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.

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.5 However, its use in the emergency room is rare; rather, it is reserved for more carefully selected patients taking part in clinical trials in intensive care units and recovery rooms.6 Clearly, these patients...
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 [SatO₂], 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, SatO₂, 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±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) 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**

<table>
<thead>
<tr>
<th>Initial conventional treatment</th>
<th>Oxygen therapy; Boussignac CPAP in patients with lung edema; Ventimask use in mild-moderate decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of inotropic drugs</td>
<td>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)</td>
</tr>
<tr>
<td>SBP &gt; 100 mm Hg NTG with/without levosimendan</td>
<td>Use levosimendan in ALE or hypertensive heart failure, de novo acute heart failure, decompenated chronic heart failure (NYHA III-IV) with only partial or no response to conventional treatment and after controlling heart rhythm and blood pressure</td>
</tr>
<tr>
<td>SBP 85-100 mm Hg</td>
<td>Levosimendan. Loading dose - with normal blood pressure: 6 µg/kg. With high blood pressure or serious worsening: 12 µg/kg. Follow with continuous infusion: 0.1 µg/kg/min. If BP falls, reduce dose of GTN and consider reducing the levosimendan perfusion dose.</td>
</tr>
<tr>
<td>SBP &lt; 85 mm Hg, signs of shock</td>
<td>Begin levosimendan administration with conventional treatment (oxygen therapy, diuretics, consider low dose GTN). No loading dose (or consider 6 µg/kg) but continuous infusion at 0.05 µg/kg/min; if there is no clinical response but hemodynamic stability is achieved, consider increasing to 0.1 µg/kg/min</td>
</tr>
</tbody>
</table>

*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.
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 1 did administration of the drug have to be suspended (Figure 2).
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 SatO\textsubscript{2}. Once admitted, patients’ symptoms did not worsen and there was no need for rescue medication. These findings agree with those of other studies.\textsuperscript{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\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 attenuated\textsuperscript{8} 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.\textsuperscript{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.\textsuperscript{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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