Clinical Evaluation of Angiotensin II Antagonist in Advanced Hypertension

MINORU YASUJIMA, KEISHI ABE, NOBUO IROKAWA, KANCHO RITSU, MASAHIDE SEINO, KEITARO SAITO, YUTAKA SAKURAI, SATORU CHIBA, TORU ITO and KAORU YOSHINAGA

Department of Internal Medicine, Tohoku University School of Medicine, Sendai

YASUJIMA, M., ABE, K., IROKAWA, N., RITSU, K., SEINO, M., SAITO, K., SAKURAI, Y., CHIBA, S., ITO, T. and YOSHINAGA, K. Clinical Evaluation of Angiotensin II Antagonist in Advanced Hypertension. Tohoku J. Exp. Med., 1977, 122 (2), 191-197 — Eighteen patients with advanced or malignant hypertension due to essential hypertension, systemic lupus erythematosus or chronic glomerulonephritis were infused intravenously with 1-Sar-8-Ile-Angiotensin II, a competitive antagonist of angiotensin II. The spectrum of responses was broad from a mild elevation to a marked fall in blood pressure. The changes in mean blood pressure caused by this peptide showed a significant correlation with the level of peripheral plasma renin activity immediately before the infusion ($r=0.5652$, $p<0.02$). This peptide infusion reduced blood pressure in 12 patients (responders), but not in 6 (non-responders). There were no differences with age, sex and severity of hypertension except for the level of peripheral plasma renin activity between the two groups. Our retrospective study showed that in 12 responders propranolol reduced blood pressure to near the normal level, while in 6 non-responders furosemide induced similar depressor response. It is concluded that the vasodepressor effect of this peptide correlates with the levels of peripheral plasma renin activity and that the responses to this drug can be used as a guide for the selection of effective antihypertensive drugs.

ang II antagonist; 1-Sar-8-Ile-Ang II; peripheral plasma renin activity; selection of antihypertensive drugs

Specific competitive antagonists of angiotensin II, angiotensin II analogues, have been developed to study the renin angiotensin system in man and experimental animals (Sweet et al. 1973; Davis et al. 1974).

An antagonist of angiotensin II has been used for detecting hyperactivity of renin-angiotensin system in hypertension (Brunner et al. 1973; Streeton et al. 1975). However, clinical studies utilizing angiotensin II antagonist have yielded conflicting results (Donker and Leenan 1974; Pettinger and Mitchell 1975; Marks et al. 1975; Geyskes et al. 1976).

Two projects of human studies have hitherto been performed with regard to depressor effects of angiotensin II antagonist. The first is an attempt to detect the patients with renovascular hypertension. The second is a trial to determine how to treat the patient, in other words, how to select effective antihypertensive drugs.

Received for publication, January 14, 1977.
drugs and how to predict surgical curability in renovascular hypertension. Furthermore, it is suggested that angiotensin II antagonist is an excellent therapeutic agent for the hypertensive crisis of malignant hypertension. Our previous study showed that 1-Sar-8-Ile-Angiotensin II reduced blood pressure in the patients with high plasma renin activity, especially in malignant hypertension.

We will report here that administration of an effective antagonist of angiotensin II, 1-Sar-8-Ile-Angiotensin II, serves as a reliable screening test to detect the degree of renin dependency in each hypertensive patient.

**Patients and Methods**

Eighteen patients with advanced or malignant hypertension were included in this study. They consisted of 12 cases of essential hypertension, 2 of systemic lupus erythematosus, and 4 of chronic glomerulonephritis. Their ages ranged from 15 to 50 years. Control systolic blood pressures varied from 172 to 241 mmHg and the diastolic blood pressures from 130 to 152 mmHg (Table 1).

**Table 1. The effective antihypertensive drugs in responders and non-responders**  
(total of 18 cases with advanced hypertension)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Blood pressure (mmHg)</th>
<th>ocular fundi</th>
<th>GFR (ml/min)</th>
<th>PRA (ng/ml)</th>
<th>1-Sar-8-Ile-Ang II</th>
<th>Propranolol (P)</th>
<th>Furosemide (F)</th>
<th>P+F</th>
<th>P+F</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>F</td>
<td>210/140</td>
<td>IV</td>
<td>4.5</td>
<td>28</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>M</td>
<td>220/130</td>
<td>III</td>
<td>32.0</td>
<td>76</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>M</td>
<td>218/132</td>
<td>IV</td>
<td>6.1</td>
<td>129</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>M</td>
<td>240/140</td>
<td>IV</td>
<td>15.0</td>
<td>32</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>M</td>
<td>198/130</td>
<td>IV</td>
<td>16.3</td>
<td>74</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>M</td>
<td>230/140</td>
<td>IV</td>
<td>29.3</td>
<td>38</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>F</td>
<td>230/152</td>
<td>IV</td>
<td>40.0</td>
<td>32</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>M</td>
<td>172/130</td>
<td>III</td>
<td>57.0</td>
<td>62</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>M</td>
<td>208/138</td>
<td>IV</td>
<td>29.6</td>
<td>240</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>M</td>
<td>198/136</td>
<td>I</td>
<td>93.8</td>
<td>60</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>M</td>
<td>230/150</td>
<td>IV</td>
<td>5.3</td>
<td>88</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>M</td>
<td>220/150</td>
<td>IV</td>
<td>25.3</td>
<td>96</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>M</td>
<td>192/132</td>
<td>III</td>
<td>22.0</td>
<td>26</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>31</td>
<td>M</td>
<td>190/130</td>
<td>III</td>
<td>19.0</td>
<td>9.6</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>M</td>
<td>204/140</td>
<td>III</td>
<td>56.0</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>F</td>
<td>216/148</td>
<td>III</td>
<td>15.0</td>
<td>10.2</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>50</td>
<td>F</td>
<td>250/130</td>
<td>I</td>
<td>42.2</td>
<td>14.4</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>30</td>
<td>F</td>
<td>208/130</td>
<td>II</td>
<td>46.2</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>#</td>
</tr>
</tbody>
</table>

(++) = very effective, (+) = effective, (-) = not effective, O = other antihypertensive drugs.

The diagnosis of essential hypertension has been made by physical and laboratory examinations, intravenous pyelography, radioisotope renography, renoscintigraphy, and determination of plasma 11-OHCS, plasma renin activity, plasma aldosterone, urinary catecholamines, and vanillyl mandelic acid. The diagnosis of systemic lupus erythematosus was made according to American Rheumatism Association's criteria, and chronic glomerulonephritis was diagnosed by biopsy of the kidney.

Every antihypertensive medication had been discontinued at least 24 hr before the study except Cases 4, 5, 9, 11 and 12, who were on antihypertensive medicines, furosemide, reserpine and hydralazine. Two patients with systemic lupus erythematosus were taking prednisolone. Ad lib intake of sodium (approximately 200 mEq per day or above) had
been allowed.

Angiotensin II antagonist, 1-Sar-8-Ile-Angiotensin II, was prepared as an injectable aqueous solution (Daichi Pharmaceutical Co., Tokyo). This solution was diluted in physiologic saline to a concentration of 10 μg/ml and infused by means of an infusion pump which had been adjusted to keep the infusion rate at 100, 200, 400, 800 and 1200 ng/kg/min. The blood pressures were monitored at 5-min intervals using a sphygmomanometer.

Measurements of plasma renin activity were carried out on samples of peripheral vein blood obtained before and during the infusion of this peptide using the radioimmunoassay of angiotensin I (Abe et al. 1972). One ml of plasma was incubated at 37°C and pH 5.5 for 6 hr with disodium ethylene diamine tetraacetic acid (EDTA) and diisopropyl fluorophosphate (DFP). The sample was then diluted tenfold with physiologic saline, and heated in a boiling water bath for 5 min. After centrifugation, angiotensin I in the supernatant was assayed radioimmunologically. The normal resting levels of plasma renin activity were between 5 and 30 ng/ml.

**RESULTS**

**Correlation between plasma renin activity and initial mean blood pressure**

Preinfusion levels of plasma renin activity were from 9.6 to 240 ng/ml and mean blood pressure ranged from 144 to 178 mmHg. Fig. 1 shows that there was no statistically significant correlation between plasma renin activity and mean blood pressure.

![Fig. 1. Correlation between plasma renin activity and initial mean blood pressure in 18 hypertensive patients.](image)

**Effect of 1-Sar-8-Ile-Angiotensin II on blood pressure**

The blood pressure responses to 1-Sar-8-Ile-Angiotensin II varied widely from a mild elevation to a marked fall. The 18 patients were classified into two groups, responders (12 patients) and non-responders (6 patients), according to the response in blood pressure. They were judged as responders when the fall in diastolic blood pressure was 10 mmHg or greater. Most patients in either group exhibited a transient pressor effect immediately after the infusion of this peptide. In the responder group, the blood pressure returned to preinfusion levels in 3–5 min and began to decline thereafter. But in the non-responder group, this
peptide showed a moderate pressor effect throughout the infusion. The average depressor effects for 12 responders were 44.8±5.3 (mean±S.E.) mmHg in systolic and 27.6±3.3 mmHg in diastolic. The greatest depressor response was 90 mmHg systolic and 69 mmHg diastolic in a patient whose preinfusion level of blood pressure was 208/138 mmHg. The least depressor response was 20 mmHg systolic and 14 mmHg diastolic in a patient whose preinfusion level of blood pressure was 196/130 mmHg.

The 6 patients classified as non-responders showed a mild pressor reaction during the infusion. Average pressor response was 14.4±10.2 mmHg systolic and 12.8±3.7 mmHg diastolic. One patient showed a slight depressor response of 14 mmHg systolic and 8 mmHg diastolic, his blood pressure being unstable during the infusion.

Ten of 12 responders had advanced or malignant hypertension. The remaining 2 responders had hypertension due to systemic lupus erythematosus. Four of 6 non-responders had hypertension due to chronic glomerulonephritis. The remaining 2 non-responders had essential hypertension in an advanced stage.

Between the two groups, there were no significant differences with regard to age, sex and severity of hypertension. Among the 12 responders, plasma renin activity was elevated in 11 and normal in 1. All 6 non-responders had normal plasma renin activity. The mean plasma renin activity in the responders was 78.1 ±16.1 ng/ml and in the non-responders 16.9±3.0 ng/ml. The difference was statistically significant. Fig. 2 shows the correlation between the infusion rates of this peptide required to cause 10 mmHg fall in diastolic blood pressure and the

![Fig. 2. Relationship between plasma renin activity and the doses of angiotensin II antagonist required to cause a drop of 10 mmHg of diastolic blood pressure in the responders.](image-url)
levels of peripheral plasma renin activity. From the figure, it is obvious that the effective dose for patients with high plasma renin activity is smaller than that for those with normal plasma renin activity. The changes in mean blood pressure for all 18 patients during 1-Sar-8-Ile-Angiotensin II infusion showed a significant correlation with the level of peripheral plasma renin activity (r=0.5652, p<0.02) (Fig. 3). The line crosses the X axis at a plasma renin activity of 30 ng/ml, the upper limit of normal value. This fact proves that all hypertensive patients with elevated plasma renin activity respond to 1-Sar-8-Ile-Angiotensin II infusion by a fall in mean blood pressure.

Retrospective studies on the effects of antihypertensive drugs including propranolol and furosemide

The retrospective study was undertaken to examine the effectiveness of antihypertensive drugs in 12 responders and 6 non-responders within 24 months after the infusion test of 1-Sar-8-Ile-Angiotensin II.

Fifteen patients (12 responders and 3 non-responders) were treated with propranolol alone in doses of 30 to 360 mg/day. In 12 responders, propranolol reduced blood pressure to near normal, but not completely normal. While in 3 non-responders propranolol did not reduce the blood pressure at all.

Six patients (2 responders and 4 non-responders) were treated with furosemide alone in doses of 40 to 360 mg/day. Furosemide reduced blood pressure in 4 non-responders, the pressure was normalized in 2 of them. In 2 responders, furosemide did not show any antihypertensive effect.

A combination therapy of antihypertensive drugs including propranolol and furosemide reduced blood pressure to normal in all non-responders, while the normalization was attained in only 4 out of 12 in responders.
DISCUSSION

It has been repeatedly reported that depressor effects of 1-Sar-8-Ile-Angiotensin II or 1-Sar-8-Ala-Angiotensin II are correlated both with renal ischemia and renin levels in the peripheral blood. Therefore, the competitive inhibition of angiotensin II seems to be useful to prove the dependency of hypertension on the renin angiotensin system and to evaluate the pathophysiological state of hypertensive patients. But our previous data showed that 1-Sar-8-Ile-Angiotensin II induced an elevation of blood pressure in some patients with renovascular hypertension with normal peripheral plasma renin levels under ad lib intake of sodium (200 to 350 mEq of sodium per day), in whom vascular reconstruction or extirpation of the affected kidney performed later led to complete normalization of the blood pressure. We therefore consider that circulating angiotensin II was not directly involved in the maintenance of high blood pressure in human chronic renovascular hypertension on an ordinary diet (Yasujima et al. 1975).

The antagonistic action of 1-Sar-8-Ile-Angiotensin II has been examined further in the present study. The fall in blood pressure during infusion of this peptide showed a significant correlation with the level of peripheral plasma renin activity (Fig. 3). In the responders, an excess of circulating angiotensin II is involved in the maintenance of high blood pressure. Furthermore the regression line crossed the X axis at a plasma renin activity of about 30 ng/ml, the upper limit of values obtained in normal subjects. Among the 6 non-responders to this peptide infusion, all patients had normal peripheral plasma renin activity. This peptide induced a significant rise in blood pressure when it was infused into them. The degree of elevation in blood pressure showed a negative correlation with levels of peripheral plasma renin activity. It seems reasonable to conclude, therefore, that the infusion of 1-Sar-8-Ile-Angiotensin II is very useful for screening the patients with high levels of peripheral plasma renin activity.

Recently, a new approach for antihypertensive therapy has been tried based on the observations that patients with a high renin activity respond to renin-suppressing drugs like propranolol (Bühler et al. 1972) whereas those with a low renin activity do not, responding instead to diuretic agents. The use of this peptide gives much information about the role of renin in causing the hypertensive state. In the present retrospective study, propranolol alone lowered blood pressure to some extent but not to normal range in all patients of responder group. While in the non-responder group, propranolol did not reduce blood pressure at all, but furosemide or combination of propranolol with furosemide lowered blood pressure to normal range. These results show that blood pressure responses to various kinds of antihypertensive drugs can be predicted according to the response to this peptide infusion. The infusion test is simple and excellent compared with the measurements of plasma renin activity.

Streeton et al. (1975) reported that angiotensin II antagonist provided effective means of recognizing angiotensinogenic hypertension and propranolol reduced blood pressure in responder group.
Laragh (1975) commented that the pharmacologic response to the angiotensin II antagonist adds evidence to the concept that two pressor mechanism, vasoconstrictors and volume factors, are involved to a varying extent in all high blood pressure situations.

In conclusion, it may be said that 1-Sar-8-Ile-Angiotensin II is a valuable means of identifying the relative contribution of vasoconstrictors and volume factors in individual hypertensive patients, in the interests of simpler and more specific long-term therapy.

Acknowledgment

We are deeply indebted to Daiichi Pharmaceutical Co., Tokyo, for the supply of 1-Sar-8-Ile-Angiotensin II.

This work was supported by the grants (No. 157229) from the Ministry of Education and for Specific Diseases from the Ministry of Health and Welfare of Japan.

References