

Preliminary clinical experience with the repetitive administration of levosimendan in patients with end-stage heart failure

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Key words:
Heart failure;
Outpatient management;
Therapy.

We present our preliminary clinical experience with the initial and repetitive administration of the novel inotropic agent levosimendan in a cohort of 20 patients with end-stage heart failure who were acutely decompensated or whose symptoms were refractory to the usual pharmacological treatments thus necessitating hospitalization. Repetitive levosimendan infusions were administered to 9 patients (minimum 2, maximum 8 pulses). The effects of this therapy on the symptomatic status, vital signs, hemodynamic performance and clinical outcomes are discussed.

(Ital Heart J 2003; 4 (Suppl 2): 45S-49S)

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Most patients with heart failure (HF) due to left ventricular systolic dysfunction respond favorably to pharmacological and non-pharmacological treatments and enjoy a good quality of life and an enhanced survival. However, some patients do not improve or experience a rapid recurrence of symptoms despite optimal medical therapy. Intravenous positive inotropic agents play an important role in the short-term management of patients with end-stage HF whose symptoms are refractory to the usual pharmacological treatments. The use of continuous intravenous inotropic support to improve symptoms, stabilize the patient and allow hospital discharge is often necessary.

Beta-adrenergic agonists and phosphodiesterase inhibitors, the most commonly used positive inotropic agents, exert their action primarily by increasing cyclic adenosine monophosphate (cAMP) and ultimately intracellular calcium concentrations. Their use is limited by several problems such as an increase in heart rate, the stimulation of arrhythmias and the development of tolerance^{1,2}. Although they can improve cardiac performance during short- and long-term therapy, long-term therapy in patients with advanced HF with these drugs has not improved their symptoms or clinical status and has been associated with a significant increase in mortality². This is the reason why the long-term use of regularly scheduled

intermittent infusions at home, in an outpatient clinic, or in a short stay unit is strongly discouraged in patients who have been successfully weaned from inotropic support, even in advanced HF².

Levosimendan is a novel calcium-sensitizing agent that exerts a positive inotropic action by increasing the sensitivity of the contractile apparatus to calcium, and unlike the cAMP-dependent positive inotropic agents, it does not cause diastolic intracellular calcium overload³. It is the only calcium-sensitizing agent that has been successfully developed as a clinically used drug. A unique property of levosimendan is that its favorable hemodynamic effects are sustained due to the long elimination half-time (70-80 hours) of its active metabolite OR-1896⁴.

Accumulating evidence from a number of clinical studies demonstrates the efficacy of levosimendan in improving the hemodynamic performance, symptomatic status and physical performance of patients with severe HF^{5,6}. Furthermore, the mortality outcomes in two sizeable studies that compared levosimendan with dobutamine in patients with severe HF and levosimendan with placebo in patients with severe HF after acute myocardial infarction were in favor of this novel drug^{7,8}.

In view of these data, we started the use of levosimendan in patients with acutely decompensated HF and in symptomatic patients with severe HF refractory to the usual phar-

macological treatments. Furthermore, we initiated a program of repetitive administration of levosimendan in patients who showed a markedly favorable clinical response after the first administration of the drug. We present the clinical experience of our Center in this manuscript.

Methods

Patient population. All patients admitted to our Department with low-output HF after March 2002 were preliminarily considered for levosimendan therapy. Patients with acutely decompensated HF or with severe symptomatic HF refractory to the usual pharmacological treatments who were judged to require hemodynamic monitoring and treatment with an intravenous positive inotropic agent were considered candidates for levosimendan therapy.

The exclusion criteria were: patients with clinical and electrocardiographic evidence of acute ischemia; precipitating and readily correctable causes of acute HF decompensation; significant mechanical obstructions affecting the ventricular filling or outflow or both; coexisting severe renal failure; coexisting severe hepatic impairment; severe hypotension; severe tachycardia; and artificial ventilation.

Drug administration. All patients were receiving optimal pharmacological therapy. They were all receiving intravenous furosemide. Angiotensin-converting enzyme inhibitors or angiotensin receptor inhibitors and beta-adrenergic receptor blockers were administered if tolerated well and not contraindicated. Digoxin, spironolactone, thiazides, anticoagulants and amiodarone were administered if indicated.

The levosimendan regimen administered in all patients was 0.1 µg/kg/min infusion for 24 hours with no loading bolus.

In patients with a systemic blood pressure < 90 mmHg intravenous dobutamine or dopamine was administered and if blood pressure increased to > 90 mmHg, levosimendan was co-administered in the usual fashion. Patients who showed a markedly favorable clinical response after the first administration of the drug were considered for repetitive administration every 4-8 weeks.

Assessments. The medical history and physical examination findings were recorded. The vital signs just prior to the first levosimendan infusion and at its completion were also recorded.

Before the first administration of levosimendan a flow-directed pulmonary artery catheter was inserted into the right heart cavities through the internal jugular or the subclavian veins, unless contraindicated. The baseline right heart pressures were measured and recorded. The right heart pressures were also measured and recorded approximately at the end of the administration of the drug in those patients who were being hemodynamically monitored.

Venous blood samples drawn before and after the first administration of the drug were sent for a full blood count and for the determination of the serum levels of urea, creatinine, electrolytes and high-sensitivity C-reactive protein (hsCRP).

Statistical analysis. The baseline characteristics were summarized using appropriate descriptive statistics. Changes in the hemodynamic status were evaluated using the paired Student's t-test. The risk of death was plotted using the Kaplan-Meier technique. The results are expressed as mean ± SD and were considered statistically significant at p < 0.05.

Results

Between March 2002 and April 2003, levosimendan was administered to 20 patients.

Table I summarizes the demographics and causes of HF in these patients. They were all males, except for 2 women (one with coronary artery disease, one with valvular disease).

Table II summarizes the concomitant drugs our patients were receiving at the initiation of the levosimendan infusion.

The NYHA functional status (before levosimendan infusion and after hospital discharge) and the vital signs just prior to and at the end of levosimendan infusion are shown in table III. The systolic and diastolic blood pressures remained largely unchanged and there was a significant improvement in the symptomatic status of the patients as measured on the NYHA scale.

Table I. Patient demographics and causes of heart failure.

	No. patients	Age (years)	NYHA class
All	20	60 ± 16 range 14-78	3.9 ± 0.3 min 3-max 4
Coronary artery disease	9	70 ± 8	3.8 ± 0.5
Dilated cardiomyopathy	7	42 ± 17	4 ± 0.0
Hypertensive cardiomyopathy	1	76	4
Valvular disease	2	52	3
Heart transplantation	1	64	4

Table II. Concomitant medications and implantable automatic cardioverter-defibrillators (IACD).

Furosemide	20 (100%)
Dose (mg)	215 ± 205 (min 60-max 750)
ACE-inhibitors/ARB	11 (55%)
Spironolactone	12 (60%)
Beta-blockers	9 (45%)
Digoxin	8 (40%)
Amiodarone	6 (30%)
IACD	5 (25%)
Co-inotropes	9 (45%)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

Table III. NYHA status and vital signs before and after the infusion of levosimendan.

	Before	After	p
NYHA class	3.9 ± 0.3	3.2 ± 0.8	0.007
SBP (mmHg)	103 ± 13	101 ± 11	0.6
DBP (mmHg)	61 ± 10	56 ± 10	0.16
HR (b/min)	83 ± 19	87 ± 20	0.22

DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

In 12 patients a complete set of paired hemodynamic measurements of the right heart pressures was obtained and the results are shown in table IV. All the right heart pressures were reduced after the infusion of levosimendan and most of these reductions reached statistical significance.

Paired echocardiographic examinations performed before and 1-10 days after the initiation of levosimendan infusion were available for 12 patients and the results for some basic echocardiographic parameters are shown in table V. There was a trend towards a reduction in the left ventricular end-systolic and end-diastolic dimensions.

Paired measurements of the standard hematological and biochemical variables before and the day after the initiation of the levosimendan infusion were obtained in 16 patients and the results are shown in table VI. The urea, creatinine, sodium and hsCRP serum levels remained unchanged. There was a non-statistically significant trend towards a reduction in the serum potassium levels. Both hemoglobin and hematocrit levels were significantly reduced after the levosimendan infusion.

The serious adverse events observed during the levosimendan infusion in our patients were: 1 death, 1 wide QRS tachycardia requiring DC-shock cardioversion, 1 systolic blood pressure drop > 20 mmHg, and 1 severe headache requiring discontinuation of the infusion.

The co-administration of levosimendan with dobutamine or dopamine was required in 9 patients due to an initially low systemic blood pressure. Table VII shows

Table IV. Right heart hemodynamics just prior and at the completion of levosimendan infusion.

	Before	After	p
Right atrium (mmHg)	16 ± 11	9 ± 6	0.069
Right ventricle (mmHg)			
Systolic	42 ± 13	39 ± 12	0.035
Diastolic	8 ± 8	7 ± 6	0.645
Mean	20 ± 8	18 ± 6	0.038
Pulmonary artery (mmHg)			
Systolic	48 ± 17	41 ± 12	0.011
Diastolic	23 ± 11	21 ± 8	0.206
Mean	32 ± 13	29 ± 9	0.140
PCWP (mmHg)	24 ± 11	20 ± 10	0.015

PCWP = pulmonary capillary wedge pressure.

Table V. Basic echocardiographic measurements before and 1-10 days after levosimendan infusion.

	Before	After	p
LVEF (%)	20 ± 8	21 ± 14	0.46
LVEDD (mm)	74 ± 12	71 ± 8	0.14
LVESD (mm)	68 ± 10	63 ± 8	0.06

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter.

Table VI. Standard hematological and biochemical variables before and the day after the initiation of levosimendan infusion.

	Before	After	p
Potassium (µmol/ml)	4.5 ± 0.8	4.1 ± 0.6	0.14
Sodium (µmol/ml)	130 ± 6	129 ± 5	0.22
Urea (mg/dl)	123 ± 62	122 ± 72	0.97
Creatinine (mg/dl)	1.7 ± 0.7	1.7 ± 0.9	0.96
Hematocrit (%)	37.7 ± 3.8	34.8 ± 4.6	< 0.001
Hemoglobin (g/dl)	12.1 ± 1.4	11.2 ± 1.7	0.003
hsCRP (mg/l)	47.5 ± 47.9	34.0 ± 36.6	0.25

hsCRP = high-sensitivity C-reactive protein.

Table VII. Selected demographic, clinical and laboratory variables in patients who received levosimendan alone or in combination with other inotropic agents.

	Levosimendan	Combination	p
Age (years)	65 ± 14	55 ± 18	0.21
NYHA class	3.8 ± 0.4	4.0 ± 0.0	0.15
SBP (mmHg)	106 ± 16	93 ± 19	0.19
DBP (mmHg)	61 ± 12	56 ± 13	0.44
HR (b/min)	79 ± 14	95 ± 26	0.15
Dose of furosemide (mg)	211 ± 245	220 ± 175	0.95
Urea (mg/dl)	102 ± 42	146 ± 72	0.17
Creatinine (mg/dl)	1.5 ± 0.6	2.0 ± 0.6	0.10
Potassium (µmol/ml)	4.2 ± 0.6	4.6 ± 0.7	0.21
Sodium (µmol/ml)	134 ± 4.5	127 ± 4.4	0.02

DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

the differences in selected demographic, clinical and laboratory characteristics between patients who received levosimendan alone or in combination with other inotropic agents. Although there were distinctive differences between these two groups, the only statistically significant variation was the lower baseline serum sodium levels in the latter group of patients.

A levosimendan infusion was re-administered at least once in 9 patients during follow-up, and in 6 of them this was planned due to the favorable clinical response seen after the first administration (Table VIII). These latter patients were readmitted according to a preplanned schedule every 4-8 weeks for 24-48 hours for the usual 24-hour infusion. In the other 3 patients the re-administration was given during an unplanned admission for decompensated HF. The fact that 3 of them died during this admission testifies to their worse condition.

The mean follow-up of our patients was 194 ± 152 days (min 1/max 406).

Table IX shows the morbidity and mortality outcomes during follow-up and according to whether they received repetitive administrations or not. The Kaplan-Meier survival curve is shown in figure 1.

Discussion

Our preliminary experience with the use of the new positive inotropic agent levosimendan is encouraging. We were able to confirm the hemodynamic improvements shown to be the result of therapy with levosimendan in other studies and clinical trials. In addition, most of our patients achieved an average of almost one NYHA class symptomatic improvement after their discharge from the index admission. These observations are important, because the cohort of patients studied are those commonly encountered in our daily clinical practice and out of the setting of clinical trials with their usually strict inclusion and exclusion criteria. These were high-risk patients requiring hospitalization and virtually all in NYHA class IV before their index admission.

The crude mortality in our patients at the end of the follow-up was 35%. We consider this satisfactory, especially when seen in perspective with the 39.4% mortality observed in the enalapril arm of the CONSENSUS study (mean follow-up 188 days)⁹. All patients randomized in the CONSENSUS study were in NYHA class IV, though, unlike our cohort of patients, they were not decompensated.

The patient who died during the levosimendan infusion had dilated cardiomyopathy with practically no myocardial contractile reserve, a left ventricular ejection fraction of 10% and an ongoing fulminant deterioration of his clinical status. He was hypotensive and another inotropic agent was co-administered. An intra-aortic balloon pump was in place, and levosimendan was administered despite the fact that his blood pressure never increased > 90 mmHg. The other observed seri-

Table VIII. Tabulation of admissions for repetitive levosimendan infusions.

No. of re-administrations	Planned	Unplanned	All
2	1	3	4
3	2	0	2
4	1	0	1
7	1	0	1
8	1	0	1
Total	6	3 (2 deaths)	9

Table IX. Mortality and morbidity outcomes in the repetitive and non-repetitive administration groups of patients.

	Repetitive (n=9)	Non-repetitive (n=11)	All (n=20)
Deaths	3	4	7
Unplanned hospital admission	1	4	5

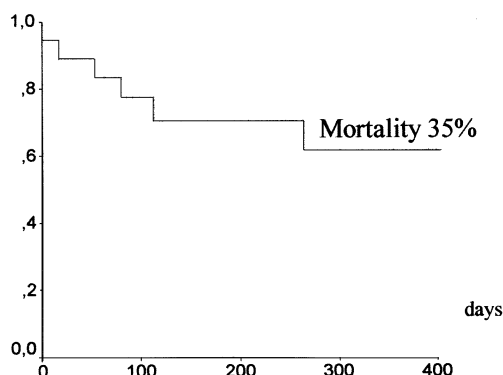


Figure 1. Mortality curve of the studied population.

ous adverse events were well tolerated and without any sequel.

A slight, not statistically significant decrease in the systolic and diastolic blood pressures and an increase in the heart rate was observed in most patients.

We observed a significant decrease in the hemoglobin levels and in the hematocrit in our patients, similar to that observed in other studies. This may be attributed to the hemodilution consequent to fluid shift into the intravascular space as a result of the cardiac output increase and vasodilation. We did not observe any significant change in the serum levels of sodium, potassium and hsCRP.

The 3 patients who received more pulses of repetitive levosimendan (8, 7 and 4 times respectively) experienced a dramatic improvement in their symptomatic status from the very first infusion and remained stable during follow-up. However, it should be stressed that patients were selected for repetitive administrations on the basis of a favorable clinical response after the first infusion. Thus, the favorable clinical outcomes observed

in these patients cannot be uncritically extrapolated to others. We chose a time window of 4-8 weeks between each pulse of levosimendan infusion because of the prolonged effect of its active metabolite OR-1896 and for logistic reasons.

The first levosimendan infusion was administered in the coronary care unit, always with invasive blood pressure monitoring and right heart pressure monitoring in most cases. The scheduled repetitive administrations of levosimendan were performed in the ward using telemetry and frequent automatic non-invasive blood pressure monitoring. We found this to be convenient and safe. None of our scheduled repetitive administration patients had to prolong their stay in the ward beyond 48 hours.

The LIDO study⁷ showed that in patients with severe, low-output HF levosimendan improved the hemodynamic performance more effectively than dobutamine and moreover, up to 6 months of follow-up, this was accompanied by a lower mortality. The RUSLAN study⁸ demonstrated the safety of levosimendan therapy in patients with HF complicating an acute myocardial infarction, which in addition produced a reduction in the risk of worsening HF and death. However, the results of adequately powered definitive mortality trials on levosimendan are still to be published. If levosimendan proves to have a neutral or favorable mortality effect in patients with severe HF, one might anticipate its widespread repetitive use for at least symptomatic relief and as a bridge to more invasive therapies such as heart transplantation.

References

1. Opasich C, Russo A, Mingrone R, Zambelli M, Tavazzi L. Intravenous inotropic agents in the intensive therapy unit: do they really make a difference? *Eur J Heart Fail* 2000; 2: 7-11.
2. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 guidelines for the evaluation and management of heart failure): developed in collaboration with the International Society for Heart and Lung Transplantation, endorsed by the Heart Failure Society of America. *Circulation* 2001; 104: 2996-3007.
3. Holubarsch C. New inotropic concepts: rationale for and differences between calcium sensitizers and phosphodiesterase inhibitors. *Cardiology* 1997; 88 (Suppl 2): 12-20.
4. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. *Circulation* 2003; 107: 81-6.
5. Slawsky MT, Colucci WS, Gottlieb SS. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. *Circulation* 2000; 102: 2222-7.
6. Nieminen MS, Akkila J, Hasenfuss G. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. *J Am Coll Cardiol* 2000; 36: 1903-12.
7. Follath F, Cleland JG, Just H, et al, for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; 360: 196-202.
8. Moiseyev V, Poder P, Andrejevs N, et al, for the RUSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSLAN). *Eur Heart J* 2002; 23: 1422-32.
9. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316: 1429-35.