International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(2):21-26

Review Article

EFFECT OF ANTIHYPERTENSIVE DRUGS ON AUTONOMIC NERVOUS SYSTEM ACTIVITY

Namita Khanna[a*], Jaswinder Singh[b]
[a]Guru Gobind Singh Medical College, Baba Farid University of Health Sciences, Faridkot, Punjab, India
[b]Khalsa College Amritsar, Punjab, India

(Received: 10 March 2013; Accepted: 10 April, 2013; Published: 28 April, 2013)

Corresponding Author's email: **dr.namitakhanna@yahoo.com**

Abstract: The autonomic nervous system is both the monitor and regulator of the 'mileu interieur. ANS regulates the activity of smooth muscle, heart, and glands of GIT, sweat glands adrenal gland and of certain endocrine organs. The assessment of autonomic nervous activity is a frequent and challenging goal of the clinical research. It has been found that hypertension is related to an interaction between the autonomic nervous system and the renin-angiotensin system, together with other factors. Various common antihypertensive drug are used for treating hypertension like *Angiotension Converting Enzyme (ACE) inhibitors e.g* captopril, enalapril, *Angiotension II receptor blockers* like losartan, candesartan *Beta blockers* e.g metoprolol, atenolol, *Calcium channel blockers like* nifedipine, amlodipine, verapamil. The emphasis is on choosing the drug that best meets each patient need, according to factors such as age, ethnicity and presence of other cardiovascular condition.

Key**words:** Hypertension; Antihypertensive drugs; Autonomic nervous system

Introduction

Hypertension is common, asymptomatic, readily detectable and usually easily treatable. It is called 'the silent killer' because it usually has no symptoms. Some people may not find out they have it until they have trouble with their heart, brain, kidneys and eyes (target organs) and in untreated cases it can cause left ventricular hypertrophy, ischaemic heart disease, myocardial infarction, heart failure, stroke or transient ischaemic attacks, kidney failure, peripheral vascular disease and retinopathy. The spectrum of mortality in untreated cases is 50% of coronary artery disease, 33% of stroke and 10-15% of renal failure. Hypertension is becoming a major concern all over the world. Because of stress and strain in the modern life, changing dietary habits, sedentary life style, obesity and smoking, the magnitude of this problem is increasing day by day.

In USA, hypertension remains the major risk factor for coronary, cerebral and renal vascular disease causing over half of all the deaths in the country. Pooling of India epidemiological studies shows that hypertension is present in 25% (34 million) urban and 10% (31.5 million) rural subjects. [1]

Hypertension is of two type 1) Primary hypertension: Although our understanding of the pathophysiology of an elevated blood pressure has increased, in 90-95% cases etiology is unknown. This is labeled as essential or primary hypertension. 2) Secondary hypertension: A very small percentage of patients exhibit associated abnormalities in hormone secretion and renal function or structural cardiac lesion, which is known as secondary hypertension. Since there is no dividing line between normal and high blood pressure, arbitrary levels have been established to define those who have an increased risk of developing a morbid cardiovascular event and/ or will clearly benefit from medical therapy. Now hypertension is defined as systolic blood pressure (BP) of 140 mm Hg or higher and diastolic of 90 mm Hg or higher in subjects (> 18 years of age) who are not taking antihypertensive medication. Both numbers are important, but in May 2003 the Seventh Report on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), from National Institutes of Heath's National Heart, Lung and Blood Institute (NHLBI), recommended systolic blood pressure as the better and much more important indicator of risk for cardiovascular disease in patients older than 50 years and has been considerably more difficult to control than diastolic hypertension. [2, 3]

Classification of Blood Pressure for Adults Aged 18 years or older according to Joint National Committee (JNC 7) report is tabulated as:

Blood Pressure	Diastolic (mm Hg)	Systolic (mm Hg
Normal	less than 80	less than 120
Prehypertension	80-89	120-139
High Stage 1	90-99	140-159
High Stage 2	100 or higher	160 or higher

Note: - When systolic and diastolic blood pressures fall into different categories, the higher category should be used to classify blood pressure level e.g. 160/80 would be stage 2 high blood pressure. There is an exception to the above definition of high blood pressure. A blood pressure of 130/80 or higher is considered high blood pressure in persons with Diabetes mellitus and chronic renal disease.

In contrast to classification provided in JNC VI report, a new category designated as pre-hypertension has been added. Patients with pre-hypertension are at increased risk for progression to hypertension; those in the 130/ 80 to 139/89 mm of Hg BP range are at twice the risk to develop hypertension as those with lower values and they require health promoting life style modifications to prevent hypertension and its related risks. The diagnosis of hypertension is confirmed by taking BP reading on at least 3 separate occasions. The blood pressure is recorded as two numbers-the systolic pressure (as the heart beats) over the diastolic pressure (as the heart relaxes between beats). The underlying defect in pathogenesis of hypertension is multifactorial and hence its management also has to be multipronged including life style modifications and antihypertensive drug therapy.[4]

Beevers et al [5] found that hypertension is related to an interaction between the autonomic nervous system and the renin-angiotensin system, together with other factors. There is transition to the high peripheral resistance and normal cardiac out put haemodynamic state characteristic of established hypertension, which is due to the development of adaptive structural changes in peripheral resistance vessels and heart. The autonomic imbalance found in hypertension and subsequent vascular and cardiac changes may explain some of association between hypertension and risk factor for coronary heart disease

Amerena and Julius observed that a high sympathetic tone in particular is responsible for many of metabolic, haemodynamic and trophic abnormalities that cluster in patient with high blood pressure.[6]

Effect of sympathetic nervous system

The sympathetic nervous system is an important regulator of circulation. Its activity is increased in hypertension and heart failure and adversely affects prognosis.[7] Hypertension is a complex disease where the high blood pressure is only one of the numerous coronary risk factors. Sympathetic over activity in hypertension, independent of the blood pressure, may be conducive to premature atherosclerosis by inducing insulin resistance and dyslipidemia. Through its trophic effect on blood vassels, sympathetic over activity potentiates vasoconstriction. This, in turn, accelerates hypertension and the metabolic syndrome. The hypertrophy of small coronary arterioles decreases the coronary reserve and enhances coronary spasmas. Tachycardia, which is due to increase sympathetic tone and a decrease parasympathetic tone, favours arrhythmias and sudden death in congestive heart failure and hypertension.

Overview of various common antihypertensive regimens:

The classical drugs like B-blockers and diuretics continue to be a mainstay of antihypertensive treatment. Calcium channel antagonists, ACE-inhibitors, postsynapticai-adrenoreceptor blocking agents have been added as valuable therapeutics to the armamentarium of antihypertensive drugs. [8]

Angiotension Converting Enzyme (ACE) inhibitors:

They are widely used in all degrees and form of hypertension. They are effective in preventing end stage renal disease in diabetes and patients of CRF. Various ACE inhibitors are captopril, enalapril, lisinopril, perindopril, and ramipril.

Angiotension II receptor blockers:

It offers all advantage of ACE inhibitors and fewer side effects. Various drugs in this group are losartan, candesartan, and irbesartan.

Diuretics:

Alone or in combinations of other drugs, they are particularly effective in the elderly and black. Various drugs are chlorthiazide, indapamide, furosemide, spironolactone, triamterene and amiloride.

Beta blocker:

They are particularly suitable in patient with myocardial ischaemia and high levels of stress. e.g. propanolol, metoprolol, atenolol.

Calcium channel blocker:

The long acting calcium channel blockers is the most popular class of agents used in treatment of hypertension. The degree of each effect depends on the class of calcium channel blocker:

a) Phenylalkylamines (e.g. verapamil) act primarily on cardiac conducting tissue, so they are used mostly as antiarrhythmic agents.
b) Dihydropyridines (e.g. nifedipine, nimodipine, amlodipine, isradipine) mostly cause vasodilation and are used for treatment of hypertension
c) Benzothiazepines (e.g. diltiazem) act preferentially on coronary vessels, so they are used as antiarrhythmic and anti-angina drugs.

3.6 Alpha blockers:

Selective alpha blockers have role in management of hypertension. alpha-Blockers inhibit the action of catecholamines at peripheral alpha-adrenergic receptors.

a) Phentolamine: a non-selective, short-acting a-blocker used in the treatment of hypertensive crises seen with phaeochromocytoma or cocaine intoxication. An intravenous dose of 1-5 mg causes a rapid reduction in blood pressure for 5-20 minutes.
b) Phenoxybenzamine: a long-acting, non-selective a-blocker that is usually used in the preoperative management of phaeochromocytoma. Starting dose is 10 mg orally.
c) Prazosin and doxazosin: selective a1-blockers that cause vasodilation. They are also used for benign prostatic hyperplasia (relaxation of urinary tract smooth muscle), congestive heart failure and Raynaud's disease. All a-blockers should be titrated carefully as first-dose hypotension can be severe. They have additional favourable metabolic effects on lipid and glucose metabolism.

Classes of antihypertensive drugs

Judicious use of appropriate drug is important to further improve the efficacy of antihypertensive treatment in

those patients who in addition to high blood pressure, also have other associated risk factors.

The various classes of antihypertensive drugs act differently in relation to autonomic nerves system activity.

Betadrenergic blockade:

Beta -Adrenoceptor antagonists as antihypertensives were introduced in the 1960s.[9] Stimulation of β-receptors in the heart, kidney and nervous system leads to increases in cardiac output, peripheral vascular resistance, sympathetic nervous system activity and renin–angiotensin–aldosterone system activity. Buhler and Haensler studied that Beta-blockers continue to be a mainstay in the treatment of chronic hypertension.[10] Raine and Pickering evaluated in hypertensive patients the cardiovascular and sympathetic response to exercise after long term betadrenergic blockade (Atenolol) and observed that heart rate and blood pressure were lower at rest and throughout the exercise in treated patients. [11] The plasma dopamine beta hydroxylase (DBH) activity was also measured as an index of changes in sympathetic activity. After exercise, plasma DBH activity was significantly increased in controls but not in treated patients. It was concluded that long term administration of beta adrenergic blockers increased myocardial repolarization time and reduces sympathetic nervous system activity. Another study conducted by Morrison et al. on hypertensive subjects to compare the responses to change in posture, cold and exercise in selective and non-selective beta-adrenoreceptor blockade in hypertension revealed that extent to pressor response to cold stimulus and to isometric and dynamic exercise were similar during selective and nonselective beta blockade and concluded such increase in blood pressure largely mediated by neural sympathetic pathway rather than by circulating epinephrine. Haemodynamic, biochemical and reflexive changes produced by atenolol before and after 4 weeks of beta-blockade in 10 patients with mild essential hypertension. Dreslinski et al. [12] observed that atenolol reduced mean arterial pressure, heart rate and cardiac index. Reflexive cardio acceleration during valsalva maneuver and upright passive tilts was blunted. No changes were observed in circulating fluid volumes.

The antihypertensive effects of calcium channel blocker (nisoldipine) and beta adrenergic blockers (Atenolol) were compared by Takasashi in patients with mild to moderate essential hypertension. The study revealed that heart rate decreased significantly in the Atenolol group but not in Nisoldipine group. The magnitude of pressor response during hand grip test tended to be smaller in both groups of patients than in the controls, with no significant difference between the treated groups.[13]

Indapamide

Noveck studied the autonomic responses in heart rate and blood pressure to valsalva maneuver before and after treatment with Indapamide (diuretics). Following treatment, responses in heart rate and blood pressure to valsalva maneuver were unaltered indicating that in hypertensive patients on indapamide, changes in vascular responsiveness occurred by mechanism independent of changes in autonomic nervous system. [14]

Enalapril and Metoprolol

The effect of autonomic nervous system following angiotensin converting enzyme inhibitors in hypertension done by Asmar et al. [15] measuring common carotid blood flow and cold pressor test in 16 patients with essential hypertension before and after 30 days treatment with angiotensin converting enzyme inhibitor (Enalapril). Enalapril decreased blood pressure and carotid vascular resistance with no significant change in heart rate. After treatment, despite a wide range of responses, the changes in systolic blood pressure to cold pressor test were significantly attenuated, whereas the heart rate responses were not and thus concluding that ACE inhibitors causes sympathio-inhibitory influences which are principally observed in stress condition. The interference to autonomic nervous system was assessed with drug effects on heart rate variability in 13 hypertensive diabetic subjects during treatment with antihypertensive drugs, metoprolol and enalapril by Salo et al. [16] It was concluded that heart rate was reduced by metoprolol and not by enalapril. The heart rate variability was not significant altered by enalapril revealing that ACE inhibitor was a more neutral treatment from the point of view of autonomic cardiac control. Zou et al. [17] compared the effect of Doxazosin and Enalpril on digital vasoconstriction and nocturnal blood pressure in hypertension Obstructive Sleep Apnea (OSA) patients. Doxazosin as compared to Enalpril has a proportionally poor effect on nocturnal BP control in OSA patients, which may be due to the enhanced sympathetic nervous system activity characteristic of this condition.

A study conducted by Piccirillo et al. on 15 elderly hypertensive men with silent myocardial ischaemia that effects of antihypertensive drugs on autonomic nervous system behaviour by means of power spectrum analysis of heart rate variability revealed that treatment with metoprolol, quinapril and amlodipine plus quinapril significantly depressed sympathetic activity.[18]

Calcium channel blockers

Calcium antagonists (calcium entry blockers, slow channel blockers) are selective inhibitors of the influx of calcium ions from the extracellular space into the cell, via the specific calcium channels in the sarcolemma. The process of calcium influx plays an important functional role in vascular smooth muscle and in various cardiac tissues, but not in skeletal muscles. Accordingly, calcium antagonists will cause vasodilatation, in particular in the arterial vascular bed, with little or no influence on capacitance vessels. Arterial vasodilatation and antihypertensive activity are common properties of all the current calcium antagonists. A depressant influence on cardiac tissues, as reflected by reductions in cardiac contractile force, HR, and A-V conduction, is limited to verapamil, diltiazem and their related successor drugs.

In most cases, they are used in the treatment of chronic hypertension as monotherapy or in combination with other drugs. Most of the dihydropyridines and also verapamil and diltiazem can be used as antihypertensives for chronic treatment. Nifedipine and possibly other dihydropyridines can also bc used in the acutetreatment of a

hypertensive emergency. Hypertensive patients with concomitant CAD may have an additional benefit from the treatment with calcium antagonists. The anti-angina] effect of the calcium antagonists is well established. In therapeutic doses they do not change plasma lipid profiles, but in various animal models their anti-atherogenie activity appears to be well established.[19]

The effect of nifedipine hydrochloride, a T-type calcium channel blockers on the sympathetic activities was investigated. It was revealed that administration of nifedipine hydrochloride decreased the heart rate in patients with high heart rate, reduced sympathetic nervous activity and enhanced parasympathetic nervous activity. [20] concluded that nifedipine may be a useful vasodilator in the management of postoperative hypertension, and is probably preferable to NP in patients with myocardial ischemia.

Cardillo et al. [21] studied the effect of sustained release verapamil therapy on blood pressure at rest and on pressor response to isometric exercise (handgrip test) in hypertensive patients and showed that there was significant reduction in resting systolic and diastolic blood pressure. Blood pressure and heart rate at peak exercise were lower after verapamil than after placebo.

A study was conducted on 23 hypertensive subjects to compare the effect of verapamil and amlodipine on the autonomic and cardiovascular stress responses. Patients performed stress tests (mental arithmetic, cold pressor and handgrip test while extra cardiovascular and haemodynamic functions were assessed non-invasively at every heart beat, during baseline, stress and recovery phases. The abnormal sympathetic stress response, which characteristics the hypertensive patients, might be affected by choice of medication. Verapamil in particular, moderated emotional arousal, the vasoconstrictive response and reduced cardiac load without lowering cardiac output demands. In contrast, in patient treated with amlodipine, in whom cardiac output response was increased, the pattern was reversed and functional cardiac load was also increased It was studied that verapamil sr/trandolapril combination therapy may be an appropriate treatment option in patients with moderate essential hypertension, particular in those who have tendency toward early morning rise in blood pressure.[22]

Another study also proved that the antihypertensive effects of amlodipine were of slow onset and long duration and were not accompanied by an increase in sympathetic activity or activation of renin angiotensin system. The comparative study of the effects of amlodipine and nifedipine retard on autonomic sympathetic nerve activity in hypertensive patient revealed that administration of amlodipine did not induce an increase in sympathetic nerve activity in essential hypertensive patients in contrast to slow releasing nifedipine. The effect of dihydropyridine (amlodipine) and a non dihydropyidine (verapamil) on autonomic functions in patients with mild to moderate hypertensive was studied and concluded that amlodipine induced a shift in sympathovagal balance as measured by heart rate variability indices and plasma norepinephrine, towards sympathetic predominance compared with vagal predominance with verapamil. Contrasting effects of verapamil and amlodipine on cardiovascular stress responses in hypertension showed that blood pressure was equally reduced by both the drugs. The systolic blood pressure, heart rate and rate-pressure product were lower with varapamil compared with amlodipine. Varapamil attenuated the increase in systolic blood pressure during sustained isometric handgrip and cold pressor test, more as compared to amlodipine. In another study to estimate the influence of therapy with amlodipine or lacidipine on heart rate variability, it was concluded that amlodipine and lacidipine reduce the influence of humoral control and sympathetic autonomic nervous system activity.[23-24]

Lacourciere et al. [25] studied that lsradipine was more effective in patients whose clinical hypertension was confinned by ambulatory BP monitoring (35) than in patients who remained normotensive by ambutatory BP monitoring criteria (41). The isradipine- treated ambulatory hypertensive group experienced significantly greater decreases in BP during 24-hour, work, awake and sleep periods than did the ambulatory normotensive group. These data suggest that sustained-release isradipine has a sustained antihypertensive effect throughout 24 hours comparable to that of isradipine given twice daily and may improve compliance with long-term treatment.

Another study conducted to study the effects of dihydropyridine calcium antagonist (cilnidipine) on autonomic function, ambulatory blood pressure and heart rate in patients with essential hypertension revealed that cilnidipne was effective antihypertensive agent and causes little influence on heart rate. During the cold pressor test, the maximum change in systolic blood pressure were significantly a lower during the treatment with cilnidipne than during the drug free period. The baroreflex sensitivity measured from the overshoot phase of valsalva maneuver did not differ significantly.[26]

Sankata et a.l evaluate the effects of amlodipine and cilnidipine on cardiac sympathetic nervous system activity, it was revealed that in patients with essential hypertension clinidipine suppressed the cardiac sympathetic overactivity more as compared to amplodipine.[27]

Sakata et al. evaluated the effects of Iosartan and its combination with quinapril on the cardiac sympathetic nervous system and neurohormonal status in essential hypertension. All patients underwent metaiodobenzyl guanidine (MIBG) imaging and neurohormonal measurements before and 3 months after treatment were assessed. It was concluded that combination therapy with Iosartan and qunapril results in higher degree of inhibition of renin angiotensin system and cardiac sympathetic activity than Iosartan and quinapril as a monotherapy. [28]

ACE inhibitor

Drugs investigated in detail and used for therapeutic purposes on a very large scale are the ACE-inhibitors, of which captopril and enalapril are the best known examples. The inhibition of the angiotensin I-converting enzyme (ACE) by these drugs suppresses the formation of angiotensin II from angiotensin I. Angiotensin II is known as a potent vasoconstrictor, which also enhances the release ofaldosterone from the adrenal cortex. In

addition, angiotensin II enhances the intensity of sympathetic stimulation in various organs and tissues, and it is considered as an important growth factor in myocardial and vascular hypertrophy. Concomitantly, the suppression of the formation of angiotensin II, as provoked by ACE inhibitors. may be expected to counteract elevated blood pressure, elevated aldosterone levels (i.e CAF), sequelae of sympathetic activation, and hypertrophy of the heart and vessels.[29]

The effects of an ACE inhibitor and calcium channel blockers on cardiovascular autonomic nervous system and carotid distensibility in patients with mild to moderate hypertension was studied and concluded that ACE inhibitor significantly improved the impairment of autonomic balance.

Few studies have reported the effects of angiotensin converting enzyme inhibitor on 24 hours blood pressure and regulation of sympathetic nervous activity in hypertensive patients with diabetic nephropathy. Using ambulatory blood pressure monitoring devices equipped with spectral analysis of heart rate variability, the effects of Perindopril (ACE inhibitor) was assessed on 24 hour blood pressure and autonomic nervous system activity in these patients. It was concluded that in patients, with diabetic nephropathy, perindopril decreased 24 hours good blood pressure. Spectral analysis suggested that this finding was partially related to inhibited sympathetic nervous system activity [29]

The influence of ACE inhibitor and angiotensin II AT^1 receptor blockade on the autonomic function and baro reflex sensitivity was investigated in hypertension. It was observed that in hypertensive patients, both the treatment with enalapril and Iosartan reduced blood pressure and had no effect on heart rate. A resetting of baro reflex function was observed during both ACE inhibition and angiotensin II AT_1 receptor blockade.[30] Effects of selective angiotensin II receptor blockade on symathetic nerve activity in primary hypertensive subjects showed that selective angiotensin II receptor blockade not only reduced blood pressure but also shifts the baro reflex set point for initiation of counter regulatory reflex responses of heart rate and blood pressure towards normal blood pressure levels It observed that behaviour of autonomic nervous system after treatment with angiotensin II converting enzyme inhibitors. It was concluded that functional autonomic adjustment after the antihypertensive treatment with ACE inhibitor was observed indicating recovery of parasympathetic tonus.[31] It has suggested that therapy with telmisartan significantly improves the sympathovagal balance increasing parasympathetic activity, and cardiac electrical stability reducing the heterogeneity of ventricular repolarization in hypertensive subjects. These effects could contribute to reduce arrhythmias as well as sudden cardiac death in at-risk hypertensive patients.[32]

Conclusion

The emphasis is on choosing the drug that best meets each patient need, according to factors such as age, ethnicity and presence of other cardiovascular condition. Treatment with metoprolol, quinapril and amlodipine plus quinapril significantly depressed sympathetic activity in elderly hypertensive patients with silent myocardial ischemia. Enalapril (an ACE inhibitor) is more neutral treatment in subjects with hypertension, diabetes and autonomic neuropathy as compared to (beta-blocker) metoprolol. ACE inhibitor (Captropril) is effective in controlling blood pressure not only in benign hypertension but also in accelerated hypertensives. Thus a review of above researches have shown modification in the autonomic nervous system activity both sympathetic as well as parasympathetic by various groups of antihypertensive agents in the hypertensive patients.

References

1. Gupta R. The JNC-7. Report and the Indian Clinician. *South Asian Journal of Preventive Cardiology*. **2004**; 8: 5-7.
2. Williams G.H. Hypertensive vascular disease. In: Isselbacher KJ, Braunwald E. Wilson JD, Martin, Fauci AS, Kasper DL. editors. Harrison's principles of Internal medicine. 13th ed. vol. 1. New York: McGraw-Hill, Inc. **1994**; 1116-1131.
3. Antonaccio M.J, Wright J.J. Renin angiotrnsin system, converting enzyme and renin inhibitors, in Antonaccio MJ (ed): Cardiovascular Pharmacology (ed 3). New York. NY. Raven., **1990**; 210-228.
4. Boon N.A, Fox K.A.A, Bloomfield P. Diseases of Cardiovascular System. In: Haslett C, Chilvers ER, Hunter JAA, Boon NA, editors. Davidson's principles and practice of medicine. 18th ed. Edinburgh: Churchill Livingston. **1999**; 191-302.
5. Beevers G, Lip GYH, O' Brien E. ABC of hypertension: The pathophysiology of hypertension *BMJ*; **2001**;322: 912-16
6. Amerena J, Julius S. The role of the autonomic nervous system in hypertension. *Hypertens Res J*; **1995**;18 (2): 99-110.
7. Binggeli C, Corti R, Sundano I, Luscher T.F, Noll G. Effects of chronic calcium channel blockade on sympathetic nerve activity in hypertension. *Hypertension*. **2002**; 39: 892.
8. Van Zwieten P.A., Van Wezel H.B. Antihypertensive Drug Treatment in the Perioperative Period. *Journal of Cardiothoracic and Vascular Anesthesia,* **1993**; 213-226
9. Prichard B.N.C, Gillam P.M.S. Use of propranolol in the treatment of hypertension. *Br Med J,* **1964**; 2:725-727,
10. Buhler F.R, Haensler G. Optimization of p-blockers for cardiovascular care. *J Cardiovasc Pharmacol* **1986**; 8:1-23
11. Raine A.E.G, Pickering T.G. Cardiovascular and sympathetic response to exercise after long-term beta-adrenergic blockade. *Brit Med. J.* **1977**; 2: 90-92.
12. Dreslinski G.R, Messerli F.H, Dunn F.G, Suarez D.H, Reisin E, Frohlich E.D Hemodynamics, Biochemical and reflexive changes produced by atenolol in hypertension. *Circulation.* **1982**;65: 1365-1368.
13. Takasashi H, Fukuyama M, Yoneda S, Okabayashi H, Yoshimura M. comparison of nisoldipine and atenolol

in the treatment of essential hypertension. *Arzneimittelforschung*. **1989**; 39: 379-82.
14. Noveck R.J, McMahan F.G, Quiros A, Giles T. Extrarenal contributions to indapamide's antihypertensive mechanism of action. *American Heart Journal*. **1983**; 106: 221-229.
15. Asmar R.G, Benetos A, Dara B, Laurent S, Safar M.E. An indirect evaluation of the effect of the autonomic nervous system following converting enzyme inhibition in hypertension. *Clin Exp Hypertens A*. **1992**; 14 (5): 853-73.
16. Salo T.M, Viikari J.S.A, Antila K.J, Voipio-Pulkki L, Jalonen J.O, Valimiki. Antihypertensive treatment and heart rate variability in diabetic patients: role of cardiac autonomic neuropathy. *J Auto Nerv Sy* **1996**; 60: 61-70.
17. Zou D, Grote L, Eder D N, Radlinski J, Hedner J A double-blind, crossover study of Doxazosin and Enalapril on peripheral vascular tone and nocturnal blood pressure in sleep apnea patients. *Sleep Medicine* **2010**;11: 325–328.
18. Piccirillo G, Bucca C, Santagada E, Monteforte G, Viola E, Durante M. The effects of antihypertensive drugs on the autonomic nervous system in elderly hypertensive patients with silent myocardial ischemia. *Arch Geront Geriat*. **1996**; 22: 119-124.
19. Weinstein D.B, Heider J.C . Antiatherogenic properties of calcium channel blockers. *Am J Med* **1988**; 84:102-108.
20. Harada K, Nomura M, Nishikado A, Uehara K, Nakaya Y, Ito S. Clinical efficacy of efonidipine hydrochloride, a T-type calcium channel inhibitor, on sympathetic activities. *Circ J***. 2003**; 67: 139-45.
21. Cardillo C, Musumeci V, Savi L, Guardigli R, Mores N, Folli G,. Effect of sustained-release verapamil therapy on the blood pressure at rest and on the pressor response to isometric exertion in hypertensive patients. European *Joural of Clinical Pharmacology*. **1988**; 34: 549-533.
22. Nazzaro P, Manazari M, Merlo M, Triggiani R, Scarano A.M, Lasciarrea. Antihypertensive treatment with verapamil and amlodipine. Their effect on the functional autonomic and cardiovascular stress responses. *European Heart Journal.* **1995**; 16: 1277-1284.
23. Lefrandt J. D, Heitmann J, Sevre K, Castellano M, Hausberg M, Fallon M . The effects of dihydropyridine and phenylalkylamine calcium antagonist classes on autonomic function in hypertension: the VAMPHYRE study. *Am J Hypertens*. **2001**;14: 1083-9.
24. Lefrandt J. D, Jorg H, Sevre K. C. M, Hausberg M, Maura F. Contrasting effects of verapamil and amlodipine on cardiovascular stress responses in hypertension. *Brit J Clin Pharmacol*. **2001**; 52: 687-692.
25. Ligtenberg G, Blankestijin P. J, Oey P. L, Klein I. H.H, Dijkhorst O LT, Boomsma F. Reduction of Sympathetic Hyperactivity by Enalapril in Patients with Chronic Renal Failure. *The new Eng. J. Of Med.* **1999**; 340: 1321-1328.
26. Minami J, Ishimitsu T, Kawano Y, Matsuoka H. Effects of amlodipine and nifedipine retard on autonomic nerve activity in hypertensive patients. *Clin Exp. Pharmacol Physiol.* **1998**; 25: 572-6.
27. Sakata K, Yoshinda H, Obayaski K, Ishikawa J, Tamekiyo H, Nawada R. Effects of Iosartan and its combination with quinapril on the cardiac sympathetic nervous system and neurohormonal status in essential hypertension. *J. Hypertens*; **2002;** 20 : 103-10.
28. Sankata K, Shirotani M, Yoshida H, Nawada R, Obayashi K, Togi K, Miho N. Effects of amlodipine and cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. *Hypertension;* **1999**; 33: 1447-52.
29. Yasuda G, Hasegawa K, Kuji T, Ogawa N, Shimura G, Umemura S. Perindopril effects of ambulatory blood pressure: relation to sympathetic nervous activity in subjects with diabetic nephropathy. *Am J. Hypertens.* **2004**; 17 (1): 14-20.
30. Guasti L, Petrozzino M.R, Mainardi L.T, Grimoldi P, Zanotta D, Garganico D. Autonomic function and baroreflex sensitivity during angiotensin-converting enzyme inhibition or angiotensin II AT-1 receptor blockade in essential hypertension patients. *Acta Cardiol.* **2001**; 56: 289-95.
31. Menezes, Ada S Jr, Moreira, H.G., Daher M.T. Analysis of heart rate variability in hypertensive patients before and after treatment with angiotensin II-converting enzyme inhibitors. *Arq Bras Cardiol;* **2004**; 83: 169-172.
32. Galetta F, Franzoni F, Fallahi P, Tocchini L, Graci F, Carpi A, Antonelli A, Santoro G. Effect of telmisartan on QT interval variability and autonomic control in hypertensive patients with left ventricular hypertrophy. *Biomedicine & Pharmacotherapy* **, 2010**; 64: 516–520.