

European Experience on the Practical Use of Levosimendan in Patients with Acute Heart Failure Syndromes

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The novel calcium sensitizer and ATP-dependent potassium channel opener levosimendan has been introduced for routine use in several European countries. Recent reports on clinical experience confirm the positive hemodynamic results and beneficial clinical effects described in the initial dose-finding and randomized comparative therapeutic trials in patients with severe low-output heart failure. In addition, studies in small series of patients with cardiogenic shock after myocardial infarction and/or surgical interventions and postinterventional myocardial dysfunction (stunning) indicate that the inotropic and vasodilating actions of levosimendan may be of value in a wider range of indications. Dose recommendations, combination with other drugs, and potential side effects are discussed in this overview. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:80G–85G)

Levosimendan is a new calcium-sensitizing drug that opens adenosine triphosphate–dependent potassium (K_{ATP}) channels with effects that increase myocardial contraction and cause vasodilation. Compared with other agents for acute heart failure syndromes (AHFS), its main potential advantages are the improvement of myocardial contractility without increasing oxygen requirements, reduction of ventricular preload, and an antistunning, anti-ischemic effect by opening K_{ATP} channels.^{1–3} This pharmacologic profile of levosimendan offers new therapeutic possibilities in patients with AHFS. In initial dose-finding^{4,5} and therapeutic trials,⁶ a rapid and prolonged hemodynamic improvement with an increase in cardiac index, reduction of pulmonary capillary wedge pressure (PCWP), and reduction of peripheral vascular resistance without proarrhythmic effects were documented. Furthermore, positive effects on long-term survival up to 6 months were observed.^{6,7}

Levosimendan is registered for clinical use in several countries in Europe, South America, and Asia. There are an increasing number of reports on practical experiences and therapeutic successes in different clinical situations. In this article, we summarize recent publications on therapeutic indications, dose schedules, outcomes, and tolerance.

Methods

Clinical reports on levosimendan therapy in patients with severe decompensated acute or chronic heart failure (HF), cardiogenic shock after myocardial infarction (MI), or car-

diac interventions and perioperative administration are reviewed. These publications were mostly smaller randomized or observational trials, with good descriptions of patient inclusion criteria, levosimendan administration, and methods of clinical and/or hemodynamic evaluation.

Therapeutic Efficacy of Levosimendan in Acute Heart Failure Syndromes

Decompensated low-output heart failure: Decompensated low-output HF is the best documented therapeutic indication for levosimendan administered as a single intravenous infusion lasting 6 to 24 hours. Patients included in the dose-finding and comparative clinical trials^{4–6} were characterized by dyspnea (New York Heart Association [NYHA] functional class III to IV) and signs of venous and pulmonary congestion accompanied by peripheral vasoconstriction. Hemodynamic inclusion criteria were reduced cardiac index (<2.5 L/min per m^2) and increased PCWP (>16 mm Hg). Patients with systolic blood pressure <90 mm Hg were excluded in these initial trials. Bolus injection followed by a continuous infusion of levosimendan resulted in a rapid increase in cardiac index with simultaneous reduction of PCWP. There were no arrhythmic complications or sinus tachycardia. A clinical improvement with regression of dyspnea and fatigue was also observed. Positive effects were maintained for 24 to 48 hours after the end of levosimendan infusion.

Changes in B-type natriuretic peptide (BNP) levels have been associated with changes in ventricular filling pressures, and growing evidence suggests that BNP may be both a useful tool to monitor therapy and a powerful prognostic marker in advanced HF. The treatment of patients with decompensated HF with levosimendan was shown to produce a significant reduction in BNP levels that was associated with significant improvements in functional status and hemodynamic measures.^{8–10} An interesting finding among

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these studies was that patients whose BNP levels were lowered to <145 pmol/L (500 pg/mL) at discharge had significantly better clinical outcomes than those whose BNP values remained at levels >145 pmol/L (500 pg/mL).^{8,10}

Initial trial results could be fully confirmed under routine clinical conditions in an ongoing prospective multicenter postlaunch trial in Portugal.¹¹ At present, >120 patients with decompensated HF (NYHA class III to IV, left ventricular ejection fraction [LVEF] <0.40) were treated by a 24-hour infusion of levosimendan (0.05 to 0.2 $\mu\text{g}/\text{kg}$ per min) with or without initial loading doses. Based on well-defined uniform criteria for subjective and objective categories of clinical improvement, a good therapeutic effect occurred in 80% of patients without serious adverse events. An important finding was the marked increase in urinary output in initially oliguric patients, with a rapid reduction of serum creatinine levels. A reduction of serum creatinine was also observed in the Levosimendan Infusion Versus Dobutamine (LIDO) trial.⁶ In several patients who were already receiving inotropic support with catecholamines, such drugs could be stopped and β -blockers readministered or initiated. Overall drug tolerance was remarkably good, with the exception of short episodes of hypotension with decreases of systolic blood pressure to <80 mm Hg in up to 33% of the patients. Hypotension could be treated by dose reduction or temporary interruption of levosimendan infusion, which later could be continued for the remaining 24-hour period. An additional therapeutic measure in such situations may be volume replacement, especially in patients with marked increases in diuresis.

Renal insufficiency commonly complicates the treatment of HF because of neurohumoral activation and inadequate organ perfusion, and it is associated with worse outcomes, including higher mortality. Levosimendan is hepatically metabolized and is suitable for use in patients with renal insufficiency. In another study from Portugal, Franco and colleagues¹² have shown that independent of baseline renal function in patients with NYHA functional class IV HF, levosimendan produced hemodynamic benefits while preserving renal status and perfusion. In this study, which included 41 patients, renal impairment was classified as mild, moderate, or severe, depending on creatinine clearance. After levosimendan therapy, patients experienced, on average, a brisk diuresis of similar magnitude independent of the degree of renal impairment (liters per 24 hours, mean [SD]): mild, 2.3 (1.02); moderate, 2.3 (0.84); or severe, 2.5 (1.96), respectively; $p = 0.914$. Consistent with the observed diuresis, mean serum BNP values rapidly decreased by similar proportions across renal impairment groups at 24 hours, indicating a decrease in myocardial wall stress. There was no compromise of perfusion or renal function as indicated by mean serum creatinine, mean arterial pressure, or heart rate at 24 hours. At discharge, all patients improved by 1 (56%) or 2 (44%) NYHA classes. The distributions across renal groups were not significantly different at 24 hours or at discharge.

A positive clinical experience was also reported by Nanas and associates,¹³ who used levosimendan in 18 pa-

tients with NYHA class IV HF previously treated with long-term intermittent dobutamine infusions. After a final dobutamine infusion at a rate of 10 $\mu\text{g}/\text{kg}$ per min, levosimendan was added with a bolus dose of 6 $\mu\text{g}/\text{kg}$ for 10 minutes followed by a continuous infusion at a rate of 0.2 $\mu\text{g}/\text{kg}$ per min for 24 hours. Hemodynamic measurements were obtained in all patients. With dobutamine alone, cardiac index increased by $>40\%$ in only 5 of 18 patients (28%), and PCWP did not change. However, at the end of combined levosimendan and dobutamine infusions, cardiac index increased $>40\%$ in 14 patients (78%, $p = 0.003$) and remained at a high level, even at 1 week of follow-up, in 11 patients (61%). PCWP also decreased $>25\%$ in 8 patients (44%) after 24 hours and was lower than baseline in 7 patients (39%) at the end of 1 week. The combined inotropic administration was well tolerated by all patients. At 7 days, symptoms also improved in all patients, and NYHA class had decreased from 4.0 to 2.94 ± 0.54 ($p = 0.001$). A total of 15 of the 18 patients could be discharged from the hospital. Thus, levosimendan may elicit a positive response, even in patients whose condition is refractory to dobutamine. Furthermore, levosimendan therapy provided clear outcome benefits, including decreased time to weaning from inotropes, shortened lengths of stay in the hospital and intensive care unit, and lower 30-day mortality, when compared with conventional intravenous inotropic agents.

Franco and coworkers¹⁴ showed that early addition of levosimendan to conventional inotropic therapy (dobutamine and/or dopamine) in patients with severe hypotension and progressive cardiogenic shock improved hemodynamic status and clinical outcomes. Patients who received levosimendan therapy (group 1, $n = 15$) required conventional inotrope support for half as long as those who were not given levosimendan (group 2, $n = 11$): 62 ± 38 hours for group 1 compared with 120 ± 48 hours for group 2, $p < 0.05$. With levosimendan treatment, hospital stay was decreased by >1 week (14 ± 5 days compared with 22 ± 8 days, $p < 0.01$) and time in the intensive care unit was decreased by 50% (5 ± 3 days compared with 9 ± 5 days, $p < 0.05$). In this group of patients, in-hospital mortality was also decreased 50% because of inclusion of levosimendan in the therapeutic regimen.

A preliminary clinical experience with repetitive administration of levosimendan in patients with end-stage HF was reported by Spargias and colleagues.¹⁵ Investigators studied 20 patients hospitalized with acute decompensation refractory to usual therapeutic agents; 12 of the 20 patients were hemodynamically monitored before, and at the completion of, levosimendan administration. Right- and left-sided filling pressures were significantly reduced without changes in blood pressure and heart rate. In 9 patients, levosimendan was repeatedly administered 2 to 8 times at intervals of 4 to 8 weeks. In 6 patients, planned readministration maintained clinical improvement, whereas in 3 patients rehospitalized for further acute clinical deterioration, repeated treatment with levosimendan could not prevent a fatal outcome. In

view of the long-lasting hemodynamic improvement because of a long-acting metabolite (half-life, approximately 80 hours),¹⁶ levosimendan appears to be a suitable drug for repetitive treatment of patients with advanced HF as a bridge to cardiac transplantation. Large-scale trials including comparison with other drugs used for similar indications should be conducted.

From the controlled and observational trials, it can be concluded that levosimendan represents an important new therapeutic option in patients with decompensated low-output congestive HF. It has advantages over current inotropic agents, such as prolonged effects after a single 24-hour infusion, without complicating cardiac arrhythmias, tachyphylaxis, or episodes of drug-induced myocardial ischemia.

Left ventricular failure in patients with acute coronary artery disease: In the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure Due to an Acute Myocardial Infarct (RUSSLAN),⁷ 402 patients with acute MI and clinical and radiologic signs of left ventricular HF within 5 days were treated with 4 different doses of levosimendan infused for 6 hours. These patients were compared with a group of 100 patients receiving a placebo infusion in addition to standard therapy. The aim of this study was to test the tolerance to this inotropic agent in patients with acute ischemia during the first 5 days. The incidence of recurrent ischemia and/or hypotension was similar in the levosimendan and placebo groups. Clinical worsening with the need for additional treatment with intravenous diuretics or other inotropes was significantly less frequent in the levosimendan group than in the placebo group (7.2% vs 13.7%, $p = 0.03$). At 14 days, mortality was lower after levosimendan than after placebo (11.7% vs 19.6%; hazard ratio, 0.56; 95% confidence interval [CI], 0.33 to 0.95; $p = 0.031$). Mortality reduction was maintained up to 180 days (22.6% vs 31.4%; hazard ratio, 0.67; 95% CI, 0.45 to 1.0; $p = 0.053$). However, an important experience in this study was a poor tolerance of the highest levosimendan dose level of 0.4 $\mu\text{g}/\text{kg}$ per min. This dose increased the incidence of hypotension and/or ischemia up to 19% compared with 10.7% to 12% in the 2 groups receiving the lower (0.1 or 0.2 $\mu\text{g}/\text{kg}$ per min) dose levosimendan and after placebo (10.8%). Thus, the importance of the upper dose limit of 0.2 $\mu\text{g}/\text{kg}$ per min should be recognized in all patients with acute myocardial ischemia.

A recent report by Sonntag and associates¹⁷ illustrates the potential utility of levosimendan in the prevention of myocardial stunning after coronary reperfusion. In 18 patients with acute coronary syndrome, levosimendan was administered at a dose of 24 $\mu\text{g}/\text{kg}$ infused over 20 minutes immediately after the completion of angioplasty. This treatment reduced the number of hypokinetic segments significantly as compared with a placebo infusion. Levosimendan-treated patients also had a lower left ventricular end-diastolic volume and higher LVEF. The myocardial protection might be a result of the K_{ATP} channel-opening

effects of levosimendan. This clinical observation is in accordance with the experimental data of Kersten and co-workers¹⁸ who showed a reduced myocardial infarct size in dogs undergoing coronary artery occlusion.

Cardiogenic shock: In the initial dose-finding and therapeutic trials in patients with decompensated HF, a systolic blood pressure <90 mm Hg was an exclusion criterion. In view of its vasodilatory and potential blood pressure-lowering effects, levosimendan alone is not a drug of first choice in cardiogenic shock. There are, however, several recent clinical observations indicating that levosimendan can improve hemodynamics, even in patients with cardiogenic shock, if it is combined with norepinephrine to maintain adequate perfusion pressures. Delle Karth and colleagues¹⁹ administered levosimendan to 10 patients with cardiogenic shock after MI or cardiac surgery who did not improve after revascularization. Patients then underwent intra-aortic balloon counterpulsation and infusion of catecholamines. First, norepinephrine was given to maintain mean arterial pressure at a level >65 mm Hg, then a levosimendan infusion was added at a dose of 0.1 $\mu\text{g}/\text{kg}$ per min without a bolus and continued for 24 hours; 7 of 10 patients were also mechanically ventilated. Patients also received volume administration to maintain cardiac filling pressures. Levosimendan treatment resulted in a significant increase in cardiac output together with a decrease in systemic vascular resistance. A total of 4 patients could be weaned from catecholamines, and all survived up to 6 months. The 6 nonsurvivors died of refractory cardiogenic shock ($n = 4$), intracerebral bleeding ($n = 1$), or mesenteric infarction ($n = 1$). In another study, Lehmann and associates²⁰ described the use of levosimendan in 18 patients after resuscitation after acute MI. Patients underwent emergency surgical revascularization followed by a combined treatment with levosimendan and norepinephrine. All patients in these series could be weaned from cardiopulmonary bypass, and 8 survived without the occurrence of multiorgan failure. A comparable experience was reported by Labriola and coworkers²¹ who treated 11 patients with cardiogenic shock after surgical interventions. In 8 patients (73%), cardiac index was increased by $>30\%$, and PCWP was reduced to <18 mm Hg within 3 hours after the start of levosimendan infusion. There are also several case reports on successful treatment of patients with various causes of cardiogenic shock by Zobel and colleagues,²² and Benlolo and associates,²³ and in a case of sepsis, by Matejovic and coworkers.²⁴ The above reports suggest that levosimendan may be successfully used in combination with catecholamines, such as norepinephrine, to treat cardiogenic shock. Nevertheless, formal controlled and comparative studies are necessary to define the place of levosimendan in such patients.

Perioperative treatment in patients undergoing cardiac surgery: Initial hemodynamic studies by Lilleberg et al²⁵ have shown that levosimendan improves hemodynamics in patients after coronary artery bypass grafting. More

recently, Ploch and Rajek²⁶ also described significant increases in cardiac output and stroke volume with decreases in systemic vascular resistance in 10 critically ill postoperative patients. In a small randomized study, Nijhawan and colleagues²⁷ compared the hemodynamic effects of 2 doses of levosimendan (0.2 or 0.3 $\mu\text{g}/\text{kg}$ per min infused for 6 hours) with that of placebo after cardiopulmonary bypass. At 15 minutes after the end of cardiopulmonary bypass, levosimendan increased cardiac output and reduced systemic vascular resistance without hypotension or tachycardia. The investigators suggested that the dose of 0.2 $\mu\text{g}/\text{kg}$ per min would be sufficient because the clinical outcome was not different in the 2 levosimendan-treated groups. Barisin and associates²⁸ tested the hypothesis that levosimendan could prevent ischemic myocardial impairment during and after off-pump coronary bypass grafting. In a randomized study, 31 patients were treated with a low (12 $\mu\text{g}/\text{kg}$) or a high (24 $\mu\text{g}/\text{kg}$) dose of levosimendan or placebo administered over 10 minutes started 20 minutes before the operation. Cardiac output and LVEF were significantly higher and systemic vascular resistance was significantly lower in patients receiving levosimendan compared with those receiving placebo. Again, the lower dose was regarded as sufficient to improve hemodynamics and to avoid hypotension and tachycardia. In this study, all patients also received an initial volume load of 500 mL before levosimendan administration.

These perioperative and postoperative studies in cardiac surgical patients indicate that levosimendan is a potentially useful drug to prevent and/or improve postoperative ischemic cardiac depression. A controlled, large-scale trial is needed to give a definitive answer about the role of levosimendan in such patients.

Dose recommendations: The optimum dose regimen and duration of administration of levosimendan should be based on the pharmacokinetic properties of levosimendan and its main pharmacologically active metabolite. The half-life of unchanged levosimendan is 1 hour, which means that a steady-state concentration is achieved within 4 hours after the beginning of infusion. However, the formation of the active metabolite (OR-1896), with a half-life of approximately 80 hours, continues to increase even after the end of a 24-hour infusion.²⁹ Because of the progressive accumulation of the metabolite, pharmacologic effects continue to increase if the drug is given for >24 hours. Kivikko and coworkers³⁰ infused levosimendan for 7 days at doses of 0.05 or 0.1 $\mu\text{g}/\text{kg}$ per min to patients with chronic HF. At the end of the infusion at 1 week, there were significant dose-dependent increases in heart rate (15 to 25 beats per minute), and systolic and diastolic blood pressures decreased by 11 ± 14 mm Hg and 11 ± 10 mm Hg, respectively. Side effects occurred in 16 of 24 patients: 1 patient experienced worsening of HF symptoms, 4 patients had cardiac arrhythmias, 3 had

hypotension, headache, and dizziness, and 2 reported angina pectoris. Therefore, prolonged infusions >24 hours should be avoided.

A controversial question is whether a loading dose is necessary to start levosimendan therapy. The loading dose is only indicated if a rapid therapeutic effect is required within the first hours before the full effect of unchanged levosimendan is reached by a continuous infusion (about 4 hours). In addition, the size of the loading dose should be adapted to the individual situation and can vary between 6 $\mu\text{g}/\text{kg}$ and 24 $\mu\text{g}/\text{kg}$ over 10 to 20 minutes. A loading dose should be avoided in patients with systolic blood pressure <90 mm Hg. The optimum maintenance dose may range from 0.05 to 0.2 $\mu\text{g}/\text{kg}$ per min. As shown by the RUSLAN trial,⁷ a dose >0.2 $\mu\text{g}/\text{kg}$ per min may result in hypotension, tachycardia, and myocardial ischemia in patients who have had a recent MI.

Combination with Other Drugs

As previously discussed, levosimendan enhances the hemodynamic effects of dobutamine. It can be combined with norepinephrine in patients with initially low systolic blood pressure to maintain adequate organ and tissue perfusion. A practical advantage of levosimendan is that its effects are not reduced or prevented by concomitant β -blocker therapy.⁶ Under the protection of levosimendan, β -blockers can be started in patients with advanced HF.

Tolerability

In general, levosimendan has been shown to be well tolerated, with most of its potential adverse effects being secondary to its vasodilating properties. Adverse events are dose related. In 972 patients treated with intravenous levosimendan in the initial clinical trials, headache occurred in 8.7% and hypotension in 6.5% of patients.³¹ Among the laboratory parameters, slight reductions in red blood cell count, hematocrit, and hemoglobin (<10%), as well as small reductions of serum potassium, were also described in 5% of patients. In contrast, serum creatinine levels significantly improved, even in patients with initially reduced renal function. Long-term electrocardiographic recordings showed no proarrhythmic effects.³²

Conclusion

The calcium sensitizer and K_{ATP} channel opener levosimendan offers new therapeutic possibilities for AHFS patients, providing symptomatic and hemodynamic im-

Table 1
Clinical use of levosimendan

Indication

- Decompensated acute heart failure with low cardiac output and high filling pressures
- Postoperative cardiac failure (stunning)
- Heart failure after acute myocardial infarction

Dosage recommendations

- Loading dose (10 min infusion)*
—6–12–(24) $\mu\text{g}/\text{kg}$ if SBP >100 mm Hg
- Continuous infusion (24 hrs)[†]
—0.05–0.2 $\mu\text{g}/\text{kg}/\text{min}$, depending on BP

Drug combinations

- Norepinephrine + levosimendan in patients with hypotension
- Dobutamine withdrawal under levosimendan

BP = blood pressure; SBP = systolic BP.

* Loading dose only if rapid effect (<2 hours) required.

[†] Prolonged infusion >24 hours leads to accumulation of long-acting metabolites.

provements within a few hours after the beginning of intravenous administration. A summary of the clinical use of levosimendan is shown in Table 1. In patients with AHFS treated with levosimendan, a survival benefit compared with dobutamine was observed in clinical trials. In several countries, the drug is already routinely used in patients with HF requiring inotropic support. Other potential indications for levosimendan include myocardial depression and stunning after coronary bypass operations or catheter revascularization. However, controlled trials of sufficient size are still lacking for these applications. Initial experience with levosimendan in combination with norepinephrine in patients with cardiogenic shock is also encouraging, but again, comparative trials are needed.

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