

Clinical Experience With Levosimendan in the Emergency Department of a Tertiary Care Hospital

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The efficacy and safety of levosimendan administration in patients with acute heart failure admitted to intensive care units has been well established. However, no information is available on the drug's beneficial effects in emergency departments. We studied 40 patients with acute heart failure who showed no or only partial improvement after conventional treatment and who received levosimendan during the period 2005-2006. The patients' mean age was 76 (9) years. The most common etiology was ischemic heart disease, and 85% of patients were in New York Heart Association (NYHA) class III or IV. The clinical response was favorable in 82% of patients, while adverse effects occurred in 18%. Some 70% were admitted to the emergency department short-stay unit. These findings indicate that levosimendan can be used safely and effectively in hospital emergency departments.

Key words: Acute heart failure. Levosimendan. Hospital emergency department.

Experiencia clínica con levosimendán en un servicio de urgencias de un hospital de tercer nivel

La eficacia y la seguridad de la administración de levosimendán en las unidades de cuidados intensivos en pacientes con insuficiencia cardíaca aguda está bien establecida, pero no hay pruebas científicas de sus efectos favorables en los servicios de urgencias (SUH). Hemos estudiado a 40 pacientes con insuficiencia cardíaca aguda con ausencia de mejoría o mejoría parcial tras tratamiento convencional a los que se administró levosimendán entre 2005 y 2006. La media de edad fue de 76 ± 9 años. La cardiopatía isquémica fue la etiología más frecuente; el 85% de los pacientes se encontraba en estadio III-IV de la New York Heart Association. La respuesta clínica fue favorable en un 82% de los pacientes y sólo un 18% presentó efectos adversos. El 70% de los pacientes ingresó en la unidad de corta estancia dependiente del SUH. Los resultados obtenidos indican que levosimendán puede utilizarse de forma segura y eficaz en los SUH.

Palabras clave: Insuficiencia cardíaca aguda. Levosimendán. Servicios de urgencias hospitalarios.

INTRODUCTION

Decompensated heart failure (DHF) is the main cause of hospitalization in patients over 65 years of age who present at hospital emergency rooms.¹ The traditional short-term objectives are the restoration of hemodynamic function and the relief of symptoms; the long-term objectives include preventing disease progression, reducing the number of readmissions, and improving the chances of survival. The therapeutic options currently available include the use of diuretics, vasodilators, and

inotropic drugs.² However, while these can be of great help in stabilizing the patient and in achieving short-term hemodynamic improvement and symptomatic relief, there is evidence that suggests they may increase mortality³ and provoke the appearance of malignant arrhythmias; their use is therefore restricted in clinical practice. However, a new group of pharmacological agents known as "calcium sensitizers" has recently appeared—of which levosimendan is the most important—that may help overcome some of these problems. Levosimendan offers short-term hemodynamic and symptomatic benefits, and improves cardiac output and coronary flow without negatively affecting survival; indeed, some authors report it to reduce mortality.⁴ The latest DHF treatment guidelines establish its use with a class IIa recommendation and a B level of evidence.² However, its use in the emergency room is rare; rather, it is reserved for more carefully selected patients taking part in clinical trials⁵ in intensive care units and recovery rooms.⁶ Clearly, these patients

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do not reflect the reality of patients with DHF presenting at the emergency room. This paper describes our experience of the use of levosimendan in patients with DHF presenting at the emergency room of a tertiary hospital.

METHODS

This prospective, descriptive study involved patients with DHF who presented at our emergency room and who received treatment with levosimendan. A protocol was designed (Table 1) in which this agent was made available to patients who did not improve, or who only partially improved, after standard treatment (oxygen, nitrates, and intravenous diuretics), or who presented with heart failure refractory to standard treatment and who fell into New York Heart Association (NYHA) functional III-IV. Patients in cardiogenic shock, with high blood potassium ($K > 5.5$ mEq/dL), uncontrolled arrhythmia, or serious valve stenosis were excluded. Levosimendan was administered as described in the protocol. During their time in the emergency room the patients were non-invasively monitored (chest x-ray, blood pressure, heart rate, breathing rate, oxygen saturation [SatO_2], and diuresis). Once stabilized, patients were transferred to the ward where blood pressure and heart rate were monitored every 8 hours. Treatment was considered effective when there was a subjective amelioration in terms of dyspnea, SatO_2 ,

and a radiological improvement. A patient's condition was considered to have worsened, or not to have improved, when there was a need to increase the dose of diuretics or nitrates, when a new drug was needed to control his/her heart failure, or when he/she died during hospitalization. The frequency of related adverse events (symptomatic hypotension, headache, tachycardia) was recorded, as well as the percentage of these problems that demanded levosimendan treatment be suspended. The sociodemographic, clinical, blood analysis, radiological, and referral destination (or immediate release) data were recorded at the time of admission. The duration of hospital stay was also recorded. Continuous variables were expressed as mean \pm standard deviation; categorical variables were recorded as number and percentage.

RESULTS

Between July 2005 and July 2006, 40 patients received treatment with levosimendan at our emergency room. Table 2 shows the characteristics of these patients, who were older than those of other studies (mean 76 years compared to 68 and 58 years)^{7,8} and suffered greater comorbidity. The most common etiology of their heart failure was ischemic. More than 80% of patients fell into NYHA functional class III-IV. Some 57% presented with a depressed left ventricular ejection fraction. All patients

TABLE 1. Action Protocol for Use With Patients Presenting With Heart Failure at the Emergency Room*

Initial conventional treatment	Oxygen therapy: Boussignac CPAP in patients with lung edema; Ventimask use in mild-moderate decompensation Diuretics (furosemide). Dose according to liquid retention: moderate, 20-40 mg iv bolus; serious, 1 mg/kg iv bolus followed by perfusion (10 mg/h) With/without GTN
Use of inotropic drugs	Acute heart failure with high blood pressure: GTN: reduction of SBP or DBP within 5 minutes by at least 30 mm Hg and then gradually to normal levels. If the response is unfavorable but the BP optimal, investigate other causes and consider use of levosimendan Acute heart failure with low or normal blood pressure: begin early levosimendan along with conventional treatment.
SBP >100 mm Hg: NTG with/without levosimendan	Use levosimendan in ALE or hypertensive heart failure, de novo acute heart failure, decompensated chronic heart failure (NYHA III-IV) with only partial or no response to conventional treatment and after controlling heart rhythm and blood pressure Levosimendan. Loading dose - with normal blood pressure: 6 $\mu\text{g/kg}$. With high blood pressure or serious worsening: 12 $\mu\text{g/kg}$. Follow with continuous infusion: 0.1 $\mu\text{g/kg/min}$. If BP falls, reduce dose of GTN and consider reducing the levosimendan perfusion dose.
SBP 85-100 mm Hg	Begin levosimendan administration with conventional treatment (oxygen therapy, diuretics, consider low dose GTN). No loading dose (or consider 6 $\mu\text{g/kg}$) but continuous infusion at 0.05 $\mu\text{g/kg/min}$; if there is no clinical response but hemodynamic stability is achieved, consider increasing to 0.1 $\mu\text{g/kg/min}$
SBP <85 mm Hg, signs of shock	Consider providing fluids or blood transfusion if required. Consider orotracheal intubation. Consider referral to intensive care or catheterization room Drugs: noradrenaline associated with levosimendan (no loading dose)

*CPAP indicates continuous positive airway pressure; ALE, acute lung edema; i.v., intravenous; GTN, nitroglycerine; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 2. General Characteristics of the Patients With Decompensated Heart Failure Who Received Levosimendan (n=40)*

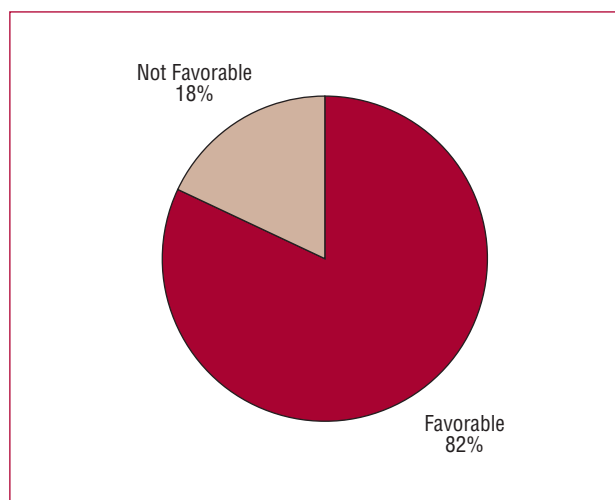
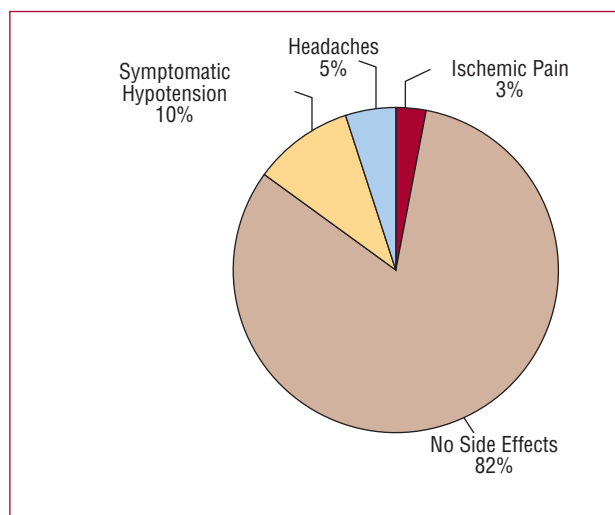
	Number, %	Mean (SD)
Age		76 (9)
Sex (male)	22 (5)	
Comorbidity		
High blood pressure	33 (82.5)	
Diabetes mellitus	26 (65)	
Kidney failure	12 (30)	
Active neoplasm	2 (5)	
Charlson index ≤ 3 points	28 (70)	
Etiology		
Ischemia	30 (75)	
Hypertensive	16 (40)	
Dilated heart failure	7 (17.5)	
Valve disease	9 (22.5)	
NYHA functional class		
II	6 (15)	
III	26 (65)	
IV	8 (20)	
LVEF <45%	23 (57.5)	
Prior treatment		
ACEi/ARA-II	36 (90)	
Diuretics	40 (100)	
Beta-blockers	24 (60)	

*ARA-II indicates angiotensin receptor antagonists I; SD, standard deviation; LVEF, left ventricular ejection fraction; ACEi, angiotensin converting enzyme inhibitors; NYHA, New York Heart Association.

TABLE 3. Clinical Situation and Treatment Administered in the Emergency Room*

	Number (%)	Mean (SD)
Systolic blood pressure		129 (28)
Heart rate		140 (20)
Breathing rate		28 (8)
Initial SatO ₂		86 (6)
SatO ₂ at 24 h		95 (6)
Chest x-ray		
Acute lung edema	13 (32.5)	
Left heart failure	27 (67.5)	
ECG		
Sinus rhythm	20 (50)	
Atrial fibrillation	15 (37.5)	
Pacemaker rhythm	5 (12.5)	
Oxygen treatment		
CPAP	8 (20)	
Conventional	32 (80)	
iv diuretics	37 (92.5)	
iv nitrates	35 (87.5)	
Levosimendan bolus		
6 $\mu\text{g/kg}$	9 (22.5)	
12 $\mu\text{g/kg}$	24 (60)	
24 $\mu\text{g/kg}$	2 (5)	
No bolus	5 (12.5)	
Maintenance dose		
0.05 $\mu\text{g/kg/min}$	10 (25)	
0.1 $\mu\text{g/kg/min}$	30 (75)	

*CPAP indicates continuous positive airway pressure; SD, standard deviation; iv, intravenous; SatO₂, oxygen saturation; ECG, electrocardiogram.

**Figure 1.** Clinical efficiency of levosimendan in patients with decompensated heart failure treated with levosimendan in the emergency room.**Figure 2.** Distribution of adverse events attributable to levosimendan administration.

followed standard maintenance treatments prior to presenting at the emergency room; a large proportion received beta blockers.

Table 3 shows the clinical characteristics of the patients and the details of the treatment administered. Patients remained in the emergency room between 4 and 6 hours. Thirty three patients showed a favorable clinical response. Four patients died due to refractory heart failure after a prolonged hospitalization period, in the course of which the perfusion with levosimendan had already been finalized) (Figure 1). Seven patients suffered adverse events directly related to the administration of levosimendan; although 2 of these suffered symptomatic hypotension only in 1 did administration of the drug have to be suspended (Figure

2). Twenty eight patients (70%) were eventually admitted to the emergency department short stay unit; the remainder were admitted to the cardiology, internal medicine or intensive care units, or to long stay hospitals. The mean length of time spent by the patients in the short stay unit was 3.5 days; these patients were later monitored by the home hospitalization unit.

DISCUSSION

Levosimendan proved to be effective in our patients with DHF, helping to achieve clinical improvements in those showing no response, or only a partial response, to conventional treatment. The drug ameliorated the patients' symptoms in the emergency room, as well as their radiological variables and SatO₂. Once admitted, patients' symptoms did not worsen and there was no need for rescue medication. These findings agree with those of other studies.⁷⁻¹⁰ The clinical benefits of levosimendan were maintained when perfusion ended.

The majority of patients tolerated the drug very well. Hypotension was the most common adverse event, although it was less common than reported in other studies^{7,8} (10% compared to 50%). This difference might be explained in that the doses used in the present study were more flexible, ie, they were adjusted to the hemodynamic situation of the patient.¹¹ Furthermore, the early use of the drug in the emergency room avoided excessive volume depletion through the use of diuretics. Unlike in these earlier studies,^{7,8} the percentage of arrhythmias recorded was low. This is probably related to the fact that continuous non-invasive monitoring was not performed on the ward in the present study, which could have led to certain adverse events not being detected. Levosimendan should therefore be used with care in situations in which continuous monitoring is not possible (eg, day hospital, or home hospitalization units).

A large number of the present patients received prior treatment with beta-blockers. In previous studies the concomitant administration of beta-blockers and levosimendan did not attenuate the effects of the latter. In fact in these patients the lowest mortality and the greatest hemodynamic benefits were seen.⁷⁻¹¹ This supports the idea that beta-blocker treatment should be maintained in patients with DHF in the emergency room. However, in patients who receive beta-blockers, the effects of dobutamine are attenuated⁸ and the beta receptors downregulated; these last 2 agents are therefore incompatible.

The majority of patients were admitted to the emergency room short-stay unit, which is associated with a home hospitalization unit. These alternative hospitalization modes—the use of which is made possible with levosimendan treatment—have been shown to reduce the mean hospital stay, to reduce the number of admissions, and to improve patient quality of life.¹²

Many of the patients presented with advanced or terminal chronic heart failure, and were highly dependent. The compassionate use of levosimendan acquires greater importance in such situations. Certainly it appears safe and effective, and its pharmacokinetics (it has an active metabolite with a half life of 80 h) allow its effects to persist even one week after perfusion is ended. This may help reduce the dependence of these patients.¹³

The present work suffers from a number of important limitations inherent in its design. Since it is a descriptive study and there is no control group, no comparisons of the results can be made. Further, neither mid-term nor long-term survival, readmissions, nor new visits to the emergency room were investigated. Patients quality of life was not investigated either. However, it would seem that levosimendan does have an important palliative and compassionate role to play in the control of DHF symptoms.

Levosimendan is safe and effective in the treatment of patients with DHF presenting at the emergency room, and should be included in treatment protocols for patients with acute heart failure or decompensated chronic heart failure in whom the response to conventional treatment is negative or only partial.

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