EPITHEORESE KLINIKES FARMAKOLOGIAS
KAI FARMAKOKINETIKES, INTERNATIONAL
EDITION 16: 75-76 (2002)

Plasma Atrial Natriuretic Peptide in Essential Hypertension after Treatment with Irbesartan

P. Kotridis[1], B. Kokkas[2], M. Karamouzis[3], G. Sakadamis[1], I. Kanonidis[1], G. Dadous[1], C. Karantona[1], O. Gouli[1], J. Karadoumanis[1], P.C. Papadopoulos[1] and C.L. Papadopoulos[1]

Departments of [1]Second Cardiology, [2]Pharmacology and [3]Biochemistry, Medical School, Aristotle University, Thessaloniki, Greece

INTRODUCTION

This study aims to investigate the antihypertensive effect of irbesartan in relation to plasma ANP concentration changes in the same category of hypertensive patients. It is known that irbesartan inhibits the activity of angiotensin II (A-II) via specific selective, noncompetitive antagonism of the A-II receptor subtype 1 (AT_1) which mediates most of the known physiological activities of A-II (1).

METHODS

Thirty male patients, mean age 58.2 years (range 42-71 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 AT_1 receptor 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 irbesartan (Aprovel, Sanofi Pharmaceutical Company) 300mg daily given per os in a single dose. Before treatment and a month after treatment, 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 as well as 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 one hour after the last drug's dose administration. 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 fell by 30.9% (from 183.3 mmHg to 126 mmHg). Mean DBP was decreased by 17.7% (from 108.3 mmHg to 89.1 mmHg) while mean plasma levels of ANP increased after treatment by 15.7% (from 48.16 pg/ml to 55.73 pg/ml). All these changes were statistically significant ($p<0.05$). LAD decreased by 1.21% (from 39.56mm to 39.08, $p<0.01$). LVESD decreased by 3.25% (from 40.83mm to 39.50mm, $p<0.001$) and LVEDD decreased by 2.7% (from 54.5 mm to 53.0, $p<0.001$).

Table 1.
Changes in the parameters studied before and after 30 days treatment with irbesartan 300mg daily for 30 days. Results expressed as mean ± SD, n: 30
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, ** p<0.01, *** p<0.001

Parameters	Before treatment	After treatment	Units	% changes
ANP	48.16±7.38	55.73±7.10	pg/mL	+ 15.71 *
LAD	39.56±9.7	39.08±0.93	mm	- 1.21 **
LVESD	40.83±1.49	39.50±1.73	mm	- 3.25 ***
LVEDD	54.50±1.89	53.08±1.83	mm	- 2.7 ***
SBP	183.3±5.52	126.6±5.5	mmHg	- 30.93 *
DBP	108.3±4.71	89.1 ±3.4	mm/Hg	- 17.72 *

DISCUSSION

After a month of monotherapy with the AT_1-blocker irbesartan, blood pressure was decreased and ANP plasma levels increased. This last finding was not the result of an increased mechanical load on the left cardiac chambers since both left atrial and left ventricular dimensions were slightly decreased. The above mentioned results indicate that the increase of ANP plasma levels is the result of a pharmacological action. There are not available references concerning such a study in hypertensive humans. Thus, it is difficult to provide an explanation concerning our findings on a cellular and molecular level. Speculations can only be done based on data derived from animals. References coming from experiments performed in hypertensive rats demonstrate that AT_1- blockers provoke an increase of the atrial immunoreactive ANP mRN levels in the left atrium (3). Our method measure both atrial and ventricular derived ANP plasm levels. Based on the fact that most of the ANP i secreted by the atrial wall, the above mentione references offer a molecular base that could sup port that irbesartan exerts its action at the level c the secretion and not at the level of the catabc lism of the ANP. On the other hand, other e> periments that have been performed in stroke prone spontaneously hypertensive rats as well a in cultured aortic smooth muscle cells have dem onstrated that AT_1 -blockers decrease the gen expression of NP-C receptor, thought to be re lated to clearance of ANP (4). Such observation indicate that AT_1 -blockers increasing action c ANP plasma levels may be related with a dimin ished clearance of the above peptide. No matte which of the mechanisms is involved, the princi pal message of this clinical trial is that AT_1 blockers like irbesartan exert part of their anti hypertensive action by increasing ANP levels.

REFERENCES

1. Gillis J., Markham A.: Irbesartan. A review of its pharma codynamic and pharmacokinetic properties and therapeuti use in the management of hypertension. *Drugs 54*: 885-90 (1997)
2. Geller D., Currie M., Wakitani K.: Atriopeptides. *Bic chem. Biophys. Res. Commun. 120*: 333-338 (1984)
3. Magga J., Kalliovalkama J., Romppanen H., et al.: Diffe ential regulation of cardiac adrenomedullin and natriureti peptide gene expression by AT1 receptor antagonism an ACE inhibition in normotensive and hypertensive rats. *Hypertens. 17*: 1543-1552 (1999)
4. Yoshimoto T., Naruse M., Naruse K., et al. : Angiotensi II- depended down regulation of vascular natriuretic peptid type C receptor gene expression in hypertensive rats. *Er docrinology 137*: 1102-1107 (1996)