EFFECT OF FELODIPINE ON THE SERUM LIPID PROFILE OF PATIENTS WITH HYPERTENSION

Maninder Kaur*, Kiranjeet Kaur, Gurdeep Kaur Bedi, Gurpreet Singh Sidhu, Roopan Sikand

Departments of Biochemistry & Cardiology, Government Medical College, Patiala.

ABSTRACT

Forty patients suffering from mild to moderate degree of hypertension were put on felodipine. Their lipid profile was analysed before the start of their therapy and consecutively at two and four months after starting felodipine. There was a statistically significant fall in the levels of serum cholesterol, serum triglycerides and serum total lipids; though no appreciable variation was observed in HDL and LDL cholesterol levels. At baseline there were a few patients who had higher than the normal range of the serum lipid profile. Analysis of these patients showed a highly significant fall in the levels of serum cholesterol, serum triglycerides, serum LDL-cholesterol and serum total lipids i.e. felodipine modified the lipid profiles of hypertensive patients in a positive way.

KEY WORDS : Felodipine, Lipid Profile, Hypertension.

INTRODUCTION

Hypertension is a major risk factor for arteriosclerosis and the beneficial effects of lowering blood pressure on the vascular morbidity and mortality are well documented and demonstrated (1). However, it is disturbing that despite a striking decrease in cerebrovascular accidents, renal failure and hypertensive cardiomyopathy as a result of controlling blood pressure, there has not been a significant decline in the incidence of myocardial infarction (2). The cause for this observation has been suggested to be due to the unfavourable effects of antihypertensive drug therapy on other cardiovascular risk factors - in particular the plasma lipids(3). Thus the antihypertensive agents chosen may negate the beneficial effects of a lower blood pressure (4).

We conducted a study to evaluate the effect of felodipine on the lipid profile of humans; as previous studies have confirmed its lipid lowering effect in experimental animals (5,6,7). This drug has

not been extensively studied in humans though one study has reported lipid neutrality of felodipine (8). Our study shows lipid lowering effect of felodipine in hypertensive patients which has not been reported earlier.

Felodipine, a new generation calcium channel antagonist, belonging to the class of dihydropyridines, is a practical advance in the treatment of hypertension(5).

MATERIALS AND METHODS

The present study comprised of 40 hypertensive patients who were referred from the Department of Cardiology, Rajindra Hospital, Patiala irrespective of the aetiology of hypertension. There were 14 males and 26 female patients included in the study group. Twenty-seven patients were having mild degree of hypertension while 13 had moderate degree of hypertension. No patient of severe hypertension was included in the study.

Before administering felodipine to the patients, baseline serum lipid profile was estimated. Consecutive estimation of lipid profile of these patients was done at two months and at four months after commencing felodipine therapy.

Address for Correspondence :

Dr. Maninder Kaur, Patiala Surgical Centre
1, Ranbir Marg, Patiala-147001 (Punjab)

The various biochemical parameters were estimated by the below stated methods to assess the serum lipid profile.

1. Serum cholesterol - colorimetric method using ferric chloride [10] (normal range = 150-250 mg%).
2. Serum triglycerides - GPO-PAP enzymatic method; procured from ERBACHEM [10] (normal range = 30-180 mg%).
3. Serum HDL-cholesterol - colorimetric method after precipitation by phosphotungstate and Mg^{2+} [10] (normal range = 29-61 mg% in males & 38-75 mg% in females).
4. Serum LDL-cholesterol was calculated by the formula:-

$$LDL\text{-cholesterol} = \text{Total cholesterol} - (\text{Triglycerides}/5 + \text{HDL cholesterol})$$
 [10] (normal range = 114-153mg%)

5. Serum total lipids - estimated by colorimetric method based on sulpho-phosphovanillin reaction [10] (normal range = 400-900 mg%).

The patients under study were divided into two groups:- Group 1. All the 40 patients as a whole. Group 2. Patients who had an abnormally high lipid profile at baseline i.e. before starting felodipine therapy.

RESULTS AND DISCUSSION

The results of our study show that:-

1. There was a statistically significant reduction in the levels of serum cholesterol, serum triglycerides and serum total lipids with felodipine therapy in group 1 patients (Table 1). The percentage lowering of serum cholesterol was 10.23% and consecutively 12.34% after 2 months and 4 months

Table 1 : Comparison of lipid profile at baseline, 2 months and 4 months post-felodipine therapy

Sr. No.	Parameter	Levels (Mean $\pm$ SD) (mg%)			Mean Change (mg%)		P-Value	
		Baseline	2 months	4 months	MC ₁	MC ₂	P ₁	P ₂
1	S. cholesterol (N=40)	260.77 $\pm$ 65.09	234.07 $\pm$ 50.66	230.47 $\pm$ 61.09	26.7 (10.23%)	30.3 (12.34%)	<0.05	<0.05
2	S. triglycerides (N=40)	217.55 $\pm$ 92.97	186.30 $\pm$ 77.56	168.45 $\pm$ 49.59	31.25 (14.36%)	49.1 (22.56%)	<0.05	<0.05
3	HDL-cholesterol (N=40)	48.67 $\pm$ 10.88	45.95 $\pm$ 3.80	46.77 $\pm$ 7.70	2.72 (5.88%)	1.90 (3.90%)	>0.05	>0.05
4	LDL cholesterol (N=40)	169.77 $\pm$ 64.32	149.47 $\pm$ 47.72	148.0 $\pm$ 46.37	20.30 (11.95%)	20.87 (12.11%)	>0.05	>0.05
5	Total lipids (N=40)	776.62 $\pm$ 155.52	686.50 $\pm$ 125.83	668.90 $\pm$ 5.24	90.12 (11.6%)	107.75 (15.69%)	<0.02	<0.01

Change in mean levels at 2 months versus baseline = MC₁
 Change in mean levels at 4 months versus baseline = MC₂
 P value comparing levels at 2 months versus baseline = P₁
 P value on comparing levels at 4 months versus baseline = P₂

Table 2 : Comparison of lipid profile at baseline, 2 months and 4 months post-felodipine therapy in patients having higher than normal baseline levels.

Sr. No.	Parameter	Levels (Mean $\pm$ SD) (mg%)			Mean Change (mg%)		P-Value	
		Baseline	2 months	4 months	MC ₁	MC ₂	P ₁	P ₂
1	S. cholesterol (N=20)	307.50 $\pm$ 57.66	258.65 $\pm$ 46.25	235.15 $\pm$ 35.90	48.85 (15.88%)	72.35 (23.52%)	<0.01	<0.01
2.	S. triglycerides (N=26)	259.11 $\pm$ 8.63	210.30 $\pm$ 7.70	184.26 $\pm$ 49.59	45.81 (17.67%)	74.85 (28.8%)	<0.05	<0.01
3.	LDL-cholesterol (N=23)	205.04 $\pm$ 62.58	169.17 $\pm$ 43.16	170.30 $\pm$ 44.36	35.87 (17.49%)	34.74 (16.94%)	<0.05	<0.05
4.	Total lipids (N=7)	1005.0 $\pm$ 64.80	830.0 $\pm$ 146.62	747.28 $\pm$ 118.56	175.0 (17.41%)	257.72 (25.57%)	<0.01	<0.001

Change in mean levels at 2 months versus baseline = MC₁
 Change in mean levels at 4 months versus baseline = MC₂
 P value comparing levels at 2 months versus baseline = P₁
 P value on comparing levels at 4 months versus baseline = P₂

post-felodipine therapy. The lowering of serum triglycerides was 14.36% and 22.56% at the same time intervals and that of serum total lipids was 11.6% and 15.69% at 2 and 4 months respectively.

2. No statistically significant change was recorded in serum HDL and LDL-cholesterol levels.

3. There was a highly statistically significant fall in the levels of all the lipid parameters in group 2 patients (Table 2). The fall in the levels of serum cholesterol was 15.88% and 23.52% after 2 months and 4 months of felodipine treatment. At the same time intervals, the fall in serum triglycerides was 17.67% and 28.8% respectively. The lowering in LDL-cholesterol was 17.49% and 16.94% after 2 months and 4 months and that of total lipids was 17.41% and 25.57% at the same time intervals. No patient had abnormally high levels of HDL-cholesterol at baseline.

Many antihypertensive drugs are known to alter lipoproteins, and this may override the benefits of blood pressure reduction (4). A review of the

effects of various antihypertensive agents on the serum lipid profile of humans is briefly given below:-

Most of the thiazides and beta-blockers have an unfavourable effect on the lipid profile (11, 12). ACE inhibitors and post-ganglionic neuron inhibitors have a neutral effect on the serum lipids (13). Alpha adrenergic blockers, centrally acting drugs and vasodilators have a beneficial effect on the serum lipid profile (14, 15). Calcium channel blockers have been reported to be mostly lipid neutral (16, 17).

Calcium channel antagonists reduce the calcium dependent vascular smooth muscle tone by direct interference with transmembrane calcium supply and thereby counteract every kind of contractile tension development in the vascular wall (9). Felodipine is an inhibitor of calcium ion influx, and blocks the transmembrane influx of calcium ions mainly in the arteriolar resistance vessels. Thus it selectively dilates arterioles with minimal or no effect on venous vessels (9).

Previous studies have confirmed the lipid lowering effect of felodipine in animals. Out of all the calcium channel blockers, felodipine was the most effective in preventing the rise in total cholesterol and triglyceride levels in fat-fed mice and had the maximum anti-atherogenic index [886% versus 303% for Clofibrate] (5). In streptozotocin induced diabetes in rats fed on high fat diet, felodipine produced a marked fall in cholesterol and triglyceride levels (6). In another study it was observed that felodipine prevented rise in levels of serum cholesterol, triglycerides, LDL-cholesterol and VLDL-cholesterol in rabbits fed on atherogenic diet. It also elevated the levels of cardioprotective HDL-cholesterol (7). In a human study consisting of diabetics and normocholesterolaemics felodipine therapy did not produce any statistically significant change in serum cholesterol and triglyceride levels. However, in hypercholesterolaemic patients, levels of serum cholesterol did fall but not significantly (8).

Mechanism of lipid lowering action of felodipine

The mechanism of bringing about this change in lipid profile is not very clear, but the following have been suggested.

(a) Activation of cellular cholesterol ester hydrolase : Eltingh (18) demonstrated that pharmacological concentrations of nifedipine and other dihydropyridines doubled the activity of rabbit smooth cell lysosomal cholesterol ester hydrolase. Smooth muscle cells enriched in lipid content showed a significant decrease in both free and ester cholesterol during 7 days incubation with dihydropyridines, presumably as a result of activation of cellular cholesterol ester hydrolase. This perhaps might be the mechanism of action by which there is reduction of serum cholesterol levels in patients on felodipine therapy.

(b) Activation of triglyceride lipase : Lopez and Klein (19, 20) reported an increase in circulating levels of epinephrine and nor-epinephrine in patients receiving amlodipine and nifedipine (dihydropyridines), which directly activate the hormone sensitive triglycerides lipase (which is present in abundance in fat cells) to cause rapid breakdown of triglycerides and mobilisation of free fatty acids-thereby leading to a fall in levels of serum triglycerides.

(c) Increase in the number of LDL receptors: Stein (21) showed that verapamil increased the LDL-cholesterol uptake and degradation by 70-200% in bovine aortic smooth muscle and endothelial cells. He postulated an increase in the number of LDL receptors on cell surface. Fillipovic (22) observed that the rate of synthesis of LDL receptors in human skin fibroblasts incubated with calmodulin antagonists (like felodipine, nifedipine) increased by 2-3 fold. Thus felodipine therapy might be increasing the LDL-cholesterol receptors on the cell surface leading to increased binding and enhancing the metabolism of LDL-cholesterol.

As there was no control group treated by placebo in this study, interference by factors other than felodipine per se cannot be entirely excluded i.e. these results regarding changes in lipid profile may be explained in part as a result of better attention given to the daily diet and exercise by the patient, though no restrictions except reduction in salt intake were advised during the course of this study.

Conclusion

Felodipine constitutes a step forward in the search for drugs which are vasoselective in action. And, if its lipid lowering effect is confirmed by various ongoing trials, it would emerge as the drug of choice in the treatment of hypertensive patients, especially those with a deranged lipid profile.

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