Endopeptidase 24.11 Inhibition by SCH 42495 in Essential Hypertension

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The detailed integrated renal, hormonal, and hemodynamic effects of acute (first dose) and established (4 days) inhibition of endopeptidase 24.11 by SCH 42495 (200 mg, every 12 hours) were documented in eight patients with essential hypertension in a double-blind, balanced random-order, crossover study. SCH 42495 suppressed plasma endopeptidase activity (>90%, \( P < .001 \)) for the duration of the dosing period. Initially, plasma atrial natriuretic factor levels increased markedly (+123%, \( P < .01 \)) and remained elevated, although to a lesser extent (+34%, \( P < .01 \)), with established enzyme inhibition. Cyclic guanosine monophosphate in both plasma and urine remained elevated throughout the treatment period. Significant augmentation of sodium excretion in excess of placebo values (96±27 mmol sodium, \( P < .001 \)) was established in the initial 24 hours of dosing but later became attenuated, with a mild antinatriuresis (\( P < .01 \)) in the latter 3 days of treatment. Blood pressure, heart rate, the renin-angiotensin-aldosterone system, and plasma norepinephrine levels were all initially (first dose) unchanged. With established enzyme inhibition (day 4), however, blood pressure was significantly lower (mean 24-hour values, 9.3±3/-3.8±1 mm Hg, \( P < .05 \) for both systolic and diastolic pressures) than matched placebo values, whereas heart rate was higher (2.7±1 beats per minute, \( P < .01 \)). Mean 24-hour values of plasma renin activity (+33%, \( P < .05 \)), aldosterone (+36%, \( P < .05 \)), and norepinephrine (+40%, \( P < .001 \)) were all clearly increased above placebo values with established enzyme inhibition. In summary, inhibition of endopeptidase 24.11 in essential hypertension leads to both acute and sustained increases in plasma atrial natriuretic factor and cyclic guanosine monophosphate, with an associated acute natriuresis. The renin-angiotensin-aldosterone and sympathetic nervous systems exhibit delayed activation, and these latter compensatory responses may limit the antihypertensive effect of endopeptidase inhibition. (Hypertension 1993;22:119-126)

KEY WORDS • membrane metalloendopeptidase • atrial natriuretic factor • renin-angiotensin system • catecholamines • natriuresis • blood pressure • hypertension, essential

The neutral metalloendopeptidase EC 3.4.24.11 (EC 24.11) initiates degradation of atrial natriuretic factor (ANF).1,2 This discovery has stimulated interest in specific inhibitors as potential therapeutic agents in hypertension.3-6 Because prolonged infusions of physiological doses of ANF in hypertensive humans and in animal models of hypertension reduce blood pressure7-9 and genetically engineered transgenic mice with an enhanced ANF productive capacity exhibit lower blood pressures than control animals,10 chronic increments in plasma and/or tissue concentrations of ANF induced by inhibition of EC 24.11 may offer a new means of lowering blood pressure.

Endopeptidase inhibition by a number of different inhibitors results in a hypotensive effect in several animal models of hypertension.11-13 In studies of normal volunteers, patients with heart failure, and patients with essential hypertension, single doses of inhibitor increase plasma ANF concentrations and induce several ANF-like end-organ effects.14-18 These include a natriuresis, increased plasma and urine concentrations of cyclic guanosine monophosphate (cGMP), and suppression of the renin-angiotensin-aldosterone system. Whereas single doses of inhibitor have little effect on blood pressure in normotensive or hypertensive humans,15-18 longer-term studies using three different endopeptidase inhibitors suggest that the blood pressure may be lowered significantly in hypertensive patients receiving orally active inhibitors administered for days or weeks.3,4,6

SCH 42495 is the oral prodrug ester of SCH 42354, a potent and selective inhibitor of EC 24.11. Preclinical studies in several animal species and models of hypertension have shown that SCH 42495 causes augmentation of plasma ANF concentrations and reduction in blood pressure.19-21

To date, there are no published data regarding the antihypertensive potential of SCH 42495 in patients with essential hypertension. Furthermore, there is a lack of detailed information on the evolution of renal, hormonal, and hemodynamic responses from the acute through the chronic phase of endopeptidase inhibition.
in such patients. We therefore performed a detailed study of the integrated effects of SCH 42495 administered over a period of 4 days to a group of patients with essential hypertension in a double-blind, placebo-controlled, crossover study.

**Methods**

The study protocol was approved by the Canterbury Area Health Board Ethics Committee, and all participants gave written informed consent. Eight white male patients with uncomplicated, mild to moderate essential hypertension underwent randomized, double-blind, crossover, placebo-controlled studies. The patients (38 to 65 years; median, 47 years; mean, 51.5 years; 65 to 91 kg; mean, 79.4 kg) received placebo or SCH 42495 (orally active inhibitor of EC 24.11, 200 mg twice daily) on separate occasions, each for 4 days. All patients were monitored before the studies for a minimum of 2 months while receiving no antihypertensive medication. Blood pressure measured by a single observer (A.M.R.) using standard mercury column sphygmomanometry was recorded repeatedly in all participants and consistently exceeded 140/90 mm Hg (10 minutes seated) on at least four consecutive occasions before entry into the study.

The experimental protocol is illustrated in Fig 1. Patients took a constant-sodium (150 mmol/d), constant-potassium (80 mmol/d), caffeine-free, and alcohol-free diet for 3 days before and throughout the treatment periods (total of 7 days for each study period). Placebo and active study periods were separated by an interval of 2 weeks. The patients were followed as outpatients from day 1 through 6 of diets. Dosing began on day 4 of diets, and capsules were taken every 12 hours at 10 AM and 10 PM. Serial 24-hour urine collections were obtained throughout the dietary period for measurements of urine volume and levels of sodium, potassium, creatinine, immunoreactive ANF, cGMP, cortisol, and aldosterone.

Before the first dose of placebo or SCH 42495 (see day 1, Fig 1), patients presented to the study facility at 8 AM, having consumed breakfast at 7 AM. They were weighed. A 21-gauge "butterfly" sampling needle was secured in a forearm vein. Blood samples were obtained after periods of supine and upright posture both before (9:30 and 10 AM) and after (3:30 and 4 PM) the first dose of SCH 42495 or placebo. The patients remained supine from 8 AM until 9:30 AM, at which time venous blood was sampled for measurements of plasma ANF, cGMP, plasma renin activity, angiotensin II, aldosterone, cortisol, catecholamines, and plasma neutral endopeptidase activity. Blood samples were collected into chilled tubes containing appropriate anticoagulants; the plasma was separated in a refrigerated centrifuge and stored at −20°C or −80°C (catecholamines) before assay by means of our established radioimmunoassay,22–26 high-performance liquid chromatography,27 and fluorescence techniques.28 The patients then sat upright for a further 30 minutes, and an additional blood sample was taken at 10 AM, followed immediately by the first dose of placebo or SCH 42495 (200 mg). Patients were quietly ambulant except for seated resting (15 minutes) measurements of blood pressure at 11:30 AM. At 3 PM, patients once again lay down, and another blood sample was obtained at 3:30 PM after half an hour in the supine position. Patients then sat upright for 30 minutes, and a blood sample was taken at 4 PM. Blood pressure and heart rate were recorded in duplicate by means of a semiauto-

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**Figure 1.** Diagram shows experimental protocol, indicating timing of diet, serial 24-hour (10 AM to 10 AM) and 6-hour (day 4) urine collections, outpatient observations (blood pressure [BP] and hormone measurements), dose times ( ), and inpatient monitoring with intra-arterial (i a) BP recordings. SCH 42495 and placebo study periods were separated by 2 weeks. Postural changes (seated and supine) are stated in text and indicated in Tables 2 and 3 and Fig 4.
mated Rose Box (Electronic Research and Development, Dunedin, New Zealand) at 8:30 AM, 9:30 AM, 10 AM, 11:30 AM, 3:30 PM, and 4 PM. Patients were then discharged home and instructed to continue taking medications at 10 AM and 10 PM daily over days 1 to 3 of dosing. On day 3 of dosing, procedures were repeated as for day 1 up to 9:30 AM only.

On day 4 (see Fig 1), patients presented to the study facility at 8 AM, having had breakfast at 7 AM. They were weighed, and an intravenous cannula was once again placed in a forearm vein for blood sampling. The nondominant brachial artery was cannulated under local anesthesia using the Seldinger technique for continuous ambulatory recording of intra-arterial pressure by the Oxford method. Patients remained supine from 8 AM until 9:30 AM, at which time blood (supine) was sampled for hormones (as above), after which they assumed the sitting position. From that point, patients stood for the first 15 minutes of each hour and remained seated for the latter 45 minutes of each hour until 9 PM, except for the period from 2 to 3:30 PM. During this period, patients underwent echocardiography and then remained supine from 3 to 3:30 PM for withdrawal of a further venous sample (supine) for measurement of plasma hormones. Snacks and meals were provided at 11 AM, 1:15 PM, and 6 PM. Patients were recumbent in bed from 9 PM to 8 AM, and blood sampling continued overnight (see Fig 2). Intra-arterial recording of blood pressure continued throughout day 4 until 10 AM on day 5.

Repeated blood samples for measurement of plasma vasoactive hormone concentrations were obtained at the times and in the postures indicated in Fig 2 and Tables 1 and 2. Split urine collections (for measurement of the variables listed for the preceding serial 24-hour urine collections) were obtained at 6-hour intervals. Estimates of glomerular filtration rate and effective renal plasma flow were obtained by inulin and \( p \)-aminohippuran clearance techniques. \( p \)-Aminohippuran and inulin infusions ran from 9 AM to 4 PM. When applicable, blood was sampled before patients stood to complete urine collections. At 10 AM on day 5, intravenous and arterial cannulas were removed, hemostasis was secured, and patients were discharged.

Data were analyzed by analysis of variance with repeated measures using program P2V of the BMDP package, with treatment (SCH 42495 or placebo), posture (when appropriate), and time as repeated-measures factors. When appropriate, mean values at specific time points were compared in a post hoc fashion by paired \( t \) test. Results are given as mean \( \pm \)SEM. A value of \( P \leq 0.05 \) was taken to indicate statistical significance.

**Results**

Studies were completed without major adverse events. A single patient experienced mild diarrhea for the first 36 hours of dosing with the active agent. Data collection was complete for all variables with the exception of plasma neutral endopeptidase activity, which was not available in one patient for technical reasons. Routine hematologic and plasma biochemical variables (hemoglobin, white cell count and differential, platelet count, plasma sodium, potassium, urea, creatinine, glucose, and liver function profile) and dipstick polyurinalysis were unchanged by SCH 42495.

Patients exhibited a decline in weight between days 1 and 4 of dosing with SCH 42495 (-1.2±0.2 kg) which exceeded that with placebo (-0.6±0.1 kg, \( P < 0.001 \)). SCH 42495 induced a striking initial excess excretion of 96±27 mmol sodium above time-matched placebo values (Fig 3, day 1 of treatment, \( P < 0.001 \)). On days 2, 3, and 4, however, a mild rebound antinatriuresis was observed, and at completion of day 4, overall excess sodium excretion had been reduced to 45±30 mmol. Excretion of immunoreactive ANF was also strikingly increased during the first day of dosing with SCH 42495 and remained somewhat above matched placebo values for the remainder of the study period (Fig 3, \( P < 0.001 \)). Similarly, urinary excretion of cGMP was higher throughout the treatment than the placebo phase (\( P < 0.001 \)). Excretion of aldosterone was initially unchanged but rose above matched placebo values for days 2, 3, and 4 of dosing (Fig 3, \( P < 0.05 \)). Urine volume was greater on the first day of SCH 42495 compared with placebo (1845±187 versus 1312±60 mL, \( P < 0.05 \)).

**Fig 2.** Line graphs show plasma endopeptidase activity (EC24.11), atrial natriuretic factor (ANF) concentrations, plasma renin activity (PRA), and norepinephrine (NE) on day 1 and days 4 to 5 of treatment with SCH 42495 (\( \bullet \)) and placebo (\( \circ \)). Arrows indicate dose times. Posture is indicated diagrammatically in the bottom panel. All four variables were significantly altered by endopeptidase inhibition (see text).
whereas the 24-hour excretion of potassium, cortisol, and creatinine were unaffected (data not shown). Urine variables measured during the split serial 6-hour urine collection periods from 10 AM on day 4 of dosing to 10 AM on day 5 revealed a mild but significant antinatriuresis (P<.05) with continuing significant stimulation of urinary cGMP and aldosterone (P<.01 for both) but no continuing effect on urine volume, potassium, or creatinine excretion (data not shown).

Table 2. Supine Hormones

<table>
<thead>
<tr>
<th>Plasma cGMP and hormones</th>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9:30 AM</td>
<td>3:30 PM</td>
<td>9:30 AM</td>
<td>3:30 PM</td>
</tr>
<tr>
<td>ANF (pmol/L)*</td>
<td>A</td>
<td>15±2</td>
<td>27±5</td>
<td>22±5</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>16±3</td>
<td>15±3</td>
<td>16±3</td>
</tr>
<tr>
<td>cGMP (pmol/mL)†</td>
<td>A</td>
<td>...</td>
<td>8.6±2</td>
<td>7.0±1.1</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>...</td>
<td>4.7±1.2</td>
<td>5.6±1.5</td>
</tr>
<tr>
<td>PRA (nmol/L/h)‡</td>
<td>A</td>
<td>0.6±0.2</td>
<td>0.6±0.1</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.8±0.2</td>
<td>0.8±0.1</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Ang II (pmol/L)</td>
<td>A</td>
<td>18±9</td>
<td>11±5</td>
<td>20±6</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>11±2</td>
<td>8±2</td>
<td>10±2</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)‡</td>
<td>A</td>
<td>219±35</td>
<td>121±20</td>
<td>298±51</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>176±22</td>
<td>132±23</td>
<td>170±17</td>
</tr>
<tr>
<td>Norepinephrine (pg/mL)‡</td>
<td>A</td>
<td>196±27</td>
<td>215±19</td>
<td>267±41</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>199±30</td>
<td>196±34</td>
<td>175±19</td>
</tr>
<tr>
<td>Epinephrine (pg/mL)</td>
<td>A</td>
<td>17±3</td>
<td>19±2</td>
<td>15±4</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>17±3</td>
<td>23±8</td>
<td>16±4</td>
</tr>
</tbody>
</table>

ANF, atrial natriuretic factor; A, active treatment (SCH 42495); P, placebo; cGMP, cyclic guanosine monophosphate; PRA, plasma renin activity; Ang II, angiotensin II. Values are mean±SEM. Arrow indicates first dose; days 1, 3, and 4 refer to day of dosing. *P<.05, †P<.001, ‡P<.01, for analysis of all serial data for each variable by analysis of variance with repeated measures.
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TABLE 1. Continued

<table>
<thead>
<tr>
<th>Time</th>
<th>Supine</th>
<th>Seated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 PM</td>
<td>6.8±0.8</td>
<td>7.5±1.5</td>
</tr>
<tr>
<td>1 AM</td>
<td>4.8±1.3</td>
<td>5.6±1.8</td>
</tr>
<tr>
<td>4 AM</td>
<td>19±5</td>
<td>17±6</td>
</tr>
<tr>
<td>8 AM</td>
<td>13±3</td>
<td>12±3</td>
</tr>
<tr>
<td>10 AM</td>
<td>137±21</td>
<td>207±34</td>
</tr>
<tr>
<td>93±9</td>
<td>126±19</td>
<td>237±63</td>
</tr>
<tr>
<td>140±25</td>
<td>5±1</td>
<td>3±1</td>
</tr>
<tr>
<td>11±3</td>
<td>10±5</td>
<td>9±5</td>
</tr>
</tbody>
</table>

pressure. SCH 42495-treated patients had a mean heart rate 2.7±1 beats per minute higher than placebo-treated patients over the 24 hours (Fig 4, P<.05). These effects of SCH 42495 on heart rate and blood pressure were similar both during daytime hours when patients were upright and during nocturnal recumbency (Fig 4).

Echocardiographic studies indicated a trend (NS) toward reduced cardiac output (4.6±0.5 versus 5.1±0.3 L/min) and slightly increased peripheral resistance (2079±297 versus 1871±19 dyne·s·cm⁻⁵), NS) with SCH 42495 compared with placebo but no appreciable differences in left atrial diameter (35±2 versus 37±2 mm), left ventricular diastolic diameter (45±2 versus 44±2 mm), or left ventricular ejection fraction (71±4% versus 73±3%).

SCH 42495 suppressed plasma neutral endopeptidase activity by more than 90% below matched placebo values on day 1 of dosing, and inhibition was similar on day 4 (Fig 2, P<.001), with only a minor tendency toward recovery between doses. Plasma ANF was markedly increased after the first dose of SCH 42495 and remained above placebo values (although to a lesser degree) during serial sampling on day 4 of dosing (Fig 2, P<.001 for first-dose effect, and P<.05 for days 4 to 5). Plasma cGMP concentrations were also increased beyond time-matched placebo values (P<.01 for first dose, P<.01 for days 4 to 5, Table 1). Plasma renin activity was unaffected by the first dose of SCH 42495 (Fig 2), but after 4 days, mean levels were 33% above time-matched placebo values (P<.05). This increase in plasma renin activity was most obvious during daylight hours when patients were upright and appeared to peak 6 hours after the morning dose of SCH 42495 (Fig 2; P<.001, treatment and time interaction). The effects of SCH 42495 on plasma angiotensin II and aldosterone paralleled those on plasma renin activity (Table 1). Diurnal changes in plasma cortisol were similar on the two study days. Plasma norepinephrine concentrations were unchanged by the first dose of SCH 42495 but were higher than matched placebo values on days 4 to 5 of dosing (P<.001, Fig 2). In contrast, plasma epinephrine concentrations remained unaffected (Table 1). Diurnal supine (9:30 AM and 3:30 PM; days 1, 3, and 4 of dosing) hormone values exhibited the same pattern of changes (Table 2) as observed for the overall series of hormone values.

Discussion

This is the first study to document, in detail, renal, hormonal, and hemodynamic responses from initial to established endopeptidase inhibition by SCH 42495 in patients with essential hypertension. The techniques used, including rigidly standardized dietary electrolyte intake and body posture, frequent hormone measurements, continuous intra-arterial pressure recordings, and the crossover design of the study, allowed detection of systematic changes in several variables of interest, whereas less robust studies have failed to detect such effects.36
TABLE 3. Outpatient Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8:30 AM</td>
<td>9:30 AM</td>
</tr>
<tr>
<td>Pre-A</td>
<td>A</td>
<td>P</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>156±5</td>
<td>155±4</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>99±1</td>
<td>98±1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64±1</td>
<td>66±2</td>
</tr>
</tbody>
</table>

Pre-A, before SCH 42495; Pre-P, before placebo; W1, washout period before either study phase (mean of four measurements); W2, washout period between study phases (mean of two measurements); A, SCH 42495; P, placebo. Day 1 indicates first day of dosing (fourth day of diet); day 3 indicates third day of dosing (sixth day of diet). Arrow shows timing of first dose. No statistically significant differences were found between SCH 42495 and placebo.

Significant natriuresis within the first 24 hours of dosing was attenuated over the subsequent 3 days of treatment. Arterial pressure was reduced and heart rate increased on days 4 to 5 of dosing. Acute pronounced enhancement of plasma ANF in association with no change in either renin-angiotensin-aldosterone system activity or plasma catecholamines with the first dose of SCH 42495 was followed by a somewhat attenuated enhancement of plasma ANF and modest but clear activation of both the renin-angiotensin-aldosterone system and plasma norepinephrine levels with more prolonged endopeptidase inhibition.

Our findings indicate that the acute natriuresis induced by endopeptidase inhibition is replaced by a lesser antiurotressis over the subsequent 3 days. In contrast, the increments in plasma and urinary ANF, in parallel with changes in plasma and urine cGMP, are sustained throughout the dosing period.

The initial natriuresis was presumably curtailed by activation of compensatory antinatriuretic systems (including the renin-angiotensin-aldosterone and sympathetic nervous systems) and the fall in renal perfusion pressure. Renal blood flow and glomerular filtration were not substantially altered, but the filtration fraction was subtly enhanced. The latter effect is commonly observed during infusion of ANF.

The initial vigorous rise in plasma ANF levels was less striking with continued administration of SCH 42495 (Fig 4), as has previously been observed. This diminishing ANF response to continued enzyme inhibition presumably reflects a reduction in endogenous secretion of ANF (rather than accelerated clearance of the peptide), since we have previously published evidence from studies of normal volunteers indicating that the plasma clearance of exogenous ANF remains demonstrably impaired rather than enhanced by chronic endopepti-
dase inhibition.\textsuperscript{32} The mechanism underlying this presumed reduction in ANF secretion is not addressed fully by the present study, but subtle contraction of circulating and atrial volumes secondary to natriuresis and falls in arterial pressure may be responsible.

In contrast to earlier studies that reported suppression of the renin-angiotensin-aldosterone system with acute endopeptidase inhibition,\textsuperscript{14,15,18} we observed no first-dose effect, and chronic dosing (4 days) clearly enhanced activity of this system (Fig 4 and Table 3). This may well reflect a response to modest sodium depletion, significant falls in arterial pressure, and activation of the sympathetic system. In addition, we and others have reported that endopeptidase inhibition modestly impairs the plasma clearance rate of angiotensin II.\textsuperscript{33} Stimulation of the renin-angiotensin-aldosterone system occurred in spite of a clear-cut rise in circulating ANF (and cGMP) levels, which, under some circumstances, has been shown to suppress both renin and aldosterone levels.\textsuperscript{31} These findings are consistent with our previous experience of chronic endopeptidase inhibition in normal volunteers and patients with hypertension receiving an alternative inhibitor.\textsuperscript{34,35}

Norepinephrine concentrations, which were unchanged with the initial dose of SCH 42495 (Fig 4), increased with sustained treatment in parallel with the rise in heart rate. This effect may well reflect a baroreceptor-mediated activation of the sympathetic nervous system, which may also have contributed to enhanced secretion of renin.\textsuperscript{36}

The many effects of endopeptidase inhibition in humans could conceivably reflect not only increases in plasma and tissue ANF but also changes in other vasoactive substrates to EC 24.11 such as bradykinin and brain natriuretic peptide. However, animal studies indicate that polyclonal anti-ANF antisera attenuate or abolish the cGMP, natriuretic, and hypotensive effects of endopeptidase inhibitors, whereas antagonists to other substrates, including bradykinin, do not.\textsuperscript{19-21,37,38} Hence, ANF is the likely predominant mediator of these end-organ effects of enzyme inhibition.

From our data it is clear that the fall in blood pressure was not mediated by suppression of the renin-angiotensin-aldosterone or sympathetic nervous systems. The delayed response of both systems suggests they are activated as a compensatory response to the inhibitor-induced natriuresis and fall in blood pressure. Such compensatory activation of counteracting systems may limit the hypotensive effects of plasma and tissue ANF levels enhanced via inhibition of EC 24.11.

Previous reports suggest that reduction of blood pressure by ANF in hypertension reflects contraction in plasma volume and cardiac output rather than reduction in peripheral vascular resistance.\textsuperscript{39} We addressed this issue by performing echocardiographic studies together with continuous intra-arterial pressure recordings. The trends toward reduced cardiac output and sustained vascular resistance are consistent with previous data obtained by invasive techniques during low-dose ANF infusions in patients with essential hypertension and in animals receiving SCH 42495,\textsuperscript{21} suggesting a similar hypotensive mechanism.\textsuperscript{39}

The possible role of endopeptidase inhibition in the management of hypertension must await the outcome of well-designed long-term trials in large numbers of patients. Despite promising results from some authors,\textsuperscript{34} other workers have observed only marginal or negligible effects on blood pressure.\textsuperscript{36} Bevan et al\textsuperscript{6} recently reported on the efficacy and tolerability of endopeptidase inhibition by candoxatril (UK 79300) in a well-designed parallel-groups study of 40 patients with essential hypertension receiving placebo or candoxatril (200 mg) every 12 hours for 28 days. Blood pressure tended to fall to a greater extent with candoxatril than with placebo, but in contrast to the current data) this pattern was statistically significant for erect systolic pressures only. Also, in contrast to our data was the absence of activation of the renin-angiotensin-aldosterone system. However, relatively infrequent sampling of data combined with the parallel-groups design and lack of standardization of dietary electrolyte intake may have obscured any effect of candoxatril on renin release. Nevertheless, as the authors state, the trial by Bevan et al\textsuperscript{6} casts "some doubt on the role of endopeptidase inhibition in the treatment of unselected hypertensive patients" when it is given as monotherapy.

It remains possible that individual endopeptidase inhibitors may vary in their ability to lower blood pressure. These drugs might differ in their potency and specificity for inhibition of EC 24.11 in different tissue sites and thereby induce varying profiles of renal, hemodynamic, and hormonal effects. Further detailed and long-term studies of a range of endopeptidase inhibitors in larger groups of patients are warranted. Finally, the potential role of endopeptidase inhibition, not only as monotherapy but also as an adjunct to established and developing modes of therapy (particularly converting enzyme inhibitors, angiotensin II antagonists, and renin inhibitors), requires careful study.

Acknowledgments

SCH 42495 was provided by Schering-Plough Corp, together with support for this work. Additional support was received from the National Heart Foundation and the Health Research Council of New Zealand. We thank the Endocrine Tests nursing staff, Mrs. Marilyn Cullens (Dietitian), and the Endocrine Assay technical staff. Mrs. Barbara Griffin provided expert secretarial assistance.

References


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_Hypertension_. 1993;22:119-126
doi: 10.1161/01.HYP.22.1.119

_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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