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Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers

Claes-Håkan Bergh[1†], Bert Andersson[1], Ulf Dahlström[2], Kolbjorn Forfang[3], Matti Kivikko[4], Toni Sarapohja[4], Bengt Ullman[5], and Gerhard Wikström[6*]

[1]Department of Cardiology, Sahlgrenska University Hospital, SE-41345 Gothenburg, Sweden; [2]Department of Cardiology, Linkoping University Hospital, S-582 52 Linkoping, Sweden; [3]Department of Cardiology, Rikshospitalet University Hospital, 0027 Oslo, Norway; [4]Department of Critical Care, R&D, Orion Pharma, PO Box 65, 02101 Espoo, Finland; [5]Department of Cardiology, Södersjukhuset, Sjukhusbacken 10, Stockholm, Sweden; and [6]Department of Medical Sciences, Kardiologi, Akademiska Hospital, Institution of Medical Science, Uppsala 751 85, Sweden

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Aims The aim of this study is to compare the effects of a 24 h intravenous infusion of levosimendan and a 48 h infusion of dobutamine on invasive haemodynamics in patients with acutely decompensated chronic NYHA class III–IV heart failure. All patients were receiving optimal oral therapy including a β-blocker.

Methods and results This was a multinational, randomized, double-blind, phase IV study in 60 patients; follow-up was 1 month. There was a significant increase in cardiac index and a significant decrease in pulmonary capillary wedge pressure (PCWP) at 24 and 48 h for both dobutamine and levosimendan. The improvement in cardiac index with levosimendan was not significantly different from dobutamine at 24 h ($P = 0.07$), but became significant at 48 h (0.44 ± 0.56 vs. 0.66 ± 0.63 L/min/m^2; $P = 0.04$). At 24 h, the reduction in the mean change in PCWP from baseline was similar for levosimendan and dobutamine, however, at 48 h the difference was more marked for levosimendan (-3.6 ± 7.6 vs. -8.3 ± 6.7 mmHg; $P = 0.02$). No difference was observed between the groups for change in NYHA class, β-blocker use, hospitalizations, treatment discontinuations or rescue medication use. Reduction in B-type natriuretic peptide (BNP) was significantly greater with levosimendan at 48 h ($P = 0.03$). According to physician's assessment, the improvement in fatigue ($P = 0.01$) and dyspnoea ($P = 0.04$) was in favour of dobutamine treatment, and hypotension was significantly more frequent with levosimendan ($P = 0.007$). No increase in atrial fibrillation or ventricular tachycardia was seen in either group.

Conclusion A 24 h levosimendan infusion achieved haemodynamic and neurohormonal improvement that was at least comparable at 24 h and superior at 48 h to a 48 h dobutamine infusion.

Keywords Levosimendan • Dobutamine • Decompensated heart failure • Invasive monitoring

Introduction

Despite optimal oral therapy, patients with acutely decompensated heart failure (ADHF) may experience periods of decompensation that require short-term therapy with positive inotropic agents. These agents may increase myocardial oxygen consumption and worsen myocardial ischaemia and, while they may improve pump function acutely and stabilize the patient's condition, there may

* Corresponding author. Tel: +46 18 611 4954, Fax: +46 18 506 640, Email: gerhard.wikstrom@medsci.uu.se

† In memoriam.

be an increased frequency of arrhythmias and death. Whether this is also the case in patients with ADHF treated with optimal dosages of β-blockers remains unclear.

Intravenous levosimendan is a novel agent developed for the short-term treatment of worsening heart failure (HF). It has been found to increase myocardial contractility via a sensitization of cardiac troponin C to calcium,[1] and to produce vasodilatation by opening the ATP-sensitive potassium channels in vascular smooth muscle cells. Levosimendan also has phosphodiesterase type III inhibitory properties at high concentrations.[2] Levosimendan induces haemodynamic improvement without an increase in myocardial oxygen consumption.[3] In randomized, double-blinded studies in patients with ADHF, intravenous levosimendan administered over 6–24 h has been shown to decrease pulmonary capillary wedge pressure (PCWP) and increase cardiac output, compared both with placebo and dobutamine.[4–6] Moreover, in a retrospective analysis of the LIDO trial, the haemodynamic advantage of levosimendan over dobutamine was accentuated in the presence of β-blockers.[6] In the SURVIVE trial, levosimendan and dobutamine had similar outcome effects,[7] but post hoc analyses showed that in patients receiving concomitant β-blockers, mortality was lower for levosimendan than dobutamine.[8]

Levosimendan may therefore offer an important alternative for the treatment of ADHF in patients on optimal conventional treatment including a β-blocker and in need of inotropic support. Because of an active long-acting metabolite (OR-1896),[9,10] the haemodynamic effects of levosimendan continue for several days after stopping the infusion. The aim of the present study was to compare the effects of a 24 h intravenous infusion of levosimendan with a 48 h infusion of dobutamine on invasive haemodynamics in patients with ADHF on optimal therapy including a β-blocker. This was the BEAT-CHF (efficacy and safety of short-term intravenous treatment with levosimendan vs. dobutamine in decompensated HF patients treated with beta-blockers) trial.

Methods

The investigation conforms to the principles outlined in the Declaration of Helsinki[11] and the principles of Good Clinical Practice within the European Union. The protocol and its amendments were approved by the local ethics committees at each centre. All patients provided written informed consent before the performance of any study procedures.

Study population

Sixty patients (29 on levosimendan and 31 on dobutamine) aged over 18 years with ADHF of ischaemic or non-ischaemic origin, in New York Heart Association (NYHA) class III–IV, despite optimized conventional treatment for HF including a β-blocker, who had been on a stable regimen for ≥3 months at an optimal dosage (in the investigator's opinion) and who might benefit from intravenous positive inotropic agents, were enrolled in 13 centres in Sweden, Norway and Iceland. Patients were required to have a left ventricular ejection fraction (LVEF) ≤ 35% within 3 months prior to inclusion, a cardiac index < 2.5 L/min/m^2, and PCWP > 15 mmHg.

The main exclusion criteria were significant mechanical obstruction affecting ventricular filling and/or outflow, systolic blood pressure (SBP) ≤ 85 mmHg, heart rate ≥ 130 b.p.m. persistent for at least 5 min and serum potassium <3.5 mmol/L or >5.4 mmol/L (or, alternatively, plasma potassium <3.4 mmol/L or >4.9 mmol/L) at screening, or severe angina pectoris during the 6 h before baseline.

Study design

This was a multinational, double-blinded, double-dummy, parallel group phase IV study. The study consisted of a screening period of up to 24 h before initiation of treatment, a study drug infusion period of 48 h, and a follow-up period of 1 month. Patients were hospitalized at a minimum for the duration of the intravenous infusion. Randomization was stratified with respect to treatment with carvedilol, as a subgroup analysis from the LIDO trial[6] suggested that carvedilol has a different haemodynamic interaction with dobutamine when compared with other β-blockers.[12] Patients within each stratum were randomly allocated to a 24 h infusion with levosimendan or a 48 h infusion with dobutamine in a 1:1 ratio. All patients received two infusions: active treatment and a placebo for the alternative treatment.

Study medication

Levosimendan or placebo for levosimendan (Orion Pharma, Espoo, Finland) was administered as an initial loading dose of 12 μg/kg delivered over 10 min followed by a continuous infusion of 0.1 μg/kg/min for 50 min. The infusion rate was increased to 0.2 μg/kg/min for a further 23 h. If dose-limiting events (DLEs) occurred (as described below) during administration of the loading dose, the loading dose was stopped. Upon resolution, the infusion could be restarted at 0.1 μg/kg/min and increased to 0.2 μg/kg/min or reduced to 0.05 μg/kg/min as appropriate. If DLEs occurred during the infusion, the dosage could be reduced to 0.1 or 0.05 μg/kg/min.

Dobutamine (Eli-Lilly, Solna, Sweden) or placebo for dobutamine (Orion Pharma, Espoo, Finland) was given as a continuous infusion without a loading dose, starting at a rate of 5 μg/kg/min for 1 h, and increased to 10 μg/kg/min for a further 47 h, unless the dosage was not tolerated during the first 60 min. If DLEs occurred during the infusion, the dosage could be reduced to 5 or 2.5 μg/kg/min.

The optimal dosage of β-blocker administered at baseline was, as far as possible, to be maintained throughout the study. If possible, diuretic treatment regimens were to remain constant.

DLEs were defined as symptomatic hypotension, heart rate ≥ 140 b.p.m. constantly over 5 min, development of angina pectoris, electrocardiographic signs of significant myocardial ischaemia, or suspicion of myocardial infarction, development of new malignant tachyarrhythmia, or excessive diuresis that was sustained despite reducing the dosage or discontinuing administration of diuretics. Hypotension was defined as 'asymptomatic' if systolic BP was ≤75mmHg but the patient had no symptoms, or 'symptomatic' if the patient had symptoms attributable to low BP in the opinion of the investigator irrespective of the blood pressure measurement. In all cases hypotension was confirmed by a second reading.

In case of worsening of ADHF, the infusion rates were to be adjusted and/or rescue treatment (e.g. dopamine or epinephrine) administered.

The infusions of both study drugs were to be discontinued permanently if the patient experienced a major cardiovascular event or serious adverse event (AE).

Efficacy and safety assessments

Haemodynamic variables were measured at baseline and at 0.5, 2, 24, and 48 h after the start of the infusion using a Swan-Ganz catheter via central access. Measurements included PCWP and mean right atrial pressure (mRAP). Arterial blood pressure was measured via an arterial catheter. Systemic vascular resistance and pulmonary vascular resistance were calculated from the measured parameters. Cardiac index was calculated from cardiac output, which was measured using the

thermodilution technique via the Swan-Ganz catheter. Mixed venous oxygen saturation (SvO_2) was measured by analysis of blood gases.

NYHA class was assessed at baseline, 48 h after the start of infusion, and at 1-month follow-up. HF symptoms (dyspnoea and fatigue) were assessed by both the patients and investigators using a 7-point scale of responses from markedly improved to markedly worse, at 48 h after the start of the infusion and at 1-month follow-up.

Changes in β-blocker therapy during the study and the need for rescue medication or other interventions were documented. Timing, duration, and the primary reason for admission for hospitalizations occurring after discharge from the initial hospitalization to the 1-month follow-up were documented and used to calculate days alive and out of hospital.

B-type natriuretic peptide (BNP) plasma levels were analysed by radioimmunoassay at a central laboratory from samples collected at baseline, 24, and 48 h after the start of the infusion and at 1-month follow-up.

Safety was followed by repeated heart rate and blood pressure measurements, AE inquiries, ECG assessments, and laboratory variables.

Statistical methods

Sample size estimation was done using nQuery Advisor® 4.0 (Statistical Solutions, Saugus, MA, USA). With a sample size of 27 in each group there was 80% power to detect a 0.75 L/min difference between treatment groups in change in mean cardiac output at two-sided 5% significance level. Calculation assumed common standard deviation (SD) of 0.95 L/min. The planned sample size in this phase IV study was originally 110 patients; however, owing to slow recruitment and on the recommendation of the steering committee, this was reduced to 60 patients (30 patients per treatment group).

The primary objective was to describe the changes, from baseline to 24 h after the start of study drug infusion, in cardiac index, and PCWP and to compare the changes between the treatment groups. With the Hochberg method, significance could be declared for both of the primary haemodynamic variables if both had two-sided $P \leq 0.050$.[13] Significance could also be declared for one of the primary haemodynamic variables if two-sided $P \leq 0.025$ was reached for one of the variables and $P > 0.05$ for the other variable. The intention-to-treat (ITT) population, comprising all randomized patients who received study medication, was used in all efficacy analyses.

Changes in both of the haemodynamic variables of the primary analysis were compared between treatment groups using analysis of variance (ANOVA) with effects for treatment, use of carvedilol at baseline and treatment-by-usage of carvedilol interaction (i.e. using an adjusted model) or the non-parametric Mann–Whitney (M-W) depending on whether the data were normally distributed. Analyses were repeated using an unadjusted model. With the exceptions listed below, secondary variables were described and analysed in the same way as the primary efficacy variable.

The changes in NYHA class from baseline to the 1-month follow-up visit were analysed using odds ratio and 95% confidence intervals (95% CIs). The change in patients' and investigators' assessment of fatigue and dyspnoea were compared between groups using the Cochran-Mantel-Haenszel row-mean score test. The proportion of patients with treatment discontinuations and/or need for rescue therapy owing to lack of efficacy at any time point were analysed using risk-ratio and 95% CIs.

For the most frequently reported AEs, the incidence was compared between groups using the χ^2 test. All statistical analyses were performed using SAS® 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient disposition and baseline characteristics

Patient enrolment was from November 2002 until April 2005. Sixty patients were randomized and patient disposition is summarized in *Figure 1*. Demographic and baseline HF characteristics were similar in both treatment groups (*Table 1*).

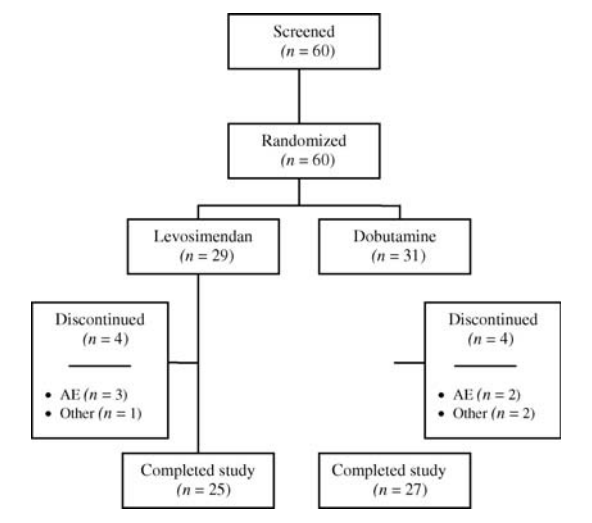

Figure 1 Patient disposition.

Table 1 Patient characteristics at baseline (ITT population)

Characteristic	Levosimendan (*n* = 29)	Dobutamine (*n* = 31)
Age (years), mean (SD)	70 (10)	71 (11)
Sex male, *n* (%)	26 (90)	25 (81)
BMI (kg/m^2), mean (SD)	27.0 (5.4)	25.7 (4.0)
Ethnic origin, *n* (%)		
Asian	0 (0)	1 (3)
Caucasian	29 (100)	27 (87)
Hispanic	0 (0)	1 (3)
Other	0 (0)	2 (7)
NYHA class, *n* (%)		
III	17 (59)	16 (52)
IV	12 (41)	15 (48)
Primary aetiology, *n* (%)		
Ischaemic	22 (76)	18 (58)
Non-ischaemic	5 (17)	11 (36)
Other	2 (7)	2 (7)
EF (%), mean (SD)	21.2 (5.8)	21.8 (6.1)

BMI, body mass index; EF, ejection fraction; NYHA, New York Heart Association; ITT, intention-to-treat.

The majority of patients in both groups (93% of levosimendan patients and 94% of dobutamine patients) achieved the target dosage within 2 h of starting the infusion. The mean continuous infusion rate administered and the duration of infusion were 0.19 μg/kg/min (SD 0.03) and 22.8 h (SD 4.4) for levosimendan and 10.1 μg/kg/min (SD 0.41) and 46.6 h (SD 7.9) for dobutamine. In total, 25 (86.2%) levosimendan patients and 27 (87.1%) dobutamine patients underwent the 1-month follow-up visit.

Efficacy

Haemodynamic assessments

Both levosimendan and dobutamine infusions induced haemodynamic improvement (*Figure 2*). At 24 h, the mean improvement in cardiac index from baseline showed a trend in favour of levosimendan over dobutamine (M-W $P = 0.066$). At 48 h, the difference between groups was statistically significant (M-W $P = 0.037$).

At 24 h, the reduction in the mean change in PCWP from baseline was similar for levosimendan and dobutamine (ANOVA $P = 0.105$) (*Table 2*). At 48 h, the difference between the groups in the mean change in PCWP from baseline was more marked for levosimendan than for dobutamine (ANOVA $P = 0.015$) (*Figure 2*).

Changes in other haemodynamic variables were generally consistent with the findings for the co-primary analyses (*Table 2*). There was no marked difference between the groups for the change in mRAP or SvO_2 from baseline.

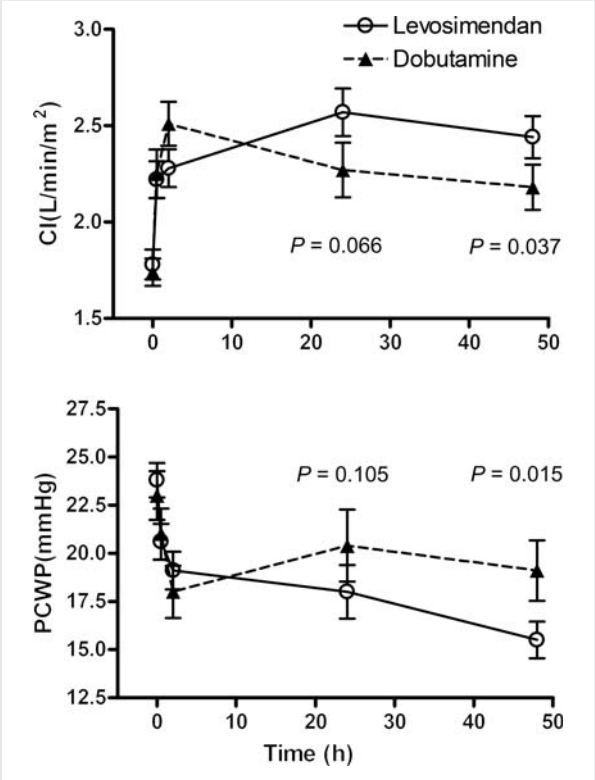

Figure 2 Mean cardiac index and pulmonary capillary wedge pressure from baseline to 48 h after the start of the study drug infusion [intention-to-treat (ITT) population].

Symptomatic improvement, hospitalizations, and concomitant medications

There was no difference between the groups in the change in NYHA class from baseline at 48 h and at 1-month follow-up.

The patients reported similar improvements in HF symptoms at 24 and 48 h in the levosimendan and dobutamine groups. According to the investigators' assessments of both fatigue and dyspnoea, the differences between the groups at 24 h were statistically significant; 93% of patients in the dobutamine group vs. 62% in the levosimendan group were reported to have improvement in fatigue ($P = 0.010$), and 87% vs. 76%, respectively, in dyspnoea ($P = 0.038$). The differences between the groups were less marked at 48 h.

There were no significant differences between groups in terms of β-blocker use at follow-up, days alive and out of hospital, and treatment discontinuations and rescue medications required owing to lack of efficacy. The mean percentage change in the dose of β-blockers from screening until the 1-month follow-up visit was 9.5% (SD 38.0) for the levosimendan group, and 21.5% (SD 128.0) for the dobutamine group ($P = 0.283$). Fourteen patients were rehospitalized (six levosimendan patients; eight dobutamine patients) and the mean number of days alive and out of hospital during the 30 days following the start of study drug infusions was similar in both treatment groups. No levosimendan patients and two dobutamine patients required rescue medication (including intravenous levosimendan, dobutamine, and crystalloids). Two levosimendan patients discontinued because of lack of efficacy compared with one dobutamine patient. The requirement for rescue medication or discontinuation owing to lack of efficacy was not statistically different between the two groups at 1-month follow-up (odds ratio 0.73, 95% CI 0.11, 4.92; $P = 0.76$, CMH test stratified for carvedilol use).

B-type natriuretic peptide

The reductions in BNP from baseline were more marked with levosimendan than with dobutamine, the difference being statistically significant at 48 h ($P = 0.03$) (*Table 3*).

Safety

Thirteen DLEs were reported for nine (31.0%) levosimendan patients and five DLEs for four (12.9%) dobutamine patients ($P = 0.09$).

The AE profiles were generally similar in both treatment groups (*Table 4*), with the exception of hypotension, which was more frequent in the levosimendan group (35% vs. 7%, respectively; $P = 0.007$) and nausea ($P = 0.032$). Cardiac arrhythmias were infrequent; ventricular tachycardia was reported in one patient from each group, and atrial fibrillation was reported in one patient from the levosimendan group. However, it should be noted that since no Holter recording or such was made during the study, this may not be entirely accurate.

Consistent with the more frequent reporting of hypotension as an AE for levosimendan patients, SBP decreased more during the infusion of levosimendan than dobutamine (*Figure 3*). The differences between groups in mean change in SBP from baseline were statistically significant at 0.5, 2, and 24 h, but not at 48 h (*Figure 3*).

Heart rate gradually increased after administration of levosimendan from 72 b.p.m. at baseline to 80 b.p.m. at 48 h. In the

Table 2 Haemodynamic values at baseline and change from baseline to 24 and 48 h (ITT population)

Time point	Levosimendan ($n = 29$)	Dobutamine ($n = 31$)	P-value[a,b]
CI (L/min/m^2)			
Baseline, mean (SD)	1.78 (0.42)	1.74 (0.40)	
24 h mean change (SD)	0.79 (0.56)‡	0.53 (0.57)‡	0.066[a]
48 h mean change (SD)	0.66 (0.63)‡	0.44 (0.56)‡	0.037[a]
PCWP (mmHg)			
Baseline, mean (SD)	23.8 (4.8)	23.0 (7.0)	
24 h mean change (SD)	−5.8 (8.2)‡	−2.6 (7.9)^{NS}	0.105[b]
48 h mean change (SD)	−8.3 (6.7)‡	−3.6 (7.6)†	0.015[b]
Heart rate (b.p.m.)			
Baseline, mean (SD)	71.7 (13.6)	74.6 (13.5)	
24 h mean change (SD)	6.5 (13.7)‡	3.0 (10.2)^{NS}	0.267[b]
48 h mean change (SD)	8.3 (8.8)‡	4.7 (9.8)†	0.166[b]
Stroke volume (mL)			
Baseline, mean (SD)	50.50 (15.33)	45.95 (15.13)	
24 h mean change (SD)	16.04 (14.42)‡	11.57 (15.84)‡	0.401[b]
48 h mean change (SD)	11.20 (14.46)‡	7.22 (13.18)†	0.660[b]
SVR ((dyne × s)/cm^5)			
Baseline, mean (SD)	1555 (519)	1742 (416)	
24 h mean change (SD)	−590 (435)‡	−477 (481)‡	0.288[b]
48 h mean change (SD)	−525 (408)‡	−426 (469)‡	0.286[a]
PVR ((dyne × s)/cm^5)			
Baseline, mean (SD)	274 (146)	348 (210)	
24 h mean change (SD)	−87 (126)†	−57 (163)^{NS}	0.652[a]
48 h mean change (SD)	−71 (152)^{NS}	−54 (149)^{NS}	0.897[b]
mRAP (mmHg)			
Baseline, mean (SD)	13.4 (6.6)	12.6 (5.7)	
24 h mean change (SD)	−3.4 (5.0)‡	−4.0 (4.8)‡	0.732[a]
48 h mean change (SD)	−3.9 (6.1)‡	−2.9 (5.5)†	0.692[a]
SvO_2 (%)			
Baseline, mean (SD)	58 (12)	58 (9)	
24 h mean change (SD)	6.9 (13)‡	8.1 (7.3)‡	0.703[a]
48 h mean change (SD)	8.0 (10)‡	6.0 (6.4)‡	0.417[b]

CI cardiac index; PCWP pulmonary capillary wedge pressure; SVR systemic vascular resistance; PVR pulmonary vascular resistance; mRAP mean right arterial pressure; SvO_2 mixed venous oxygen saturation; NS, non-significant.
Statistical testing is performed between-treatment groups at given time ([a]M-W test; [b]ANOVA) and within-treatment groups as baseline vs. post drug using ANOVA ($^{\dagger}P < 0.05$; $^{\ddagger}P < 0.01$; $^{NS}P < \geq 0.05$).

dobutamine group, HR was 75 b.p.m. at baseline, peaked at 2 h (84 b.p.m.), and decreased to 79 b.p.m. at 48 h. The difference at 48 h was not statistically significant.

Two patients died during the study (one levosimendan, one dobutamine) and one patient (levosimendan group) died three days after discontinuing the study.

There were no significant differences in any of the laboratory variables measured.

Discussion

The primary objective of this study was to demonstrate a significantly greater improvement in PCWP and/or cardiac index at 24 h after the start of the infusion for levosimendan compared with dobutamine in patients who had NYHA stage III–IV ADHF despite optimal oral treatment, including a β-blocker. Both treatments induced haemodynamic improvement in these patients. Even though the primary objective was not met, a trend in favour of levosimendan was seen at 24 h after the start of study drug infusion. This was consistent with previous findings in the LIDO study, where levosimendan showed a significantly greater decrease in PCWP and a significantly greater increase in cardiac output.[6] Further, this difference became significant at 48 h, even though levosimendan was only administered for 24 h and dobutamine for 48 h. Two factors, the concomitant β-blockade diminishing effect on dobutamine and the formation of an active metabolite of levosimendan, probably account for these findings.

Although pharmacokinetic parameters were not measured in the present study, previous studies have shown that levosimendan has an active metabolite (OR-1896), which has a considerably

Table 3 B-type natriuretic peptide values (ng/mL) at baseline, change from baseline to 24, and 48 h after the start of the infusion, and at the 1-month follow-up (ITT population)

Time point	Levosimendan ($n = 29$)	Dobutamine ($n = 31$)	*P*-value[a]
BNP (ng/mL)			
Baseline, mean (SD)	1114 (1214)	979 (748)	
24 h mean change (SD)	−432 (727)	−324 (533)	0.248
48 h mean change (SD)	−507 (785)	−260 (475)	0.029
1 month mean change (SD)	−206 (1094)	52 (471)	0.138

[a]ANOVA.

Table 4 Incidence of adverse events (>2 subjects) from the start of study drug infusion to the 1-month follow-up visit (ITT population)

Event	Number (%) of subjects		
	Levosimendan ($n = 29$)	Dobutamine ($n = 31$)	*P*-value[a]
Total subjects with at least 1 AE	22 (75.9)	21 (67.7)	
Hypotension	10 (34.5)	2 (6.5)	0.007
Insomnia	4 (13.8)	3 (9.7)	0.620
Nausea	4 (13.8)	0 (0.0)	0.032
Cardiac failure	3 (10.3)	4 (12.9)	0.758
Headache	3 (10.3)	1 (3.2)	0.269
Urinary tract infection	3 (10.3)	1 (3.2)	0.269
Hypokalaemia	1 (3.4)	2 (6.5)	0.594
Cough	1 (3.4)	2 (6.5)	0.594

[a]χ^2 test, where the incidence was more than two subjects in at least one treatment group.

longer elimination half-life than the parent drug (about 80 vs. 1 h).[9,10] In line with the present findings, a 24 h levosimendan infusion has previously been shown to maintain the haemodynamic effects at a similar level at 24 and 48 h,[10] with the effects lasting for about 7 days.[14] The haemodynamic effects of dobutamine may diminish owing to tachyphylaxis,[15,16] but in the present study this was not seen, and cardiac index and PCWP were at similar levels at 24 and 48 h in the dobutamine group.

The haemodynamic changes observed at 24 h in the β-blocked patients in the LIDO study showed an improvement in cardiac index, which was similar in magnitude to the improvement observed in this study. However, in the LIDO study, the dobutamine patients did not respond as well as the levosimendan patients. In contrast, in the present study, cardiac index improved to a similar extent in both the levosimendan and dobutamine groups at 24 h. The total dose of dobutamine over the first 24 h of the infusion was somewhat higher in the present study compared with LIDO, so the higher dosage might explain the greater improvements in the dobutamine group in the present study. However, a more likely explanation for these minor differences between the groups is the relatively small number of patients in both the LIDO subgroup and the present study.

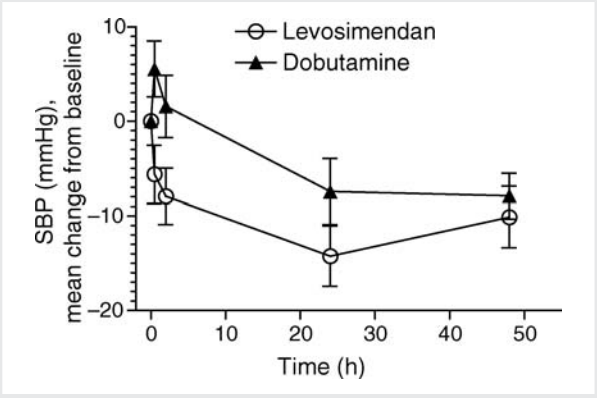

Figure 3 Mean change from baseline in systolic blood pressure at baseline and at 0.5, 2, 24, and 48 h after start of the study drug infusion (ITT population).

Previous studies with levosimendan have demonstrated a reduction in plasma BNP concentrations, correlating with improvements in haemodynamic status in ADHF patients.[7] Consistent with these findings, BNP levels were lower during levosimendan treatment and the difference between treatments was statistically significant at 48 h in the present study.

In both treatment groups, the majority of patients reported either improved or unchanged HF symptoms (dyspnoea and fatigue). According to the physician's assessment, a greater proportion of patients in the dobutamine group were reported to have an improvement in these symptoms. The pharmacodynamic profile of dobutamine is consistent with a short-term experience of improvement. As patients in the study were mostly confined to bed rest, changes in dyspnoea rating should be interpreted with caution.

Consistent with the more frequent reporting of hypotension as an AE for levosimendan patients (35%), SBP decreased more during the infusion of levosimendan than dobutamine. This is in contrast to the SURVIVE study, where a similar proportion of patients experienced hypotension as an AE (16% for levosimendan and 14% for dobutamine). Generally, the tolerability of levosimendan and dobutamine were similar and mortality rates were low in both groups.

In the present study, mean heart rate increased with both levosimendan and dobutamine (8 and 5 b.p.m. at 48 h, respectively), with the highest heart rate observed during dobutamine infusion at 2 h, similar results were reported in the LIDO and SURVIVE studies.

Limitations

Because of slow recruitment, the study was terminated before the prespecified number of patients had been included, which weakened the scientific conclusions of the study. The two study drugs, levosimendan and dobutamine have different pharmacokinetic and pharmacodynamic profiles, resulting in a different duration of effect. This was compensated for by administering the two drugs for different lengths of time, but it is possible that the duration of effect may still have been different.

Conclusions

In conclusion, in HF patients experiencing acute decompensation while receiving optimal β-blocker therapy, a 24 h levosimendan infusion achieved haemodynamic and neurohormonal improvement that lasted beyond the infusion period. The improvement with levosimendan was at least comparable to a 48 h dobutamine infusion at 24 h after the start of the infusion and superior at 48 h. This lasting effect is corroborated by clinical observations indicating a practical advantage over dobutamine.

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