

Levosimendan in Acute Heart Failure: Past, Present, and Future

Juan F. Delgado

Unidad de Insuficiencia Cardíaca y Trasplante, Servicio de Cardiología,
Hospital Universitario 12 de Octubre, Madrid, Spain.

Acute heart failure (AHF) is one of the main causes of cardiovascular morbidity and mortality. After diagnosis of AHF and during the first year of follow-up, 45% of the patients will be admitted to hospital at least once and mortality can be as high as 40%.¹

Therapeutic approaches are therefore needed to alleviate symptoms, stabilize the hemodynamics of the patients, and improve their quality of life and survival.

Interest in clinical investigation in the field of AHF is very recent. Thus, unlike chronic heart failure, the scientific evidence to support therapeutic action is not extensive. In fact, the first clinical guidelines for management of AHF were not published until 2005.¹

Inotropic Treatment of Acute Heart Failure

Inotropic drugs are one of the therapeutic options for treating AHF due to systolic dysfunction. In recent decades, clinical experience has supported the use of these drugs and adrenergic stimulants such as dobutamine have come to be used more than phosphodiesterase III inhibitors, such as milrinone. However, the clinical information we have on the efficacy and safety of these therapeutic groups is limited and sometimes suggests they may have negative effects.^{2,3}

The intravenous use of inotropic drugs is indicated in patients with AHF and peripheral hypoperfusion (hypotension, deterioration of renal function, or cutaneous signs of poor peripheral perfusion), regardless of whether pulmonary or systemic congestion is present, and in those with AHF unresponsive to diuretics and vasodilators.⁴ This indication is recommendation level IIa with a level of evidence C.¹

SEE ARTICLE ON PAGES 338-45

Correspondence: Dr. J.F. Delgado.
Unidad de Insuficiencia Cardíaca y Trasplante. Servicio de Cardiología.
Hospital Universitario 12 de Octubre.
Avda. de Córdoba, s/n. 28041 Madrid. España.
E-mail: jdelgado.hdoc@salud.madrid.org

Initial Clinical Development of Levosimendan

A new pharmacological group of positive inotropics known as calcium sensitizers has recently appeared. The main representative of this new group is levosimendan. The clinical development of this agent has gained the interest of clinicians thanks to the efficacy and safety of this drug in the inotropic treatment of patients with AHF.

Levosimendan exerts its influence on the cardiovascular system through 2 mechanisms of action. It improves myocardial wall motion by sensitizing troponin C to calcium and it exerts an arterial and venous vasodilatory effect through activation of adenosine triphosphate (ATP) sensitive potassium channels of vascular smooth muscle cells.⁵

With this dual mechanism of action, the hemodynamic effects of the drug are, on the one hand, increased cardiac load and, on the other, decreased pulmonary capillary wedge pressure, and pulmonary and systemic vascular resistance. An antiarrhythmic effect and certain properties for reversing myocardial stunning have also been attributed to the drug.⁵⁻⁸

Moreover, thanks to the hemodynamically active metabolite denominated OR-1896, the hemodynamic effect of levosimendan is sustained and may even persist more than a week after a single intravenous administration.⁹

The results obtained in clinical trials that have been published (LIDO,⁸ RUSSLAN¹⁰) or communicated at conferences (CASINO¹¹) suggest that levosimendan is more effective than dobutamine in AHF^{8,11} and that mortality is lower compared with dobutamine^{8,11} and placebo.¹¹ According to these findings, levosimendan is the inotropic drug of choice for patients with AHF and signs of peripheral hypoperfusion (recommendation level IIa, level of evidence B).¹

Levosimendan has also been used in other types of acute circulatory failure, such as low cardiac output after heart surgery.¹² The study by Álvarez et al,¹³ published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, is an example of the interest generated by this new drug in other areas of intensive care medicine. We will return to this article later.

Current Situation: Levosimendan After the REVIVE and SURVIVE Studies

Two important studies with levosimendan for the treatment of AHF (REVIVE II and SURVIVE) were presented recently at the American Heart Association Meeting in Dallas.^{14,15}

The REVIVE II study assessed the effects of levosimendan plus conventional therapy versus conventional therapy alone in 600 patients hospitalized for severe AHF (those with left ventricular ejection fraction <35% who were symptomatic after 48 h of appropriate treatment with diuretics and vasodilators). The primary endpoint was a clinical one that comprised a composite of improvement or deterioration based on the clinical course of the patient during the first 5 days after infusion of the drug. The clinical benefit, though modest, was greater in patients treated with levosimendan—in absolute terms, 6% more patients improved and 7% fewer deteriorated in the levosimendan group compared to patients on conventional treatment ($P=.015$). Moreover, 15% of patients treated with levosimendan needed rescue therapy compared to 26% in the conventional therapy arm.

Other results worthy of mention are a decrease in brain natriuretic peptide (BNP) of approximately 250 g/mL and 2 days shorter hospital stay for patients treated with levosimendan.

On the other hand, it is important to note that 50% of patients in the levosimendan group and 36% of those in the conventional group presented hypotension as an adverse effect. Atrial and ventricular arrhythmias also appear more frequently in patients in the levosimendan group compared to the conventional treatment group. Although the REVIVE II study was not designed to evaluate mortality, mortality at 90 days was defined as a secondary endpoint. Forty-five patients died in the levosimendan group compared to 35 in the conventional treatment group, although these differences were not statistically significant.

The second of these studies is the SURVIVE study, which was designed specifically to determine the effect on survival of intravenous inotropic treatment after 6 months of follow-up in 1327 patients with AHF. The study population had very advanced disease—the left ventricular ejection fraction was less than 30% and AHF was symptomatic. These patients had not responded to treatment with diuretics and/or intravenous vasodilators and they presented with oliguria, resting dyspnea, or severe hemodynamic dysfunction confirmed by pulmonary artery catheterization.

The study hypothesis was that randomization to receive a single dose of levosimendan would reduce mortality at 6 months by 25% with respect to randomization to receive dobutamine. Although the primary endpoint was not met, fewer patients on levosimendan died compared to dobutamine at 5 days, 2

weeks, 1 month, and 6 months after infusion of the drug. The relative reduction in mortality at these times in the levosimendan group was 27%, 14%, 13%, and 6.4%, respectively, although these differences were not statistically significant. Other findings of note were the regional differences in mortality among participating countries, the greater benefit of levosimendan in acute decompensation of chronic heart failure compared to patients with de novo AHF, and the slightly higher incidence of atrial fibrillation in the levosimendan-treated group compared to the dobutamine-treated group (9% vs 6%).

Critical Analysis of the REVIVE and SURVIVE Studies

The results of the REVIVE II and SURVIVE studies were surprising. First, they did not reflect the perceived clinical benefit in the countries that have approved the use of levosimendan¹⁶⁻¹⁸ and, second, they contradicted to a certain extent trends observed in pilot studies.^{8,10,11} We will try to explain how these discrepancies might have produced about.

Acute heart failure is a complex condition with a variety of causes. Severity is variable, and can range from mild decompensation of chronic heart failure with congestion at rest to cardiogenic shock. The disease severity between these 2 extremes is continuous and this severity is not adequately captured by the clinical variables used for the selection criteria for the clinical trials. Therefore, the first possible explanation of the discrepancy between the results of earlier studies and these recent ones is based on how the study population was selected. Although patients presented with AHF in all of the studies, the clinical condition of those in the LIDO study (selected with hemodynamic criteria before randomization) was not the same as those in the REVIVE study (selected with clinical criteria).

Second, unlike chronic heart failure, there is no universally accepted treatment for AHF. Many of the therapeutic regimens (for example, dose, route of administration, frequency of dosing, and type of diuretic) have scarce evidence to support them and practice may vary from region to region (for example, in the use of beta-blockers). In fact, regional differences in the use of beta-blockers may account for the differences in the results obtained in different countries participating in the SURVIVE study, as the benefit of levosimendan compared to dobutamine in patients treated with beta-blockers has been documented.⁸

The third aspect that should be taken into account when discussing the design of the REVIVE and SURVIVE studies is the high doses of levosimendan used, both as a loading dose and for maintenance. The use of a loading dose was a requirement of the health authorities as the evidence available when the studies

were designed suggested that such a regimen should be used.^{8,10} However, this may have had a negative effect on clinical outcome. It was known that the risk/benefit ratio (particularly for hypotension) is higher with higher loading doses and maintenance doses.¹⁰ Thus, administration of the loading dose to patients in the REVIVE study, with a systolic blood pressure between 85 mm Hg and 130 mm Hg was associated with hypotension in up to 50% of the patients treated with levosimendan compared to 36% of those who received standard therapy. This can be interpreted 2 ways. Administration of a potent vasodilator such as levosimendan to this group of patients was obviously responsible for a higher incidence of hypotension than in placebo. The fact that hypotension was still reported in 36% of those who did not receive levosimendan, i.e. those on placebo, can only be explained by the inclusion criterion that required intravenous diuretic treatment to be optimized. This requirement may have caused a high rate of relative intravascular volume depletion in both groups. At this point, we should be aware that, in previous studies showing clinical and hemodynamic benefit of levosimendan, pulmonary artery catheterization was used to confirm sufficient preloading before treatment.⁸ These 2 factors together—relative volume depletion and administration of a vasodilator at a high loading dose—clearly favored the appearance of hypotension. Hypotension is well known to have deleterious effects in patients with AHF and could be associated with the appearance of atrial and ventricular arrhythmias and also with worse survival.

Future

The findings of the initial studies with levosimendan have obviously not been reproduced in the 2 large studies (REVIVE and SURVIVE) designed specifically to provide confirmation, or at least, the findings have not been as positive as was hoped. Although these discrepancies may be explained by different study designs, another alternative or complementary explanation is that the real clinical benefit provided by levosimendan is less than was expected.

In any case, we must inevitably conclude that the clinical development of levosimendan has yet to be completed. This is despite the fact that the AHF drug supported by the most extensive scientific evidence is levosimendan, with more than 3000 patients studied in randomized clinical trials.

Further clinical trials are clearly necessary with placebo, dobutamine, or intravenous vasodilators. But these new studies, in view of what we have now learned, should address some particular points. First, they should include better defined patients (disease severity, cause, and clinical situation) within the broad and complex range of patients with AHF. Second, they should include patients with less severe AHF, who are, those not in

danger of cardiogenic shock. Third, studies should be stricter about permitted concomitant treatments to provide a better idea of the positive and negative effects of the therapeutic intervention under assessment. Finally, the study design should allow for flexible dosing (both loading and maintenance) of levosimendan to more closely mimic how cardiovascular agents are actually used in daily clinical practice.

Along these lines, Álvarez et al¹³ report a modest but novel and elegant contribution to the clinical development of levosimendan in a specific indication—low cardiac output syndrome after extracorporeal circulation. This syndrome has many causes (myocardial damage related to cardioplegic protection, ischemia, and reperfusion) and may affect 10% of patients undergoing extracorporeal circulation with mortality among those affected being as high as 17%.¹⁹ The study published in this issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA* is a prospective, randomized design with consecutive patients that compared the hemodynamic changes under treatment with levosimendan or dobutamine in 41 patients with low cardiac output syndrome after extracorporeal circulation. The clinical and hemodynamic profile (baseline and progression) suggests that the patients included were those with less severe presentation of this syndrome. Of the study population, 16% assigned to levosimendan were excluded because of hypotension, probably related to an unnecessary loading dose. In the dobutamine group (inotropic control), a low dose was used (7.5 g/kg/min), which probably explains why 20% of patients assigned to this group were excluded because of persistence of low cardiac output syndrome. From the hemodynamic results obtained in treated patients, it was concluded that levosimendan showed certain advantages over dobutamine in the treatment of low cardiac output syndrome in that levosimendan improved the cardiac output index. The two drugs showed a similar safety profile.

Conclusion

To conclude, with the current evidence it is not possible to recommend levosimendan to all patients with AHF. However, when inotropic treatment is considered necessary, levosimendan remains an excellent therapeutic option, particularly in patients without hypotension or relative depletion of the intravascular volume.

Although levosimendan is a drug supported by extensive scientific evidence, new clinical studies would be desirable to complete its clinical development.

REFERENCES

1. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G et al. Executive summary of the guidelines on the

- diagnosis and treatment of acute heart failure. *Rev Esp Cardiol*. 2005;58:389-429.
2. Thackray S, Easthaugh J, Freemantle N, Cleland JG. 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;4:515-29.
3. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541-7.
4. Crespo Leiro M, Paniagua Martín M. Tratamiento de la insuficiencia cardíaca refractaria o avanzada. *Rev Esp Cardiol*. 2004;57:869-83.
5. Tamargo J, López-Sendón J. Bases y evidencias clínicas de los efectos de los nuevos tratamientos farmacológicos en la insuficiencia cardíaca. *Rev Esp Cardiol*. 2004;57:447-64.
6. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. *Circulation*. 2000;102:2222-7.
7. Michaels AD, McKeown B, Kostal M, Vakharia KT, Jordan MV, Gerber IL, et al. Effects of intravenous levosimendan on human coronary vasomotor regulation, left ventricular wall stress, and myocardial oxygen uptake. *Circulation*. 2005;111:1504-9.
8. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. 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.
9. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. *Circulation*. 2003;107:81-6.
10. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J*. 2002;23:1422-32.
11. Coletta AP, Cleland JGF, Freemantle N, Clark AL. Clinical trials update from the European Society of Cardiology Heart Failure meeting: SHAPE, BRING-UP 2 VAS, COLA II, FOSIDIAL, BETACAR, CASINO and meta-analysis of cardiac resynchronisation therapy. *Eur J Heart Fail*. 2004;6:673-6.
12. Siirilä-Waris K, Suojäranta-Ylinen R, Harjola V-P. Levosimendan in Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2005;19:345-9.
13. Álvarez J, Bouzada M, Fernández AL, Caruezo V, Taboada M, Rodríguez J, et al. Comparación de los efectos hemodinámicos del levosimendán con la dobutamina en pacientes con bajo gasto después de cirugía cardíaca. *Rev Esp Cardiol*. 2006;59:338-45.
14. Bermejo J, Segovia J, Alfonso F. Resúmenes de los ensayos clínicos presentados en las Sesiones Científicas de la American Heart Association 2005 (Dallas, Texas, Estados Unidos, 13-16 noviembre 2005). *Rev Esp Cardiol*. 2006;59:143-53.
15. Cleland JGF, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, AS-TAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail*. 2006;8:105-10.
16. Silva Cardoso J, Ferreira J, Prazeres de Sá E, Martins de Campos J, Fonseca C, Lousada N, et al. O levosimendan na prática quotidiana de cuidados intensivos. Fundamentação, métodos e organização do Estudo Portland. *Rev Port Cardiologia*. 2004;23:1431-43.
17. Follath F, Franco F, Cardoso JS. European experience on the practical use of levosimendan in patients with acute heart failure syndromes. *Am J Cardiol*. 2005;96:80-5.
18. Parissis JT, Filippatos G, Farmakis D, Adamopoulos S, Paraskevaidis I, Kremastinos D. Levosimendan for the treatment of acute heart failure syndromes. *Expert Opin Pharmacother*. 2005;6:2741-51.
19. Rao V, Ivanov J, Weisel RD, Ikonomidis JS, Christakis GT, David TE. Predictors of low cardiac output syndrome after coronary artery bypass. *J Thorac Cardiovasc Surg*. 1996;112:38-51.