

Is There a Role for Levosimendan in Hospital Emergency Departments?

To the Editor:

We read with interest the article by Llorens-Soriano et al,¹ in which they report their experience with levosimendan and conclude that it is a safe and effective therapeutic option for the treatment of acute heart failure (AHF) in hospital emergency departments. The purpose of this letter is to reflect on certain aspects of the above mentioned article.

In the first place, there are notable differences between the indications for levosimendan in the clinical practice guidelines² and the protocol followed by the authors.¹ Whereas the guidelines recommend its use in heart failure with symptomatic reduced cardiac output secondary to left ventricular dysfunction with no severe hypotension, the authors of the above mentioned study consider its use in multiple clinical situations, including AHF with a left ventricular ejection fraction (LVEF) >45% and hypotension, or shock.

To date, no scientific evidence is available regarding the use of levosimendan in patients with AHF and conserved systolic function. It is therefore surprising that more than 40% of the patients included in the study belonged to this subgroup. The administration of levosimendan is known to produce a reduction in peripheral vascular resistance and an improvement in the parameters of diastolic function.³ However, at the present time diuretics and vasodilators have been shown to be highly effective in these patients and currently form the treatment of choice in this context.⁴ Additionally, the results of the study offer serious doubts about their scientific validity: the lack of a control group, the inconsistency of the inclusion criteria (not all the patients received diuretics), the low risk profile of the study population (only 30% had acute pulmonary edema), and the lack of precision in the definition used for "lack of response to the drug" are all important aspects that should have been taken into account. The clinical practice guidelines² contraindicate the use of levosimendan in patients with cardiogenic shock. Nonetheless, recent studies in patients with ischemic cardiogenic shock and low cardiac output after heart surgery have shown promising results.^{5,6}

In our opinion, levosimendan should be used after optimal patient selection, which requires suitable co-ordination between the various different services. To this extent, an echocardiogram may prove extremely useful. The following factors have recently been suggested to be associated with a favorable therapeutic response⁷: decompensated chronic heart failure, ischemic

etiology, NYHA Class III/IV, absence of concomitant treatment with vasodilators or antiarrhythmic drugs, and systolic blood pressure >100 mm Hg. Another important aspect to consider is the dosage of this drug. In the REVIVE and SURVIVE studies, the relative depletion of intravascular volume secondary to diuretic therapy, together with the administration of a high loading dose, favors the onset of hypotension and is probably associated with worse survival.⁸ The authors of this study, like us, are in favor of using a more flexible dose of levosimendan depending on the hemodynamic status of the patient, as well as its early use in order to avoid situations of excessive volume depletion caused by the use of diuretics.

In conclusion, we would like to emphasize the need for adequate identification of those patients who might benefit from this promising drug, which, pending the results of further studies, should have its use restricted to the indications already approved in consensus guidelines. Additionally, it would seem reasonable to perform an echocardiogram prior to the administration of this drug and to have better co-ordination between the various hospital services involved in treating these patients.

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REFERENCES

1. Llorens-Soriano P, Carbajosa-Dalmau J, Fernández-Cañadasa J, Murcia-Zaragoza J, Climent-Payá V, Laghzaouia F, et al. Experiencia clínica con levosimendán en un servicio de urgencias de un hospital de tercer nivel. *Rev Esp Cardiol*. 2007;60:878-82.
2. Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Guías de Práctica Clínica sobre el diagnóstico y tratamiento de la insuficiencia cardíaca aguda. Sumanariced version. *Rev Esp Cardiol*. 2005;58:389-429.
3. 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.
4. Anguita M, Ojeda S. Tratamiento médico de la insuficiencia cardíaca por disfunción diastólica. *Rev Esp Cardiol*. 2006;6:53-8.
5. Álvarez, J, Bouzada M, Fernández AL, Caruezo V, Taboada M, Rodríguez J, et al. Comparación de los efectos hemodinámicos del levosimendan con dobutamina en pacientes con bajo gasto después de cirugía cardíaca. *Rev Esp Cardiol*. 2006;59:338-45.
6. Matejovic M, Krouzecky A, Radej J, Novak I. Successful reversal of resistant hypodynamic septic shock with levosimendan. *Acta Anaesthesiol Scand*. 2005;49:127-8.

7. Parissis JT, Farmakis D, Bistola V, Adamopoulos S, Kremastinos DT. Levosimendan for the treatment of acute heart failure syndromes: time to identify subpopulations of responding patients. *Am J Cardiol*. 2007;99:146-7.
8. Delgado JF. Levosimendán en la insuficiencia cardíaca aguda: pasado, presente y futuro. *Rev Esp Cardiol*. 2006;59:309-12.

scenes found with AHF in the emergency department, independently of the type of cardiac dysfunction. Its use in cardiogenic shock is documented in different studies and in the recent recommendations arising from expert agreements.^{2,3}

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Response

To the Editor:

The question posed by the authors is interesting, although at the same time disappointing, because at no point do they suggest an answer. In order to provide an answer, it would have been necessary to be aware of our situation: the patient with acute heart failure (AHF) in Spanish emergency wards presents a different profile to the patient usually seen on the cardiology ward or in the office, and even different to the patients who form the object of the guidelines for AHF. A recent multicenter study carried out in Spain¹ comes to the conclusion that patients with AHF in the emergency ward are older (a population considered by the guidelines to be special), and have a high degree of comorbidity, functional, and social deterioration, and previous diagnoses of chronic heart failure (CHF), as well as presenting functional decompensation or progression even though most of them receive a correct pharmacological treatment. Moreover, as they are patients with CHF, most are unaware of the type and degree of cardiac dysfunction, and when this is known, both systolic and diastolic dysfunction are predominant. Fewer than 3% undergo an echocardiographic study in the emergency wards, and fewer than 10% are admitted to the cardiology ward, which shows that AHF is very important in the emergency wards and that the treatment of these patients is no less important.

The clinical practice guidelines on AHF must be understood to provide advice on the management of these patients, and we should be able to adapt this advice to the circumstances of our environment and not treat it as dogma for the attendance of our patients. Our working protocol coincides with the current recommendations drawn up by experts in cardiology, emergency medicine and intensive medicine for the early stages of AHF, during which levosimendan is administered to patients who remain symptomatic after initial conventional therapy and in the case of shock associated with vasopressors.^{2,3}

There are currently more than 3000 patients who have been included in randomized clinical trials, in whom the efficacy and safety of levosimendan have been demonstrated, without mentioning observational studies and case series. It is the first inodilator to improve diastolic dysfunction and left ventricular filling pressures and increases contractility with little consumption of energy, all of which are ideal effects for the different

REFERENCES

1. Llorens P, Martín FJ, González-Armengol JJ, Herrero P, Jacob J, Álvarez AB, et al. Perfil clínico de los pacientes con insuficiencia cardíaca en los servicios de urgencias: datos preliminares del estudio EAHFE (Epidemiology Acute Heart Failure Emergency). *Emergencias*. 2008 [In press].
2. Mebazaa A, Gheorghiade M, Piña I, Harjola VP, Hollenberg S, Follath F, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Crit Care Med*. 2008;36 Suppl: S129-30.
3. Parissis JT, Farmakis D, Nieminen M. Classical inotropes and new cardiac enhancers. *Heart Fail Rev*. 2007;12:149-56.