Original article

Outpatients repeated infusion of levosimendan in end-stage chronic heart failure: an efficacy and safety trial

Summary
In patients with chronic heart failure (HF) the effects of inotropic therapy are still uncertain; aim of our study is to evaluate the safety and efficacy of periodic infusion of levosimendan (LS) in outpatients (pts) with chronic end stage HF. We treated 10 pts with 2 or more admissions in hospital for HF during the previous 12 months (mts), with periodic infusion (every 3 weeks) of LS. Comparing the 8 mts before and after this therapy, the number of admissions and the number of days of hospitalization for HF showed a significant reduction. BNP dosage showed a non significant trend towards a reduction of BNP level in the first 6 mts. The periodic use of LS is safe and effective in reducing re-admissions for worsening HF at least in the first eight mts of therapy.

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Giorgio Bartesaghi, Fabrizio Morandi, Silvia Longoni, Andrea Pozzi, Laura Gaiara, Jorge A. Salerno-Uriarte
Dipartimento di Scienze Cardiovascolari Università degli Studi dell'Insubria - Ospedale di Circolo Fondazione Macchi, Varese.

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Fabrizio Morandi
U.O Cardiologia
Ospedale di Circolo Fondazione Macchi
Viale Borri 57
21100 Varese
e-mail: fabiomora@libero.it

Patients with chronic end-stage heart failure (HF) remain symptomatic despite optimized medical therapy; in these patients the aim of physician is to improve the quality of life and inotropic drugs, such as dobutamine[1-4], can help to reach this target, although some studies demonstrated an increased mortality for proarrhytmic effects[5,6]. Levosimendan is a new drug for acute heart failure with inotropic, vasodilatatory and metabolic properties without proarrhytmic effects[7]. In literature there are only few experiences with repetitive infusion of Levosimendan in chronic heart failure, in inpatients and for few months; they demonstrated an improvement in symptoms and NYHA class[8-13]. The aim of our experience is to demonstrate the safety and utility of Levosimendan in repetitive infusions for several months in outpatients with chronic end-stage heart failure.

Methods

Between June 2004 and June 2008 we treated with periodic infusions of Levosimendan 10 patients (age 41-77 years old) with end-stage chronic heart failure due to left ventricular (LV) systolic dysfunction. All patients had a left ventricular ejection fraction <30% with dyspnoea on minimal exertion or at rest (NYHA class IV in 7 pts and NYHA class III in 3 pts) (table 1). The aetiology of the LV dysfunction was ischemic in 6 pts, idio-

pathic and valvular in two cases respectively; one of these pts had a Marfan syndrome with a prosthetic mitral valve and an aortic prosthetic tube. Patients were currently on optimal medical treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, beta-blockers unless not tolerated, aldosterone antagonists, digitalis and diuretics and all received periodic clinic evaluation in our heart failure ambulatory in some cases also with telemonitoring. All had an ICD, 4 had also a biventricular pacemaker; two pts were on heart transplant list and for other two pts the inclusion on transplant list was denied because of comorbidity; for other pts the transplant chance was not possible for age limit.

Levosimendan was given as a 10-minute bolus of 6 or 12 ug/kg/min followed by continuous infusion for 24 hours at a rate of 0,1 ug/kg/min in 4 pts; 6 pts were treated without bolus. Afterwards, they received every 3 weeks, 6,25 mg of Levosimendan ev. at a rate of 0,1 ug/kg/min; during the follow-up, if the symptoms and signs of heart failure improve only for few days the infusion was performed every two weeks. In absence of improvement, Levosimendan was increased to 12,5 mg every two weeks. Worsening heart failure was defined as increased symptoms with or without new hospitalization, but with increased oral furosemide dosage (at least 50 mg/day) or need of furosemide or vasodilator ev. All patients but one, during the previous 12 months had 2 or more admissions in hospital for HF and these patients at the beginning of this study were admitted for acute heart failure; one pts had no hospitalisation for HF in the previous 12 months, but we decided to start with the protocol considering his poor quality of life. In 8 patients a long-term access catheter was implanted (port-a-cath Celsite®) and the subsequent infusions were made by portable infusion pump (CADD Legacy 1 6400 SIMS DELTEC, INC) as outpatients. That is, every three or two weeks our pts reach our department for a brief visit and to perform an electrocardiogram and blood analysis; after that, we applied the infusion pump and patients returned home. The day after, the pump was removed by our nurses in hospital or by the patient or relatives at home, previously instructed in aseptic care of the central access site and line. In patients without long-term access catheter, the infusion were performed as inpatients through a peripheral vein. BNP dosage was available only in 6 patients and was performed before the starting of this protocol and before the subsequent infusions. In nine patients a right-sided cardiac catheterization was performed to evaluated hemodynamic parameters at baseline and after 24 h from the beginning of the treatment.

Table 1. Baseline characteristic.

Age	67±11
Male/female	10/0
Ischemic/non ischemic	6/4
Ejection fraction %	20,5±3,6
LVTDD mm	71,2±10,52
LVTDVml	240,3±48,18
ACE-inhibitors	10/10
ARB	1/10
Beta-blockers	8/10
Aldosterone antagonist	8/10
Digitalis	9/10
Diuretics	10/10

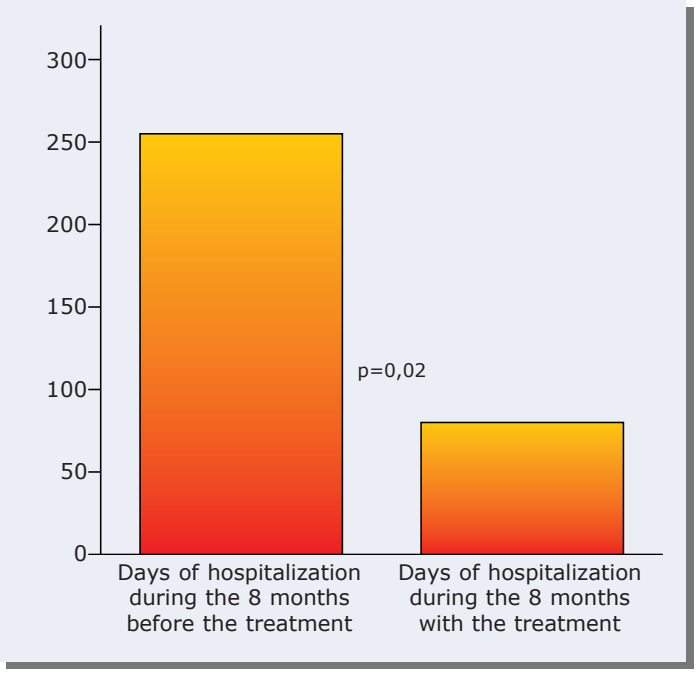
Results

Cardiac index (CI) and cardiac output (CO) were very low at baseline and improved significantly at 24 h; pulmonary wedge pressure (PWP) decreased after Levosimendan but not significantly (table 2).

The mean follow-up was 18±9 months (range 8-35 months); during the follow-up 2 pts died for refractory heart failure after 10 and 35 months respectively of therapy and one pt died for sudden death after 31 months of therapy. Another pt received heart transplant after 15 months of follow up and in another one we stopped the treatment after 22 months as required by the Heart Transplant Center; after two months the pt died for refractory heart failure. We compared the number of hospitalization and the days of hospitalization for all patients during the eight months before and after this therapy; before, we observed 20 admissions in hospital for heart failure with 256 days of hospitalization, and during the protocol the admissions in hospital were 6 with 80 days of hospitalization. Intermittent infusion of Levosimendan showed a significant reduction of hospitalization ($p = 0,02$) and of days of hospitalization ($p = 0,02$) for heart failure during the first 8 months (figure 1).

BNP level reduced during the first 9 months, but this trend was not statistically significant (see fi-

Figure 1. Days of hospitalization during the 8 months before the treatment and during the 8 months with the treatment.



gure 2); notably in these months we observed a significant reduction of hospitalization as showed before. At three months of follow-up all pts had an improvement of NYHA class of at least one point and after 12 months this improvement was still present in 4 pts.

Left ventricular echocardiographic parameters as ejection fraction (EF), telediastolic diameter (LVTDD) and telediastolic volume (LVTDV) at baseline and after 12 months didn't show significantly improvement.

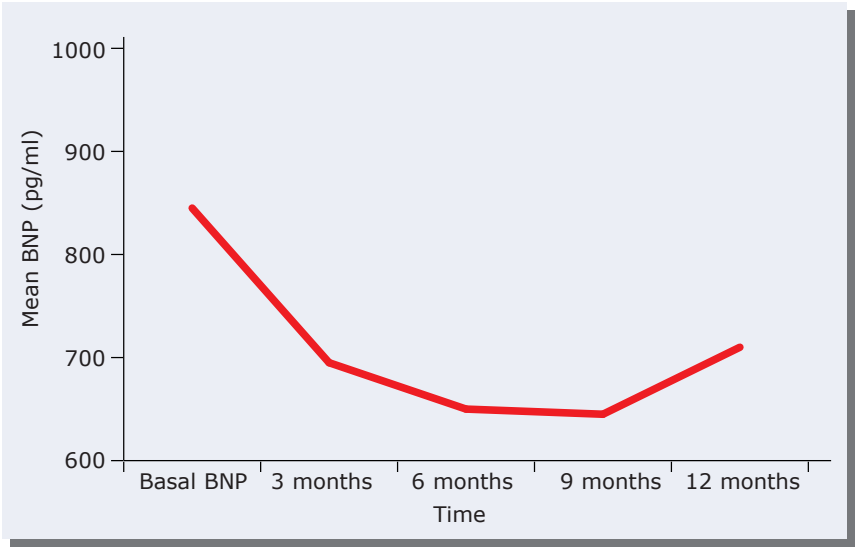
One patient, who did not tolerate beta-blocker, began therapy with bisoprololo without complication during the period of treatment with Levosimendan; this is an advantage of inotropic therapy with agent without beta-agonistic activity, as already demonstrated with PDE-inhibitor[14]. During the follow-up we had no adverse events: no hypotension, no infection and no problem with the management of the pump at home. This therapy didn't show proarrhytmic complication; all pts had an ICD, and during the therapy only two pts had ICD intervention. One pt during the 2 months before the therapy showed 8 episodes of DC-shock and during 35 months of follow-up 4 episodes after 6, 15, 24 and 30 months; in this pt, therapy with Levosimendan seemed reduce ventricular arrhythmic episodes, probably because of improvement of hemodynamic conditions. In another pts, the number of arrhythmic episodes were the same before and during the Levosimendan therapy (one episode per month).

We tried to compare the hemodynamic parameters in pts with ischemic cardiomyopathy (6 pts) and in pts with non ischemic cardiomyopathy (4 pts); only the ischemic pts had significant improvement of cardiac index and of cardiac output. Furthermore, during the follow-up, two of the non ischemic pts needed an increase in Levosimendan dosage with successful, both after 4 months of therapy; at the end of the follow-up they were treated respectively for 8 and 12 months with the augmented dose. Among ischemic pts, three needed an increase in Levosimendan dosage, but after a longer period than non ischemic pts. These increase were made after 12, 24, and 31 months from the beginning of the therapy, and after few months clinical condition worsened irreversibly: one pts had cardiac transplantation after 3 month and the others died after 1 and 4 months respectively. We hypothesize that ischemic pts have more benefit than non ischemic pts from Levosimendan, both in acute and in chronic condition.

Table 2. Hemodynamic parameters at baseline and after 24 hours; * = p <0,01.

	Baseline	+ 24 h
Cardiac output	3,09±1	3,96±1,2*
Cardiac index	1,84±0,3	2,4±0,5*
Pulmonary wedge pressure	22,6±11,4	16,63±3,81
Mean pulmonary pressure	25,8±8,5	25,33±6,9
Mean sistemic pressure	78,8±6	75,1±7,5
Central venous pressure	7,2±4,7	6,1±4,8

Figure 2. BNP trend during the first 12 months of therapy.



Discussion

We think that in patients with chronic end-stage heart failure inotropic therapy can improve quality of life and reduce hospitalization as demonstrated in previous study with dobutamine[1-4], even if, in these studies, dobutamine demonstrated an increase in mortality due to proarrhytmic events[5,6]. Levosimendan is a new inotropic agent with a minor proarrhytmic effects, with vasodilatatory and metabolic effects; these properties make it a good agent for repeated infusions. At present, there are in literature only few[9-13] experiences with repetitive infusions of Levosimendan in chronic end-stage heart failure, with different protocol and results. Our protocol is the first with Levosimendan infusion as outpatient and the follow-up is longer than that of previous study; the mean follow-up of our pts is 18±9 months with a range of 8-35 months. During the follow-up 2 pts died for refractory heart failure (after 10 and 35 months of therapy), and 1 pt died for sudden death (after 31 months of therapy); another pts died for refractory heart failure but the therapy was stopped 2 months before the death (after 22 months from the beginning of the infusion) as required by the heart transplant centre. We demonstrated a reduction in the number of hospitalization and in the days of hospitalization for heart failure at least during the first 8 months of therapy; we think that this effect is not due to a more closed observation of these pts because all received, before the beginning of this therapy, periodic evaluations in our heart failure ambulatory, with rapid clinical re-evaluation (within 24 hour) in the case of worsening dyspnoea and four pts had also daily home telemonitoring. Besides, BNP level, available only in six pts, showed a trend in reduction during the first 9 months of therapy. The reduction of the hospitalisation and the transient reduction of BNP denote the possibility to delay only for few months the progression of the disease, improving in these months the quality of life without effect on mortality. It's difficult to explain the so long follow-up of two of our pts; we tried too delay the infusion of Levosimendan in these pts and stopped it but without success, with worsening dyspnoea and increasing diuretic dosage.

Echocardiographic parameters, as LVTDD, LVTDV, EF, did not show improvement during the follow-up, as we expected, even if, other clinical reports demonstrated an improvement of these parameters[9,10]; in our opinion, in pts with very low ejection fraction, very large ventricular volume, often associated with regional dyssinchrony, is not realistic to evaluate by echocardiogram any change in these parameters induced by inotropes. In this experience, with a long follow-up, repeated infusion resulted safe without hypotensive, infective and arrhythmic complication. Only two pts had arrhythmic episodes during the follow-up, but in one pts, after the beginning of the therapy with Levosimendan, the incidence of ventricular arrhythmic episodes decreased, probably because the improvement of hemodynamic conditions. In the second pt, the number of arrhythmic episodes were the same before and during the Levosimendan therapy (one episode per month).

The positive effect of Levosimendan in these pts is due not only to its inotropic activity but also to vasodilator effect and probably also to its metabolic effect as anti-stunning agent. That is, Levosimendan improves the contractility of hiberrnating area without an increase in oxygen consumption and without proarrythmic effects. Ac-

cording to this hypothesis, Levosimendan could have a better action in pts with ischemic left ventricular dysfunction than in pts with a non ischemic left ventricular dysfunction. We tried to compare the hemodynamic parameters in pts with ischemic left ventricular dysfunction with that of the pts with non ischemic heart disease and we notice a significant improvement in cardiac output and in cardiac index only in pts with ischemic heart disease. Bedsides, during the follow-up, 5 pts needed an augmented dose of Levosimendan; 2 of these pts were non-ischemic and needed this modification of the therapy only after 4 months from the beginning, 3 of these pts were ischemic and needed the augmentation after 12 months. This could support the previous hypothesis, but at present is only sensation.

Conclusion

Our study demonstrated the safety of Levosimendan treatment in repetitive infusion in particular with an outpatient management; with our protocol we obtain a reduction of hospitalisation the main target in pts with end-stage chronic heart failure. However, we think that the real role of Levosimendan and in general of inotropic agents in pts with refractory heart failure remain at present again a "dark side of the moon". TiM

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