A review of levosimendan in the treatment of heart failure

Hulya Akhan Kasikcioglu
Nese Cam

Siyami Ersek Thoracic and Cardiovascular Surgery Center, Istanbul, Turkey

Abstract: Heart failure is a relatively important public health problem due to its increasing incidence, poor prognosis, and frequent need of re-hospitalization. Intravenous positive inotropic agents play an important role in treating acute decompensation of patients with heart failure due to left ventricular systolic dysfunction. Although frequently used, the inotropic agents β-adrenergic agonists and phosphodiesterase inhibitors seem effective for improving symptoms in the short term; it has been shown that they increase morbidity and mortality by elevating intracellular cyclic adenosine monophosphate (cAMP) and calcium levels. Levosimendan is a new positive inotropic agent having ATP-dependent potassium-channel-opening and calcium-sensitizing effects. In studies on its effects without increasing intracellular calcium concentrations and on its effects that depend on available intracellular calcium levels, it has been shown to have favorable characteristics different from those of current inotropic agents, which exert their effects by increasing calcium concentrations. This study aims to review other important studies about levosimendan by revealing the underlying mechanisms of its activity, efficiency, and safety.

Keywords: heart failure, positive inotropic therapy, levosimendan

Introduction

Heart failure is a growing problem for both individuals and public health especially as the elderly population is increasing (McKee et al 1971; Mosterd et al 1999). According to the World Health Organization, it is estimated that there are 22.6 million heart failure patients worldwide (McMurray et al 2000; Cleland et al 2001). Especially, in European countries, myocardial dysfunction due to coronary heart disease is the most frequent reason for heart failure in patients under the age of 75 (Sutton 1990).

Moreover, regardless of the underlying cause, the prognosis of heart failure patients is relatively poor. For example, nearly 40% of severe heart failure patients die within a year of acute exacerbation (Cowie et al 2000). Furthermore, it is a relatively important public health problem with respect to re-hospitalization and prolonged hospitalization frequency.

In the treatment of acute decompensation of heart failure caused by left systolic dysfunction, intravenous positive inotropic agents are playing an important role in eliminating hemodynamic abnormalities and improving symptoms (Cowie et al 2000; Slawsky et al 2000).

Indeed, currently the most used intravenous inotropic agents in clinical practice include β-adrenergic agonists and phosphodiesterase inhibitors. β-adrenergic receptor agonists trigger calcium influx into the myocytes by increasing intracellular cAMP levels through cyclic adenosine monophosphate (cAMP) production. Phosphodiesterase inhibitors do the same thing by inhibiting its degradation (Colucci et al 1986; Cody 1988; Packer 1993). Increased intracellular calcium levels increase cellular energy need, resulting in an increase of myocardial oxygen consumption (Colucci et al 1986; Slawsky et al 2000). Moreover, it is reported that increased intracellular cAMP and Ca^{+} concentration are cardiotoxic (Lee and Downing 1980;

Correspondence: Hulya Akhan Kasikcioglu
Resitpasa caddesi Salkim sokak No=2/5, Posta kutusu 9 Avcilar- 34840 Istanbul-Turkey
Tel +90 21634 05316
Fax +90 21634 05316
Email hulyakasikcioglu@yahoo.com

Stevenson 1998). Elevated intracellular calcium concentrations trigger arrhythmias by affecting myocytes' electrophysiology (Packer and Leier 1987; Ferric et al 1990). As a result, this condition further increases cellular energy need and myocardial oxygen consumption (Hasenfuss et al 1989; Haikala et al 2000). Although these agents seem useful during the acute exacerbation of heart failure in the short term, it was reported that they cause progression in and increased mortality from the disease (Dies et al 1986; Ferrick et al 1990; Felker et al 2003; Abraham et al 2005).

Thus, in the meantime, attention is focused on the calcium-sensitizing agents that enhance cardiac performance without increasing intracellular calcium and cAMP levels. Among these groups of agents, levosimendan and pimobendan are known as calcium sensitizers that are available for clinical practice.

Mechanism of action

Levosimendan has a dual mechanism of action: (1) This agent sensitizes troponin C to calcium in a manner dependent on the calcium concentration, thereby increasing the effects of calcium on cardiac myofilaments during systole and improving contraction at low energy cost (Hasenfuss et al 1998; Janssen et al 2000). (2) During diastole, sensitization is diminished due to a plunge in calcium concentration level which does not cause a deterioration of diastolic relaxation but, on the contrary, does cause an improvement (Pagel et al 1997; Janssen et al 2000; Tachibana et al 2005). Since levosimendan does not cause any diastolic calcium overload, unlike other inotropic agents, it is also does not cause any cardiac myocyte dysfunction, arrhythmia, or an increase of energy consumption (Hasenfuss et al 1995). The enhanced calcium myofilament responsiveness mediated by levosimendan results in increased cross bridge formation and greater contractility. Because levosimendan-enhanced cross bridge formation depends on the presence of calcium, there is no impairment of myocardial relaxation during diastole (Haikala and Linden 1995; Gheorghiade et al 2005). In addition, preclinical studies indicate that levosimendan may enhance myocardial relaxation and diastolic function (Gheorghiade et al 2005; Tachibana et al 2005).

Moreover, levosimendan also opens ATP-dependent potassium (K) channels in myocytes and vascular smooth muscle cells, which results in vasodilatation (Yokoshiki et al 1997; Pataricza et al 2000; Kaheinen et al 2001). This reduces preload and afterload, and increases coronary and other organ blood flow (Harkin et al 1995; Yokoshiki and Sperelakis 2003; Michaels et al 2005).

Cardio protective effect

During the acute exacerbation of heart failure, accelerated cellular loss occurs due to deterioration of ischemia, mechanical strain, neurohormones production, inflammation and oxidative stress, and progressive myocardial failure. It is suggested that on these patients, levosimendan exerts its cardio protective effect by activation of ATP-dependent K (K_{ATP}) channels which inhibit mitochondrial apoptotic pathway (Maytin and Colluci 2005).

Furthermore, in a study by Nieminen et al (2000), it was shown that levosimendan did not increase troponin T levels which were manifestations of myocardial injury. In addition to its well-described hemodynamic effects, levosimendan also activates K_{ATP} channels both in plasma membrane and in mitochondrial matrix of cardiac myocytes (Maytin and Colluci 2005; Kopustinskiene et al 2001). It is now recognized that the activation of mitochondrial K_{ATP} channels in cardiac myocytes is an important and potent cardio protective mechanism (O'Rourke 2004). Apoptosis is an energy-dependent process mediated by a highly organized biochemical cascade. Although ischemia is an important cause of apoptosis, several additional apoptotic stimuli, including oxidative stress, mechanical strain, and neurohormones (eg, norepinephrine and angiotensin) have been identified and are believed to contribute to progressive myocyte loss during chronic heart failure (Rossig et al 2004; Maytin and Colluci 2005).

Anti-inflammatory effect

It has been reported that elevated circulatory levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) increase the apoptosis of cardiac myocytes and endothelial cells by increasing oxidative stress and lead to the suppression of myocardial contractility, and that they have a role in the clinical and hemodynamic deterioration of heart failure (Seta et al 1996; Sasayama et al 1999). Elevated levels of TNF-α and IL-6 have been associated with increased morbidity and mortality in patients with advanced heart failures (Levine et al 1990; Torre-Amione et al 1996; Tsutamoto 1998; Plenz et al 2001). Recent studies show that therapies that decrease cytokine levels may improve the clinical picture and ventricular functions in patients with congestive heart failure (Gullestad et al 2001; Skudicky et al 2001).

Some other studies indicate that levosimendan exerts anti-apoptotic and anti-inflammatory effects by decreasing the circulatory pro-inflammatory cytokines and soluble

apoptosis mediators (Parissis et al 2004; Avgeropoulou et al 2005; Kyrzopoulos et al 2005).

Effects on matrix metalloproteinase

It has been concluded that levosimendan decreases the levels of matrix metalloproteinases, which regulate extracellular matrix metabolism, and play an important role in the left ventricular remodeling in chronic heart failure (McMurray and Pfeffer 2002; Tziakas et al 2005). Therefore, it is suggested that levosimendan may show pleiotropic effects that may affect myocardial remodeling (Tziakas et al 2005).

Neurohormonal effect

It is known that neurohormonal changes occur in acute heart failure and strong vasoconstrictors, epinephrine and norepinephrine, are increased as a response to the decreased cardiac output. In fact, increased epinephrine and norepinephrine levels are prognostic markers showing a decrease in survival rates (Cohn et al 1984; Kaye et al 1995; Bristow et al 2004). Also, it has been shown that levosimendan in therapeutic dosages does not increase epinephrine and norepinephrine concentrations (Nicklass et al 1999; Nieminen et al 2000). In addition, it has been determined that levosimendan decreases plasma endotelin-1 concentrations in patients with severe heart failure (Nicklas et al 1999).

B type natriuretic peptide level (BNP) is one of the best prognostic markers in heart failure. It has been demonstrated that during treatment of decompensated chronic heart failure, the changes in BNP levels were strongly predictive for mortality and early re-hospitalization (Cheng et al 2001). It has been proved that levosimendan leads to a marked decrease in BNP levels and supports clinical improvement in these patients (Avgeropoulou et al 2005; Kyrzopoulos et al 2005; Moertl et al 2005; Parissis et al 2005).

Effects on coronary circulation

It has been determined that administration of intravenous levosimendan has a direct vasodilator effect on conductance and resistance of coronary arteries (Gruhn et al 1998). It has been suggested that levosimendan exerts this effect by opening ATP-sensitive K channels in vascular smooth muscles (Gruhn et al 1998; Kaheinen et al 2001). It has been demonstrated that coronary artery flow was increased and coronary artery resistance was reduced during levosimendan infusion (Michaels et al 2005).

Also, in another study conducted with positron emission tomography imaging in heart failure patients, levosimendan increased myocardial blood flow compared to placebo (Ukkonen et al 2000).

In a study by De Luca et al (2005) on patients with LV dysfunction following myocardial infarction just after primary percutaneous coronary intervention, it was determined that levosimendan infusion improved hemodynamic parameters and coronary flow reserve.

Anti-stunning effect

Abnormal calcium homeostasis and decreased sensitivity of contractile proteins against calcium are important factors for the development of myocardial stunning (Bolli 1990; Bolli and Marban 1999). Therefore, it is suggested that calcium-sensitizing agents may improve the functions of stunned myocardium (Soei et al 1994). To clarify, Sonntag et al (2004), in a study in which the patients undergoing angioplasty following acute coronary syndrome were examined, showed that levosimendan improved systolic performance of the stunned myocardium without worsening diastolic functions.

Hemodynamic effects/influence on systolic function/influence on diastolic function

Although levosimendan causes vasodilatation by opening ATP-dependent K channels in vascular smooth muscle cells, this does not only result in a reduction of preload and afterload but it also creates a positive inotropic effect (Harkin et al 1995). It was determined in multicenter large scale studies conducted on patients with heart failure that levosimendan reduced pulmonary capillary wedge pressure (PCWP), right atrial, pulmonary arterial and mean arterial pressures, and peripheral vascular resistance (PVR), whereas it increased cardiac index (Nieminen et al 2000; Slawsky et al 2000; Follath et al 2002).

As is the case with other drugs having potent vasodilator activity, levosimendan increases intrapulmonary shunting. However, in contrast to these drugs, it does not reduce arterial oxygen saturation (Lilleberg et al 1998).

In a study by Sonntag et al (2004) with patients undergoing percutaneous transluminal coronary angioplasty due to acute coronary syndrome, levosimendan infusion after 10 minutes following successful intervention reduced the number of hypokinetic segments. As an indicator of improved systolic functions, increase of ejection fraction, and decrease of end diastolic volume, single-beat elastance,

and upward/leftward shift of the systolic part of the pressure–volume loop have been observed.

One of the most important indicators of improved contractile functions with levosimendan infusion is the increase in exercise capacity. In a tissue Doppler echocardiography study conducted by Kasikcioglu et al (2005), there was a significant increase in the exercise capacity assessed by 6 minute walking test parallel to the increase of systolic myocardial velocity for mitral annulus as an indicator of the increase in contractile functions.

Calcium-sensitizing agents may not have negative effects on diastolic functions although they improve systolic function by increasing the affinity of troponin C to calcium both in systole and diastole (Haikala and Linden 1995). Sensitization is calcium-concentration dependent; sensitization of contractile apparatus is done in systole but not in diastole. This leads to an inotropic effect without impairing diastolic relaxation (Hasenfuss 1998; Haikala and Pollesello 2000; Cleland et al 2004; Sonntag et al 2004). Indeed, unlike the effects of other calcium sensitizers, the effect of levosimendan is dependent on intracellular calcium levels, and it does not worsen diastolic functions even though there are studies showing its positive effects on diastolic functions (Haikala et al 1995; Sonntag et al 2004; Kasikcioglu et al 2005; Parissis et al 2005). Also, levosimendan decreases the index of diastolic relaxation, indicating that levosimendan seems to improve the systolic performance of stunned myocardium without impairing diastolic function (Hasenfuss 1998; Haikala and Pollesello 2000; Sonntag et al 2004; De Luca et al 2006)

Anti-arrhythmic effect

Another study, in which the patients with normal cardiac functions were examined, showed that levosimendan shortened atrial, atrioventricular node, and ventricular effective refractory period (Toivonen et al 2000). On patients with atrial fibrillation, it is reported that levosimendan may not only increase ventricular rate by accelerating atrioventricular conduction but it may also induce an increase in heart rate by shortening the sinus node recovery time (Toivonen et al 2000). Although it has no influence on the uncorrected QT interval it is reported that it may prolong corrected QT interval in doses higher than the therapeutic levels (Singh et al 1999).

Ambulatory electrocardiographic and electro-physiological evaluation did not detect any pro-arrhythmic effect of intravenous levosimendan (Singh et al 1999). On the other hand, the REVIVE study showed that the rate of ventricular tachycardia, atrial fibrillation, and ventricular extra-systoles in the levosimendan group were increased compared with placebo (Packer et al 2005).

Pharmacokinetics and metabolism

Levosimendan has an elimination half-life of 1 hour (Kivikko et al 2002a, 2002b). However, the half-lives of its two circulating metabolites, OR-1855 and its acetylated form OR-1896, range between 70 and 80 hours (Kivikko et al 2002a, 2002b). These metabolites reach their maximum serum concentration 2 days after completion of a 24-hour intravenous levosimendan infusion (Sundberg et al 1998). Since the OR-1896 metabolite is hemodynamically active, with properties similar to those of levosimendan, the hemodynamic effects of levosimendan should theoretically persist for at least 7–10 days following the intravenous infusion (Kivikko et al 2002a, 2002b).

Combinations with other drugs

It was demonstrated that the combination of levosimendan and dobutamine is relatively safe and effective on patients with severe heart failure (Nanas et al 2004, 2005). It can be combined with norepinephrine in patients with initially low systolic blood pressure to maintain adequate organ and tissue perfusion (Delle Karth et al 2003; Lehmann et al 2004). Although beta blocker use decreases the inotropic and vasodilator effects in patients taking dobutamine, no reduction in levosimendan level was reported (Follath et al 2002). It is reported that concomitant use of levosimendan with angiotensin-converting enzyme inhibitors and nitrates may increase the hypotension and tachycardia effects of levosimendan (Antila et al 1996; Sundberg et al 2000)

Clinical studies

The studies demonstrate that the efficacy and safety of levosimendan and are important and guiding factors for the current clinical practice. The results are summarized in Table 1.

A multicenter, placebo-controlled, randomized study conducted by Nieminen et al (2000) to determine the therapeutic dose range of levosimendan enrolled 151 patients with New York Heart Association (NYHA) class II-IV heart failure with ischemic origin. Five different dose regimes of levosimendan (10-minute loading dose of 3, 6, 12, 24, or 36 $\mu g\,kg^{-1}$ followed by a 24-hour infusion of 0.05,

0.1, 0.2, 0.4, or 0.6 $\mu g\,kg^{-1}\,min^{-1}$) were compared with placebo and dobutamine (6 $\mu g\,kg^{-1}\,min^{-1}$). When all levosimendan groups were evaluated, it was determined that reported hemodynamic targets were attained in more than 50% of the patients. At all doses of levosimendan, response rates were significantly greater than those of placebo ($p=0.038$ at the lowest dose and $p\leq0.005$ at all other doses). This study concluded that 6–24 $\mu g\,kg^{-1}$ loading dose of levosimendan for 10 minutes followed by 0.05–0.2 $\mu g\,kg^{-1}\,min^{-1}$ infusion was well tolerated, with favorable hemodynamic effects.

A multicenter, double-blind, placebo-controlled, randomized study conducted by Slawsky et al (2000), with the objective of determining the short-term hemodynamic and clinical effects of levosimendan, enrolled 146 NYHA class III-IV heart failure patients with pulmonary capillary wedge pressure ≥15 mmHg and a cardiac index of ≤2.5 L $min^{-1}\,m^{-2}$. In this study, patients were randomized 2:1 to receive intravenous levosimendan or placebo. Levosimendan was initiated as a bolus of 6 $\mu g\,kg^{-1}$, followed by a continuous infusion, initially at a rate of 0.1 $\mu g\,kg^{-1}\,min^{-1}$. At hourly intervals, a repeat bolus (6 $\mu g\,kg^{-1}$) was given and the infusion rate was increased by increments of 0.1 $\mu g\,kg^{-1}$. Uptitration was continued until a maximum dose of 0.4 $\mu g\,kg^{-1}\,min^{-1}$ was achieved or until a dose-limiting event occurred. Patients were administered 6-hour infusions and hemodynamic measurements were obtained at baseline, at the end of each hourly uptitration for hours 1–4, and at hours 5.5 and 6. The symptoms of dyspnea and fatigue were evaluated by the patient and the physician at baseline and at the sixth hour. Levosimendan was associated with dose-dependent increases in stroke volume and cardiac index that were significantly different from the effects of placebo at all doses tested. In addition, levosimendan was associated with dose-dependency, which significantly decreased PCWP at all doses. Assessments of dyspnea and fatigue at the sixth hour demonstrated that levosimendan was associated with significantly improved dyspnea and a trend towards improved fatigue. The results of this study showed that levosimendan causes a rapid dose-dependent improvement in hemodynamic functions and in clinical picture without any significant increase in adverse events in patients with decompensated heart failure.

After completion of 6-hour infusions, 85 patients were completely infused as open label for 24 hours and the patients were randomized 1:1 in a double-blind manner. In one group, the infusion was discontinued and then maintained with placebo whereas levosimendan was maintained for 24 hours in the other group (Kivikko et al 2003). The objective of this study was to determine whether the hemodynamic effects of levosimendan were sustained during a long-term infusion and beyond the discontinuation of infusion. At the conclusion of the study, it was demonstrated that hemodynamic effects continued at least 24 hours after 24-hour infusion. A series of adverse events may be seen in infusions prolonged for more than 24–48 hours due to excess metabolite accumulation, and the 24-hour duration is safe and effective.

The Levosimendan Infusion versus Dobutamine in severe low-output heart failure (LIDO) study is a multicenter, double-blind, double-dummy, randomized study in low-output heart failure patients. It was designed to compare the clinical and hemodynamic effects of levosimendan and dobutamine (Follath et al 2002). A total of 203 patients with severe low-output heart failure (left ventricular ejection fraction [LVEF] <0.35, cardiac index (CI) <2.5 L $min^{-1}\,m^{-2}$, and PCWP<15 mmHg) were included in the study. A levosimendan 24 $\mu g\,kg^{-1}$ loading dose is maintained with a 24-hour infusion with 0.1 $\mu g\,kg^{-1}\,min^{-1}$ dose. Dobutamine was administered in 5 $\mu g\,kg^{-1}\,min^{-1}$ dose. Infusion rates were doubled after 2 hours on 69 patients randomized to levosimendan and on 40 patients randomized to dobutamine whose cardiac output had not risen by more than 30%. Among the doses used in this study, the cardiac-output-enhancing effect (29% increase over baseline for levosimendan compared with a 22% increase for dobutamine, $p=0.05$) and PCWP-lowering effect of levosimendan (28% decrease over baseline for levosimendan compared with a 13% decrease for dobutamine, $p=0.03$) were greater than those of dobutamine. In this study, it was shown that 6 hours after the infusion had been completed, the effects of levosimendan were still continuing whereas dobutamine hemodynamic effects had disappeared. Clinical symptoms of dyspnea and fatigue tended to improve more with levosimendan than they did with dobutamine but these differences were not significant.

It was also demonstrated that 180-days mortality was lower in the levosimendan group compared with dobutamine group (mortality rate in levosimendan and dobutamine patients were 26% and 38% respectively, $p=0.029$).

The Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure Due to an Acute Myocardial Infarct (RUSSLAN) evaluated different doses of levosimendan versus placebo in subjects with heart failure following an acute myocardial infarction (Moiseyev et al 2002). This study was double-blind and

Table 1 Several aspects concerning levosimendan and guidelines for its current clinical practice

Trial	Enrollment	Aim	Primary endpoint	Secondary endpoint	Selected results	Conclusion
Nieminen et al (2000)	Dobutamine: 20 Levo: 95 (5 different dose groups) Placebo: 21 Vehicle: 15	Define the therapeutic dose range of levo	Achieving ≥1 of the following: ≥15% increase in SV, ≥40% increase in CO, ≥25% decrease in PCWP, or ≥50% decrease in PCWP during 2 consecutive measures.	Changes in hemodynamic indices (HR, PAP, PVR, RAP, MBP and total peripheral resistance)	Primary endpoint: all levo groups ≥50% vs placebo 27% (p<0.001)	Dosing of levo with a 10-min bolus of 6–24 μg kg^{-1} followed by an infusion of 0.05–0.2 μg $kg^{-1}min^{-1}$ is well tolerated and leads to favorable hemodynamic effects
Slawsky et al	Levo: 98 Placebo: 48	Short-term hemodynamic and clinical effects of levo	% of patients with an increase in SV or a decrease in PCWP of ≥25% at 6 h	The change in SV and PCWP over time and change in the symptoms of dyspnea or fatigue as assessed by patient and clinician	SV: levo 56% vs placebo 4% (p<0.001)PCWP: levo 43% vs placebo 15 % (p<0.001) Change in SV: levo increased 13±1 mL vs placebo decreased −1±2 mL (p<0.001)	Levo causes a rapid dose-dependent improvement in hemodynamic function in patients with decompensated heart failure
Kivikko et al	Levo: 98 (for 6 h) Placebo: 48 (up to 24 h) Levo: 43 Placebo: 42	Determine whether the hemodynamic effects of levo are sustained during continuous infusion for up to 48 h	Hemodynamic effects of levo and metabolite (OR-1896) at 24 h		CO: levo continuation increased 0.5±0.2 L min^{-1} vs levo withdrawal 0.2±0.2 L min^{-1} (p=0.333) PCWP: levo continuation decreased 0.3±0.8 mmHg vs levo withdrawal increased 0±0.8 mmHg (p=0814)	After a 24 h infusion, the hemodynamic effects are maintained for at least an additional 24 h. In most cases, the infusion of levo need not to be extended beyond 24 h
LIDO	Levo: 103 Dobutamine: 100	To compared the effects of levo and dobutamine on hemodynamic performance and clinical outcome	Hemodynamic improvement at the end of infusion (≥30% increase in CO, ≥25% decrease in PCWP)	Other hemodynamic measures (SV, CI, PAP, RAP, HR, BP, TPR) Mortality at 31 and 180 d	Levo (28%) vs dobutamine (15%) achieved hemodynamic endpoint (p=0.022) mortality at 180d: levo (26%) vs dobutamine (38%) (p=0.029)	Levo improved hemodynamic performance more effectively than dobutamine. This benefit was accompanied by lower mortality in the levo group than in the dobutamine group for up to 180 d
RUSSLAN	Levo: 402 Different doses groups: I: 6 μg kg^{-1} + 0.1 μg $kg^{-1}min^{-1}$ II: 12 μg kg^{-1}+0.2 μg $kg^{-1}min^{-1}$ III: 24 μg kg^{-1}+0.2 μg $kg^{-1}min^{-1}$ IV: 24 μg kg^{-1}+0.4 μg $kg^{-1}min^{-1}$ Placebo 102	To evaluate the safety and efficacy of levo in patients with left ventricular failure complicating AMI	Hypotension or myocardial ischemia at 6 h	Combined risk of death or worsening HF at 6 and 24 h , clinical change at the end of the infusion, and mortality at 14 and 180 d	Hypotension or ischemia was similar all groups (p=0.319) death or worsening HF at 24 h: levo 4% vs placebo 8.8% (p=0.044)mortality at 14d: levo 11.7% vs 19.6% (p=0.031) mortality at 180d: levo 22.6%, vs placebo 31.4% (p=0.053)	Levo at doses 0·1–0·2 μg $kg^{-1}min^{-1}$ did not induce hypotension or ischemia and reduced the risk of worsening HF and death in patients with left ventricular failure complicating AMI

Abbreviations: ADHF, acute decompensated heart failure; AMI, acute myocardial infarction; BP, blood pressure; BNP, B-Type natriuretic peptide; CI, cardiac index; CO, cardiac output; d, days; EF, ejection fraction; h, hours; HF, heart failure; HR, heart rate; h, hour; levo, levosimendan; mo, months; TPR, total periferic resistance; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SV, stroke volume.

Table 1 *Continued*

Trial	Enrollment	Aim	Primary endpoint	Secondary endpoint	Selected results	Conclusion
CASINO 6	Levo: 100 Dobutamine: 100 Placebo: 99	To compare the safety and efficacy of levo, dobutamine, and placebo in patients with decompensated HF	Combination of mortality and rehospitalization for worsening HF		Mortality at 1mo: levo 6.1% (p=0.1 vs placebo and p=0.04 vs dobutamine), dobutamine 12.8% and placebo 8.2% mortality at 6 mo: levo 15.3% (p= 0.0001 vs dobutamine and p=0.04 vs placebo), 39.6% for dobutamine and 24.7% for placebo	Study stopped early for survival benefit
REVIVE	REVIVE-1 Levo: 51 Placebo: 49	To evaluate the length of intensive care and hospitalstay in ADHF	Clinical composite at 5 d	Length of the stay in the hospital and intensive care unit	Levo 49% vs placebo 33% improved by clinical composite (p =0.23)	Pilot study to evaluate end point for REVIVE- 2
	REVIVE-2 Levo: 299 Placebo: 301	To evaluate the effects of levo plus standard therapy compared with standardtherapy alone over the clinical course of ADHF	Changes in symptoms, death, or worsening HF over 5–4 d longer than the infusion,		At day 5, 33% more patients in the levo group had improved and 30% fewer of them had worsened compared with patients in the control group (p=0.015).	
SURVIVE	Levo: 664 Dobutamine:663	To demonstrate a 25% reduction in mortality for levo compared with dobutamine	All-cause mortality at 180 d	The number of days alive and out of the hospital during the 180 d of the trial, all-cause mortality during 31 d, cardiovascular mortality during 180 d, and global assessment at 24 h	At 5 d, 2 w, 1 and 6 mo mortality in the levo group was reduced by 27%, 14%, 13%, and 6.4% respectively, compared with the dobutamine group. These differences did not reach statistical significance	SURVIVE is the first study to examine mortality for an extended period following treatment of ADHF

Abbreviations: ADHF, acute decompensated heart failure; AMI, acute myocardial infarction; BP, blood pressure; BNP, B-Type natriuretic peptide; CI, cardiac index; CO, cardiac output; d, days; EF, ejection fraction; h, hours; HF, heart failure; HR, heart rate; h, hour; levo, levosimendan; mo, months; TPR, total periferic resistance; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SV, stroke volume.

placebo-controlled. This is the first and the largest study, conducted with 504 patients comprising four different levosimendan dose groups and a placebo group. No significant differences among the five treatment groups were observed in the proportion of patients experiencing hypotension or ischemia (primary endpoint). Nonetheless, a greater incidence of arterial hypotension and ischemia was observed among patients who received the highest doses of levosimendan (bolus, 24 $\mu g\,kg^{-1}$; infusion, 0.4 $\mu g\,kg^{-1}\,min^{-1}$) compared with the patients who received the highest doses of placebo. In 14 days, the mortality rate in the levosimendan group was 11.7% compared with 19.6% in the placebo group (p=0.03). However, there was no statistically significant difference between two dose groups in terms of 180-day mortality (p=0.053). In this study, although there is no significant improvement in patients' complaints during levosimendan infusion periods, the worsening of heart failure in 6 hours (p=0.033) and in 24 hours (p=0.044) were significantly less when compared with those of placebo group.

The Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study (CASINO) is a randomized, double-blind, double-dummy, and parallel-group study (Zairis et al 2004). This study was designed to compare the safety and efficacy of levosimendan, dobutamine, and placebo on patients with decompensated heart failures. Patients with NYHA class IV heart failure and LVEF ≤35% were recruited for the study in which levosimendan, dobutamine, or placebo infusions were administered. The study was originally designed to recruit 600 patients; however, it was stopped prematurely after 299 patients had been enrolled, due to a clear mortality benefit in favor of the levosimendan group. Levosimendan showed a significant survival benefit on these patients whereas dobutamine appeared to increase mortality. After 1 month, the mortality rates were 6.1% for levosimendan (p=0.1 compared with placebo and p=0.04 compared with dobutamine), 12.8% for dobutamine, and 8.2% for placebo treatment. After 6 months, the mortality rates were 15.3% for levosimendan (p=0.0001 compared with dobutamine and p=0.04 compared with placebo), 39.6% for dobutamine, and 24.7% for placebo treatment. However, it should be noted that these data have not yet been published by a peer-reviewed journal.

The Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short-Term Treatment of Decompensated Heart Failure (REVIVE) was a double-blind, placebo-controlled, large-scale study (Packer et al 2005). Patients with acute decompensated heart failure, LVEF≤35%, and having resting dyspnea despite intravenous diuretics were included in this study. Patients were randomized to receive either a levosimendan bolus (6–12 $\mu g\,kg^{-1}$) followed by a stepped dose regimen of levosimendan (0.1–0.2 $\mu g\,kg^{-1}\,min^{-1}$) for 24 hours plus standard therapy, or a placebo infusion for 24 hours plus standard therapy. The REVIVE-1 study is the pilot study consisting of the first 100 patients of this study. This pilot study was designed to compare the intensive care unit and hospital stays between levosimendan and placebo groups and to test the feasibility of clinical composite endpoint instead of hemodynamic measurement which was employed as an endpoint in previous studies in this patient group (Garrat et al 2004; Johansson et al 2004). This study concluded that for the patients with acute heart failures, the intensive care unit stay in levosimendan group is 1 day shorter than that of the standard treatment group. This clearly shows that the hospitalization costs may be reduced by adopting levosimendan treatment.

After the completion of the REVIVE-1 enrollment, the REVIVE-2 study enrolled 600 patients (Packer et al 2005). The objective of new endpoints used in this study is to detect the alterations of patients' symptoms and clinical conditions. Thus, the patients were divided in three groups as worsening, stable, and improving according to their clinical picture. In this study, on the fifth day 33% more patients in the levosimendan group had improved and 30% fewer of them had worsened compared with patients in the control group (p=0.015 for both differences). Worsening acute heart failure requiring rescue intravenous therapy developed in 15% of patients in the levosimendan group and 26% of patients in the control group. The secondary endpoint of 90-day all-cause mortality rate was 15.1% in the levosimendan group and 11.6% among other control groups.

The Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support Study (SURVIVE) is a randomized, double-blind, double-dummy, prospective, controlled study (Mebazaa 2005; Mebazaa et al 2005). A total of 1327 patients hospitalized for acute decompensated heart failure, LVEF≤30%, not responding to intravenous diuretics and vasodilator therapy were included in the study. The primary endpoint of SURVIVE was all-cause mortality in 180 days, and the study was also designed to demonstrate a 25% lower mortality rate in the levosimendan group than that of the dobutamine group, following a single intravenous infusion. This study is the first trial using mortality as the primary endpoint in evaluating the efficacy (Mebazaa 2005;

Mebazaa et al 2005). Secondary endpoints for this trial include the number of days alive and out of the hospital during the 180 days of the trial, all-cause mortality during 31 days, cardiovascular mortality during 180 days, and global assessment at 24 hours. Patients were randomized to either dobutamine (minimum dose 5 $\mu g\,kg^{-1}\,min^{-1}$) or levosimendan bolus (12 $\mu g\,kg^{-1}$) followed by a stepped dose regimen of levosimendan (0.1–0.2 $\mu g\,kg^{-1}\,min^{-1}$). Both treatment groups also received standard care. After 5 days, 2 weeks, 1 month, and 6 months following the study drug infusion, mortality rate in the levosimendan group was reduced by 27%, 14%, 13%, and 6.4%, respectively, compared with that of the dobutamine group. These differences did not reach statistical significance. A secondary endpoint of BNP was significantly reduced in the levosimendan arm compared with the dobutamine arm.

Tolerability

Levosimendan is generally well tolerated. Most of its adverse effects are dose-related and due to its vasodilator effect (Lehtonen et al 1995). The most frequent adverse events associated with levosimendan include headache (5%), hypotension (5%), dizziness (1%–10%), and nausea (1%–10%) (Nieminen et al 2000; Slawsky et al 2000; Follath et al 2002; Moiseyev et al 2002; Sandel et al 2004). Among laboratory parameters, slight decreases of red blood cell count, hematocrit, and hemoglobin (10%), and, particularly in higher doses group, a slight decrease of serum K levels have been reported (Nieminen et al 2000). Serum creatinine levels were affected positively even among the patients with baseline renal function impairment (Follath et al 2002; Franco et al 2003).

Overall, studies demonstrated that levosimendan did not deteriorate or trigger myocardial ischemia (Follath et al 2002). However, excess reductions of blood pressure may decrease coronary perfusion pressure and provoke ischemia (Cleland et al 2004).

Although less arrhythmia was reported in clinical studies comparing levosimendan and dobutamine with placebo, ventricular tachycardia (25% vs 17%) and atrial fibrillation (8% vs 2%) were more frequent in the levosimendan group compared with the standard treatment group in the REVIVE II study (Nieminen et al 2000; Follath et al 2002; Moiseyev et al 2002; Packer et al 2005). In the SURVIVE study, atrial fibrillation (9.1% vs 6.1%) and ventricular tachycardia (7.9% vs 7.3%) were more frequent in the levosimendan group compared with the dobutamine group (Mebazaa 2005).

Dose recommendations

If rapid onset of action is desired, 6–24 $\mu g\,kg^{-1}\,min^{-1}$ is administered in 10–20 minutes according to the clinical picture of the patient. In patients with systolic blood pressure <90 mmHg, a loading dose should be avoided. An optimum maintenance dose of 0.05–0.2 $\mu g\,kg^{-1}\,min^{-1}$ is recommended. In doses above 0.2 $\mu g\,kg^{-1}\,min^{-1}$, adverse events may be seen more frequently (Moiseyev et al 2002). Since the half-life of its metabolites is longer, it was shown that the accumulation of metabolites during prolonged infusions enhances the adverse events. Therefore, infusions longer than 24 hours are not recommended (Kivikko et al 2003).

Place in clinical practice

Clinical studies have show that the use of levosimendan is safe and effective in postponing heart failure and in heart failure following acute myocardial infarction (Moiseyev et al 2002; Sonntag et al 2004). Although some studies have shown that levosimendan may be used in patients with shock, acute heart failure guidelines published by the European Society of Cardiology recommend its use on patients having symptomatic, low-output heart failure secondary to systolic dysfunction which is not accompanied by severe hypotension (Delle Karth et al 2003; Lehmann et al 2004; Nieminen et al 2005). Use on patients with a systolic blood pressure below 85 mmHg is not recommended (Nieminen et al 2005).

Conclusion

Levosimendan is a new inodilator agent for the therapy of end-stage heart failure, acting by calcium sensitization; it also causes vasodilatation by opening K channels. However, several recent studies showed different unexpected results, contrary to mechanism of its action. Further clinical trials may help to clarify its effects on mortality and use in clinical practice.

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