ORIGINAL RESEARCH PAPER

Volume-6 | Issue-10 | October-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF CHANGES IN SERUM LEVELS OF THYROID HORMONES IN HYPERTENSIVE PATIENTS RECEIVING CALCIUM CHANNEL BLOCKERS

Endocrinology

Dr Pruthvi Desireddy Senior Resident, Department of Pharmacology, Osmania Medical College.

Dr Praveena Gungam Senior Resident, Department of Pharmacology, Osmania Medical College.

Dr Swathi Rapole Senior Resident, Department of Pharmacology, Osmania Medical College.

Dr Preethi Kola Senior Resident, Department of Pharmacology, Osmania Medical College.

ABSTRACT

Amlodipine is the commonly used Calcium channel blocker. Calcium channel blockers are known to intervene with functioning of various hormonal systems. Hypothyroidism is a commonly prevailing disorder in adult Indian population. Knowledge on Drug induced hypothyroidism, though not a major cause of hypothyroidism, holds an important role in preventing the iatrogenic introduction of disease. This study was taken up to observe the effects of Amlodipine on long term usage in hypertensive patients. A comparative prospective observational study carried out in medical outpatient department in Osmania General Hospital, Hyderabad, for a duration of 6 months showed a significant decrease in T3 and T4 levels and increase in TSH levels. Calcium channel blockers, in particular Amlodipine caused significant increase in TSH and decrease in T3, T4 hormones on administration for a period of 6 months in comparison to Enalapril.

KEYWORDS

INTRODUCTION:

Hypertension holds a major disease burden in India with a prevalence of 40.8% in urban population and 17.9% in rural population between 2000-2012[1]. Cardiovascular morbidity and mortality increase as both systolic and diastolic blood pressures rise. The first line category of drugs for control of hypertension for patients <55 years are ACEI and for patients >55 years are Calcium channel blockers[2]. Amlodipine is the commonly used Calcium channel blocker. Calcium channel blockers being the mainstay of hypertension treatment, behold with them various side effects and adverse effects. These might be due to universal distribution of various types of Calcium channels in human biological systems. Calcium channel blockers are known to intervene with functioning of various hormonal systems. Their effect on Thyroid gland has been studied since 1986[3].

Hypothyroidism is a commonly prevailing disorder in adult Indian population. Iodine intake ceases to be the sole etiological contender for thyroid disorders in urban areas. Prevalence of hypothyroidism in urban population is found to be 10.95%. In particular, female population being involved is 5.02%[4]. India being in post iodization phase still faces the problem of goiter [5]. Identifying multiple risk factors and plausible underlying mechanisms is warranted.

Knowledge on Drug induced hypothyroidism, though not a major cause of hypothyroidism, holds an important role in preventing the iatrogenic introduction of disease. A wide variety of chemical agents may inhibit one or more of the metabolic steps involved in thyroid hormone synthesis and release. Although many of the drugs implied to cause thyroid malfunctioning, may not result in frank hypothyroidism, almost all have induced goiter in animals or man[6,7].

In the earlier studies, effect of Amlodipine on thyroid gland were not studied in human subjects. Few studies where humans were volunteers, the commonly employed drug Amlodipine was not the study drug. There were reports of hypothyroidism in patients using Amlodipine to FDA[8]. Based on the previous studies on animals an effect on thyroid hormones is anticipated due to the blockade of L-type calcium channels caused by Amlodipine[9,10]. Hence this study was taken up to observe the effects of Amlodipine on long term usage in hypertensive patients. The present study involves Hypertensive patients attending Medical OP who are prescribed Amlodipine for the control of hypertension and patients on Enalapril as hypertensive therapy.

AIMS AND OBJECTIVES:

- To evaluate the effect of Amlodipine on the serum levels T3, T4 and TSH in hypertensives
- To compare the effects of Enalapril on Serum levels of T3, T4 and TSH in hypertensives
- To compare the effects of Amlodipine and Enalapril on serum levels of T3, T4 and TSH.

MATERIALS AND METHODS:

A prospective observational study was carried out in medical outpatient department in Osmania General Hospital, Hyderabad, for a duration of 6 months.

After approval from Institutional Ethics Committee, patients attending Medical out patient Department were screened for Hypertension and inclusion and exclusion criteria. Hypertensive patients were examined by the consultant physician to rule out secondary hypertension. Systolic and diastolic blood pressure was measured in right arm, sitting posture by auscultatory method using standard mercury sphygmomanometer. Two recordings of blood pressure were taken at an interval of 15 min by the same physician. After initial screening, the demographic data, past medical history, family history, findings of physical examination and clinical examination are recorded in the case report form.

139 patients were enrolled for the study and informed written consent was taken from the patients. Patients on Tab Amlodipine 10 mg OD, 63 in number, included in Group A and 62 Patients on Tab Enalapril 5 mg, taken as Group B were evaluated after excluding dropouts. The patients received hypertensive therapy as per the assessment of the treating physician. No changes were made in the treatment decision and schedule as part of the study.

Routine investigations were done for the patients like blood urea, serum creatinine, lipid profile and thyroid profile in particular for the study. 5ml Blood samples were drawn by taking all aseptic precautions in fasting state for lipid profile and thyroid profile. Baseline T3, T4 and TSH level estimations were done and these levels were taken as baseline levels. The patients were called for review with filled and empty blisters of the tablets at the end of 3rd and 6th months for evaluation by the physician and repeat investigations. Compliance to study medicines is measured by pill count during each follow up. Values are compared with baseline values.

T3, T4 and TSH levels were estimated by Chemiluminisence method (Beckman Coulter), which is an automated immunoassay analyzer.

Inclusion criteria:

- Age group 30 to 80 years
- Either sex.
- Patients diagnosed with mild and moderate hypertension with systolic BP > 139 and <180 & Diastolic BP >89 and < 110
- Introducing Tab Amlodipine 10 mg or Tab Enalapril 5 mg as part of hypertensive treatment regime.
- Patients with normal thyroid profile
- Patients with normal renal and liver function tests
- Patients with normal cardiac function

Exclusion criteria:

- Pregnant and lactating females.
- Patients with Secondary hypertension.
- Patients with abnormal thyroid profile.
- Patients with severe hypertension.
- Patients with abnormal renal or hepatic profile
- Patients with Diabetes Mellitus
- Patients with other conditions taking drugs which have proven effect on thyroid hormone levels (Iodides, Sulfonamides, Thiourea, Methimazole, Aminotriazole, Lithium, Thiocyanates, Perchlorates, Phenobarbital, Benzodiazepines, Spironolactone and Retinoids)

Results were analysed using GraphPad Prism 6.0 h software for Mac Os X. Paired t test to compare within the group and unpaired t test for intergroup analysis was used, with level of significance 0.05.

RESULTS:

Newly diagnosed hypertensive patients who were prescribed Tab Amlodipine 10mg OD (GROUP A) and Tab Enalapril 5 mg OD (GROUP B) as monotherapy for control of hypertension were included in this study. Total number of patients participated in the study was 125. Number of patients in Group A were 63 and the number of patients in Group B were 62.

Table 1 shows the effect of Amlodipine and Enalapril on T3 levels. In Group A decrease of T3 levels was observed. Mean ± SD of T3 levels of patients in Group A at 0 month was 1.593 ± 0.1923. Similarly at the end of 3 months and 6 months was 1.492 ± 0.275 and 1.415 ± 0.332 respectively. Mean ± SD of T3 levels in Group B patients at 0, 3 and 6 months was 1.357 ± 0.250, 1.333 ± 0.184 and 1.3719 ± 0.215 respectively.

TABLE 1: EFFECT OF AMLODIPINE AND ENALAPRIL ON SERUM T3 LEVELS (MEAN ± SD) IN ng/ml

S NO	STUDY GROUP	0 MONTH (Baseline)	AFTER 3 MONTHS	AFTER 6 MONTHS
1	GROUP A	1.5931±0.192	1.4926±0.275**	1.4158±0.332**
	p value		<0.05	<0.05
2	GROUP B	1.358±0.250	1.333±0.184*	1.3719±0.215*
	p value		>0.05	>0.05

*** p < 0.01 – Highly Significant * p <0.05 – Significant * p >0.05- Not Significant

GROUP A – patients administered Amlodipine 10 mg OD
GROUP B – patients administered Enalapril 5 mg OD

The decreases in T3 values at the end of 3rd and 6th month were compared with Baseline Values. p values for Amlodipine group were 0.0426 at 3 months and 0.00043 at 6 months when compared with Baseline levels, which were < 0.05 and hence significant. Whereas p values for Group B were not significant (0.515 and 0.688 at the end of 3rd and 6th months compared to Baseline values) as p > 0.05.

Table 3 shows the Mean levels of serum T4 levels – base line levels, levels after 3 months and levels after 6 months. p value < 0.05 is taken as level of significance

TABLE 3: EFFECT OF AMLODIPINE AND ENALAPRIL ON SERUM T4 LEVELS (MEAN±SD) IN ug/ml

S NO	STUDY GROUP	0 MONTH (Baseline)	AFTER 3 MONTHS	AFTER 6 MONTHS
1	GROUP A	9.336±1.292	8.858±1.42***	8.340±2.07***
	p value		< 0.01	< 0.01
2	GROUP B	7.256±1.26	7.323±1.224*	7.297±1.315*
	p value		> 0.05	> 0.05

*** p < 0.01 – Highly Significant ** p <0.05 – Significant * p >0.05- Not Significant

GROUP A – patients administered Amlodipine 10 mg OD
GROUP B – patients administered Enalapril 5 mg OD

For Group A, Mean ± SD were 8.85±1.421 and 8.34±2.071 at 3 months and 6 months respectively compared to 9.33±1.29 at 0 month (Baseline Value). Mean values of T4 levels at the end of 3rd and 6th months when compared with Baseline values, p values obtained were 0.025 and 0.00013. In Group A, p values show significant decrease in the levels of T4. For group B, p values at the end of 3rd and 6th months obtained were 0.13 and 0.45. p values being highly significant for Group A failed to show significance for Group B.

Table 4 shows the Mean levels of serum TSH levels – base line levels, levels after 3 months and levels after 6 months. p value < 0.05 is taken as level of significance

TABLE 4: EFFECT OF AMLODIPINE AND ENALAPRIL ON SERUM TSH LEVELS (MEAN±SD) IN ug/ml

S NO	STUDY GROUP	0 MONTH (Baseline)	AFTER 3 MONTHS	AFTER 6 MONTHS
1	GROUP A	1.898±0.938	2.266±0.776 ***	2.457±1.366 ***
	p value		< 0.01	< 0.01
2	GROUP B	2.684±1.065	2.735±0.983*	2.770±1.070*
	p value		> 0.05	> 0.05

*** p < 0.01 – Highly Significant ** p <0.05 – Significant * p >0.05- Not Significant

GROUP A – patients administered Amlodipine 10 mg OD
GROUP B – patients administered Enalapril 5 mg OD

Group A shows gradual rise in TSH values. Mean ± SD of TSH values for Group A being 2.266 ± 0.77 and 2.457 ± 1.366 at 3rd and 6th month respectively. Baseline Values being 1.898 ± 0.93. For Group B Mean ± SD at 0,3 and 6 months were 2.684 ± 1.06, 2.735 ± 0.98 and 2.770 ± 1.070. But the rise in values was not significant for Group B. p values at 3rd and 6th months were 0.0004 and 0.0002 for group A, and 0.191 and 0.068 for group B. Hence Group A is showing significant rise in TSH levels.

Table 5 showing average difference between baseline values and after 6 months for T3, T4 and average difference between after 6 months values and Baseline values for TSH in both the groups with SD.

TABLE 5: AVERAGE DIFFERENCE BETWEEN BASELINE AND AFTER 6 MONTH VALUES OF T3, T4 AND TSH (MEAN ± SD)

S NO	STUDY GROUP	0 MONTH (Baseline)	AFTER 3 MONTHS	AFTER 6 MONTHS
1	GROUP A	0.177±0.04	0.995±0.22	0.558±0.14
2	GROUP B	0.05±0.013	0.89±0.48	0.08±0.04
3	P VALUE	<0.01***	<0.01***	<0.01***

*** p < 0.01 – Highly Significant ** p <0.05 – Significant * p >0.05- Not Significant

GROUP A – patients administered Amlodipine 10 mg OD
GROUP B – patients administered Enalapril 5 mg OD

Mean values of difference of T3 values of both groups at baseline level and after 6 months was also calculated and compared taking using unpaired t test. Table-5 shows the mean of difference between baseline values and after 6 months values of T3, T4 and TSH parameters. p value <0.01 shows the significant increase in TSH levels and significant decrease in T3 and T4 levels in Group A when compared with Group B

DISCUSSION:

Discovery of the key role of Calcium channels in cellular signaling have brought together with them solutions to poorly managed medical conditions. In 1940's Sodium was considered as major ion in cellular signaling[11]. Role of calcium and calcium channels was not considered of major importance. Once the role of calcium channels was discovered it simultaneously led to the discovery of calcium channel antagonists.

Calcium channel blockers exert a wide variety of influences on

biological systems. Their effects are therapeutically employed for the treatment of various conditions like Angina, Arrythmias, Hypertension, Raynauds syndrome, Migraine, Mountain sickness and as Tocolytics.

Calcium channel blockers are the main stay of pharmacotherapy of hypertension. Calcium channel blockers lower blood pressure by relaxing arteriolar smooth muscle and decreasing peripheral resistance.

Calcium channel blockers are structurally of 3 types. Dihydropyridines, Phenylalkylamines and Benzothiazepines. The latter two groups being broadly categorized as Non-Dihydropyridines. Tachycardia being a major side effect is seen with Dihydropyridine group, which is due to adrenergic stimulation of SA node. Tachycardia due to Dihydropyridines is typically modest. This effect is not seen with with Non-Dihydropyridine groups like Verapamil and Diltiazem. Amlodipine, Felodipine, Isradipine, Nicardipine and Nimodipine are second generation 1,4 Dihydropyridine calcium channel blockers with long plasma half lives. Amlodipine, which is a long acting Calcium channel blocker (With plasma half life of 35 hours) is commonly employed for control of blood pressure.

Emphasis is laid upon appropriate control of hypertension, which if not under control may lead to various neurological and cardiovascular sequelae. Incidence of cardiovascular events being more in comparison to neurological sequelae. In the treatment of hypertension, the strategy for therapeutic evaluation has been based on the simple concept that lowering blood pressure will result in a decrease in the incidence of stroke, myocardial infarction, renal failure, and death.

Various modalities of pharmacotherapy of Hypertension are associated with various side effects. The commonly employed drugs are Amlodipine and Enalapril.

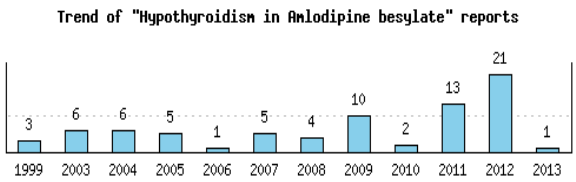
Calcium channel blockers are known to cause various hormonal effects as shown by various studies. David Serfas et al., in their case report on Pheochromocytoma summarized that calcium channel blockade plays a role in suppression of adrenal hormone secretion thereby relieving symptoms[12].

Similarly effect of calcium channel blockers was studied on various hormonal secretions including pituitary hormones like Thyroid stimulating hormone, Follicle stimulating hormone, Luteinizing hormone and gonadotropin releasing hormone. Their effect was also studied on Parathyroid hormone, aldosterone and hormone secretion[13,14,15].

It still poses a challenge to determine at which level of hypothalamo-pituitary glandular axis the effect of calcium channel blockers is predominant enough to cause clinical effects.

Based on the adverse events reported by patients using Amlodipine Besylate to FDA from the year 1999 to 2013, 17,622 people reported side effects out of which 77(0.44 %) patients reported to have hypothyroidism.[8]

FIGURE 13: FDA Report of Trend of Hypothyroidism in Amlodipine besylate[8]



Most of the patients (33.33%) seemed to have developed Hypothyroidism after its use for more than 6 months, among whom males were 54.17% and females 45.83%. 80% who developed hypothyroidism belonged to age group of above 50 years and 7% of the patients belonged to age group of 40-49 years[8].

Hypothyroidism is affecting over 1% of the general population and about 5% of individuals over age 60 years[2]. Despite being iodine replete, goiter continues to be prevalent in mild to moderate degree of endemicity in most states of India[18-20]. The degree of severity ranges from mild and unrecognized hypothyroid states to striking myxedema. Thyroid hormone deficiency affects almost all body functions.

Patients typically have nonspecific symptoms of hypothyroidism that include weight gain, fatigue, lethargy, depression, weakness, dyspnea on exertion, dry skin, headache, paresthesias, cold intolerance, carpal tunnel syndrome, and Raynaud syndrome. Physical findings can include bradycardia, diastolic hypertension, thin & brittle nails, thinning of hair, peripheral edema, puffy face & eyelids, and skin pallor. Delayed relaxation of deep tendon reflexes may be present.

Subclinical hypothyroidism and Hypothyroidism are associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels[22]. Low-T3 is a strong predictor of death in cardiac patients[23]. Preexistent coronary artery disease and heart failure may be exacerbated by levothyroxine therapy. This holds importance when the patient is being prescribed with a drug for cardiovascular condition, and the drug prescribed interferes with thyroid hormone functioning. Patients with severe hypothyroidism have an increased susceptibility to bacterial pneumonia. Hence it becomes important to know the effects of commonly used antihypertensive Amlodipine on Thyroid profile as previous studies and FDA reports show the development of hypothyroidism on prolonged usage of the drug.

An open label prospective observational study was carried out in General Medicine OPD, Osmania General Hospital, Hyderabad. 430 patients were screened for inclusion and exclusion criteria and their eligibility to be included in the study. A total of 139 patients were eligible to participate in the study. Informed consent was taken for their participation in the study. Among 139 patients, 69 patients were prescribed Tab Amlodipine 10 mg OD, and 70 patients with Tab Enalapril 5mg OD by the physician.

Patients were instructed to inform, if they were treated with any other medication in a period of 6 months from the start of the study, due to ineffective control of hypertension. A total of 63 patients were finally evaluated from Amlodipine group after excluding the 6 dropouts. And a total of 62 patients remained in Enalapril group after 8 dropouts. Dropouts were mainly because of inclusion of another drug in the treatment protocol due to ineffective control of hypertension. Of 63 patients on Amlodipine, 28 were females and 35 males. In Enalapril group, there were 25 females and 37 males. All these patients were evaluated for a period of 6 months. Patients on Amlodipine were categorized into GROUP A and patients on Enalapril into GROUP B.

It was observed that there were more number of males in each study group. Mean age group of patients included in Group A was 45.49 and Group B was 43.95. In the study population, 30 % of patients in Group A were between the ages 42 and 54 years and 30 % of patients in Group B were between ages 29 and 41 years.

For both the groups T3, T4 and TSH levels were estimated at the beginning of the study. These were taken as Baseline values. Values of T3, T4 and TSH at the end of 3 months and 6 months were compared with the baseline values of each group.

There was adequate control of Blood pressure in both the groups when they were evaluated at the end of 3 and 6 months. At the end of 6 months results were tabulated and were analysed using Two tailed Paired T test.
A decrease in T3 levels was observed in 39 patients (Males 23 & Females 16) in Group A among whom 15 patients showed a decrease of more than 0.5 ug/ml in 6 months period. While 26 patients in Group B showed a decrease in T3 levels out of which only 2 patients showed a decrease of more than 0.5 ug/ml.

A decrease in T4 levels was observed in 51 patients (Males 29 & Females 22) in Group A among whom 9 patients showed a decrease of more than 3 ug/ml in 6 months period. While 35 patients in Group B showed a decrease in T4 levels out of which no patient showed a decrease of more than 3 ug/ml.

An increase in TSH levels was observed in 43 patients in Group A (Males 25 & Females 18) among whom 15 patients showed an increase of more than 1 ug/ml in 6 months period. While 37 patients in Group B showed an increase in TSH levels whereas only 1 patient showed an increase of more than 1 ug/ml.

Therefore decrease in T3, T4 and increase in TSH was significant in the present study for the time period the patients were evaluated. But it failed to show significant association for the development of subclinical hypothyroidism in the 6 months period of time. Further studies with longer duration of exposure may determine the relation of subclinical hypothyroidism and the drug used. Due to limitations of the present study this could not be evaluated.

In the present study mean age ± SD of patients showing increase in TSH levels in Group A is 46.465 ± 10.52. Mean age ± SD of patients showing decrease in T3 and T4 are 46.58 ± 9.83 and 46.37 ± 10.31 respectively.

Results of the present study are consistent with S R Mittal et al., where one month oral therapy with calcium channel blockers caused significant ($p < 0.001$) decrease in serum levels of triiodothyronine and thyroxine and significant increase in serum levels of thyroid stimulating hormone in rabbits. They have observed low serum levels of triiodothyronine and thyroxine in some of their patients receiving calcium channel blockers. But could not evaluate due to several limitations[9].

Results are also consistent with the study conducted by R J Kaur et al., where it was found that on continuous daily administration of calcium channel blockers there was a gradual fall in levels of T3 and T4 with rise in TSH levels in comparison to the baseline value taken before initiating the drug therapy ($p < 0.01$) in rats[10].

Amlodipine was not the drug of interest in both the previous studies mentioned. Humans were not the study subjects employed as well. Present study conducted in human subjects employing Amlodipine as the treatment drug, confirms the association of decrease in T3, T4 and increase in TSH levels.

Contrary to these findings Yamada et al., says calcium channel blockers cause significant suppression of TRH stimulated TSH secretion. Drugs used were Nifedipine and Nicorandil. They studied on healthy human volunteers. Their findings could not be analyzed in the present study as no significant decreases in TSH levels were observed. Response to TRH was not evaluated in the present study[3].
Margaret A Shupnik et al., studied the role of L-type calcium channels in TRH induced TSH beta promoter activity in rat thyrotropes. This causes the synthesis and release of TSH. This study inferred that calcium channel blockers play a role in decreasing the TSH beta promoter activity and hence decreased secretion of TSH. These findings are in contrary to the present study where calcium channel blockers show increased TSH levels[16].

Johannes et al., in their study on healthy human male volunteers observed the effect of Verapamil and Diltiazem (Non Dihydropyridine) on the release of pituitary hormones in response to TRH. It was significantly proved that pituitary cells exhibit differential susceptibility to the drugs used. While Verapamil caused suppression of the pituitary hormones, Diltiazem failed to do so[13].

Hence it is not predictable at which stage of Hypothalamo-pituitary-thyroid axis, calcium channels blockers act to produce their effects. According to Yamada et al., where Nifedipine was employed as the drug under observation was given in dose of 10 mg and TSH levels measured after 40 minutes. They observed that Calcium channel blockers suppressed TRH stimulated TSH secretion at pituitary level[3].
Margaret A Shupnik et al., also concludes the same while he studied the effects of Nimodipine on Transfected cells. The transcription rate of the homologous gene in normal thyrotropes was measured by nuclear run-off assays. Bay K8844, an L channel agonist, stimulated TSH beta gene transcription 8-fold, and TRH stimulation of TSH beta gene transcription was partially blocked by Nimodipine, an L channel antagonist[16].

G Brabant et al., in their study showed that pulsatile release of TSH was significantly decreased when Nifedipine was given to human volunteers[24]
Since drugs causing hypothyroidism effect at various stages including Iodide uptake, oxidation and organification of iodine, altering the concentration of TBG (Thyroxine binding globulin), by inhibiting T3 and T4 binding in serum and by increased cellular binding of T3 and T4. It becomes difficult to interpret at which stage drug is acting to cause hypothyroidism.

S R Mittal et al., and R J Kaur et al., in their studies talked about role of calcium channel blockers in the synthesis and secretion of T3 and T4 at glandular level in rabbits and rats respectively. While the former studied the effects of Nifedipine, Verapamil and Diltiazem for a period of 1 month the latter studied the effects of same drugs for a period of 3 months. Both the studies showed a significant decrease in T3 and T4 and increase in TSH levels at the end of the study[9,10].

Frank A. Verhoeven et al., described the role of calcium channel blockers in inhibiting the hormone uptake by end organs. They studied on Rat cardiomyocytes employing Nifedipine and Verapamil as the drugs under study. They observed that inhibitory effects of Calcium channel blockers on T3 uptake by Cardiomyocytes are not due to their effects on Calcium influx but due to their interference with T3 carrier in the plasma membrane[25].

Duncan J Topliss et al., studied on rat hepatoma and myeloblastoma cell lineages using Verapamil, Diltiazem and Nifedipine along with Calmodulin Antagonists. They observed that uptake of T3 is inhibited by both the groups of drugs significantly[17].

Fontes et al., in their study observed that prevalence of subclinical hypothyroidism was higher in Diabetic group and Amlodipine in this group caused decrease in TSH causing Secondary Hypothyroidism. This study contradicts the findings of present study where increase in TSH levels was observed. In the present study Diabetics were not included as Type 2 Diabetes Mellitus being an Autoimmune Condition is associated with autoimmune Thyroiditis where TSH levels are decreased[26].

From the above discussion it is apparent that calcium channel blockers act at multiple levels of Hypothalamo-pituitary-thyroid axis, and causes various changes in serum Thyroid hormone levels. The present study could not analyze at which stage Amlodipine is acting to cause the changes in thyroid profile. This study is confined to the effect of Amlodipine on thyroid hormone levels, irrespective of their effect on hypothalamus and pituitary hormones.

Findings of this study warrant careful follow up of patients being treated with Amlodipine for long-term. Calcium channel blockers are first line drugs employed for patients aged 55 years or older. Thiazide diuretics/ ACEI/ARB's are prescribed to patients as second line treatment to patients in whom hypertension is not controlled by single drug. Thiazide diuretics are associated with S/E like edema, electrolyte imbalance etc. ACEI and ARBs are associated with electrolyte disturbances. The findings of present study propose the importance of serum thyroid hormone level follow up for patients who are prescribed Amlodipine.

Limitations of the present study include small sample size, open label design, duration of study being short, and effect of single daily dose of 10 mg is evaluated. Though the duration of the present study being long in comparison to previous studies, evaluation for longer periods of exposure to the drug might reveal underlying risk epidemiologically. Large randomized blinded studies are required to confirm the results of this study. Larger studies where 5mg daily dose is taken into consideration may bring out the effects of smaller doses, if any.

SUMMARY:

An open label, prospective observational study involving 125 patients was conducted in Medicine OP in Osmania General Hospital. Patients were divided into two groups with Group A on Amlodipine as hypertension treatment and Group B on Enalapril as Hypertension treatment.

There were 63 patients in Group A and 62 in Group B. in both the study groups there were more number of Males. In Study Group A Maximum number of patients were in age group 42-54 years and in Group B 30-42 years.

T3, T4 and TSH levels at Baseline and after 3 and 6 months were compared within the group using Paired T test with 0.05 as level of significance. Results showed a significant increase in TSH and significant decrease in T3 and T4 levels at the end of 3 and 6 months in Group A. There was no significant increase or decrease in T3, T4 and TSH in Group B.

Decrease in T3 and T4 levels of Group A was compared with decrease in T3 and T4 levels in Group B using Unpaired T test. This showed a significant decrease of T3 and T4 levels in Group A.

Increase in TSH levels of Group A was compared with increase in TSH levels in Group B using Unpaired T test. This showed a significant increase of TSH levels in Group A.

Though the results showed significant changes in Thyroid profile in Group A it failed to show an association between Subclinical hypothyroidism and Group A.

Further studies with larger sample size and for longer period of observation are necessary to confirm the above results.

CONCLUSION:

Calcium channel blockers, in particular Amlodipine causes significant increase in TSH and Decrease in T3, T4 hormones on administration for a period of 6 months in comparison to Enalapril. Hence frequent follow up of thyroid profile is proposed for patients using Amlodipine for long term. Large sample, randomized and blinded studies are required to confirm the results.

REFERENCES:

1. Midha T, Nath B, Kumari R, Rao YK, Pandey U. Prevalence of hypertension in India: A meta-analysis. World J Meta-Anal. 2013 Aug 26;1(2):83-9. http://www.cnki.com.cn/Article/CJFDTotal-HZFX201302003.htm
2. Maxine A Papadakis, Stephen J Mcphee Current Medical Diagnosis and Treatment.Mc graw Hill; 2015, pg 457
3. Yamada M, Mori M, Yamaguchi M, Akiyama H, Shiono S, Kobayashi I, Kobayashi S. Thyrotropin- releasing hormone stimulation of thyrotropin secretion is suppressed by calcium ion antagonists that block transmembrane influx and intracellular mobilization of calcium ion in human subjects. J Endocrinol Invest. 1986 Jun;9(3):227-31. https://link.springer.com/article/10.1007/BF03348105
4. Unnikrishnan AG, Kalra S, Sahay RK, Bantwal G, John M, Tewari N. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. Indian J Endocr Metab 2013;17:647-52. doi: 10.4103/2230-8210.113755 doi: 10.4103/2230-8210.113755
5. Das S, Bhansali A, Dutta P, Aggarwal A, Bansal MP, Garg D, Ravikiran M, Walia R, Upreti V, Ramakrishnan S, Sachdeva N. Persistence of goitre in the post-iodization phase: micronutrient deficiency or thyroid autoimmunity?. The Indian journal of medical research. 2011 Jan;133(1):103. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100137/
6. Vagenakis AG, Braverman LE. Drug induced hypothyroidism. Pharmacology & Therapeutics. Part C: Clinical Pharmacology and Therapeutics. 1976 Dec 31;1(1):149-59. https://doi.org/10.1016/S0362-5486(76)80011-8
7. Capen CC. Mechanisms of chemical injury of thyroid gland. Progress in clinical and biological research. 1993 Dec;387:173-91 http://europepmc.org/abstract/med/7526405
8. Study of possible correlation between hypothyroidism and amlodipine http://factmed.com/report-AMLODIPINE-causing-HYPOTHYROIDISM.php
9. Mittal SR, Mathur AK, Prasad N. Effect of calcium channel blockers on serum levels of thyroid hormones. Int J Cardiol 1993;38:131-2. https://doi.org/10.1016/0167-5273(93)90171-C
10. Kaur RJ, Mehta B, Ambwani SR, Gehlot A. Effect of calcium channel blockers on the serum levels of thyroid hormone. Int J Basic Clin Pharmacol 2013;2:476-9. http://imsear.hellis.org/handle/123456789/153913
11. Tsien RW, Barrett CF. A brief history of calcium channel discovery. InVoltage-Gated Calcium Channels 2005 Jan 1 (pp. 27-47). Springer US. https://link.springer.com/chapter/10.1007/0-387-27526-6_3
12. Serfas D, Shoback D, Lorell B. Phaeochromocytoma and hypertrophic cardiomyopathy: apparent suppression of symptoms and noradrenaline secretion by calcium-channel blockade. The Lancet. 1983 Sep 24;322(8352):711-3. https://doi.org/10.1016/S0140-6736(83)92250-X
13. Veldhuis JD, Borges JI, Drake CR, Rogol AD, Kaiser Dl, Thorner MO. Divergent Influences of the Structurally Dissimilar Calcium Entry Blockers, Diltiazem and Verapamil, on Thyrotropin-and Gonadotropin-Releasing Hormone-Stimulated Anterior Pituitary Hormone Secretion in Man. The Journal of Clinical Endocrinology & Metabolism. 1985 Jan;60(1):144-9. https://doi.org/10.1210/jcem-60-1-144
14. Cooper CW, Borosky SA, Farrell PE and Steinsland OS. Effects of the calcium channel activator Bay-K 8644 on in vitro secretion of calcitonin & parathyroid hormone. Endocrinol 1986;118:545-9 https://doi.org/10.1210/endo-118-2-545
15. StojilkovićSS,Izumi SI, Catt KJ. Particip ation of voltage-sensitive calcium channels in pituitary hormone release. Journal of Biological Chemistry. 1988 Sep 15;263(26):13054-61. https://www.ncbi.nlm.nih.gov/pubmed/2458342?dopt=Abstract
16. Shupnik MA, Weck J and Hinkle PM. Thyrotropin (TSH) releasing hormone stimulates TSH beta promoter activity by two distinct mechanisms involving calcium influx through type Ca2+ channels and protein kinase C. Mol Endocrino. 1996;10(1): 90-9 https://doi.org/10.1210/mend.10.1.8838148
17. Topliss DJ, Scholz GH, Kolliniatis E, Barlow JW, Stockigt JR. Influence of calmodulin antagonists and calcium channel blockers on triiodothyronine uptake by rat hepatoma and myoblast cell lines. Metabolism. 1993 Mar 31;42(3):376-80. https://doi.org/10.1016/0026-0495(93)90090-B
18. Chandra AK, Bhattacharjee A, Malik T, Ghosh S. Goitre prevalence and iodine nutritional status of school children in a sub-Himalayan tarai region of eastern Uttar Pradesh. Indian Pediatr 2008; 45 : 469-74. https://www.indianpediatrics.net/june2008/june-469-474.htm
19. Chandra AK, Tripathy S, Lahari D, Mukhopadhya S. Iodine nutritional status of school children in rural area of Howrah District in West Bengal. Indian J Physiol Pharmacol 2004; 48 : 219-24. https://doi.org/10.1093/tropej/fmm063
20. Kapil U, Singh P, Pathak P, Singh C. Assessment of iodine deficiency disorders in district Bharatpur, Rajasthan. Indian Pediatr 2003; 40 :147-9. https://indianpediatrics.net/feb2003/feb-147-149.htm
21. Kamath R, Bhat V, Rao RSP, Acharya D, Kapil U, Kotian MS, et al. Prevalence of goiter in school children in Balgaum district. Indian J Pediatr 2009; 76 : 825-8. https://link.springer.com/article/10.1007%2Fs12098-009-0101-6?LI=true
22. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Annals of Internal Medicine. 2008 Jun 3;148(11):832-45 http://annals.org/aim/article/741243/meta-analysis-subclinical-thyroid-dysfunction-risk-coronary-heart-disease-mortality
23. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L. Low-T3 syndrome a strong prognostic predictor of death in patients with heart disease. Circulation. 2003 Feb 11;107(5):708-13. http://circ.ahajournals.org/content/107/5/708.full
24. Brabant G, Prank K, Hoang-Vu C, Hesch RD, MÜHLEN AV. Hypothalamic Regulation of Pulsatile Thyrotopin Secretion. The Journal of Clinical Endocrinology & Metabolism. 1991 Jan;72(1):145-50. https://doi.org/10.1210/jcem-72-1-145
25. Verhoeven FA, Moerings EP, Lamers JM, Hennemann G, Visser TJ, Everts ME. Inhibitory effects of calcium channel blockers on thyroid hormone uptake in neonatal rat cardiomyocytes. American Journal of Physiology-Heart and Circulatory Physiology. 2001 Nov 1;281(5):H1985-91 http://ajpheart.physiology.org/content/281/5/H1985.short
26. Fontes R, Denardin O P, Souza J D, Almeida A P M, Cerquiera A C B. Prevalence of subclinical hypothyroidism in diabetic patients over 60 years using specific diagnostic criteria for elderly patients, and the impact of treatment on the diagnosis. American association for clinical chemistry. 2015. https://www.aacc.org/science-and-practice/annual-meeting-abstracts-archive