EFFECT OF TELMISARTAN ON SERUM LIPID PROFILE IN PATIENTS WITH HYPERTENSION AND DYSLIPIDEMIA

*Vanitha M1, Vijayal K2

1Department of Pharmacology, Osmania Medical College, Hyderabad
2Department of Pharmacology, Dr VRK Women’s Medical College & Research Institute, Hyderabad

*Corresponding author email: hayavanitha@yahoo.in

ABSTRACT

Background and Objectives: Hypertension and dyslipidemia are two major risk factors for cardiovascular disease and they commonly occur together. Management of dyslipidemia in a hypertensive patient significantly reduces the total cardiovascular risk. Telmisartan is an Angiotensin receptor blocker with a partial agonistic action on PPAR-γ. In the present study, the effect of Telmisartan on serum Lipid Profile was evaluated in hypertensive patients who also have associated Dyslipidemia and also the efficacy of Telmisartan in reducing systolic and diastolic BP was assessed in these patients. Materials and Methods: A total of 50 outpatients from the medical outpatient department of Gandhi Hospital, Secunderabad, were enrolled into the study. These patients had grade I essential Hypertension and mild dyslipidemia. After the study period of 24 weeks, the efficacy of Telmisartan in reducing serum lipid profile was evaluated apart from its effect on reducing systolic and diastolic BP. Results: Telmisartan was very effective in reducing serum triglycerides (27 % ↓, P<0.01), VLDL-C (27 % ↓, P<0.01), LDL-C (22% ↓, P<0.01). It also decreased serum cholesterol by 16% (P<0.01). HDL-C increased by 14% (P<0.05). Telmisartan in a dose of 40-80 mg/day, significantly reduced both systolic BP by 18 %( P<0.01) and diastolic BP by 12 %( P<0.01) Conclusion: In our study, Telmisartan proved to be effective not only in controlling BP, but had a favorable effect on lipid profile also So, in conclusion, all the patients with uncomplicated Hypertension and mild dyslipidemia can be effectively treated with Telmisartan.

Key words: Telmisartan, Hypertension, Dyslipidemia, Serum lipid profile

INTRODUCTION

Coronary heart disease continues to be the leading cause of morbidity and mortality in the world1. Several factors increase the risk of CHD such as hypertension, advancing age, dyslipidemia, type 2 diabetes mellitus, family history of coronary artery disease, cigarette smoking, obesity etc.. Hypertension and dyslipidemia are the most common risk factors for cardiovascular disease. It is found that hypertensive patients have lower levels of HDL-cholesterol and higher levels of triglycerides compared to normal individuals. In patients with
hypertension, dyslipidemia substantially increases the cardiovascular risk. So, there is a need for disciplined diet plan and appropriate pharmacological therapy in these patients. The exact pathophysiology by which dyslipidemia may be involved in the development of hypertension is not well established. Lipid disorders cause endothelial dysfunction and this may become manifest as hypertension. Education therapy for hypertension and dyslipidemia is becoming more complicated, as over two-thirds of patients require two or more anti-hypertensive agents and at least one lipid lowering agent. The mechanism of action of majority of anti-hypertensive drugs in use today is to primarily target the factors which contribute to development of increased blood pressure. They do not in any way modify the pathophysiological mechanisms causing dyslipidemia. Angiotensin II receptor blockers (ARB) are efficient anti hypertensive agents that act through inhibition of AT$_1$ receptors. In experimental models, as well as in some clinical trials, ARBs have been found to significantly affect lipid metabolism. More precisely; ARBs improved the overproduction and accumulation of TGL in the liver, in experimental models, through mechanisms independent of their hypotensive action. Furthermore, there are preclinical studies showing that telmisartan exerts a favourable effect on lipid abnormalities, due to its partial activation of peroxisome proliferator-activated receptor-gamma (PPAR-$\gamma$). The finding that Telmisartan acts as both an ARB and a partial agonist of PPAR-$\gamma$ has important implications in the prevention of atherosclerosis and cardiovascular disease. Moreover, it has been shown that activation of PPAR-$\gamma$, downregulates the expression of angiotensin II type I receptor and modifies the effects of angiotensin II on intracellular signaling pathways. Telmisartan is a potent, insurmountable and highly selective antagonist of AT$_1$ receptors, with a long terminal elimination half-life, Telmisartan is capable of activating the nuclear peroxisome proliferator-activated receptor (PPAR) - $\gamma$ also, in addition to blocking the angiotensin II type I receptor. PPAR-$\gamma$ is a nuclear transcription factor that exists in the form of a heterodimer complex with the retinoid X receptor- $\alpha$. Activation of PPAR-$\gamma$ causes the receptor complex to affect the expression of key target genes that mediate beneficial effects on glucose and lipid metabolism. Evidence for the importance of PPAR-$\gamma$ in regulating key features of the metabolic syndrome comes from the studies of individuals with mutated forms of the receptor. Such individuals exhibit multiple features of the metabolic syndrome, including severe insulin resistance, hypertriglyceridemia, elevated concentrations of non esterified fatty acids, low concentrations of HDL cholesterol and hypertension. In fact PPAR-$\gamma$ is an important target for drugs used in the treatment of insulin resistance, diabetes mellitus and the metabolic syndrome. Thiazolidinedione PPAR-$\gamma$ activators, pioglitazone and rosiglitazone are currently available, and these agents have been shown to increase the insulin sensitivity and decrease FA and triglyceride concentrations in patients with type 2 diabetes.

In contrast to other ARBs, relatively low concentrations of telmisartan were also found to increase the expression of phosphoenol-pyruvate carboxykinase (PEPCK) gene in human visceral adipocytes. PEPCK is a key target gene that contributes to the ability of PPAR-$\gamma$ activators to reduce the FA levels. Further evidence that telmisartan activates PPAR-$\gamma$ comes from the findings that telmisartan induces adipocyte differentiation in vitro and is more effective than other ARBs in reducing serum concentrations of glucose, insulin and triglyceride in rats maintained on a diet rich in fats carbohydrates. In contrast to glitazones, telmisartan is a selective PPAR-$\gamma$ modulator that activates only a subset of genes targeted by the full PPAR-$\gamma$ agonists and that’s why it has fewer adverse effects compared to.
to full PPAR-γ agonists. Telmisartan is highly lipophilic, and has a high mean volume of distribution of 460-510 L. This high apparent volume of distribution and the lipophilic nature of telmisartan suggest that it may have greater capacity to enter intracellular compartments and gain better access to PPAR-γ than other ARBs.

MATERIALS AND METHODS

The present study was conducted in the Departments of Pharmacology and Medicine, Gandhi Medical College and Gandhi Hospital, Secunderabad. 50 newly diagnosed cases of essential hypertension, having dyslipidemia were included in the study. The patients were enrolled from the medical OPD and the study was conducted in the period from October 2010 to May 2011. After getting approval from the Institutional Ethics Committee, newly diagnosed cases of grade I essential hypertension were first screened for dyslipidemia by doing serum lipid profile after overnight fasting for about 10 hrs. Those patients having both hypertension and dyslipidemia were included in the study.

Exclusion criteria: Patients with Diabetes mellitus, secondary causes for hypertension, Hepatic or renal insufficiency, coronary artery disease or cerebrovascular diseases were excluded from the study. The age of the patients ranged from 38-65 years with a mean of 52 ± 1.2 years and consisted of 31 males (62%) and 19 females (38%). In each case after the informed consent was obtained, a detailed clinical history was taken. All the patients underwent complete clinical examination including recording of pulse, B.P, detailed clinical examination of respiratory system, cardiovascular system and central nervous system. The biochemical investigations including Blood sugar, serum creatinine and serum lipid profile were done. LFT, TSH, X-ray chest and resting 12 leads electrocardiogram were done in all the patients. Serum lipid profile was repeated at the end of 24 weeks. All the patients were started on Telmisartan 40 mg orally once daily. They were followed up with BP recording once in 15 days and the dose of telmisartan titrated according to the response.

RESULTS

Initial lipid profile: The initial total serum cholesterol in the patients ranged between 171-281 mg/dl with a mean of 218.86 ± 3.91. The initial serum triglycerides ranged between 93-275 mg/dl with a mean of 170.8 ± 5.25. The initial LDL-C, ranged between 107-197 mg/dl with a mean of 144.08 ± 3.65. The initial HDL-C, ranged between 32-58 mg/dl with a mean of 40.62 ± 0.76. The initial VLDL-C, ranged between 19-55 mg/dl with a mean of 34.16 ± 1.04. All the parameters including total Cholesterol, LDL-C, Serum Triglycerides, HDL-C and VLDL-C, were marginally higher in female patients, when compared with male patients.

Lipid profile after 24 weeks: (Table1): After 24 weeks of study period, the mean Total Cholesterol decreased significantly from 218.86 mg/dl to 185.06 mg/dl (15% ↓, P<0.01). The mean Serum Triglycerides decreased significantly from 170.8 mg/dl to 123.86 mg/dl (27% ↓, P<0.01). The mean LDL-C decreased significantly from 144.08 mg/dl to 112.5 mg/dl (22% ↓, P<0.01). The mean HDL-C increased from 40.62 mg/dl to 47.5 mg/dl (14% ↑, P<0.05). The mean VLDL-C decreased from 34.16 mg/dl to 25.06 mg/dl (27% ↓, P<0.01).

Blood Pressure initial Vs after 24 weeks: (Table2) The initial systolic BP ranged from 140-160 mm Hg with a mean of 149.96 ± 1.0 mm Hg and the initial diastolic BP ranged from 80-99 mm Hg with a mean of 92.88 ± 0.52 mm Hg. After 24 weeks of treatment with Telmisartan, the mean systolic BP in the patients decreased significantly from 149.96 mm Hg to 122.72 mm Hg (18% ↓, P<0.01). Similarly, the mean DBP also decreased from 92.88 mm Hg to 81.92 mm Hg (12% ↓, P<0.01).
Table 1: Lipid profile initial vs after 24 weeks

<table>
<thead>
<tr>
<th>Lipid parameters (mean values mg/dl)</th>
<th>Initial</th>
<th>After 24 weeks</th>
<th>% of ↓</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>218.86± 3.91</td>
<td>185.06±5.29</td>
<td>15%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Serum Triglycerides</td>
<td>170.8±5.25</td>
<td>123.86±0.52</td>
<td>27%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>LDL – Cholesterol</td>
<td>144.08± 3.65</td>
<td>112.5±6.11</td>
<td>22%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HDL – Cholesterol</td>
<td>40.62± 0.76</td>
<td>47.5±3.12</td>
<td>↑ - 14%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>VLDL – Cholesterol</td>
<td>34.16± 1.04</td>
<td>25.06±1.42</td>
<td>27%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Table 2: Blood pressure initial vs after 24 weeks

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial</th>
<th>After 24 weeks</th>
<th>% of ↓</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Systolic BP (mm Hg)</td>
<td>149.96± 1.0</td>
<td>122.72±3.4</td>
<td>18%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean Diastolic BP (mm Hg)</td>
<td>92.88 ± 0.52</td>
<td>81.92±2.33</td>
<td>12%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

DISCUSSION

Hypertension is not the only determinant of cardiovascular damage and the propensity of a subject to develop atherosclerotic vascular disease is markedly affected by the presence of other risk factors such as age, gender, obesity, smoking, diabetes and dyslipidemia. There is no doubt that the management of lipid disorders in hypertensive patients ameliorates their total cardiovascular risk. Clinical trials suggest that some antihypertensive agents may have a beneficial effect on lipid metabolism through various possible mechanisms. Telmisartan is an unique angiotensin receptor blocker (ARB) with an additional PPAR-γ modulating action. It is possible that the lipid lowering effect of Telmisartan is due to numerous mechanisms. The ARBs activate PPAR-γ which regulates lipid metabolism; thereby reduce triglyceride and LDL-C levels. Furthermore, there is experimental evidence suggesting an interaction between angiotensin system and lipid metabolism. The ARBs reduce the AT-II mediated endothelial injury and lipid peroxidation by blocking the AT₁ receptor.

Telmisartan is commonly prescribed for grade I essential hypertension in the medical outpatient department. In the present study, the effect of long term administration of Telmisartan on serum lipid profile was evaluated. The patients who were enrolled into the study had both hypertension and dyslipidemia. Also, the efficacy of Telmisartan in reducing both systolic and diastolic BP was evaluated in this study. In the present study, there was significant effect on serum lipid profile in the patients, who were given Telmisartan 40-80 mg/day, for 6 months. The total serum cholesterol decreased by 16 %(P<0.01), LDL-C by 22% (P<0.01), serum triglycerides decreased by 27 %(P<0.01) and VLDL-C decreased by 27 %(P<0.01). The HDL-C increased by 14 %(P<0.05). This favourable effect on serum lipid profile was in addition to the proved effect of Telmisartan as an antihypertensive drug. Telmisartan in a dose of 40-80 mg/day, significantly reduced both systolic BP by 18 %(P<0.01) and diastolic BP by 12 %(P<0.01). In our study, Telmisartan was well tolerated, except for some minor and transient side effects like headache, dizziness and fatigue in a few patients.

The significant effect of Telmisartan on serum lipid profile in the present study is supported by preclinical studies conducted on rabbits and also...
by STAR trial, (Saga Telmisartan Aggressive Research Study), a single arm, prospective, multicentric clinical trial conducted in Japan on 197 patients with hypertension and dyslipidemia.

CONCLUSION

In our study, Telmisartan proved to be effective not only in controlling BP, but had a favorable effect on lipid profile also. Telmisartan treatment results in amelioration of cardiovascular risk factors, not only through arterial pressure regulation but also through reduction of serum lipid profile. So, in conclusion, all the patients with uncomplicated hypertension and dyslipidemia without other associated risk factors can be effectively treated with Telmisartan.

ACKNOWLEDGEMENT

The authors are thankful to Management and staff of Medical Out Patient Department, Gandhi Hospital, Secunderabad, Andhra Pradesh, for providing necessary facilities to carry out the research work.

REFERENCES