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ORIGINAL ARTICLE

The Efficacy And The Safety Of A Fixed Dose Combination Of Amlodipine And Atorvastatin In Hypertensives With Dyslipidaemia

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ABSTRACT

Introduction: It was claimed that the amlodipine/atorvastatin combination improved the patient's achievement of national-guideline-recommended blood pressure and lipid target levels and exhibited a safety profile consistent with its parent compounds. The present study has been undertaken to evaluate the efficacy and the safety of a fixed dose combination of amlodipine with atorvastatin in the Indian population.

Methods: The study was designed as a prospective, open labeled, noncomparative trial in 35 adult patients of mild to moderate essential hypertension with dyslipidaemia. The blood pressure criteria for inclusion was >140/90mmHg and less than 180/110mmHg. The dyslipidaemia criteria was LDL cholesterol>130mg/dl and triglycerides more than 150mg/dl. The patients were screened at baseline visit (Day 0) and at visit 2 (Day 4). The supine blood pressure was recorded by taking the mean of three readings. The blood pressure was measured again after a week during the placebo period (visit 3, day 10, week 1). The active medication (Combination of 5mg of amlodipine and 10mg of atorvastatin) started at visit 4 (day 17, week 2). The blood pressure was measured again during visit 5 (day 31, week 4), visit 6 (day 45, week 6) and visit 7 (day 60, week 8) by using the same instrument at all visits.

Results: A total of 35 patients were included in the study, out of which 27 were males and eight were females. The average decrease of supine blood pressure from the baseline recording was 10.3$\pm$ 3.62mmHg at the end of treatment, which was statistically highly significant (p=0.005). The average decrease of diastolic blood pressure was 9.51$\pm$2.13mmHg at the end of the treatment, which was also statistically highly significant (p=0.0002). A statistically significant decrease in the levels of total cholesterol and LDL cholesterol were observed during the treatment. The most common adverse events were hyponatraemia (25.93%), head ache (22.22%) and hypoglycaemia (22.22%).

Conclusion: To conclude, the concomitant administration of amlodipine and atorvastatin is well tolerated and effective in reducing both blood pressure and lipid levels and in helping patients achieve their goals in cases of hypertension and dyslipidaemia.

Key words: *Amlodipine, atorvastatin, hypertension, dyslipidaemia.*

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Introduction:

The benefits of lowering blood pressure (BP) in patients with hypertension and lowering cholesterol in patients with dyslipidaemia are well known and well studied. However, worldwide, many patients with hypertension have concomitant dyslipidaemia, which places them at a greater risk for cardiovascular disease as compared to patients with just one risk factor. In order to prevent cardiovascular events, it is essential to effectively manage the overall risk of cardiovascular disease[1]. However, despite guideline recommendations to this effect, the current management of the major, modifiable cardiovascular risk factors such as hypertension and dyslipidaemia is disconnected and patient adherence to therapy is poor. This is particularly important for patients with multiple cardiovascular risk factors, who are often prescribed multiple medications. Polypharmacy and complex treatment regimens have been identified as important, modifiable risk factors for medication noncompliance. The use of fixed-dose combinations in this regard may have advantages[2] like simplification of therapy, increased patient compliance, reduction of total daily dose and adverse effects and the reduction of the overall cost of therapy. These fixed-dose combinations are valuable only when they have been developed, based on sound rational pharmacokinetic and pharmacodynamic criteria and when claims for their benefits have been supported by evidence-based data and well-designed clinical studies.

Amlodipine/atorvastatin is a combination of two drugs, amlodipine, a long acting dihydropyridine calcium channel blocker and atorvastatin, a synthetic HMG-CoA reductase inhibitor. The amlodipine/atorvastatin combination is indicated for patients who require simultaneous treatment with both drugs. Clinical trials have demonstrated that amlodipine plus atorvastatin can be safely co-administered across the dose range. Single-pill amlodipine/atorvastatin reduces both BP and cholesterol and may help to improve the management of patients with concomitant hypertension and dyslipidaemia[3],[4]. It was claimed that the amlodipine/atorvastatin combination improved the patient's achievement of national-guideline-recommended blood pressure and lipid target levels and exhibited a safety profile consistent with its parent compounds. The present study has been undertaken to evaluate the efficacy and the safety of a fixed dose combination of amlodipine with atorvastatin in the Indian population.

Methods:

The study was designed as a prospective, open labeled, noncomparative trial in 35 adult patients of mild to moderate essential hypertension with dyslipidaemia. The study protocol was approved by the institutional ethics committee and the written informed consent was taken from each patient. The study included both sexes, newly diagnosed hypertensives, as well as those who were on antihypertensive therapy. Freshly diagnosed patients of dyslipidaemia, as well as those who showed inadequate response to the previous therapy were included in the study. The blood pressure criteria for inclusion was >140/90mmHg and less than 180/110mmHg. The dyslipidaemia criteria was LDL cholesterol>130mg/dl and triglycerides more than 150mg/dl. Patients with severe hypertension, cardiac failure, acute myocardial infarction, stroke, uncontrolled diabetes mellitus, grade III retinopathy, papilloedema, renal/hepatic impairment, psychiatric illness, history of major surgery during the previous 3 months, known hypersensitivity to amlodipine or statins and those who are on concurrent NSAIDs were excluded from the study. Women of child bearing potential, as well as lactating mothers were also not included in the study.

The patients were screened at baseline visit (Day 0) and blood samples for haematology, hepatic/renal function tests and lipid profile

were collected. The presence of any concomitant diseases and concomitant medications were recorded. At visit 2 (Day 4), supine blood pressure was recorded by taking the mean of three readings. The patients were advised to discontinue their previous antihypertensive and lipid lowering medications and they were put on placebo tablets for 2 weeks. Dietary modifications also advised during this visit. Blood pressure was measured again after a week during the placebo period (visit 3, day 10, week 1). Active medication (Combination of 5mg amlodipine and 10mg atorvastatin) started at visit 4 (day 17, week2). At this visit, the patients were withdrawn from the study if their blood pressure and lipid profile were within the normal limits. Blood pressure was measured again during visit 5 (day 31, week 4), visit 6 (day 45, week 6) and visit 7 (day 60, week 8) by using the same instrument at all visits. The patients were advised to get the used container of study medication during each visit to check for compliance. The adverse events reported or detected during examination were recorded with all the relevant details. All laboratory investigations were repeated again at the end of the study i.e. at visit 7.

Statistical analysis was done by using the Student's 't'test. P values less than 0.05 were considered as statistically significant.

Results:

A total of 35 patients were included in the study, out of which 27 were males and eight were females. [Table/Fig 1] shows the demographic characteristics of the patients. The mean age of the patients was 60.43± 2.25 years. The mean body mass index was 24.84±0.52kg/m^2.

[Table/Fig 1]: Demographic characteristics of the patients

Characteristics	Value
Age	60.4+2.25
Males(n%)	19(70.37)
Females(n(%))	8(29.63)
Body mass index(mg/m^2)	24.84±0.52
Diabetes mellitus(n(%))	23(85.19)
Ischaemic heart disease	7(25.93)
Duration of hypertension(years)(mean)	2.96
Baseline systolic BP(mmHg)	155.37+ 3.01
Baseline diastolic BP(mmHg)	93.37+2.17
Baseline cholesterol (mg/dl)	240.11+9.87
Baseline LDL cholesterol(mg/dl)	154.69+ 7.88
Baseline triglycerides(mg/dl)	225.66±32.98
Baseline HDL cholesterol(mg/dl)	40.46±2.13

All values are expressed as mean± SE

The average duration of hypertension is 2.96 years. 23 patients were diabetic and 7 had ischaemic heart disease. 28 patients entered into active medication visit, out of which one was withdrawn at visit 6 due to adverse events. Two patients were withdrawn at visit 2, as their BP and lipids were normal after placebo. One of the patients was withdrawn at visit 2 because of adverse events. Three patients were lost to follow up after visit 3.

The mean blood pressure and mean lipid values at different visits are shown in [Table/Fig 2] and [Table/Fig 3] respectively. [Table/Fig 4] shows the mean changes in blood pressure and [Table/Fig 5] shows the mean changes in the lipid profile at different visits from the baseline to the end of treatment.

[Table/Fig 2]: Changes in blood pressure from baseline to end of treatment

Week	Blood pressure (mm of Hg)		t value	p value	95% Confidence interval of the difference	
					Lower	Upper
Week 1	Systolic	156.06± 2.45	0.04	0.97	-5.54	5.78
	Diastolic	86.91±2.18	-4.49	0.000**	-9.39	-3.53
Week 2	Systolic	158.91+2.8	1.16	0.26	-2.27	8.21
	Diastolic	90.06+ 1.74	-2.07	0.047*	-6.56	-5.05
Week 4	Systolic	150.71+3.84	-1.39	0.18	-12.96	2.5
	Diastolic	87.64+1.76	-3.31	0.003**	-9.28	-2.18
Week 6	Systolic	143.5+3.42	-3.71	0.001**	-19.32	-5.56
	Diastolic	83.07+1.54	-6.82	0.000**	-13.4	-7.2
Week 8	Systolic	144.26±3.4	-3.49	0.002**	-18.51	-4.8
	Diastolic	83.11±1.7	-6.14	0.000**	-13.69	-6.83

Values were expressed as mean± SE t=Student 't' test*Significant ** Very highly significant

The average decrease of supine blood pressure from the baseline recording was 10.3± 3.62mmHg at the end of the treatment, which was statistically highly significant ($p<0.001$). The average decrease of diastolic blood pressure was 9.51±2.13mmHg at the end of the treatment, which was also statistically highly significant ($p<0.001$). Significant blood pressure reduction was evident 6 weeks onwards.

[Table/Fig 3]: Changes in lipid levels from baseline to the end of treatment

Week	Lipid levels (mg/dl)		t value	p value	95% Confidence interval of the difference	
					Lower	Upper
Week 4	Total cholesterol	236.94±7.81	-0.44	0.66	-17.81	11.46
	LDL	164.5±10.23	1.04	0.31	-9.36	28.98
	Triglycerides	196.40+21.18	-1.50	0.14	-68.92	10.42
	HDL	40.91+2.56	0.19	0.85	-4.35	5.24
Week 8	Total cholesterol	166.36+5.89	-12.76	0.000**	-85.62	-61.89
	LDL	90.96+6.12	-10.62	0.000**	-76.04	-51.42
	Triglycerides	168.39+22.84	-2.55	0.02*	-103.29	-11.25
	HDL	48.43+3.5	2.32	0.03*	0.92	15.01

Values were expressed as mean± SE t=Student 't' test*Significant ** Very highly significant

A statistically significant decrease in the levels of total cholesterol, LDL cholesterol and triglycerides were observed during the treatment. At the end of the treatment, the decrease in total cholesterol level was found to be 78.15± 8.31 mg/dl, in LDL cholesterol level was found to be 63.74 ±8.26mg/dl and in triglyceride levels was found to be 58.51±17.91mg/dl. HDL levels were found to be increased by 4.9±1.44mg/dl at the end of the treatment, which was statistically significant (p=0.03).

[Table/Fig 4]. Mean changes in blood pressure from baseline to end of the treatment.

Mean changes in BP	Week 1	Week 2	Week 4	Week 6	Week 8
Systolic BP(mmHg)	0± 3.19	-5 ±2.77	3.63± 4.06	11.85± 3.81	10.3 ±3.62
Diastolic BP(mmHg))	6.7± 2.02	2.22± 2.32	4.81± 2.05	9.23± 2.09	9.52 ±2.13

All values are expressed as mean± SE

[Table/Fig 5]. Mean changes in lipid levels from baseline to end of treatment.

Mean changes	Week 4	Week 8
Total cholesterol(mg/dl)	6.41 ±7.1	78.15± 8.31
LDL cholesterol(mg/dl) (	-8.41± 8.55	63.74± 8.26
Triglycerides(mg/dl)	25.85 ±25.94	58.52 ±17.91
HDL cholesterol(mg/dl)	-1.04 ±1.61	-4.93± 1.44

All values are expressed as mean± SE

The decrease in total cholesterol and LDL cholesterol was highly significant (p<0.001), whereas the drop in triglyceride levels was also showed statistical significance (p=0.03). 59.26% patients achieved blood pressure goals and 77.77% of the patients achieved low-density lipoprotein cholesterol goals.

[Table/Fig 6] Incidence of adverse events

Adverse event	Number of patients(n=27)	Percentage
Hyponatremia	7	25.93
Headache	6	22.22
Hypoglycemia	5	18.52
Pedal edema	3	11.11
Giddiness	3	11.11
Weakness	3	11.11
Exertional dyspnoea	2	7.41
Flatulence	2	7.41
Arthralgia	2	7.41
Myalgia	2	7.41
Elevated serum creatinine	2	7.41
Elevated creatine kinase	1	3.7
Elevated serum bilirubin	1	3.7
Hypokalemia	1	3.7
Itching	1	3.7
Postural hypotension	1	3.7
Cramps of legs	1	3.7
Constipation	1	3.7

Both the goals were achieved in 55.55% of the patients. The mean blood pressure reduction was 10.3/9.5 mm Hg and the mean LDL-C reduction was 63.74mg/dl (41.4%) after 8 weeks of treatment.

The adverse events which were reported were minor. The incidence of the adverse events (AEs) is shown in [Table/Fig 6]. The most common AEs were hyponatraemia (25.93%), head ache (22.22%) and hypoglycaemia (22.22%).

Among the patients who developed hyponatraemia, 2 were receiving diuretics and 3 were on ACE inhibitors. The patients who presented with hypoglycaemia were diabetics on insulin/oral hypoglycaemic agents. Other less common AEs which were reported were pedal oedema, giddiness, myalgia, arthalgia, flatulence, weakness, hypokalaemia and elevated serum creatinine.

Discussion:

Guidelines stress the importance of the simultaneous management of multiple cardiovascular risk factors. This can in part be achieved by the coadministration of lipid-lowering and antihypertensive treatments. Adherence to treatment notably improved when therapy was initiated simultaneously[5]. Amlodipine and atorvastatin have been demonstrated in numerous clinical trials to be highly effective in lowering blood pressure and low-density lipoprotein cholesterol. The amlodipine/atorvastatin single pill has been shown to achieve national-guideline-recommended blood pressure and lipid target levels and exhibits a safety profile which is consistent with its parent compounds[4],[6],[7].

The results of the present study have shown that the combination of atorvastatin and

amlodipine is well tolerated and is effective in reducing blood pressure, as well as in improving lipid profile. A statistically highly significant reduction in both systolic and diastolic blood pressure, as well as a highly significant reduction in LDL cholesterol was observed at the end of 8 weeks of treatment. Atorvastatin and amlodipine have each been shown to have beneficial effects on the endothelium *in vitro* and they may have a greater effect on blood pressure reduction[8]. The results of Atorvastatin and Amlodipine in patients with elevated lipids and hypertension (the AVALON study[6]) showed that 5 mg of amlodipine, administered once daily in combination with 10 mg of atorvastatin I was an effective treatment for concomitant hypertension/dyslipidaemia. AVALON was the first of a series of trials of concomitant cholesterol/blood pressure lowering with atorvastatin plus amlodipine, but the last in which the 2 agents were administered separately. In subsequent trials, a single-pill, dual-therapy approach, combining amlodipine and atorvastatin was used and this combination was approved by the United States Food and Drug Administration.

Results from an international study program showed that the single-pill fixed-dose combination of the amlodipine/atorvastatin therapy was an effective treatment that simultaneously reduced two modifiable risk factors, hypertension and low-density lipoprotein cholesterol levels and reduced the calculated risk for a fatal cardiovascular event by 29%-52%.[8] The present study showed that 59.26% of the patients achieved blood pressure goals and 77.77% of the patients achieved low-density lipoprotein cholesterol goals, as defined by the sixth report of the Joint National Committee on the Prevention, Detection, and the Treatment of High Blood Pressure (JNC VI)[9] or their LDL-cholesterol goals, as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III,[10]. Both the goals were achieved in 55.55% of the patients in the present study. In agreement with our results, the GEMINI study showed that 57.7% of the patients achieved both blood pressure and low-density lipoprotein cholesterol goals, 62.9% of the subjects in the JEWEL I study and 50.6% of the patients in the JEWEL II study achieved both country-specific blood pressure and LDL-cholesterol goals after 16 weeks of treatment with the same combination[7]. Neutel GM etal[11] showed that dual goal attainment was significantly greater with amlodipine/atorvastatin as compared with placebo at week 4, with further improvements at week 8. Erdine S et al [12] showed that after 14 weeks treatment, 55.2% of patients reached both blood pressure and lipid goals, 61.3% patients reached the blood pressure goal and 87.1% patients reached the lipid goal (34.0% were at lipid goal at baseline). They observed mean blood pressure reduction was 20.2/11.4 mm Hg and the mean reduction in LDL-C was 41.0%. In contrast to these results, our study showed lesser mean blood pressure reduction (10.3/9.5 mm Hg) and mean LDL-C reduction of 63.74mg/dl (41.4%) after 8 weeks of treatment. Comparatively, the shorter duration of the study may be responsible for a lesser reduction in the mean blood pressure in our study.

Earlier studies have demonstrated that amlodipine/atorvastatin has the same safety profile as its individual components and can be administered safely across the dosage range[4],[5],[6],[7],[11],[12]. The side effects of amlodipine/atorvastatin are similar to those for each component, most commonly abdominal pain, constipation, dyspepsia, oedema, flatulence and headache. The serious but rare side effects included hepatotoxicity and rhabdomyolysis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and cardiac failure. In the GEMINI study[12], 64.1% of patients reported at least one adverse event. The most commonly reported adverse events were respiratory tract infection (11.9%), peripheral oedema (8.8%), headache (5.4%) and myalgia (4.2%). The incidence of serious adverse events during the study appeared to be low (2.7%), with no events attributable to the study drug. There were no serious events that correlated with myopathy, myositis, rhabdomyolysis or abnormal/increase in alanine aminotransferase, aspartate aminotransferase or creatinine phosphokinase. Our study has also shown a similar pattern of adverse events. One of the commonest adverse event seen in the present study was hyponatraemia, which was not observed in the

earlier studies. Among the 7 patients who presented with hyponatraemia, 2 patients were on diuretics and 3 were on ACE inhibitors, which could have been the cause of the hyponatraemia. In the remaining two patients, the cause of hyponatraemia could not be identified. Hyponatraemia could not be attributed to the environmental conditions, as the study was conducted during the winter season. Hence, the relationship of hyponatraemia with the study medication may be possible. As per the literature, amlodipine was not associated with hyponatraemia. Serious adverse events did not occur in the present study. Though the incidence of hypoglycaemia was also more in the present study, this cannot be attributed to the study medication, as these patients were diabetics who were on insulin/oral hypoglycaemic agents.

The limitations of the present study should be considered. The number of patients in the study was very small to draw any valid conclusions. The duration of treatment was comparatively shorter in our study.

To conclude, the concomitant administration of amlodipine and atorvastatin is well tolerated and effective in reducing both blood pressure and lipid levels and in helping patients achieve their goals in cases of hypertension and dyslipidaemia. Amlodipine combined with atorvastatin has been demonstrated to reduce cardiovascular events in hypertensive patients at high cardiovascular risk and the single-pill formulation has the potential to improve adherence and decrease prescription costs. These potential benefits are associated with important implications because hypertensive patients with additional risk factors represent a large proportion of those at risk for cardiovascular events.

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