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Study the Combined Effects of Amlodipine and Simvastatin on Lipid Profile in Hypertensive Obese Patients

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SUMMARY

A study was conducted to evaluate the combined effect of Amlodipine and Simvastatin on the lipid levels of hypertensive obese patients. Amlodipine belongs to the dihydropyridine subclass of calcium antagonist whereas Simvastatin is a competitive inhibitor of HMG-CoA (3Hydroxy 3Methyl Glutaryl Coenzyme A) reductase. Three group of patients of both gender comprises 40 in each were included. Group A (hypertensive obese patients) was given amlodipine, group B (obese patients) was given simvastatin and group C (hypertensive obese patients) was given combination of amlodipine and simvastatin. Blood pressure was checked and tests for serum Cholesterol, serum Triglycerides and serum Lipoprotiens (HDL, LDL) was carried out by Standard kit methods (Merck). The patients were evaluated three times i.e. before giving the medicines 0 week, at 6^{th} and 12^{th} week. The patients were advised to take fat free diet and a morning walk. Mean blood pressure of both male and female patients was significantly reduced. It was observed that combined therapy of Amlodipine and Simvastatin, significantly decreased the level of serum cholesterol, triglycerides and LDL-Cholesterol and significantly increased the level of HDL-Cholesterol in both sexes, but they did not show any significant synergistic effect as compared to the levels of these parameters in group A (amlodipine) as well as in group B (simvastatin). A significant weight reduction is observed in male patients which may be due to low calorie diet and physical exercise. It is therefore concluded that synergism with Amlodipine and Simvastatin is not significant as the major action of Amlodipine is on blood pressure and the major effects of Simvastatin is on lipid profile and also reduced the body weight, if patients used calorie restricted diet with some morning walk.

Key words: Amlodipine, Simvastatin, Lipid Profile, Hypertension, Obesity.

INTRODUCTION

Hypertension is the most common cardiovascular disease. Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, cardiac failure and stroke[1].

In more than 95 % of cases a specific underlying cause of hypertension cannot be found. Such patients are said to have essential hypertension. Effective pharmacologic lowering of blood pressure has been shown to prevent damage to blood vessels and to substantially reduce morbidity and mortality rates[2].

Amlodipine belongs to the dihydropyridine subclass of calcium antagonist. It is a potent peripheral and coronary vosodilator with selectivity for vascular smooth muscle and minimal effect on myocardial contractility or cardiac conduction[3].

Calcium Channel Blockers drugs such as Amlodipine inhibits the Ca^{2+} component of ionic currents carried in the cardiac action potential. Because of this activity these drugs are also referred to as slow channel blockers, calcium channel antagonist and calcium entry blockers[4].

Amlodipine is effective and well tolerated in patients with mild or moderate hypertension as a single agent therapy[5], or in combination with other drugs[6]. It produces both peripheral arterial vasodilatation and coronary dilatation. However there is less reflex tachycardia with Amlodipine possibly because the long half-life produces minimal peaks and troughs in plasma concentration[7].

Amlodipine reduces the mean triglycerides and very low-density lipoproteins levels in hypertensive patients with high baseline values of lipid profile while the changes in lipids and lipoproteins were not significant after Amlodipine

treatment with medium baseline values of lipid profile[8]. It provided an additional benefit with decreased low-density lipoprotein cholesterol level[9].

Simvastatin is a competitive inhibitor of HMG-CoA (3Hydroxy 3Methyl Glutaryl Coenzyme A) reductase. HMG-CoA reductase mediates the first commited step in sterol biosynthesis. Simvastatin is structural analog of HMG-CoA intermediate that is formed by HMG-Co A reductase in the synthesis of Mevalonate[10].

Simvastatin is a safe and efficacious lipid lowering drug[11]. HMG-CoA reductase inhibitors are effective in the prevention of cardiovascular events and regression of atherosclerotic lesions evaluated by angiography[12]. It is quite effective in reducing Low Density Lipoprotein (LDL) levels. It appears to be twice as effective as Lovastatin at doses of 40 mgs/day. The lowering of LDL-Cholesterol primarily is due to decrease in LDL particle number, although there also is a slight decrease in the cholesterol content of the LDL particle and a small decrease in VLDL Cholesterol. Triglyceride concentration also decline by 10-30% reflecting the decrease in VLDL levels. Of great importance is the fact that HDL-Cholesterol levels typically rise 8-10%[7]. However the adverse effects of Simvastatin are increase in hepatic transaminases in serum and myopathy[13].

Purpose of the study

Present study was designed to find out the combined effect of Amlodipine and Simvastatin on lipid profile in hypertensive obese patients.

PATIENTS AND METHODS

The study was done on three groups. Group A (Amlodipine) Forty patients (20 male and 20 female) with mild or moderate essential hypertension were included. Serum Cholesterol, serum Triglycerides and serum Lipoprotiens (HDL, LDL) was carried out at 0 week (before giving Amlodipine) and then after 12 weeks of Amlodipine therapy with the dose of 5mg / day by Standard kit methods (Merck). Group B (Simvastatin) Forty obese patients (20 male and 20 female) were included. Patients were advised to take fat free diet and a morning walk. Serum Cholesterol, serum Triglycerides and serum Lipoprotiens (HDL, LDL) was carried out at 0 week (before giving Simvastatin) and then after 12 weeks of Simvastatin therapy with the dose of 10mg / day by Standard kit methods (Merck). Group C (Amlodipine and Simvastatin) Forty hypertensive obese (20 male and 20 female) patients were included. In each case a detailed personal, past and family history was obtained and physical examination for body weight and blood pressure was recorded.

The hypertensive obese patients were evaluated three times i.e. before giving combination of Amlodipine and Simvastatin, 0 week and then after 6 and 12 weeks with the dose of 5mg/day of Amlodipine and 10mg/day of Simvastatin. The patients were advised to take fat free diet and a morning walk. They were checked physically for weight and blood pressure and biochemical investigations. Venous blood was collected from the anticubital vein after an overnight fast and analysed. Effort was made to minimize the dropouts. Serum Cholesterol, serum Triglycerides and serum Lipoprotiens (HDL, LDL) was carried out at o week and then after 12 weeks by Standard kit methods (Merck).

RESULTS

The values of the age, body weight and blood pressure at 0 week after 6 and 12 weeks was noted. (Table 1) It was observed that the mean age of male patients was 40 years and of female patients was 45 years. Mean body weight of male patients was 214 lbs and of female patients was 178 lbs at zero week, after six weeks of administration of Amlodipine and Simvastatin it was 203 lbs of male patients and 169 lbs of female patients, after twelve weeks it was 194 lbs of male patients and 163 lbs in female patients. Mean blood pressure at 0 week in male patients was 160/105 mmHg and 155/105 mmHg of female patients, after six weeks it was 130/85 mm/Hg in male patients while 135/85 mmHg in female patients and after 12 weeks of administration of Amlodipine and Simvastatin mean blood pressure of male patients was 125/80 mmHg whereas in female patients it was 120/80 mmHg. This showed a highly significant reduction of blood pressure ($P<0.001$) in both sexes and significant reduction ($P<0.01$) in weight in male patients after twelve weeks of administration of Amlodipine and Simvastatin.

The levels of serum cholesterol, serum triglyceride and serum lipoprotiens (HDL and LDL) in male patients before 0 week and then after twelve weeks of Group A (Amlodipine), Group B

Table 1: **Mean age, body weight and blood pressure in male/female patients before (0 week) and after (6, 12 weeks) taking a combination of Amlodipine and Simvastatin.**
Values expressed in mean ± SEM. No. of cases in (parentheses).

Time Period	Male (20)			Female (20)		
	Age (Years)	Weight (lbs)	B.P (mmHg)	Age (Years)	Weight (lbs)	B.P (mmHg)
0 weeks	40.95±1.77	214.55±3.86	160/105±1.95/1.41	45.00±1.64	178.6±6.04	155/105±1.98/1.06
6 weeks		203.00±7.70	130/85±1.11/0.98**		169.2±5.74	135/85±1.56/1.14**
12 weeks		194.6±7.39*	125/80±1.47/0.97**		163.6±5.66	120/80±1.54/0.85**

* P< 0.01=significant difference; ** P< 0.001= Highly significant difference

Table 2: **Level of total serum cholesterol, HDL-Cholesterol, LDL-Cholesterol and triglyceride in male patients of group A, group B and group C.**
Values expressed as mean±.SEM

Parameters	Weeks	Group A (Amlodipine)	Group B (Simvastatin)	Group C (Amlodipine +Simvastatin)
Total cholesterol (mg/dl)	0 week	227.85±8.07	240.28±3.55	238.6±5.14
	12 weeks	192.05±7.35**	215.52±4.00**	206.82±4.47**
HDL-cholesterol (mg/dl)	0 week	45.40±1.13	25.55±0.49	35.70±0.75
	12 weeks	43.15±1.06	35.29±0.71**	39.29±1.16**
LDL-cholesterol (mg/dl)	0 week	143.25±5.87	201.72±3.23	172.4±3.21
	12 weeks	111.15±5.67**	160.86±3.50**	141.06±3.31**
Serum Triglyceride (mg/dl)	0 week	174.65±14.02	170.88±7.72	170.05±7.81
	12 weeks	152.20±10.47	122.88±5.00**	133.80±6.22**

**P<0.001=Highly significant difference

Table 3: **Level of total serum cholesterol, HDL-Cholesterol, LDL-Cholesterol and triglyceride in female patients of group A, group B and group C.**
Values expressed as mean±.SEM

Parameters	Weeks	Group A (Amlodipine)	Group B (Simvastatin)	Group C (Amlodipine +Simvastatin)
Total cholesterol (mg/dl)	0 week	211.20±7.59	245.50±4.30	228.5±3.8
	12 weeks	184.65±6.58**	225.20±4.90**	205.20±3.56**
HDL-cholesterol (mg/dl)	0 week	43.30±1.20	30.00±0.60	36.20±0.76
	12 weeks	40.65±2.35	39.90±0.75**	41.0±1.02*
LDL-cholesterol (mg/dl)	0 week	135.70±7.95	200.50±5.20	166.47±4.25
	12 weeks	116.20±5.00*	165.60±5.00**	142.51±3.62**
Serum Triglyceride (mg/dl)	0 week	160.50±13.99	115.50±3.00	137.3±7.63
	12 weeks	136.57±10.85	93.22±1.50**	115.22±5.31*

**P<0.001=Highly significant difference; * P< 0.01=significant difference

(Simvastatin) and Group C (Combination of Amlodipine and Simvastatin) were noted. (Table 2) Group A showed a significant reduction (P<0.001) in levels of serum cholesterol and serum LDL-Cholesterol and non-significant reduction in serum triglyceride and serum HDL-Cholesterol between 0-12 weeks. Group B showed a significant reduction (P<0.001) in levels of serum cholesterol, serum LDL-Cholesterol and in serum triglyceride while serum HDL-Cholesterol was significantly increased (P<0.001) between 0-12 weeks while, Group C showed a significant reduction (P<0.001) in levels of serum cholesterol, serum LDL-Cholesterol and in serum triglyceride while serum HDL-Cholesterol was significantly increased (P<0.001) between 0-12 weeks.

The levels of serum cholesterol, serum triglyceride and serum lipoprotiens (HDL and LDL) in female patients before 0 week and then after twelve weeks of Group A (Amlodipine), Group B (Simvastatin) and Group C (Cmbination of Amlodipine and Simvastatin) were noted. (Table 2) Group A showed a significant reduction ($P<0.001$) in levels of serum cholesterol and serum LDL-Cholesterol and non-significant reduction in serum triglyceride and serum HDL-Cholesterol between 0-12 weeks. Group B showed a significant reduction ($P<0.001$) in levels of serum cholesterol, serum LDL-Cholesterol and in serum triglyceride while serum HDL-Cholesterol was significantly increased ($P<0.001$) between 0-12 weeks while, Group C showed a significant reduction ($P<0.001$) in levels of serum cholesterol, serum LDL-Cholesterol and in serum triglyceride while serum HDL-Cholesterol was significantly increased ($P<0.001$) between 0-12 weeks.

DISCUSSION

In this study we assessed the change in lipid profile before and after giving combination of Amlodipine and Simvastatin to hypertensive obese patients. Amlodipine (calcium channel blocker) is effective in mild to moderate hypertension as a single agent therapy or in combination with other drugs by blocking L-type calcium channels leading to peripheral and coronary vasodilatation. The antiatherosclerotic effect is mediated through a reduction in blood pressure and / or a decrease in vascular smooth muscle cell migration / proliferation along with a possible direct effect[14].

A no of studies[10,12,13] confirmed inhibitory effect of Simvastatin on HMG-CoA reductase. (3Hydroxy 3Methyl Glutaryl Coenzyme A) Although Simvastatin is a safe and efficacious lipid lowering drug but it can cause myopathy syndrome[13].

In present study we also suggested a light exercise (morning walk) with medicine. Body weight was also checked during treatment with Amlodipine and Simvastatin. It was observed that body weight was significantly reduced in male patients. The effect of Simvastatin on reduction of body weight was not reported but it was observed that changes in lipid profile also effects body weight. It may be an insulin distinct resistance related metabolite syndrome characterized by dyslipidemia and obesity in both sexes[14]. Another study found that beside medication life style changes are advocated as a first line of treatment for dyslipidaemia and obesity. They found that more intense life style intervention may be effective at improving blood lipids and quality of life[15]. Another study also found that a comprehensive life style intervention can substantially lower blood pressure in hypertensive adults[16]. It is reported that daily walking reduces visceral adipose tissue areas and improves insulin resistance in obese subjects[17].

A comprison of the level of lipid profile reduction with Group A (Amlodipine) as compared to Group B (Simvastatin) was also determined. It was observed that decreased level of cholesterol in male patients was more in case of Amlodipine (35mg/dl) as compared with Simvastatin (25mg/dl). In case of female patients decreased level of cholesterol was more with Amlodipine as compared with Simvastatin. The reason may be that the initial level of serum cholesterol was very high (240mg/dl) in group of patients taking Simvastatin as compared to group of patients (227mg/dl) taking Amlodipine. Decreased level of triglyceride in case of male patients was more (48mg/dl) with Simvastatin as compared with Amlodipine (22mg/dl). On the other the decreased level of triglyceride in case of female patients was more or less same.

Decreased level of LDL-Cholesterol was also observed when one group of male patients treated with Amlodipine and another group of male patients with Simvastatin. It was found that the level of LDL-Cholesterol was more decreased (41mg/dl) in male patients with Simvastatin as compared with Amlodipine. Like male patients, in female patients the decreased level of LDL-Cholesterol was more with Simvastatin as compared with Amlodipine.

Increased level of HDL-Cholesterol in case of male patients was more (10mg/dl) with Simvastatin as compared with Amlodipine (2mg/dl) Like male patients, in female patients the level was also markedly increased (9mg/dl) with Simvastatin than with Amlodipine (3mg/dl).

Present study found that combined therapy of Amlodipine and Simvastatin, although decreased the level of serum cholesterol (32mg/dl), serum triglycerides (37mg/dl), and LDL-Cholesterol (31mg/dl), but they did not show any significant synergistic effect as compared to the individual levels of these parameters in Group A (Amlodipine) as well as in Group B (Simvastatin) in male patients.

On the other increased level of HDL-Cholesterol (4mg/dl), was observed in case of combined therapy in male patients but this did not show any synergism. Like male patients, in female patients the decreased levels of serum cholesterol, serum triglyceride, serum LDL-Cholesterol and increased level of serum HDL-Choesterol were more or less same.

Reason may be that Amlodipine is actually a calcium channel blocker and its major effect is on blood pressure. It may effect on lipid profile but the effect is not very much significant. On the other Simvastatin is a lipid-lowering drug; its effect is more as compared to Amlodipine. Therefore the combined therapy of Amlodipine and Simvastatin does not show any significant synergism.

So far no work has been done on effects of combination of Amlodipine and Simvastatin on lipid profile in hypertensive patients. Therefore a further study is needed to observe the influence of base line values on lipid and lipoprotein changes during combination of Amlodipine and Simvastatin treatment in hypertensive patients. However it is concluded that combination of Amlodipine and Simvastatin reduces serum cholesterol, serum triglycerides, and serum LDL-Cholesterol significantly and a significant increase in serum HDL-Cholesterol in both sexes.

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