Hemodynamic and Neurohumoral Effects of Continuous Infusion of Levosimendan in Patients With Congestive Heart Failure

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OBJECTIVES
We sought to define the therapeutic dose range of levosimendan in patients with New York Heart Association class II–IV heart failure of ischemic origin.

BACKGROUND
Levosimendan is a calcium sensitizer for treatment of acute decompenated heart failure.

METHODS
A double-blind, placebo-controlled, randomized, multicenter, parallel-group study included 151 adult patients. Levosimendan was given as a 10-min intravenous bolus of 3, 6, 12, 24 or 36 μg/kg, followed by a 24-h infusion of 0.05, 0.1, 0.2, 0.4 or 0.6 μg/kg/min, respectively. Dobutamine, for comparative purposes, was given as an open-label infusion (6 μg/kg/min).

RESULTS
The response rate to levosimendan ranged from 50% at the lowest dose to 88% at the highest dose (compared with placebo 14%, dobutamine 70%). A dose-response relationship was demonstrated for levosimendan on increases in CO and SV, and reductions in PCWP during the infusion (for all, p ≤ 0.001). Headache (9%), nausea (5%) and hypotension (5%) were the most frequently reported adverse events at higher dosages.

CONCLUSIONS
Dosing of levosimendan with a 10-min bolus of 6 to 24 μg/kg followed by an infusion of 0.05 to 0.2 μg/kg/min is well tolerated and leads to favorable hemodynamic effects. (J Am Coll Cardiol 2000;36:1903–12) © 2000 by the American College of Cardiology

Intravenous inotropic therapy is indicated to correct the hemodynamic disturbances encountered in end-stage congestive heart failure (CHF), in the management of acute exacerbations of chronic CHF and as a “bridge” to heart transplantation (1). Drugs currently used for these purposes include the beta-agonist inotropes, such as dobutamine, and phosphodiesterase inhibitors such as milrinone. The positive inotropic actions of these agents are based on increased intracellular calcium concentrations that may enhance myocardial energy consumption and arrhythmias. In addition, the use of beta-mimetics is limited by tachyphylaxis. Short-term parenteral use of beta-agonists or phosphodiesterase inhibitors improves hemodynamics in patients with advanced CHF, but the longer term oral use of several of these drugs has been associated with worsened mortality (2,3).

Increasing myocyte sensitivity to calcium is an alternative basis for positive inotropy (4). This approach, in theory, has the advantage that the contractile performance of the failing heart can be enhanced with little increase in total myocardial energy demand and with a decreased potential for arrhythmias (5,6). Levosimendan promotes inotropy by stabilizing troponin C in a configuration that enhances the calcium sensitivity of cardiac myofilaments (7–9). Unlike other calcium sensitzizers, this effect of levosimendan is shown to be dependent on the concentration of intracellular ionized calcium. As a result, levosimendan is shown to increase cardiac contractile force during systole but not to impair ventricular relaxation (10,11). Furthermore, levosimendan opens adenosine triphosphate-dependent potassium channels, leading to vasodilatation (12,13). Levosimendan is a selective inhibitor of phosphodiesterase III in vitro, but at therapeutic doses its inotropic effects are independent of cAMP (14).

We report the results of a study conducted to determine the therapeutic dose range of intravenous levosimendan in patients with New York Heart Association (NYHA) functional class II–IV heart failure. Participation in the study was restricted to patients with heart failure of ischemic etiology, in order to detect any potential of levosimendan to induce myocardial ischemia. Dobutamine was used as a
positive control in this placebo-controlled randomized study.

METHODS

Patients. A group of 151 patients with stable CHF (NYHA class II or IV) of ischemic origin was recruited from a total of 12 centers in Finland, Sweden, Germany and The Netherlands between April 1994 and October 1996. Participating patients were 18 to 85 years old, had left ventricular ejection fraction <40% as determined by echocardiography (according to Simpson’s rule or the arealength method), left ventricular angiography or multiple-gated acquisition of left ventricular function by nuclear imaging, were in sinus rhythm and weighed not more than 110 kg with a body-mass index not exceeding 35 kg/m². Patients were required to have had unchanged medication for at least one week before enrollment and not have an acute need for intravenous inotropics.

The main exclusion criteria were myocardial infarction, stroke or hospitalization for any disabling disease other than CHF (including angina pectoris) during the three months before enrollment; systolic blood pressure <100 mm Hg or >200 mm Hg; recent symptomatic ventricular tachyarrhythmia; heart rate (HR) <50 or >100 beats/min at rest; second- or third-degree atrioventricular block; renal insufficiency (serum creatinine >150 μmol/L); abnormal liver function (serum alanine transaminase levels more than twice the upper reference limit); chronic pulmonary disease; hemodynamically significant obstructive valvular disease or use of amiodopine or class IC antiarrhythmics. Women with childbearing potential were ineligible.

Patients were in a stable condition at rest without the use of long-acting nitrates. To standardize concomitant medications, it was recommended that all angiotensin-converting enzyme inhibitors be changed to enalapril (5 to 20 mg daily) one week before the study day. Oral nitrates were withheld during the study day. Patients were allowed to take beta-blockers during the study at half the dose used previously. Calcium antagonists (amlodipine was an exclusion criterion) were withheld one week before the study day. Angiotensin-converting enzyme inhibitors and beta-blockers were preferred if a patient required anti-ischemic or antihypertensive therapy. Diuretic dose was adjusted at the prestudy visit and kept stable. Digitalis glycosides were not taken during the morning of the study day, but discontinuation was considered unethical because many CHF patients have atrial fibrillation.

After approximately 25 patients had entered the study it became apparent that the clinical eligibility criteria favored patients with low pulmonary capillary wedge pressures (PCWPs). The protocol was amended to permit recruitment of patients with class IV heart failure; the acceptable left ventricular ejection fraction was lowered to 35% and the requirement of sinus rhythm was abolished.

Study procedure. Pretreatment hemodynamic parameters were measured 2 h after the introduction of a Swan–Ganz catheter and 30 min before starting study medication (−30 min) with repeat measurements 20 and 10 min before starting treatment (−20 and −10 min). Baseline level was taken as the mean of the measurements at −20 and −10 min. Infusion of the study drug was then started via the sheath of the Swan–Ganz catheter by a calibrated infusion pump to ensure as stable a baseline as possible (15). Any other spontaneous changes during infusion were encountered by large control groups.

Patients were randomized to receive double-blind levosimendan (Simdax™, Orion Pharma, Finland), double-blind placebo, open-label vehicle or an open-label infusion of dobutamine (Dobutrex™, Eli Lilly, Indianapolis, Indiana), which was given at a constant rate of 6 μg/kg/min without a loading dose. Levosimendan treatment was started with loading doses of 3, 6, 12, 24 or 36 μg/kg administered in 10 min, followed by infusion of levosimendan at rates of 0.05, 0.1, 0.2, 0.4 or 0.6 μg/kg/min, respectively. For pharmaceutical reasons, the double-blind placebo contained less ethanol than levosimendan. Therefore, a separate ethanol vehicle group (see earlier) was included as an additional negative control group. Because dobutamine was given without a bolus dose, this treatment was not blinded.

Study treatment was stopped for 1 h and then resumed at half the previous rate if any of the following conditions were met: HR reduced to <50 beats/min or increased >20% from baseline for 10 consecutive min; systolic blood pressure reduced to <90 mm Hg for 5 min or symptomatic hypotension; cardiac output (CO) increased by >40% compared with baseline; PCWP reduced by ≥50% from baseline in two consecutive measurements; or the development of adverse events related to use of study medication. In addition, study treatment was discontinued if symptomatic ischemia (angina with an ST-segment depression >0.2 mV in precordial leads [Marquette Electronics, Series 8000; version 5.80]), sustained ventricular tachycardia (>150 beats/min for 30 s) or clinically more severe arrhythmia, second- or third-degree atrioventricular block, or any severe adverse event was recorded.

Right atrial pressure (RAP), pulmonary artery pressure (PAP) and PCWP were measured at 0 min (immediately after the bolus dose) and 30 min, at 1, 2, 4, 8, 23, 23.5 and 24 h from the start of the infusion, and at 1 and 2 h after...
completion of the infusion. CO was measured in triplicate by the thermodilution technique at the same times as the hemodynamic recordings were measured, and HR was measured from ECG recordings of six consecutive QRS complexes. Stroke volume (SV) was calculated from the CO and HR. Systolic and diastolic blood pressures (Korotkoff phase V) were measured to an accuracy of 2 mm Hg, always from the same arm, by auscultation with an automatic or semiautomatic manometer with the patient in the supine position; mean blood pressure (MBP) was derived from these measurements. The ECG was recorded continuously throughout the study day via the V2 and V5 precordial leads.

Blood samples for the determination of plasma epinephrine, norepinephrine, renin and atrial natriuretic peptide levels were taken immediately before infusion, after 30 min and 8 h postinfusion, and 2 h postinfusion. Samples were stored at −70°C until use, when they were prepared by centrifugation (3,000 rpm × 10 min). Catecholamines were assayed by high-pressure liquid chromatography (ESA Model 5100 A Coulochem with Beckman Ultrasphere C-18 column and dihydroxybenzylamine as the assay standard) at the University of Turku, Turku, Finland. Atrial natriuretic peptide and renin were quantified by radioimmunoassay (Oy Medix Ab, Helsinki, Finland).

An adverse event inquiry was undertaken before the start and after the termination of infusion. Patients were followed up for medical examination, adverse event inquiry and the determination of blood chemistry variables for two to nine days after the study.

Efficacy criteria. The primary efficacy variable was the proportion of patients in each treatment group who responded to treatment by attaining one or more of the following four prespecified end points: 1) a ≥15% increase in SV at 2 to 3 h; 2) a ≥25% decrease in PCWP (and ≥4 mm Hg) at 2 to 3 h; 3) a ≥40% increase in CO (with a change in HR of <20%) leading to a reduction in the dose of study medication at any time during the infusion; 4) a ≥50% decrease in PCWP during two consecutive measurements leading to a reduction in the dose of study medication at any time during the infusion. Changes from baseline of the three hemodynamic components of this primary end point were also analyzed.

Secondary efficacy end points included changes in directly measured or derived hemodynamic indices (HR, PAP, PVR, RAP, MBP and total peripheral resistance). In addition, the following post-hoc analyses were undertaken: patients aged <65 years versus ≥65 years, PCWP <15 mm Hg versus ≥15 mm Hg, MBP <95 mm Hg versus ≥95 mm Hg, men versus women, and use versus nonuse of beta-blockers or digitalis.

Statistical methods. The primary measure of efficacy specified in the protocol was a “responders analysis” based on a combination of prespecified changes in CO, PCWP and SV. All analyses were based on the intention-to-treat principle. A last-observation-carried-forward approach was used if hemodynamic data were missing.
The sample size calculation was based on the binomial distribution and on the assumptions that under one of the doses of levosimendan the response rate is at least 50% and that of placebo 5%. In the final protocol the two-sided type I error was set to 5% and the type II error to 10%, which gave a group size of 19 patients with a total of 152 patients in a balanced design of eight parallel groups.

Two analyses were conducted to test for the significance of differences among the treatment groups: 1) tests of the significance of differences among all eight treatment groups using the Cochran-Mantel-Haenszel test, controlling for center. If the overall test was significant, pairwise comparisons were carried out, again controlling for center; 2) tests of the relation between dose and response for levosimendan, using Spearman’s correlation coefficient based on six treatment groups (placebo [i.e., a zero dose of levosimendan] and five levosimendan doses).

Changes in the hemodynamic components of the primary end point (CO, PCWP and SV) and changes in secondary hemodynamic variables were compared across the treatment groups using an analysis of covariance model with effects for treatment, center and treatment-by-center interaction adjusted for baseline value. Changes from baseline values were calculated as the least square means. The significance of observed differences between treatments in the change from baseline was evaluated by an analysis of covariance procedure controlling for treatment, center and treatment-by-center interaction and using the baseline value as a covariate. The frequency of adverse events was compared using Fisher exact test. Descriptive statistics were used to examine alterations in laboratory variables during treatment. Analysis of ECG data was based on the Cochran-Mantel-Haenszel test, controlling for center.

Statistical significance was originally defined by an alpha-value of 0.05 or less in two-tailed tests. An interim analysis of the data was undertaken after 28 patients had completed the study, however, and the protocol was modified. The alpha-level associated with the primary end point was therefore adjusted to 0.025. An alpha-level of 0.05 was retained for other analyses.

Ethanol vehicle had no significant effect on any hemodynamic variables studied (data not shown) and thus the placebo and vehicle results are pooled in the major analyses.

**ETHICAL CONSIDERATION.** The study followed the principles of the Declaration of Helsinki of the World Medical Assembly with amendments. The protocol was approved by local Ethics Committees according to national regulations. Informed written consent was obtained from all participating patients or their proxies. The study was monitored in accordance to Good Clinical Practice guidelines in the European Community.

## RESULTS

### Demographic and baseline features.**
Baseline characteristics of the 151 patients are summarized in Tables 1 and 2. Most of the patients (n = 132) were male, most (n = 147) had class III CHF and all but one (an Asian) were Caucasian. There were no statistically significant intergroup differences.

### Efficacy. **Response rate.** Favorable hemodynamic responses to levosimendan were observed in at least 50% of patients at all doses studied, with a clear dose-response relationship (Fig. 1). Response rates obtained with all doses of levosimendan studied were significantly greater than the response rate seen with placebo (p = 0.038 at lowest dose; p ≤ 0.005 at all other doses). The response rate obtained with dobutamine (70%) was significantly greater than with placebo (27%; p < 0.001) but did not significantly differ from any dose of levosimendan. The response rate to levosimendan was higher among those patients with a baseline PCWP ≤ 15 mm Hg than in patients with a lower PCWP (placebo-adjusted rate 86% vs. 29%; p = 0.037). No significant variations in response rates were discovered in other patient subgroups.

### Principal Hemodynamic Indices. Levosimendan exerted a dose-dependent effect on CO, SV and PCWP (for all, p < 0.001 for linear dose trend) (Table 2). At 23 h to 24 h, all doses of levosimendan produced significantly larger

### Table 2. Patients’ Baseline Hemodynamics and Changes After 24 h Infusion of Study Medication

<table>
<thead>
<tr>
<th>Group</th>
<th>CO (L/min)</th>
<th>ΔCO at 23–24 h</th>
<th>SV (ml)</th>
<th>ΔSV at 23–24 h</th>
<th>PCWP (mm Hg)</th>
<th>ΔPCWP at 23–24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-value for linear dose trend</strong></td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dobutamine (n = 20)</td>
<td>4.3 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>62 ± 4</td>
<td>3.5 ± 2.3</td>
<td>16 ± 2</td>
<td>−1.3 ± 1.2</td>
</tr>
<tr>
<td>LS 0.6 μg/kg/min (n = 14)</td>
<td>4.5 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>61 ± 4</td>
<td>3.5 ± 3.8</td>
<td>15 ± 3</td>
<td>−7.1 ± 1.8</td>
</tr>
<tr>
<td>LS 0.4 μg/kg/min (n = 23)</td>
<td>4.6 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>62 ± 4</td>
<td>7.6 ± 3.1</td>
<td>17 ± 2</td>
<td>−5.7 ± 1.2</td>
</tr>
<tr>
<td>LS 0.2 μg/kg/min (n = 19)</td>
<td>5.1 ± 0.4</td>
<td>0.7 ± 0.2</td>
<td>70 ± 4</td>
<td>−1.8 ± 2.5</td>
<td>13 ± 2</td>
<td>−5.0 ± 1.2</td>
</tr>
<tr>
<td>LS 0.1 μg/kg/min (n = 23)</td>
<td>4.8 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>66 ± 4</td>
<td>−1.8 ± 2.5</td>
<td>16 ± 1</td>
<td>−4.5 ± 1.2</td>
</tr>
<tr>
<td>LS 0.05 μg/kg/min (n = 16)</td>
<td>4.2 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>63 ± 6</td>
<td>0.6 ± 2.5</td>
<td>14 ± 2</td>
<td>−3.8 ± 1.1</td>
</tr>
<tr>
<td>Placebo (n = 20)</td>
<td>4.7 ± 0.3</td>
<td>−0.3 ± 0.2</td>
<td>69 ± 4</td>
<td>−6.8 ± 2.0</td>
<td>12 ± 1</td>
<td>0.6 ± 1.0</td>
</tr>
<tr>
<td>Vehicle (n = 15)</td>
<td>5.2 ± 0.3</td>
<td>−0.1 ± 0.2</td>
<td>78 ± 5</td>
<td>−4.4 ± 3.2</td>
<td>13 ± 1</td>
<td>−0.9 ± 0.8</td>
</tr>
</tbody>
</table>

Dosages of levosimendan refer to continuous infusion. See text for details of bolus starting doses.

CO = cardiac output; HR = heart rate; LS = levosimendan; MBP = mean blood pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SV = stroke volume. Data are mean ± SEM.

(continued on next page)
Table 2. Continued

<table>
<thead>
<tr>
<th>PAP (mm Hg)</th>
<th>ΔPAP at 23–24 h</th>
<th>RAP (mm Hg)</th>
<th>ΔRAP at 23–24 h</th>
<th>MBP (mm Hg)</th>
<th>ΔMBP at 23–24 h</th>
<th>HR (beats/min)</th>
<th>ΔHR at 23–24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 ± 2</td>
<td>0.002</td>
<td>0.018</td>
<td>27 ± 2</td>
<td>0.002</td>
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</tbody>
</table>

decreases in PCWP than dobutamine (p < 0.044 for all doses of levosimendan) and infusions of 0.4 and 0.6 µg/kg/min produced significantly larger increases in CO (p < 0.001 and p = 0.003, respectively). There were no significant differences in SV changes between the dobutamine and levosimendan groups at any time. The CO increase is due partly to heart rate increase (Table 2), especially with higher dosing levels.

**Secondary efficacy variables.** MEASURED HEMODYNAMIC VARIABLES. There was a significant linear relationship between levosimendan dose and the change in HR at 23 h to 24 h (p = 0.002) (Table 2). A significant linear trend was also demonstrated for reduction in mean PAP during levosimendan therapy (p = 0.002). The decrease in mean PAP in the dobutamine group was small and did not differ significantly from that seen with placebo (p = 0.845). Overall effects on RAP were small, but there was a significant linear relationship between levosimendan dose and change in mean RAP (p = 0.018). Levosimendan infusions of 0.2 to 0.6 µg/kg/min produced significantly larger decreases in mean RAP than dobutamine (p ≥ 0.032).

**DERIVED HEMODYNAMIC VARIABLES (MBP, PVR AND TOTAL PERIPHERAL RESISTANCE).** There was a significant relation between levosimendan dose and change in MBP at 23 h to 24 h (p = 0.012) (Table 2) even though consistent and substantial (>5 mm Hg) decrease in MBP were recorded only with levosimendan infusions of 0.4 µg/kg/min or more. The reduction in MBP observed in the dobutamine group was not statistically different from that seen with placebo.

Total peripheral resistance response at 23 h to 24 h was significantly related to the levosimendan dose (p < 0.001), with reductions ranging from approximately 7% at 0.05 µg/kg/min to approximately 33% at 0.4 µg/kg/min. Levosimendan infusions of 0.4 and 0.6 µg/kg/min produced significantly larger decreases in total peripheral resistance than dobutamine infusion (p < 0.001 for both doses). Mean change in PVR in patients treated with levosimendan exhibited a significant linear relationship (p = 0.005). The mean decrease in PVR seen in the dobutamine group was not greater than that observed in the placebo group (p = 0.119) and was significantly smaller than with levosimendan 0.4 or 0.6 µg/kg/min (p < 0.001).

**TIME-COURSE OF HEMODYNAMIC EFFECT.** Additional analyses conducted to describe fully the hemodynamic effects of levosimendan indicated that the magnitude of the treatment effect of levosimendan on hemodynamic indices, notably decrease in PCWP, tended to become larger with time (Fig. 2), whereas the effect of dobutamine was attenuated. The effect of levosimendan on SV was more variable because of an excessive reduction in preload in some patients. Linear dose-response trends were demonstrated for levosimendan during the first 30 min of treatment, corresponding to the phase of bolus infusion (p < 0.001 for CO, PCWP, MBP and HR; p > 0.2 for SV), though in pairwise comparisons the treatment effect on HR was statistically significant only at the highest bolus studied (36 µg/kg; p = 0.008).

**NEUROHORMONES.** There were some statistically significant changes in plasma atrial natriuretic peptide levels during the infusion of levosimendan but no significant changes in plasma epinephrine (Table 3). Two hours after termination of the infusion a statistically significant increase in norepinephrine levels was seen in patients who received levosimendan 0.05, 0.01 and 0.6 µg/kg/min (p ≤ 0.002). No dose relation was evident for the effect on norepinephrine. Plasma renin levels were reduced in patients who received the lower doses of levosimendan and increased at higher doses (0.4 or 0.6 µg/kg/min) and in those who received dobutamine. Most of the changes were on the order of 10% to 20% of baseline levels, though the treatment effects of higher dose levosimendan (0.4 and 0.6 µg/kg/min) and dobutamine were larger (~23% to 40%) and statistically significant (p ≤ 0.007) at 30 min and 8 h.

**SAFETY EVALUATION.** Overall, 29% of patients treated with levosimendan experienced at least one adverse event during the study day, compared with 35% of patients treated with dobutamine and 20% of patients who received placebo. The adverse events most frequently recorded in levosimendan-treated patients (regardless of relation to study medication) were headache, hypotension and nausea (n = 9, 5 and 4, respectively). Hypertension was reported only in the dobutamine group (n = 2), and was, with tachycardia (n = 2), the most often recorded adverse event in dobutamine-treated patients.
Tachycardia (HR increase >20% from baseline) and systolic blood pressure <90 mm Hg were the two most frequent protocol-defined dose-limiting events. Tachycardia occurred in one patient who received levosimendan 0.05 μg/kg/min, in three patients in each of the 0.1 and 0.2 μg/kg/min groups, in four patients in each of the 0.4 and 0.6 μg/kg/min groups, in five patients receiving dobutamine and in one patient who received placebo. Low systolic blood pressure was recorded in eight patients treated with levosimendan (one each in the 0.1 and 0.6 μg/kg/min groups, two in the 0.2 μg/kg/min group and four in the 0.4 μg/kg/min group) and in one patient treated with dobutamine. Tests for a levosimendan dose-relation to tachycardia or low systolic blood pressure were not statistically significant (p > 0.1). Heart rate was reduced to <50 beats/min in one patient who received levosimendan 0.6 μg/kg/min.

There were no deaths during the treatment day, but two patients died during follow-up. One of these patients had received dobutamine and had experienced a worsening of CHF during the follow-up period. The other had received levosimendan 0.1 μg/kg/min and died following an acute myocardial infarction.

LABORATORY SAFETY INDICES. There were no clinically meaningful alterations in any laboratory safety parameters during the study day. Reductions in red blood cell count (10% to 39%; p ≤ 0.012), hematocrit (<10%; p ≤ 0.011) and hemoglobin (<10%; p ≤ 0.01) were seen at the higher levosimendan doses (0.2 to 0.6 μg/kg/min).

Small (~5%), but statistically significant (p < 0.05) reductions in serum potassium occurred with the higher doses of levosimendan. One case of hypokalemia in a patient treated with levosimendan 0.2 μg/kg/min was reported during the follow-up period. There were no increases in creatinine kinase MB isoenzyme or troponin-T in patients who received levosimendan.

ECG RECORDINGS. The mean duration of the RR interval was reduced by 113 ± 85 ms during levosimendan treatment, with evidence of a dose-effect relationship (p = 0.002). The RR interval was also shortened in all other treatment groups (dobutamine 29 ± 18 ms, placebo 15 ± 17 ms; vehicle 37 ± 14 ms). There were no substantial effects of treatment on the QRS and PQ intervals in any treatment group. QT interval (corrected for HR) was increased by 15 ± 20 ms with levosimendan 0.4 μg/kg/min and by 45 ± 10 ms with levosimendan 0.6 μg/kg/min (p = 0.008 for linear dose trend).

Ventricular extrasystoles and ventricular tachycardia were recorded in the ambulatory ECG more often with dobutamine than with other treatments. An increased frequency of ventricular dysrhythmias was noted at the highest dose of levosimendan used (0.6 μg/kg/min). No differences in the frequency of atrial arrhythmias were observed between the groups and there was no evidence of a dose relationship.

DISCUSSION

There have been few controlled studies on prolonged infusions of any intravenous drug indicated for the short-
Figure 2. Time course of levosimendan treatment effects on pulmonary capillary wedge pressure (A), stroke volume (B) and heart rate (C). Data are placebo-adjusted means ± SEM. Dosages of levosimendan (LS) refer to continuous infusion; see text for details of bolus starting doses. Open circle = levosimendan 0.05 µg/kg/min; open triangle = levosimendan 0.1 µg/kg/min; open square = levosimendan 0.2 µg/kg/min; open diamond = levosimendan 0.4 µg/kg/min; upside-down triangle = levosimendan 0.6 µg/kg/min; closed circle = dobutamine.
Table 3. Plasma Neurohormone Levels at Baseline, After 30 min (end of bolus injection phase), 8 h, and at 26 h (2 h After Completion of Infusion Phase)

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo/vehicle</th>
<th>LS 0.05 µg/kg/min</th>
<th>LS 0.1 µg/kg/min</th>
<th>LS 0.2 µg/kg/min</th>
<th>LS 0.4 µg/kg/min</th>
<th>LS 0.6 µg/kg/min</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP (ng/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>149 ± 22 (n = 33)</td>
<td>90 ± 14 (n = 16)</td>
<td>153 ± 21 (n = 22)</td>
<td>78 ± 13 (n = 16)</td>
<td>132 ± 20 (n = 23)</td>
<td>137 ± 37 (n = 13)</td>
<td>151 ± 27 (n = 20)</td>
</tr>
<tr>
<td>30 min</td>
<td>151 ± 23 (n = 35)</td>
<td>107 ± 17 (n = 16)</td>
<td>135 ± 15 (n = 22)</td>
<td>74 ± 12 (n = 16)</td>
<td>103 ± 16* (n = 22)</td>
<td>151 ± 43 (n = 13)</td>
<td>144 ± 21 (n = 20)</td>
</tr>
<tr>
<td>8 h</td>
<td>163 ± 24 (n = 34)</td>
<td>76 ± 10* (n = 16)</td>
<td>124 ± 21* (n = 20)</td>
<td>68 ± 13* (n = 16)</td>
<td>96 ± 201* (n = 20)</td>
<td>129 ± 35 (n = 12)</td>
<td>152 ± 22 (n = 16)</td>
</tr>
<tr>
<td>26 h</td>
<td>144 ± 19 (n = 34)</td>
<td>78 ± 12 (n = 15)</td>
<td>117 ± 16 (n = 22)</td>
<td>58 ± 9 (n = 15)</td>
<td>131 ± 42 (n = 14)</td>
<td>105 ± 26 (n = 12)</td>
<td>173 ± 32 (n = 15)</td>
</tr>
</tbody>
</table>

Epinephrine (nmol/L)

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo/vehicle</th>
<th>LS 0.05 µg/kg/min</th>
<th>LS 0.1 µg/kg/min</th>
<th>LS 0.2 µg/kg/min</th>
<th>LS 0.4 µg/kg/min</th>
<th>LS 0.6 µg/kg/min</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.06 ± 0.19 (n = 33)</td>
<td>2.13 ± 0.28 (n = 14)</td>
<td>2.60 ± 0.25 (n = 21)</td>
<td>2.57 ± 0.38 (n = 16)</td>
<td>2.84 ± 0.46 (n = 19)</td>
<td>2.12 ± 0.30 (n = 12)</td>
<td>2.91 ± 0.41* (n = 15)</td>
</tr>
<tr>
<td>30 min</td>
<td>2.03 ± 0.17 (n = 34)</td>
<td>2.21 ± 0.25 (n = 14)</td>
<td>2.65 ± 0.28 (n = 20)</td>
<td>2.67 ± 0.24 (n = 16)</td>
<td>2.91 ± 0.35 (n = 19)</td>
<td>3.19 ± 0.61† (n = 10)</td>
<td>2.97 ± 0.54† (n = 15)</td>
</tr>
<tr>
<td>8 h</td>
<td>1.95 ± 0.18 (n = 33)</td>
<td>2.52 ± 0.31 (n = 14)</td>
<td>2.88 ± 0.28 (n = 19)</td>
<td>2.78 ± 0.23 (n = 16)</td>
<td>2.84 ± 0.48 (n = 17)</td>
<td>3.31 ± 0.42 (n = 11)</td>
<td>2.92 ± 0.51 (n = 13)</td>
</tr>
<tr>
<td>26 h</td>
<td>2.02 ± 0.17 (n = 34)</td>
<td>2.84 ± 0.36† (n = 14)</td>
<td>3.19 ± 0.26† (n = 20)</td>
<td>2.70 ± 0.31 (n = 14)</td>
<td>2.66 ± 0.39 (n = 14)</td>
<td>3.00 ± 0.43† (n = 12)</td>
<td>3.01 ± 0.42 (n = 15)</td>
</tr>
</tbody>
</table>

Epinephrine (nmol/L)

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<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.20 ± 0.03 (n = 33)</td>
<td>0.17 ± 0.05 (n = 14)</td>
<td>0.21 ± 0.03 (n = 21)</td>
<td>0.21 ± 0.07 (n = 16)</td>
<td>0.22 ± 0.04 (n = 19)</td>
<td>0.34 ± 0.10 (n = 12)</td>
<td>0.21 ± 0.03 (n = 15)</td>
</tr>
<tr>
<td>30 min</td>
<td>0.22 ± 0.03 (n = 34)</td>
<td>0.17 ± 0.04 (n = 14)</td>
<td>0.21 ± 0.04 (n = 20)</td>
<td>0.27 ± 0.06 (n = 16)</td>
<td>0.19 ± 0.03 (n = 19)</td>
<td>0.25 ± 0.06 (n = 10)</td>
<td>0.20 ± 0.04 (n = 15)</td>
</tr>
<tr>
<td>8 h</td>
<td>0.19 ± 0.02 (n = 33)</td>
<td>0.17 ± 0.04 (n = 14)</td>
<td>0.19 ± 0.02 (n = 21)</td>
<td>0.28 ± 0.06 (n = 16)</td>
<td>0.16 ± 0.03 (n = 17)</td>
<td>0.31 ± 0.10 (n = 11)</td>
<td>0.21 ± 0.03 (n = 13)</td>
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<td>26 h</td>
<td>0.24 ± 0.03 (n = 34)</td>
<td>0.18 ± 0.03 (n = 14)</td>
<td>0.28 ± 0.04 (n = 19)</td>
<td>0.30 ± 0.06 (n = 14)</td>
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<td>0.25 ± 0.05 (n = 12)</td>
<td>0.54 ± 0.29 (n = 15)</td>
</tr>
</tbody>
</table>

*p < 0.05 for levosimendan versus pooled placebo/vehicle groups; †p = 0.004 for levosimendan versus pooled placebo/vehicle group. Data represent mean ± SEM. Dosages of levosimendan refer to continuous infusion; see text for details of bolus starting doses.

ANP = atrial natriuretic peptide; LS = levosimendan.
with other data indicating that the effects of levosimendan on myocardial performance are energy neutral (25), as well as providing assurance that vasodilatation caused by levosimendan does not compromise myocardial perfusion.

**STUDY LIMITATIONS.** Efforts were made to minimize hemodynamic variability among patients in order to facilitate precise examination of dose-response relationships. Thus, patients were required to have been clinically stable for 1 month and to be receiving standardized medications for CHF. The initial eligibility criteria resulted, however, in the recruitment of patients with low PCWP. The protocol was therefore amended to permit the recruitment of patients with NYHA class IV. In addition, the left ventricular ejection fraction criterion was lowered to <35%. There is no reason to believe that the dose-finding results of the current study are not applicable to patients with more severe pump failure, but an explicit proof of this assumption is desirable.

Patients received their assigned doses of the study medication without uptitration. This fulfills the requirements of a dose-response study but does not represent the clinical situation in which therapy with a positive inotropic drug would normally be initiated at low dose and titrated until the desired effects were achieved. The present trial provides little information about the feasibility or safety of uptitration of levosimendan. Conversely, the study design permitted dose reductions: this reflects clinical practice and ensured patient safety. Dose reductions complicated the analysis of dose-responsiveness, however, and may have concealed the magnitude of the treatment effect on those parameters that were used to mandate dose adjustment.

Despite these limitations, the results of this study clearly demonstrate that intravenous administration of levosimendan for 24 h produces favorable dose-dependent hemodynamic effects in Caucasian male patients with stable moderate-to-severe CHF, and defines the tolerated dose range for this agent i.e., preferred starting dose of a bolus of 6 to 24 μg/kg in 10 min followed by infusion rates of 0.05 to 0.2 μg/kg/min.

**Acknowledgments**

The contribution of the patients and investigators to this study is greatly appreciated.

**STUDY LOCATIONS AND INVESTIGATORS**

("PRINCIPAL INVESTIGATOR")

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**REFERENCES**


