Use of levosimendan in critically ill patients with severe aortic stenosis and left ventricular dysfunction

European Heart Journal: Acute Cardiovascular Care
1(4) 281–284

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DOI: 10.1177/2048872612467294

acc.sagepub.com

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Abstract

Congestive heart failure and left ventricular dysfunction in the setting of severe aortic stenosis are associated with a high mortality rate. Evidence on optimal medical therapy is scanty. Vasodilators were traditionally considered to be contraindicated in severe aortic stenosis, albeit this concept has recently been challenged. The use of levosimendan, which has positive inotropic, vasodilatory and cardioprotective properties seems attractive. We describe a small series of exceedingly ill patients with severe aortic stenosis and left ventricular dysfunction, in different clinical settings (acute heart failure, cardiogenic shock and difficult-to-wean ventilatory support), in which levosimendan was successfully used.

Keywords

Severe aortic stenosis, left ventricular dysfunction, levosimendan

Received: 17 July 2012; accepted: 18 October 2012

Introduction

Severe aortic stenosis (AS) carries a dismal prognosis when associated with congestive heart failure, with a mean survival of less than two years in conservatively treated patients.¹ Aortic valve replacement (AVR) is the most effective treatment but, as soon as left ventricular (LV) systolic dysfunction ensues, the perioperative mortality rate increases up to 25%,¹ and can reach 50% if congestion cannot be relieved.²

Balloon valvulotomy has been recommended in this situation as a bridge to surgery, yet it is associated with a high rate of procedural complications and poor long-term results.³

Therefore, the quest for an effective medical therapy to improve cardiac function in these critically ill patients continues.

Dobutamine has been studied during stress echocardiography in patients with severe AS and reduced LV ejection fraction (LVEF). However, it is contraindicated if there is coronary artery disease (CAD), since it may induce arrhythmias and myocardial ischemia.⁴

While drugs with vasodilator effects have traditionally been contraindicated in severe AS,⁵ this concept has recently been challenged, as sodium nitroprusside has been shown to have beneficial hemodynamic effects in severe decompensated AS, providing an effective bridge to AVR

or oral vasodilator therapy.⁶ However, nitroprusside's narrow therapeutic window and possibility of triggering cardiac ischemia mandates caution.⁷

Being an inodilator, levosimendan has the potential benefit of adding an inotropic effect to the vasodilator action,⁸ bringing together the best of dobutamine and nitroprusside.

We describe three critically ill patients with severe AS and LV dysfunction in which levosimendan was successfully used.

Case reports

Case 1

A 65-year-old male patient was admitted at the Intensive Cardiac Care Unit (ICCU) with new onset New York Heart

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Association (NYHA) class IV acute heart failure. Physical examination showed: atrial flutter (120 beats per min); blood pressure 150/90 mmHg and markedly elevated jugular venous pressure. Echocardiography revealed a mildly dilated non-hypertrophied LV, with severely impaired systolic function (LVEF<20%) and high filling pressures ($E/E' = 20$); aortic valve was calcified with an area of 0.6 cm² and 16 mmHg mean aortic gradient (mAG). Coronary angiography showed one vessel diseased. Despite successful electrical cardioversion and intravenous furosemide with negative fluid balance, the patient remained in NYHA class IV. Therefore, 0.1 mcg/Kg/min intravenous levosimendan was started, leading to marked diuresis and significant improvement in dyspnea. The patient was discharged at day 18 on medical therapy. One month post-discharge, he was in NYHA class II, and there was remarkable improvement in echocardiographic parameters: LVEF was 50%; aortic valve area of 0.85 cm² with 43 mmHg mAG. At this time, percutaneous coronary angioplasty was performed followed by successful AVR surgery.

Case 2

An 85-year-old male with known CAD and chronic kidney disease was admitted in cardiogenic shock. Echocardiography showed mildly dilated, globally hypokinetic LV (LVEF 30%); heavily calcified aortic valve, area of 0.6 cm² and 21 mmHg mAG; and moderate-severe mitral regurgitation. Dobutamine, noradrenaline and furosemide infusions were administered. Since there was no diuretic response, ultrafiltration was started. Within six hours the patient resumed diuresis. Clinical improvement was observed, however we could not wean off the vasopressor support. On levosimendan infusion, we were able to withdraw dobutamine and noradrenaline gradually. No further inotropic support was needed thereafter. Control echocardiography revealed increases in LVEF (35%) and mAG (33 mmHg), indicating true AS and the presence of contractile reserve. Considering the remarkable clinical and echocardiographic improvement, the patient was proposed for AVR. However, as hospitalization was complicated with nosocomial urosepsis, worsening the fragile state of the patient, he was discharged on medical therapy, passing away one month later.

Case 3

A 67-year-old male patient with known severe AS, two-vessel CAD and systolic dysfunction was admitted to the emergency department with acute pulmonary edema. Some minutes following admission, he suffered cardiac arrest. After successful resuscitation, he was transferred to ICCU on mechanical ventilation and noradrenaline infusion. Echocardiography showed LVEF 30%; 36 mmHg mAG and high LV-filling pressures with a restrictive pattern.

Although vasopressor support was withdrawn, every attempt to wean him off the ventilator was unsuccessful due to severe pulmonary congestion. As a last resort, levosimendan infusion was started at 0.1 mcg/Kg/min. 24 hours later, invasive ventilation support was weaned. LV systolic function and mAG increased to 43% and 47 mmHg respectively. The patient underwent successful AVR and myocardial revascularization.

Discussion

Patients with heart failure due to severe AS combined with LV dysfunction present the dual challenge of treating heart failure and preventing peri-operative complications if cardiac surgery is undertaken. To the best of our knowledge, our case reports are among the very few in which levosimendan has been used in this clinical setting.^{9,10}

Levosimendan is characterized by a dual mechanism of action. It sensitizes troponin C to calcium in a manner dependent on calcium concentration, improving contraction at low energy cost, and leads to vasodilatation through the opening of ATP-sensitive potassium channels.^{8,11} Through the combined inotropic and vasodilatory effects, levosimendan increases cardiac output without significantly increasing myocardial oxygen demand.⁸

The beneficial effect of levosimendan in the treatment of heart failure due to severe LV systolic dysfunction is already well documented.¹² However, patients with severe AS have been excluded from studies.

Pathophysiologically, levosimendan appears to be a promising alternative to dobutamine, the only inotrope thoroughly studied in AS.⁴

Traditionally, drugs with vasodilator properties have been contra-indicated in severe AS⁵ because of concern that they may precipitate life-threatening hypotension. Recently, this concept has been challenged in the UNLOAD study,⁶ which showed for the first time that the administration of nitroprusside to patients with severe AS and severe LV dysfunction dramatically improved cardiac output, providing an effective bridge to AVR or oral vasodilator therapy. The rationale is that, in the setting of impaired contractility, the LV is exquisitely sensitive to afterload excess,¹³ and reduction in this excess leads to proportional increase in cardiac output, preventing the development of hypotension.¹⁴

The use of levosimendan, which has positive inotropic, vasodilatory and cardioprotective effects, is therefore attractive. In addition, the long-lasting pharmacodynamic effects of its metabolite OR-1896 (7–9 days) may help to maintain improved cardiac performance.¹⁵

Our patients were exceedingly ill. Nevertheless, following 24 hours of levosimendan infusion there was a significant clinical and echocardiographic improvement. Furthermore, levosimendan, used without a loading dose and at a maximum rate of 0.1 mcg/Kg/min, was well

tolerated, as neither arrhythmias nor hypotension were recorded during the entire monitoring period.

Discrimination between true and pseudo AS in patients with severe systolic dysfunction is nowadays performed with stress echocardiography with dobutamine.⁴ In Case 1 we were faced with this differential diagnosis since after successful cardioversion the patient persisted with reduced LVEF. Levosimendan was our option due to its long-lasting positive effects on myocardial function and coronary blood flow. Nevertheless, we believe that the outstanding improvement in systolic function was the sum of all the actions taken.

Scarce reports suggest that levosimendan can improve hemodynamics even in patients with cardiogenic shock when combined with catecholamines to maintain adequate perfusion pressures,^{16–18} as in Case 2.

Regarding Case 3, recent reports highlighted the potential benefit of levosimendan in difficult-to-wean patients due to heart failure.^{19–21} It counteracts the effects of cardiopulmonary interactions, like the increase in systemic venous return and LV afterload present during weaning off ventilation, by enhancing cardiac contractility and reducing systemic and pulmonary vascular resistance, thus decreasing LV-filling pressures and afterload.²²

The high cost of levosimendan has frequently been taken into consideration when discussing the treatment of very severe patients with poor prognosis. However, overall costs must also take into consideration the savings in length of stay in the ICCU.

In conclusion, levosimendan rapidly and markedly improved cardiac function in our patients with decompensated heart failure due to severe LV dysfunction in the context of severe AS. It provided a safe and effective bridge to AVR or oral therapy in these critically ill patients.

We hope our clinical experience will influence other investigators in pursuing the validation of levosimendan application in this clinical setting since, until randomized clinical trials are done, the beneficial role of this drug in this specific population cannot be definitely determined.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

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