones during hypoglycemia was enhanced by beta adrenoceptor blockade [2]. 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 [8, 9]. Propranolol is a non-selective beta-adrenergic receptor blocking agent commonly used in the treatment of hypertension. It has no other autonomic nervous system activity and act as competitive antagonist which specifically competes with beta-adrenergic receptor stimulating agents for available beta-receptor sites. When access to beta-adrenergic receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. Glipizide, a potent second generation sulfonyle ureas belongs 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. Both the drug metabolized in liver by cytochrome P450 enzyme system [10, 11].

Present study is intended to investigate the possible drug interaction between propranolol and glipizide, which may be useful for the clinically to readjust the dose of glipizide, when they are used along with propranolol.

MATERIALS AND METHODS

Drugs and chemicals

Standard drugs propranolol and glipizide are obtained form Cipla Laboratories, Mumbai and Sun Pharmaceuticals Pvt. Ltd., Mumbai respectively as a gift sample. Streptozotocin procured from Sigma-Aldrich, Banglore. Potassium oxalate, sodium fluoride and other chemicals were obtained from Hi-Media lab. Ltd, Mumbai, and were of analytical grade. Glucose estimation kit purchased from Span Diagnostic Ltd, Bengalore.

Animals

Albino rats of either sex weighing between 150-200 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 (No. 557/02/c/CPCSEA) was obtained as per the prescribed guidelines.

Study procedure

Effect of propranolol and glipizide individually and in combination were tested in healthy and diabetic rats. Diabetes was induced to a group of animals by injecting 55 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 glucose oxidase/peroxidase (GOD/POD) method, which is compared with fasting blood sugar level. Individual effect of propranolol and glipizide on blood sugar level were tested after administration of single dose in animals, whereas the influence of repeated treatment of propranolol for seven days on the hypoglycemic effect of glipizide was studied.

Influence of propranolol and glipizide on blood glucose levels in healthy and diabetic animals

Healthy normal animals were divided into three groups each consists six rats. Vehicle, propranolol (10mg/kg, *b.w.*), glipizide (10mg/kg, *b.w.*) administered orally to different groups of animals. Blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0 and 30.0 hrs and glucose levels were analyzed by GOD/POD method. The same experiment was repeated with the diabetic animals.

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

Animals were divided into two group contain six animals each. Group I contain healthy and group II contain diabetic animals. All the animals received propranolol (8mg/kg) per day orally for one week. After 18 hrs of fasting, on the 8^{th} day, '0' hour blood samples were collected for determining fasting blood glucose levels. Propranolol (8mg/kg) was given first followed by the administration of glipizide (10mg/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 autoanalyser (ERBA Mannheim) and the percentage reduction in blood glucose levels at time "t" was calculated by using the following equation.

$$\text{Percentage of Blood glucose reduction at time 't'} = [(A - B)/A] \times 100$$

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 propranolol, glipizide on blood glucose level and effect of repeated treatment of propranolol 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 propranolol as a single dose did not produce any significant change in blood glucose level in normal and diabetic animals, where as antidiabetic drug glipizide produce significant decrease in blood glucose level. Administration of propranolol for 8 days has enhanced the hypoglycemic effect of glipizide up to one hour and afterwards it had reduced the hypoglycemic effect of glipizide through out 30 hrs of study, but repeated administration of propranolol significantly increased the hypoglycemic activity of glipizide in diabetic animals.

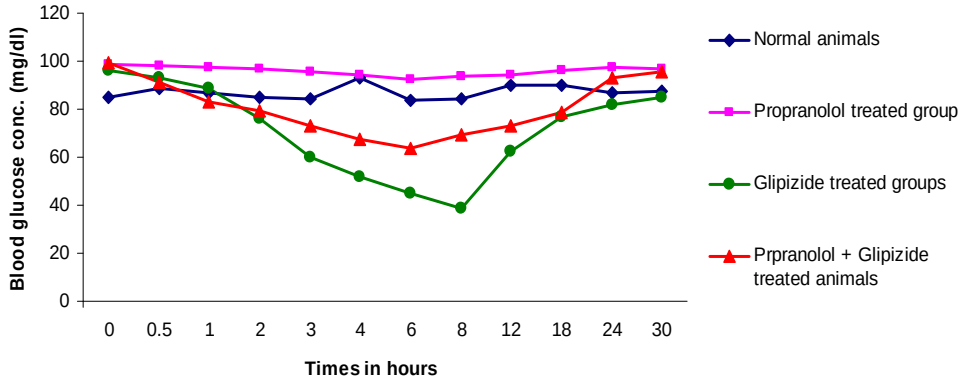

Figure 1: Effect of propranolol, glipizide alone and there combination on blood glucose level in healthy albino rats

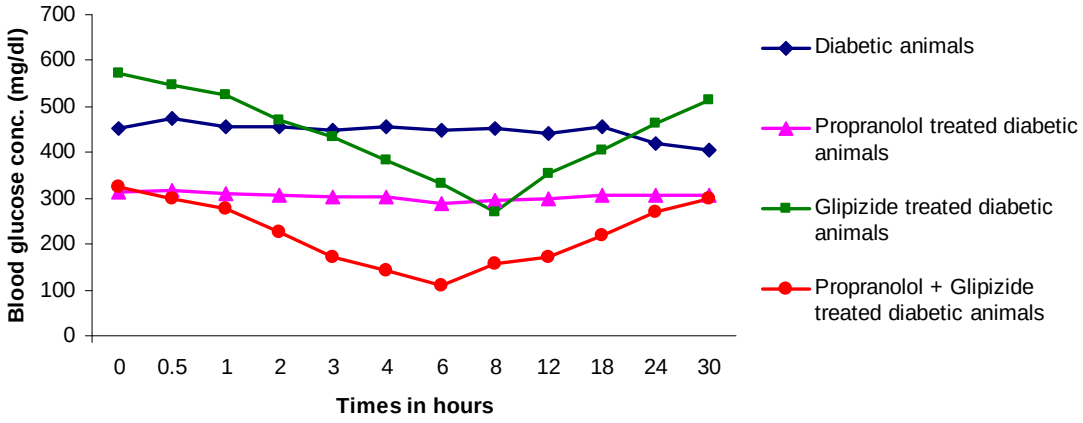

Figure 2: Effect of propranolol, glipizide alone and there combination on blood glucose level in diabetic animals

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 propranolol, glipizide alone as a single dose and in combination in normal and diabetic rats. In case of diabetic animals, propranolol potentiate the peak effect (i.e., reduction in blood glucose level is 66.16%±0.89 after

6 hrs) and duration of action 24 hrs and glipizide significantly. But there was no significant change in onset time.

Table 1. Antidiabetic effect of propranolol and glipizide alone and in combination in healthy albino rats

Time in hrs	Percentage reduction in blood glucose level (Mean±SEM)			
	Vehicle	Propranolol	Glipizide	Propranolol+Glipipzide
Fasting	0.00	0.00	0.00	0.00
0.5	-4.60±2.41	0.75± 0. 15	3.18±0.22	7.93± 1.54*
1.0	-1.95±3.28	1.15± 0. 32	7.95±0.36	16.25± 1.49
2.0	0.46±3.09	1.70± 0. 46	20.63±1.77	20.21± 1.01
3.0	0.45±3.55	3.19± 0. 56	37.46±1.26	25.90± 1.22**
4.0	-9.14±3.38	4.47± 0. 57	46.23±1.80	32.21± 1.14***
6.0	1.84±3.58	6.12± 0. 58	53.29±1.61	35.67± 0. 93***
8.0	1.17±2.06	5.24± 0. 50	59.92±1.10	30.23± 1. 28***
12.0	5.78±2.64	4.44± 0. 54	34.99±1.27	26.60± 0.84**
18.0	-5..90±1.77	2.62± 0.69	19.81±0.98	20.51± 0.86
24.0	-1.90±2.06	1.47± 0. 53	14.83±1.15	6.19± 2.14**
30.0	-3.18±2.31	1.96± 0.17	11.13±1.28	3.82± 0.97**

Table 2. Antidiabetic effect of propranolol and glipizide alone and in combination in diabetic albino rats

Time in hrs	Percentage reduction in blood glucose level (Mean±SEM)			
	Vehicle	Propranolol	Glipizide	Propranolol+Glipipzide
Fasting	0.00	0.00	0.00	0.00
0.5	-4.97±3.87	0.53±0.12	4.37±0.52	8.17±0.13
1.0	-0.83±1.24	1.15±0.12	8.47±0.38	18.03±0.25***
2.0	-0.92±0.77	1.52±0.26	18.17±0.55	30.24±0.64 ***
3.0	0.52±0.73	2.83±0.38	24.40±0.68	47.09±1.59 ***
4.0	-0.94±0.81	3.61±0.14	33.05±0.79	56.68±0.51***
6.0	0.71±0.69	7.42±0.29	41.70±1.09	66.16±0.89***
8.0	-0.17±0.54	5.61±0.39	52.86±1.19	53.39±0.84
12.0	2.41±0.38	4.26±0.40	38.44±1.80	47.14±1.20 ***
18.0	-1.21±1.06	2.39±0.32	29.31±1.78	32.73±1.48
24.0	7.27±1.34	1.80±0.19	19.25±1.39	16.84±1.12
30.0	10.33±1.33	1.81±0.27	10.17±0.82	8.42±0.95

The risk of retinopathy, stroke, 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 [12, 13, 14]. Results suggested that propranolol and glipizide did not have any potential drug interaction on single administration. However, repeated treatment of propranolol enhance hypoglycemic effect of glipizide up to one hour followed reduced hypoglycemic effect of glipizide through out the study period in normal animals. While in diabetic animals repeated administration of propranolol followed by glipizide potentiated the hypoglycemic activity.

Non-selective beta blocker can delay the return of insulin induced low blood sugar levels to normal in healthy and diabetic animals [15]. 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 propranolol group [10, 13]. These effects may be one of the reasons for the diminished hypoglycemic effect of glipizide after repeated administration of propranolol in healthy albino rats after a period of one hour. In addition literature review that indicated concomitant administration of propranolol and glipizide does not interfere with disposal of propranolol and atenolol, excluding possibility of any pharmacokinetic interactions [16].

CONCLUSION

The present study may suggest that during simultaneous treatment of antihypertension and diabetes with propranolol and glipizide the dose and frequency of administration of glipizide 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.

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