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Effect of Losartan on Different Biochemical Parameters in Essential Hypertensive Patients

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The renin–angiotensin system (RAS) provides the most powerful regulation of blood pressure and angiotensin II is the primary mediator in this system. The binding of angiotensin II to AT_1 receptors produces a number of potentially harmful effects that include increase in blood pressure, progression of atherosclerosis, myocardial and vascular hypertrophy. Losartan was the first ARB and found to reduce the risk of stroke, new onset of diabetes and to have a proven benefit in stroke. The present study was designed to evaluate the effect of losartan on different biochemical parameters *viz;* blood sugar, lipid profile, uric acid and serum electrolytes. 29 newly diagnosed patients of either gender with essential hypertension were included in the study. Baseline readings of lipid profile, serum electrolytes, fasting blood sugar and uric acid were recorded before starting losartan monotherapy and were repeated after six months.After comparing the means, it was revealed that there was a significant increase in HDL cholesterol and a significant decrease in serum uric acid levels after six months of losartan therapy. No significant difference was found in blood sugar and electrolyte levels.These findings suggest that losartan can be an attractive option for the treatment of hypertension and for metabolic syndrome.

Keywords: Losartan,essential hypertension, lipid profile, blood sugar level, serum electrolytes, serum uric acid.

Hypertension being a common health problem, is usually a progressive disorder, and one of the leading causes of death and disability worldwide. It is a major risk factor for cardiovascular diseases[1,2]. Lowering of elevated blood pressure decreases morbidity from cardiovascular, cerebral and renal failure[3]. Essential hypertension is a condition where the cause for rise in blood pressure is not known[4]. The beneficial effects of antihypertensive agents on cardiovascular system can be counter balanced by the induction of metabolic disorders. The modifications in various metabolic parameters like lipids, serum electrolytes, serum uric acid, blood sugar level etc. are responsible for different adverse drug reactions of antihypertensive drugs. It might also have potential to produce secondary morbidities after long term use. Several studies comparing antihypertensive agents have shown differences in risk reduction in cardiovascular diseases

(CVD) with a similar blood pressure lowering effect, suggesting that specific pharmacological mechanisms may be involved[2,3].

The renin angiotensin aldosterone system (RAAS) is targeted by some of the most widely used antihypertensive medication classes like angiotensin receptor blockers (ARBs), aldosterone antagonists,angiotensin converting enzyme inhibitors (ACEIs) and direct rennin inhibitors[5,6]. ARBs are increasingly used in the treatment of hypertension because of fewer side effects with blood pressure lowering abilities. The first ARB discovered was losartan. It is a competitive antagonist and an inverse agonist, about 10,000 times more selective for AT_1 than AT_2 receptors. It generates active metabolite which is more potent andnon-competitively blocks the AT_1 receptor with higher affinity. Blockade of AT_1 receptors causes inhibition of vasoconstriction, sodium retention and reduces blood pressure[7,8].

The present study was designed to evaluate the effect of losartan monodrug therapy on different biochemical parameters. Various studies carried out with losartan showed no significant changes in the biochemical parameters. However, there have also been some studies which have shown significant favorable changes in the various parameters[9]. Therefore, the present study was designed to observe the effect of losartan on different biochemical parameters in essential hypertension.

MATERIALS AND METHODS

The present work was an open prospective study conducted in an OPD of medicine department of 50 bed multi-specialty private hospital in western Maharashtra. Newly diagnosed patients of either sex were selected as per JNC 8. The patients with either gender in the age group 18-70 years were included in the study, who were newly diagnosed as per JNC 8, stage I and II of essential hypertension without comorbidities. The patients excluded from the study were the subjects taking hypolipidemic, hypoglycemic, uricosuric drug therapy, subjects administered with combination/multidrug antihypertensive treatment, subjects on chronic drug therapy, taking steroids or estrogen, subjects with any hepatic or renal diseases, pregnant, lactating females,women on contraceptives and subjects with chronic history of smoking and alcoholism.

Twenty-nine newly diagnosedpatientswith mild to moderate hypertension were enrolled after taking informed and written consent. Before administering losartan, baseline blood pressure and biochemical parameters like lipid profile, serum electrolytes (sodium, potassium and calcium) uric acid, fasting blood sugar level (BSL) were recorded. 12-14 hours of overnight fasting blood sample was taken for laboratory investigation. Mono therapy with losartan (Dose range: 20- 50 mg OD) was started and follow up of measurement of blood pressure was carried out every month. The same biochemical parameters were measured after six months of losartan mono drug therapy. Institutional Ethics Committee Approval was taken prior to the initiation of the study. Study protocol and informed consent forms were also approved by Ethics Committee. Statistical analysis was done using version 20.0 SPSS software. Student's 'paired t' test was applied for statistical analysis of

Table 1. Effect of losartan on lipid profile

Losartan (n=29) 20mg – 50mg -value		Mean ± SD Before	After	t – value	p
Lipid Profile (mg/dl)	TC	191.59±26.40	188.69±23.39	0.8400	0.4070
	TG	118.97±14.05	118.24±11.82	0.4200	0.6780
	HDL	43.97±7.58	47.79±8.12***	"4.5400	<0.0001
	LDL	123.79±22.40	117.24±17.01	1.9900	0.0560
	VLDL	23.82±2.79	23.6±2.38	0.5000	0.6240

Student's paired t-test: *** p< 0.0001
TC- Total Cholesterol, TG-Triglycerides, VLDL-Very low density lipoproteins, LDL- Low density lipoproteins, HDL- High density lipoproteins

Table 2. Effect of losartan on serum electrolytes, Serum uric acid and Fasting blood sugar level

Losartan (n=29) 20mg – 50mg -value		Mean ± SD Before	After	t – value	p
Electrolytes (mEq/ L)	Na+	139.51±3.66	138.41±3.05	1.5400	0.1350
	K+	4.13±0.36	4.04±0.25	1.3100	0.2000
	Ca++	9.47±0.60	9.53±0.51	?0.6900	0.4940
SUA (mg/ dl)		4.02±0.72	3.61±0.45***	4.7600	<0.0001
Fasting BSL (mg/ dl)		83.97±12.66	81.21±11.44	1.7200	0.0970

Student's paired t-test: *** p< 0.0001
Na+- Sodium, K+- Potassium, Ca++- Calcium, SUA- Serum Uric acid,BSL- Blood sugar level.

data. The data was expressed as mean ± SD with t- value, p- value, and p< 0.05 was considered as statistically significant.

RESULTS

In the present study, it was observed that there was non-significant decrease in TC, TG, VLDL, LDL and very highly significant increase in HDL. Very highly significant decrease in serum uric acid (SUA) level was observed with losartan monotherapy.There was non-significant decrease in fasting BSL after receiving losartan. There were no changes in sodium, potassium and calcium levels.

DISCUSSION

Effects on Lipids

Dyslipidemia is more common in untreated hypertensives than normotensives.An increase in lipid level is seen as the blood pressure (BP) is increased. Many studies have shown that TC, TG and virtually all fractions of lipoproteins are frequently abnormal among hypertensive patients when compared to the normal population[10]. High levels of serum cholesterol are known to increase the risk of developing macrovascular complications such as coronary heart disease and stroke. Plasma HDL levels are inversely related to the risk of atherosclerosis and CVD[11]. The main objective of this study is to compare baseline levels of lipid profile with lipid levels obtained after six months of losartan mono drug therapy[12].

The present study showed that on administration of losartan, there was a slight decrease in the levels of TC, TG, LDL and VLDL. However these changes were statistically insignificant while there was a significant increase in HDL levels.There are numerous studieswhich are in line with the present study result[13, 14, 15]. An increase in adiponectin levels have also been observed with ARBs[16]. They are reported to be linked to an elevation in HDL cholesterol[17]it is an observation that supports our present findings.

Hanefeld M *et al* in their study, observed the effect of ARB (Valsartan) on lipid profile. There were no significant changes in levels of TG, VLDL and marked decrease in LDL levels were seen with valsartan monotherapy. According to them, the possible mechanism that contributed to the beneficial effects on lipids was a reduction in catecholamine levels by AT_1 receptors antagonists [18].

Various studies are in contrast to the present study findings[19, 20]. This contrast may arise due to variation between doses and the duration of drug treatment in various studies.

The wide uses of ARBs for the treatment of hypertension and hypertension related organ damage have succeeded in reducing the onset of cardiovascular diseases, preventing organ damage and cardiac death. These beneficial effects of ARBs are largely dependent upon their primary effects on lowering of blood pressure. This group of agents exerts a wide variety of biological effects on vascular metabolism including antioxidative and anti-inflammatory actions.[21] These pleotropic actions therefore play a role in cardiovascular protection.

Effects on blood sugar levels

In the present study, a slight decrease in blood sugar levels were observed, though insignificant. There are number of studies which demonstrate that ARBs do not show any significant

changes in blood sugar levels[13, 14, 22]. Certain studies stated that treatment for longer periods or with higher doses, was associated with a significant fall in the BSL[23]. The fall in BSL, be it significant or non significant, can be explained on the basis of following mechanisms:-

Activation of PPARgamma

Peroxisome Proliferator – activated receptor gamma (PPARgamma) represent a family of ligand activated nuclear receptors involved in glucose and lipid metabolism[22, 24, 25]. Pharmacological activation of PPARgamma improves glucose tolerance and insulin sensitivity in type 2 diabetes patients, thus proving that PPARgamma agonists are clinically useful in ameliorating type 2 diabetes[26]. Another underlying mechanism possibly involved in the reduction of new onset diabetes is RAS inhibition[27]. From a theoretical point of view, preventing type 2 diabetes mellitus by RAS inhibition may result from a preservation of â cell function and/ or an enhancement of insulin sensitivity, thereby decreasing the need for pancreatic insulin secretion[28]. Targeting RAS may lead to alterations in microcirculation and changes in ionic status that indeed could potentially affect the islet insulin secretion as well as the cellular insulin action. However unexpected insulin mechanism may also play a role, as newly recognized components of the RAS have been observed to modulate cardiovascular and renal regulation or even adipocyte turnover[29]. Besides, a pure hemodynamic effect on cellular insulin action, by blocking angiotensin II has also been described[30].

Therapy with ARBs shows improvement in glucose metabolism. Large clinical trials have evaluated the effects of ARBs on cardiovascular end points. An analysis of comorbidity showed that such therapy with ARBs substantially lowers the risk for type 2 diabetes when compared with other antihypertensive drugs and placebo[31].

Hyperuricemia has been associated with endothelial dysfunction, impaired oxidative metabolism, stimulation of granulocyte adherence, increased platelet aggregation and all these are implicated in the pathogenesis of hypertension. Hyperuricemia may be a precursor of hypertension or be a reflection of subclinical renal dysfunction may cause both increase in serum uric acid level and increase in blood pressure[32].Elevated serum uric acid in hypertensive patients has been associated with 3-5 folds increased risk of coronary artery disease or cerebrovascular disease compared with normal uric acid level. Lowering serum uric acid level might be beneficial in slowing progression of CVD (Cardiovascular Disease) in hypertensive patients.[33, 34]

Several mechanisms could be linked with ARBs Effect on angiotensin receptor blocker (ARBs) on SUA

Theelevated uric acid defined as e" 7mg /dl levels has been linked to multiple comorbiditiesincluding gout, hypertension, chronic kidney disease (CKD), diabetes, obesity & heart failure.[35, 36, 37,38]

In our study, a highly significant fall in serum uric acid (SUA) level was observed with losartan monotherapy. There are numerous studies which shows that ARBs and in particular losartan demonstrates a significant reduction in SUA levels[39]. The mechanism involved in this process may be explained as follows:

Mode of action is by reabsorption of uric acid transporter $URAT_1$ and secretion via other transporters. $URAT_1$ mainly contributes to renal absorption of uric acid across the apical membrane of proximal tubular epithelial cells. Since $URAT_1$ is an anion/ uric acid exchanger and compounds like PZA (Pyrazine carboxylic acid) and lactic acid stimulate the reabsorption of acid, modulation of $URAT_1$ may occur due to reduction and increment of SUA levels by cis inhibition and trans stimulation of $URAT_1$ respectively by ARBs. Losartan exhibited inhibitory effects on the uptake of uric acid by $URAT_1$. The hypouricemic effect of Losartan may be due to the fact that Losartan targets the urate anion exchange and decrease urate absorption in the proximal convoluted tubule. As a result, urate excretion is increased which leads to increased renal uric acid excretion[40]. However, there are certain studies that show ARBs do not any effect on SUA levels[41]. Such studies are in contrast with our study findings.

Effect of ARBs on serum electrolytes (Na^+, K^+, Ca^{++})

Losartan showed no change in sodium, potassium and calcium levels

There are studies which display non significant changes in serum electrolytes on treatment with ARBs. The present study shows

a decrease in sodium levels, but notsignificant. This decrease can be explained by the action of ARBs in promoting renal excretion of sodium and water (natriuretic and diuretic effect) by blocking the effect of angiotensin II in the kidney and by blocking ang II stimulation of aldosterone secretion[42]

In some studies, hyperkalaemia has been observed on the treatment of ARBs, which can be explained on the basis of following mechanism: -

Bakris GL *et al* investigated the impact of ACEI and ARBs on potassium in renal failure. They exhibited that in presence of renal insufficiency, the ARBs do not raise serum K^+ (to the same degree as ACEIs). Effect on serum K^+ is related to a relatively smaller reduction in plasma aldosterone by ARBs and not related to changes in GFR. Thus, treatment with ARBs, especially in patients with renal insufficiency is less likely to affect the serum K^+ levels[43].

In present study, ARBs have shown, a non significant decrease in levels of potassium wherein the values lie within normal limits.

CONCLUSION

The results of present study are an important step to understand in a better way the clinical efficacy of losartan especially in hypertensive Indian population. In conclusion, losartan is efficacious antihypertensive but offers highly significant increase in HDL and highly significant decrease in SUA level.

Thus the metabolic effect of antihypertensive drugs could be of special importance in long term treatment of essential hypertension. It suggests that losartan is an attractive option for treatment of hypertension as well as in hypertension associated with hyperuricemia, CKD, gout, hyperlipidemia, type 2 diabetes patients and in patients with metabolic syndromes. Losartan appears to have renoprotective effect due degree of reduction in SUA levels.

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