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Plasma atrial natriuretic peptide levels in essential hypertension after treatment with verapamil

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SUMMARY

The aim of this study was to evaluate the long term effects of the selective Ca^{2+}- blocker verapamil on atrial natriuretic peptide (ANP) levels in patients with moderate essential hypertension. The drug was given orally in a daily dose of 300 mg for 30 days. At the end of this clinical trial, plasma ANP levels increased by 16.14% despite the drop in blood pressure while left atrial and ventricular diameters remained unchanged. These findings indicate that the increase of ANP plasma levels is not the result of a mechanical load on the left cardiac chambers but the result of a pharmacological action. These observations also indicate that verapamil exerts part of its antihypertensive action by increasing ANP plasma levels.

INTRODUCTION

In a study that has been carried out for a decade in our clinic, we have investigated the action of different antihypertensive drugs on the blood level of atrial natriuretic peptide (ANP) in patients having a moderate degree of uncomplicated essential hypertension and undergoing long term treatment with the drug. We have already found that drugs like cilazapril, an angiotensin converting enzyme inhibitor (ACEI), bisoprolol, a selective β_1-adrenergic selective blocker and celiprolol, a β_1-blocker/β_2-agonist increase ANP plasma levels while blood pressure is decreased. We have also found that this effect was not the result of an increased mechanical load but rather, caused by a pharmacological action. (1-4)

Calcium entry blockers exert their antihypertensive action in a non direct neural or hormonal way. It is therefore interesting to investigate whether any long-term effect on ANP plasma levels is exerted by them.

Verapamil is a Ca^{2+}-entry blocker with mild inhibiting actions on α_2- adrenoceptor (5). There are few studies concerning the action of Ca^{2+}-entry blockers on ANP plasma levels and none of them concerns a long-term treatment with verapamil. Thus, this study aims to investigate the long-term antihypertensive effect of verapamil in relation to plasma ANP concentration changes essential hypertensive patients.

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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 for treatment with Ca^{2+}- blockers. Informed consent and ethical approval had been obtained.

All patients had normal renal function as determined 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 the SPECT (thalium-201) exercise test. Any treatment that some of these patients were receiving prior to their inclusion in 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 dose and in the form of slow releasing 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 a 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}I) radioimmunoassay (RIA) system according to the manufacturer's instructions (6). The results obtained (mean ± SD) were expressed as pg/mL. Normal values calculated in 10 male healthy individuals, mean age 51 years (range 30-60), in our laboratory were 35.3 ± 9.5 pg/mL.

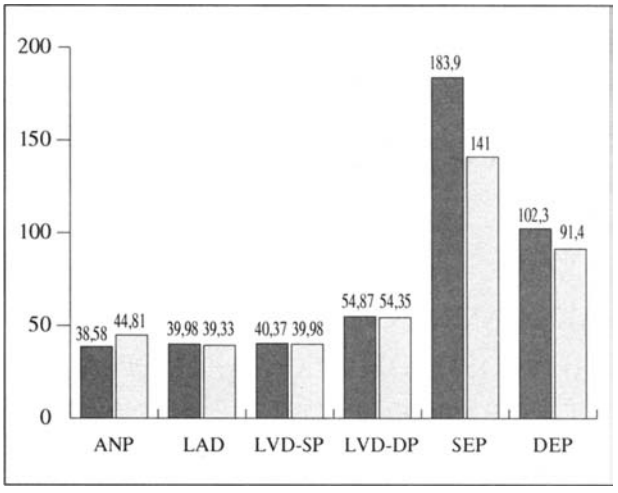

Fig. 1: Schematic representation of the changes in the parameters studies before and after 30 days treatment with verapamil 240mg daily for 30 days. ANP: atrial natriuretic peptide (plasma concentration in pg/mL), LAD: left atrial diameter (mm), LVESD: left ventricular end systolic diameter (mm), LVEDD: left ventricular end diastolic diameter (mm), SBP: systolic blood pressure (mmHg), DBP: blood pressure (mmHg).

Comparison of the values obtained before and after treatment was carried out for each parameter using the Student's pair t- test.

RESULTS

Results are shown in detail in table I (mean values± SD). 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 I: 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

We investigated the long - term effect of verapamil, a Ca^{2+}-blocker, on a group of patients with uncomplicated moderate essential hypertension. 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 no available publications concerning such a study with verapamil in hypertensive humans. There is only one study reporting that verapamil did not change ANP plasma levels after 2 and after 24h of its administration (7). There are also some studies with conflicting results concerning 1,4-dihydropyridines, another category of Ca^{2+}-blockers with increased angioselectivity. Iwasaki T. et al. report that nifedipine acutely increased ANP in normal subjects but not in hypertensive ones. Shigematsu S. et al. (9) report that the same drug's acute effects were a rise of ANP plasma levels in young and old normotesive subjects but not in young hypertensive patients and half of the old patients while Rappelli A. et al. say that in hypertensive patients a rise of circulating ANP was among the acute effects of nifedipine (10). According to Shamis A. et al. (7), such a short-term enhancement of ANP levels is related to the initial diuretic and natriuretic effects of dihydropyridines. Colantonio D. et al. also report that a short- term treatment of hypertensive patients with nifedipine 30mg/d did not modify plasma ANP levels (11). According to Cerasola G. et al. (12), felodipine during a long-term administration to essential hypertensive patients caused a transient increase in circulating ANP. On the contrary, Lehnert G. et al. (13) suggest that a long-term treatment of hypertensive patients with nitrendipine resulted in a decrease of ANP plasma levels.

It is dificult to say whether 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. Studies performed in neonatal rat ventricular cardiomyocytes have demonstrated that nifedipine-sensitive calcium channels are involved in ANP release (14). Similar findings are reported from experiments performed in perfused beating rabbit atria (15). Such observations do not favor a stimulatory effect of verapamil on ANP secretion. An inhibitory effect of verapamil on ANP catabolism seems to be more reasonable. There are no available data 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 demonstrated that some categories of antihypertensive drugs like β-adrenergic blockers and AT_1 -blockers increase ANP plasma levels not only by increased secretion (16,17) but also by decreasing the gene expression of the NP-C receptor, thought to be related to clearance of ANP (18,19,20).

Regardless of the mechanisms is involved, the principal message from our study is that verapamil exerts part of its antihypertensive action by increasing ANP levels.

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