Original Article

Repeated Infusions of Levosimendan: Well Tolerated and Improves Functional Capacity in Decompensated Heart Failure – A Single-Centre Experience

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Background: **Levosimendan is a novel agent used in the treatment of patients with decompensated heart failure to enhance cardiac contractility. Recent clinical studies have demonstrated that single doses of levosimendan have positive symptomatic and haemodynamic benefits, few have explored the efficacy and safety of intermittent repeated doses of levosimendan.**

Aims: **In this prospective study we document our single-centre experience of repeated administration of levosimendan to patients with decompensated heart failure.**

Methods: **Prospective data were collected and analysed with respect to New York Heart Association (NYHA) class, mean arterial pressure (MAP), brain natriuretic peptide levels (BNP) and adverse events.**

Results: **Forty-four consecutive patients with decompensated heart failure received repeated doses of levosimendan. The mean dosing interval was 66.2 (12) days. All patients had documented evidence of impaired left ventricular function, with a mean ejection fraction (EF) of 23.7% (2.2). Fifty-eight percent were NYHA class IV, mean age 50 (2.4), 82% were male. A significant drop in BNP levels and improvement in NYHA class was seen post-infusion. In general, levosimendan was well tolerated with 130 (83.5%) infusions completed without an adverse event. Twenty-five percent of patients were bridged to cardiac transplant or left ventricular assist device (LVAD) insertion. Four patients received 12 infusions, in total in the community.**

Conclusion: **The majority of repeated levosimendan infusions were well tolerated, reduced BNP and improved NYHA functional class. In selected patients it can be administered in the community. Further investigation is required to assess the efficacy and safety of this approach.**

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Keywords. Heart failure; Cardiomyopathy; Levosimendan; Repeated doses; BNP; NYHA class

Introduction

Treatment options for patients with severe heart failure refractory to conventional medical therapy are limited. The use of inotropic agents such as phosphodiesterase inhibitors and adrenergic agonists produce favourable haemodynamic effects but none result in consistent improvements in symptoms and may result in shortened survival.[1–3] These drugs exert their positive inotropic effects by increasing intracellular calcium, which increases myocardial energy consumption and this may explain the deleterious effects of these compounds.[4]

Levosimendan is a new calcium-sensitising drug which increases myocardial contractility without promoting intracellular calcium accumulation.[5] Its clinical effects are mediated by the parent compound and its active metabolite OR-1896 which peaks 72 hours after a 24 hour intravenous infusion.[6] Improvement in haemodynamic parameters are sustained for at least seven days.[7] Recent clinical studies have demonstrated that a single 24 hour infusion of levosimendan, in patients with decompensated heart failure of ischaemic and non-ischaemic aetiology increases cardiac output, reduces cardiac filling pressures, improves symptoms and reduces short-term morbidity when compared to dobutamine or placebo,[8–10] although all-cause mortality at 180 days is not affected.[11]

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Few studies have explored the efficacy and safety of intermittent repeated doses of levosimendan and to our knowledge there have been no reports of levosimendan being given in the out-patient setting.[12,13] In this prospective observational study we describe our single-centre experience of administering repeated doses of levosimendan to patients with decompensated heart failure.

Methods

Patient Selection

Patients with decompensated heart failure with a left ventricular ejection fraction (EF) ≤35% and an elevated B-type natriuretic peptide (BNP) ≥150 ng/L who failed to respond to manipulation of oral therapy and intravenous diuretics were considered for levosimendan infusion. Patients who showed symptomatic benefit after the first dose of levosimendan, together with a reduction in BNP levels and NHYA score, were considered for further doses of levosimendan if clinical evidence of decompensation subsequently ensued.

Levosimendan Administration

Levosimendan was given as a 10 minute intravenous bolus injection of 6–12 μg/kg in 46 (35%) administrations followed by a continuous 24 hour infusion, initially at a rate of 0.1 μg/kg/min; the rate was up-titrated hourly by 0.1 μg/kg/min if systolic BP ≥ 90 mmHg to a maximum rate of 0.4 μg/kg/min. A total dose of 12.5 mg was administered per infusion. In 102 (65%) doses no bolus injection was given and infusions were commenced at 0.1 μg/kg/min for an hour and then titrated as above (Table 1). Initial 24 hour infusions were administered in hospital. Four patients, who were haemodynamically stable during their initial infusion, received subsequent infusions as an out-patient using a Graseby CADD-Legacy™ PLUS pump. The mean infusion duration was 16.8 (0.5) h (range 5–32 h).

Data Analysis

We prospectively collected data on all patients receiving a levosimendan infusion for decompensated heart failure from 1st June 2002 to 1st July 2006. Data was collected on NYHA class, BNP levels, serum creatinine and mean arterial pressure (MAP), pre- and post-levosimendan infusion. Adverse events and mortality were recorded. Data were entered on to a computerised database. Categorical variables were compared between groups by Fisher's exact test. Differences between groups were assessed by a paired two-tailed *t*-test. Continuous variables are expressed as mean (standard error of the mean (SEM)). A value of $p < 0.05$ was considered significant.

Table 1. *Administration*

	No. of Infusions
Loading dose over 10 min (mcg/kg/min)	
Nil	102 (65%)
6	45 (29%)
12	9 (6%)
Peak-dose for maintenance infusions (mcg/kg/min)	
0.1	44 (28%)
0.2	94 (60%)
0.4	16 (10%)

Table 2. *Aetiology of Heart Failure*

	N	%
Ischaemic	21	48
Non-Ischaemic:	23	52
Idiopathic	11	
Valvular	5	
Post-viral	4	
Truncus arteriosus	1	
Post-transplant vascular rejection	1	
Becker's muscular dystrophy	1	

Results

Forty-four patients received a total of 156 doses of levosimendan in the 48-month study period. The mean age of the subjects was 50 (2.4) and the majority were male (82%). All patients had documented evidence of significantly impaired left ventricular systolic function, with a mean EF on transthoracic echocardiogram calculated by Simpson's biplane method of 23.7% (2.2). Patient status prior to infusion: NYHA Class IV 58% ($n = 90$), Class III 41% ($n = 64$) and Class II 1% ($n = 2$). All subjects were receiving maximally tolerated doses of ACE inhibitors, beta-blockers, angiotensin II blockers, diuretics and spironolactone. There was a similar distribution between ischaemic and non-ischaemic aetiology (Table 2). Six (4%) infusions were administered concomitantly with a dobutamine infusion.

Twenty-one (47.7%) patients received two infusions of levosimendan, with seven (25.9%) receiving more than five infusions (Fig. 1). The mean dosing interval was 66.2 (12.0) days. One subject received 26 infusions over a two-year period whilst awaiting availability of a destination LVAD. Four patients received a total of 12 infusions as an out-patient using a Graseby CADD-Legacy™ PLUS pump.

Pre- and post-infusion BNP levels were available in 24 patients (40 infusions). BNP levels were not measured in the remaining 20 patients (116 infusions) as a local assay of BNP did not become available until 2003. There was a significant reduction in BNP levels collected 5.4 (0.7) days post-levosimendan infusion;

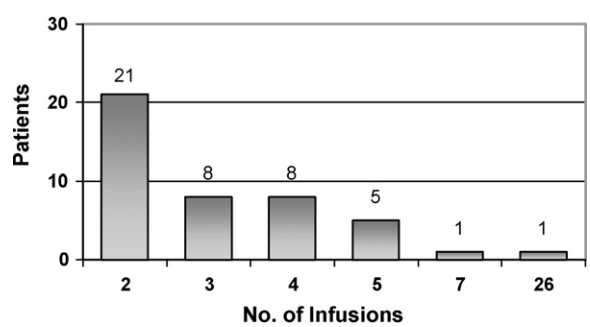

Figure 1. *Number of infusions per patient.*