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Original Article

Assessment of Effect of Atenolol and Enalapril on Trace Elements in Pre and Postmenopausal Women with Essential Hypertension

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ABSTRACT

Background: *Studies conducted in recent times have reported the involvement of trace elements in the pathogenesis of certain cardiovascular diseases particularly hypertension. So, the present study was planned to evaluate the influence of the antihypertensive drugs enalapril and atenolol on blood pressure and serum concentration of zinc, magnesium, lead, aluminum and vanadium.* ***Methods:*** *For the study, selection of 30 pre and 30 post-menopausal women patients with mild to moderate essential hypertension and 60 normal controls for both the groups was done. The age group of premenopausal hypertensive women was 30-50 years and for postmenopausal hypertensive women it was 50-70 years. Atenolol (10-40 mg/day) was prescribed to half of the patients from both the study groups and the other half was prescribed Enalapril (5-20mg/day). The assessment of trace elements was done during the follow up before and after 3, 6, 12 months of treatment.* ***Results:*** *Effectiveness of both the drugs, Atenolol and Enalapril were found equal in deceasing blood pressure. A significant increase in the serum level of lead ($P<0.05$), significant decrease in the level of Magnesium ($P<0.05$), non-significant increase in the level of zinc and no change in the level of Vanadium and aluminum was observed in newly diagnosed pre-and postmenopausal women with essential hypertension as compared to normal control.* ***Conclusions:*** *There is association of high level of blood lead and low level of magnesium to essential hypertension in pre and postmenopausal women without any renal disease. High plasma vanadium levels were not found in hypertensives with normal renal functions with respect to control.*

Key words: *Atenolol, Electrolytes, Enalapril*

INTRODUCTION

Hypertension is a chronic disease known to be one of the major factors for cardiac ischemia and the main risk for cerebrovascular disease.[1] Due to these risks there is a great need to control hypertension with multiple approaches based method. Studies conducted in recent times have reported the involvement of trace elements in the pathogenesis of certain cardiovascular diseases particularly hypertension.[2,3] A highly significant correlation between concentrations of electrolytes in serum and the systolic and diastolic blood pressure had been reported by epidemiological studies and it was shown that blood pressure is high in subjects with electrolyte imbalance as compared to normal contols.[4,5]

Magnesium is found in the inner surface of cell membrane and is involved in permeability of calcium and sodium.[6] Deficiency of magnesium is a common occurrence and studies have related deficiency of magnesium to increased susceptibility to diseases like hypertension, cardiovascular diseases, insomnia, etc.[7,8] Blood pressure can be reduced with supplementation of magnesium salts for an appropriate period.[9]

Zinc is a trace element with some important functions in the human. Its role in bone formation, cell mediated immunity, host defense and tissue growth has been widely studied.[10] There is a direct correlation of serum zinc with plasma angiotensin converting enzyme activity because it is

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the only metal present in molecular structure of angiotensin converting enzyme. Studies have related repeatedly lower levels of zinc in patients with hypertension than in controls.[11]

Lead is a toxic element, having adverse effects on the body even at low levels of exposure.[12] Blood level of lead is directly correlated to both systolic and diastolic blood pressures. Lead is known to be a potent inhibitor of Na-K-ATPase.[13] Synergistically inhibitor action of lead and endogenous Na-K-ATPase inhibits non competitively with respect to potassium.[14] Endothelins and the level of reactive oxygen species are increased directly by lead while due to increased reactive oxygen species, the endothelial derived relaxation factor is secondarily decreased.[15] These studies suggests that there is a possibility that lead may be the primary cause for the essential hypertension.

Vanadium (V) is a trace element. Vanadium has been widely researched in recent years. In patients with renal insufficiency, studies have showed increased plasma vanadium concentration. Studies have also reported that increments in the arterial blood pressures may be caused because of increased lead and vanadium concentration in plasma.[16]

Some of the anti-hypertensive drugs presently used (including diuretics, β-blockers, calcium antagonists and ACE-inhibitors), can modify the patient's biochemical parameters, lipid profile and change serum and intra-erythrocyte concentrations of zinc, magnesium and aluminum.[17] Investigations of effects of β-blockers, ACE-inhibitors on levels of circulating magnesium, zinc and aluminum are very few in number.[18] So, the present study was planned to evaluate the influence of the antihypertensive drugs Enalapril and atenolol on blood pressure and serum concentration of zinc, magnesium, lead, aluminum and vanadium.

METHODS

The study was conducted in the medicine department of the institution. For the study, selection of 30 pre-and 30 post-menopausal women patients with mild to moderate essential hypertension and 60 normal controls for both the groups were selected. The age group of premenopausal hypertensive women was 30-50 years and for postmenopausal hypertensive women it was 50-70 years. Clinical criteria were used for selection of all the patients. Patients were informed to avoid any change in their dietary habits and exercise regime during the time of the study. Atenolol (10-40 mg/day) was prescribed to half of the patients from both the study groups and the other half was prescribed Enalapril (5-20mg/day). The assessment of trace elements was done during the follow up before and after 3, 6, 12 months of treatment. Blood sample for the biochemical analysis was taken only in the morning after a minimum of 12 hours fasting. Atomic absorption spectrophotometer (ELICO SL-93) by the method of Parkin et al. was used for measurement of plasma concentration of lead, aluminum, zinc, vanadium and magnesium. Heparin bulb was used for the collection of blood samples. Samples were run on atomic absorption spectrophotometer and readings were obtained for the analysis of trace element before treatment and after 3, 6, 12 months of treatment and compared with normal control. Expression of data was done as mean $\pm$SD. Paired 't' test was used for the analysis of trace elements in normal control and essential hypertensive pre-and postmenopausal women. Statistical significance was also observed before and after treatment in both pre-and postmenopausal women patients using paired 't' test. Statistical significance was considered as $p< 0.05$.

RESULTS

Effectiveness of both the drugs, Atenolol and Enalapril were found equal in deceasing blood pressure. A significant increase in the serum level of lead ($P<0.05$), significant decrease in the level of Magnesium ($P<0.05$), non-significant increase in the level of zinc and no change in the level of Vanadium and aluminum was observed in newly diagnosed pre-and postmenopausal women with essential hypertension as compared to normal control. After treatment with atenolol, there was no significant decrease in the level of lead (139$\pm$17 to 135$\pm$15 µg/l and 140 $\pm$ 18 to 136 $\pm$16.0 µg/l), aluminum (3.55$\pm$ 1.0 to 3.1$\pm$0.77 µg/l and 3.83 $\pm$ 0.99 to 3.15$\pm$0.81 µg/l), magnesium (2.33$\pm$0.31 to 2.24$\pm$0.29 mg/dl and 2.33$\pm$0.31 to 2.30$\pm$0.24 mg/dl) and significant decrease in the level of zinc (112.11$\pm$30 to 102$\pm$21 µg/dl and 115 $\pm$27 to 103 $\pm$23 µg/l, $P<0.05$) in pre-and postmenopausal essential hypertensive women respectively.

On treatment with Enalapril, it was observed that there was no significant decrease in the level of lead(136 $\pm$ 21 to 134 $\pm$ 18 µg/l and 138+22 to 135+17.5 µg/l), aluminum(3.61 $\pm$ 0.9 to 3.3 $\pm$ 0.81 µg/l and 3.77 $\pm$ 1.0 to 3.19 $\pm$ 0.82 µg/l), significant decrease in the level of zinc (119 $\pm$ 24 to 109 $\pm$ 19 µg/l and 117 $\pm$ 29 to 107 $\pm$ 24 µg/l , $P<0.05$), and significant increase in the level of magnesium (2.35 $\pm$ 0.26 to 3.30 $\pm$ 0.32 mg/dl and 2.39 $\pm$ 0.30 to 3.1 $\pm$ 0.22 mg/dl, $P< 0.05$) in pre and postmenopausal essential hypertensive patients respectively.

DISCUSSION

In the present study, it is observed that there is an increased level of serum lead, zinc and decreased level of magnesium which demonstrates an imbalance of trace elements in pre-and postmenopausal essential hypertensive women.

For the treatment of hypertension, atenolol and Enalapril are extensively used.[19] It is important to study the effects of long term usage of these drugs as these drugs are prescribed for regular usage and necessary steps should be taken to cure any induced mineral imbalance.

Both the antihypertensive drugs compared in this study are equally effective in controlling the blood pressure. The comparison of effects of these drugs on the level of plasma zinc, magnesium, vanadium, aluminum and lead in pre-and post-menopausal women was also done with the normal control. Hypertensive patients and normotensive control

had almost similar serum concentration of vanadium and aluminum.[20] There was a high concentration of serum zinc in the pre-and post-menopausal hypertensive women. After treatment with atenolol and Enalapril serum zinc was decreased significantly in our subjects. A similar study was conducted by O'Conner et al and he reported no effect on serum zinc concentration in patients with captopril and propranolol treatment.[21] Goliak et al, obserevd increase in the urinary zinc excretion with treatment of captopril and enalapril.[22] In the present study, we also observed significantly decrease in the serum zinc concentration with antihypertensive treatment. As the enzyme ACE is dependent on zinc concentration, so the possible increase in urinary zinc excretion by Enalapril may decrease the activity of ACE indirectly. So, it is evident from these findings that ACE activity in patients with essential hypertension can be increased can be increased by oral supplementation of zinc sulphate. Although few investigators found just opposite to happen.[23]

Table 1. Effect of Atenolol and Enalapril on the level of Lead, Aluminum, Vanadium, Zinc and Magnesium in pre-and postmenopausal women with essential hypertension

	ESSENTIAL HYPERTENSIVE WOMEN			
	PRE-PR **Premenopausal women**		**Postmenopausal women**	
	ATENELOL	**ENALAPRIL**	**ATENELOL**	**ENALAPRIL**
Lead-BT	139±17*	136±21*	140±18*	138±22*
3 months	138±16	135±20	139±17.1	137±20
6 months	136±16.6	135±19	137±16.2	136±19
12 months	135±15	134±18	136±16.0	135±17.5
Aluminum-BT	3.55±1.0	3.61±0.9	3.88±0.99	3.77±1.0
3 months	3.33±0.83	3.45±0.85	3.49±0.95	3.44±0.97
6 months	3.2±0.8	3.41±0.82	3.27±0.88	3.21±0.94
12 months	3.1±0.77	3.3±0.77	3.15±0.81	3.19±0.82
Vanadium-BT	3.95±1.8	3.99±1.7	3.80±1.9	3.83±2.0
3 months	3.92±1.7	3.97±1.6	3.78±1.8	3.82±1.8
6 months	3.93±1.7	3.95±1.7	3.77±1.8	3.80±1.7
12 months	3.93±1.8	3.96±1.7	3.78±1.7	3.79±1.7
Zinc-BT	112.11±30	119±24	115±27	117±29
3 months	110±27	17±23	112±25	115±27
6 months	109±24	115±21	110±24	112±26
12 months	102±21*	104±19*	103±23*	105±24*
Magnesium-BT	2.33±0.31*	2.5±0.26*	2.33±0.31*	2.52±0.30*
3 months	2.31±0.30	2.7±0.30	2.32±0.28	2.45±0.27
6 months	2.29±0.28	3.1±0.33	2.38±0.26	2.6±0.25
12 months	2.24±0.29	3.3±0.34*	2.28±0.24	2.9±0.22*

* P<0.05

Figure 1. Effect of Atenolol and Enalapril on concentration of Lead in pre-and postmenopausal essential hypertensive women

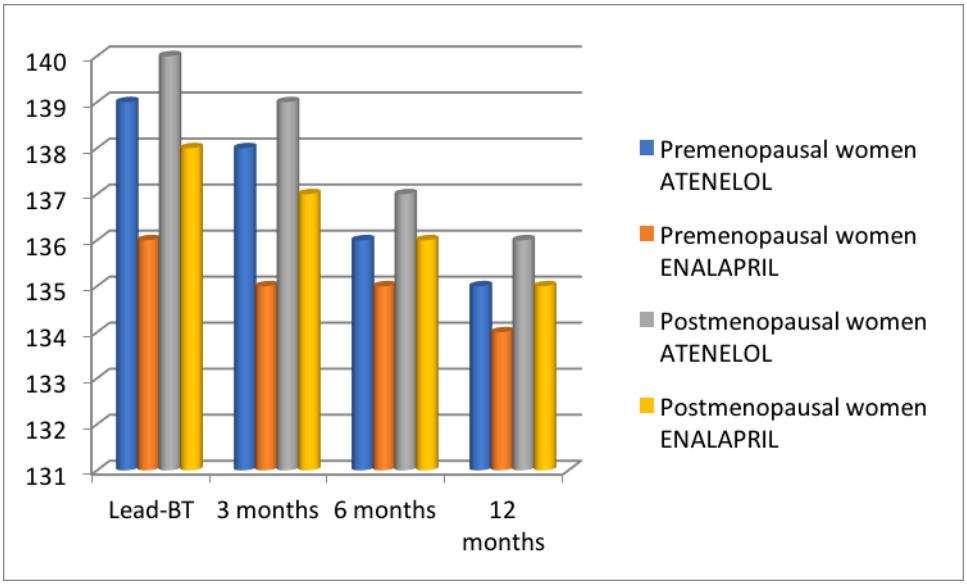
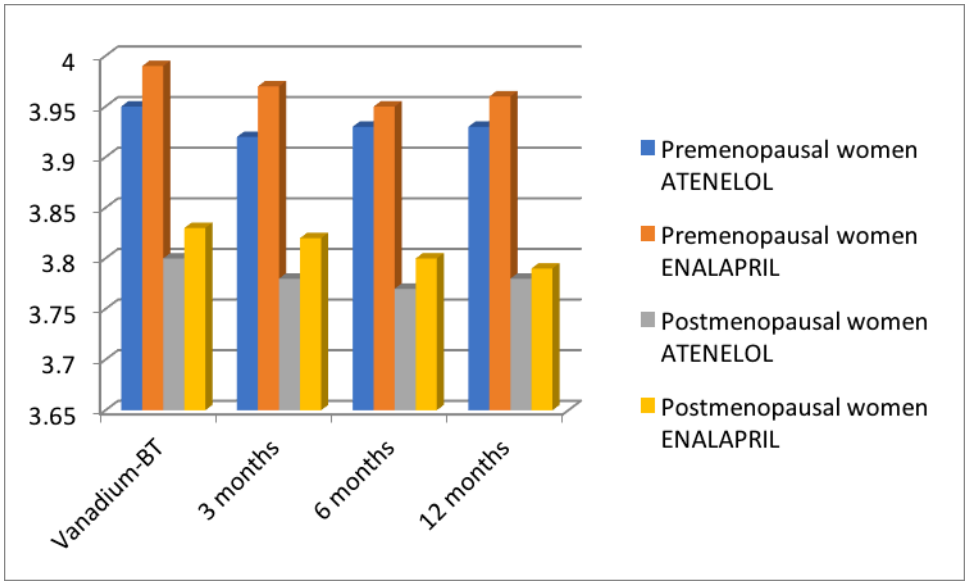


Figure 2: Effect of Atenolol and Enalapril on concentration of Vanadium in pre-and postmenopausal essential hypertensive women



The activity of aldosterone and plasma renin and diastolic blood decreases significantly on administration of zinc. Even though activation of ACE is dependent on zinc, there is an evidence of saturation of enzyme by its cofactor. Increased urinary excretion of zinc in our subjects is evident from the significant decrease in mean serum zinc after treatment with Enalapril for 3, 6, 12 months.[24] An adequate intake of dietary zinc shall be insured in patients with hypertension, especially treated with Enalapril to avoid the undesirable effects of hypozincemia. There would also be an increase in the effectiveness of Enalapril with adequate intake of zinc by enhancement of the blockade of ACE.[25]

Hypertensive patients had significantly decreased concentration of magnesium as compared to controls. Studies conducted by Altura et al and Resnick et al are in conformity to these findings.[26,27] An important role is played by magnesium ions by activation of Na-K ATPase pump which regulates transport of sodium and potassium across the membrane. Intracellular and plasma levels of magnesium ions are inversely related to an increase in blood pressure.[28]

After treatment with atenolol, serum levels of magnesium did not change significantly. The results of Cocco et al are in agreement with these findings.[29]

After six months, there was decrease in the level of serum magnesium with comparison to three months' level. After treatment for 12 months, there was significant increase in the serum magnesium levels as compared to basal levels. This finding agrees with those of Miroslav Simunic et al.[30]

In a study conducted by Anguis Rubio et al, oral supplementation with magnesium lead to increase in the apolipoprotein A-1/B ratio, a 27% decrease in the triglycerides and very low density lipoprotein cholesterol and tended to increase serum HDL-cholesterol in patients with ischaemic heart disease and myocardial infarction.[31]

A hypothesis that deficiency of magnesium participates in the pathogenesis of ischaemic heart disease by altering the composition of circulating lipids in a way that predisposes the patient to atherosclerosis is supported by these findings. Hence, an effective non-pharmacological treatment for pre- and postmenopausal essential hypertensive women is supplementation of dietary magnesium to them.[32]

Some investigations have revealed that deficiency of magnesium sensitizes people to acute or prolonged stress and supplementation of suitable magnesium compounds to them are a powerful means for imcreasing stress resistance e.g. by prventing cardiovascular damage.[33]

The blood lead levels of pre-and postmenopausal hypertensive women were significantly increased as compared to normal controls before antihypertensive treatment. Increased levels of blood lead in essential hypertensive as compared to controls indicate that there is an association between increased blood pressure and lead levels in pre-and postmenopausal hypertensive women with normal renal functions. Reports from US survey are in agreement to these resuts which showed a significant association between blood lead and systolic and diastolic blood pressure.[34] Hence, it is evident that lead may increase the risk for hypertension.

There was no significant decrease in the levels of lead in pre-and postmenopausal essential hypertensive women on treatment with atenolol and Enalapril. So, some suggestions were made to supplement magnesium in case of lead induced hypertension. But, inspite of non-significant decrease in the lead level, both the drugs, atenolol and Enalapril were found to be effective in lowering blood pressure effectively. In the present study, we observed a non-significant variation in the level of blood vanadium and aluminum with respect to normal control. So, this suggests that the vanadium and aluminum in high blood pressure of pre-and postmenopausal women is of doubtful significance. It was observed that both the drugs atenolol and Enalapril were unsuccessful in lowering the levels of

vanadium, aluminum and lead upto significant levels on 3,6, 12 months of treatment. Some other research findings also showed very similar trends for essential hypertension.[35] Premenopausal women because of presence of estrogen are more protective against imbalance trace elements. The changes induced in the body due to estrogen are well documented. These changes include an increase in HDL-cholesterol and reduction in LDL and triglycerides in the plasma. Also, enhanced sensitivity to insulin, enhanced glucose metabolism and reduction in the LDL-oxidation are observed. In other studies, the development of atherosclerosis is retarded due to increased secretion of nitric oxide in arterial endothelium.[36]

CONCLUSION

There is association of high level of blood lead and low level of magnesium to essential hypertension in pre-and postmenopausal women without any renal disease. High plasma vanadium levels were not found in hypertensives with normal renal functions with respect to control.

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