Effect of Inhibition of Endopeptidase 24.11 on Responses to Angiotensin II in Human Volunteers

A. Mark Richards, Gary A. Wittert, Eric A. Espiner, Timothy G. Yandle, Hamid Ikram, and Chris Frampton

The effects of endopeptidase 24.11 inhibition on angiotensin-induced changes in plasma angiotensin II, aldosterone, and atrial natriuretic factor concentrations and blood pressure were assessed in normal volunteers. Two groups, each consisting of eight normal volunteers, received stepwise infusions of angiotensin II (2, 4, and 8 ng/kg per minute) on day 5 of dose administration with 25 mg every 12 hours (group 1) or 100 mg every 12 hours (group 2) of an oral inhibitor of endopeptidase 24.11 (UK 79300, candoxatril) or placebo in balanced randomized, double-blind, placebo-controlled crossover studies. Both doses of candoxatril significantly enhanced plasma angiotensin II concentrations during infusions (group 1, p<0.01; group 2, p<0.01; overall treatment effect for combined data, p<0.001). This effect was most pronounced at the highest dose of angiotensin II (treatment–time interaction, p<0.0001 for combined data) and tended to be more marked with the higher dose of candoxatril (treatment–group interaction, p=0.08). The pressor response to angiotensin II was clearly enhanced by the lower dose of candoxatril; peak systolic and diastolic pressures exceeded placebo values by approximately 10 mm Hg (p<0.001 and p<0.05 for systolic and diastolic pressures, respectively). This effect of candoxatril was absent in group 2, which (unlike group 1) had exhibited a modest natriuretic response (sustained cumulative negative sodium balance, −70±21 mmol; p<0.01) to the higher dose of inhibitor. Baseline plasma aldosterone concentrations and the incremental aldosterone response to angiotensin II infusions were not significantly altered by low-dose (group 1) candoxatril. Basal aldosterone levels were slightly enhanced by the higher dose of inhibitor (p<0.05), but the incremental response to angiotensin II infusions was unchanged. Pretreatment with candoxatril caused plasma atrial natriuretic factor to rise above baseline values during angiotensin infusions (p<0.001, combined data). Inhibition of endopeptidase 24.11 significantly reduced clearance of infused angiotensin II in association with an enhanced pressor response to exogenous angiotensin when the inhibitor was given in doses below natriuresis. For cases in which a sufficient inhibitor was administered to elicit natriuresis, pressor responses did not change despite augmented plasma angiotensin II. These data carry implications for the potential therapeutic use of endopeptidase inhibitors in high and low renin states. (Circulation Research 1992;71:1501–1507)

Key Words • endopeptidase 24.11 • angiotensin II • atrial natriuretic factor • natriuresis • blood pressure

Inhibition of endopeptidase EC 3.4.24.11 (endopeptidase 24.11) may be of therapeutic value in hypertension and heart failure.1–4 Endopeptidase 24.11 appears to play a central role in the initial degradation of atrial natriuretic factor (ANF).5–7 Endopeptidase 24.11 inhibitors have been shown to enhance plasma ANF and induce ANF-like end-organ effects in animals as well as both normal volunteers and patients with hypertension and heart failure.2–4,8 ANF exerts beneficial hemodynamic effects in hypertension and heart failure,9,10 but data have been limited because of the peptide’s short half-life and the necessity for parenteral administration. Therefore, orally active endopeptidase 24.11 inhibitors may offer a method for testing the effects of chronic enhancement of ANF bioactivity in cardiovascular disease.

However, ANF is not the sole vasoactive substrate for endopeptidase 24.11.1 Others include angiotensins (Ang[s]) I and II,11,12 bradykinin, and substance P.1 Therefore, the net hemodynamic effect of endopeptidase 24.11 inhibition may well depend on the proportional effects of vasopressor and vasodilator substrates. Ang II is a potent endogenous pressor peptide, and possible direct or indirect enhancement or antagonism of this hormone by endopeptidase 24.11 inhibition is of potential clinical significance. Therefore, we studied the effect of subnatriuretic and natriuretic doses of the endopeptidase 24.11 inhibitor candox-
angiotensin II on Ang II-induced changes in blood pressure and hormones.

Materials and Methods

The study protocol was approved by the Canterbury Area Health Board Ethics Committee, and all participants gave informed written consent. Two groups, each consisting of eight normal male volunteers, received stepwise infusions of Ang II on day 5 of dose administration with 25 mg every 12 hours (group 1, aged 19–25 years; weight, 68–92 kg [median, 79.8 kg]) or 100 mg every 12 hours (group 2, aged 19–23 years; weight, 60–83 kg [median, 70.2 kg]) of oral candoxatril or matched placebo in balanced randomized, double-blind, placebo-controlled crossover studies. Active and placebo study phases were separated by 2 weeks. Doses were taken at 10:00 AM and 10:00 PM. Volunteers were studied under standardized conditions of diet, posture, room temperature, and time of day. All of them took constant sodium (150 mmol/day) and potassium (80 mmol/day), caffeine and alcohol-free diets for 3 days before and throughout the period of dose administration. All food and fluids were provided from our metabolic kitchen. Serial 24-hour urine samples were collected throughout the dietary period for measurement of volume, creatinine, sodium, and potassium.

On day 5 of dose administration with candoxatril or placebo, subjects were given breakfast at 8:30 AM in the research facility. Candoxatril (dose 9) or placebo was taken at 10:00 AM. Subjects were recumbent from 10:00 AM to 12:30 PM, i.e., for the duration of Ang II infusions. Ang II (Hypertensin, Ciba-Geigy, Basel, Switzerland) was dissolved in Haemaccel (1,000 ng/ml) and administered at 2, 4, and 8 ng/kg per minute for 30 minutes at each dose (11:00 AM to 12:30 PM) by syringe pump (Treonic IP4, Vickers Medical, Basingstoke, UK). Blood pressure and heart rate were measured in duplicate at 10-minute intervals from 10:30 AM to 12:30 PM (semi-automated Rose Box). Serial blood samples were taken by means of a 21-gauge “butterfly” needle placed in a superficial vein of the arm opposite to that used for the administration of the infusion. Samples were taken at 10:30 AM, 11:00 AM, 11:30 AM, 12:00 PM, and 12:30 PM for measurement of plasma concentrations of Ang II, aldosterone, and ANF.14-16 For each hormone, all samples from a given subject were assayed together to eliminate the potentially confounding effects of interassay variation. Intra-assay variation was greatest for plasma ANF (coefficient of variation, 8%) and least for aldosterone (%). Samples of all Ang II infusates were also assayed for Ang II concentrations. The metabolic clearance rate of Ang II was calculated according to the following equation:

\[ \text{MCR} = \frac{\text{infusion rate/steady state plasma concentrations}}{\text{plasma ANF}} \]

For this calculation endogenous plasma Ang II was assumed to be fully suppressed, and plasma Ang II concentrations were assumed to be at steady state at the end of each 30-minute constant infusion period.

Analysis by high-performance liquid chromatography (HPLC) and subsequent radioimmunoassay (to identify genuine Ang II and its metabolites) was performed on plasma samples obtained during a similar protocol conducted in a group of patients with hypertension. In this later experiment we administered similarly timed incremental infusions of Ang II to patients pretreated with placebo or candoxatril according to a similar protocol used with our normal volunteers. Plasma samples were obtained from the peak Ang II infusion dose phase. They were transported in deep-frozen condition to the Cleveland Clinic (Cleveland, Ohio) and underwent analysis according to previously described methods.17

Data were analyzed for groups 1 and 2, separately and together, by paired t-test (where appropriate) and analysis of variance (or covariance where appropriate) using program P2V of the BMDP package, with the group (where appropriate) as a between-subjects factor and treatment (candoxatril or placebo), and time as repeated-measures factors.18

Results

Data were complete with the exception of plasma aldosterone concentrations in one volunteer in group 2, in whom an idiosyncratic interaction with the aldosterone radioimmunoassay yielded fallacious plasma aldosterone values. Studies were completed without adverse events.

Pre-dose administration (i.e., day 3 of standard diets) 24-hour urine indexes that included volume, sodium, potassium, and creatinine did not differ either between groups or between study phases within either group.19

Candoxatril induced modest natriuresis in group 2 (a cumulative negative sodium balance of 70±21 mmol was established by 48 hours of commencement of dose administration and sustained throughout the dosing period; p<0.01) but not group 1 (intergroup comparison, p<0.05).

Baseline and intrainfusion values of plasma Ang II and aldosterone concentrations are listed in Table 1 and/or illustrated in Figure 1. Basal levels of angiotensin and aldosterone were unchanged by the lower dose (group 1) of candoxatril. Group 2 showed a trend toward higher basal levels of angiotensin (Figure 1 and Table 1, p=NS) and a significant increase in basal plasma aldosterone concentrations (p<0.05), which was consistent with the modest sodium depletion induced by the higher dose of candoxatril. Measured infusate concentrations of Ang II were similar for both candoxatril and placebo phases of the studies for both groups (1,119±41 and 1,139±35 ng/ml for candoxatril and placebo phases, respectively, in group 1; 985±45 and 1,013±36 ng/ml for candoxatril and placebo phases, respectively, in group 2; p=NS for all comparisons of candoxatril versus placebo and group 1 versus group 2).

Candoxatril clearly enhanced achieved plasma Ang II concentrations particularly at higher angiotensin infusion rates (Figure 1). This effect tended to be more pronounced in group 2. Table 2 gives mean±SEM metabolic clearance rates (MCR) for Ang II for each rate of Ang II infusion for both groups. Mean placebo-phase metabolic clearance of Ang II tended to be greater in group 1 than group 2. This was presumed to reflect the greater median body mass in group 1 together with the effect of chance biological variation, because there were no other indicators of fundamental baseline differences between the two groups (Table 1). Significant reductions in the MCR of Ang II were observed during the 4 and 8 ng/kg per minute doses of
Ang II in group 1 and for all three doses of Ang II in group 2.

HPLC analysis followed by radioimmunoassay (Dr. Mark Chappell, Cleveland Clinic Foundation, Cleveland, Ohio)\(^{18}\) revealed similar chromatographic profiles of Ang II and metabolites (Ang[3–8] and Ang[2–8]) in samples taken during infusions with and without candoxatril pretreatment. The ratio of octapeptide to metabolites was similar in both study phases, with increased immunoreactivity present for all moieties in the active phase. Therefore, levels of authentic Ang II were clearly enhanced by candoxatril.

Plasma aldosterone concentrations showed the expected dose-related increases during the stepwise Ang II infusions (Figure 1). In group 2, plasma aldosterone values were modestly but significantly increased by candoxatril before and during angiotensin infusions (Figure 1, \(p<0.05\)). However, in both groups the incremental response of plasma aldosterone to successive doses of Ang II was not altered by candoxatril despite the higher achieved plasma Ang II values (Figure 1).

The pressor response to Ang II was clearly enhanced by the lower dose of candoxatril (group 1, Figure 2). Both systolic and diastolic pressures were significantly

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Hormones, Blood Pressure, and Heart Rate (Mean±SEM)</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>P</td>
</tr>
<tr>
<td>Angiotensin II (pmol/l)</td>
<td>18±3</td>
<td>17±2</td>
</tr>
<tr>
<td>Aldosterone (pmol/l)</td>
<td>144±20</td>
<td>160±24</td>
</tr>
<tr>
<td>ANF (pmol/l)</td>
<td>6±1</td>
<td>7±1</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>113±3</td>
<td>111±2</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>58±3</td>
<td>58±5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>61±3</td>
<td>60±3</td>
</tr>
</tbody>
</table>

A, pretreatment with 25 mg candoxatril (group 1) or 100 mg bd (group 2); P, placebo; ANF, atrial natriuretic factor; bpm, beats per minute. All hormone values are the mean of values at 10:00 AM (–30 minutes) and 11:00 AM (time 0) before commencement of angiotensin II infusions. Blood pressure and heart rate values are the mean of serial 10-minute mean recordings from 10:30 to 11:00 AM.

\(^{*}p<0.05\) for A vs. P.

\(n=8\) for all values except for group 2 aldosterone (\(n=7\)).

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** Line graphs showing plasma angiotensin II (Ang II, AII) and aldosterone concentrations (mean±SEM) in two groups of normal volunteers receiving stepwise infusions of Ang II on day 5 of dose administration with candoxatril. Group 1 (left panels) received 25 mg every 12 hours of candoxatril (△) and placebo (○). Group 2 (right panels) received 100 mg every 12 hours of candoxatril (△) and placebo (○). Doses were given at 10:00 AM. Achieved plasma Ang II concentrations were increased by candoxatril (\(p<0.001\) and \(p<0.01\) for groups 1 and 2, respectively; \(p<0.001\) for combined data), with the augmentation being significantly greater at the higher Ang II infusion rates (treatment–time interaction, \(p<0.06\) and \(p<0.001\) for groups 1 and 2, respectively; \(p<0.0001\) for combined data). Plasma aldosterone was significantly increased by candoxatril in group 2 (\(p<0.05\)) but not group 1 (\(p=NS\), although data from both groups combined indicated a significant overall treatment effect (\(p<0.05\)). The incremental response was unaffected in both groups. No significant treatment–time interactions were observed for aldosterone.
TABLE 2. Metabolic Clearance of Angiotensin II (Liters per Minute, Mean±SEM)

<table>
<thead>
<tr>
<th>Angiotensin II dose (ng/kg per minute)</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>6.6±2.7</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Group 1 (n=8)</td>
<td>4.5±0.4 (-32%)</td>
<td>4.7±0.8 (-22%)</td>
<td>5.3±0.4 (-15%)</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>3.5±0.4</td>
<td>4.3±0.3</td>
<td>4.9±0.2</td>
</tr>
<tr>
<td>Group 2 (n=8)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>2.8±0.3 (-20%)</td>
<td>3.5±0.3 (-19%)</td>
<td>3.6±0.2 (-27%)</td>
</tr>
</tbody>
</table>

P, placebo; A, pretreated with canoxatril (group 1, 25 mg every 12 hours; group 2, 100 mg every 12 hours).

†Bracketed values indicate percentage reduction in mean clearance rate from time-matched placebo values.

Increased above placebo values, and this effect was most obvious at the highest angiotensin infusion rate, when both variables exceeded matched placebo values by approximately 10 mm Hg (Figure 2). Conversely, no augmentation of the pressor effect to Ang II was observed in group 2. The expected fall in heart rate occurred during Ang II infusions and was not significantly altered by canoxatril.

ANF significantly increased above baseline values during Ang II infusions in both study phases in group 1 but only with canoxatril pretreatment in group 2 (Figure 3).

Discussion

Chronic dose administration with both subnatriuretic and natriuretic doses of the orally active inhibitor of endopeptidase 24.11, canoxatril, enhanced achieved plasma immunoreactive Ang II concentrations during angiotensin infusions in these two groups of normal volunteers. Basal (endogenous) Ang II concentrations increased above placebo values, and this effect was most obvious at the highest angiotensin infusion rate, when both variables exceeded matched placebo values by approximately 10 mm Hg (Figure 2). Conversely, no augmentation of the pressor effect to Ang II was observed in group 2. The expected fall in heart rate occurred during Ang II infusions and was not significantly altered by canoxatril.

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were not altered in group 1 and showed only a nonsignificant upward trend in group 2, suggesting that the effect on metabolism of Ang II (at least as reflected in steady state plasma concentrations) may not be apparent until high levels of this enzyme substrate are present. When acute infusions of exogenous Ang II increased plasma Ang II levels to the pathophysiological range, endopeptidase 24.11 inhibition reduced calculated metabolic clearance by approximately 20%. The means used to calculate the MCR of Ang II probably systematically underestimated clearance through the assumption that basal endogenous Ang II levels were completely suppressed throughout Ang II infusions. Endogenous Ang II levels would be expected to decline secondary to the "short loop" negative feedback effect of exogenous Ang II on renin secretion, but the extent of this suppression in our current experiment is uncertain. The degree to which this factor may differ in the presence and/or absence of endopeptidase inhibition (and the consequent potential distortion of comparisons of MCR) is unknown.

The possibility that the enhanced angiotensin immunoreactivity observed during peptide infusions represented the accumulation of cross-reacting angiotensin metabolites (with reduced or negligible bioactivity) has been assessed by means of HPLC analysis of samples taken during a similar experiment performed in patients with essential hypertension. Again, in the presence of candoxatril the achieved plasma immunoreactive Ang II level was significantly enhanced, particularly at the highest dose of exogenous angiotensin infusions. HPLC coupled to a radioimmunoassay (RIA) (using an antiserum distinct from that used in our own RIA) confirmed that the increased Ang II immunoreactivity we have observed includes enhanced levels of the octapeptide and does not simply reflect cross-reacting inactive metabolites of angiotensin or other interfering moieties. The clearly enhanced pressor response to Ang II infusions observed in group 1 also suggests that the measured peptide retains bioactivity and is therefore likely to be intact Ang II. The mechanisms whereby candoxatril impairs metabolic clearance of Ang II cannot be definitively stated from our current data. However, because endopeptidase 24.11 cleaves Ang II at the Tyr-Ile bond in vitro,11 it seems probable that the inhibitor impedes Ang II degradation by tissue endopeptidases, at least when plasma Ang II is acutely increased threefold to fivelfold.

In contrast to group 1, enhanced Ang II levels during infusions in group 2 subjects were not associated with an enhanced pressor response. Although the reason for this difference is unclear from our studies, several factors could contribute to this phenomenon. First, unlike group 1, subjects in group 2 who received the higher dose of candoxatril were mildly sodium depleted (relative to placebo status)—circumstances that are known to reduce the pressor response to Ang II.20,21 Second, in group 2 the diurnal endogenous Ang II levels during dose administration with candoxatril tended to be higher than control levels,19 whereas in group 1 subjects values were closely matched in active and placebo phases. Such a trend to higher plasma and/or tissue Ang II in group 2 (if sustained) may downregulate vascular Ang II receptors and diminish the pressor response to infusions given after 5 days of candoxatril treatment. Third, with higher doses of candoxatril, enhancement of tissue and plasma (Figure 3) ANF may counteract the pressor action of Ang II, e.g., by reducing plasma volume22 and/or partially opposing the action of Ang II on vascular smooth muscle cells.

Despite augmented Ang II levels at high Ang II infusion rates, the plasma aldosterone incremental response was unaffected by candoxatril pretreatment in both groups. Furthermore, group 2 subjects with mild sodium depletion, which is known to increase glomerulosa sensitivity to Ang II,20 showed a similar Ang II/aldosterone dose–response relation. Because even small increments in plasma ANF may reduce aldoste-
rone secretion in normal and hypertensive men, it is possible that enhanced plasma ANF levels before and/or during Ang II administration in candoxatril-treated subjects (Figure 3) act to reduce the aldosterone response. However, the tissue (adrenal glomerulosa) level of ANF may be more important. In studies of diurnal plasma ANF levels during chronic (4-day) candoxatril treatment, increases in plasma and urine cGMP (an ANF second messenger) are greater and more sustained than those of plasma ANF. These findings suggest that some of the actions of endopeptidase inhibition may be mediated by promotion of ANF bioactivity at the tissue level rather than through changes in steady state plasma concentrations of ANF.

ANF levels were modestly but significantly enhanced in a dose-related fashion by Ang II infusions. This may reflect Ang II–induced increases in peripheral arterial resistance and decreases in venous capacitance, which lead to increased central blood volumes and atrial pressures, with consequent increases in ANF secretion. Ang II may also alter regional vascular resistance and reduce blood flow to sites of ANF clearance. Therefore, endopeptidase 24.11 inhibition may enhance the ANF secretory response to Ang II through both the increase in achieved levels of angiotensin and the delay of enzymatic degradation and metabolic clearance of ANF.

Endopeptidase 24.11 inhibition is evidently not synonymous with pure enhancement of ANF. The present findings raise the possibility that the therapeutic efficacy of endopeptidase 24.11 inhibition in hypertension and heart failure may be modulated by sodium status and baseline activity of the renin-angiotensin-aldosterone system (RAAS). Patients with high-renin hypertensive states such as renovascular hypertension, malignant-phase hypertension, hypertension secondary to renin-secreting tumors, or the more common high-renin essential hypertension may show significant enhancement of plasma Ang II with administration of an endopeptidase inhibitor. This could conceivably maintain or exacerbate the hypertensive state depending on the strength of concomitant opposing vasodepressor influences (which include the simultaneous effect on plasma and tissue ANF levels). Conversely, in volume-expanded states with low renin activity and high basal ANF levels, the hypotensive effect of endopeptidase inhibition may be potentiated. In support of these proposals, endopeptidase 24.11 inhibitors have a significant blood pressure–lowering effect in the volume-expanded DOC-salt rat hypertensive model. To our knowledge, data from models of renovascular hypertension are not yet available. Spontaneously hypertensive rats (SHR) have been reported to show a fall in blood pressure with endopeptidase inhibition, although contrary findings have also been published.

The renin-angiotensin-aldosterone system is also activated in patients with deteriorating heart failure and animal models of heart failure. Many of the adverse manifestations of heart failure seem secondary to raised RAAS activity and are ameliorated by converting enzyme inhibition. Candoxatril has caused beneficial hemodynamic effects when given to heart failure patients in acute single-dose studies. However, the more long-term effects of endopeptidase 24.11 inhibition on RAAS activity in heart failure remain undetermined. It may be necessary to coadminister converting enzyme inhibitors or Ang II antagonists to gain optimum benefit from the use of endopeptidase inhibition in heart failure and hypertension.

The current data are derived from contrived circumstances in which plasma Ang II concentrations were rapidly elevated from normal to pathophysiological levels, and it remains to be confirmed that endopeptidase 24.11 inhibition will continue to significantly delay metabolic clearance of Ang II in the medium or longer term with more gradual or subtle elevation of endogenous angiotensin II, and, if so, whether such an action would be sufficient to exert significant hemodynamic effects. However, the potential importance of the observed interaction indicates that carefully controlled trials (of a range of endopeptidase inhibitors) that incorporate monitoring of both clinical status and neurohumoral status will be required to establish the appropriate role, if any, of endopeptidase 24.11 inhibitors in the management of cardiovascular disease.

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References

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