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Plasma Atrial Natriuretic Peptide Levels in Essential Hypertension after Treatment with Verapamil

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INTRODUCTION

This study aims to investigate the long-term antihypertensive effect of verapamil in relation to plasma ANP concentration changes on essential hypertensive patients. Verapamil is a Ca^{2+}-entry blocker with mild inhibiting actions on α_2-adrenoceptor (1). Calcium entry blockers exert their antihypertensive action in a non direct neural or hormonal way. It is therefore interesting to investigate if any long-term effect on ANP plasma levels is exerted by them. There are few references concerning the action of Ca^{2+}-entry blockers on ANP plasma levels and no one of them concerns a long-term treatment with verapamil.

MATERIALS AND METHODS

Thirty male patients, mean age 59.83 years (range 49-74 years) with mild to moderate uncomplicated essential arterial hypertension were included in the study. The above patients satisfied the criteria for inclusion in treatment with Ca^{2+}- blockers. All patients had a normal renal function as it was detected by conventional biochemical tests and by the radioisotopic investigation. Echocardiographically, all patients had normal systolic ventricular function; no evidence of ischemia was detected by means of ECG or SPECT (thalium-201) exercise test. Any treatment that some of these patients were receiving prior to their inclusion to the present study was discontinued for 2 weeks. After that period, all patients were started on verapamil 240 mg daily (isoptin, Knoll Pharmaceutical Company) given per os in a single doşe and in the form of slow release tablets. Before treatment and a month after it, the following parameters were measured: Systolic blood pressure (SBP), diastolic blood pressure (DBP), left atrial diameter (LAD),left ventricular end systolic (LVESD) and end diastolic (LVEDD) diameters, and ANP plasma concentration. The determination of these parameters was carried out with the patients in the supine position after a rest period of 30 minutes each time. Blood pressure was determined using a mercury sphygmomanometer. Left atrial and ventricular dimensions were measured echocardiographically in the parasternal long axis position. ANP was measured in blood specimens taken by venous puncture. Quantitative determination of human ANP was made by radioimmunoassay procedure using an ANP (^{125}J) radioimmunoassay (RIA) system according to the manufacturer's instructions (2).

RESULTS

Mean SBP was decreased by 23.28% (from 183.8 mmHg to 141.0 mmHg). Mean DBP was also decreased by 10.65% (from 102.3 mmHg to 91.4 mmHg) while mean plasma levels of ANP increased after treatment by 16.4% (from 38.58 pg/ml to 44.81 pg/ml). All these changes were

statistically significant ($p<0.05$). LAD as well as LVEDD and LVESD remained unchanged.

Table 1
Changes in the parameters studied before and after 30 days treatment with verapamil 240mg daily for 30 days. (means ± SD, n: 30)

Parameters	*Before treatment*	*After treatment*	*Units*	*% changes*
ANP	38.58±7.42	44.81±6.04	pg/mL	+ 16.14 *
LAD	39.98±1.12	39.33±1.35	mm	N.S
LVD-SP	40.37±1.22	39.98±1.67	mm	N.S
LVD-DP	54.87±1.62	54.35±1.57	mm	N.S
SBP	183.8±11.83	141.0±7.5	mmHg	- 23.28 *
DBP	102.3±6.44	91.4 ±2.8	mm/Hg	-10.65 *

ANP, atrial natriuretic peptide (plasma concentration) ; LAD, left atrial diameter; LVESD, left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure. * $p < 0.05$, N.S : No Significant

DISCUSSION

After a month of monotherapy, left atrial and ventricular dimensions remained unchanged, blood pressure decreased and ANP plasma levels increased. The above mentioned results indicate that the increase of ANP plasma levels is the result of a pharmacological action and not the result of a mechanical load on the left cardiac chambers since their dimensions remained unchanged. There are not available references concerning such a study with verapamil in hypertensive humans. There are some references with conflictive results concerning studies with 1,4-dihydropyridines, another category of Ca^{2+}-blockers with increased angioselectivity.(3-8). It is difficult to say if the increasing effect of verapamil on ANP plasma levels is the result of a stimulatory secretory effect or the result of an inhibitory effect on the catabolism of this peptide. An inhibitory effect of verapamil on ANP catabolism seems to be more reasonable. There are not available references concerning such an effect of calcium blockers on ANP catabolism. On the other hand, experiments that have been performed in animals or in cultured aortic smooth muscle cells derived from animals, have demonstrate that some categories of antihypertensive drugs like β-adrenergic blockers and AT_1 -blockers increase ANP plasma levels not only by increased secretion (9,10) but also by decreasing the gene expression of NP-C receptor, thought to be related to clearance of ANP (11-13). No matter which of the mechanisms is involved, the principal message from our study is that verapamil exerts part of its antihypertensive action by increasing ANP levels.

REFERENCES

1. Papadopoulos C.L., Kokkas B., Kotridis P., et al.: Plasma atrial natriuretic peptide in essential hypertension after angiotensin converting enzyme inhibition. *Intern. J. Angiology 4*: 44-45 (1995)
2. Geller D., et al.: Atriopeptides. *Biochem. Biophys. Res. Commun. 120*: 333-338 (1984)
3. Iwasaki T. et al.: Effects of calcium antagonists and nitroglycerin on atrial natriuretic peptide in normal subjects and patients with essential hypertension. *Angiology 40*: 24-28 (1989)
4. Shigematsu S. et al.: Differential effects of nifedipine on plasma atrial natriuretic peptide in normal subjects and hypertensive patients. *Angiology 43*: 40-46 (1992)
5. Rappelli A., et al.): Increase of plasma atrial peptide levels after sublingual administration of nifedipine in essentially hypertensive patients. *Int. J. Cardiol. 25*: 25-28 (1989)
6. Colantonio D., et al.: Short term effects of atenolol and nifedipine on atrial natriuretic peptide, plasma renin activity, and plasma aldosterone in patients with essential hypertension. *J. Clin. Pharmacol. 31*: 238-242 (1991)
7. Cerasola G., et al.: Effects of felodipine on natriuresis, atrial natriuretic factor, the renin-angiotensin-aldosterone system, and blood pressure in essential hypertension. *Clin. Ther. 10*: 694-703 (1988)
8. Lehnert H., et al.: Effects of nitrendipine on blood pressure, renin-angiotensin system and atrial natriuretic peptide in hypertensive type I diabetic patients. *Horm. Metab. Res. 25*: 24-28 (1993)
9. Shields P., Glembotski C.: Regulation of atrial natriuretic factor secretion from neonatal rat primary atrial cultures by activators of protein kinases A and C. *J. Biol. Chem. 264*: 9322-9328 (1989)
10. Magga J., et al. (1999): Differential regulation of cardiac adrenomedullin and natriuretic peptide gene expression by AT1 receptor antagonism and ACE inhibition in normotensive and hypertensive rats. J. Hypertens., 17:1543-1552 (1999)
11. Yoshimoto T. et al.: Angiotensin II-depended down regulation of vascular natriuretic peptide type C receptor gene expression in hypertensive rats. *Endocrinology 137*: 1102-1107 (1996)
12. Yoshimoto T. et al.: Beta-adrenergic antagonist propranolol potentiates hypertensive action of natriuretic peptides. *Eur. J. Pharmacol. 12*: 61-66 (1998)
13. Yoshimoto T. et al.: Potentiation of natriuretic peptide action by beta-adrenergic blocker carvedilol in hypertensive rats: a new antihypertensive mechanism. *Endocrinology 139*: 81-88 (1998)