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Levosimendan

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Contents

Abstract

▲ Levosimendan, a pyridazinone-dinitrile derivative, is a calcium sensitiser with additional action on adenosine triphosphate (ATP)-sensitive potassium channels. It is used intravenously (IV) for the treatment of decompensated cardiac failure.

▲ At therapeutic doses, levosimendan exhibits enhanced contractility with no increase in oxygen demands. It also produces antistunning effects without increasing myocardial intracellular calcium concentrations or prolonging myocardial relaxation. Levosimendan also causes coronary and systemic vasodilation.

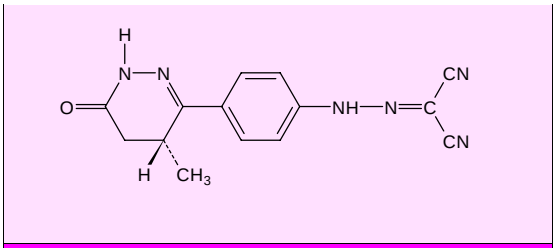
▲ In patients with decompensated congestive heart failure (CHF), IV levosimendan significantly reduced the incidence of worsening CHF or death.

▲ IV levosimendan significantly increased cardiac output or cardiac index and decreased filling pressure in the acute treatment of stable or decompensated CHF in large, double-blind, randomised trials and after cardiac surgery in smaller trials.

▲ Levosimendan is well tolerated, with the most common adverse events (headache, hypotension, nausea) being secondary to vasodilation. It has not been shown to be arrhythmogenic.

▲ Levosimendan has shown no clinically important pharmacokinetic interactions with captopril, felodipine, β-blockers, digoxin, warfarin, isosorbide-5-mononitrate, carvedilol, alcohol (ethanol) or itraconazole.

Features and properties of levosimendan (OR-1259)	
Indications	
Heart failure (CHF)	Launched (intravenous)
Mechanism of action	
Calcium sensitisation and activation of ATP-sensitive potassium (K_{ATP}) channels	Enhanced contractility via sensitising of cardiac myofilaments to calcium in troponin C and vasodilation via opening of K_{ATP} channels
Dosage and administration	
Usual dosage in clinical trials	6 to 12 μg/kg loading dose over 10 min followed by 0.05-0.2 μg/kg/min as a continuous infusion
Route of administration	Intravenous
Pharmacokinetic profile (in patients with CHF)	
Volume of distribution (steady state)	19.5L
Plasma protein binding	97-98%
Bioavailability	85% (oral)
Total clearance	0.18 L/h/kg (3 ml/min/kg)
Elimination half-life	≈1h
Adverse events	
Most frequent	Headache, hypotension, nausea



Levosimendan

Congestive heart failure (CHF) is a complex cardiovascular disorder with many possible causes. Symptoms usually result from left ventricular dysfunction which is associated with progressive alterations in the geometry of the left ventricle (LV). This cardiac remodelling decreases LV contractility and increases the haemodynamic stresses on the heart and is thought to be due, at least partly, to increases in levels of circulating neurohormones. Therapy can be aimed at increasing myocardial contractility via inotropes, decreasing pre- or afterload via vasodilators or altering the process of cardiac remodelling via drugs such as β-blockers and ACE inhibitors.[1]

The short term treatment of decompensated (unstable) CHF with intravenous (IV) inotropes is well established.[2,3] However, results from longer term clinical trials involving oral inotropic drugs have been disappointing. Digoxin has been shown to decrease morbidity but not mortality in patients in sinus rhythm[4] and the phosphodiesterase (PDE) inhibitor milrinone was shown to increase morbidity and mortality, probably via arrhythmogenesis.[5]

The calcium sensitisers, a new class of IV agents for decompensated heart failure, are a heterogeneous group of drugs that increase myocardial contractility without increasing cytosolic calcium release.[6-8] By reducing myocardial energy demand it is hoped that these drugs will avoid the serious arrhythmogenic effects seen with inotropic agents.

Levosimendan, a pyridazinone-dinitrile derivative, is a calcium sensitiser in cardiac muscle that produces enhanced myocardial contractility. In addition, levosimendan possesses vasodilatory effects attributed to the activation of adenosine triphosphate (ATP)-regulated potassium (K_{ATP}) channels.[9] It can be administered IV, which makes it a therapeutic option for acute decompensated heart failure.

1. Pharmacodynamic Profile

Established positive inotropic drugs exert their effects by increasing intracellular concentrations of free calcium, which has been shown to markedly increase myocardial energy consumption.[10] Increased intracellular calcium may be caused by an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP), which can be induced by β-adrenergic stimulation or by decreasing the catabolism of pre-existing cAMP via PDE inhibition.[8]

Mechanism of Action

- At therapeutically relevant concentrations, levosimendan, the active enantiomer of simendan, induces enhanced contractility mainly via its calcium sensitising actions. Levosimendan appears to increase myofilament calcium sensitivity by binding to cardiac troponin C in a calcium-dependent manner.[11,12] This stabilises the calcium-induced conformational change of troponin C,[13,14] thereby changing actin-myosin cross-bridge kinetics without appearing to increase the cycling rate of the cross-bridges or myocardial ATP consumption.[6] This mechanism of action appears to differ from that seen with other calcium sensitisers such as pimobendan and EMD 53998.[15-17]

- A concern regarding calcium sensitisers has been the possibility that they will delay the dissociation of calcium from the contractile apparatus, leading to slowing of ventricular relaxation which is often already impaired in end-stage heart failure.[3] Levosimendan has been shown to decrease or have no effect on myocardial relaxation time in a study involving instrumented dogs[17] and in *in vitro* studies involving failing human myocardium[18] and guinea-pig hearts.[19]

- The mechanism responsible for this phenomenon is not definitely known but is thought to be due,

at least in part, to levosimendan binding strongly to troponin C in the presence of high systolic intracellular calcium concentrations and binding less avidly when cytosolic calcium levels decrease during diastole.[6]

• Levosimendan also causes vasodilation which may be attributed to the opening of K_{ATP} channels.[20-25] Many, but not all,[26] *in vitro* studies using levosimendan (0.1 to 1 μmol/L) have shown that vascular smooth muscle relaxation may be induced by hyperpolarisation of myocytes secondary to activation of glibenclamide (glyburide)-sensitive potassium channels.[20-25] Another potential mechanism for the *in vivo* vasodilatory activity of levosimendan is the blockade of endothelin-1 release.[26]

Haemodynamic Effects

Effects of Enhanced Contractility

• The dose-dependent enhanced contractility effects of levosimendan shown in *in vitro*[7,27,28] and *in vivo*[17,29-33] have been confirmed in clinical trials in which single IV doses of levosimendan 0.25 to 5mg were given to healthy men,[34,35] patients with left ventricular dysfunction[36] and patients who had undergone coronary artery bypass.[37] Furthermore, a dose-dependent relationship was demonstrated for continuous infusion (up to 24 hours) levosimendan on a number of haemodynamic parameters in several large, well controlled clinical trials in patients with heart failure (also see section 3 and fig. 1 for specific haemodynamic data).[38-40]

• In a dose-ranging study in 24 patients with left ventricular dysfunction[36] [most were New York Heart Association (NYHA) class II], levosimendan 0.25 to 4mg bolus increased cardiac output. When compared with baseline values, cardiac output and heart rate increased significantly in the 2 and 4mg groups. The increase in cardiac output in the 0.25 and 0.5mg groups was significant without increasing heart rate when compared with placebo and there was no significant change in cardiac output in the 1mg group.

Effects on Myocardial Energetics and Coronary Blood Flow

• In 23 patients undergoing elective cardiac surgery, IV administration of levosimendan 8 or 24 μg/kg had no significant effect on myocardial oxygen consumption or on the utilisation of free fatty acids, lactate, pyruvate and glucose. Arterial and coronary sinus blood samples were taken at regular intervals before and during drug administration and myocardial oxygen and substrate utilisation was then calculated by measuring the differences between the blood samples from these 2 sites. Stroke volume increased significantly with both doses of levosimendan (63 to 66 and 62 to 72ml for levosimendan 8 and 24 μg/kg, respectively, *vs* 59 to 57ml for placebo, $p < 0.05$). An increase in cardiac output occurred at both levosimendan doses. Heart rate was also increased significantly (by a maximum of 11 beats/min, $p < 0.05$ *vs* placebo).[37]

• In this study, the overall increase from baseline in coronary blood flow after levosimendan 8 or 24 μg/kg was 28 and 42 ml/min, with a mean increase of 35 ml/min. Coronary vascular resistance and coronary perfusion pressure decreased significantly ($p < 0.05$ *vs* placebo) with both doses.[37]

• Myocardial oxygen consumption in 8 patients with recently decompensated CHF was assessed using dynamic positron emission tomography (PET) plus pulmonary artery catheterisation in a double-blind, randomised, placebo-controlled, crossover study. Levosimendan administered as an 18 μg/kg loading dose over 10 minutes followed by an infusion of 0.3 μg/kg/min for about 5 hours increased mean LV myocardial blood flow from 0.76 to 1.02 ml/min/g ($p < 0.05$ *vs* placebo) and had no significant effect on myocardial oxygen consumption. LV mechanical efficiency was unchanged but right ventricular efficiency increased by 24% ($p < 0.05$ *vs* placebo).[41]

• IV levosimendan administered as an 18 μg/kg loading dose over 10 minutes followed by an infusion of 0.3 μg/kg/min for 2 hours demonstrated neutral effects on myocardial energetics (assessed by measuring myocardial oxygen consumption

using dynamic PET) in 6 healthy male volunteers in a nonblind study.[42] Sodium nitroprusside 1 μg/kg/min (n = 5) or dobutamine 5 μg/kg/min (n = 5), both as constant rate infusions, were also assessed. The effects of sodium nitroprusside on myocardial energetics were neutral, whereas dobutamine significantly enhanced cardiac contractility at the expense of excessively increased oxygen consumption.[42]

Vasodilatory Effects

- Levosimendan 0.1 μmol/L to 3 mmol/L caused complete relaxation of porcine coronary arteries[24,26] and human venous capacitance vessels[23] *in vitro*. Infusions of levosimendan 1, 2 or 4 μg/kg/min over 10 minutes reduced systemic and coronary vascular resistance in dogs ($p < 0.05$ *vs* control).[43]

- Levosimendan (6.5 and 25 μg/kg bolus) significantly reduced systemic vascular resistance in healthy volunteers ($p < 0.05$ *vs* placebo).[34] In patients, the drug decreased systemic vascular resistance[36,37] and pulmonary vascular resistance (PVR; see next subsection).[37] Bolus doses of levosimendan significantly decreased pulmonary capillary wedge pressure (PCWP; 0.5, 1, 2 and 4mg doses) and right atrial pressure (2 and 4mg doses) in patients with LV dysfunction ($p < 0.05$ *vs* placebo for both parameters).[36]

- Furthermore, in large (n = 146 to 151), double-blind, randomised, multicentre trials in patients with heart failure,[39,40] continuous infusion of levosimendan (10-minute loading dose of 3, 6, 12, 24 or 36 μg/kg followed by a 24-hour infusion of 0.05 to 0.6 μg/kg/min,[39] or at a mean infusion rate of 0.26 μg/kg/min for 6 hours[40]) decreased PCWP and systemic vascular resistance (see also section 3).

Effects on Pulmonary Circulation

In addition to the systemic vasodilatory effects observed with levosimendan, the drug also decreases PVR and pulmonary artery pressure (PAP).

- In 23 anaesthetised patients given bolus levosimendan (8 or 24 μg/kg) immediately after coronary bypass surgery, PVR decreased significantly (by 22 and 27%, respectively; $p = 0.0004$) whereas an increase was observed with placebo. At both levosimendan doses, PAP decreased by 2mm Hg.[37]

- In patients with NYHA III or IV heart failure who received a 6-hour infusion of levosimendan titrated at doses of 0.1 to 0.4 μg/kg/min, mean PAP decreased at all infusion rates, with a maximal decrease of 6mm Hg at 6 hours (versus an increase of 1mm Hg for placebo, $p < 0.001$). Levosimendan decreased PVR, with a maximal decrease of 80 dyne • sec • cm^{-5} (compared with an increase of 33 dyne • sec • cm^{-5} for placebo, $p < 0.001$).[40]

- A significant ($p = 0.002$) linear reduction in mean PAP was seen during levosimendan therapy (a 10-minute loading dose of 3 to 36 μg/kg followed by a 24-hour infusion of 0.05 to 0.6 μg/kg/min) in patients with NYHA III heart failure of ischaemic origin. In comparison, the decrease in mean PAP in dobutamine (6 μg/kg/min) recipients was small and did not differ from that in placebo recipients. Similarly, the mean decrease in PVR in levosimendan-treated patients exhibited a significant linear relationship ($p = 0.005$). In contrast, the mean decrease in PVR in the dobutamine group was similar to that observed with placebo and was significantly ($p < 0.001$) smaller than with levosimendan 0.4 or 0.6 μg/kg/min.[39]

Effects on Diastolic Function

- Levosimendan 24 μg/kg as a bolus dose had no clinically relevant influence on diastolic function in 16 patients who had undergone successful percutaneous transluminal coronary angioplasty (PTCA).[44] Levosimendan increased chamber compliance in late diastole, indicating improved LV filling; the effects of placebo (n = 8) were similar.

- In 10 patients with heart failure, levosimendan 3.75 μg/min as a bolus dose infused intracoronarily had no effect on Tau (τ; the time constant of LV isovolumic relaxation). At a dose of 12.5 μg/min, levosimendan decreased τ ($p = 0.007$), indicating a mild positive lusitropic effect.[45]

Anti-Ischaemic Effects

The calcium sensitivity of the myofilaments in the ischaemic myocardium is decreased[8] mainly because of the acidic intracellular pH. As levosimendan is a calcium sensitiser, it produces anti-ischaemic effects; these effects have been demonstrated in animal studies. Although the anti-ischaemic effects of levosimendan have not been studied specifically in patients, available data indicate the lack of an ischaemic effect.

- Levosimendan perfusion (at a concentration of 1×10^{-7} or 5×10^{-6} mol/L) significantly decreased infarct size ($p < 0.05$ *vs* controls) in isolated rabbit hearts in which acute regional ischaemia was induced by coronary artery ligation. This effect was thought to be partly due to an increase in coronary blood flow, but an oxygen-sparing effect secondary to myofilament calcium sensitisation was also postulated.[46,47]

- In isolated guinea-pig hearts, levosimendan produced anti-ischaemic effects in a manner that was independent of coronary flow. These effects were postulated to be due to the opening of K_{ATP} channels.[31]

- Levosimendan significantly decreased infarct size when compared with placebo ($p < 0.05$) in dogs in which the left anterior descending coronary artery was occluded for 60 minutes and then reperfused for 3 hours. Animals were randomised to receive continuous IV levosimendan (24 μg/kg loading dose followed by 0.4 μg/kg/min infusion) or placebo, in the presence or absence of glibenclamide (glyburide), for 15 minutes before the coronary artery occlusion until the start of reperfusion.[48]

- In 147 patients with CHF, no changes in levels of troponin T and creatine kinase MB subunit (CK-MB) [specific and sensitive markers of myocardial damage] were observed after levosimendan 0.05 to 0.6 μg/kg/min was infused for 24 hours.[39]

- A slight decrease in mean CK-MB values (specific data not reported) was observed in 504 patients with LV failure due to an acute myocardial infarction who received placebo or levosimendan as a loading dose of 6 to 24 μg/kg followed by a 6-hour infusion of 0.1 to 0.4 μg/kg/min.[49]

Antistunning Effects

There is *in vitro* evidence to suggest that myocardial stunning (reversible myocardial contractile dysfunction secondary to ischaemia) may be caused, at least partly, by abnormal intracellular calcium homeostasis, including decreased myofilament calcium sensitivity.[50]

- Myocardial stunning was produced in anaesthetised dogs by subjecting them to multiple periods of coronary artery occlusion and reperfusion. Three hours later, levosimendan (1.5 to 12 μg/min) administered directly into the area of stunned myocardium via intracoronary catheter markedly improved the contractility of the stunned myocardium without causing any systemic or coronary haemodynamic changes. This effect was presumed to be due to localised calcium sensitisation.[51]

- In patients who had undergone successful PTCA, levosimendan 24 μg/kg as a bolus dose ($n = 16$) improved the function of the stunned myocardium, as evidenced by a significant reduction in the number of hypokinetic segments (-2.4) compared with placebo ($n = 8$; +0.8; $p = 0.0111$). There was no observed influence on chamber compliance.[44]

Effects on Arrhythmias

Theoretically, increased contractility that does not increase potentially arrhythmogenic intracellular concentrations of cAMP or calcium should not predispose the myocardium to arrhythmias.[52]

- The effect of levosimendan 300 nmol/L or dobutamine 0.1 μmol/L on the incidence of ischaemic/reperfusion arrhythmias has been evaluated in the Langendorff-perfused guinea-pig heart model. Reperfusion ventricular tachycardia (but not ventricular fibrillation) developed in 25% of control hearts ($n = 8$). Levosimendan-treated hearts ($n = 6$) had no ischaemic or reperfusion arrhythmias whereas 83% of hearts treated with dobutamine ($n = 6$) developed reperfusion ventricular tachycardia and 33% developed reperfusion ventricular fibrillation (both $p < 0.05$ *vs* control).[31]

• Levosimendan 0.1 μmol/kg infused IV in dogs (n = 6) 10 minutes prior to a 25-minute occlusion of the left anterior descending coronary artery, resulted in a 0% incidence of ventricular fibrillation versus 50% with milrinone 0.1 μmol/kg (n = 6) and 40% in controls (n = 10; p-values not stated). Ventricular tachycardia was seen in 83, 67 and 90% of the levosimendan, milrinone and control groups, respectively.[53]

• In placebo-controlled trials in patients treated with continuous IV levosimendan for 6 to 24 hours at doses of 0.05 to 0.2 μg/kg/min, the corrected QT interval was not significantly prolonged compared with placebo. Indeed, the uncorrected QT interval was shortened with levosimendan.[49]

• No increase in the frequency of nonsustained ventricular tachycardia was found in an analysis of pooled ambulatory electrocardiograph data from 10 studies which included data from 386 patients with heart failure who received IV levosimendan at different doses. There was no evidence of any increase in the development of new supraventricular or ventricular tachyarrhythmias, including torsade de pointes, in patients who did not exhibit these abnormalities at baseline.[54]

• An intracardiac electrophysiology study in 10 patients evaluated for rhythm disorders indicated that levosimendan at plasma concentrations of about 110 ng/mL exerted electrophysiological effects, although the magnitude of the effects at the ventricular level were not substantial (see section 4 for further details).[55]

Neurohumoral Effects

• In a nonblind, placebo-controlled, crossover study, IV levosimendan boluses of 6 or 25 μg/kg produced no appreciable stimulation of the sympathoadrenal system in 14 healthy men at rest; levels of adrenaline, noradrenaline and atrial natriuretic peptide (ANP) were unchanged. After exercise, there was a slight decrease in ANP levels and a significant increase in noradrenaline levels with levosimendan 25 μg/kg (7.8 to 9 nmol/L; $p < 0.001$ *vs* placebo), but adrenaline levels were unchanged.[34]

• In a randomised, multicentre, placebo-controlled trial involving 151 patients with stable heart failure, IV levosimendan (loading dose followed by an infusion of 0.05 to 0.6 μg/kg/min for 24 hours) did not affect adrenaline levels and tended to decrease plasma ANP levels. Two hours after the termination of the infusion, noradrenaline levels were significantly increased at the 0.05, 0.01 and 0.6 μg/kg/min doses of levosimendan ($p \leq 0.002$). Plasma renin levels were reduced in patients who received the lower doses of levosimendan and increased at higher doses (0.4 or 0.6 μg/kg/min).[39]

• Noradrenaline and adrenaline levels decreased by 16 and 27%, respectively, in 85 patients with severe low-output heart failure who received levosimendan 0.1 to 0.2 μg/kg/min for 24 hours. Similar decreases were observed in 81 patients treated with dobutamine 5 to 10 μg/kg/min for 24 hours.[49]

• In another study, no changes in plasma noradrenaline levels were observed in 62 patients with heart failure (NYHA III to IV) given levosimendan at titrated doses of 0.1 to 0.4 μg/kg/min or placebo (n = 30).[56] In addition, a significant ($p = 0.008$ *vs* baseline; $p = 0.001$ *vs* placebo) reduction (11%) in endothelin-1 levels was observed 6 hours after starting the levosimendan infusion (n = 67) compared with no change in placebo-treated patients (n = 31). At 24 hours after starting the levosimendan infusion, endothelin-1 levels decreased a further 16% from the 6-hour levels ($p < 0.0001$ *vs* baseline).[56]

Duration of Action

• In general, the effect of 5-minute loading doses of levosimendan on haemodynamic parameters (e.g. cardiac output, ejection fraction and PCWP) was clearly visible at the end of the infusion. The effect peaked at 10 to 30 minutes after the infusion, with the duration of action about 1 to 2 hours.[36,37]

• No attenuation of the haemodynamic response was observed in patients with moderate heart failure during a continuous 24-hour infusion of levosimendan 0.05 to 0.6 μg/kg/min[39] or in patients

with severe heart failure during continuous infusion of levosimendan 0.1 to 0.2 μg/kg/min for 48 hours. In addition, no attenuation of the effect of levosimendan on PCWP and stroke volume was observed up to 48 hours after stopping the infusion.[49]

2. Pharmacokinetic Profile

The pharmacokinetic properties of IV levosimendan have been evaluated in healthy volunteers[57-60] and in patients with mild (NYHA class II)[57] or severe (NYHA class IV)[61] CHF. In addition, the pharmacokinetics of IV levosimendan as a 10 minute bolus infusion have been evaluated in patients with renal[62] or hepatic[49] failure and in children aged 3 months to 6 years.[63] The pharmacokinetic profile of oral levosimendan has also been characterised in healthy volunteers[58] and in patients with mild CHF.[57]

Absorption and Distribution

- Levosimendan exhibits linear pharmacokinetics.[49,60] In a dose-ranging study, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased linearly with the dose in 10 healthy volunteers.[49] Dose proportionality has also been observed in patients with CHF after single IV infusions of levosimendan ranging from 0.25 to 4mg.[49]

- Levosimendan is distributed rapidly to a small volume; the distribution half-life ($t_{½\alpha}$) of unchanged drug was 0.26 and 0.1 hours in patients with mild and severe CHF, respectively.[57,64]

- The volume of distribution (V_{ss}) at steady state for unchanged drug was 19.5 and 21.9L in patients with CHF and healthy volunteers, respectively.[57]

- About 97 to 98% of levosimendan was bound to plasma proteins in patients with CHF and healthy volunteers.[57,65]

- $AUC_{0-\infty}$ values were 29.7 and 36 μg · L/h in patients with mild or severe CHF, respectively, given levosimendan 0.5mg.[57,64]

- The bioavailability of levosimendan was about 85% in healthy volunteers and patients with CHF after administration of solution, conventional tablet or capsule formulations.[57,58] Levosimendan was absorbed rapidly, with C_{max} reached in 0.5 to 1 hours after administration of oral formulations.[57,58]

Metabolism and Elimination

- The elimination half-life ($t_{½\beta}$) was approximately 1 hour in patients with mild or severe CHF.[57,61] Total clearance (CL_{tot}) was 0.18 L/h/kg (3 ml/min/kg) in patients with severe CHF.[61]

- Levosimendan is completely metabolised, with negligible amounts of unchanged drug found in urine and faeces.[49,66]

- In humans, the main metabolites of levosimendan are conjugates of the glutathione pathway, cyclic or N-acetylated cysteine or cysteinylglycine derivatives. These are biologically inactive, intermediate metabolites.[49,67]

- Animal models have shown that levosimendan is also reduced (to OR-1855) in the lower parts of the gastrointestinal tract; OR-1855 is absorbed and further acetylated to OR-1896.[67,68] The latter metabolite is biologically active at therapeutic concentrations with a pharmacological profile resembling that of levosimendan.[69,70]

- The metabolites OR-1855 and OR-1896 are formed slowly.[58] The potentially longer half-lives of these 2 metabolites may prolong the haemodynamic effects of levosimendan after elimination of the parent drug.[68]

Special Populations

- The clearance of unchanged drug in patients with mild to moderate renal failure was not statistically significantly different from that in healthy controls (CL_{tot} 22.8 *vs* 16.7 L/h and $AUC_{0-\infty}$ 27.8 *vs* 32.5 μg · L/h for patients *vs* healthy group).[62]

- In addition, compared with healthy volunteers, the pharmacokinetic properties of levosimendan as a loading dose were not statistically significantly

different in patients with mild to moderate hepatic impairment or in children with congenital heart disease. However, since the metabolites are not formed in detectable amounts after a single dose, the pharmacokinetic properties of plasma metabolites is unknown in these patient groups.[49,62,63]

• There were significant differences in plasma levels of levosimendan between healthy male (n = 8) and female (n = 3) volunteers given a single 0.5mg bolus injection over 10 minutes, with women having a larger AUC (37.2 *vs* 52.6 μg • h/L, $p < 0.05$).[64] However, when adjusted for bodyweight, there were no statistical differences in pharmacokinetic parameters between males and females; no dosage adjustments for gender are deemed necessary.[61]

3. Therapeutic Trials

Congestive Heart Failure

IV levosimendan has been evaluated for the acute treatment of patients with decompensated (unstable) CHF in several large, multicentre, randomised, double-blind trials compared with placebo[40,71] or dobutamine.[38] The efficacy of IV levosimendan has also been compared with placebo or dobutamine in a randomised, double-blind, parallel group, multicentre trial in patients with stable heart failure (NYHA class III or IV).[39]

Decompensated Heart Failure

• In the Levosimendan Infusion versus Dobutamine (LIDO) trial (published as an abstract), patients (n = 203) with severe, low-output decompensated CHF were randomised to IV levosimendan (an initial loading dose of 24 μg/kg followed by a 24-hour infusion of 0.1 to 0.2 μg/kg/min) or dobutamine (continuous IV infusion of 5 to 10 μg/kg/min for 24 hours).[38] Significantly more patients treated with levosimendan than dobutamine achieved an increase from baseline in cardiac index ≥30% and a decrease in PCWP ≥25% (primary efficacy measure) [28 *vs* 15%, p = 0.022].[38]

• At 30-day follow-up in the LIDO trial,[38] the relative risk of worsening heart failure or death was significantly lower with levosimendan than with dobutamine (p = 0.039). Seven of 103 (6.8%) patients treated with levosimendan and 17 of 100 (17%) patients in the dobutamine group had worsening heart failure or died during the 24-hour infusion plus a 30-day follow-up period (p = 0.039).[38]

• 504 patients with decompensated CHF after acute myocardial infarction received 1 of 4 different doses of IV levosimendan or placebo in the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct (RUSSLAN) trial (published as an abstract).[71] Levosimendan was administered as a loading dose of 6, 12, 24 or 24 μg/kg followed by a 6-hour infusion of 0.1, 0.2, 0.2 or 0.4 μg/kg/min, respectively. During the first 24 hours there was a significant (p = 0.044), dose-related decrease in the combined risk of worsening heart failure or death in patients treated with levosimendan (4.0 *vs* 8.8% in the placebo group).[49,71] At 14 days, overall mortality was lower in patients treated with levosimendan than in placebo recipients (11.4 *vs* 19.6%, p = 0.029).[71]

• Levosimendan, administered as a continuous infusion for 6 hours (mean dose 0.26 μg/kg/min), increased the cardiac index by 0.7 L/min/m^2 when compared with baseline in 146 patients with CHF ($p \leq 0.001$ *vs* placebo). The increase in cardiac index was primarily due to changes in stroke volume, which increased by 13ml from baseline ($p \leq 0.001$ *vs* placebo). The levosimendan group also experienced a 6mm Hg decrease in PCWP ($p \leq 0.001$) and a 514 dyne • sec • cm^{-5} decrease in systemic vascular resistance when compared with baseline (both $p \leq 0.001$ *vs* placebo).[40]

• At 6 hours, patients receiving placebo were discontinued from the trial. The dose of levosimendan was reduced by 50% in the remaining patients and administered for a further 18 hours (total of 24 hours) in a single-blind manner. At 24 hours, patients were randomised, in a double-blind manner, to continue levosimendan (n = 42) or placebo (n = 43) for an additional 24 hours (total of 48 hours). Haemodynamic effects observed with levosi-

mendan at 6 hours were maintained at 24 and 48 hours.[49]

Stable Heart Failure

• In a trial involving 151 patients, 5 different dosage regimens of levosimendan (10-minute loading dose of 3, 6, 12, 24 or 36 μg/kg followed by a 24-hour infusion of 0.05, 0.1, 0.2, 0.4 or 0.6 μg/kg/min; the latter 2 are not recommended dosages of levosimendan) were compared with dobutamine (given in a nonblind manner as a continuous infusion of 6 μg/kg/min for 24 hours) and placebo. At least 50% of patients treated with levosimendan (all doses) had a favourable haemodynamic response [defined as attaining at least 1 of the following prespecified end-points: ≥15% increase in stroke volume at 23 to 24 hours; ≥25% decrease in PCWP (and ≥4mm Hg) at 23 to 24 hours; ≥40% increase in cardiac output (with a change in heart rate of <20%); ≥50% decrease in PCWP during 2 consecutive measurements leading to a reduction in the dose of study medication at any time during the infusion]. At all doses of levosimendan, response rates were significantly greater than with placebo ($p = 0.038$ at the lowest dose and $p \leq 0.005$ at all other doses). The response rate with dobutamine (70%) did not differ significantly from that obtained with any dose of levosimendan (range: 50% at lowest to 88% at highest dose).[39]

• Cardiac output increased with all doses of levosimendan ($p < 0.001$ and $p < 0.003$ *vs* dobutamine for levosimendan 0.4 and 0.6 μg/kg/min, respectively; fig. 1a). There were no significant differences in stroke volume changes between the levosimendan and dobutamine groups at any time (fig. 1b). PCWP was significantly decreased with all doses of levosimendan, presumably secondary to vasodilation, compared with dobutamine ($p < 0.044$; fig. 1c).[39]

After Cardiac Surgery

Despite cardioplegic protection, a variable degree of myocardial stunning, which frequently requires inotropic support, usually follows cardiac surgery. Levosimendan does not increase myocardial intracellular concentrations of calcium and has been shown to have coronary artery vasodilating properties via activation of K_{ATP} channels (see section 1).[24,37,41] Therefore, levosimendan may be beneficial with regard to haemodynamics and myocardial energetics after cardiac surgery.[37]

• After cardiopulmonary bypass (CPB), 18 patients were randomised to receive IV placebo, low dose (18 μg/kg loading dose followed by a 0.2 μg/kg/min infusion) or high dose (36 μg/kg loading dose followed by a 0.3 μg/kg/min infusion) levosimendan, 15 minutes before and continued for 6 hours after CPB in a double-blind manner. When comparing pre-CPB values with those obtained 15 and 60 minutes post-CPB, both doses of levosimendan significantly increased cardiac output ($p < 0.05$ *vs* placebo). The maximum increase in cardiac output was seen in high dose recipients 15 minutes after the discontinuation of CPB (cardiac output increased from 4.2 to 7.9 L/min). Heart rate was significantly greater only with the higher dose of levosimendan compared with placebo during the first hours after CPB ($p < 0.05$ *vs* placebo).[72]

• As discussed in section 1, levosimendan 8 or 24 μg/kg improved cardiac performance without increasing myocardial oxygen consumption or changing myocardial substrate utilisation in 23 patients undergoing elective coronary artery bypass graft surgery.[37]

4. Tolerability

• Levosimendan has been shown to be well tolerated, with most adverse events being secondary to its vasodilating properties.[73] Adverse events related to levosimendan were dose related.[49]

• Headache (8.7%) and hypotension (6.5%) were the most common treatment-emergent adverse events in 972 patients treated with IV levosimendan during clinical trials. Treatment-emergent adverse events occurring in >2% of levosimendan recipients in all IV clinical trials are shown in figure 2.[49]

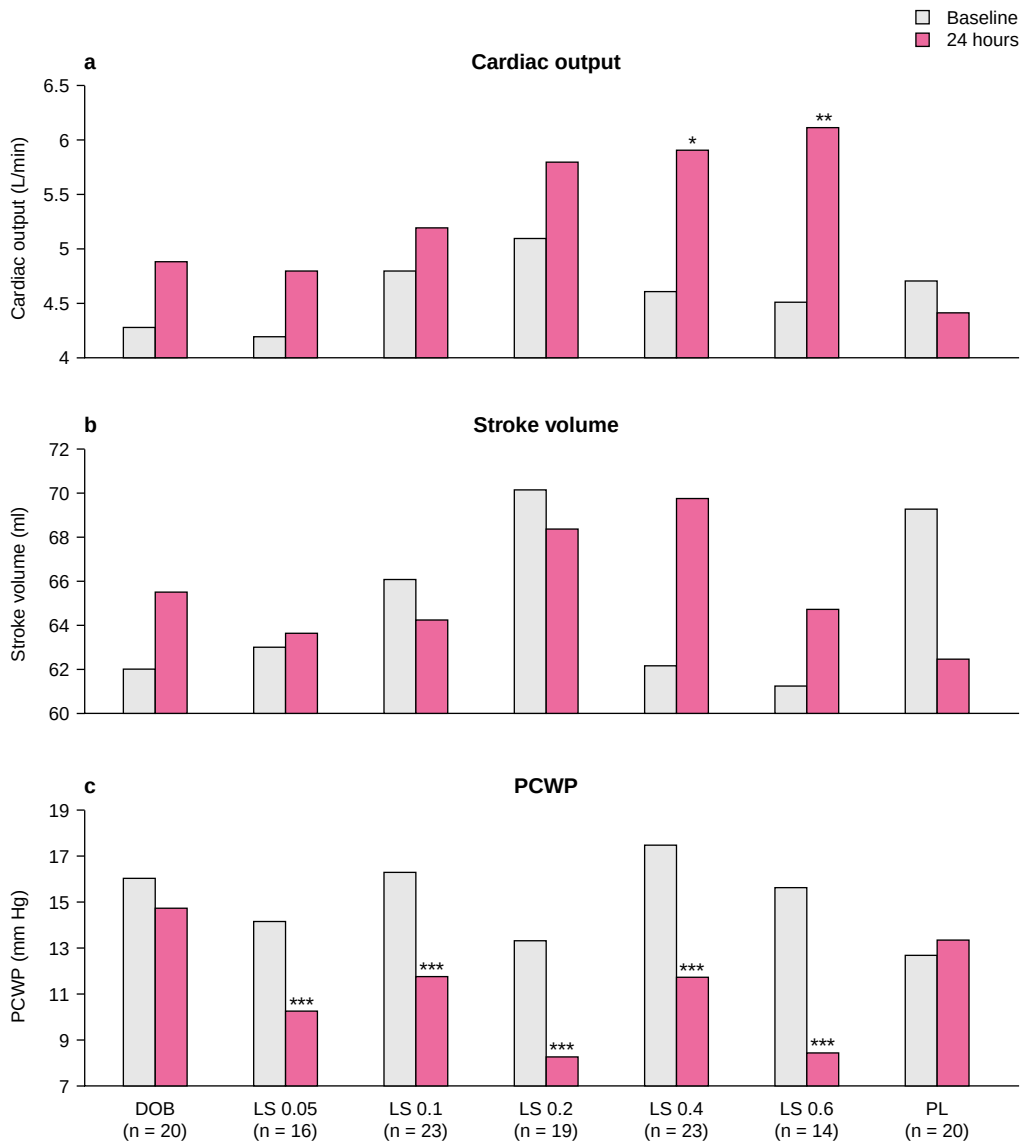


Fig. 1. Effects of levosimendan (LS), dobutamine (DOB) or placebo (PL) on (**a**) cardiac output, (**b**) stroke volume and (**c**) pulmonary capillary wedge pressure (PCWP). 151 patients with stable congestive heart failure received LS as a 10-minute loading dose (3, 6, 12, 24 or 36 μg/kg) followed by a 24-hour infusion (0.05, 0.1, 0.2, 0.4 or 0.6 μg/kg/min) [the latter 2 are not recommended dosages of LS], a 24-hour infusion of DOB at 6 μg/kg/min (nonblind) or PL in a randomised, double-blind trial. Haemodynamic changes were recorded via a right heart catheter at regular intervals from 30 minutes to 24 hours after the start of the infusion and cardiac output was measured by thermodilution. At 24 hours, cardiac output and stroke volume had decreased and PCWP increased from baseline in PL recipients (statistical data not reported).[39] * $p < 0.001$, ** $p < 0.003$, *** $p < 0.044$ *vs* DOB.

• In the LIDO trial, patients who received levosimendan had significantly fewer serious adverse events (6.8%) than patients treated with dobutamine (18.4%; $p < 0.05$).[38]

• In the RUSSLAN trial, there were no significant differences between the combined levosimendan group and placebo in the proportion of patients with LV failure after myocardial infarction who experienced ischaemia and/or hypotension (13.4 *vs* 10.8%). A possible dose-response relationship was attributed to the high frequency of ischaemia and hypotension (19%) associated with the highest levosimendan infusion rate (loading dose of 24 μg/kg over 10 minutes followed by a maintenance infusion of 0.4 μg/kg/min for 6 hours; not the recommended levosimendan dosage).[49]

• Overall, 29% of levosimendan-treated patients (10-minute IV loading dose of 3 to 36 μg/kg followed by 0.05 to 0.6 μg/kg/min for 24 hours; n = 95) experienced at least 1 adverse event during the study day compared with 35 and 20% of patients treated with placebo (n = 20) or dobutamine (6 μg/kg/min; n = 20), respectively, in a randomised, double-blind, parallel group, multicentre trial in patients with stable heart failure (NYHA class III).[39] Headache (9%), hypotension (5%) and nausea (4%) were the most frequently reported adverse events in levosimendan-treated patients (regardless of relation to study medication).

• During this study, there were no clinically relevant alterations in any laboratory parameters.[39] At higher levosimendan doses (0.2 to 0.6 μg/kg/min), reductions in red blood cell count (10 to 39%; $p \leq 0.012$), haematocrit (<10%; $p \leq 0.011$) and haemoglobin (<10%; $p \leq 0.01$) were observed. Small (≈5%) but statistically significant ($p < 0.05$) reductions in serum potassium occurred at higher levosimendan doses.

• Similar changes in laboratory parameters were observed in pooled data from 3 of the large clinical trials conducted in patients with heart failure. In addition, median increases in blood glucose levels were greater in the levosimendan group (1.1 mmol/L) compared with placebo (0.56 mmol/L; $p = 0.035$) or dobutamine (no change; $p = 0.034$).[49]

• In an electrophysiological study, 10 patients with normal cardiac function received IV levosimendan infused at a loading dose of 18 μg/kg for 10 minutes followed by 0.4 μg/kg/min infused continuously for 32 to 43 minutes (yielding plasma concentrations of ≈110 ng/mL, above the therapeutic range). Levosimendan enhanced impulse formation and conduction in cardiac slow-response tissue, enhanced recovery of excitability in the myocardium and possibly delayed ventricular repolarisation. However, the effects on the ventricle were not substantial, indicating a low likelihood of serious cardiac arrhythmias.[55]

5. Drug Interactions

Cardiovascular Drugs

• Levosimendan produced no significant adverse haemodynamic effects when administered concomitantly with captopril in 22 evaluable patients with CHF (NYHA class II or III) in a double-blind, randomised trial. Patients received single IV doses of levosimendan 1 or 2mg or placebo before and after a 2-week course of oral captopril (dose titrated up to 50mg twice daily according to clinical response).[74]

• Potential interactions between felodipine [a substrate of cytochrome P450 (CYP) 3A4] and oral levosimendan were investigated in a double-blind, randomised, crossover trial in 24 patients with ischaemic heart disease.[75] The trial consisted of four 7- to 10-day treatment periods during which the patients received placebo, levosimendan 0.5mg 4 times daily with or without felodipine 5mg once daily, or felodipine 5mg alone (washout period not stated). Both drugs increased heart rate after submaximal exercise. At rest, heart rate increased by 5 to 8 beats/min for levosimendan, 0 to 6 beats/min with felodipine and 6 to 10 beats/min for both drugs combined. Levosimendan alone or in combination with felodipine did not have any effect on exercise capacity in these patients.[75]

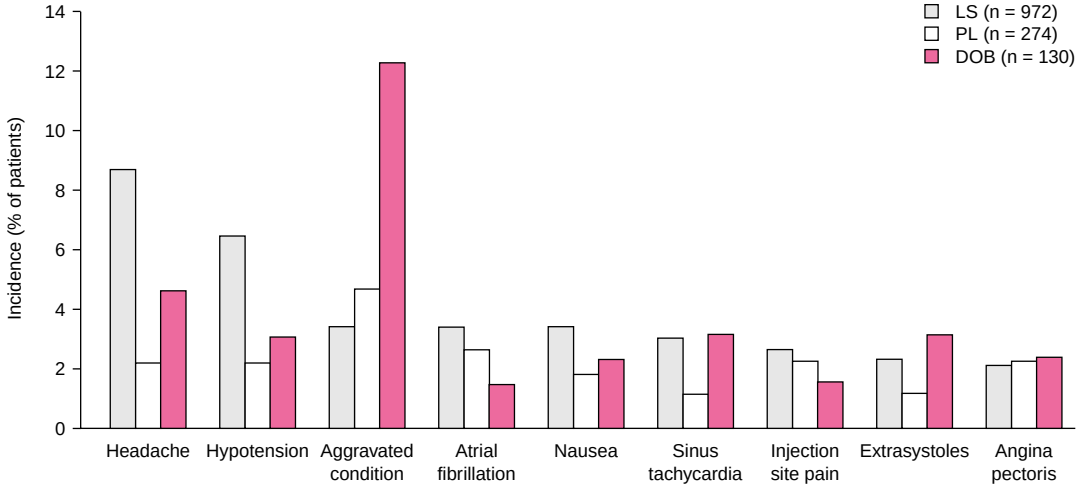


Fig. 2. Treatment-emergent adverse events associated with levosimendan (LS), placebo (PL) or dobutamine (DOB) in 1376 patients with heart failure. Data are pooled from all clinical studies of intravenous LS and represent adverse events occurring in >2% of LS recipients. Dosages of LS and DOB were not stated.[49]

• The pharmacokinetics of levosimendan were not affected when the drug was coadministered with β-blockers (specific drugs not reported; n = 32) or digoxin (n = 87) [drug dosages not stated] in a population pharmacokinetic analysis of patients with heart failure.[49]

• Drug plasma protein binding and measures of blood coagulation were largely unaffected by concomitant administration of oral levosimendan and warfarin 25mg in 10 healthy volunteers. Pharmacokinetic parameters of levosimendan were also unaltered, although the $t_{½\beta}$ of warfarin was significantly shorter (37.3 *vs* 40.8h, $p < 0.05$) and volume of distribution (Vd) larger (7.4 *vs* 6.1L) when both agents were coadministered versus warfarin alone. Single doses of warfarin were administered alone and on day 4 of a 9-day course of levosimendan 0.5mg 4 times daily in a randomised, crossover manner.[65,76]

• Isosorbide-5-mononitrate 20mg or placebo was given orally, in a randomised, double-blind, crossover manner, to 12 healthy men in combination with IV levosimendan (12 μg/kg loading dose over 10 minutes plus 0.2 μg/kg/min infusion for a total time of 2 hours). The only additive effect seen with combined levosimendan and isosorbide-5-mononitrate was an increase in orthostatic heart rate (40 beats/min *vs* a respective 30, 28 and 22 beats/min increase with levosimendan, isosorbide-5-mononitrate or placebo alone).[77]

• The concomitant administration of carvedilol had no significant effects on the contractility and vasodilatory effects of levosimendan in 12 healthy volunteers.[78] Subjects received levosimendan as a 2mg IV bolus or placebo before and at the end of a 7- to 9-day treatment period with carvedilol.

Other Drugs

• IV levosimendan was shown to have no clinically important interactions with alcohol (ethanol) in a randomised, double-blind, crossover study involving 12 healthy male volunteers. Apart from a decrease in the central compartment Vd (14.3 *vs* 10.8L, $p < 0.05$), alcohol caused no significant

changes to the pharmacokinetics/pharmacodynamics of levosimendan. Likewise, levosimendan did not alter the elimination of, or potentiate the psychomotor changes induced by, alcohol.[59]

- A 5-day course of oral itraconazole (a CYP3A4 inhibitor) 200mg in a double-blind, placebo-controlled, crossover trial had no significant effects on the pharmacokinetics of single-dose oral levosimendan 2mg in 12 healthy volunteers.[66]

6. Levosimendan: Current Status

Levosimendan is a calcium sensitiser that works via a dual mechanism of action that provides enhanced contractility and vasodilation. It increases myocardial contractility without increasing myocardial oxygen demand through calcium sensitisation and produces venous, arterial and coronary vasodilation through activation of K_{ATP} channels in smooth muscle. Administered intravenously, levosimendan is an effective and well tolerated drug for the treatment of cardiac failure; it has shown no proarrhythmic activity in short term trials and has no short term effect on mortality and no adverse effect on long term survival. IV levosimendan received its first marketing approval in Sweden for the short term treatment of critically ill patients hospitalised due to acute decompensated heart failure.[79] Registration is ongoing in other European countries and Latin American, Pacific, Asian and African nations. In the US, levosimendan is in late phase clinical development.

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