Beneficial Renal and Hemodynamic Effects of Omapatrilat in Mild and Severe Heart Failure

Richard W. Troughton,* Miriam T. Rademaker,* James D. Powell, Timothy G. Yandle, Eric A. Espiner, Christopher M. Frampton, M. Gary Nicholls, A. Mark Richards

Abstract—Omapatrilat is a member of the new drug class of vasopeptidase inhibitors that may offer benefit in the treatment of heart failure (HF) through simultaneous inhibition of angiotensin-converting enzyme and neutral endopeptidase. We examined the effects of omapatrilat in a placebo-controlled crossover study using a pacing model of HF. Seven sheep were paced sequentially at 180 bpm (mild HF) and then 225 bpm (severe HF) for 7 days each. Omapatrilat (0.005 mg/kg) or vehicle was administered by intravenous bolus on days 4 to 7 of each paced period. Omapatrilat lowered mean arterial and left atrial pressure and increased cardiac output acutely and chronically in both mild and severe HF (P<0.01 for all). Plasma atrial and brain natriuretic peptide and cGMP levels were stable acutely (P=NS), while brain natriuretic peptide increased after repeated dosing in severe HF (P<0.05). Plasma renin activity rose, whereas angiotensin II and aldosterone levels fell after acute and repeated dosing in both states (P<0.01 for all). Omapatrilat increased urinary sodium excretion by day 7 in both mild and severe HF (P<0.05). Effective renal plasma flow and glomerular filtration rate increased or were stable after omapatrilat in mild and severe HF after both acute and repeated dosing. Omapatrilat exhibited pronounced acute and sustained beneficial hemodynamic and renal effects in both mild and severe heart failure. (Hypertension. 2000;36:523-530.)

Key Words: vasopeptidase inhibitor ■ peptides ■ kidney ■ renin ■ angiotensin ■ aldosterone

The neurohormonal response to cardiac injury is pivotal to the development and progression of cardiovascular disease,1 including heart failure (HF).2–4 Modulation of this response remains a key target for therapeutic intervention.5–9 Omapatrilat is a member of the new drug class vasopeptidase inhibitors, which may offer additional benefit in the treatment of HF.10 It inhibits both angiotensin-converting enzyme (ACE) and neutral endopeptidase,10 the latter participating in the metabolism of the cardiac natriuretic peptides,11,12 as well as angiotensin II (Ang II) and other vasoactive hormones.13 The expected result is simultaneous amelioration of the vasoconstrictor, sodium-retaining actions of the renin-angiotensin-aldosterone (RAA) system and potentiation of the vasodilator, natriuretic actions of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide, and the kinins.10 Dual inhibition offers potential advantages over inhibition of either enzyme alone.14–17 A major potential benefit of vasopeptidase inhibitors in the treatment of HF is preservation or even enhancement of renal function15,18 compared with ACE inhibitor therapy alone.15,19,20 Omapatrilat has demonstrated potent hypotensive effects across the spectrum of renin and volume-dependent models of hypertension.21 Early results in HF suggest beneficial hemodynamic and urinary effects14,18,22 mediated by synergistic ACE and neutral endopeptidase inhibition.23 The inhibition of metalloprotease by BMS 186716 in randomized exercise and symptoms study (IMPRESS) reported a greater improvement in New York Heart Association class and reduction in a combined mortality/hospitalization end point for patients with systolic HF receiving omapatrilat compared with ACE inhibitor alone.24 We examined the effects of first and repeated doses (over 4 days) of omapatrilat on renal function, hemodynamic indices, and neurohormones in an ovine model of mild and severe HF.

Methods

The Animal Ethics Committee of the Christchurch School of Medicine approved the study. Seven Coopworth ewes (weighing 45 to 60 kg) were instrumented, as previously described, via left lateral thoracotomy under general anesthesia induced by thiopental (17 mg/kg) and maintained with halothane and nitrous oxide.25 The animals recovered over 14 days before the study protocol began and during the study were held in metabolic cages with free access to water. They consumed a normal laboratory diet of chaff and pellets (40 mmol/d of Na+, 200 mmol/d of K+), supplemented with an additional 40 mmol NaCl tablets administered orally each morning. Urine was collected continuously via urethral catheter. Omapatrilat was provided by Bristol Myers Squibb. Pilot doses (10 to 100 μg/kg IV bolus) in 6 paced sheep with fully developed HF produced profound falls in mean arterial pressure (MAP) and renal impairment, ranging from a reversible rise in plasma creatinine to

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Predosing Baseline Values for Omapatrilat and Vehicle Phases

<table>
<thead>
<tr>
<th>Predosing Baseline</th>
<th>180/min Baseline</th>
<th>225/min Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Omapatrilat</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>93.8±3.0</td>
<td>91.6±2.4</td>
</tr>
<tr>
<td>Left atrial pressure, mm Hg</td>
<td>2.9±0.4</td>
<td>2.9±0.3</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.3±0.3</td>
<td>3.3±0.3</td>
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<tr>
<td><strong>Hormones</strong></td>
<td></td>
<td></td>
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<tr>
<td>ANP, pmol/L</td>
<td>23.5±4.4</td>
<td>27.2±6.6</td>
</tr>
<tr>
<td>BNP, pmol/L</td>
<td>5.5±1.5</td>
<td>7.5±2</td>
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<tr>
<td>cGMP, nmol/L</td>
<td>10.6±1.6</td>
<td>10.1±1.2</td>
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<tr>
<td>PRA, nmol/L·h</td>
<td>0.71±0.14</td>
<td>0.41±0.07</td>
</tr>
<tr>
<td>Ang II, pmol/L</td>
<td>30.0±4.4</td>
<td>28.2±21</td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td>477±71</td>
<td>341±46</td>
</tr>
<tr>
<td>Cortisol, pmol/L</td>
<td>75.8±20.3</td>
<td>61.9±16.6</td>
</tr>
<tr>
<td>Endothelin, pmol/L</td>
<td>1.5±0.3</td>
<td>1.7±0.3</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>92.5±11.5</td>
<td>103.4±8.1</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>127.3±19.8</td>
<td>106.6±8.7</td>
</tr>
<tr>
<td>ERPF, ml/min</td>
<td>678±129</td>
<td>655±67</td>
</tr>
<tr>
<td>Urinary cGMP, nmol</td>
<td>1.8±0.5</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>Net cGMP, nmol</td>
<td>0.5±0.3</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>24-h urinary volume, mL</td>
<td>1338±217</td>
<td>1324±187</td>
</tr>
<tr>
<td>24-h urinary Na, mmol</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Plasma Na, mmol/L</td>
<td>144.6±0.9</td>
<td>142.1±1.3</td>
</tr>
</tbody>
</table>

Values (mean±SEM) are shown for predosing, after 4 days of pacing at 180 bpm (mild HF), and after 4 days of pacing at 225 bpm (severe HF).

*P<0.05 compared with vehicle at same time.

†P<0.01 compared with vehicle at same time.

‡P<0.05 compared with predosing in same phase.

§P<0.01 compared with predosing in same phase.

¶P<0.05 compared with 180 bpm in same phase.

#P<0.01 compared with 180 bpm in same phase.

Fulminant, fatal renal failure. A dose of 5 μg/kg produced significant hemodynamic effects, preserved renal function, and resulted in significant diuresis and natriuresis.

**Study Protocol**

After the postoperative recovery period, HF was induced, as previously described,26 by left ventricular pacing at 180 bpm for 7 days (mild HF) and then at 225 bpm for an additional 7 days (severe HF). All sheep developed the hemodynamic, hormonal, and metabolic hallmarks of mild and severe low-cardiac-output HF (Table).26 The sequence was repeated after a 7-day nonpacing rest period. In a crossover design randomized for order, each animal received either vehicle (10 mL of 10% sodium bicarbonate) or omapatrilat (0.005 mg/kg) as a single intravenous bolus (administered via left atrial line) at 11 AM on days 4 to 7 of each pacing week. No treatment was given on days 1 to 3 of each week or in the nonpacing rest week. Hemodynamic measurements were determined by on-line computer-assisted analysis by methods previously described.27 In each 7-day pacing period, hemodynamic recordings (MAP, left atrial pressure, cardiac output, and heart rate) were taken with the sheep standing quietly in the metabolic cage, on day 0 (predosing); on day 4 at pretreatment baseline (the mean of 4 measurements made at 15-minute intervals for the hour before bolus administration was used in analysis); and then at 30, 60, 90, 120, 240, and 360 minutes after treatment; and on days 5 to 7, immediately before and 1 hour after treatment. The latter provided data 24 hours after the previous dose of omapatrilat and 1 hour after the current dose.

Blood for plasma hormone assays and biochemistry was drawn from the left atrial catheter immediately after hemodynamic recordings. Samples were taken in each pacing week on day 0 (predosing); on day 4 at pretreatment baseline (the mean of 2 samples taken at −30 minutes and immediately before bolus administration) and at 30, 60, 120, 240, and 360 minutes after treatment; and on days 5 to 7 at baseline and 1 hour after treatment. Blood was drawn into tubes on ice, centrifuged immediately at 4°C, and stored at −80°C until analyzed. Hormones assayed included plasma Ang II, ANP, BNP, cGMP, aldosterone, cortisol, endothelin, and an index of plasma renin activity (PRA), as previously described.15 Samples from individual sheep were assayed together to avoid interassay variability; intra-assay coefficients of variation were all <9%. Twenty-four-hour urine collections were obtained before pacing and on days 3 to 7 of each week of pacing. On day 4 of pacing, urine was collected in the hour before treatment and at 1, 2, 4, and 6 hours after treatment. Urinary volumes were noted and measurements made of concentrations of sodium, potassium (IL 943 autocal flare photometer Instrumentation Laboratories), creatinine (standard Jaffe method), and cGMP (assayed as for plasma). Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by inulin and para-aminohippurate clearance methods27 on days 0 (predosing baseline), 4 (baseline and 1, 2, 4, and 6 hours after treatment with omapatrilat...
or vehicle), and 7 (baseline and 1 hour after treatment) in each pacing week.

Statistical Analysis
Statistical analysis was performed with the Systat statistical package. Repeated-measures ANOVA was used to compare the effects of omapatrilat versus vehicle. To account for minor differences at baseline and allow comparison of the effect over 4 days of omapatrilat and vehicle administration, results are expressed as the change from baseline on day 4 before treatment (expressed as mean ± SEM). Statistical significance was assumed at \( P < 0.05 \).

Results

Baseline Indices
Baseline values on day 0 (prepacing) were matched between vehicle and omapatrilat phases (Table). There were no significant differences between day 4 predose baseline values of hemodynamic, hormonal, and renal variables in vehicle compared with omapatrilat phases, except plasma aldosterone and 24-hour urinary sodium excretion in the severe HF phase (Table). No effect of order of administration (omapatrilat versus vehicle) was demonstrated.

Hemodynamics

Compared with placebo, the first dose of omapatrilat on day 4 of pacing caused an acute fall in MAP during mild and severe HF (\( P < 0.01 \) and \( P < 0.001 \), respectively) (Figure 1). On days 5 to 7 of pacing (days 2 to 4 of treatment) during omapatrilat treatment, baseline (predose) MAP levels were lower than vehicle in both HF states (\( P < 0.001 \)). Omapatrilat caused a further acute fall in MAP on days 5 to 7 in both states compared with vehicle (\( P < 0.01 \)). After omapatrilat, left atrial pressure fell acutely from baseline in mild and severe HF compared with vehicle (both \( P < 0.001 \)). Predose baseline left atrial pressure fell progressively with omapatrilat in both phases (\( P < 0.001 \) for both). Omapatrilat caused a further acute fall in left atrial pressure on days 5 to 7 in both states (\( P < 0.05 \) versus vehicle). Cardiac output increased acutely in mild and severe HF after omapatrilat compared with vehicle (\( P < 0.05 \) for both). Cardiac output tended to fall at baseline (predose) during vehicle phase and to decline further 1 hour after vehicle administration. Cardiac output remained stable (mild HF) or increased (severe HF) from baseline on day 4 during the remainder of the omapatrilat treatment week (\( P < 0.001 \)). Furthermore, cardiac output rose acutely after omapatrilat on day 7 (\( P < 0.01 \) for both HF states versus vehicle). The absolute change in these hemodynamic variables was not statistically different between mild and severe HF.
Neurohormonal Effects

The first dose of omapatrilat produced an acute rise in PRA in both states compared with vehicle ($P<0.01$ for both), with a more marked effect in severe HF ($P<0.05$) (Figure 2). Baseline (predose) levels of PRA on days 5 to 7 were similar for mild and severe HF and not significantly different between omapatrilat and vehicle phases. However, the acute rise in PRA after successive omapatrilat doses ($P<0.01$; both states versus vehicle) became more marked in mild than severe HF ($P<0.05$). Plasma Ang II levels fell acutely after the first dose of omapatrilat in both phases ($P<0.01$ for both), again more markedly in the severe state ($P<0.05$). Baseline Ang II levels on day 5 to 7 were lower with omapatrilat than vehicle in both HF states ($P<0.05$), with further pronounced falls after omapatrilat, especially in severe HF ($P<0.05$). Plasma aldosterone levels fell acutely in both HF states ($P<0.001$ for both), more so in severe HF ($P<0.01$). During treatment with omapatrilat, baseline aldosterone levels on day 7 were lower than pretreated baseline levels versus vehicle ($P<0.01$), more so in severe HF ($P<0.001$), and fell acutely after omapatrilat in both phases ($P<0.01$ for both). Plasma levels of the cardiac peptides ANP and BNP and second messenger cGMP were unchanged compared with vehicle after the first dose of omapatrilat. Baseline ANP and BNP levels on day 5 to 7 were lower with omapatrilat than vehicle in both HF states ($P<0.05$), with further pronounced falls after omapatrilat, especially in severe HF ($P<0.05$). Plasma cGMP levels were lower during treatment with omapatrilat compared

Figure 2. Effects of acute and repeated dosing with omapatrilat on change in plasma levels of ANP, BNP, cGMP, renin activity (PRA), Ang II, and aldosterone in mild and severe HF. Results are expressed as mean±SEM.
with vehicle ($P=\text{NS}$) and tended to rise on day 7 with omapatrilat, mirroring BNP ($P=\text{NS}$) (Figure 2).

Renal Effects

Urinary volume was maintained after the first dose of omapatrilat in mild and severe HF compared with placebo ($P=\text{NS}$) (Figure 3). Daily urinary volume increased in both HF states with omapatrilat ($P=0.005$ versus vehicle), more markedly and in stepwise fashion in severe HF (up to 3000 mL on day 7; $P<0.05$ compared with mild). Urinary sodium excretion increased from baseline in both mild and severe HF after the first dose of omapatrilat ($P<0.01$ versus vehicle for both). Daily sodium excretion also was higher after repeated dosing with omapatrilat compared with placebo ($P<0.05$ versus vehicle; Figure 3). ERPF was increased by the first dose of omapatrilat in mild and severe HF ($P<0.001$ for both versus vehicle) (Figure 4), with a greater effect in mild HF ($P=0.03$). Baseline predose ERPF increased with repeated doses of omapatrilat and fell with placebo ($P<0.01$). ERPF rose acutely with omapatrilat on day 7 in severe HF ($P<0.05$) and was maintained in mild HF compared with vehicle. GFR and net renal production of cGMP were sustained at or above time-matched vehicle levels with acute and repeated administration of omapatrilat in both mild and severe HF (Figure 4).

Discussion

HF is characterized by neurohormonal activation.\textsuperscript{2,3} With increasing severity of left ventricular dysfunction, the deleterious effects of increasing RAA system activity and other vasoconstrictor hormones outweigh the beneficial actions of
increased levels of the cardiac peptides and other vasodilator hormones.² ACE inhibitors, now established as frontline therapy for systolic HF⁷ and vascular disease,¹ demonstrate the benefit of inhibiting the RAA system. Paradoxically, any benefits from ACE inhibitor in moderate to severe left ventricular dysfunction occur notwithstanding a fall in circulating levels of the cardiac peptides, and diuretics likewise reduce their levels.²⁹,³⁰ There have been concerns regarding the effects of ACE inhibitor on renal function in more severe grades of HF, particularly in diabetics, when high diuretic doses are required, or if there is concomitant renovascular disease.¹⁹,²⁰ Vasopeptidase inhibitors act on both ACE and neutral endopeptidase, producing simultaneous reduction in Ang II formation and augmentation of circulating cardiac peptide levels.¹⁰ As has been demonstrated with omapatrilat and other agents, synergistic dual inhibition can produce potent antihypertensive actions, beneficial renal effects, and other potential benefits.¹⁰,¹⁵,¹⁷,¹⁸ There is, however, little information on their effects in HF under vehicle-controlled conditions. We examined the effects of the vasopeptidase inhibitor omapatrilat in an established pacing model²⁶ of both mild HF, in which there is sodium balance and activation of the cardiac peptides but not the RAA system, and severe HF, in which there is activation of both cardiac peptides and the RAA system and also marked sodium retention and volume overload.³¹ Omapatrilat induced substantial, well-tolerated, beneficial hemodynamic effects. The absolute changes in MAP, left atrial pressure, and cardiac output with omapatrilat were similar in both phases, and therefore the relative changes were greater in severe HF, likely reflecting greater activation of both the RAA system and the cardiac peptides in this state.²⁶ A continuing trend for falling left atrial pressure and rising cardiac output with repeated doses of omapatrilat was most marked in severe HF. Stable baseline levels were

Figure 4. Effects of acute and repeated dosing with omapatrilat on ERPF, GFR, urinary cGMP excretion, and net urinary cGMP excretion in mild and severe HF. Results are expressed as mean±SEM.
not achieved in either HF state after 4 doses. The effects of each dose of omapatrilat on hemodynamic variables was sustained, in most instances, for 24 hours, and further acute improvements were seen 1 hour after the subsequent bolus injection of omapatrilat.

Omapatrilat produced falls in Ang II and aldosterone, most profound in severe HF, with levels falling within 1 hour after the first dose of omapatrilat and remaining suppressed thereafter. After the first dose of omapatrilat, plasma levels of ANP, BNP, and second messenger did not change relative to vehicle, although there was a trend to lower levels in severe HF. This effect, of preserved ANP and BNP levels despite significant falls in left atrial pressure and MAP, is similar to that seen in other studies with combined ACE and neutral endopeptidase inhibition and differs from isolated ACE inhibition, which usually causes distinct, statistically significant falls in plasma levels of the cardiac peptides, or isolated neutral endopeptidase inhibition, in which ANP and BNP may be augmented or remain stable. Baseline levels of the cardiac peptides and cGMP were lower on day 2 with omapatrilat, probably reflecting hemodynamic changes leading to reduced atrial and ventricular distending pressure (the major stimulus to cardiac peptide secretion). However, within several days treatment levels increased both before and after dosing. It is possible that once the hemodynamic effects of omapatrilat are fully established, the effect of neutral endopeptidase inhibition on peptide clearance begins to predominate over the initial reduction in secretion (which reflects initial cardiac decompression), with consequent net increase in tissue and plasma cardiac peptides and cGMP. If so, greater cardiac peptide augmentation may occur with further doses once stable hemodynamics are established.

Omapatrilat produced beneficial renal effects. Despite falls in renal perfusion pressure, urinary volume and sodium excretion were maintained or increased after administration of omapatrilat in both mild and severe HF. This likely reflects neutral endopeptidase inhibition. Although isolated ACE inhibition may produce transient, minor natriuresis in mild HF, this is unlikely in severe HF, when GFR is low and often falls further with ACE inhibition. These results are consistent with a recent study in mild HF that demonstrated augmented natriuresis by omapatrilat compared with pure ACE inhibitor (fosinoprilat). In our study, despite significant hemodynamic changes and falling renal perfusion pressure, ERPF increased with omapatrilat, most markedly in mild HF. While this pattern could be consistent with isolated ACE inhibition, the trend to improvement of GFR in severe HF is not an expected ACE inhibitor effect and presumably reflects neutral endopeptidase inhibition. By contrast with these results, our previous studies in this severe HF model demonstrated a progressive decline in endogenous creatinine clearance with repeated doses of the ACE inhibitor captopril. The beneficial renal hemodynamic effects of omapatrilat in this study may be mediated by local enhancement of ANP, BNP, or urodilatin levels within the kidney. ANP increases efferent glomerular arteriolar tone, one mechanism by which GFR may be maintained in the current setting.

Our study did not allow direct comparison of omapatrilat with pure ACE inhibition. Nevertheless, there is clear evidence of dual neutral endopeptidase and ACE inhibition. While some effects of omapatrilat in this study could be attributed to its powerful ACE inhibitor action, other effects, such as early maintenance and later enhancement of plasma cardiac peptide levels and, more particularly, the diuresis/natriuresis in both mild and severe HF, are not consistent with pure ACE inhibitor. Our results are consistent with recently presented studies comparing omapatrilat with ACE inhibitor in large-animal models, in which omapatrilat produced similar hemodynamic and natriuretic effects in mild HF, effects that were blocked by specific natriuretic peptide receptor antagonism.

Omapatrilat offers potential treatment benefits in HF and hypertension. This is the first study to demonstrate the beneficial effects of its dual actions in both mild and severe HF. These actions, including substantial hemodynamic effects to reduce preload and afterload, preservation of renal blood flow and GFR, and augmentation of natriuresis even in severe HF, indicate that omapatrilat may add benefit beyond current treatment.

Acknowledgments

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References


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