Levosimendan use in several scenarios of Acute Heart Failure

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Abstract

In countries where it is available, early levosimendan infusion can be considered for patients who remain symptomatic with dyspnea at rest despite initial therapy, particularly those with a history of chronic heart failure or chronically treated with beta-blockers. Hypotensive patients or patients with active ischemia are not the best candidates for levosimendan administration and should have these problems addressed first.

Acute heart failure (AHF) syndromes are defined as gradual or rapid change in signs and symptoms of heart failure (HF) requiring urgent therapy. This is the most common reason for hospital admission among patients above 65 years of age. HF hospitalizations continue to increase each year and account for 75% of hospital costs. HF incidence continues to increase because of several therapeutic advances in the management of acute myocardial infarction (AMI), which are leading to improved survival in patients with impaired cardiac function, and also due to an increasingly aging population.

These syndromes are heterogeneous, encompassing an entire spectrum of patients where symptoms may be predominantly congestive, or in more advanced disease, related to low cardiac output (CO).

The past decade witnessed an increased interest in AHF because the need for early intervention and patient stabilization was recognized to improve symptoms; restore oxygenation and organ perfusion; avoid or limit cardiac, renal and other organ damage; and initiate long-term therapies that may improve outcome.

Unfortunately, in the absence of knowledge about causes of AHF that may benefit from specific treatment, improving patient survival has been difficult, and AHF continues to carry an ominous prognosis. This is particularly true for AHF with low CO, where low systolic blood pressure at admission has been shown to be a major outcome determinant and where mortality is above 20% at 6 months.

HF patients with normal or low systolic blood pressure usually have a lower left ventricular ejection fraction and frequent signs of organ hypoperfusion. These patients, who often present with hyponatremia, low peripheral temperature, renal failure, and vasodilator intolerance, are more likely to receive inotropes for lack of an alternative therapeutic option, and have the highest in-hospital mortality rate among AHF patients. Usual inotropes or inodilators like beta-adrenergic agonists and phosphodiesterase (PDE) inhibitors acutely lower filling pressures and enhance CO, improving hemodynamics and symptoms. According to an increasing number of reports in the literature, these agents, however, have been consistently associated with a detrimental effect on survival rates, regardless of the dosage used. They exert a positive inotropic action primarily by increasing cyclic adenosine monophosphate (cAMP) and intracellular calcium concentration in cardiac myocytes, but in severe HF their use may be limited by heart rate increase, arrhythmia stimulation, and by a reduced effect due to beta-adrenergic desensitization.

Given the limitations of high-dose diuretic and vasodilator use in these patients, several new pharmacologic and nonpharmacologic interventions have been introduced, while others are under development or in preclinical investigation for treatment of pulmonary and systemic congestion and restoration of CO in the setting of AHF.

Among these, levosimendan, the most studied calcium sensitizer, introduced in several countries for treatment of acutely decompensated HF, has both inotropic and vasodilatory effects. It differs from classic inodilators because of...
its ability to improve myocardial efficiency without increasing myocardial oxygen demand, its antistunning properties, its effects on coronary blood flow, and its lack of negative lusitropic effects. Several studies have shown significant benefit in decreasing congestion, improving CO, and clinical outcome, although a recent large trial failed to confirm long-term survival benefit. The European Society of Cardiology indicates the use of levosimendan in AHF patients to treat symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction without severe hypotension.

In this paper, we intend to review its use in several clinical scenarios of acute heart failure.

**Pharmacology and Mechanism of Action**

Its chemical name is \( \text{[(R)-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)-phenyl hydrazono] propanedinitrile} \). The drug is a levo-isomer of racemic simendon, a pyridazinone-dinitril derivative. Simendon is a racemic compound made of 2 enantiomers: dextrosimendan and levosimendan.

Livosimendan belongs to the so-called group of “calcium sensitizers” that includes several other substances that share the ability of increasing sensitivity of myofilaments to calcium, leading to increased myocardial contraction without increasing intracellular cyclic adenosine monophosphate or intracellular calcium concentration, possibly with some PDE inhibitory effects. This concept seems to be associated with fewer adverse effects, lower arrhythmogenic potential, and a favorable effect on myocardial oxygen consumption compared with traditional inotropes or inodilators.

Livosimendan displays calcium-dependent binding to the N-terminal domain of cardiac troponin C (TnC) with a higher affinity at high calcium concentrations and a lower affinity at low calcium concentrations. By stabilizing the calcium-TnC complex, levosimendan inhibits the troponin I (TnI) effect and prolongs the actin-myosin cross-bridge association rate. This positive inotropic effect is obtained without increasing intracellular calcium concentration or with a significant increase in myocardial oxygen demand, usually seen with other inotropes.

Beneficial effects of levosimendan are also related to its vasodilatory effects of systemic, coronary, pulmonary, renal, splanchnic, and cerebral arteries, and of systemic and portal veins. This effect is mediated by an adenosine tri-phosphate (ATP) dependent potassium channel-opening effect in an ATP-dependent manner in arterial smooth muscle cells of the small-resistance arterioles by a calcium-activated potassium and voltage-dependent potassium channel-opening effect in large conductance arterioles. Membrane hyperpolarization induced by the open potassium channels inhibits calcium entry and activates sodium-calcium exchange, decreasing intracellular calcium and inducing vasodilatation.

This induced decrease in right and left ventricular afterload seems to be beneficial in failing hearts.

Livosimendan has about a 1.3-hour half-life. The drug is metabolized by the liver and has 2 active metabolites, OR-1855 and OR-1896, with a long half-life, 75-78 hours, which are excreted by the kidney and prolong the duration of the hemodynamic effects of their parent compound. This long half-life is markedly increased in patients with severe chronic renal failure or end-stage renal disease who are undergoing hemodialysis as compared with healthy subjects.

**Clinical Studies**

**Acute Heart Failure**

Several clinical trials have shown the beneficial effect of levosimendan on short-term hemodynamic and clinical signs in patients with AHF. Kivikko et al reported a 40% increase in CO and 30% decrease in pulmonary capillary wedge pressure (PCWP) after 24-hour infusion in class III-IV HF patients. The Levosimendan Infusion versus DObutamine (LIDO) study enrolled 203 patients with severe low-output HF and compared the effects of levosimendan with those of dobutamine in a double-blind fashion over 24 hours. The primary end point of hemodynamic improvement (an increase of 30% or more in CO, and a decrease of 25% or more in PCWP) was achieved by 28% of the levosimendan patients and 15% of the dobutamine patients (p = 0.022). Interestingly, a subgroup analysis demonstrated that the use of beta-blockers enhanced the hemodynamic effects of levsimendan but reduced the hemodynamic effects of dobutamine. In this study, levosimendan treatment was also associated with a significant decrease in mortality. At 31 days, all-cause mortality was significantly lower with levosimendan compared with dobutamine [hazard ratio 0.43 (95% CI 0.18-1.00) p = 0.049]. The patients were also followed retrospectively for 180 days, and this analysis revealed that 26% of the levosimendan patients had died compared with 38% in the dobutamine group [hazard ratio 0.57 (95% CI 0.34-0.95) p = 0.029].

Importantly, the inodilatory effects of levosimendan were accentuated by concomitant use of beta-blocking agents in the LIDO study. In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial, levosimendan significantly improved a composite of clinical signs and symptoms of acute decompensated HF over 5 days as assessed by patients and their physicians. In the Survival Of Patients With Acute Heart Failure In Need Of Intravenous Inotropic Support (SURVIVE) study, a statistically significant difference was seen early during the first 5 days, especially in patients chronically treated with a beta-blocker, but it was not evident in the 180-day survival.

In advanced chronic HF patients awaiting cardiac transplantation, levsimendan improves renal function during the 3 months that follow drug administration.

**After Percutaneous Coronary Intervention or after Coronary Artery Bypass Grafting**

Levosimendan improves coronary blood flow, decreases myocardial oxygen extraction, and improves ischemic myocardium performance. This was first shown in animals and healthy humans but was later shown in patients with congestive HF, AMI, and after percutaneous coronary intervention (PCI) of AMI patients.
with LV dysfunction, improving the left ventricular diastolic function of stunned myocardium in these patients.

In patients undergoing elective coronary artery bypass grafting (CABG), levosimendan increases CO and stroke volume and decreases systemic vascular resistance without increasing myocardial oxygen consumption or causing myocardial substrate utilization to deteriorate.

Diastolic Heart Failure

In animal and human preclinical studies, levosimendan has been shown to improve diastolic function, and its inotropic effect is associated with an increased rate of relaxation and reduced relaxation time, thus improving diastolic filling.

In severe HF patients with restrictive left ventricular filling assessed both by pulsed-wave Doppler echocardiography of the mitral flow and simultaneous pulmonary artery catheterization, levosimendan improved both systolic and diastolic function increasing left ventricular filling, stroke volume (-24% ± 9) and CO (29% ± 14) while decreasing PCWP (-29% ± 6). The percentage changes of the early/late transmitral diastolic peak flow velocity (E/A) ratio and the percentage changes of the isovolumetric relaxation time were independent predictors of the increase in CO in this series.

Peripartum Cardiomyopathy

Using new drugs in patients with rare diseases is always difficult, and only a few anecdotal reports are available describing the successful use of levosimendan in peripartum cardiomyopathy patients. AHF is a life-threatening event that rarely occurs during or after childbirth. In these published reports, in patients with a severe episode of AHF, levosimendan improved cardiac performance that was associated both with symptomatic relief and hemodynamic or echocardiographic improvement in ventricular function. Levosimendan induced a steady decline of increased PCWP, followed by a definitive increase in cardiac stroke volume and patient recovery.

Right Heart Failure and Cardiogenic Shock

Levosimendan has also been used to restore right or left ventricular function in patients after cardiac surgery and in unresponsive cardiogenic shock patients after heart transplantation primary graft failure.

In patients with low-output syndrome during or after open-heart surgery, although levosimendan use improves the hemodynamic and functional status of both groups of patients, it may be associated with increased survival and shorter ICU and hospital stay if started early, in the operating theater, instead of later, when patients are dependent on classical inotropic support and IABP.

In patients with acute respiratory distress syndrome (ARDS), pulmonary hypertension and right ventricular dysfunction have been associated with poor outcomes. In a prospective, randomized, placebo-controlled, pilot study, of septic shock patients requiring mechanical respiratory support due to ARDS, levosimendan was shown to decrease mean pulmonary artery pressure, pulmonary vascular resistance index and right ventricular end-systolic volume, increasing CO, right ventricular ejection fraction, and mixed venous oxygen saturation.

Therapeutic Use

Treatment with levosimendan is usually initiated with a 10 minute loading bolus of 3 to 6 mcg/kg followed by a 24-hour continuous infusion of 0.05 to 0.2 mcg/kg per min. If the patient has hypotension, one should either skip the loading dose or associate norepinephrine in low doses. If there are signs of volume responsiveness, cautious fluid administration under adequate monitoring should be considered. Most patients show improvement in hemodynamic function during the next 24 hours, usually heralded by a marked increase in urinary output and a significant decrease in PCWP. This diuretic effect is often the cause of electrolyte imbalance that has been associated with arrhythmia. Pre-emptive magnesium and potassium administration under adequate monitoring should be considered to prevent hypokalemia and arrhythmia unless there is a contraindication such as renal failure.

As a powerful vasodilator, levosimendan may be a harmful drug. Although this drug exerts little influence on myocardial oxygen demand per se, in patients with active ischemia or obstructive coronary artery disease, levosimendan induced hypotension, especially in the hypovolemic patient, may precipitate tachycardia, aggravate ischemia, and increase myocardial damage, worsening long-term prognosis. Hypotensive patients or patients with active ischemia are not the best candidates for levosimendan administration and should have these problems addressed first.
References


Review Article

Tavares et al

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