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Vasopeptidase Inhibition With Omapatrilat in Chronic Heart Failure: Acute and Long-Term Hemodynamic and Neurohumoral Effects

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OBJECTIVES We investigated the acute and long-term hemodynamic and neurohumoral effects of the vasopeptidase inhibitor omapatrilat in human heart failure.

BACKGROUND Angiotensin-converting enzyme (ACE) inhibition constitutes a major advance in the treatment of chronic heart failure (CHF). Simultaneous inhibition of both neutral endopeptidase and ACE with omapatrilat may represent a new treatment strategy in CHF.

METHODS Three hundred and sixty-nine patients with symptomatic heart failure were randomized to double-blind treatment with omapatrilat (first 190 patients: 2.5 mg, 5 mg or 10 mg; last 179 patients: 2.5 mg, 20 mg or 40 mg once daily) for 12 weeks.

RESULTS Acutely, the 10 mg, 20 mg and 40 mg doses of omapatrilat produced greater reductions in pulmonary capillary wedge pressure (PCWP), systolic blood pressure (SBP) and systemic vascular resistance compared with 2.5 mg. Higher doses were associated with greater increases in vasodilator and natriuretic peptides, in addition to ACE inhibition. After 12 weeks, omapatrilat 20 mg and 40 mg showed greater falls from baseline in PCWP (40 mg: 0 h to 12 h average change -7.3 ± 0.8 mm Hg) and SBP (40 mg: -11.7 ± 1.7 mm Hg) than 2.5 mg (both $p < 0.01$ vs. 2.5 mg). The incidence of adverse experiences and patient withdrawal were similar in all groups.

CONCLUSIONS In CHF, the acute hemodynamic benefit seen with higher doses of omapatrilat was associated with increases in plasma vasodilator and natriuretic peptide levels in addition to ACE inhibition. After 12 weeks, the hemodynamic benefit was maintained. Omapatrilat may be a promising new agent in CHF. (J Am Coll Cardiol 2002;39:2034–41) © 2002 by the American College of Cardiology Foundation

Angiotensin-converting enzyme (ACE) inhibition constitutes a major advance in the treatment of chronic heart failure (CHF), with symptomatic improvement and some survival gains (1). However, despite the first line use of ACE inhibitors and, more recently, beta-adrenergic blocking agents, the prognosis of CHF remains poor (1,2).

The natriuretic peptides are counter-regulatory to the renin-angiotensin system, causing vasodilation, diuresis and natriuresis (3–5). Augmentation of their levels with exogenously administered atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) has resulted in a reduction in filling pressures, natriuresis and diuresis in acute studies in CHF (4,5). However, their therapeutic usefulness is limited by a short half-life, due to rapid degradation by neutral endopeptidase (NEP) (6). Other NEP substrates include bradykinin (7) and adrenomedullin (ADM) (8).

Omapatrilat is the first of a new class of drugs known as vasopeptidase inhibitors, which simultaneously inhibit both NEP and ACE, resulting in increased levels of natriuretic peptides and bradykinin, with a reduction in angiotensin II (9,10). In patients with heart failure, omapatrilat therapy for 24 weeks showed a similar increase in week 12 exercise tolerance but conferred more benefit than lisinopril in the composite of death, hospital admission or discontinuation of study treatment for worsening heart failure (11).

The purpose of this multicenter study was to evaluate the hemodynamic and neurohumoral effects, safety and tolerability of increasing doses of omapatrilat after a single oral dose and after 12 weeks of once-daily oral therapy in patients with symptomatic heart failure.

METHODS

Study design. Patients with stable symptomatic heart failure (New York Heart Association functional class II to IV),

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ADM = adrenomedullin
ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
cGMP = cyclic 3′,5′-guanosine monophosphate
CHF = chronic heart failure
CI = cardiac index
ET-1 = endothelin-1
NEP = neutral endopeptidase
PCWP = pulmonary capillary wedge pressure
SBP = systolic blood pressure
SVR = systemic vascular resistance

left ventricular ejection fraction ≤40% and in sinus rhythm were eligible for enrollment in this multicenter double-blind, randomized study. The protocol was approved by local ethical committees, and all patients gave written, informed consent.

Studies in normal human volunteers have shown evidence of significant ACE inhibition with 2.5 mg to 75 mg doses of omapatrilat (12,13), while dose-related NEP inhibition, as measured by changes in urinary ANP and urinary cyclic 3′,5′-guanosine monophosphate (cGMP), was shown from the 7.5-mg to the 75-mg dose (12). In contrast, the 2.5-mg omapatrilat dose, although showing selective ACE inhibition, did not change urinary ANP and cGMP. Since ethical considerations excluded a placebo control, the 2.5-mg dose was used as an active control.

The study was conducted in two sequential, separate panels. In panel I, patients were randomized to omapatrilat 2.5 mg, 5 mg or 10 mg once daily. In panel II, patients were randomized to omapatrilat 2.5 mg, 20 mg or 40 mg once daily. An analysis of safety data from the completed panel I was performed before panel II started. Patients who were in panel I were not eligible for panel II.

After enrollment, there was a 2- to 14-day single-blind placebo lead-in period, where patients were stabilized on diuretics and concomitant cardiac medications, with doses remaining stable for ≥2 days before right heart catheterization. Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists were withdrawn for at least four days before randomization. Patients were admitted for right heart catheterization, performed at least 12 h before baseline measurements. After an overnight fast, a minimum of two baseline recordings (30 min apart with <10% variability) with mean pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg; cardiac index (CI) ≤3.0 l/min/m^2 and SBP ≥90 mm Hg were required to enter the 24-h hemodynamic assessment phase.

Patients who qualified were then randomized to double-blind therapy. Repeat hemodynamic measurements were made at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 9 h, 12 h and 24 h after the first dose of the study drug. All other cardiac medications were withheld over the 24-h period of hemodynamic monitoring.

Subjects were continued for 12 weeks on double-blind study drug. All other medications (except ACE inhibitors or angiotensin II receptor antagonists) were restarted and continued throughout the 12 weeks. Outpatient evaluations were performed at weeks 1, 2, 4, 6 and 8. Up to four supplemental doses of diuretics were permitted for worsening heart failure, with no supplemental doses permitted within 72 h before hemodynamic measurements. Patients were withdrawn from the study if an increase in the daily maintenance dose of diuretic or other heart failure medication was required. The diuretic dose could be decreased to correct serum creatinine >3.0 mg/dl (265 μmol/l) or to correct symptomatic hypotension.

After 12 weeks, patients underwent a second right heart catheterization. On the morning of the next day, the study medication was administered after two consecutive predose recordings showed ≤10% variability in PCWP and CI; repeat measurements were performed over a similar 24-h period as on day 1. All other medications were withheld during the 24-h period.

Methodology. Hemodynamic assessment was performed the day after placement of a balloon-tipped thermodilution catheter in the pulmonary artery. Pulmonary arterial pressures and electrocardiogram were measured continuously, cardiac output was measured by the thermodilution technique, and arterial blood pressures by brachial sphygmomanometry. All measurements were performed in triplicate in the semisupine position. Cardiac index and systemic vascular resistance (SVR) were calculated using standard formulas (14). Physician and subject assessments of the change in functional status were performed at three months or on withdrawal from study using a global assessment scale: improved (greatly, moderately or slightly), unchanged or worsened. Subjects participating in the neurohormonal substudy had venous blood drawn during both hemodynamic monitoring periods (day 1 and week 12), predose and at 3 h, 12 h and 24 h after dose.

Measurement of plasma ANP, BNP, cGMP, ADM, aldosterone, endothelin-1 (ET-1), renin and ACE activity was performed by radioimmunoassay, and norepinephrine and epinephrine by higher performance liquid chromatography (12,15–21). All samples were analyzed in duplicate. Intraassay coefficients of variation were <9%.

Statistical analysis. The primary efficacy measure was the change from baseline in PCWP determined at week 12. A sample size of 45 subjects per group in panel I and 35 subjects per group in panel II was planned to allow detection with power = 0.80 of a 4.3 mm Hg (4.9 mm Hg in panel II) mean difference in PCWP between the high and low dose groups (standard deviation of difference assumed = 7.3 mm Hg).

A time-weighted average change from baseline (baseline defined as the day 1 predose value) was calculated for each hemodynamic parameter, averaged over the first 12 h after the first dose (acute response) and over the first 12 h after the last dose (week 12 response). The acute and week 12

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Table 1. Baseline Demographics

	Panel I			Panel II		
Omapatrilat Dose	**2.5 mg**	**5 mg**	**10 mg**	**2.5 mg**	**20 mg**	**40 mg**
Total No.	**63**	**66**	**61**	**59**	**58**	**62**
Age (yrs), mean (SD)	60.4 (11.5)	59.6 (12.8)	62.2 (12.7)	58.7 (11.1)	61.0 (10.5)	60.3 (11.2)
NYHA functional class (%)						
II	22 (35)	17 (26)	28 (46)	26 (44)	29 (50)	23 (37)
III	37 (59)	46 (70)	29 (48)	32 (54)	27 (47)	34 (55)
IV	4 (6)	3 (5)	4 (7)	1 (2)	2 (3)	5 (8)
LVEF (%), mean (SD)	23.3 (8.5)	24.3 (7.7)	23.4 (7.7)	23.1 (6.6)	25.6 (7.9)	23.5 (8.5)
CHF duration (months), mean (SD)	43.8 (39.0)	38.6 (33.0)	42.1 (46.9)	43.9 (38.9)	45.9 (50.0)	47.6 (40.9)
Etiology of heart failure						
Ischemic	35 (56%)	45 (68%)	36 (59%)	40 (68%)	33 (57%)	37 (60%)
Idiopathic	18 (29%)	15 (23%)	16 (26%)	14 (24%)	15 (26%)	18 (29%)
Hypertensive	7 (11%)	4 (6%)	7 (11%)	5 (8%)	8 (14%)	5 (8%)
Valvular	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	1 (2%)	2 (3%)	2 (3%)	0 (0%)	2 (3%)	4 (2%)
Baseline hemodynamic measurements, mean (SE)						
PCWP (mm Hg)	21.6 (0.7)	23.2 (0.9)	22.9 (1.0)	22.4 (0.8)	22.2 (0.9)	22.2 (0.7)
CI (l/min/m^2)	2.29 (0.06)	2.22 (0.06)	2.18 (0.06)	2.27 (0.06)	2.39 (0.06)	2.30 (0.06)
SBP (mm Hg)	129.2 (2.5)	127.2 (2.2)	132.0 (2.7)	131.8 (2.6)	135.3 (2.9)	129.6 (2.7)
MSAP (mm Hg)	94.2 (1.4)	92.8 (1.3)	94.8 (1.6)	95.5 (1.8)	94.9 (1.8)	93.9 (1.8)
SVR (dynes.s/cm^5)	1,645 (51)	1,607 (53)	1,715 (67)	1,602 (55)	1,577 (61)	1,612 (54)
Previous cardiovascular medications						
Beta-blockers	9 (14%)	15 (23%)	8 (13%)	20 (34%)	20 (34%)	21 (34%)
Diuretics	58 (92%)	62 (94%)	54 (89%)	52 (88%)	54 (93%)	59 (95%)
ACE inhibitors	55 (87%)	60 (91%)	54 (89%)	51 (86%)	48 (83%)	50 (81%)
A II inhibitors	7 (11%)	6 (9%)	4 (7%)	6 (10%)	6 (10%)	7 (11%)

A II = angiotensin II; ACE = angiotensin-converting enzyme; CHF = congestive heart failure; CI = cardiac index; LVEF = left ventricular ejection fraction; MSAP = mean systolic arterial pressure; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; SVR = systemic vascular resistance.

time-weighted changes were each evaluated by analysis of covariance, with resulting comparisons of each dose group to its corresponding 2.5 mg control group made using Fisher least significant difference test. Comparisons were made within panels only, so as to reflect the manner in which the randomization was performed. All tests were two-sided with alpha = 0.05. To maintain control of the type I error at alpha, pairwise testing to the 2.5 mg control dose was performed in a sequential manner, from the highest dose on down, with the testing sequence stopping upon identifying a dose with a nonsignificant ($p > 0.05$) result.

For neurohormones the change from baseline (baseline defined as the day 1 predose value) was calculated for each parameter at 3 h, 12 h and 24 h after the first dose of study medication and at the same time points after the last dose of study medication at week 12. A 95% confidence interval for the mean change at each time point compared with the 2.5-mg control was calculated for each dose group.

New York Heart Association functional changes, as well as assessments of change in heart failure status, were compared among dose groups within each panel using the Cochran-Mantel-Haenszel test. For describing safety, including the incidence of adverse events, data from the two 2.5-mg dose groups were pooled.

RESULTS

Of the 565 patients who were enrolled, 369 met the entrance criteria, with 190 randomized in panel I of the study and 179 in panel II (Table 1). Nine patients did not complete the first 24-h assessment, and 79 discontinued before week 12. Hemodynamic data were available for the first 24 h and after 12 weeks of therapy in 360 and 281 patients, respectively. Fifty-nine patients in panel I and 44 patients in panel II (divided evenly among dose groups) completed the neurohormonal substudy.

Hemodynamic measurements. After the initial dose of omapatrilat, the 0-h to 12-h average reduction in PCWP from baseline was significantly greater in the 10 mg, 20 mg and 40 mg groups (all $p < 0.01$ vs. 2.5 mg) (Table 2). After 12 weeks of therapy, the 0-h to 12-h average reduction in PCWP from baseline (baseline defined as the day 1 predose value) was significantly greater with the 20 mg and 40 mg doses (both $p < 0.01$ vs. 2.5 mg) (Fig. 1a). Cardiac index did not change with higher doses compared with 2.5 mg acutely, or after chronic therapy.

Dose-related falls in systolic blood pressure (SBP) were seen acutely. On day 1, the 0-h to 12-h average reduction in SBP from baseline was significantly greater in the 10 mg, 20 mg and 40 mg groups (all $p < 0.01$ vs. 2.5 mg). After 12 weeks, greater falls from baseline in SBP were seen with

Table 2. Average Changes From Baseline in Hemodynamic Variables

	Panel I			Panel II		
	2.5 mg	5 mg	10 mg	2.5 mg	20 mg	40 mg
PCWP (mm Hg)						
0–12 h Δ day 1	−3.2 ± 0.5	−3.8 ± 0.5	−5.9 ± 0.5†	−3.6 ± 0.4	−7.2 ± 0.4†	−7.5 ± 0.4†
24 h day 1	−2.4 ± 0.7	−1.6 ± 0.7	−3.6 ± 0.7	−2.6 ± 0.7	−3.6 ± 0.7	−3.4 ± 0.7
Predose week 12	−2.0 ± 1.0	−3.2 ± 1.0	−4.3 ± 1.0	−2.5 ± 1.0	−3.4 ± 1.1	−3.4 ± 1.1
0–12 h Δ week 12	−5.0 ± 0.8	−5.5 ± 0.8	−7.1 ± 0.9	−3.6 ± 0.8	−7.1 ± 0.8†	−7.3 ± 0.8†
CI (l/min/m^2)						
0–12 h Δ day 1	0.07 ± 0.03	0.11 ± 0.03	0.13 ± 0.03	0.10 ± 0.04	0.14 ± 0.04	0.07 ± 0.04
24 h day 1	0.09 ± 0.05	0.16 ± 0.05	0.17 ± 0.05	0.09 ± 0.05	0.21 ± 0.05	0.11 ± 0.05
Predose week 12	−0.08 ± 0.07	0.10 ± 0.07	0.11 ± 0.08	0.14 ± 0.06	0.20 ± 0.07	0.17 ± 0.06
0–12 h Δ week 12	0.00 ± 0.07	0.12 ± 0.07	0.15 ± 0.07	0.12 ± 0.06	0.21 ± 0.06	0.15 ± 0.06
SBP (mm Hg)						
0–12 h Δ day 1	−4.9 ± 1.1	−7.1 ± 1.1	−13.3 ± 1.2†	−4.3 ± 1.2	−13.5 ± 1.2†	−14.9 ± 1.2†
24 h day 1	−4.6 ± 2.0	0.4 ± 2.0	−7.7 ± 2.1	−3.8 ± 1.8	−3.8 ± 1.6	−5.6 ± 1.5
Predose week 12	−4.5 ± 1.6	−1.5 ± 1.6	−6.2 ± 1.7	−2.0 ± 2.1	−4.5 ± 2.2	−5.6 ± 2.1
0–12 h Δ week 12	−8.6 ± 1.6	−5.8 ± 1.7	−11.4 ± 1.7	−4.6 ± 1.7	−10.7 ± 1.7*	−11.7 ± 1.7†
MSAP (mm Hg)						
0–12 h Δ day 1	−3.9 ± 0.8	−5.0 ± 0.8	−9.5 ± 0.8†	−3.4 ± 0.8	−10.3 ± 0.8†	−11.5 ± 0.8†
24 h day 1	−2.2 ± 0.9	0.1 ± 0.8	−4.5 ± 0.9	−2.0 ± 1.1	−3.3 ± 1.2	−4.2 ± 1.1
Predose week 12	−4.4 ± 1.3	−0.3 ± 1.3	−2.9 ± 1.3	−1.7 ± 1.4	−4.0 ± 1.5	−5.1 ± 1.4
0–12 h Δ week 12	−6.9 ± 1.2	−3.6 ± 1.2	−7.1 ± 1.2	−4.1 ± 1.2	−8.5 ± 1.2*	−9.9 ± 1.2†
SVR (dynes.s/cm^{-5})						
0–12 h Δ day 1	−99 ± 27	−146 ± 27	−234 ± 28*	−94 ± 30	−209 ± 31*	−190 ± 30*
24 h day 1	−76 ± 39	−81 ± 37	−182 ± 39	−71 ± 40	−181 ± 40	−112 ± 39
Predose week 12	8 ± 57	−30 ± 57	−119 ± 59	−118 ± 50	−116 ± 52	−181 ± 30
0–12 h Δ week 12	−77 ± 46	−99 ± 47	−199 ± 49	−146 ± 43	−175 ± 42	−199 ± 42
HR (beats/min)						
0–12 h Δ day 1	1.5 ± 0.8	0.4 ± 0.8	−1.2 ± 0.8	0.7 ± 0.7	0.3 ± 0.7	−1.7 ± 0.6*
24 h day 1	4.1 ± 1.0	3.2 ± 0.9	0.5 ± 1.0	1.4 ± 1.0	4.1 ± 1.0	2.6 ± 1.0
Predose week 12	−1.6 ± 1.3	−2.4 ± 1.3	−2.2 ± 1.3	−2.3 ± 1.3	−2.4 ± 1.4	−5.6 ± 1.3
0–12 h Δ week 12	−0.2 ± 1.2	−0.8 ± 1.3	−0.7 ± 1.3	−1.4 ± 1.2	−1.9 ± 1.2	−3.3 ± 1.2
PADP (mm Hg)						
0–12 h Δ day 1	−1.9 ± 0.4	−2.9 ± 0.4	−5.4 ± 0.4*	−2.4 ± 0.4	−5.5 ± 0.4†	−5.8 ± 0.4†
24 h day 1	−0.9 ± 0.7	−1.2 ± 0.7	−3.5 ± 0.7	−1.9 ± 0.7	−1.2 ± 0.8	−2.4 ± 0.7
Predose week 12	−1.3 ± 0.9	−1.9 ± 0.9	−3.8 ± 0.9	−1.9 ± 1.0	−2.5 ± 1.0	−2.6 ± 1.0
0–12 h Δ week 12	−3.3 ± 0.8	−3.7 ± 0.8	−5.7 ± 0.8	−2.9 ± 0.8	−5.9 ± 0.8*	−5.0 ± 0.8
MRAP (mm Hg)						
0–12 h Δ day 1	−0.9 ± 0.3	−1.6 ± 0.3	−1.7 ± 0.3	−0.8 ± 0.2	−2.4 ± 0.2†	−2.3 ± 0.2†
24 h day 1	−0.3 ± 0.5	−1.1 ± 0.5	−1.3 ± 0.6	−2.1 ± 0.5	−1.2 ± 0.6	−1.3 ± 0.6
Predose week 12	−1.4 ± 0.5	−0.9 ± 0.8	−1.2 ± 0.6	−1.2 ± 0.6	−1.5 ± 0.7	−0.4 ± 0.6
0–12 h Δ week 12	−2.0 ± 0.5	−1.5 ± 0.5	−1.9 ± 0.6	−1.1 ± 0.5	−2.8 ± 0.5*	−1.8 ± 0.5

Average changes from predose day one baseline (mean ± SEM). 0–12 hΔ day 1 = 0–12 h average change after first omapatrilat dose; 24 h day 1 = change at 24 h after first dose; predose week 12 = change from predose day 1; 0–12 hΔ week 12 = 0–12 h average change after final omapatrilat dose. *$p < 0.05$; †$p < 0.01$, vs. 2.5 mg dose.
HR = heart rate; MRAP = mean right atrial pressure; PADP = pulmonary artery diastolic pressure. Other abbreviations as in Table 1.

both the 20 mg ($p < 0.05$) and 40 mg ($p < 0.01$) doses compared with 2.5 mg (Fig. 1b).

On day 1, SVR fell more with the 10 mg, 20 mg and 40 mg doses (all $p < 0.05$ vs. 2.5 mg). At week 12, SVR tended to fall in all groups; reductions from baseline in SVR with higher doses of omapatrilat were not significantly greater than in the 2.5-mg groups. Acutely, heart rate was reduced more in the 40-mg group ($p < 0.05$ vs. 2.5 mg), with no difference after chronic dosing.

Neurohormones. On day 1, changes in neurohormones occurred mainly at 3 h after dose (Table 3). By 12 h all neurohormones had returned to baseline levels, except plasma ACE activity and plasma renin. Plasma ACE activity decreased from baseline in all dose groups, with a greater reduction seen at all dose groups above 2.5 mg. Plasma renin increased from baseline at 12 h and 24 h in all dose groups except 2.5 mg. Greater increases in plasma ANP were seen at 3 h with 10 mg (22 ± 8 pmol/l), 20 mg and 40 mg doses compared with the 2.5 mg control groups. This was mirrored by dose-related increases in the plasma second messenger cGMP. Brain natriuretic peptide also increased at 3 h with 10 mg (7 ± 2 pmol/l) and 40 mg compared with 2.5 mg. The 40-mg dose also caused a greater rise in plasma ADM at 3 h versus 2.5-mg control, with no difference in aldosterone. Plasma ET-1 and norepinephrine both showed an initial rise at 3 h with 40 mg compared with 2.5 mg.

After 12 weeks of chronic therapy, the increase in plasma renin from predose day 1 baseline levels was higher with 40 mg (2.2 ± 0.5 nmol/l/h) compared with 2.5 mg (0.1 ±

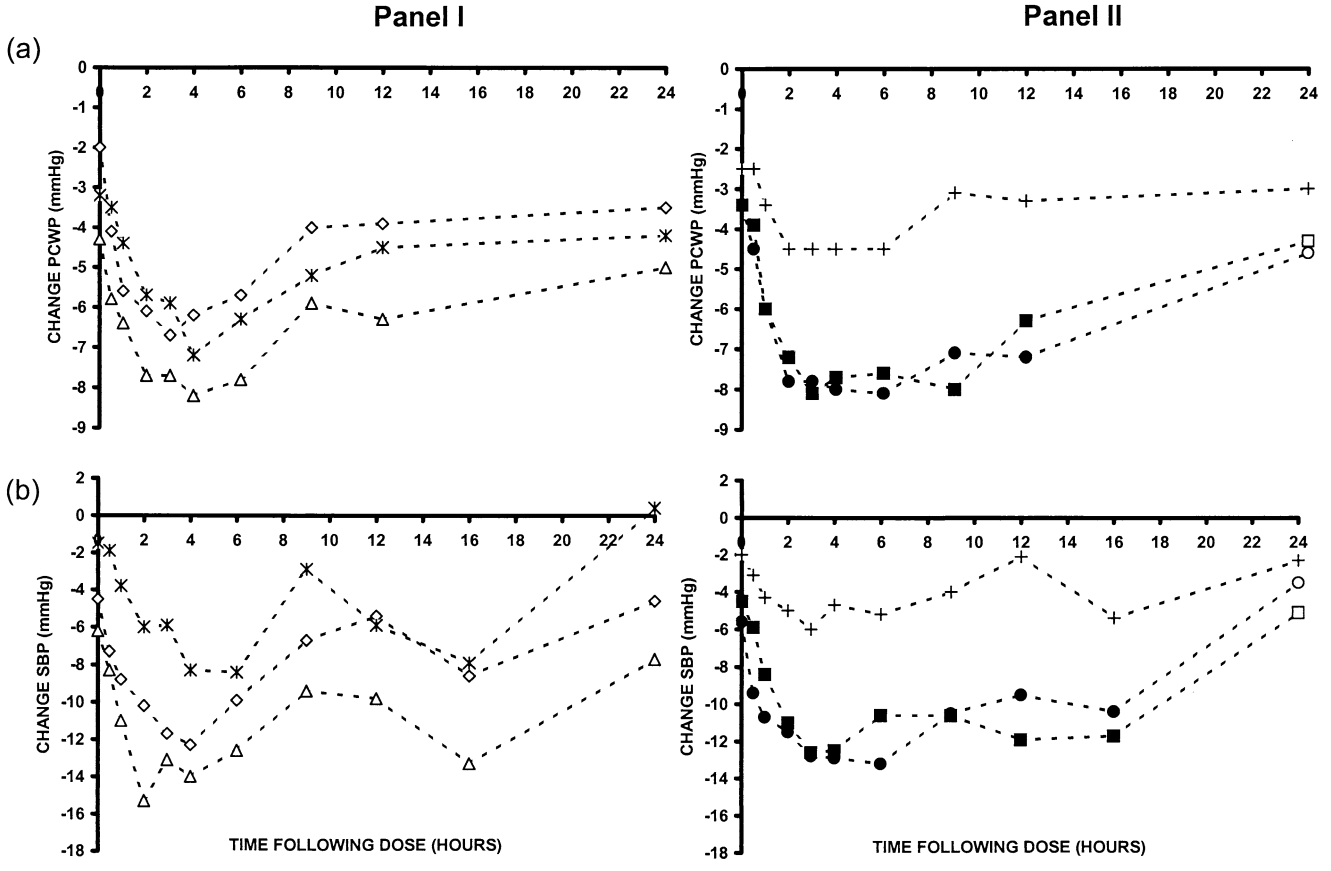

Figure 1. Change from pretreatment day 1 baseline levels in pulmonary capillary wedge pressure (PCWP) **(a)** and systolic blood pressure (SBP) **(b)** after the final dose of omapatrilat at 12 weeks. **Panel I**: **open diamond** = 2.5 mg; **star** = 5 mg; **open triangle** = 10 mg. **Panel II**: **+** = 2.5 mg; **open square** = 20 mg; **open circle** = 40 mg. **Shaded symbols** indicate a significant difference ($p < 0.05$) in the 0-h to 12-h average change from predose day 1 for omapatrilat dose compared with the respective 2.5 mg group.

0.6 nmol/l/h, mean difference 2.3 nmol/l/h; 95% confidence interval: 0.6 to 3.8) and remained elevated at all time points after final dose. Plasma ACE activity decreased 3 h after final dose in the 10 mg, 20 mg and 40 mg (−21 ± 1.0 nmol/ml/min) groups compared with 2.5 mg (−11 ± 1 nmol/ml/min) (mean difference −9.8 nmol/ml/min; 95% confidence interval: −14 to −6). Atrial natriuretic peptide tended to increase at 3 h with 40 mg (56 ± 21 pmol/l) compared with 2.5 mg (1 + 23 pmol/l) (mean difference 55 pmol/l; 95% confidence interval: −9 to 118). There were no changes in any other neurohormone (including ET-1 and norepinephrine) at 12 weeks.

Safety and tolerability. Nine patients were withdrawn after the first dose. Four withdrew due to first-dose hypotension, but there were no serious consequences (Table 4). Incidence of first dose hypotension was 0% on 2.5 mg, 3% on 5 mg, 9.8% on 10 mg, 5.2% on 20 mg and 8.1% on 40 mg. Angioedema was reported in one subject, after the first dose of omapatrilat 40 mg.

Over the 12 weeks, there were eight deaths spread evenly among the groups. The percentage of patients who discontinued was similar in all groups (Table 4). Overall adverse experiences occurred with a similar frequency in all groups. The incidence of symptomatic hypotension at any time over 12 weeks was 4.9% on 2.5 mg, 7.6% on 5 mg, 16.4% on 10 mg, 20.7% on 20 mg and 12.9% on 40 mg. The overall incidence of cough was 11.4%, with 9.8% on 2.5 mg, 12.1% on 5 mg, 11.5% on 10 mg, 6.9% on 20 mg and 17.7% on 40 mg. Exacerbation of heart failure was seen in 30.3% on 2.5 mg; 27.3% on 5 mg; 26.2% on 10 mg; 25.9% on 20 mg and 19.4% on 40 mg (p = NS). New York Heart Association functional class improved in all groups, with no difference between groups for the physician and subject global assessments of change in heart failure status.

DISCUSSION

Vasodilation and fluid volume are regulated by a number of interrelated neurohumoral systems, including the renin-angiotensin-aldosterone system and the natriuretic peptides. This study evaluated the hemodynamic effects of the vasopeptidase inhibitor omapatrilat and its effect on these systems.

Acute effects. The 2.5-mg control dose caused a fall in plasma ACE activity, without changes in plasma natriuretic peptide levels, consistent with the action of an ACE inhibitor. The degree of ACE inhibition intensified as the dose was increased, resulting in beneficial hemodynamic

Table 3. Changes From Baseline in Plasma Neurohormones at 3 h on Day 1 (Panel II)

	Dose (mg)	Changes at 3 h From Predose Baseline	Difference (95% CI) vs. Omapatrilat 2.5 mg
ANP (pmol/l)	2.5	6 ± 11	
	20	48 ± 11	43 (11, 74)
	40	53 ± 10	47 (17, 77)
BNP (pmol/l)	2.5	−0 ± 2	
	20	4 ± 2	4 (−1, 9)
	40	8 ± 2	9 (4, 13)
cGMP (nmol/l)	2.5	3 ± 2	
	20	8 ± 2	5 (1, 10)
	40	12 ± 2	9 (5, 14)
ADM (pmol/l)	2.5	1 ± 1	
	20	4 ± 1	3 (0, 7)
	40	6 ± 1	5 (2, 9)
ACE activity	2.5	−10 ± 1	
(nmol/ml/min)	20	−20 ± 1	−10 (−13 to −7)
	40	−22 ± 1	−12 (−15 to −8)
RENIN (nmol/l/h)	2.5	0 ± 1	
	20	2 ± 2	2 (−1 to 5)
	40	3 ± 1	3 (0 to 6)
ALDO (pmol/l)	2.5	−79 ± 21	
	20	−104 ± 20	−25 (-83, 32)
	40	−42 ± 19	36 (−20, 92)
ET-1 (pmol/l)	2.5	0.0 ± 0.1	
	20	0.4 ± 0.1	0.3 (0.0 to 0.7)
	40	0.8 ± 0.1	0.7 (0.4 to 1.1)
NOREPI (pmol/l)	2.5	−80 ± 170	
	20	30 ± 166	111 (−360 to 590)
	40	440 ± 160	523 (60 to 980)
EPI (pmol/l)	2.5	−43 ± 27	
	20	−22 ± 26	21 (−55 to 97)
	40	27 ± 25	70 (−4 to 140)

Changes in plasma neurohormones for panel II at 3 h on day 1 (Mean ± SEM).
ACE = angiotensin-converting enzyme; ADM = adrenomedullin; ALDO = aldosterone; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; cGMP = cyclic guanosine monophosphate; CI = confidence interval; EPI = epinephrine; ET-1 = endothelin-1; NOREPI = norepinephrine.

effects. Despite this, increasing the dose above 10 mg did not result in further dose-related peak hemodynamic effects, but higher doses of omapatrilat influenced several other vasoactive hormone systems. Increases in ANP and BNP acutely with plasma second messenger cGMP suggest the presence of NEP inhibition, in addition to ACE inhibition. Neurohormonal changes at 3 h coincided with reductions in left ventricular filling pressures and SVR. By 12 h after dose, plasma neurohormones had returned towards baseline, despite the persisting falls in PCWP, SVR and mean atrial pressure. This may reflect reduced secretion in response to improved hemodynamics or decreased NEP inhibition. Increases in plasma ET-1 at 3 h acutely suggests inhibition of the degradation of ET-1 due to NEP inhibition (22). Baroreceptor-mediated sympathetic discharge, in response to the significant fall in blood pressure, may have contributed to the acute increase in norepinephrine at 3 h with the 40-mg dose, in contrast to no change with epinephrine.

Chronic treatment. After chronic therapy, continued ACE inhibition was evident with increases in plasma renin and reductions in plasma ACE activity in all groups. With the highest dose, ANP tended to increase 3 h after dose at week 12. Importantly, there were no increases in potentially deleterious hormones such as endothelin and norepinephrine with chronic dosing. After 12 weeks, the hemodynamic improvements were sustained up to at least 12 h, suggesting lack of tolerance with chronic therapy. Greater falls were seen in higher dose groups for PCWP, SBP and mean systolic arterial pressure. The lack of further dose-related peak hemodynamic effects from 10 mg to 40 mg may be due to a combination of factors. Possible tissue NEP inhibition, in addition to ACE inhibition, may have occurred with the lower doses. Although the 0 h to 12 h average reduction in SVR in the 40-mg group at week 12 was similar to day 1, increased chronic effects of the 2.5-mg ACE inhibitor control may have negated a significant dose-related change. Fewer patients in panel I received chronic beta-blockade, which may have enhanced the 10-mg effect. Although no difference in CI occurred between high and low dose groups, CI appeared to increase in most groups acutely and with chronic therapy.

Omapatrilat acutely increased plasma levels of ADM, another potent renal vasodilating and natriuretic peptide (8). Higher doses of omapatrilat have been shown to have a natriuretic effect in CHF (14), which may be, in part, due to local renal effects of both natriuretic peptides and ADM.

Safety and tolerability. The first dose was safely tolerated by most patients. First dose hypotension was generally minor, transient and well tolerated but resulted in treatment withdrawal of four patients. It is likely that hypotension would be less common in clinical practice where dose titration would be used. Only three additional withdrawals for hypotension occurred over the 12 weeks. The incidence of withdrawal for any reason with chronic therapy was similar in all groups. The strict study criterion of no increase in maintenance diuretics and the requirement for repeat invasive catheterization both may have affected the withdrawal rate. The incidence of cough appeared to be similar to previously published ACE inhibitor studies (23). Angioedema occurred in one patient of 369 patients randomized.

Study limitations. The use of an active control limb, the finding that most patients were receiving an ACE inhibitor before enrollment and the short washout period are all likely to have resulted in underestimation of the magnitude of drug effect, especially as some variables such as CI and SVR may worsen over time with placebo (24). However, it is not ethically permissible to include a chronic placebo arm (25). The small numbers in the neurohormone substudy may not be representative of the group as a whole. In addition, the variable number of withdrawals among treatment groups over 12 weeks may have affected the validity of the week 12 results. The duration of plasma NEP inhibition appeared to be shorter than that of plasma ACE inhibition, suggesting more frequent dosing; however, tissue NEP inhibition was not measured.

Table 4. Reason for Discontinuation of Patients Randomized

	Omapatrilat Dose				
	2.5 mg	**5 mg**	**10 mg**	**20 mg**	**40 mg**
Acute dose					
Number of patients randomized	122	66	61	58	62
Number of subjects discontinued following first dose	2	1	1	2	3
First dose hypotension			1	2	1
First dose heart failure	1	1			
Angioedema					1
Angina					1
Hypertension	1				
Over 12 weeks					
Number of subjects discontinued over 12 weeks	23 (18.9%)	17 (25.8%)	15 (24.5%)	12 (20.7%)	12 (19.4%)
Death	2	2	1	2	1
Hypotension	1		2	1	
Worsening heart failure	10	9	4	2	4
Angina			1		
Myocardial infarction	1				
Rhythm disturbance	1	2	1	1	
Worsening renal function					1
Other causes	8	4	6	6	6
Number of patients completing 12 weeks	97 (79.5%)	48 (72.7%)	45 (73.8%)	44 (75.8%)	47 (75.8%)

CONCLUSIONS

In patients with mild-to-moderate CHF, the vasopeptidase inhibitor omapatrilat results in acute beneficial hemodynamic changes that are maintained after chronic dosing with no attenuation of effect. Acute increases in plasma natriuretic peptide levels with higher doses, despite a reduction in left ventricular filling pressures, are indicative of NEP inhibition. No adverse neurohumoral effects were seen with chronic therapy. Results from a larger trial, adequately powered for morbidity and mortality end points (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events [OVERTURE]), are now awaited to assess the long-term clinical efficacy of omapatrilat in CHF.

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APPENDIX

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