*ejpmr, 2018,5(4), 467-471*

**SJIF Impact Factor 4.897**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

**Research Article**

**ISSN 2394-3211**

**EJPMR**

# EFFECT OF ENALAPRIL, LOSARTAN ALONE AND IN COMBINATION ON BLOOD GLUCOSE, SERUM INSULIN AND SERUM CORTISOL IN RABBITS.

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**Article Received on 09/01/2018** **Article Revised on 01/03/2018** **Article Accepted on 21/03/2018**

## ABSTRACT

**Introduction:** Diabetes is a growing epidemic in greatest number of cases being expected in China and India. Enalapril and Losartan one of the most commonly used antihypertensives were reported to cause hypoglycemia. **Material and Methods:** 24 albino rabbits were selected after screening and randomized in 4 groups, control (gum acacia), Enalapril, Losartan and combination of Enalapril and Losartan. At zero hours blood collected for baseline investigations, subsequently food administered, followed by drug administration to respective groups. Blood collected at zero (baseline), 1, 2 and 4 hours for blood glucose, serum insulin and serum cortisol levels. **Results:** The blood glucose levels in Enalapril group was 82.76±0.60, in Losartan (84.85±0.61) and combination of Enalapril and Losartan group (81.26±0.58) showed statistically significant reduction at 1 hour compared to control (98.76±0.64) and similar results were seen at 2 and 4 hours of administering the medication. The Serum Insulin levels in Enalapril (9.93±0.11), Losartan (9.73±0.11) and combination (10.31±0.17) showed statistically significant reduction as compared to control (7.82±0.22) at 1 hour and similar results were seen at 2 and 4 hours. The Serum Cortisol levels in Enalapril (2.36±0.26), Losartan(2.53±0.30) and combination (2.18±0.28) showed statistically significant ($p<0.05$) reduction at 1 hour as compared to control (3.94±0.38) and similar results were also at 2 and 4 hours. **Conclusion:** Enalapril, Losartan, alone and in combination has antihyperlycemic effect, this can be used in patients having hypertension with impaired glucose tolerance. These medications also have a chance of causing hypoglycaemia at high doses.

**KEYWORDS:** Antihyperglycemic, Enalapril, Losartan, Hypoglycemia, Rabbits.

## INTRODUCTION

Diabetes Mellitus (DM) is a growing epidemic not only in developed but also in developing world. The worldwide prevalence of DM in 20–79 years of age was 6.4% affecting almost 285 million in 2010 this is going to increase to 7.7% by 2030.[1,2] The greatest number of cases being expected in China and India. High frequency of impaired glucose tolerance, ranging from 3.6-9.1% indicate the potential for further rise in diabetes mellitus in the coming decades.[3,4] The prevalence of diabetes in India currently is reported to be around 13-15% and is among the highest in the world. The Indian population has increased susceptibility to diabetes mellitus with enormous potential for further rise in prevalence diabetes shown by high frequencies of impaired glucose tolerance. Prevalence of Type 2 Diabetes will grow more rapidly in India than any other developing or developed nation.[5]

When patient presents with the diagnosis of hypertension (HT) with DM, multiple drug therapy consisting of the oral hypoglycaemic drug along with an antihypertensive drug is used for the treatment of DM & HT respectively.[6] This increases the economic burden on the patients, poor patient compliance and increased side effects.

Antihypertensive medications like Beta blockers and Calcium channel blockers have an increase risk of developing diabetes, thus reduction in hypertension alone is not the factor to prevent new onset diabetes.[7] While antihypertensives that act on renin angiotensin aldosterone system inhibition has shown to have beneficial effect on risk of diabetes by 25%.[8] Currently no single drug is available to treat hypertensive patients with impaired glucose tolerance (IGT), while the number of individuals with IGT worldwide is enormous and

approximately 5% of them develop diabetes each year.[9] There is also no available single drug which can be useful for the management of both, HT and DM, patients with metabolic syndrome, pre-diabetic with mild to moderate hypertension. Angiotensin Receptor Blockers (ARB) medication that is Losartan and Angiotensin Converting Enzyme inhibitors (ACEI) medication that is Enalapril both the medications act on Renin Angiotensin Aldosterone System (RAAS). Thus study was undertaken to study effect of Enalapril and Losartan alone and in combination on blood glucose, serum insulin and serum cortisol in albino rabbits.

## MATERIALS AND METHODS

The study was approved by Institutional Animal ethical committee of medical college and tertiary care hospital. The study site was Central animal house of a medical college and tertiary care hospital.

We used the maximum dose of Enalapril (40 mg), losartan(100mg) in humans and interpolated that to the dose in rabbits based on surface area. From the interpolation the dose of Enalapril (40 mg) was 1.9mg/kg/day, losartan (100mg) (4.6mg/kg/day) and combination (Enalapril 1.9mg/kg/day + Losartan 4.6mg/kg/day). The above medications were administered orally in the respective dose as a suspension in 2% gum acacia. 2% Gum acacia was used as vehicle control. The above medications was made in a volume of 5 ml and administered as a single dose with the help of feeding catheter and syringe.[10,11]

In our study 24 New Zealand Albino rabbits of either gender and having body weight >1.5 kilogram (kg) (1.5-5) and >24 weeks (6months-3years) of age were randomly chosen and divided into 4 groups (n=6). These albino rabbits used in the study were given water ad libitum and were fed on uniform standard diet for two weeks and then screened for the study. The animals raised in central animal house were used in the study. The rabbits were placed in comfortable restraining cages to avoid undue excitement. Selected rabbits were screened for blood glucose level by glucometer and those having normal levels were included for randomization.

All the rabbits selected in the study were fasted for 24 hours with free access to water, after 24 hours of fasting, about 3-5 ml blood was collected from lateral marginal vein of the ear for baseline investigations, fasting blood glucose, serum insulin and serum cortisol, this reading was considered as zero hour reading. Following this all animals were fed with same quantity of standard diet. After feeding, rabbits were given a single oral dose of 2% gum acacia, Enalapril, Losartan, and combination of Enalapril and Losartan to their respective group in the above mentioned doses. Study groups and medication dosages are given in table 1. After giving the medications only water was given and food was withheld till the last blood sample has been taken. Blood samples were drawn from all groups for estimation of blood glucose, serum insulin and serum cortisol at 1, 2 and 4 hours from the time control and test drugs were administered to their respective groups. The care and use of rabbits used in the study was done according to guidelines by animal ethical committee and Committee for the Purpose of Control and Supervision of Experiments guidelines.[12] Blood was placed in neatly labelled fluoride & plain tubes. Blood samples were kept at room temperature for coagulation to be completed, subsequently samples were subjected to centrifugation and supernatant plasma and serum was separated. Blood was sent for investigations to Central Laboratory and Lifeline laboratory, Mumbai.

**Table 1: Study groups and drug dosages.**

| Sr no. | Group | Medications |
|---|---|---|
| 1) | Group I (C) | Control 2% gum acacia |
| 2) | Group II (E) | Enalapril (1.9mg/kg/day) |
| 3) | Group III (L) | Losartan (4.6mg/kg/day) |
| 4) | Group IV (E+L) | Enalapril (1.9mg/kg/day) + Losartan (4.6mg/kg/day) |

Blood glucose was estimated by Glucose – oxidase method. Insulin estimation was done by using Solid Phase Radio Immuno Assay kit. Cortisol estimation was done by CLIA (Chemi luminescent Immuno Assay).

### Statistical analysis

All quantitative data is presented as mean $\pm$ standard deviation (SD). The p value of $< 0.05$ was considered as significant for all the tests applied. The groups were compared using one way ANOVA test with post hoc Tukey's test.

## RESULTS

The effect of test medications on BGL (blood glucose levels) at different time intervals is given in table 2. Effect of test medications on Serum Insulin at different time intervals is given in table 3. Effect of test medications on Serum cortisol at different time intervals is given in table 4. The values in table are expressed as mean $\pm$ S.D.

**Table 2: Effect of Medications on blood glucose at different time intervals.**

| Group | Blood Glucose (mg/dl) | | | |
|---|---|---|---|---|
| | **0 hour** | **1 hour** | **2 hour** | **4 hour** |
| Group I (C) | 82.55±0.58 | 98.76±0.64 | 96.23±0.52 | 94.55±0.54 |
| Group II (E) | 84.65± 0.58 | 82.76±0.60 ** | 78.32±0.55*** | 75.43±0.52*** |
| Group III (L) | 84.02±0.57 | 84.85±0.61** | 80.18±0.63*** | 77.08±0.67*** |
| Group IV (E+L) | 86.24±0.54 | 81.26±0.58*** | 77.97±0.58*** | 75.26±0.85*** |
| **P value** | 0.6742 | 0.0006 | < 0.0001 | < 0.0001 |

*P<0.05, **P<0.01, *** P<0.001, when compared to Group I (C).

**Table 3: Effect of Medications on serum insulin at different time intervals.**

| Group | Serum Insulin (μ IU/ml) | | | |
|---|---|---|---|---|
| | **0 hour** | **1 hour** | **2 hour** | **4 hour** |
| Group I (C) | 6.23±0.21 | 7.82±0.22 | 7.56±0.21 | 7.22±0.27 |
| Group II (E) | 6.21±0.19 | 9.93±0.11*** | 9.51±0.17*** | 9.31±0.26*** |
| Group III (L) | 6.27±0.20 | 9.73±0.11*** | 9.38±0.23*** | 9.13±0.15*** |
| Group IV (E+L) | 6.13±0.19 | 10.31±0.17*** | 10.04±0.22*** | 9.66±0.17*** |
| **P** | 0.9704 | < 0.0001 | < 0.0001 | < 0.0001 |

*P<0.05, **P<0.01, *** P<0.001, when compared to Group I (C).

**Table 4: Effect of Medications on serum cortisol at different time intervals.**

| Groups | Serum Cortisol (mcg/dl) | | | |
|---|---|---|---|---|
| | **0 hour** | **1 hour** | **2 hour** | **4 hour** |
| Group I (C) | 5.32±0.25 | 3.94±0.38 | 4.12±0.27 | 4.31±0.29 |
| Group II (E) | 5.35±0.19 | 2.36±0.26*** | 2.75±0.28*** | 2.87±0.30** |
| Group III (L) | 5.29±0.21 | 2.53±0.30*** | 2.83±0.33** | 3.08±0.32** |
| Group IV (E+L) | 5.60±0.18 | 2.18±0.28*** | 2.56±0.27*** | 2.78±0.38*** |
| **P** | 0.6666 | < 0.0001 | < 0.0001 | < 0.0001 |

*P<0.05, **P<0.01, *** P<0.001, when compared to Group I (C).

## DISCUSSION

Currently ACI and ARB are used alone or in combination in hypertensive patients with diabetic nephropathy. Combination of ACE inhibitor with ARB is used in patients with uncontrolled hypertension who are on single Medication therapy, in heart failure.[7]

There were several case reports of patients having episodes of severe hypoglycaemia in hypertensive‘s who were given large doses of ACEI or ARBs for hypertensive emergencies in diabetics as well as in non-diabetics.[13,14] Hypoglycaemia was noted in type 1 and type 2 diabetics when an ACE inhibitor was added to their therapeutic regimen, in which withdrawal of hypoglycaemic medications became necessary.[15,16] Similar instances of a reduction in blood sugar in both non-diabetic and diabetic patients given Enalapril, have occurred.[17] The clinical trial of Studies Of Left Ventricular Dysfunction reported reduction of new cases of diabetes that was statistically significant in patients that were using medication of Enalapril.[18,19] Also Meta-analysis by Bjergaard suggests that RAAS inhibition significantly reduces incidence of type 2 diabetes mellitus in patients diagnosed with hypertension and those diagnosed with congestive cardiac failure.[20,21] However some studies like STOP (Swedish Trial in Old Patients with Hypertension) -2 trial failed to show any protective effect of ACEIs against the development of type 2 diabetic patients.[18,19] In study by Arivazhahan it was suggested that high dose of enalapril can be considered as an important component of therapeutic regimens to combat dyslipidaemia weight gain, hyperglycaemia and seen in metabolic syndrome.[22] In study by Pinheiro Resveratrol and enalapril were used in mice and they improved the glucose and lipid levels in mice.[23]

In our study Enalapril and Losartan individually and in combination at high dose showed statistically significant attenuation in rise of blood glucose levels, decrease in serum cortisol levels and increase in serum insulin and the maximum activity at 1 hour after giving the medication. This coincides with the peak serum value of Enalapril and Losartan.[24]

In animal studies angiotensin had shown to be responsible for vasoconstriction in the endocrine pancreas. ACE inhibition and angiotensin two receptor blockade had caused increase in islet blood flow. Study by McCall in which angiotensin two was infused in healthy humans that resulted in blunting of insulin secretion. Hypertensive patients were administered oral or intravenous glucose followed by infused of ACE inhibition medications, this resulted in insulin secretion and especially improvement of the first phase.[25]

Normal islet function involves increased insulin secretion by beta cells from pancreas in response to

hyperglycemia.[26] In study by Bindom Angiotensin two has been known to decrease the blood flow to islet cells and thereby decreasing the insulin secretion. ACEI or ARBs mediated vasodilatation lead to increased blood flow in pancreas which could cause an increase in insulin secretion and preservation of islet function in diabetes.[6,27] Thus by the mechanism of decreasing ACE and blocking AT two there can be increase in insulin secretion. Serum cortisol is produced as a compensatory hormone in response to stress due to hypoglycaemia. Hormones like cortisol and growth hormone have been shown to limit hypoglycemia that occurs in study on healthy humans after prolonged infusion of intravenous insulin. In study by Reynolds subjects had significantly higher plasma cortisol that were glucose intolerant.[28,29]

Evidence suggests that the pancreas has a local renin-angiotensin system. In perfused preparations of pancreas angiotensin two infusion has shown to decrease insulin secretion. ACE inhibition medication causes vasoconstriction in endocrine pancreas whereas angiotensin two receptor blockade preferentially increase islet blood flow. Angiotensin two on perfused pancreas preparations had delayed the first phase of insulin release seen with response to glucose.[25]

One of the mechanism by which ACE inhibitors and ARB cause hypoglycaemia is through reduction of compensatory hormone cortisol. ACE inhibitor medications has been reported to attenuate counter regulatory hormones like cortisol, catecholamines and adrenocorticotropic hormone.[30] In a study by Deninger et al on Losartan reduces symptoms and counter regulatory responses during hypoglycemia in healthy patients.[15] In a study by Navarro with fructose feed rats showed that Angiotensin two played an important role in both the BP elevation and increase in persistent blood glucose. This effects were decreased when fructose fed rats were given Losartan in high dose as compared to placebo.[31]

ACE inhibitors attenuate endothelial dysfunction and improve glucose metabolism thus importantly reducing blood glucose levels and incidence of new onset diabetes. ACE catalyzes the conversion of Angiotensin I to Angiotensin II which causes vasoconstriction, by the same mechanism it inhibits glucose metabolism and increases blood glucose. The relevance of the reduced generation of Angiotensin II by the action of ACE-inhibitors can be seen from studies showing that Angiotensin II receptor antagonists exhibit almost the same effects in reducing hypertension and blood glucose as those elicited by ACE inhibitors.[32]

Combined ACEI and ARB has greater effect than monotherapy on blood pressure and left ventricular hypertrophy in sponataneously hypertensive rats. ACE inhibitors decrease the level of ACE and ARB block the AT II receptors, although both the medications have different mechanism of action but both act on the same pathway that is RAS system and on consecutive steps.[33] This might be the reason that the combination is not having additive effect on serum insulin and serum cortisol levels. Rabbits are the animals of choice for normoglycemic animal model as they have been used for standardization of Insulin for many years and also for the ease in handling. As rabbits have a stable blood glucose and repeated blood collection can be done, so it was selected for the study.[11]

Hypoglycaemia was noted in type 1 diabetics when an ACE inhibitor was added to their therapeutic regimen; it was also seen in a type 2 diabetic, in whom withdrawal of hypoglycaemic drugs became necessary. Similar instances of a reduction in blood sugar in both non-diabetic and diabetic patients given Enalapril, an ACEI have occurred.[14,15,16] These medications can be used in patients with untreated essential hypertension tend to develop higher fasting as well as higher postprandial insulin levels than normotensive patients. Patients in young age group suffer from Metabolic syndrome which consists of hyperglycemia, hypertension, central obesity, hypertriglyceridemia and low high-density lipoproteins cholesterol.[6]

Clinical evaluation of patients on Enalapril, losartan and combination may be followed for benefits on blood glucose. Those are newly prescribed should be prescribed keeping in mind the effect on blood glucose. Thus further studies are needed to elicitate long term action of these medications.

**ACKNOWLEDGEMENT**

The authors would like to acknowledge the guidance and support of Dr.S.B.Patel, Professor and Head, Department of Pharmacology, Grant Governmental Medical College and Sir JJ Group of Hospitals, Mumbai.

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