Hemodynamic Effects of Tezosentan, an Intravenous Dual Endothelin Receptor Antagonist, in Patients With Class III to IV Congestive Heart Failure

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Background—Endothelin-1, a powerful mediator of vasoconstriction, is increased in patients with congestive heart failure and appears to be a prognostic marker that strongly is correlated with the severity of disease. However, little is known about the potential immediate beneficial effects of acute blockade of the endothelin system in patients with symptomatic left ventricular dysfunction. We assessed the hemodynamic effects and safety of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with moderate to severe heart failure.

Methods and Results—This randomized placebo-controlled study evaluated the hemodynamic effects of 6-hour infusions of tezosentan at 5, 20, 50, and 100 mg/h compared with placebo in 61 patients with New York Heart Association class III to IV heart failure. Plasma endothelin-1 and tezosentan concentrations were also determined. Treatment with tezosentan caused a dose-dependent increase in cardiac index ranging from 24.4% to 49.9% versus 3.0% with placebo. Tezosentan also dose-dependently reduced pulmonary capillary wedge pressure and pulmonary and systemic vascular resistances, with no change in heart rate. No episodes of ventricular tachycardia or hypotension requiring drug termination were observed during tezosentan infusion. Tezosentan administration resulted in dose-related increased plasma endothelin-1 concentrations.

Conclusions—The present study demonstrated that tezosentan can be safely administered to patients with moderate to severe heart failure and that by virtue of its ability to antagonize the effects of endothelin-1, it induced vasodilatory responses leading to a significant improvement in cardiac index. Further studies are under way to determine the clinical effects of tezosentan in the setting of acute heart failure. (Circulation. 2001;103:973-980.)

Key Words: endothelin • hemodynamics • heart failure

Treatment of the symptoms of acute heart failure requires rapid improvement in the hemodynamic profile of the patient without further aggravation of the cardiac status. Conventional pharmacological management of heart failure includes the use of diuretics, positive inotropes, vasodilators, and inotropes in combination or as single therapy.1–4 The beneficial effects of these agents must be balanced against potential side effects, including the activation of neurohormones, risk of hypotension, possibility for arrhythmia, and deleterious cardiac effects. Despite obvious advances in the management of this important clinical syndrome, new and novel pharmacological agents for its treatment are still needed.

Endothelin (ET)-1, a powerful mediator of vasoconstriction, is increased in patients with heart failure,6 and progressively higher plasma concentrations are found in patients as their functional status deteriorates.6,7 ET-1 binds to 2 receptors, ET A and ET B .8 ET A receptors are found in smooth muscle cells and mediate vasoconstriction and proliferation.9 Under physiological conditions, ET B receptors, present in the brain, endothelium, and certain smooth muscle cells, play a role in endothelium-dependent vascular smooth muscle relaxation.10 In experimental heart failure, ET B receptor expression is upregulated, and these receptors become capable of mediating vasoconstriction and participate in the development of cardiac fibrosis.11–14 These findings suggest that both ET A and ET B receptors may play roles in the pathophysiological effects of excess ET-1. Therefore, it seems reasonable to postulate that dual ET A/ET B receptor antagonists might have specific advantages in heart failure, such as improving central and peripheral hemodynamics and blunting vascular hypertrophy and remodeling. Short-term studies with 2 oral long-
acting ET receptor antagonists (bosentan and LU135252) developed for the treatment of chronic heart failure support the notion that antagonism of the effects of excess ET-1 improves hemodynamics.15-17

Tezosentan (Ro 61-0612) is a highly specific potent ET receptor antagonist that inhibits ET-1 binding to both ET A and ET B receptors.18 Tezosentan has been optimized for clinical use in acute indications requiring the rapid onset of action. It is water soluble, thus allowing intravenous administration, and a short half-life facilitates adjustment of its hemodynamic effects. Tezosentan was found to be pharmacologically active with a rapid onset of action in several animal models of heart failure, ischemic renal failure, and hypertension.18 The present study was designed to assess the acute hemodynamic actions of tezosentan and its safety in patients with moderate to severe heart failure.

Methods

This was a double-blind, randomized, placebo-controlled study of 4 dosages of tezosentan infused over 6 hours with hemodynamic measurements performed during the infusion. The study, approved by the respective ethical committees, was conducted in parallel at 2 centers: Baylor College of Medicine, Houston, Tex, and The Cleveland Clinic Foundation, Cleveland, Ohio. All patients gave written informed consent.

Study Patients

The study population included males and females (surgically sterile, postmenopausal, or on contraceptives) between the ages of 18 to 70 years with New York Heart Association (NYHA) class III to IV congestive heart failure (CHF) caused by ischemic or nonischemic heart disease and a left ventricular ejection fraction <35%. To qualify for enrollment, patients who were undergoing clinically indicated right heart catheterization for either heart transplant evaluation or acute heart failure were required to have a pulmonary capillary wedge pressure (PCWP) >18 mm Hg and a cardiac index (CI) <2.5 L·min⁻¹·m⁻². All patients must have been receiving established medications for heart failure, including a diuretic and an ACE inhibitor, unless intolerance or contraindication could be documented. The dosages of background medications must have been stable for ≥1 week before the initiation of the study. Exclusion criteria included severe hypertension, clinically significant hypotension (systolic blood pressure <85 mm Hg), myocardial infarction within the last 4 weeks, unstable angina, hemodynamically relevant cardiac arrhythmias, and other serious systemic diseases.

Study Procedures

Qualified patients were randomized to receive 1 of 4 dosages of tezosentan infused over 6 hours with hemodynamic measurements performed during the infusion port of the Swan-Ganz catheter at a constant rate of 0.133 mL/min for 6 hours. The infusion rate could be decreased by half in the event of a leaky catheter. Patients were monitored in the intensive care or heart failure unit for the entire duration of the study. After the infusion, patients remained overnight in the hospital and were discharged after a follow-up check.

Hemodynamic Measurements

Hemodynamic variables were assessed 30 minutes before (first baseline measurement), immediately before (second baseline measurement), and every 30 minutes during the 6-hour infusion. Cardiac output was determined by the thermodilution technique. PCWP, systolic and diastolic pulmonary artery pressures, and mean right atrial pressure were obtained during expiration. Arterial pressures were measured with a pressure transducer in the arterial line. Heart rate was derived from the continuously monitored ECG. CI, stroke index, and systemic and pulmonary vascular resistances were calculated according to standard formulas.

Neurohormone and Pharmacokinetic Measurements

Blood samples for ET-1 and tezosentan assessments were taken through the cordis sheath of the catheter at 0, 1, 3, 6, 7, 8, and 20 to 24 hours after the start of the infusion. Plasma ET-1 concentrations were determined by a quantitative sandwich enzyme immunoassay with chemiluminescence (R&D Systems Europe), with a lower limit of quantification of 0.16 pg/mL. Plasma tezosentan concentrations were determined by using a validated liquid chromatography–tandem mass spectrometry method with a limit of quantification of 2.50 ng/mL.

Safety Data

Adverse events were monitored throughout the infusion and until discharge. Serious adverse events, whether related or unrelated to treatment, that came to the attention of the investigator within 28 days after stopping treatment were also reported. ECG, routine clinical laboratory tests (hematology, multipanel blood chemistry, and urinalysis), and vital signs (blood pressure and pulse rate) were assessed at baseline and at follow-up (discharge).

Statistical Analysis

All patients were included in the safety analysis. For hemodynamic evaluation, 4 patients (1 from each tezosentan dosage group) were excluded from the primary (per-protocol) analysis because of major protocol violations that could interfere with evaluation of the drug. The decision to exclude these patients was made before the results of the double-blind study were revealed. The primary efficacy parameter was mean change from baseline to the end of infusion (hour 6) in CI for each tezosentan group compared with placebo, which was tested by use of the Dunnett 1-tailed test (α = 0.05); the corresponding 2-tailed 90% confidence limits derived from the Dunnett test were calculated. As a confirming analysis, 2-tailed 95% Dunnett confidence limits were also calculated. Mean changes from baseline to hour 6 for secondary variables (PCWP, pulmonary artery pressures [systolic, diastolic, and mean], mean right atrial pressure, arterial pressures [systolic, diastolic, and mean], heart rate, stroke index, and vascular resistances [systemic and pulmonary]) were displayed with 95% confidence limits. Demographic, baseline, pharmacokinetic, pharmacodynamic, and safety parameters were analyzed descriptively or tabulated.

Results

A total of 61 patients were randomized into the present study. All patients were included in the safety analyses, but 1 patient from each tezosentan group was excluded from efficacy analyses: 3 were excluded because of protocol-prohibited concomitant medication (furosemide), and 1 was excluded because a leaky catheter resulted in an incorrect infusion rate. The decision to exclude these patients was made before revealing the results and was based on the supposition that the violations could interfere with the ability to interpret the actual hemodynamic effects of tezosentan. In all parameters assessed, results from the intent-to-treat analysis, which included all enrolled patients, were very similar to those of the standard analysis in the present study; statistical results were identical with 2 exceptions: changes from baseline (1) in
pulmonary vascular resistance with 5 mg/h tezosentan and (2) in mean pulmonary arterial pressure with 50 mg/h did not reach statistical significance in the intent-to-treat population.

No patients were prematurely discontinued from the present study. Despite the small number of patients, the 5 treatment groups were fairly well matched, with the exception of heart failure cause (Table 1). A greater proportion of patients in the 50 and 100 mg/h tezosentan groups had ischemic heart disease than in other groups, and correspondingly fewer had dilated cardiomyopathy. The mean age of patients in the treatment groups ranged from 55 to 64 years. Most patients were male (73% to 92%) and white (54% to 73%).

All patients in the study were taking concomitant medications for CHF before the study with no obvious differences among treatment groups (Table 1). Nearly all patients were taking furosemide (range 85% to 100%), a few were taking torsemide or bumetanide, >73% were taking digoxin, and 73% to 100% were taking an ACE or angiotensin II inhibitor.

### Hemodynamic Effects

#### Cardiac Index

At baseline, CI was similar in all treatment groups, ranging from 1.78±0.11 L · min⁻¹ · m⁻² in the 100-mg/h group to 2.04±0.09 L · min⁻¹ · m⁻² in the 20-mg/h group (Table 2). Tezosentan infusion produced a dose-dependent increase in CI (Figure 1). The improvement in CI was apparent as early as 30 minutes and peaked within the first 90 to 120 minutes of drug infusion. Compared with placebo, the increases in CI observed in the tezosentan groups were clearly larger, reaching statistical significance with the 100-mg/h infusion (treatment effect, 0.72 L · min⁻¹ · m⁻²). At hour 6 of the infusion, the change (mean±SE) from baseline in CI was significant in each tezosentan-treated group (26.9±6.8%, 24.4±8.8%, 30.9±13.6%, and 49.9±13.9% for 5, 20, 50, and 100 mg/h, respectively).
respectively). In contrast, the change from baseline in the placebo group was not significant (3.0±6.1%). Dose-trend analysis of the change from baseline to the end of treatment (hour 6) in CI with the 4 tezosentan dosages showed a significant dose relationship ($P=0.038$).

Other Hemodynamic Variables
Treatment with each of the 4 dosages of tezosentan resulted in decreases in PCWP, mean pulmonary artery pressure, and systemic and pulmonary vascular resistances (Figure 2). The change from baseline to hour 6 for each of these parameters was significant in most tezosentan-treated groups but was not significant in the placebo group (Table 2).

Treatment with tezosentan was associated with small decreases from baseline in mean blood pressure, occurring primarily within the first 90 minutes of infusion and reaching statistical significance only in the 100-mg/h group (Table 2, Figure 3A). No instances of symptomatic hypotension were observed, and no dose reduction was needed. There were no significant changes in heart rate as assessed by continuous telemetry in the tezosentan-treated groups (Table 2, Figure 3B).

Safety of Tezosentan
As would be expected in this patient population, there were many adverse events reported. The incidence of adverse events (including those considered unrelated to the study drug) in the tezosentan groups ranged from 38.5% to 81.8%. All combined, 62.0% of the patients receiving tezosentan (n=50) experienced at least 1 adverse event compared with 63.6% in the placebo group (n=11). Overall, there were few adverse events considered treatment-related, and no apparent relationship to dose was observed for any individual event (Table 3). There was no evidence of a rebound effect (eg, worsening of heart failure) either within the first 24 hours after the start of infusion or the next 28 days. No deaths occurred during treatment. One patient awaiting cardiac transplantation who had received tezosentan (100 mg/h) experienced ventricular fibrillation and died 5 days after the end of infusion, but the death was considered unrelated to tezosentan.

During the 28 days after the infusion, 3 (27%) of the 11 patients on placebo and 9 (18%) of the 50 patients on
Pharmacokinetic and Pharmacodynamic Variables

The plasma concentration of tezosentan was dose dependent, with near maximum concentrations reached within the first hour of the infusion (Figure 4A). When the infusion was stopped, tezosentan concentration rapidly declined to near baseline (zero) within 1 hour, consistent with the short half-life of the drug.

Plasma concentrations of ET-1 rapidly increased during infusion with tezosentan in a dose-dependent manner (Figure 4B). When the infusion was stopped, ET-1 concentrations...
rapidly decreased within the first 2 hours in tezosentan-treated patients.

Discussion
This double-blind placebo-controlled study in patients with moderate to severe CHF demonstrated that intravenous infusion of the dual ET receptor antagonist tezosentan resulted in rapid dose-dependent improvements in central and peripheral hemodynamic parameters and was well tolerated. The effect of tezosentan on CI, the primary efficacy parameter, was evident after only 30 minutes and was statistically significant at the 6-hour end point. Tezosentan also dose-dependently decreased PCWP, pulmonary artery pressures, systemic and pulmonary vascular resistances, and blood pressure but had no consistent effect on heart rate.

The likely mechanism by which tezosentan improved CI is the antagonism of the vasoconstrictor effect of ET-1. ET receptors are present in both arterial and venous vessels, and the hemodynamic responses to tezosentan suggest that it blocks these receptors in both arteries and veins. Another potential benefit of ET receptor antagonism may be related to its effect on the contractile state of the heart. Although ET-1 exerts positive inotropic effects in normal myocardium, experimental and clinical evidence suggests that in failing myocardium, ET-1 exerts negative inotropic effects. Accordingly, antagonizing the deleterious actions of excessive ET-1 may represent an attractive therapeutic strategy.

Table 3. Summary of AE

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=11)</th>
<th>5 mg/h (n=13)</th>
<th>20 mg/h (n=14)</th>
<th>50 mg/h (n=12)</th>
<th>100 mg/h (n=11)</th>
<th>All (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with ≥1 AE, n (%)</td>
<td>7 (63.6)</td>
<td>5 (38.5)</td>
<td>10 (71.4)</td>
<td>7 (58.3)</td>
<td>9 (81.8)</td>
<td>31 (62.0)</td>
</tr>
<tr>
<td>Injection site pain, n (%)</td>
<td>1 (9.1)</td>
<td>2 (15.4)</td>
<td>...</td>
<td>...</td>
<td>1 (9.1)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Chest pain, n (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1 (8.3)</td>
<td>...</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Muscle cramps, n (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1 (8.3)</td>
<td>2 (18.2)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Lung infiltration, n (%)</td>
<td>1 (9.1)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>2 (18.2)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>2 (18.2)</td>
<td>2 (4.0)</td>
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AE indicates adverse event. Only individual AEs reported on study days 1 or 2 for ≥1 patient in any 1 treatment group are included.
ET-1 in patients with heart failure may restore contractile properties of the failing myocardium. Regardless of the mechanism by which tezosentan improved hemodynamics, it was achieved in the absence of significant hypotension or arrhythmia.

In the failing myocardium, experimental and patient data suggest an alteration in ET receptor sensitivity, such that the response to ET₄ receptor stimulation is diminished and the activation of ET₄ receptors is enhanced, resulting in a relatively greater vasocostrictor response.33 Additionally, both the ET₄ and ET₆ pathways may contribute to myocardial hypertrophy in vivo,24–29 as suggested by the proliferation of vascular smooth muscle cells and increased collagen turnover caused by long-term in vitro exposure to ET.30,31 Therefore, the ability of tezosentan to compete for both ET₄ and ET₆ receptors18 may be more advantageous than selective antagonism of either receptor.

Short-term goals of heart failure management are to relieve symptoms such as shortness of breath, decreased exercise tolerance, and lower-extremity edema and to improve functional capacity and quality of life. Long-term goals include decreasing mortality and slowing or reversing the underlying cardiac structural abnormalities. Conventional treatment, including the use of catecholamine-like drugs, phosphodiesterase inhibitors, nitrates, direct vasodilators, and diuretics, has achieved only limited success, inasmuch as this syndrome continues to carry an extremely poor prognosis. Moreover, these drugs are capable of inducing significant ischemia, increasing the incidence of arrhythmia,32 and producing symptomatic hypotension.33 In the case of nitrates, continuous therapy can provoke the development of early tolerance.34 Therefore, the ideal agent should substantially improve hemodynamics without a significant effect on ischemic burden or arrhythmogenicity and should maintain its effectiveness.

Studies with oral ET receptor antagonists such as bosentan15,16 (mixed receptor antagonist) and LU13525217 (selective ET₄ receptor) indicate that short-term treatment with bolus intravenous or oral dosages is associated with improved systemic and pulmonary hemodynamics. The short-term effects are promising, but these compounds are being developed for the chronic treatment of heart failure. Only long-term studies will determine whether the short-term effects translate into long-term benefit. In contrast, tezosentan is being developed specifically for the short-term intravenous treatment of acute heart failure; therefore, its immediate hemodynamic effects will determine its value in the setting of acute heart failure.

In summary, the present study demonstrated that dual ET receptor antagonism in patients with moderate to severe heart failure led to an improved hemodynamic profile and was safe and well tolerated. Moreover, these observations add to the already impressive body of evidence supporting the importance of the ET system in the pathophysiology of heart failure. Finally, the present study provides the rationale for conducting larger studies to define the full clinical benefits of tezosentan in patients with acute heart failure.

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