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Evaluation of the Effect of Perindopril and its Combination with Oral Anti-Diabetic Drugs on Blood Sugar Levels in Diabetic Wistar Rats

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Abstract
It is well known scientifically that ACE (Angiotensin converting enzyme) inhibitors prevent the development and progression of incipient or established nephropathy and delay the progression of diabetic retinopathy hence these drugs are routinely prescribed with the oral anti-diabetic drugs in these conditions. The actual scenario of impact of ACE inhibitors on blood glucose is still controversial therefore current study was undertaken to investigate the effect of Perindopril on blood glucose level and interaction with the oral anti-diabetic drugs in alloxan induced diabetic rats. Rats were classified into Ten groups (n = 6) where group I –II represent normal and group III –X represent diabetic rats. Perindopril doses (0.8 mg/kg body weight) were administered to both normal and diabetic rats. In diabetic groups, the Perindopril was also given with the Oral anti-diabetic drugs to check-out any alteration in blood glucose level .All drugs administered orally once a day for 13 days and then Oral Glucose Tolerance Test (OGTT) was conducted. It was observed that in normal rats the Perindopril insignificantly ($P>0.05$) reduced the blood glucose level at all time points. In contrast, Perindopril showed significant ($P\leq0.01$ and $P\leq0.001$) anti-hyperglycemic activity at all time points when given either alone or with the Oral anti-diabetic drugs respectively in alloxan-induced diabetic rats. Hence the present study concluded that the Perindopril has anti-hyperglycemic activities which accentuate the effect of oral anti-diabetic drugs in diabetic rats significantly. .

Keywords: Perindopril; Blood glucose; Diabetic wistar rats; Oral anti-diabetic drugs.

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INTRODUCTION

Diabetes mellitus (DM) has been considered as one of the major health concerns all around the world today [1-2]. Experimental animal models are one of the best strategies for the understanding of patho-physiology of diseases in order to design and develop new drugs [3-4]. Numerous animal models have been developed for the past few decades for studying DM and testing anti-diabetic agents via chemical, surgical and genetic manipulations. One of the most potent methods to induce experimental DM is chemical induction by alloxan [5-6] which is a well- known diabetogenic agent widely used to induce Type II diabetes in experimental animals [7].

DM describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Approximately 140 million people worldwide suffer from diabetes [8-9] which is a leading cause of morbidity and mortality in the United States. DM is often complicated by micro- and macro-vascular involvements which contribute to the damage of one or more target organs. Diabetic nephropathy (DN) is a well-known micro-vascular complication of diabetes and is responsible for 40% – 50% of all cases of end stage renal disease (ESRD) in the United States adult population [10-11]. In the past 2 decades, there has been a continual increase in the incidence of ESRD among patients with diabetes, predominantly those with type 2 diabetes [12-13].

Pharmaceutically, drugs for treating DM fall into several categories: Firstly, drugs that primarily stimulates insulin secretion by binding to the sulfonylurea receptor, for example: Sulfonylureas which remain as the most widely prescribed drugs for treating hyperglycemia. The Meglitinide analog such as Repaglinide and Nateglinide, also bind the sulfonylurea receptor and stimulate insulin secretion. Secondly, drugs that primarily lowers glucose levels by acting on hepatic muscle and adipose tissue, for example: Metformin works in the liver while Thiazolidinediones, such as Pioglitazone and Rosiglitazone appear to have their main effect on skeletal muscle and adipose tissue. Thirdly, drugs that principally affect the absorption of glucose, for example: α- glucosidase inhibitors such as Acarbose and Miglitol. Fourthly, drugs that mimic incretin effect or prolong incretin action: Glucagon-like peptide-1 (GLP-1) receptor agonists and DPP-4 (Di-peptidyl peptidase-4) inhibitors are good examples for this category. Other drugs such as pramlintide decrease blood glucose level by suppressing glucagon and slowing gastric emptying.

Current therapeutic options focused on delaying the progression of DN. This includes intensive blood glucose control, improved blood pressure control, interruption of the Renin-angiotensin –aldosterone system (RAAS) using angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin type-1 (AT_1) receptor blockers (ARB) along with dietary modification and cholesterol-lowering agents [14]. Despite the aggressive multi-factorial interventions, DN remains the single leading cause of ESRD in the United States.

In diabetic patients, ACE inhibitors prevent the development and progression of incipient or established nephropathy [15-16] and delay the progression of diabetic retinopathy [17].The ACE inhibitors/ARB have been recommended as the treatment of choice for all patients with diabetic nephropathy regardless of the diabetes type [18].

The pharmacological treatment of DM requires a continued monitoring for optimal blood sugar level in patients because strict blood sugar regulation can prevent many of the complications of diabetes like retinopathy, neuropathy, nephropathy and vascular abnormalities. Avoidance of hypoglycemia is also important to prevent convulsion, coma and death. It is therefore necessary to know the interactions of various pharmacological agents with anti-diabetic agents which would be very helpful for clinician to avoid or at least to minimize the previous complications by optimizing the doses and the schedule of drugs administration or by using alternative drugs.

Diabetes and hypertension are both independent risk factors for cardiovascular diseases and the risk is even more when accompanied by nephropathy. Cardiovascular causes account for more than half of the mortality associated with nephropathy [19]. As ACE inhibitors are the first line of drugs for hypertension in diabetes and routinely prescribed with the anti-diabetic drugs, it is therefore worthy to investigate the interaction between them. The actual impact of ACE inhibitors on blood glucose is contradicted because some studies have showed the hypoglycemic activity but some are in favor of neutral activity. Many of the previous studies were made on the effect of Captopril which is prototype of the ACE inhibitor. Thus, this study was planned to investigate interactions of Perindopril with various oral hypoglycemic agents on experimental animal.

.MATERIALS AND METHODS

Animals:

The study was conducted on male and female albino wistar rats weighing 150-250 gm. The animals were made available in the Central animal house, GSVM Medical College, Kanpur, Uttar Pradesh, India. Rats were housed in polypropylene cages and maintained under standard conditions (room temperature 25± 3º

C, 35-60% humidity and 12 h light /dark cycle), fed in standard pellet diet and drinking water *ad libitum*. The study was approved by the Institutional Animal Ethics Committee (IAEC), GSVM Medical College, Kanpur, India. The procedures were conducted in accordance with the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) [20] while handling experimental animals.

Induction of Experimental Diabetes:

Diabetes was induced in albino rats by a single intra-peritoneal injection of aqueous alloxan monohydrate (135 mg/kg body weight) (Sigma Chemical Co. USA) [21]. Blood samples were collected before and after the administration of alloxan to know the status of diabetes. After two days, diabetes was confirmed by testing blood glucose level using glucometer and they were further maintained for four days for well establishment of diabetes. Finally, animals with blood glucose level more than 200 mg/dl (moderate diabetes) were selected for the experiment.

Drugs and chemical agents:

Alloxan- alloxan monohydrate (Sigma) (dose-135 mg/kg body weight/rat),ACE inhibitor- Perindopril (Torrent) (dose of 0.8 mg /kg body weight /day /rat), Oral anti-diabetics drugs- (a) Biguanides- Metformin (Bristol-Myers Squibb) (225 mg /Kg body weight /day /rat), (b) Second generation Sulfonylureas- Gliclazide (Torrent) (22 mg/ Kg body weight/day /rat) (c) Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ) agonists-Pioglitazone (Zydus Cadila) (4 mg /kg body weight/day /rat).

The doses of the drugs were calculated by extrapolating the therapeutic dose to rat dose on the basis of body surface area ratio (conversion factor 0.18 for rats) by referring to the table of "Paget & Barns"(Paget and Barnes, 1964).[22]

Experimental Design:

Rats were classified into Ten groups (n = 6) where group I –II represent normal and group III –X represent diabetic rats. Rats in Group I (NC) received 1 ml sterile water and served as normal control. Rats of Group II (N+PP) received Perindopril only. Rats of diabetic Group III (DC) received 1 ml sterile water and considered as diabetic control. Rats of diabetic Group IV (D+PP) treated with Perindopril only, Group V (D+M) received Metformin only, Group VI (D+G) received Gliclazide only and Group VII (D+P) treated with Pioglitazone only. The oral anti-diabetic drugs treated groups (Group V – VII) served as positive control for the rest of the groups respectively (Group VIII, IX and X). Rats of diabetic Group VIII (D+M+PP) were treated with both Perindopril and Metformin, Group IX (D+G+PP) treated with Perindopril and Gliclazide together and Group X (D+P+PP) treated with Perindopril and Pioglitazone. The animals of all groups received the doses orally for 13 consecutive days and at the end of the experiment an Oral Glucose Tolerance Test (OGTT) [23] was conducted and blood glucose estimation was done in all groups.

Oral Glucose Tolerance Test:

After an overnight fasting, '0' min blood samples (0.2 ml) were taken from the all groups by orbital sinus puncture [24]. Glucose solution (2 g/kg of 25% w/v) was administered orally in OGTT. Three more samples were taken at '30' min, '60' min and '120' min after glucose administration.

Blood Glucose Estimation:

Blood samples (0.2 ml) were collected and then centrifuged at 3000 rpm for 10 min. The clear supernatant layer was taken to estimate the blood glucose level. The plasma blood glucose levels were determined by Glucose-Oxidase-Peroxidase (GOD–POD) method [25]. Span diagnostic reagent kit (code no. B 0112) was used for the estimation of the blood glucose level.

Statistical analysis:

Data were expressed as mean ± standard error of mean (SEM). Statistical comparisons were performed by independent student t-test. Results were considered to be significant when P values were less than 0.05 ($P<0.05$).

RESULTS

Effect on Normal Rats:

Perindopril shows significant changes on blood glucose levels in normal rats as seen **Table 1**. It is observed that Perindopril, in a dose of 0.8 mg/ kg body weight, slightly reduced the blood glucose level at all of time points insignificantly ($P>0.05$). It means that it exerts some insignificant hypoglycemic activity in normal rats.

S.N.	Groups	Serum glucose level (mg/dl)			
		0 min (Fasting)	30 min	60 min	120 min
I	I(NC)	78.33±3.19	100.66±2.71	91.50±1.66	85.66±2.98
2	II(N+PP)	71.66±2.44 (8.51%)	94.66±0.88 (5.96%)	89.16±1.51 (2.55%)	81.66±3.10 (4.66%)

Table 1: Effect of Perindopril on blood glucose level in normal rats Values are expressed as Mean ±S.E (% reduction); (n=6)

Effect on Alloxan Induced Diabetic Rats:

The effect of 13-day administration of Perindopril and Oral anti-diabetic drugs on blood glucose levels in alloxan induced diabetic rats is shown in Table 2. It is noteworthy to mention that Perindopril has showed

significant anti-hyperglycemic effect in diabetic rats. The highest percentage of blood glucose reduction was obtained at 120 min and found to be 26.55%. The other obtained results were found to be 8.39% at 0 min, 8.73% at 30 min and 14.45% at 60 min. The results were significant ($P < 0.05$) at 0 and 30 min and highly significant ($P < 0.01$ and $P < 0.001$) at 60 and 120 min. Table 2 also indicates that Metformin, Gliclazide and Pioglitazone have significant hypoglycemic activities at all-time points in alloxan induced diabetic rats which is universal.

S.N.	Groups	Serum glucose level (mg/dl)			
		0 min (Fasting)	30 min	60 min	120 min
1	III(DC)	254.16±6.12	286.16±5.33	345.83±8.10	350.83±6.71
2	IV(D+PP)	232.83±2.85 ** (8.39%)	261.16±5.81 ** (8.73%)	295.83±17.37 * (14.45%)	257.66±4.63 *** (26.55%)
3	V(D+M)	224.00±3.69 ** (11.86%)	254.83±8.85 * (10.94%)	288.83±6.30 *** (16.48%)	228.50±5.28 *** (34.86%)
4	VI(D+G)	226.66±5.03 ** (10.81%)	256.83±9.11 * (10.24%)	290.16±0.83 *** (16.09%)	229.50±6.09 *** (34.58%)
5	VII(D+P)	226.83±5.38 ** (10.75%)	256.56±8.63 * (10.34%)	293.00±2.39 *** (15.27%)	230.33±5.25 *** (34.34%)

Table 2: Effect of Perindopril and Oral anti-diabetic drugs on blood glucose level in Alloxan-induced diabetic rats
Values are expressed as Mean ± S.E (% reduction); (n=6), Significance levels as compared to control (* P ≤0.05** P≤0.01*** P≤0.001)

Table 3 represents the Interaction of Perindopril with the Oral anti-diabetic drugs in alloxan induced diabetic rats. Significant changes in serum glucose levels were seen with respect to the positive control groups. It was revealed that blood glucose level is decreased due to Perindopril at all-time points, in all groups, significantly (P≤0.001). In comparison of group V (D+M) & group VIII (D+M+R), group VI (D+G) & group IX (D+G+R) and group VII (D+P) & group X (D+P+R), Perindopril exhibited the highest hypoglycemic activity at 'O' min (fasting time point) with reduction of 32.07%, 34.04% and 27.99% respectively.

S.N.	Groups	Serum glucose level (mg/dl)			
		0 min (Fasting)	30 min	60 min	120 min
I	V(D+M)	224.00±3.69	254.83±8.85	288.83±6.30	228.50±5.28
2	VIII(D+M+P)	152.16±3.40 *** (32.07%)	185.33±2.38 *** (27.27%)	224.16±4.74 *** (22.39%)	163.83±5.47 *** (28.30%)
3	VI(D+G)	226.66±5.03	256.83±9.11	290.16±0.83	229.50±6.09
4	IX(D+G+PP)	149.50±4.55 *** (34.04%)	194.66±4.11 *** (24.20%)	225.00±3.41 *** (22.45%)	183.33±5.38 *** (20.11%)
5	VII(D+P)	226.83±5.38	256.56±8.63	293.00±2.39	230.33±5.25
6	X(D+P+PP)	163.33±4.34 *** (27.99%)	201.83±5.63 *** (21.33%)	218.83±4.67 *** (25.31%)	167.00±4.58 *** (27.49%)

Table 3: Interaction of Perindopril with the Oral anti-diabetic drugs in Alloxan induced diabetic rats
Values are expressed as Mean ± S.E (% reduction); (n=6), Significance levels as compared to control (* P ≤0.05 ** P≤0.01 *** P≤0.001)

DISCUSSION

Our study has evaluated the significant interaction of Perindopril with different groups of Oral hypoglycemic drugs in alloxan induced diabetic rats. As it has been widely accepted that alloxan selectively destroys the insulin-producing β-cells found in the pancreas, hence it is used to induce diabetes in laboratory animals. The toxic affect of alloxan on β-cells involve oxidation of essential sulphydryl (-SH groups), inhibition of glucokinase enzyme, generation of free radicals and disturbances in intracellular calcium homeostasis [26-27]. The underlying mechanism involves the selective uptake of the compound due to its structural similarity to glucose as well as the highly efficient uptake mechanism of the pancreatic beta-cells[28-29].The Moderate diabetic animals are recommended for use in testing drugs for use in Type II DM[30]. Hence in this research, moderate diabetes was induced by alloxan monohydrate doses of 135 mg/kg body weight.

In light of results, the study indicates that the ACE inhibitor Perindopril did not exhibit significant reduction in blood glucose levels in normoglycemic rats but it showed significant anti-hyperglycemic activity in diabetic rats where it enhanced the hypoglycemic activity of all of the three Oral anti-diabetic drugs (Metformin,Gliclazide and Pioglitazone). The Metformin delays the absorption of glucose from

the gastrointestinal tract, increases the insulin sensitivity of cells, suppresses hepatic gluconeogenesis [31-32] and enhances glucose transport in fat tissue and muscles [33]. It does not usually lower the blood glucose concentrations in non-diabetic subjects. The Gliclazides stimulate insulin secretion in the β-cells and inhibit glycogenolysis and gluconeogenesis in the liver. Through improving insulin binding to surface receptors, they also enhance the insulin sensitivity of target cells. It has been demonstrated that Pioglitazone decreases plasma glucose levels by improving insulin sensitivity[34]. The present findings suggest that Perindopril may have insulin sensitivity potentiating properties in type 2 diabetes mellitus. Moreover, it enhanced the anti-hyperglycemic activities of Metformin, Glicalzide and pioglitazone, probably by same mechanism. The results are being strengthened by previous studies which documented the potential for ACE inhibitor-associated hypoglycemia but majority of these are with the use of Captopril[35-36].The mechanism of drug-induced hypoglycaemia is not well defined, it is proposed that the increase in bradykinins associated with ACE inhibitor use may cause an increase in insulin sensitivity[37-38]. In contrast, Wiggam *et al* demonstrated that ACE inhibitors have no impact on hepatic or peripheral insulin sensitivity[39]. The results are also consistent with our previous studies with other different ACE inhibitors like Ramipril, Enalapril and Lisinopril in diabetic rats. (40-42)

Although the present findings confirm the anti-hyperglycemic potential but the precise mechanism of its action requires further studies for appropriate elucidation. The limitation of our study is small sample size due to ethical reason.

CONCLUSION

The present study shows that the ACE inhibitor "Perindopril" lower blood glucose levels in alloxan induced diabetic rats in significant manner. Also, it augments the blood glucose lowering effect of Metformin, Gliclazide and Pioglitazone. It is therefore advisable to prescribe and use of ACE inhibitors with anti-diabetic drugs carefully with necessary dose adjustment to avoid adverse hypoglycemic episodes in diabetic individuals. Because of the contradicting information available, the actual impact of ACE inhibitors on blood glucose is not clear. Hence it is important to have a clear cut picture on the effect of ACE inhibitors on blood glucose level in large sample size of animals and subsequently on human being by state of art modern scientific techniques to investigate the exact mechanism of action involved in the anti-hyperglycemic activity of ACE inhibitors.

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