Effectiveness and Safety of Levosimendan in Clinical Practice [13]

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ABSTRACT

Background: In previous randomized studies levosimendan improved hemodynamics and clinical course, with a still unclear effect on prognosis. There are, however, few data regarding its effects when used in daily practice.
Aims: We evaluated the clinical effectiveness and safety of levosimendan in the treatment of acute systolic heart failure (SHF) in daily practice conditions.
Methods: In this prospective, multicenter, nonrandomized trial, a continuous infusion of levosimendan (0.05 µg/kg/min-0.2 µg/kg/min) was administered for 24 hours. An optional loading dose of 12 µg/kg over 10 minutes was used. The primary combined endpoint of clinical effectiveness (as defined by a eight-variable clinical score) and safety (defined by the absence of serious adverse events) was assessed at 24 hours after the beginning of treatment; a second similar primary combined endpoint was assessed at 5 days.
Results: One hundred and twenty-nine consecutive patients requiring inotropes despite optimal oral background heart failure therapy were recruited. The primary endpoint was reached in 80.6% at 24 hours and in 79.7% at 5 days. During the six months before levosimendan the number of patient days of hospitalization for heart failure was 14.9±14.6 versus 3.1±7.6 during the six months

RESUMO

Eficácia e segurança do levosimendam na prática clínica

Indrodução: Em estudos randomizados prévios, o levosimendan melhorou a evolução clínica e o estado hemodinâmico dos doentes, com um efeito prognóstico ainda não totalmente esclarecido. Existem, contudo, poucos dados relativos aos seus efeitos clínicos, quando usado na prática diária.
Objectivo: Avaliámos a eficácia clínica e a segurança do levosimendam no tratamento da insuficiência cardíaca aguda sistólica em condições de prática clínica diária.
Métodos: Neste estudo prospectivo, multicêntrico e não randomizado, foi administrada uma perfusão contínua de levosimendam (0,05 µg/Kg/min-0,2 µg/Kg/min) durante 24 horas. Foi administrado um bólus de 12 µg/Kg durante 10 minutos de forma opcional. O objectivo primário combinado de eficácia clínica (definido por uma pontuação de oito variáveis) e de segurança (definido pela ausência de efeitos adversos graves) foi avaliado às 24 horas após o início do tratamento; um segundo objectivo primário combinado similar foi avaliado aos cinco dias de tratamento.
Resultados: Foram recrutados 129 doentes consecutivos que necessitavam de fármacos inotrópicos apesar da terapêutica optimizada

following levosimendan (p<0.001).
Conclusions: In daily practice, levosimendan was clinically effective and safe in 80.6% and 79.7% of patients with acute SHF at 24 hours and 5 days respectively after the beginning of treatment. A marked reduction in the number of days of hospitalization for heart failure was also seen during the subsequent six months.

para a insuficiência cardíaca. O objectivo primário foi atingido em 80,6% às 24 horas e em 79,7% aos cinco dias. A média de dias de hospitalização por doente nos seis meses precedentes ao uso de levosimendam foi de 14.9±14.6 *versus* 3.1±7.6 dias nos meses subsequentes ao seu uso (p<0,001).
Conclusões: Na prática clínica diária, o levosimendam foi eficaz e seguro em 80,6% e 79,7% dos doentes com insuficiência cardíaca sistólica aguda às 24 horas e aos 5 dias, respectivamente, após o início do tratamento. Também ocorreu uma redução marcada do número de dias de hospitalização nos seis meses subsequentes.

INTRODUCTION

Inotropic agents are indicated in acute heart failure with systolic dysfunction in the presence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary edema refractory to diuretics and vasodilators at optimal doses[1,2]. However, concern exists regarding a possible negative impact on prognosis caused by inotropes acting through the adrenergic pathway[3-5], since they may induce ventricular arrhythmias and myocardial ischemia[6]. These negative effects may be linked to levels of cytoplasmic calcium and cyclic-AMP concentrations since adrenergic agonists result in an abundance of these signaling molecules[3-5]. In addition, negative prognosis following administration of adrenergic agonists, i.e. traditional inotropes, may be correlated with a disturbance of the myocardial oxygen supply/consumption balance[3,6-8]. Levosimendan acts through different mechanisms[6-8]: it increases cardiac contractility by enhancing the sensitivity of troponin C to calcium, and produces vasodilatation through the opening of ATP-sensitive potassium channels[6-8]. Levosimendan does not increase cytoplasmic calcium or cyclic-AMP concentrations and the myocardial oxygen supply/consumption balance is not disturbed[7,8]. Several recent randomized studies have addressed the clinical effects of levosimendan[9-13]. In the REVIVE study it improved the clinical course, compared to placebo, in patients with worsening heart failure[9], in the LIDO study levosimendan improved hemodynamic performance more effectively than dobutamine in patients with severe low-output heart failure[10]. In the RUSSLAN study levosimendan, as compared to placebo, did not increase the incidence of clinically significant hypotension or of myocardial ischemia (in doses up to 0.2 µg/kg/min, although higher doses did) in patients with left ventricular failure complicating an acute myocardial infarction[11]. In the latter two studies and also in CASINO[12] levosimendan reduced six-month mortality[10,11], although this was not seen when the drug was compared with dobutamine in acute decompensated heart failure in the SURVIVE study[13]. There are, however, few data regarding its clinical effectiveness and safety in an everyday clinical setting. We therefore conducted the Portuguese Study on the Tolerability, Safety and Effectiveness of Levosimendan in Daily Clinical Practice (PORTLAND) to test the hypothesis that in day-to-day practice, under less controlled conditions

than those of the above studies, levosimendan is both effective and safe for the treatment of systolic acute heart failure.

METHODS

Patients. This prospective, multicenter, nonrandomized clinical trial was performed in the intensive care units of 15 departments of cardiology or internal medicine[14].

Eligible patients were those admitted to hospital with NYHA functional class III-IV heart failure, left ventricular ejection fraction ≤0.40 and evidence of decompensation (as documented by the presence of pulmonary or systemic congestion, or symptoms and signs of low cardiac output, despite maximally tolerated oral therapy) which in the investigator's opinion would require treatment with inotropes. At screening patients should be taking an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin-II receptor antagonist (ARB), unless contraindicated or not tolerated, and optimal oral therapy for heart failure which could include beta-blockers, diuretics, digoxin and spironolactone.

Criteria for exclusion were: shock or marked hypotension (systolic blood pressure <85 mmHg) not responsive to intravenous fluids; significant uncontrolled tachyarrhythmia (rapid-response atrial fibrillation/flutter, supraventricular tachycardia, ventricular tachycardia); resting or post-infarction angina; documented history of torsades de pointes; mechanical obstruction of ventricular filling or ejection; severe renal failure of non-prerenal cause (serum creatinine >3 mg/dl); significant liver damage (liver transaminases three times above the upper normal limit) and/or liver failure (prothrombin time three seconds above the upper normal limit in the absence of anticoagulant therapy); hypokalemia (serum potassium <3.5 mEq/L) not responsive to potassium supplements; significant anemia (serum hemoglobin <9 g/dl); pregnancy or breast-feeding; hypersensitivity to levosimendan or any of its excipients.

The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964;ii:177). The study protocol was reviewed and approved by the Ethics Committee of each participating institution and all patients gave their informed consent.

Study protocol. The treatment with levosimendan started with an optional loading dose of 12 µg/kg for 10 minutes and was followed by a continuous infusion of 0.05 µg/kg/min, 0.1 µg/kg/min or 0.2 µg/kg/min of levosimendan for 24 hours, via a peripheral or central vein[11]. The decision to administer or withhold the loading dose, and the choice of the maintenance dose, were at the discretion of the investigators, based on their clinical assessment of the patients. An initial maintenance dose of 0.1 µg/kg/min was suggested; if after 30 to 60 minutes the response was considered excessive, due to the occurrence of tachycardia or hypotension, it was suggested that the dose be reduced to 0.05 µg/kg/min; if the effects persisted, the drug could be discontinued; in the event of hypotension persisting despite discontinuation of levosimendan, in principle the drug should not be replaced by another with a similar hemodynamic profile (for example dobutamine or a phosphodiesterase inhibitor [PDEI]); if the patient was dehydrated, a saline infusion was suggested. Only in cases of marked hypotension (systolic blood pressure <80 mmHg) or of less severe but symptomatic hypotension was ACEI or beta-blocker therapy modified and/or vasopressors, such as dopamine or norepinephrine, administered; in such circumstances invasive hemodynamic monitoring would be considered[11]. If the initial maintenance dose was well tolerated and a greater hemodynamic effect was desired, increasing to 0.2 µg/kg/min could be considered[11].

After the administration of levosimendan the patients underwent clinical, hematological, biochemical, urinary output and continuous ECG monitoring, together with noninvasive assessment of blood pressure, for a suggested period of 72 hours. Oximetric monitoring was also recommended. Invasive monitoring was not required.

Assessments. The patients were evaluated at baseline (before starting levosimendan) and at 24 hours and 5 days after the start of levosimendan. Further visits were performed at 3 months and at the end of the six-month follow-up. Baseline evaluation included medical history and physical examination, ECG and 2D echocardiogram and blood sampling for assessment of standard laboratory variables as detailed elsewhere[11]. At 24 hours and 5 days symptoms and signs of heart failure were assessed, adverse events,

concomitant medication and previous 24-hour urinary output were recorded, and an ECG and blood analysis were performed; arrhythmia alarms and heart rate and blood pressure trends of the previous 24 hours were also reviewed[11]. The number and length of hospital readmissions and mortality were recorded at three- and six-month evaluations[11].

Study endpoints. The proportion of patients in whom levosimendan was both clinically effective and safe at 24 hours after the initiation of the infusion was one of the two primary endpoints of the study; the second primary endpoint was the proportion of patients in whom both clinical effectiveness and safety were observed at 5 days after the initiation of levosimendan infusion.

Table I Assessment criteria for clinical parameters used to evaluate clinical effectiveness of the treatment at 24 hours and 5 days versus baseline.

Group I – subjective parameters			
	Improvement	No change	Worsening
NYHA functional class	↓≥1 class	←→	↑ ≥1 class
Patient self-evaluation	↓≥1 class	←→	↑ ≥1 class
Group II – objective parameters			
	Improvement	No change	Worsening
Body weight	↓≥1 kg	←→	↑ ≥1 kg
Pulmonary congestion	↓ ≥1 class	←→	↑ ≥1 class
Previous 24-hour urine output	↑ ≥20%	←→	↓ ≥20%
Serum creatinine	↓ ≥0.1 mg/dl	←→	↑ ≥0.1 mg/dl
Oral HF medication	Initiation of ACEI or BB	←→	---
IV HF medication	Suspension of inotrope or vasopressor or ↓ of its previous dose	←→	1- Addition of inotrope or vasopressor or ↑ of its previous dose. 2- Need for hemodynamic or ventilatory mechanical support. 3- Initiation of iv diuretics more than 72 hours after start of levosimendan

ACEI: angiotensin-converting enzyme inhibitors; BB: beta-blockers; HF: heart failure; IV: intravenous; ↑: increase; ←→: unchanged; ↓: decrease

A score incorporating two subjective and six objective parameters assessed clinical effectiveness. *Table I* lists these parameters and the assessment criteria for each at 24 hours and at 5 days versus baseline values. Levosimendan was considered to have produced clinical improvement, i.e. was effective, when there was improvement in one or more group I (subjective) parameters, accompanied by improvement in one or more group II (objective) parameters, as long

as all other parameters remained unchanged[11]. The safety of levosimendan was established by the absence of any serious adverse event with a probable or undetermined causal relationship with the drug.

In order to evaluate the primary combined endpoint the patients were distributed in a 2x2 table according to the treatment outcome in relation to clinical effectiveness and safety (*Table II*). Achievement of the primary endpoint was calculated by the frequency in cell A.

Table II Distribution of patients according to treatment outcome in relation to safety and clinical effectiveness

		Safety	
		Without SAE	With SAE
Clinical effectiveness	Clinical improvement	A	D
	No clinical change	B	E
	Clinical deterioration	C	F

SAE: serious adverse event with a probable or undetermined causal relationship with levosimendan

Prospectively defined secondary endpoints were changes from baseline to 24 hours and from baseline to 5 days in: NYHA functional class; patient self-evaluation symptom class (see definitions below); body weight; pulmonary congestion (see definitions below); previous 24-hour diuresis; serum creatinine; oral medication for heart failure; and intravenous medication for heart failure. Additional secondary endpoints were: tolerability of levosimendan (defined by occurrence of adverse effects); safety of levosimendan (defined by occurrence of serious adverse events with a probable or undetermined causal relationship with levosimendan); the number and length of hospital readmissions due to heart failure during the six months following levosimendan (compared with the six months prior to treatment).

Definitions. In order to establish a classific-ation of patient self-evaluation the patients were simply asked "How do you feel?" (no prompting was given) and the answer was classified as follows: class 1 – very well; class 2 – well; class 3 – reasonable; class 4 – poorly; class 5 – very poorly. The presence of rales over the lung fields detected by auscultation was used to classify pulmonary congestion as follows: class 0 – none; class 1 – present in the basal third of the pulmonary fields; class 2 – present in two thirds; class 3 - present in three thirds.

Statistical analysis. Quantitative variables

(continuous and discrete) were described by calculating the frequency of observations (n), means and standard deviation. They were compared between groups using the Student's t test adjusted for paired samples or the Wilcoxon non-parametric test when the hypothesis of normality was rejected. This was analyzed using the Shapiro-Wilks test. The tests were two-tailed, with a level of significance of five percent. Qualitative variables (ordinal and nominal) were described by calculating the frequency of observations (n) and relative frequency (%). Ordinals were compared using the Wilcoxon non-parametric test. Nominals were analyzed by the McNemar test for paired samples. The tests were two-tailed, with a level of significance of five percent. A Kaplan-Meier curve was used to describe the distribution of time to death from any cause in the six months following treatment with levosimendan.

RESULTS

Clinical characteristics. A total of 129 consecutive patients were enrolled between November 15 2001 and December 31 2003. Baseline characteristics are summarized in *Table III*. At baseline 66% of the patients were taking iv diuretics and 47% were taking nitrates.

Table III **Baseline characteristics of the patients.**

Number of patients	129
Age (yr)	63±14
Gender (male/female)	76%/24%
Cause of acute heart failure: ischemic/other	48%/52%
Acute decompensation of chronic heart failure	81%
Acute *de novo* heart failure	19%
Number of HF admissions per patient during the previous year	2±1.2
NYHA functional class III/IV	19%/81%
Left ventricular ejection fraction (%)	24±7
Systolic blood pressure (mmHg)	104±17
Diastolic blood pressure (mmHg)	64±14
Heart rate (beats/min)	86±18
Serum creatinine (mg/dl)	1.54±0.66
Serum sodium (mEq/l)	135±6.0
ACEI/ARB	92%
Beta-blockers	45%
Spironolactone	58%
Digitalis	58%
Oral diuretics (other than furosemide)	22%
IV diuretics	66%
Nitrates	47%
IV inotropes (total)	19%
Dobutamine alone	8%
Dopamine alone	8%
Dobutamine in combination with dopamine	3%

Data are presented as mean value ±SD.

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor antagonists; HF: heart failure; IV: intravenous; NYHA: New York Heart Association.

Levosimendan infusion. Levosimendan was used in 104 (81%) patients as first line therapy, in 16 (12%) to substitute other ongoing inotropes and in nine (7%) in combination with other inotropes. No invasive monitoring was performed in 61% of cases. In 35% of the patients no loading dose of levosimendan was used, due to baseline systolic blood pressure values approaching 85 mmHg or to a baseline clinical status that, in the investigators' opinion, did not require a rapid peak of levosimendan at the cost of the risk of hypotension. The maintenance dose was 0.05 µg/kg/min in 16%, 0.1 µg/kg/min in 71% and 0.2 µg/kg/min in 13% of the patients (Figure 1). The mean maintenance dose was 0.1±0.04 µg/kg/min. Only eight (6%) did not complete the 24-hour infusion, with six of these cases due to hypotension.
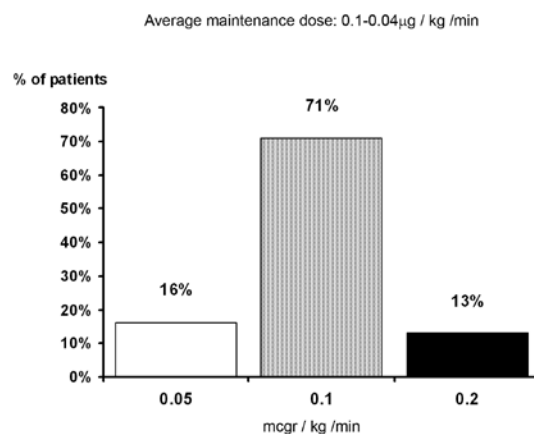

Figure 1. **Maintenance dose of levosimendan infusion.**

Endpoints. The primary combined endpoint of clinical effectiveness and safety was reached in 104 (80.6%) of 129 patients (95% CI: 73.8%-87.4%) at 24 hours and in 102 (79.7%) of 128 patients (95% CI: 73.2%-87.1%) at 5 days; in one patient information regarding the primary endpoint at 5 days was not available.

During the first 24 hours after the initiation of levosimendan there was a rapid increase in diuresis (urine output = 2512±1107 ml) in formerly oliguric patients and a fall in serum creatinine levels that was maintained at day 5 (**Table IV**). A consistent improvement in each of the individual subjective and objective parameters used to evaluate clinical effectiveness was observed at 24 hours and at 5 days compared to baseline (**Table IV**). As a consequence, due to the improvement in clinical condition, at 24 hours

occurred in eight (6%) patients (*Table V*) during the first 5 days of follow-up: in 5 (63%) cases they consisted of hypotension that was considered sufficiently severe to endanger the patient's life and thus required therapy. All these cases of severe hypotension resolved favorably.

During the first 5 days of follow-up heart rate did not increase (*Table VI*), nor did the incidence of supraventricular arrhythmias, or nonsustained ventricular tachycardias (*Table VII*). QTc interval showed no significant change during this period;

Table IV Clinical effectiveness of the treatment: improvement in subjective and objective parameters observed at 24 hours and at 5 days compared to baseline.

	Baseline	24 hours	p	5 days	p
NYHA functional class	3.8±0.5	3.1±0.7	p<0.001	2.7±0.8	p<0.001
Patient self-evaluation class	4.5±0.6	3.5±0.9	p<0.001	2.9±1.1	p<0.001
Body weight (kg)	69.5±11.0	67.9±10.9	p<0.001	67.3±10.7	p<0.001
Pulmonary congestion class	1.2±0.8	0.6±0.6	p<0.001	0.4±0.6	p<0.001
Previous 24-hour urine output (ml)	1482.0±817.1	2512.0±1106.8	p<0.001	1947.2±1050.1	p=0.001
Serum creatinine (mg/dl)	1.54±0.66	1.44±0.67	P=0.001	1.41± 0.64	p=0.009

NYHA: New York Heart Association.

Table V Severe adverse events with a probable or uncertain causal relationship with levosimendan during the first 5 days of follow-up

Type of SAE	Number of patients with SAE	Relationship of SAE with levosimendan
Severe hypotension	5	Probable: 3 cases. Uncertain: 2 cases
Severe hypokalemia	1	Probable
Ventricular fibrillation	1	Uncertain
Worsening of HF+VF	1	Uncertain

HF: heart failure; SAE: Serious adverse event with a probable or undetermined causal relationship with levosimendan; VF: ventricular fibrillation

after the initiation of levosimendan 27 (20.9%) patients showed an improvement in therapy profile, as defined in Table I: 19 of the 25 (76%) patients receiving inotropes at baseline were no longer receiving these drugs at 24 hours; despite the baseline severity of acute heart failure and the fact that at baseline 92% of patients were already taking an ACEI/ARB, and 45% were taking a beta-blocker, at 24 hours these drugs had been initiated in an additional 11 (8.5%) patients (three of whom belonged to the previous group of 19 that had stopped inotropes). At 24 hours there was no change in the number of patients on iv diuretics compared to baseline (p=0.180) and fewer patients were taking iv nitrates compared to baseline (p=0.008).

Severe adverse events with a probable or uncertain causal relationship to levosimendan

at 24 hours, but not at 5 days, serum potassium levels were lower than at baseline; serum hemoglobin showed a modest decrease during the first 5 days of follow-up (*Table VI*).

During the first 24 hours we observed a decrease in systolic blood pressure (SBP) (*Table VI*) and an increase in the incidence of significant hypotensive episodes (SBP <80 mmHg for more than three minutes) (*Table VII*). Only two of these were symptomatic (dizziness and syncope). In the majority of the significant hypotensive episodes no therapy was needed; levosimendan was withdrawn in six of these patients, in five of whom an iv saline infusion was initiated; in four cases dopamine or norepinephrine were used. All significant hypotension episodes resolved favorably. The excess in hypotensive episodes disappeared after day 1 (*Table VII*) and systolic

Table VI Heart rate, systolic blood pressure, QTc, serum potassium and hemoglobin at 24 hours and at 5 days compared to baseline.

	Baseline	24 hours	p	5 days	p
Heart rate (beats/min)	86±18	85±16	p=0.150	83±15	p=0.086
Systolic blood pressure (mmHg)	104±17	100±16	p=0.009	101±17	p=0.079
QTc (ms)	425±48	430±48	p=0.100	427±42	p=0.747
Serum potassium (mmol/l)	4.4±0.7	4.0±0.4	p<0.001	4.2±0.5	p=0.057
Hemoglobin (g/dl)	12.7±1.9	12.2±1.7	p<0.001	12.2±1.8	p<0.001

Table VII Supraventricular arrhythmias (atrial fibrillation/flutter, or supraventricular tachycardia), nonsustained ventricular tachycardias, significant hypotensive episodes (systolic blood pressure <80 mmHg for >3 min) and angina during the first 24 hours after levosimendan and during the period between 24 hours after levosimendan and day 5, compared to the 24 hours before levosimendan.

	24h before LEVO	24h after LEVO	p (24h after LEVO vs. 24h before LEVO	From 24h after LEVO to day 5	p (From 24h after LEVO today 5 vs. 24h before LEVO)
SVA (% of patients)	29%	27%	p=0.371	30%	p=0.999
NSVT (% of patients)	12%	10%	p=0.772	8%	p=0.227
SHE (% of patients)	10%	31%	p<0.001	11%	p=0.791
Angina (% of patients)	5%	1%	p=0.125	3%	p=0.687

LEVO: levosimendan; NSVT: nonsustained ventricular tachycardias; SHE: significant hypotension episodes; SVA: supraventricular arrhythmias.

blood pressure at day 5 was similar to that at baseline (*Table VI*). The number of patients presenting angina did not increase significantly during the initial 5 days of follow-up (*Table VII*). Only one patient had a new onset of angina: this was a post-myocardial infarction angina, occurring at day four after levosimendan, which was reported by the investigators as unlikely to be related to the drug administration.

The median duration of the index hospitalization (when levosimendan was administered) was six days (minimum two and maximum 60 days), three of which were in intensive care units (minimum one and maximum 24 days). In 77% of patients the index hospitalization was less than ten days.

Comparing the six months before with the six months after the initiation of levosimendan therapy (in patients alive without a heart transplant or other cardiac surgery, at the end of the six-month follow-up and in whom heart failure was present since at least six months before levosimendan), the number of heart failure hospitalizations per patient was 1.3±1.0 versus 0.4±0.7 (p<0.001); the number of days of hospitalization for heart failure per patient was 14.9±14.6 versus 3.1±7.6 (p<0.001); the percentage of patients hospitalized at least once was 81% before versus 29% after levosimendan (p<0.001).

The percentage of patients who died or received heart transplants was 21% and 29% at 3 months and six months of follow-up respectively.

DISCUSSION

The need for observational studies. There is frequently a delay of several years before the positive results of randomized clinical trials (RCTs) are translated into routine clinical practice[15]. Among other reasons, this probably stems from the fact that clinicians often feel that the non-selected patients they deal with in everyday practice are not comparable to the highly selected populations of clinical studies[16-18]. Although these trials have led to major advances in the treatment of heart failure, some authors believe that we should nevertheless recognize their limitations[16-18]. These relate to the rigorous selection of the patients included and therefore in these authors' opinion studies involving patients who are more typical of those encountered in routine practice are required[16-18]. Another important issue is the so-called external validity of RCTs, that is, whether or not their results apply to a similar population in the community[19]. Apparently this is not always the case[19]. One explanation is that patients included

in the trials received better medical care; the standard of care in a trial may not reasonably be expected in practice[19]. In Desmond Julian's opinion "we must be circumspect in translating trials into clinical practice"[19]. This reinforces the role of observational studies.

Randomized studies of levosimendan in acute heart failure. Although objective evidence in favor of levosimendan has accumulated in recent years[6-8,10,11], some cooling in enthusiasm regarding this drug occurred after the presentation of neutral results on mortality, when levosimendan was compared with dobutamine in the SURVIVE study[13]. However, other recent trials showed that levosimendan was well tolerated in patients after an acute myocardial infarction[11], and in chronic decompensated heart failure[10], had a stronger hemodynamic effect than dobutamine[10] (and this effect, unlike with dobutamine, was not hampered by beta-blockers), induced a more marked and sustained decrease in BNP levels than dobutamine[13], improved clinical course[9], had a favorable impact on hospitalizations[9,10] and was cost-effective versus dobutamine[20] and, in LIDO and CASINO[9,12], when compared with dobutamine, and used in moderate doses, had a positive impact on prognosis. The European Society of Cardiology's guidelines on acute and on chronic heart failure incorporate some of these findings[1,21]. However, these developments have yet to be widely implemented in clinical practice. The purpose of our study was to determine whether the benefits demonstrated in randomized studies would translate into two outcomes that are important for physicians and their patients in day-to-day practice conditions: clinical improvement and absence of serious adverse events.

Primary endpoint. The recent European Society of Cardiology guidelines on acute heart failure[1] indicate that, together with an improvement in hemodynamic parameters, the immediate goals for the treatment of acute heart failure include improvement in symptoms[1] and a reduction in the clinical signs of heart failure[1]. A favorable safety and tolerability profile is also essential for any treatment[1]. Our primary endpoint evaluated these clinically relevant aspects in regard to levosimendan therapy. Given that our study was nonrandomized, an effort was made to define a rigorous method of classification while maintaining simplicity in clinical criteria in

order to reduce the risk of bias in the participants. Eight subjective and objective variables were used, which, when analyzed together, enabled a more accurate understanding of the patient's response to treatment. The occurrence of serious adverse events was the chosen indicator of safety. To strengthen the latter parameter, we included not only serious adverse events considered to have a causal relationship with levosimendan, but also those for which the relation was undetermined. Data on readmissions for heart failure during a six-month period were used as a measure of medium-term outcome[1,6,22,23].

This study in the context of the literature on levosimendan. Other multicenter studies have assessed the efficacy and safety of levosimendan in patients with decompensated low output chronic heart failure. Their primary endpoints consisted of the evaluation of changes in hemodynamic parameters at six[24] or 24 hours[10,25] after the beginning of the infusion. In addition to being nonrandomized, our study differs from these works[10,24,25] by the fact that, like in REVIVE[9], it had a clinical rather than a hemodynamic primary endpoint; taking into account the pharmacokinetics of levosimendan and its metabolites[7,8] we chose to evaluate this primary combined endpoint not only at 24 hours, but also at the end of a longer period of 5 days. The population included in our study is most comparable to those in LIDO and in REVIVE in terms of baseline demographics, clinical characteristics and concomitant therapy.

Clinical effectiveness. We showed that in daily practice conditions a 24-hour infusion of levosimendan was clinically effective and safe in the majority of patients with acute systolic heart failure. These positive results were observed at 24 hours and were sustained at day 5, long after the end of the infusion. Our observations are consistent with those of the above-mentioned randomized studies[9,10,24,25]. There was an improvement in a number of meaningful clinical endpoints, including heart failure symptoms and signs and markers of renal function. The improvement in symptoms is important, since thus far there is little evidence that other inotropes can achieve this goal[8]. In REVIVE, LIDO and the study by Slawsky et al. [9,10,24], there was an improvement in heart failure symptoms with levosimendan. In the RUSSLAN[11] study, symptom improvement was not observed, but the patient population in

RUSSLAN differed from that in our study since it included only post-myocardial infarction patients and the duration of the levosimendan infusion was limited to 6 hours.

Renal function. The improvement in renal function is also important since renal deterioration is associated with increased mortality[26]. Contrary to our experience with levosimendan, other new therapies for acute heart failure, such as the vasodilator nesiritide, have a negative impact on renal function[27].

Safety. As in other studies[10,11,24,25], levosimendan was overall well tolerated by our patients. Few presented serious adverse events.

Angina. It is important to note that, unlike with other inotropes[6], the incidence of angina did not increase during the initial 5-day follow-up. This is in agreement with published data showing no increase in the recurrence of myocardial ischemia with levosimendan[11].

Arrhythmias. In our study the percentage of patients presenting atrial fibrillation or ventricular tachycardias also did not increase during the first 5 days compared to baseline. Atrial fibrillation episodes occurred more frequently with levosimendan than with placebo in REVIVE[9], and with dobutamine in SURVIVE[13]. Ventricular tachycardia was more frequent with levosimendan than with placebo in REVIVE[9], but not more than with dobutamine in SURVIVE[13]. This discrepancy between our results and those of REVIVE and SURVIVE may be related to the higher infusion rates of levosimendan used in these two studies (0.2 µg/kg/min as opposed to 0.1 µg/kg/min in PORTLAND). In fact our results were in agreement with what was expected taking into account the fact that intracellular calcium and cyclic-AMP did not increase with levosimendan[6-8] and the previous observation that there is no pro-arrhythmic effect associated with this drug[28,29].

Hypotension and hypokalemia. The most frequent adverse events in our study were hypotension and hypokalemia. These occurred most frequently during the first 24 hours after the initiation of levosimendan. Hypotension was probably related to vasodilatation and massive diuresis induced by levosimendan, and hypokalemia a consequence of the latter. Hypotension was also very frequent in REVIVE and SURVIVE (more frequent with levosimendan than with placebo, in REVIVE, but not more than with dobutamine, in SURVIVE) and was not reported in significant numbers in previous studies[10,11]. Once again the high fixed loading dose and infusion rate of levosimendan in REVIVE and SURVIVE may have played a role. It thus seems advisable to avoid loading doses in patients with systolic blood pressure <90mmHg and to use initial low infusion rates that can be increased later if hypotension does not ensue and a stronger effect is needed. Monitoring of patients' blood pressure and volume status during levosimendan therapy, and volume replacement as needed, are essential. Serum potassium monitoring is also warranted.

Hospitalizations. Hospital stay after levosimendan administration was brief, usually shorter than the 9.5 days mean duration of heart failure hospitalizations in Portugal[30]. Hospital admissions represent about 75% of total expenditure on heart failure[1,31]. Therefore, the marked reduction in heart failure hospitalizations during the subsequent 6 months indicates that levosimendan can help decrease the total costs involved in the management of patients with heart failure who need inotropic support. This decline in hospitalizations is also compatible with a beneficial effect of levosimendan on the pathophysiology of heart failure, since it differs from the high rate of hospital readmissions usually observed after acute heart failure episodes[1,32]. Since levosimendan improves hemodynamics[7,8,10,24,25] and diminishes neurohormonal activation[7-9,13,25,33], it may diminish necrosis and apoptosis during acute heart failure episodes. Thus it would be conceivable that, by protecting the myocardium, a 24-hour infusion of levosimendan could have a favorable impact on new episodes of acute heart failure, and possibly mortality, during the following 6 months. This is similar to the observation that the administration of a thrombolytic drug during an acute myocardial infarction can influence 1-year prognosis[34].

Mortality. In our study, the rate of death or transplantation at 6 months was 29%, a value similar to the 26% mortality rate at 6 months observed in the levosimendan arm of LIDO, a study that showed superiority of levosimendan versus dobutamine in terms of prognosis[10].

Limitations. Our study has several limitations.

The small sample size calls for the confirmation of the results by a larger trial.

The fact that the study was neither blind nor

controlled carries the risk that observations may, at least in part, be due to a placebo effect or to investigator bias. However, we believe our methodology helped to minimize this potential bias.

It could be argued that many patients admitted with acute heart failure improve with standard therapy. However the patients included in our study were judged by the investigators to need inotropic therapy precisely because they were not improving with standard therapy, i.e. iv diuretics or nitrates. Most of the improvement in the measured subjective and objective parameters occurred during the first 24 hours after the initiation of levosimendan (*Table IV*). At 24 hours there was no increase in the number of patients on iv diuretics and fewer patients were on iv nitrates compared to baseline. So the temporal relationship between clinical improvement and levosimendan administration is, in the present case, in favor of the existence of a causal relationship.

Concomitant inotropes. Since 25 (19%) patients were on concomitant dobutamine and/ or dopamine at baseline (*Table III*) it could be questioned whether the results observed at 24 hours and 5 days can be attributed to levosimendan alone or to the other inotropes. Several considerations are useful when analyzing this issue: 1 - The half-life of dobutamine is 2.4±0.7 minutes and that of dopamine is 120 minutes[35]. 2 - The half-life of levosimendan is 1.1±0.2 hours at a regimen of 0.05 µg/kg/min[36], which means that a steady state concentration is reached at 4 hours after the beginning of the infusion[8,37]. 3 - Levosimendan has an active metabolite, OR-1896, with peak serum concentration occurring one to two days after the cessation of a 24-hour infusion[8]; it has an elimination half-life of approximately 80 hours[8], allowing the pharmacologic effects to persist for approximately 1 week[8]. 4 - In all but one of the 16 (12%) patients in whom levosimendan was used to replace other inotropes, these agents were stopped 2-4 hours after the initiation of levosimendan. Considering points 1 and 2, the effects observed in these 15 patients at 24 hours and 5 days cannot plausibly be attributed to the inotropes that were replaced by levosimendan, since their pharmacological action had ended long before. The remaining patient maintained dopamine throughout the 5-day follow-up and reached the primary combined endpoint at 24 hours and at day 5. 5 - As to the 9 (7%) patients in whom levosimendan was used in combination with other inotropes, 5 maintained the inotropes at 24 hours (three of whom reached the primary endpoint at 24 hours) and four were still taking inotropes at day 5, none of whom reached the primary endpoint at that time. To summarize, only four (4%) of the 104 patients reaching the primary endpoint at 24 hours, and one (1%) of the 102 that did the same at 5 days, were taking a concomitant inotrope at that point. We cannot exclude the possibility that, in these few patients, the results were due to the combination of the effects of levosimendan with those of the other concomitant inotropes. However, the percentage of patients reaching the primary endpoint who were under the effect of levosimendan and another inotrope is so small that it is hardly conceivable that the overall results of the study are not due to levosimendan and its metabolites.

CONCLUSIONS

Previous double-blind, randomized, controlled studies showed that levosimendan had a positive impact in hemodynamics and clinical course, with a still unclear effect on prognosis[9-13,24,25]. Our study shows that clinical efficacy and safety, seen when levosimendan was used at moderate doses in randomized studies, can be observed in day-to-day practice conditions, when the infusion regimens and the optional use of a loading dose of the drug are adapted to the patients' condition. The fact that it was possible to administer levosimendan without invasive monitoring in the majority of patients shows that the use of the drug can be safely extended to centers with less extensive monitoring capabilities.

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APPENDIX

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REFERENCES

1. Nieminen MS, Böhm M, Cowie MR, et al, on behalf of The Task Force on Acute Heart Failure of the European Society of Cardiology. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. Eur Heart J 2005;26:384-416.

2. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA Guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). J Am Coll Cardiol. 2004;44:671-719.

3. Thackray S, Eastaugh J, Freemantle N, Cleland JGF. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure: a meta-regression analysis. Eur J Heart Fail 2002;4(4):515-31.

4. Hampton JR, van Veldhuisen DJ, Kleber FX, et at. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure: Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II). Lancet 1997;349:971-77.

5. Packer M, Carver JR, Rodeheffer RJ, et at. Effect of oral milrinone on mortality in severe chronic heart failure: the

PROMISE Study Research Group. N Engl J Med 1991;325:1468-75.

6. Greenberg B, Borghi C, Perrone S. Pharmacological approaches for decompensated heart failure: a role for the calcium sensitizer, levosimendan? Eur J Heart Fail 2003;5:13-21.

7. Figgitt DP, Gillies PS, Goa KL. Levosimendan. Drugs 2001;61(5):613-627.

8. Cleland JGF, McGowan J. Levosimendan: a new era for inodilator therapy for heart failure. Curr Opinion Cardiol 2002;17:257-265.

9. Packer M and the REVIVE II Trial Investigators. REVIVE II: multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Circulation 2005;112:3363[abstr].

10. Follath F, Cleland JGF, Just H, et al for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360:196-202.

11. Moiseyev VS, Poder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. Eur Heart J 2002;23:1422-32.

12. Cleland JGF, Ghosh J, Freemantle N, Kaye GC, Nasir M, Clark AL, Coletta AP. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-LIPIDS and cardiac resynchronisation therapy in heart failure. Eur J Heart Fail 2004;6:501–508.

13. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs Dobutamine for patients with Acute Decompensated Heart Failure. The SURVIVE Randomized Trial. JAMA 2007;297:1883-91.

14. Silva-Cardoso J, Ferreira J, Prazeres-Sá E, et al., on behalf of the PORTLAND study investigators. Levosimendan in daily intensive care practice – the experience of 15 centers. Background, methods and organization of the PORTLAND study. Port J Cardiol 2004;23(11):1431-1443.

15. Ceia F, Fonseca C, Mota T, et al, on behalf of the EPICA investigators. Prevalence of chronic heart failure in Southwestern Europe: The EPICA study. Eur J Heart Fail 2002;4:531-9.

16. Mosterd A. Heart failure in the population at large; news from the real world. Eur Heart J 1999;20:398-399.

17. McMurray J. Heart failure: we need more trials in typical patients. Eur Heart J 2000;21:699-700.

18. Masoudi FA, Havraneck EP, Wolf P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J 2003;146(2):250-257.

19. Julian D. Are the results of clinical trials a reliable guide for your practice? http://www.incirculation.net/10674_85999.aspx. Accessed on 16 March 2007.

20. Cleland JGF, Takala A, Apajasalo M, Zethraeus N, Kobelt G. Intravenous levosimendan treatment is cost-effective compared with dobutamine in severe low-output heart failure: an analysis based on the international LIDO trial. Eur J Heart Fail 2003;5:101–108.

21. The Task Force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). Eur Heart J 2005;26:1115-1140.

22. Metcalfe C, Thompson SG, Cowie MR, Sharples LD. The use of hospital admission data as a measure of outcome in clinical studies of heart failure. Eur Heart J 2003;24:105-12.

23. Arnold JMO, Bennett SJ, Cinquegrani MP, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure. J Am Coll Cardiol 2005;46(6):1179-1207.

24. Slawsky MT, Colucci WS, Gottlieb S, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000;102:2222-27.

25. Nieminen M, Akkila J, Hasenfuss G, et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000;36:1903-12.

26. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients > or = 65 years of age with heart failure. Am J Cardiol 2000;85:1110-1113.

27. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487-1491.

28. Singh BN, Lilleberg J, Sandell EP, et al. Effects of levosimendan on cardiac arrhythmia: electrophysiologic and ambulatory electrocardiographic findings in phase II and phase III clinical studies in cardiac failure. Am J Cardiol 1999;83(12B):16-20.

29. Lilleberg J, Ylonen V, Lehtonen L, Toivonen L. The calcium sensitizer levosimendan and cardiac arrhythmias: an analysis of the safety database of heart failure treatment studies. Scan Cardiovasc J 2004;38:80-4.

30. Diário da República 2003;I-Série-B;Nº30 – 30 de Fevereiro de 2003.

31. O'Connel JB. The economic burden of heart failure. Clin Cardiol 2000;23:6-10.

32. Cleland JGK, Gemmel I, Khand A, Boddy A. Is the prognosis of heart failure improving? Eur J Heart Fail 1999;1:229-241.

33. Parissis JT, Panou F, Farmakis D, et al. Effect of levosimendan on markers of left ventricular diastolic function and neurohormonal activation in patients with advanced heart failure. Am J Cardiol 2005;96:423-426.

34. Antman EM. ST-elevation myocardial infarction: management. In: Zipes DP, Libby P, Bonow RO, Braunwald, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia: Elsevier Saunders Inc. 2005;1167-1226.

35. Thomas S, Sonnenblick WH. In: Frishman WH, Sonnenblick EH, eds. Cardiovascular Pharmacotherapeutics. New York: McGraw Hill Inc. 1996;1595-1609.

36. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikainen P. Pharmacodynamics and safety of a new calcium sensitizer, levosimendan, and its metabolites during an extended infusion in patients with severe heart failure. J Clin Pharmacology 2002;42:43-51.

37. Follath F, Franco F, Silva-Cardoso J. The European experience on the practical use of levosimendan in patients with acute heart failure syndromes. Am J Cardiol 2005;96(6):80-85.