Original Article

Biochemistry

To Study Biochemical Effects of Optimized Product Ramipril 1.25mg Tablet with Essential Hypertension

1. Abdul Latif 2. Asnad 3. Abid Karim 4. Muhammad Ishaq 5. Israr Ahmed Akhund

1. Assoc. Prof. of Medicine 2. Asstt. Prof. of Biochemistry 3. Asstt. Prof. of Forensic Medicine
4. Prof. of Surgery 5. Prof. of Physiology, Jinnah Medical College, Peshawar

ABSTRACT

Introduction: Hypertension is one of the strongest modifiable risk factors for cardiovascular and kidney disease and has been identified as the leading risk factor for mortality. The reduction of blood pressure lower than 130/85 mmHg provides additional benefits regarding both protection of organs and cardiovascular mortality. Angiotensin converting enzyme inhibitors have been shown to block the activation of the renin-angiotensin system in the plasma as well as in the vascular wall.

Objective: The objective of this double-blind, comparative study evaluating the biochemical effects of optimized Ramipril 1.25mg tablet 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 January 2011 to August 2011.

Materials and Methods: This was multicenter randomized, double-blind, comparative study. Patients were randomized to receive 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 optimized Ramipril 1.25mg tablets showed antihypertensive property. No significant variations of blood glucose and different parameters of lipid profile were observed during the eight weeks of treatment**.**

Conclusion: We can suggest that the high antihypertensive efficacy, good tolerability and no biochemical effects of the optimized Ramipril 1.25mg (F-4) 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: hypertension, Ramipril, Biochemical effects.

INTRODUCTION

Hypertension is one of the strongest modifiable risk factors for cardiovascular and kidney disease and has been identified as the leading risk factor for mortality[1].In European countries the prevalence of hypertension in adults is estimated to be approximately 44%.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.[3-8]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[9, 10].Combination therapies reduced B.P to a greater extent than with amlodipine besylate alone as indicated with benazepril hydrochloride with valsartan and with perindopril[11.12]Treatment with the ACE inhibitor ramipril reduced cardiovascular mortality and morbidity in abroad range of patients at high risk for cardiovascular events.[13.] In many uncontrolled studies on antihypertensive therapies, a reduction in echocardiographically determined LVM has been observed. The results from a recent review [14]suggest that most of the therapeutic classes that are currently used to decrease blood pressure, ie, 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.[15-20] In one of these trials,[15] 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,[16-20] 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.[21.] Therefore, the objective of this comparative study evaluating the biochemical effects of optimized Ramipril 1.25mg(F-4) with placebo in the treatment of patients with essential hypertension.

MATERIALS AND METHODS

This was multicenter, randomized, placebo-controlled, comparative study. Patients were randomized to receive optimized Ramipril (1.25 mg) (F-4) 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 January 2011 to August 2011, Patients were selected from four different hospitals of orange Town and 80 patients were selected for the study. Therefore 80patients were effectively analyzed for efficacy and tolerability the analysis of antihypertensive efficacy and biochemical effects of a therapeutic regimen 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

The patients treated with optimized Ramipril 1.25mg tablet (F-4) alone, blood pressure reduction was lower, although significant; reaching values of 139.9 ± 11.3 / 89.9 ± 5.5 mmHg ($p < 0.05$ versus Placebo) by the end of eight weeks of treatment.

Table No.1. Baseline characteristics

	Ramipril (F-4) (n=60)	Placebo (n=20)
Age (years)	50.2 ± 9.3	51.5 ± 9.8
Male / Female (%)	43.4 / 56.6	35.0 / 65.0
Body weight (Kg)	68.9 ± 13.5	71.2 ± 12.2
BMI (kg/m2)	27.5 ± 3.8	27.8 ± 3.4

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 was observed and different parameters of lipid profile were also observed during the eight weeks of treatment with antihypertensive regimen used. Thus, the drug regimens used may be considered neutral as regards glucose and plasma lipid metabolism profile because drug used at low doses.

Table No.2: Baseline Biochemical characteristics

	Ramipril (F-4) (n=60)	Placebo (n=20)
	Fasting Blood Glucose(mg/dl)	
Baseline	96.4 ± 11.5	98.1 ± 8.8
Week 8	94.5 ± 11.9	97.9 ± 9.2
	Total Cholesterol (mg/dl)	
Baseline	194.2 ± 43.2	194.2 ± 33.3
Week 8	199.8 ± 43.5	193.8 ± 32.4
	LDL - Cholesterol (mg\dl)	
Baseline	113.4 ± 34.1	116.9 ± 25.9
Week 8	115.9 ± 34.5	115.8 + 24.7
	HDL - Cholesterol (mg\dl)	
Baseline	51.9 ± 13.1	48.9 ± 11.7
Week 8	50.8 ± 12.8	48.1 ± 11.2
	Triglycerides (mg\dl)	
Baseline	136.2 ± 88.5	144.5 ± 88.1
Week 8	135.1 ± 89.2	143.2 ± 88.9

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 .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 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 Ramipril 1.25mg at low doses has a very good biochemical profile with a low incidence of adverse events. The good biochemical profile of 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 in another study. 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. 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 the high antihypertensive efficacy, good tolerability and no biochemical effects of the optimized Ramipril 1.25mg (F-4) 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.

REFERENCES

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. The Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347–60.
2. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, et al. Hypertension and blood pressure levels in 6 European countries, Canada, and the US. JAMA 2003;289:2363–9.
3. Sykowsky PA, D'Agostino RB, Belanger AJ, Kannel WB. Secular Trends in Long Term Sustained Hypertension, Long Term Treatment and Cardiovascular Morbidity. The Framingham Heart Study 1950-1990. Circulation 1996; 93: 697-703.
4. MacMahon S, Peto R, Cutler J, et al. Blood Pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias. Lancet 1990; 335: 765-77.
5. IV Diretrizes Brasileiras de Hipertensão Arterial - Sociedade Brasileira de Hipertensão;Sociedade Brasileira de Cardiologia e Sociedade Brasileira de Nefrologia. Hipertensão 2003;5(4):126-63.
6. Chobaniam AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure- JNC 7. Hypertension 2003, 42: 1206-52.
7. European Society of Hypertension - European Society of Cardiology guidelines for management of arterial hypertension. J Hypertens 2003;21: 1011-53.
8. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, et al on behalf of HOT Study group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 1998; 351: 1755-62.
9. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27:1341-1381.
10. Smith SC Jr, Allen J, Blair SN, AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006; 113:2363-2372.
11. Khalida B, Najaf AG, Naheed A. Comparative studies of cimetidine derivative "temalastine" for potential energy calculation by Kitaigorodskii and lennard-jones functions. Pak J Biochem Mol Biol 2010; 43: 81-86.
12. Afshan N, Naheed A, Khalida B, Najaf AG and Farhat B. Conformational analysis geometry optimization) of nucleosidic antitumor antibiotic showdomycin by Arguslab 4 software. Pak J Pharmacol 2009; 22:78-82.
13. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects ofan angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascularevents in high-risk patients: the Heart Outcomes Prevention EvaluationStudy Investigators. N Engl J Med 2000;342:145–153
14. Dahlöf B, Pennert K, Hansson L. Regression of left ventricular hypertrophy: a meta-analysis. Clin Exp Hypertens 1992;14:173-180.
15. MacMahon SW, Wilcken DEL, Macdonald GJ. The effect of weight reduction on left ventricular mass: a randomized controlled trial in young, overweight hypertensive patients. N Engl J Med 1986;314:334-339.
16. Dittrich HC, Adler J, Ong J, Reitman M, Weber M, Ziegler M. Effects of sustained-release nicardipine on regression of left ventricular hypertrophy in systemic hypertension. Am J Cardiol 1992; 69: 1559-1564.
17. Ferrara LA, de Simone G, Mancini M, Fasano ML, Pasanisi F, Vallone G. Changes in left ventricular mass during a double-blind study with chlorthalidone and slow-release nifedipine. Eur J Clin Pharmacol1984;24:525-528.

18. Ferrara LA, Fasano ML, de Simone G, Soro S, Gagliardi R. Antihypertensive and cardiovascular effects of nitrendipine: a controlled study vs placebo. Clin Pharmacol Ther 1985;38:434-438.
19. Genovesi-Ebert A, Marabotti C, Palombo C, Ghione S, Cattaneo G, Noseda A, et al. Effect of a new multifactorial antihypertensive on heart morphology and function in mild to moderate essential arterial hypertension. Eur Heart J 1992; 13(suppl A):45-48.
20. zlachcic J, Tubau JF, Vollmer C, Massie B. Effect of diltiazem on left ventricular mass and diastolic filling in mild to moderate hypertension. Am J Cardiol 1989;63:198-201.
21. Dahlöf B. The importance of the renin-angiotensin system in reversal of left ventricular hypertrophy. J Hypertens 1993;11:S29-S35.

Address for Corresponding Author:
Prof. Dr. Muhammad Ishaq
Chairman & Founder
Jinnah Medical College Warsak Road, Peshawar.
Contact No: 0333-9152060