Hemodynamic and Antihypertensive Effects of the New Oral Angiotensin-Converting-Enzyme Inhibitor MK-421 (Enalapril)

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SUMMARY The antihypertensive, hemodynamic, and humoral effects of the new converting-enzyme inhibitor enalapril (MK-421) were assessed by sequential studies during 3 months of uninterrupted treatment (20 mg twice daily) in 10 hypertensive patients. Six achieved good blood pressure (mean arterial pressure) control with enalapril alone (from 126 ± 7.0 mm Hg pretreatment to 105 ± 1.6 mm Hg at 3 months, p < 0.05). The other four required the addition of diuretics (hydrochlorothiazide 25 mg orally twice daily) at different stages of follow-up, with resultant blood pressure control (128 ± 9.6 mm Hg pretreatment to 113 ± 1.9 mm Hg at 2 months after the addition of diuretics). Neither the acute nor long-term blood pressure response could be predicted from the pretreatment levels of plasma renin activity. The blood pressure reduction during enalapril therapy was characterized by a decrease in total peripheral resistance (53 ± 2.5 U·M² pretreatment to 38 ± 3.0 U·M² at 3 months, p < 0.05) with no significant change in cardiac output or heart rate. This lack of reflex tachycardia could not be ascribed to baroceptor dysfunction since the response to head-up tilt (the increase in diastolic blood pressure, in heart rate, and in plasma catecholamines) was normal and not significantly different from pretreatment response. Average blood volume did not change (91% ± 4.3% of normal in the pretreatment period to 93% ± 2.9% after 3 months of therapy, p = NS) despite the significant lowering of arterial pressure with enalapril alone (n = 6). This could have been possibly related to the reduction in plasma aldosterone (12.6 ± 2.3 to 8 ± 0.9 ng/dl, p < 9.95) induced by treatment. In conclusion, the hemodynamic consequences of blood pressure reduction by enalapril were similar to those produced by other converting-enzyme inhibitors and angiotensin II antagonists. These findings suggest that the hemodynamic effects of enalapril were related to interference with the generation of angiotensin II rather than a direct action of the drug.

(Hypertension 6: 167-174, 1984)

KEY WORDS • hypertension • cardiac output • blood volume • renin-angiotensin • aldosterone

ENALAPRIL maleate (MK-421) is a newly introduced orally active antihypertensive agent designed to inhibit angiotensin-converting enzyme. Its structure is, however, sufficiently different from that of the other oral converting-enzyme inhibitor, captopril, to warrant close examination as to whether its effects are similar. If the effects of both drugs were mediated by exactly the same mechanism, they would be expected to produce the same hemodynamic changes in association with blood pressure reduction. On the other hand, significant differences might raise the question of specificity or potency of effect related to the composition of the drug.

Previous studies have established the efficacy of enalapril in lowering angiotensin II levels and blood pressure, but have not fully characterized the systemic hemodynamic events that accompany blood pressure response. The present investigation was undertaken to define more precisely the sequence of hemodynamic changes occurring with enalapril in hypertensive patients. Noninvasive radionuclide hemodynamic measurements (Stewart-Hamilton formula for cardiac output and centroid method for pulmonary mean transit time) allowed repeated observations at intervals of 6 hours, 4 days, 1 month, and 3 months of therapy. Our results indicated that blood pressure reduction during enalapril therapy was related mostly to reduction of peripheral resistance. Further, acquired resistance to its antihypertensive effects occurred in three subjects.
Despite maintained inhibition of angiotensin-converting enzyme; restoration of blood pressure control in these patients by the addition of diuretics was associated with a reduction in total peripheral resistance without significant changes in blood volume or cardiac output.

Material and Methods

Patients

Ten patients with essential hypertension, all Caucasians, were included in this study (two women and eight men). Their age varied from 33 to 65 years. All previous medications (hydrochlorothiazide, beta-blockers, and vasodilators) were discontinued at least 2 weeks before the start of the present study (or until stabilization of body weight and blood pressure levels).

Protocol

The trial was initiated by placebo treatment (one tablet twice daily for 3 days) while the patients were in the hospital and after they were equilibrated on a constant diet containing 100 mEq sodium and 80 mEq potassium daily. The first hemodynamic study was performed during placebo treatment 6 hours after the last pill. The following morning these studies were repeated 6 hours after the first dose of active MK-421 (20 mg). The 6-hour interval and dosage were chosen because preliminary dose-response studies in five patients showed that this was the period for the maximal sustained antihypertensive effect of the drug.

All hemodynamic measurements were performed in the morning (8–9 am) after an overnight fast except for water; all hemodynamic studies were performed in our laboratory at the same time of day and under the same conditions to allow comparison among patients and subjects with normal values. Similarly, blood samples for renin, catecholamines, and aldosterone were obtained from study subjects and normal volunteers under the same circumstances to avoid a possible confounding effect of circadian changes.

On the day of each hemodynamic measurement (active or placebo), blood pressure was recorded repeatedly before the dose and every 2 hours thereafter for 12 hours; in addition, blood pressure was measured frequently during the hemodynamic test (10–12 measurements), and the average was used to derive other hemodynamic indices. After the initial active dose, maintenance therapy was started with 20 mg twice a day, and the hemodynamic tests were repeated on the 4th day of active therapy, again 6 hours after the last dose. The patients were then discharged from the hospital; hemodynamic tests were repeated at the end of Months 1 and 3 in patients whose blood pressures were less than 140/90 mm Hg. In patients whose blood pressure rose > 140/90 mm Hg at any time during follow-up, a hemodynamic test was repeated just before adding diuretics (hydrochlorothiazide 25 mg twice daily); studies were repeated in these patients at 5 days and 2 months after the addition of the thiazide.

Methodology

After 30 minutes of supine rest, blood volume was measured using radioiodinated human serum albumin (RISA), as previously described, and expressed as a percentage of normal for the laboratory to allow inclusion of both males and females. Blood samples were also obtained for determination of the drug levels (MK-421), of circulating angiotensin converting-enzyme activity (ACE), and of circulating aldosterone. Cardiac output was measured in duplicate by noninvasive radionuclide first-pass technique (Stewart-Hamilton formula) using 99m Tc-HSA as previously described in detail; 4, 5 the method was repeatedly validated in our laboratory. 4, 6 Ejection fraction (gated blood pool technique) was then obtained making use of the same circulating radioisotope dose. Blood pressure (cuff method) and heart rate (LII EKG) were recorded repeatedly during the test, and average values were used for calculation of derived indices by classical formulas. 1

Orthostatic responses were studied by head-up tilt test (60° for 10 minutes) because earlier studies with other converting-enzyme inhibitors have raised some concerns regarding orthostatic hypotension with converting-enzyme inhibition 1 and because heart rate changes were nonsignificant despite the reduction in blood pressure. Tilt tests were done immediately following each hemodynamic study; blood pressure (cuff method), heart rate (lead II EKG), and blood samples for plasma catecholamines (norepinephrine + epinephrine) were obtained in the supine position and again after 10 minutes of head-up tilt at 60°.

Analytical Procedures

Plasma renin activity was measured using radioimmunoassay of angiotensin I liberated after 1 hour of incubation at pH 7.4. 10 Plasma aldosterone was measured by radioimmunoassay as previously described in detail; 10 plasma catecholamines were determined by radioenzymatic assay. 11 Normal values for our laboratory for the three assays ranged from 0.6 to 1.6 ng/ml, 0 to 15 ng/dl, and 250 to 650 ng/liter, respectively. Angiotensin converting-enzyme activity was determined by hydrolysis of a synthetic tripeptide after the method of Cushman and Cheung. 12 Blood levels of MK-421 were determined by radioimmunoassay. 13

Statistical Analysis

Data are reported as means ± 1 standard error (SE). Results were assessed by analysis of variance to evaluate changes occurring in the same patients having repeated measurements and by t test for differences between groups. 14 Correlation coefficients were calculated by standard methods. The probability factor was considered significant if p < 0.05. Statistical analysis was performed with the help of the PROPHET system, a national computer resource supported by the Biotechnology Resources Program, Division of Research Resources, National Institutes of Health, Bethesda, Maryland.
Results

Clinical Course of Blood Pressure Response

In response to the first dose, nine patients exhibited a reduction in mean arterial pressure (MAP) from 125 ± 5 to 103 ± 3.2 mm Hg (p < 0.01). Blood pressure reduction was maintained in these nine patients with continued oral therapy for 4 days (102 ± 2.5 mm Hg, p < 0.01 from control). With further follow-up, however, three of the nine patients (late nonresponders) had a gradual blood pressure rise (> 10 mm Hg MAP), two after 1 month and one after 3 months of therapy.

In the tenth patient, MAP was not reduced (129 mm Hg before, 121 mm Hg 6 hours after the initial 20 mg MK-421, and 127 mm Hg after 5 days of maintenance therapy). This patient, as well as the three late nonresponders, showed a reduction in blood pressure when hydrochlorothiazide (25 mg twice daily) was added to the converting-enzyme inhibitor (121 ± 2.7 mm Hg before and 113 ± 1.9 mm Hg 2 months after addition of the diuretic).

In summary, six of 10 patients could maintain adequate blood pressure control for 3 months, whereas the other four required the addition of a diuretic at some point during that same period.

Blood Levels of MK-421 and Humoral Changes

Table 1 shows the serum levels of the active metabolite of enalapril determined at the time of the hemodynamic studies. Relatively stable steady-state levels were apparently achieved by the 4th day of treatment; the levels obtained in all patients were comparable regardless of their pressure response.

Within 6 hours of the first dose, plasma renin activity (PRA) rose while plasma aldosterone fell. These changes were sustained throughout the period of follow-up (Table 2) as was the profound suppression of measurable serum angiotensin converting-enzyme activity to barely detectable levels. These findings were taken to indicate effective oral absorption of the drug and adequate inhibition of circulating converting enzyme. A correlation was found between pretreatment PRA and the change in MAP. However, the statistical significance of that correlation was derived from one data point, the patient with a PRA of 35 ng/ml/hr (Figure 1). Including this patient, the r value of the correlation attained 0.8; however, without her, the r value fell to insignificant levels (r = 0.07 for the blood pressure change 6 hours after the first dose, r = 0.48 after 4 days of treatment, and r = 0.19 when calculated after 1 month of therapy, p = NS for all).

Hemodynamic Response

First Dose Effect

Hemodynamic studies were obtained 6 hours after the initial dose in only nine of 10 patients (including the nonresponder). The pattern of hemodynamic response in these nine patients is summarized in Figure 2. In the eight “responders,” both MAP and total peripheral resistance were reduced (from 121 ± 3.0 to 104 ± 3.3 mm Hg and from 57 ± 1.9 to 47 ± 1.68 U·M² respectively, p < 0.01 for both) while cardiac output and heart rate did not change significantly. The ratio of cardiopulmonary volume to total blood volume remained unchanged (15.9% to 16.4%). Responses to head-up tilt were normal (ΔDBP = +6 ± 2 mm Hg, ΔHR = +17 ± 3 bpm, Δ plasma NE = +202 ± 24 ng/liter, p < 0.01 for all). These responses during active enalapril therapy were not significantly different from the responses to tilt during the placebo period.

Long-Term Studies

Hemodynamic studies were obtained during prolonged follow-up in all 10 patients. These fell into the following groups: 1) six patients who had responded initially (R) and maintained this response during the 3 months of therapy (R-R); 2) three patients who had...
Correlation between pretreatment plasma renin activity (PRA) and the change in mean arterial pressure (ΔMAP) after 4 days of maintenance therapy with MK-421 (20 mg twice daily). ■ represents one patient with a pretreatment PRA of 35 ng/ml/hr; the statistical significance of the correlation (0.80) was derived from this data point.

Figure 1. Six hours after the first 20 mg dose of MK-421, only one patient (○—○) did not show significant change in blood pressure (MAP). In the other eight patients, the reduction in MAP was associated with a decrease in total peripheral resistance (TPR) while cardiac index (CI) and heart rate (HR) did not change significantly. In the tenth patient, hemodynamic measurements could not be obtained 6 hours after the first dose.

responded initially, but showed subsequently a gradual rise in pressure (R-NR) requiring the addition of a diuretic after 1 month in two and after 3 months in the third; and 3) one patient whose blood pressure was not reduced in response to the first dose and had to be given hydrochlorothiazide from the 5th day of follow-up.

The hemodynamic data obtained in the six responders (R-R) are summarized in Table 2; blood pressure reduction was associated with a sustained significant decrease in total peripheral resistance. Cardiac output was essentially unchanged in three patients (−180 to +170 ml/min/M²), but increased in the other three (+430 to +1370 ml/min/M²) so that the average change with treatment for the group was not significant. Heart rate was not significantly increased; neither mean transit time nor ejection fraction (which were normal to start with) changed significantly during the 3 months of follow-up (Table 2).

In the other three patients (R-NR), cardiac output and total blood volume increased to above pretreatment levels, when blood pressure rose after an initial reduction. However, this subsequent rise of pressure could not be ascribed to the increase in cardiac output since a similar increase in flow was observed in some patients (three of six) who maintained their initial pressure response (Figure 3). In this respect, changes in cardiac output during treatment correlated significantly in all patients with the changes in blood volume ($r = 0.72, p < 0.05$) (Figure 4), but the determinants of blood volume expansion in these patients could not be identified. In fact, plasma aldosterone was equally re-
HEMODYNAMIC EFFECTS OF MK-421/Fouad et al.

During long-term treatment, blood pressure (MAP) rose after initial control in three patients (O), after 1 month of maintained treatment in two, and after 2 months of maintained treatment in the third patient. These three patients were therefore considered "late nonresponders." This rise in MAP was related to an increase in cardiac index (CI), whereas total peripheral resistance (TPR) remained reduced. They are compared to three other patients (*) in whom blood pressure control was maintained; the increase in cardiac index was associated with a further reduction of TPR. Changes in ACE and plasma aldosterone were similar in the two groups. C = pre-MK-421; 1 = time of best blood pressure response; 2 = time of no response (O) or Month 3 (*).

The secondary rise of blood pressure in these patients could not be related to other factors such as escape from blockade of converting enzyme (PRA remained elevated and circulating ACE markedly suppressed) (Figure 3), or increased sympathetic nervous system activity, or increased aldosterone (aldosterone plasma levels remained significantly reduced below control) (Figure 3). In addition, enalapril blood levels in these patients were not significantly different from those of responders (Table 1).

Diuretics, hydrochlorothiazide 25 mg twice daily, were added to enalapril to either obtain (one patient) or restore (three patients) adequate blood pressure control. In all, the reduction in arterial pressure (which occurred within 5 days in three, but was delayed in the fourth) was associated with a reduction in peripheral resistance while cardiac output and blood volume were essentially unchanged (Figure 5).

In response to tilt, diastolic blood pressure, heart rate, and plasma norepinephrine increased to a level comparable to those observed during placebo therapy. Altogether, adrenergic responses did not appear to be altered by enalapril; differences in blood pressure response among patients could not be explained by differences in adrenergic activity (Table 3). The same results were obtained in those patients who required diuretics in addition to MK-421.

Side Effects

Only two patients developed a temporary (2–3 weeks) complaint of loose stools, which disappeared spontaneously and did not require change in dosage. No skin rash, decrease in white cell count, or other side effects were observed over this period of follow-up. No orthostatic hypotension was observed in patients on enalapril alone or in combination with diuretics either during head-up passive tilt or from standing blood pressure measurements obtained during office visits.

Discussion

Enalapril is a newly developed inhibitor of angiotensin-converting enzyme. Because it requires hydrolysis to an active form, its onset of action takes several hours

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\Delta CI (L/min) = 3.0 \quad 2.5 \quad 2.0 \quad 1.5 \quad 1.0 \quad 0.5 \quad 0.5 \quad -0.5 \quad -1.0
\]

\[
\Delta TBV (%N) = 10 \quad 15 \quad 20 \quad 25 \quad 30
\]

\[
r = 0.72 \quad p < 0.05
\]

\(\bullet = \text{responders}; \quad O = \text{delayed nonresponders}; \quad * = \text{initial nonresponder.}\)
after oral administration. The data obtained in our patients showed that ACE was reduced to almost undetectable levels as early as 6 hours after the first dose and remained low during prolonged therapy. The PRA increased in all patients. Both findings (ACE and PRA levels) could therefore be used as an index of drug absorption and patient compliance. There was no correlation in our patients, however, between these changes and blood pressure response; nor could the secondary rise of pressure during treatment (n = 3) be related to escape from the effective inhibition of circulating converting enzyme by enalapril (Figure 3).

Hemodynamically, the initial blood pressure reduction (6 hours after the first dose) was due to a reduction in total peripheral resistance without significant alterations in heart rate or cardiac output, a pattern fundamentally identical to that induced by angiotensin antagonists that do not stimulate catecholamine release from adrenal medulla15,16 and by captopril,17-20 a structurally different angiotensin converting-enzyme inhibitor. This lack of change in heart rate was also reported during long-term treatment with these agents.15-20 Its cause is not yet clear; data from this study suggested that it could not be related to interference with sympathetic activity21,22 since the response of diastolic blood pressure, heart rate, and plasma catecholamines to postural stimuli (head-up tilt) remained normal.23,24 Since vasodilators that have additional venodilating effects are not known to produce reflex sympathetic stimulation and therefore do not induce tachycardia,25 the effects of enalapril on the cardiopulmonary volume to total blood volume ratio (CPV/TBV) were studied. This ratio reflects the distribution of blood volume between central and peripheral circulation26 and could be used as an index of venous tone. The lack of significant alteration in this ratio thus suggested that enalapril has no venodilating effects in hypertensive patients. This is not surprising since the effects of angiotensin II on venous tone have not been proven.27

In three patients, blood pressure gradually rose after initial reduction despite the continuation of the same dose. Cardiac output and blood volume had increased compared to their levels when blood pressure was reduced. It would have been plausible to deduce that the escape from initial blood pressure control was related to blood volume expansion, as was previously described with other vasodilators.28 However, three of the patients who maintained blood pressure reduction (R-R) also showed blood volume expansion and cardiac output increase. Further, in that regard, the restoration of blood pressure control by the addition of hydrochlorothiazide in the late nonresponders was achieved via reduction of peripheral resistance (Figure 5), while cardiac output and blood volume were not significantly changed. We have observed the same pattern of response to salt restriction in hypertensive patients treated with captopril.29 The early (5 days) reduction of resistance in that circumstance contrasts with the pattern of response in untreated hypertensive patients subjected to similar salt restriction or diuretic treatment.31 The latter's response was characterized by an early reduction of cardiac output while peripheral resistance increased. It is possible, therefore, that the early reduction of total peripheral resistance achieved by adding diuretics to captopril or enalapril was related to simultaneous converting-enzyme inhibition. In

**Table 3. Response to Head-Up Tilt in Hypertensive Patients Treated with MK-421 (20 mg Twice Daily)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 9)</th>
<th>6 hrs (n = 9)</th>
<th>4 days (n = 9)</th>
<th>30 days (n = 8)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔDBP (mm Hg)</td>
<td>+2 ± 3</td>
<td>+6 ± 2</td>
<td>+5 ± 2</td>
<td>+5 ± 3</td>
</tr>
<tr>
<td>Δplasma NE (ng/liter)</td>
<td>+178 ± 41</td>
<td>+202 ± 24</td>
<td>+163 ± 73</td>
<td>+267 ± 54</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>+14 ± 2</td>
<td>+17 ± 3</td>
<td>+18 ± 2</td>
<td>+14 ± 2</td>
</tr>
</tbody>
</table>

*One patient (not included) was taking diuretics. NE = norepinephrine; HR = heart rate, DBP = diastolic blood pressure.
summary, the secondary rise of pressure during treatment was not an inevitable result of volume expansion. Its mechanism was more complex and linked to the possibility of accommodating increases in blood volume and cardiac output by appropriate variations in peripheral resistance.

There was no correlation in our patients between pretreatment PRA levels and either the early (6 hours) or late (4 days and 1 month) blood pressure response to enalapril, although they showed a wide range of pretreatment PRA (0.7 to 5.0 ng/ml/hr). The correlation obtained by the inclusion of only one patient with very high PRA level (35 ng/ml/hr) was considered to represent a mathematical rather than a biologic significance (Figure 1). This lack of correlation persisted when tested at the time of maximum blood pressure response irrespective of the duration of therapy. A similar independence of blood pressure response from pretreatment PRA was reported by Gavras et al. This finding is somewhat different from previous experience with captopril. Studies from most laboratories including our own and have demonstrated a highly significant correlation between baseline PRA and the early response to captopril. This correlation gradually diminished to statistical nonsignificance with maintained treatment in the experience of most but not all centers. This discrepancy between the two converting-enzyme inhibitors may reflect the operation of secondary mechanisms of blood pressure regulation that are recruited in response to interference with the generation of angiotensin II. Perhaps the relatively gradual onset of action during MK-421 administration allows these mechanisms to obscure the early relationship between PRA levels and the blood pressure effects of inhibition of the renin-angiotensin system. Alternatively, the small number of patients may have been insufficient to demonstrate this relationship.

In conclusion, enalapril proved to be an effective antihypertensive agent that lowered blood pressure by reducing peripheral resistance. The lack of associated tachycardia could add to its potential value as an unloading agent for the treatment of congestive heart failure. Many of its effects resembled those of captopril and other converting-enzyme inhibitors; this similarity suggests that the effects of both drugs were related to their inhibition of converting enzyme; since the two are structurally quite different from each other. Some additional features were observed: the slow onset of hemodynamic effect, the long duration of action, and the lack of correlation of even early blood pressure reduction with either ACE reduction or pretreatment PRA levels.

Acknowledgments

The authors thank Merck Sharp and Dohme, particularly Richard Davies, M.D., Ph.D., and John Irvin, M.D., Ph.D., for the free supply of MK-421 and for the analysis of blood levels of MK-421; Mary-Kay DePaul, R.N., Kathy Rojc, R.N., and Jay Cology, C.N.M.T., for technical assistance; and Aldona Raulinaitis for secretarial help.

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F M Fouad, R C Tarazi, E L Bravo and S C Textor

Hypertension. 1984;6:167-174
doi: 10.1161/01.HYP.6.2.167

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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