Omapatrilat Versus Lisinopril
Efficacy and Neurohormonal Profile in Salt-Sensitive Hypertensive Patients

Vito M. Campese, Kenneth C. Lasseter, Carlos M. Ferrario, William B. Smith, Michael C. Ruddy, Clarence E. Grim, Ronald D. Smith, Ramon Vargas, Michael F. Habashy, Ole Vesterqvist, Carol L. Delaney, Wei-Chi Liao

Abstract—Omapatrilat, a vasopeptidase inhibitor, simultaneously inhibits neutral endopeptidase and ACE. The efficacy and hormonal profile of omapatrilat and lisinopril were compared in salt-sensitive hypertensive patients. On enrollment, antihypertensive medications were withdrawn, and patients received a single-blind placebo. On day 15, salt-sensitivity determinations were made. Salt-sensitive hypertensive patients returned within 5 to 10 days for baseline evaluations of ambulatory diastolic blood pressure, ambulatory systolic blood pressure, and atrial natriuretic peptide. Salt-sensitive hypertensive patients were randomized to receive double-blind omapatrilat (n=28) or lisinopril (n=33) at initial doses of 10 mg for 1 week, increasing to 40 and 20 mg, respectively, for an additional 3 weeks. Ambulatory blood pressure and urinary atrial natriuretic peptide were assessed at study termination. Both omapatrilat and lisinopril significantly reduced mean 24-hour ambulatory diastolic and systolic blood pressures; however, omapatrilat produced significantly greater reductions in mean 24-hour ambulatory diastolic blood pressure (P=0.008), ambulatory systolic blood pressure (P=0.004), and ambulatory mean arterial pressure (P=0.005) compared with values from lisinopril. Both drugs potently inhibited ACE over 24 hours. Omapatrilat significantly (P<0.001) increased urinary excretion of atrial natriuretic peptide over 0- to 24-hour (3.8-fold) and 12- to 24-hour (2-fold) intervals; lisinopril produced no change. Omapatrilat significantly (P<0.001) increased urinary excretion of cGMP over the 0- to 24- and 4- to 8-hour intervals compared with that from lisinopril. Neither drug had a diuretic, natriuretic, or kaliuretic effect. In conclusion, in salt-sensitive hypertensive patients, omapatrilat demonstrated the hormonal profile of a vasopeptidase inhibitor and lowered ambulatory diastolic and systolic blood pressures more than lisinopril. (Hypertension. 2001;38:1342-1348.)

Key Words: omapatrilat ■ lisinopril ■ vasopeptidase inhibitor ■ salt sensitivity

Vasopeptidase inhibitors (VPIs) are innovative drugs that inhibit 2 key enzymes, neutral endopeptidase (NEP) and ACE. The result is an increase in vasodilatory peptides (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], bradykinin, and adrenomedullin) and inhibition of the production of the vasoconstrictor angiotensin II. The physiological effects of ANP and BNP include vasodilation and inhibition of the renin-angiotensin-aldosterone system.

The metabolism of ANP and BNP involves 2 main pathways: an enzymatic degradation by NEP 24.11 and a receptor-mediated clearance process via the clearance receptor.

NEP 24.11 is widely distributed throughout the body and is particularly present at the level of the brush border membranes in the proximal tubule of the kidney. Inhibition of NEP produces increases in plasma ANP concentrations and urine sodium and volume excretion and a decrease in blood pressure (BP) in deoxycorticosterone acetate–salt uninephrectomized rats.

NEP inhibitors, when given alone, have not been effective as long-term antihypertensive agents in humans, perhaps because of compensatory reflex renin-angiotensin-aldosterone system activation. These limitations may be overcome by VPIs through their additional ability to inhibit ACE and to potentiate the kallikrein-kinin system, resulting in additional vasodilation.

Patients with salt-sensitive hypertension (SSH) do not respond as well to ACE inhibitor monotherapy as hypertensive patients who are not salt sensitive. In response to a high dietary salt intake, SSH patients exhibit salt retention and an increase in renal vascular resistance compared with salt-resistant hypertensive patients. Moreover, black SSH patients manifest a paradoxical decrease in ANP plasma levels after a

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sodium load.\textsuperscript{16} Because of the above-described pharmacological properties, VPIs have the potential to be particularly efficacious in SSH patients. The VPI sampatrilat produced a sustained antihypertensive activity in black hypertensive patients, a patient population with a high prevalence of salt sensitivity.\textsuperscript{17} Omapatrilat has similar inhibition constants for both NEP and ACE and is effective in low-, normal-, and high-renin models of hypertension.\textsuperscript{18} Clinical efficacy appears to be independent of age\textsuperscript{19} and ethnicity and may be independent of renin and salt status.\textsuperscript{20}

The principal objective of the present study was to compare the effect of omapatrilat and lisinopril in SSH patients in terms of effects on 24-hour mean ambulatory BP (ABP) and 24-hour urinary excretion of the vasodilator ANP.

### Methods

The applicable institutional review board approved these studies. All patients provided written, informed consent. Enrolled in this study were patients with seated diastolic BP of 95 to 110 mm Hg who were 18 to 78 years of age.

After a 2- to 3-week single-blind placebo lead-in period (period A), 104 of the original 167 patients were admitted to the Clinical Research Center to determine their salt-sensitivity status. A total of 63 patients were excluded before randomization because they did not qualify for the protocol (n=40), were poorly compliant (n=7), requested withdrawal for unspecified reasons (n=9), had other personal reasons (n=6), or experienced an adverse event (n=1). On the first day (saline day), intravenous infusion of 2 L normal saline (0.9% sodium chloride at a rate of 500 mL/h for 4 hours beginning at \(8:00\) AM) and a dietary sodium intake of 200 mmol/d were given to achieve a high total body sodium state. BP was measured in the seated position before and 4 hours after infusion. On the following 2 days, volume depletion was achieved with a combination of low-sodium diet (20 mmol/d) and furosemide (40 mg every 4 hours from 10:00 AM to 6:00 PM). Dietary protein (90 g) and potassium (70 mmol/d) remained constant throughout the salt-sensitivity classification regimen.

Salt sensitivity was ascertained by a comparison of the mean arterial pressure (MAP) calculated from the 10 BP readings obtained in the sodium-loaded state beginning after the saline infusion with the mean MAP of 10 BP readings after sodium and volume depletion. Individuals with a decrease in MAP of \(\geq\)10 mm Hg after sodium and volume depletion compared with that at the end of the saline infusion were considered salt sensitive.\textsuperscript{21} The remaining patients were considered salt resistant and were excluded from the rest of the study. Of the 104 patients tested, 62 were salt sensitive (50% black, 18% white, 32% other ethnic background) and 42 were salt resistant (50% black, 38% white, 12% other ethnic background).

All the SSH patients were readmitted to the Clinical Research Center to determine baseline urinary ANP, cGMP, and ambulatory BP measurements (period B). Sixty-one of the 62 SSH patients were randomized. Twenty-eight SSH patients received omapatrilat 10 mg/d for the first week, followed by 3 weeks of 40 mg/d omapatrilat, and 33 SSH patients received lisinopril 10 mg/d for the first week, followed by 20 mg for the next 3 weeks (period C). The demographics of these 2 patient populations are detailed in Table 1. A total of 57 patients completed the study; 4 patients discontinued therapy early in the study: 2 because of adverse events, 1 for personal reasons, and 1 because of poor compliance.

Ambulatory BP monitoring was performed on the nondominant arm with a device (Space Labs 90207) precalibrated by the manufacturer and validated by mercury sphygmomanometer before each initiation.

The 24-hour urine samples were collected before and after treatment to measure volume, creatinine, urinary electrolytes (sodium, potassium, and chloride), and urinary excretion of ANP (ng/interval), cGMP (\(\mu\)mol/interval), and aldosterone. Separate urinary

### Table 1: Demographic Characteristics of Patients Who Entered Salt-Sensitivity Classification and Randomized Patients in Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Salt Sensitive</th>
<th>Salt Resistant</th>
<th>Treatment Group, SSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=62)</td>
<td>(n=42)</td>
<td>Omapatrilat</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>53±9.5</td>
<td>53±9.3</td>
<td>53±8.8</td>
</tr>
<tr>
<td>Range</td>
<td>33–77</td>
<td>36–78</td>
<td>33–70</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>36 (58)</td>
<td>22 (52)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Women</td>
<td>26 (42)</td>
<td>20 (48)</td>
<td>13 (46)</td>
</tr>
<tr>
<td><strong>Ethnic group, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (18)</td>
<td>16 (38)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Black</td>
<td>31 (50)</td>
<td>21 (50)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (32)</td>
<td>5 (12)</td>
<td>10 (36)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>57</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>87.4±17.5</td>
<td>88.8±20.9</td>
<td>84.3±15.7</td>
</tr>
<tr>
<td>Range</td>
<td>61.7–144.9</td>
<td>55.0–146.3</td>
<td>61.7–113.9</td>
</tr>
<tr>
<td><strong>Duration of hypertension, mo (n)</strong></td>
<td>5.5 (20)</td>
<td>4.5 (13)</td>
<td></td>
</tr>
<tr>
<td><strong>Trough seated DBP, mm Hg</strong></td>
<td>(n=23)</td>
<td>(n=33)</td>
<td></td>
</tr>
<tr>
<td>Mean±SD baseline</td>
<td>98.4±6.7</td>
<td>98.6±8.9</td>
<td></td>
</tr>
<tr>
<td><strong>Trough seated SBP, mm Hg</strong></td>
<td>(n=28)</td>
<td>(n=33)</td>
<td></td>
</tr>
<tr>
<td>Mean±SD baseline</td>
<td>152.7±16.8</td>
<td>150.7±22.7</td>
<td></td>
</tr>
<tr>
<td><strong>Mean±SD change in MAP, mm Hg (SD)</strong></td>
<td>19.2±9.4</td>
<td>3.2±6.5</td>
<td></td>
</tr>
</tbody>
</table>
samples were obtained between 0 and 4, 4 and 8, 8 and 12, 12 and 20, and 20 and 24 hours. Creatinine clearance was calculated with a standard formula. Plasma was collected in a Vacutainer tube containing K3 EDTA as an anticoagulant and aprotinin for measurement of ANP (pg/mL) and cGMP (nmol/L). Plasma for ACE activity was obtained with a Vacutainer tube containing heparin. Blood samples were collected at baseline before dosing and at the end of the study, both before and 4 hours after dosing.

Urinary and plasma ANP levels were measured by radioimmunoassay after solid-phase extraction. Urinary and plasma cGMP levels were measured by radioimmunoassay by use of the kit from Dupont Medical Products after dilution and ethanol extraction, respectively. Urinary aldosterone was measured by radioimmunoassay with the Aldosterone Coat-a-Count Kit (Diagnostics Product Corporation). Plasma ACE activity was determined by use of a validated radioenzyme assay adapted from a kit previously available from HYCOR Biomedical Inc using the synthetic substrate Hip-Gly-Gly.

All statistical analyses were carried out with SAS/STAT, version 6.08. ANOVA was performed on the 24-hour changes in ambulatory BP monitoring, ANP, and cGMP, including treatment as a factor and baseline value as a covariate. The adjusted treatment means were compared at the 2-sided 5% level of significance and a 95% confidence interval (CI) obtained for their difference. The 95% CI was also calculated for the differences between treatment effects on 0- to 4- and 12- to 24-hour urinary ANP (ng per interval), 0- to 24- and 12- to 24-hour urinary cGMP excretion, and peak (4 hour) and trough (0 hour) plasma ANP concentration.

Results
In the study, 28 patients were randomized to omapatrilat; 33 patients, to lisinopril treatment. There were no differences in age, body weight, body mass index, gender, and ethnic distribution between patients in the 2 groups. Baseline demographics are summarized in Table 1.

Comparison of the Antihypertensive Efficacy of Omapatrilat and Lisinopril
There were no statistically significant differences in baseline BP between the 2 treatment groups. Decreases in ambulatory DBP (ADBp) and SBP (ASBP) were observed after omapatrilat and lisinopril treatment, and the decreases were all statistically significant at the 5% level. Omapatrilat 40 mg produced significantly greater reductions than lisinopril 20 mg in ADBP, ASBP, and ambulatory MAP (AMAP). These differences in adjusted mean change from baseline between omapatrilat and lisinopril were as follows: for ADBP, 4.2 mm Hg (95% CI, 1.1 to 7.3; \( P = 0.008 \)); for ASBP, 8.2 mm Hg (95% CI, 2.7 to 13.7; \( P = 0.004 \)); and for AMAP, 5.6 mm Hg (95% CI, 1.8 to 9.3; \( P = 0.005 \)). Omapatrilat 40 mg achieved greater reductions in ABP than lisinopril 20 mg at almost every hour after dosing on day C28 (Figures 1 and 2). Mean hourly ADBP was ≤90 mm Hg for 21 of the 24 hours with omapatrilat compared with 18 of the 24 hours with lisinopril. Mean hourly ASBP was ≤140 mm Hg for 17 of the 24 hours with omapatrilat compared with 9 of the 24 hours with lisinopril. The decreases in ADBP and ASBP...
after omapatrilat treatment were not associated with changes in mean 24-hour heart rate. These data are summarized in Table 2.

**Pharmacodynamics**

**ACE Activity**

Both omapatrilat and lisinopril produced significant inhibition of ACE activity. At 0 hours on day C28, the mean percent inhibition compared with baseline was 88% for the lisinopril treatment group versus 69% for the omapatrilat treatment group. The mean percent changes from baseline for the 2 treatments were about the same at 4 hours after dosing (Figure 3).

**Urinary Excretion of ANP**

Omapatrilat increased urinary excretion of ANP, whereas lisinopril had no effect. For the 0- to 24-hour interval, omapatrilat produced a 3.8-fold increase over baseline in the 24-hour urinary excretion profile of ANP; the impact of lisinopril was negligible (Figure 4). The difference in adjusted mean change from baseline between omapatrilat and lisinopril was 42.8 ng/24 h (95% CI, 49.9 to 35.7), which was statistically significant ($P<0.001$). For the 0- to 4- and 12- to 24-hour intervals, all increases for omapatrilat were statistically significant ($P<0.001$). At the end of the interdose interval (20 to 24 hours), there was a 9% decrease in the lisinopril group but a persistent 68% increase in the omapatrilat group (Table 3).

**Plasma ANP**

On day C28, peak (4 hour) plasma ANP concentrations were increased in the omapatrilat group and were slightly decreased for the lisinopril group (Table 4).

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**TABLE 2. Efficacy of Omapatrilat and Lisinopril on 24-Hour ABP and Heart Rate**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Omapatrilat 40 mg (n=28)</th>
<th>Lisinopril 20 mg (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour ADBP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (day B1), mean±SD</td>
<td>93.7±9.1</td>
<td>91.8±9.7</td>
</tr>
<tr>
<td>Day C28 treatment, mean±SD</td>
<td>84.3±10.4</td>
<td>86.8±10.5</td>
</tr>
<tr>
<td>Adjusted mean change* (95% CI)†</td>
<td>-9.3‡ (-11.6 to -6.9)</td>
<td>-5.1‡ (-7.1 to -3.1)</td>
</tr>
<tr>
<td>24-hour ASBP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (day B1), mean±SD</td>
<td>152.9±20.1</td>
<td>147.8±16.1</td>
</tr>
<tr>
<td>Day C28 treatment, mean±SD</td>
<td>137.3±19.6</td>
<td>140.7±19.2</td>
</tr>
<tr>
<td>Adjusted mean change* (95% CI)†</td>
<td>-15.4§ (-19.6 to -11.3)</td>
<td>-7.2§ (-10.8 to -3.7)</td>
</tr>
<tr>
<td>24-hour AMAP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (day B1), mean±SD</td>
<td>113.4±11.8</td>
<td>110.4±10.4</td>
</tr>
<tr>
<td>Day C28 treatment, mean±SD</td>
<td>102.0±12.7</td>
<td>104.7±12.3</td>
</tr>
<tr>
<td>Adjusted mean change* (95% CI)†</td>
<td>-11.3</td>
<td>(-14.2 to -8.5)</td>
</tr>
<tr>
<td>24-hour heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (day B1), mean±SD</td>
<td>72.8±8.4</td>
<td>72.2±8.5</td>
</tr>
<tr>
<td>Day C28 treatment, mean±SD</td>
<td>72.2±7.7</td>
<td>72.3±8.2</td>
</tr>
<tr>
<td>Unadjusted mean±SD change</td>
<td>-0.6±4.7</td>
<td>0.1±4.2</td>
</tr>
</tbody>
</table>

*Baseline-adjusted mean.
†Estimate and 95% CI based on adjusted means.
‡$P=0.008$, §$P=0.004$, ||$P=0.005$.
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Omapatrilat increased 0- to 24-hour urinary excretion of ANP by 0.30 μmol/24 h from baseline, whereas lisinopril decreased the excretion by 0.11 μmol/24 h (Figure 5). The difference in adjusted mean change from baseline between omapatrilat and lisinopril was 0.40 ng/24 h (95% CI for change, ng/24 h 1.7–1.9).

**Urinary cGMP**

Omapatrilat increased 0- to 24-hour urinary excretion of cGMP by 0.30 μmol/24 h from baseline, whereas lisinopril decreased the excretion by 0.11 μmol/24 h (Figure 5). The difference in adjusted mean change from baseline between omapatrilat and lisinopril was 0.40 ng/24 h (P<0.001).

**Urinary Aldosterone**

Mean 24-hour urinary aldosterone excretion was decreased from baseline by 22% and 27% with omapatrilat and lisinopril, respectively. Decreases in mean urinary aldosterone were also observed during the 0- to 4-, 4- to 8-, and 12- to 24-hour collection intervals.

**Urine Volume and Urinary Excretion of Electrolytes and Creatinine**

There were no substantial changes from baseline in the 0- to 4-hour urinary excretion of electrolytes or urinary volume, and no substantial differences were observed between treatments (Table 5). Similarly, there were no substantial changes from baseline in the 0- to 24-hour results for both treatments (Table 6) and no substantial differences between treatments. Although on average creatinine clearance increased 8 mL/min for the omapatrilat group and decreased 6 mL/min for the lisinopril group, these modest changes were not statistically significant.

**Safety and Tolerability**

Both omapatrilat and lisinopril were generally safe and well tolerated. There were 56 treatment-related adverse events, 28 with lisinopril and 28 with omapatrilat. The most frequently reported adverse events were musculoskeletal pain (4 lisinopril-treated patients) and cough (3 lisinopril-treated patients, 1 omapatrilat-treated patient). Other drug-related adverse events included dyspepsia/heartburn and dizziness. Treatment for 1 patient was discontinued because of angioedema of the lip after treatment with omapatrilat. There were no deaths. In addition, there were no clinically significant laboratory abnormalities observed in these patients.

**Discussion**

In the present study, the effects of omapatrilat and lisinopril were compared in SSH patients. Compared with lisinopril, omapatrilat produced clinically and statistically greater reductions from baseline in ADBP, ASBP, and AMAP over the 24 hours after dosing. As a result of its greater efficacy, omapatrilat achieved hourly mean ADBP ≤90 mm Hg and hourly mean ASBP ≤140 mm Hg for a greater number of hourly recordings on day C28. In a preliminary report, omapatrilat 80 mg administered once daily for 10 weeks to patients with mild to moderate hypertension was statistically more effective in reducing ASBP, ADBP, AMBP, and ambulatory pulse pressure than lisinopril 40 mg over 24 hours.

Omapatrilat demonstrated the properties of a VPI in this patient population, including inhibition of NEP, evidenced by the increased urinary excretion of ANP and cGMP, and 40-mg/day dosing for 10 weeks.
inhibition of ACE. As expected, lisinopril inhibited only ACE. Neither omapatrilat nor lisinopril caused diuresis, natriuresis, or kaliuresis after long-term dosing (Tables 5 and 6). The lack of natriuresis after omapatrilat despite a decrease in urinary aldosterone and an increase in plasma and urinary ANP is difficult to explain. Our protocol did not allow us to achieve sodium balance before the study and to accurately measure the short-term effects of omapatrilat on sodium excretion and sodium balance. Thus, the greater antihypertensive efficacy of omapatrilat versus lisinopril is probably due primarily to the vasodilatory effects of NEP inhibition, but a natriuretic effect cannot be completely excluded on the basis of our studies.

Conclusions

Omapatrilat demonstrated the hormonal properties of a VPI in SSH patients, namely enhanced urinary excretion profiles of ANP and cGMP characteristic of NEP inhibition and potent inhibition of ACE. The absence of natriuresis in the presence of enhanced urinary and plasma ANP in the omapatrilat-treated patients remains unexplained. Lisinopril was shown to be a potent inhibitor of ACE activity. However, in SSH patients, significantly greater reductions in mean 24-hour ADBP, ASBP, and AMAP were achieved with omapatrilat 40 mg than with lisinopril 20 mg. Because neither agent produces diuresis, natriuresis, or kaliuresis, the greater BP-lowering effect of omapatrilat compared with lisinopril in SSH may be due primarily to the added vasodilatory effects of NEP inhibition.

Acknowledgments

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References

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