Acute Hemodynamic and Clinical Effects of Levosimendan in Patients With Severe Heart Failure

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Methods and Results—One hundred forty-six patients with New York Heart Association functional class III or IV heart failure (mean left ventricular ejection fraction 21±1%) who had a pulmonary capillary wedge pressure ≥15 mm Hg and a cardiac index ≥2.5 L·min⁻¹·m⁻² were enrolled in a multicenter, double-blind, placebo-controlled study and randomized 2:1 to intravenous infusion of levosimendan or placebo. Drug infusions were uptitrated over 4 hours from an initial infusion rate of 0.1 μg·kg⁻¹·min⁻¹ to a maximum rate of 0.4 μg·kg⁻¹·min⁻¹ and maintained at the maximal tolerated infusion rate for an additional 2 hours. Levosimendan caused dose-dependent increases in stroke volume, cardiac index, and mean arterial pressure. These hemodynamic effects appeared to be accompanied by symptom improvement and were not associated with a significant increase in the number of adverse events. Levosimendan may be of value in the short-term management of patients with decompensated heart failure. These hemodynamic effects appeared to be accompanied by symptom improvement and were not associated with a significant increase in the number of adverse events. Levosimendan may be of value in the short-term management of patients with decompensated heart failure. (Circulation. 2000;102:2222-2227.)

Key Words: heart failure • inotropic agents • vasodilation • calcium

Intravenous positive inotropic agents play an important role in the short-term management of patients with decompensated heart failure due to left ventricular (LV) systolic dysfunction. β-Adrenergic agonists and phosphodiesterase inhibitors, the most commonly used positive inotropic agents, exert a positive inotropic action primarily by increasing cAMP in cardiac myocytes. Although β-adrenergic agonists and phosphodiesterase inhibitors are effective positive inotropic agents, their use may be limited by several problems. First, because cAMP and calcium mediate diverse biological and physiological actions, the clinical effects of these drugs are relatively nonspecific. Increases in heart rate and the stimulation of arrhythmias limit dosing and can result in serious adverse effects, including myocardial ischemia and sudden death. Second, because of desensitization of the β-adrenergic pathway, the positive inotropic effects of agents that act through this pathway may be reduced in patients with severe heart failure.

Calcium-sensitizing agents exert a positive inotropic action by increasing the sensitivity of the contractile apparatus to calcium. Theoretically, such agents may increase myocardial contractility without increasing intracellular cAMP or calcium and therefore might avoid major limitations of cAMP-dependent agents. Although calcium-sensitizing agents are theoretically attractive, to date none has been successfully developed as a clinical agent. Levosimendan is a new calcium-sensitizing agent that binds to troponin C. We conducted a randomized placebo-controlled trial of the short-term intravenous infusion of levosimendan in 146 patients with decompensated heart failure due to LV systolic dysfunc-

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The goals of the present study were to determine whether levosimendan improves hemodynamic function and ameliorates the symptoms of dyspnea and fatigue.

Methods

Patient Population
Study subjects were recruited from patients with systolic LV dysfunction and New York Heart Association functional class III or IV symptoms of heart failure who were admitted to the hospital for management of decompensated heart failure. Patients were screened for the study if they were currently on treatment with diuretics and ACE inhibitors and had documented LV ejection fractions of ≤30% by echocardiogram or radionuclide ventriculogram in the preceding 6 months. Patients were considered candidates for randomization if they had a pulmonary capillary wedge pressure (PCWP) ≥15 mm Hg along with a cardiac index (CI) ≤2.5 L · min⁻¹ · m⁻².

Exclusion criteria included the following: significant ischemic heart disease (defined as angina-limited exercise or unstable angina); documented acute myocardial infarction (MI) within the previous 8 weeks; uncorrected primary stenotic valve disease; uncorrected thyroid disease; obstructive cardiomyopathy; pericardial disease; amyloidosis; active myocarditis; malfunctioning artificial heart valve; symptomatic primary pulmonary disease; chronic obstructive pulmonary disease requiring long-term treatment with β-agonists, theophylline, or corticosteroids; serious arrhythmias, defined as a history of ventricular flutter or fibrillation other than that occurring within 24 hours after acute MI; history of sudden cardiac death or symptomatic ventricular tachycardia within 3 months before study entry (patients with a history of symptomatic ventricular tachycardia or cardiac arrest who had implantable defibrillators that had not discharged within the preceding 6 months were allowed in the study); resting heart rate >115 bpm for at least 10 minutes on repeated measurements; second- or third-degree atrioventricular block, unless the patient had a functioning implanted pacemaker; supine systolic blood pressure <85 mm Hg or >200 mm Hg; primary renal or hepatic impairment (creatinine >2.5 mg/dL or aspartate aminotransferase/alanine aminotransferase >2 times upper limit of normal, respectively); uncorrected hypokalemia or hyperkalemia (potassium <3.5 mmol/L or >5.5 mmol/L); or treatment with another investigational agent within 30 days before study entry. The trial was conducted at 20 study centers.

The protocol was approved by the Institutional Review Board of each participating center and was carried out in accordance with institutional guidelines. All patients gave informed written consent before entering the study.

Study Protocol
Patients were randomized 2:1 to receive intravenous levosimendan or placebo. Levosimendan was initiated as a bolus of 6 μg/kg, followed by a continuous infusion, initially at a rate of 0.1 μg · kg⁻¹ · min⁻¹. At hourly intervals, a repeat bolus (6 μg/kg) was given, and the infusion rate was increased by increments of 0.1 μg/kg. Uptitration was continued until a maximum rate of 0.4 μg · kg⁻¹ · min⁻¹ was achieved (hour 4) or a dose-limiting event occurred. Dose-limiting events were defined as follows: (1) a heart rate >130 or an increase in heart rate of >15 bpm above baseline for 10 minutes, (2) symptomatic hypotension or a drop in systolic blood pressure to <75 mm Hg, (3) a decrease in PCWP to ≤10 mm Hg, or (4) any adverse event that, in the opinion of the site investigator, required drug dose modification. If a dose-limiting event occurred, the study drug was discontinued until the event resolved and was then restarted at the next lower dose.

Hemodynamic measurements were obtained at baseline, at the end of each hourly uptitration for hours 1 to 4, and at hours 5 and 6. The measurements at 5.5 and 6 hours were averaged. The symptoms of dyspnea and fatigue were evaluated by the patient and the physician at baseline and hour 6 by using a scale of 1 (none) to 5 (severe). At hour 6, after hemodynamic measurements and the symptom evaluation were completed, the blind was opened. Patients randomized to placebo were discontinued from the study and were begun on standard treatment, and patients randomized to levosimendan were continued on open-label drug.

Concomitant Medications
Patients were required to have been on stable ACE inhibitor doses for at least 5 days before entering the study. Patients on digoxin were required to have been on a stable dose for at least 2 weeks before study entry. Stable diuretic dosing was not required, and intravenous diuretics were allowed up to 6 hours before patient entry into the study. Use of calcium channel blockers and β-blockers was permitted if the duration of therapy was at least 1 week before enrollment in the study. Patients treated with class IC antiarrhythmics were excluded from the study. Amiodarone use was allowed as long as the patient had been on a stable dose for at least 2 months before study entry. Medications that could affect hemodynamic measurements, such as ACE inhibitors, diuretics, nitrates, antiarrhythmics and digoxin, were held until completion of the 6-hour measurements. A light liquid meal was allowed during the first 4 hours of the protocol.

Statistical Analysis
The primary end point was defined as the proportion of patients with an increase in stroke volume (SV) or a decrease in PCWP of ≥25% at 6 hours. Secondary end points were the change in SV and PCWP over time and change in the symptoms of dyspnea or fatigue as assessed by patient and clinician. Two-way ANOVA was used to compare continuous variables with effects for treatment, center, and treatment-by-center interaction. Categorical measurements were analyzed by the Cochran-Mantel-Haenszel (CMH) test. For hemodynamic data, the CMH test was used to detect treatment differences in percent change from baseline. Treatment-by-center interaction. The frequency of adverse event incidence rates between treatment groups was compared by the Fisher exact test.

Results

Baseline Characteristics
One hundred forty-six patients were randomized to treatment (n=98) or placebo (n=48). The groups were similar with regard to age and sex distribution, cause of heart failure, New York Heart Association functional classification, and LV ejection fraction (Table 1). Baseline hemodynamics were consistent with decompensated heart failure with depression.

| TABLE 1. Baseline Characteristics of Study Population |
|----------------|----------------|----------------|
|               | Placebo | Levosimendan | P |
| No. of patients | 48     | 98            |
| Age, y         | 56±2   | 58±1          | 0.72 |
| Sex, % male    | 83     | 81            | 0.68 |
| NYHA functional class, % | 67 | 66            | 0.90 |
| III             | 33     | 34            |
| Cause of heart failure, % | CAD | 56          | 62 | 0.59 |
| IV              | 44     | 38            | 0.28 |
| LV ejection fraction, % | 20±1 | 21±1          | 0.80 |

NYHA indicates New York Heart Association; CAD, coronary artery disease; and DCM, dilated cardiomyopathy.
The levosimendan infusion rate at 6 hours averaged 0.26±0.08 μg · kg⁻¹ · min⁻¹, with 70% of patients at the maximal infusion rate of 0.4 μg · kg⁻¹ · min⁻¹. Levosimendan increased SV in a dose-dependent manner during uptitration, and the effect was sustained from the completion of uptitration to 6 hours (Figure 1A). SV increased (versus placebo) at the lowest infusion rate (0.1 μg · kg⁻¹ · min⁻¹) and increased further with uptitration to a maximal increase of 13±1 mL at 6 hours (versus −1±2 mL for placebo). At 6 hours, SV increased by ≥25% in 56% of levosimendan patients versus 4% of placebo patients (P<0.001). Heart rate did not increase at the 2 lowest infusion rates of levosimendan (Figure 1B) but increased with further uptitration to a maximal increase of 6±1 bpm at 6 hours (versus 1±1 bpm for placebo). CI increased at all infusion rates, achieving a maximal increase of 0.7±0.1 L · min⁻¹ · m⁻² at 6 hours (Figure 1C).

Mean PCWP decreased at the lowest infusion rate and decreased further with uptitration, with a maximal decrease of 6±1 mm Hg at 6 hours (versus 0±1 mm Hg for placebo) (Figure 2A). PCWP decreased by ≥25% in 43% of levosimendan patients versus 15% of placebo patients (P<0.001). Mean right atrial pressure in patients receiving levosimendan decreased at all infusion rates, with a maximal decrease of 3±0±1 mm Hg at 6 hours (versus an increase of 1±1 mm Hg for placebo). Mean pulmonary arterial pressure decreased at all infusion rates, with a maximal decrease of 6±1 mm Hg at 6 hours (versus an increase of 1±1 mm Hg for placebo) (Figure 2B). Levosimendan caused a modest decrease in mean arterial pressure, with a maximum decrease of 4±1 mm Hg at hour 6 (versus an increase of 1±1 mm Hg for placebo) (Figure 2C). Levosimendan decreased systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), with a maximal decrease in SVR of 514±50 dyne · s · cm⁻⁵ (versus an increase of 41±72 dyne · s · cm⁻⁵ for placebo) and a maximal decrease in PVR of 80±13 dyne · s · cm⁻⁵ (versus an increase of 33±19 dyne · s · cm⁻⁵ for placebo) (Figures 3A and 3B, respectively).

Symptom Assessment
At hour 6, dyspnea was improved in the levosimendan group (P=0.037 versus placebo), with more patients reporting improvement in dyspnea (29% versus 15%) and fewer reporting worsening (9% versus 17%). There was a trend toward improvement in fatigue (P=0.057), with more patients in the levosimendan group reporting improvement (42% versus 22%). The physicians likewise judged that dyspnea was improved (P=0.001), with more patients rated as improved (37% versus 9%) and fewer as worse (11% versus 22%). Similarly, there was a trend toward improvement in the physician rating of fatigue (P=0.067), with more patients judged as improved (42% versus 29%) and fewer as worse (8% versus 18%).
Over the 6 hours of double-blind drug infusion, adverse events were reported in 17% of levosimendan patients and 19% of placebo patients. Two patients in the levosimendan group had nonsustained ventricular tachycardia. Four patients (4%) in the levosimendan group were permanently withdrawn from the drug because of (1) failure to respond, (2) increased pulmonary congestion and decreased cardiac output, (3) increase in heart rate ≥15 bpm, and (4) throat pain with ischemic ECG changes. Two patients (4%) were discontinued from placebo because of (1) worsening clinical condition and (2) increased pulmonary congestion. Twenty-nine levosimendan patients did not achieve the maximal infusion rate of 0.4 μg·kg⁻¹·min⁻¹. In 19 patients, the uptitration was ended because of achievement of a predetermined hemodynamic goal (ie, a decrease in PCWP to ≤10 mm Hg). The uptitration was ended because of a sustained increase in heart rate ≥15 bpm in 5 patients, an increase in ventricular ectopy in 1 patient, an error in 1 patient, and investigator judgment in 1 patient.

### Discussion

This double-blind randomized trial demonstrates that levosimendan exerts potent hemodynamic actions in patients who are admitted to the hospital with decompensated heart failure due to LV systolic dysfunction. Levosimendan increased SV and CI by 28% and 39%, respectively, while causing only a small (8%) increase in heart rate. Levosimendan also decreased left and right heart filling pressures and systemic arterial pressure. These hemodynamic effects appeared to be accompanied by improvements in dyspnea and fatigue and were not associated with a significantly higher number of adverse events.

Levosimendan has been shown to improve both systolic and diastolic function in dogs with pacing-induced heart failure.
Levosimendan causes vasodilation, which has been attributed to doses increased heart rate as well.\textsuperscript{15} 

0.25 and 0.5 mg selectively increased SV, whereas higher study performed in 24 patients with reduced LV ejection decreasing the sensitivity to calcium.\textsuperscript{22} At higher concentrations, levosimendan increased coronary blood flow without increasing myocardial oxygen consumption.\textsuperscript{14} In a dose-findinglevosimendan increased CI without increasing heart rate.\textsuperscript{13} When administered as a bolus to patients shortly after coronary bypass surgery, levosimendan increased coronary blood flow without increasing myocardial oxygen consumption.\textsuperscript{14} In a dose-finding study performed in 24 patients with reduced LV ejection fraction, a single bolus infusion of levosimendan at doses of 0.25 and 0.5 mg selectively increased SV, whereas higher doses increased heart rate as well.\textsuperscript{15} 

In vitro, levosimendan exerts several pharmacological activities, that may contribute to its hemodynamic effects in patients. Levosimendan increases the sensitivity of myocardial filaments to calcium.\textsuperscript{3,16,17} Hasenfuss et al\textsuperscript{17} found that in muscle strips from failing human hearts, levosimendan caused an upward shift in the force-frequency relationship. On average, the magnitude of the increase in twitch tension, relative to intracellular calcium, was higher with levosimendan than with the phosphodiesterester inhibitor milrinone. It is thought that levosimendan increases calcium sensitivity by binding to troponin C.\textsuperscript{11} Consistent with this thesis is the observation that levosimendan does not impair myocardial relaxation.\textsuperscript{17–20} Levosimendan causes vasodilation, which has been attributed to the activation of potassium-dependent ATP channels\textsuperscript{21} and decreasing the sensitivity to calcium.\textsuperscript{22} At higher concentrations, levosimendan can inhibit phosphodiesterase III in myocardium\textsuperscript{23} and vascular smooth muscle.\textsuperscript{24} 

We cannot determine the relative contributions of these pharmacological actions to the hemodynamic and symptomatic effects observed in the present study. However, it is noteworthy that the effect of levosimendan on SV occurred at lower infusion rates than the effect on heart rate. Likewise, the increase in SV (29%) at the highest infusion rate was larger than the corresponding increase in heart rate (8%). Consequently, the increase in CI can be attributed primarily to the increase in SV. This dissociation of the effects on SV and heart rate is consistent with the expected hemodynamic pattern of a calcium-sensitizing agent. However, because SVR also decreased at all infusion rates, indicative of arterial dilation, it is possible that some, or even all, of the increase in SV reflects a decrease in LV afterload.

The short-term therapy of decompensated heart failure has traditionally focused on the improvement of hemodynamic function. However, in the majority of cases, the primary goal of such therapy is to rapidly alleviate symptoms. Both patients and physicians rated dyspnea improved in more levosimendan patients, and there was a trend for more improvement in fatigue, as assessed by both patient and physician. Although patient and physician were blind to drug treatment at 6 hours, the fact that the physicians, and possibly the patients, were aware of the hemodynamics could have biased their assessment of symptoms. Despite the bias in symptom assessment imposed by a study in which hemodynamic effects are known, the symptom assessment data are consistent with the observed hemodynamic actions of the drug and suggest that levosimendan can alleviate symptoms in patients with decompensated heart failure. Levosimendan infusion was well tolerated. The drug was withdrawn in only 1 patient because of tachycardia. Although tachycardia limited levosimendan up titration in 5% of patients, this did not occur until the dose was increased to 0.3 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}. However, significant hemodynamic benefit occurred at lower doses. There were no significant differences in the frequency or types of adverse events in the treatment groups. However, increased ventricular ectopic activity was observed in 3 patients on levosimendan. Because of the forced-titration design in the present study, dose-related events may be more common than in usual clinical practice when titration is guided by the therapeutic response. Nevertheless, experience with longer treatment periods in a larger number of patients will be needed to determine clinical safety.

In summary, the present study demonstrates that levosimendan causes a rapid dose-dependent improvement in hemodynamic function in patients with decompensated heart failure. Although the mechanism of action cannot be determined from these data, the observed hemodynamic effects are consistent with the known pharmacological actions of this drug as a calcium sensitizer and direct vasodilator. The drug was well tolerated and appeared to improve symptoms of dyspnea and fatigue. Thus, levosimendan may be of value in the short-term treatment of patients with decompensated heart failure.

Appendix: Investigators
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