Original Article

Biochemistry

Biochemical Evaluation of Amlodipne / Ramipril in Combination with Essential Hypertension

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ABSTRACT

Introduction: The reduction of blood pressure lower than 130/85 mmHg provides additional benefits regarding both protection of organs and cardiovascular mortality. Amlodipine is a calcium channel-blocking agent with vasodilator activity and Ramipril is ACE inhibitor.

Objective: the objective of this double-blind, comparative study evaluating the biochemical effects of Amlodipine 5mg and Ramipril 1.25mg in combination and as monotherapy in adult patient with essential hypertension.

Study Design. Double-blind, comparative study

Place and Duration of Study: This study was conducted at the Department of Biochemistry, University of Karachi from December 2010 to September 2011.

Materials and Methods: This was multicenter randomized, double-blind, comparative study. Patients were randomized to receive Amlodopine (5mg) once daily, Ramipril (1.25 mg) once daily and combination of amlodipine 5mg with Ramipril 1.25 mg once daily for 8 weeks and at the end of study biochemical evaluation was done

Results: In the patients treated with combination of Amlodipine 5mg and Ramipril 1.25mg tablets showed synergetic effect and no significant biochemical effects

Conclusion: We can suggest that good tolerability and no biochemical & hematological effects of combination of Amlodipine 5mg and Ramipril 1.25mg to formulate in a single dosage forms (tablet) because it is an excellent option for the treatment of hypertension in a wide range of hypertensive patients, with a high potential to reduce cardiovascular risks.

Key Words: Amlodipine, hypertension, Ramipril, Biochemical effects.

INTRODUCTION

An adequate blood pressure is a treatment of hypertension and it is the risk of cardiovascular morbidity and mortality so proper therapy is essential. And the reduction of blood pressure lower than 130/85 mmHg provides additional benefits regarding both protection of organs and cardiovascular mortality. Guidelines of World Health Organization for the treatment of hypertension that is, 130/85 mmHg which is lower than the previous limit of 140/90 mmHg.[1-6.] Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. It may be used alone or in combination with other antihypertensive agents. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours and is well tolerated as monotherapy and in combination with other drugs without orthostatic hypotention[7.] ACE inhibitors, or angiotensin converting enzyme inhibitors (i.e. Enalapril, Ramipril, Captropril) reduce peripheral vascular resistance via blockage of the angiotensin converting enzyme. This action reduces the myocardial oxygen consumption, thereby improving cardiac output and moderating left ventricular and moderating left ventricular and vascular hypertrophy. ACEIs are recommended in current clinical practice guidelines for secondary prevention in patients with cardiovascular disease[, 8, 9.] Combination therapies reduced B.P to a greater extent than with amlodipine besylate alone as indicated with benazepril hydrochloride with valsartan and with perindopril[10, 11]. In many uncontrolled studies on antihypertensive therapies, a reduction in echo cardio graphically determined LVM has been observed. The results from a recent review [12]suggest that most of the therapeutic classes that are currently used to decrease blood pressure, i.e. angiotensin-converting enzyme (ACE) inhibitors, β-blockers, calcium antagonists, and more controversially, diuretics, seem to be able to reduce LVH. However, only six placebo-controlled trials have been reported, five of which assessed calcium antagonists.[13-18] In one of these trials,[13] significant LVM regression in the treatment group compared with the placebo group was associated with body weight reduction but not antihypertensive treatment. In the other five trials,[14-18] the results were analyzed separately for each group, with no intergroup comparisons. Although no direct comparative trial has been performed, ACE inhibitors are thought to have a more pronounced effect on LVH regression than the other drug classes, and this raises the question of the role of the renin-angiotensin system in this disease.[19] Therefore, the objective of this double-blind,

comparative study evaluating the biochemical effects of Amlodipine 5mg and Ramipril 1.25mg in combination and as monotherapy in adult patient with essential hypertension..

MATERIALS AND METHODS

This was multicenter randomized, double-blind, comparative study. Patients were randomized to receive Amlodipine (5mg) once daily, Ramipril (1.25 mg) once daily and combination of amlodipine 5mg with Ramipril 1.25 mg once daily for 8 weeks and at the end of study biochemical evaluation was done. The study was conducted in Department of Biochemistry, University of Karachi from December 2010 to September 2011.Patients were selected from four different hospitals of orange Town and 80 patients were selected for the study. Therefore 201patients were effectively analyzed for efficacy and tolerability the analysis of antihypertensive efficacy and biochemical effects of a therapeutic regimens in the long term becomes important. The primary efficacy variable was change from baseline in MSDP at the end of study. Secondary variable was change in mean sitting systolic blood pressure from baseline. Safety biochemical parameters (complete blood count, renal function, liver function, electrolytes, protein profile, and enzymes) and electrocardiogram at rest were also determined in all patients at the baseline (week O) and at the 8th week of antihypertensive treatment. At the same time points, glucose metabolism parameter values and plasma lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) were also recorded. Biochemical parameters were determined using an automated method.

RESULTS

In the patients treated with combination of Amlodipine 5mg and Ramipril 1.25mg tablets blood pressure reduction was significantly lower, reaching values of 130.4 ± 10.2 / 84.1 ± 7.4 mmHg by the end of eight weeks of treatment. Variations in blood pressure measurement in the standing position during treatment were similar to those recorded in the sitting position, and no episode of orthostatic hypotension was reported in either of the therapeutic regimen. No significant variation in leg volume measurement was observed among the both groups studied during the eight weeks of treatment. No significant variations of blood glucose and different parameters of lipid profile were observed during the eight weeks of treatment with any of the three antihypertensive regimens used. Thus, the drug regimens used may be considered neutral as regards glucose and plasma lipid metabolism profile because both classes of drugs used at low doses.

Table No.1: Baseline Characteristics

	Amlodipine (n=67)	Ramipril (n=67)	Amlodipine + Ramipril (n=67)
Age (years)	50.2 ± 9.3	51.5 ± 9.8	53.4 ± 9.5
Male / Female (%)	43.4 / 56.6	35.0 / 65.0	31.6 / 68.4
Body weight (Kg)	68.9 ± 13.5	71.2 ± 12.2	69.7 ± 10.9
BMI (kg/m2)	27.5 ± 3.8	27.8 ± 3.4	27.3 ± 3.5

Table No.2: Biochemical baseline characteristics

	Amlodipine (n=67)	Ramipril (n=67)	Amlodipine + Ramipril (n=67)
	Fasting blood glucose(mg/dl)		
Baseline	98.0 ± 12.5	96.8 ± 8.9	94.9 ± 9.6
Week 8	96.5 ± 11.9	97.2 ± 10.2	97.1 ± 10.8
	Total Cholesterol (mg/dl)		
Baseline	195.1 ± 44.2	199.0 ± 36.4	193.5 ± 41.4
Week 8	199.8 ± 43.6	193.8 ± 35.2	187.9 ± 40.7
	LDL - Cholesterol (mg\dl)		
Baseline	115.9 ± 32.4	120.8 ±130.5	119.2 ± 31.4
Week 8	117.2 ± 33.1	112.5 ± 28.7	118.0 ± 30.2
	HDL - Cholesterol (mg\dl)		
Baseline	51.5 ± 13.2	50.2 ± 12.4	52 ± 11.5
Week 8	52.2 ± 10.9	52.0 ± 13.2	51.9 ± 11.8
	Triglycerides (mg\dl)		
Baseline	137.2 ± 87.1	147.7 ± 98.1	150.9 ± 120.5
Week 8	132.5 ± 85.3	147.2 ± 96.9	149.8 ± 115.7

DISCUSSION

The baseline characteristics of the population included in the study are shown in Table No.1. We can observe that the groups were not different in relation to age, body mass index and weight, heart rate, and systolic and diastolic pressure values In the patients treated with combination of Amlodipine 5mg and Ramipril 1.25mg tablets blood pressure reduction was significantly lower, reaching values of 130.4 ± 10.2 / 84.1 ± 7.4 mmHg by the end of eight weeks of treatment. It means that patients treated with Amlodipine 5mg tablet alone, and Ramipril 1.25mg tablet alone, achieve previous

blood pressure level. i.e 140/ 90 mm Hg. And when the patients treated with combination (Amlodipine 5mg & Ramipril 1.25mg) showed synergetic effect as compare to Amlodipine 5mg & Ramipril 1.25mg alone that was achieve new blood pressure limits i.e. 130/ 85 mmHg. Biochemical effects on glucose and lipid-Glucose and plasma lipid metabolism parameter values assessed at the baseline and at the 8th week of treatment with the three drug regimens are shown in Table 2. No significant variations of blood glucose and different parameters of lipid profile were observed during the eight weeks of treatment with any of the three antihypertensive regimens used. Thus, the drug regimens used may be considered neutral as regards glucose and plasma lipid metabolism profile because both classes of drugs used at low doses. It is important to point out that blood pressure reduction provided by the treatment with the combination of Amlodipine 5mg and Ramipril 1.25mg did not cause any secondary increase in sympathetic activity, since no significant variations of heart rate occurred. In addition to a high efficacy in reducing blood pressure, keeping it at controlled levels, an antihypertensive drug should also have a good biochemical profile, since the presence of adverse effects may decrease the degree of compliance of the patient to the therapeutic regimen, thus ultimately leading to treatment dropout24. Our results showed that the combination of Amlodipine 5mg and Ramipril 1.25mg at low doses has a very good biochemical profile with a low incidence of adverse events. The good biochemical profile of the combination Amlodipine 5mg and Ramipril 1.25mg may be explained by the use of lower doses of each of the hypotensive drugs, since the existence of a strong relation between the dose of the hypotensive drug and the frequency of adverse events is known. We evaluate biochemical effects especially glucose and lipids. And we also evaluate hematogical profile. Because alterations in these parameters are very frequently observed in hypertensive patients. Incidentally, hypertension is frequently associated to the metabolic syndrome; also, the frequency of this association increases with age. However, some drugs used in the treatment of hypertension, such as diuretics and beta blockers, are known to be able to promote harmful alterations in lipid metabolism, especially in glucose metabolism. The pharmacologic agents of the class of calcium channel antagonists, in turn, have a neutral metabolic profile. In our study, we observed that the use of the fixed combination of Amlodipine 5mg and Ramipril 1.25mg did not change parameters of either glucose metabolism or plasma lipids, thus having a neutral biochemical profile even when used for 8 weeks. Based on these results we can suggest that this therapeutic modality is safe and adequate for the treatment of hypertension in patients with metabolic syndrome, diabetes mellitus and dyslipidemia.

CONCLUSION

We can suggest that good tolerability and no biochemical & hematological effects of combination of Amlodipine 5mg and Ramipril 1.25mg to formulate in a single dosage forms (tablet) because it is an excellent option for the treatment of hypertension in a wide range of hypertensive patients, with a high potential to reduce cardiovascular risks.

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