Case Report

Treatment of cardiogenic shock with levosimendan in combination with β-adrenergic antagonists

J. A. Alhashemi*

Department of Anesthesia and Critical Care, King Abdulaziz University, King Abdulaziz University Hospital, PO Box 31648, Jeddah 21418, Saudi Arabia

*E-mail: jalhashemi@kau.edu.sa

Levosimendan, a calcium sensitizer, was used in combination with β-adrenergic antagonists in a man aged 56 yr with cardiogenic shock, complicating acute myocardial infarction, who developed severe tachycardia after dobutamine administration. The patient’s trachea was intubated, his lungs were ventilated, and he was started on dopamine 5 μg kg⁻¹ min⁻¹ and dobutamine 5 μg kg⁻¹ min⁻¹ titrated to a mean arterial pressure ≥65 mm Hg. He progressively became tachycardiac (>120 beats min⁻¹) with a cardiac index (CI) of 1.4 litre min⁻¹ m⁻² despite adequate preload. Levosimendan 6 μg kg⁻¹ was administered intravenously over 10 min followed by a continuous infusion of 0.2 μg kg⁻¹ min⁻¹ for 24 h. Within 30 min, the patient’s CI increased to 2.2 litre min⁻¹ m⁻², but the heart rate (HR) also increased from 142 to 155 beats min⁻¹. Esmolol 1 mg kg⁻¹ i.v. was administered with a consequent transient decrease in HR to 110 beats min⁻¹ without adverse haemodynamic effects; however, HR increased again shortly afterwards. Carvedilol 3.125 mg orally twice a day was then administered, and the dose was increased to 6.25 mg orally twice daily on the following day. Subsequently, HR decreased over time and both catecholamines were discontinued 14 h after starting levosimendan infusion. The trachea was extubated within 20 h and the patient was discharged to the ward on day 4 after admission. In conclusion, levosimendan in combination with a β-adrenergic antagonist may have beneficial effects in patients with cardiogenic shock who exhibit tachycardia in response to inotropic agents.


Keywords: complications, myocardial infarction; heart arrhythmia, tachycardia; heart, dobutamine; heart, esmolol; pharmacology, agonists adrenergic

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Levosimendan is a new inotropic agent that is used in the treatment of acute and chronic heart failure.¹ It increases myocardial contractility by enhancing the sensitivity of the myocardial muscles to intracellular calcium without increasing intracellular calcium concentration.² In addition, this drug decreases cardiac workload by opening ATP-dependent potassium channels in vascular smooth muscles, resulting in systemic vasodilation and cardiac afterload reduction.² These two mechanisms of action produce enhanced cardiac output without increasing myocardial oxygen demand,³ an effect that is not observed with other inotropic agents. Although the safety and efficacy of levosimendan has been demonstrated in different patient populations with congestive heart failure,¹ ³ ⁴ there is little information about its use in patients with cardiogenic shock. Furthermore, the use of this drug in combination with β-adrenergic blocking agents in patients with cardiogenic shock has not been described previously. In this report, levosimendan was administered to a patient with cardiogenic shock complicating acute myocardial infarction. This resulted in an exacerbation of the patient’s pre-existing tachycardia which was then successfully treated by the addition of β-adrenergic antagonists.

Case history

A man aged 56 yr and weighing 63 kg presented to the emergency room with acute retrosternal chest pain of 7 h duration. He had had non-insulin-dependent diabetes mellitus for 14 years, but had no history of hypertension, angina or congestive heart failure. On physical examination, the heart rate (HR) was 110 beats min⁻¹, blood pressure (BP) was 110/61 mm Hg, ventilatory frequency was 20 bpm and SpO₂ was 98% on 8 litre min⁻¹ oxygen. Lungs were clear to auscultation and cardiac examination was normal. A 12-lead ECG demonstrated changes of acute anterior wall (V₂–V₆)
myocardial infarction, and laboratory investigations revealed increased serum troponin I (3.9 μg litre\(^{-1}\); normal range 0–0.05 μg litre\(^{-1}\)) and normal renal function. The patient received alteplase followed by heparin infusion, was admitted to the intensive care unit (ICU) and was prescribed atenolol 25 mg orally once daily. Two hours later, the patient became tachypneic at 27 breaths min\(^{-1}\), Sp\(_O_2\) fell to 91% on F\(_{\text{IO}}\) of 0.5, BP 108/65 mm Hg and HR 112 beats min\(^{-1}\). Auscultation revealed an S\(_3\) gallop, without murmurs, and bilateral basal crepitations, and the chest radiograph showed pulmonary oedema. The patient had no chest pain and there were no new changes on the ECG. Atenolol was stopped and frusemide 40 mg i.v. every 8 h was administered. However, the patient remained tachypneic at 28–32 breaths min\(^{-1}\) with Sp\(_O_2\) 90–92% on 50% oxygen despite an average urine output of 100 ml h\(^{-1}\). Repeat troponin I measurement at 4 h showed increased levels to 326.7 μg litre\(^{-1}\). Twelve hours later, BP and Sp\(_O_2\) had decreased to 88/42 mm Hg and 88%, respectively, ventilatory frequency had increased to 41 bpm and HR remained at 114 beats min\(^{-1}\). There were no electrolyte disturbances and the patient’s arterial blood gas showed pH 7.34, \(P_{aO_2}\) = 9.2 kPa, \(P_{CO_2}\) = 4.5 kPa and [HCO\(_3^\-\)] = 21.2 mmol litre\(^{-1}\). The trachea was then intubated and the lungs were mechanically ventilated. In addition, dopamine 5 μg kg\(^{-1}\) min\(^{-1}\) and dobutamine 5 μg kg\(^{-1}\) min\(^{-1}\) were administered, and were titrated to keep mean arterial pressure ≥65 mm Hg. When the dobutamine dose was increased to 7 μg kg\(^{-1}\) min\(^{-1}\), the patient’s HR progressively increased to >120 beats min\(^{-1}\) despite a central venous pressure (CVP) of 12 mm Hg. This precluded further increments in dobutamine dose. Transthoracic echocardiography demonstrated severe hypokinesia of the septum, the apex and the anterolateral and inferior walls with an ejection fraction of 15–20%. Cardiac chambers were normal in diameter, and there were no valvular abnormalities or pericardial effusion. A non-invasive cardiac output monitor (NICOM, Novametrix Medica Systems Inc., Wallingford, CT) showed a cardiac index (CI) of 1.4 litre min\(^{-1}\) m\(^{-2}\). The patient’s serum lactate was 2.1 mmol litre\(^{-1}\) and the central venous oxygen saturation (S\(_{CVO_2}\)) was 60%. Levosimendan 6 μg kg\(^{-1}\) was administered as a bolus infusion over 10 min, followed by a continuous infusion of 0.2 μg kg\(^{-1}\) min\(^{-1}\). The patient’s CI increased to 2.2 litre min\(^{-1}\) m\(^{-2}\) and the S\(_{CVO_2}\) increased to 70% within 30 min of starting levosimendan infusion, and the serum lactate level decreased to 1.0 mmol litre\(^{-1}\) after 6 h of therapy. On the other hand, the patient’s pre-existing tachycardia was exacerbated and the HR further increased from 142 to 155 beats min\(^{-1}\) within 30 min of administering levosimendan. However, the rhythm remained sinus, there were no new changes on the ECG and the patient’s CVP remained at 8 mm Hg. Esmolol 1 mg kg\(^{-1}\) i.v. was administered and the HR decreased transiently to 110 beats min\(^{-1}\) without adverse haemodynamic effects; however, it increased again shortly afterwards. Carvedilol 3.125 mg orally twice daily was then administered and was increased to 6.25 mg orally twice daily on the following day. Subsequently, the HR progressively decreased over time without any major change in the patient’s haemodynamic profile. Dopamine and dobutamine requirements decreased to 2 μg kg\(^{-1}\) min\(^{-1}\) and 5 μg kg\(^{-1}\) min\(^{-1}\), respectively, within 4 h of starting levosimendan infusion, and both drugs were discontinued at 10 h. Weaning from mechanical ventilation was begun 10 h after commencing levosimendan infusion and the trachea was extubated 10 h later. Serum troponin I levels measured at 24 and 48 h after presentation were 223.3 μg litre\(^{-1}\) and 58.9 μg litre\(^{-1}\), respectively. The patient was discharged to the medical ward on captopril and carvedilol on day 4, and he left the hospital on day 7 after his initial presentation. His discharge 12-lead ECG continued to show Q-waves in V\(_2\)–V\(_6\) chest leads.

**Discussion**

Cardiogenic shock complicating acute myocardial infarction is a challenging condition to treat. Vasopressors and inotropic agents required to increase perfusion pressure and cardiac output also increase myocardial oxygen demand\(^5\) and could potentially worsen ongoing myocardial ischaemia. Furthermore, these drugs may impair diastolic relaxation\(^6\) by increasing intracellular calcium concentration in myocytes. In contrast, levosimendan does not increase myocardial oxygen demand\(^7\) nor does it impair diastolic relaxation.\(^2\) These features in combination with its vasodilatory properties make levosimendan a promising agent in the management of patients with cardiogenic shock.

In the patient described here, the observed baseline tachycardia was most likely a compensatory mechanism for the low cardiac output, and it was exacerbated by the β-adrenergic stimulant effects of dopamine and dobutamine. It is unlikely that the increase in HR was due to hypovolaemia since the patient’s CVP remained at 7–8 mm Hg for several hours after dobutamine was first administered. Despite an adequate CVP and dobutamine, the patient’s CI remained very low. This may have been because the dobutamine dose was insufficient to improve cardiac performance, but it was not possible to increase the dose because of the patient’s tachycardia. A higher dose of dobutamine could have increased the CI, but at the expense of increased HR and myocardial oxygen consumption\(^5\), both of which would have deleterious effects on the patient’s underlying myocardial ischaemia.

We chose to use levosimendan as it has been shown to be safe in patients with acute myocardial infarction,\(^4\) it has anti-ischaemic effects\(^7\) and it does not increase myocardial oxygen consumption\(^7\) or have β-adrenergic stimulant effects. It was administered in a small loading dose\(^8\) of 6 μg kg\(^{-1}\) to avoid the decrease in BP that has been observed with higher loading doses.\(^2\) There was a significant improvement in CI within 30 min of levosimendan administration, but HR increased. This is in keeping with the observations of

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**Levosimendan and β-blockers for cardiogenic shock**

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Kivikko and colleagues, who reported a mean increase of 10 beats min⁻¹ following levosimendan administration, and Slawsky and coworkers, who demonstrated an 8% increase in HR in patients who received levosimendan 6 μg kg⁻¹ bolus followed by an infusion of 0.4 μg kg⁻¹ min⁻¹ compared with placebo. Although the exact mechanism of the tachycardia observed in association with levosimendan administration remains to be determined, a plausible explanation is the vasodilatory effects of the drug and the reduction in systemic vascular resistance with consequent reflex increase in HR. However, it is unlikely that hypovolaemia had contributed to levosimendan-associated tachycardia in the patient described here because there was no change in the CVP values for several hours after the HR had increased further. Furthermore, subsequent β-adrenergic blockade would have resulted in a significant decrease in BP and/or CI if the patient had been hypovolaemic, and this was not the case in this patient. The decrease in CVP observed 17 h after levosimendan administration was probably due to the diuresis that occurred with the improvement in CI. This reduction in CVP was treated with bolus administration of 500 ml of 6% hydroxyethyl starch which raised the CVP to 9 mm Hg.

Although the CI improved after levosimendan administration, controlling the patient’s HR was important in order to decrease myocardial oxygen demand and to allow better ventricular filling and improved coronary perfusion. Since levosimendan has no β-adrenergic action, we chose intravenous esmolol because of its short half-life in case it produced unwanted haemodynamic effects. Esmolol transiently decreased the patient’s HR without adverse effects on CI or BP. However, it is possible that the haemodynamic effects of esmolol were attenuated by the dopamine and dobutamine infusions. Nevertheless, the patient was subsequently started on carvedilol while still on levosimendan infusion. The patient’s HR gradually decreased over time without a change in either CI or BP. The findings of Follath and colleagues, who demonstrated that the concomitant use of β-adrenergic antagonists does not affect the haemodynamic effects of levosimendan in patients with heart failure, support this observation. In contrast, β-blockade attenuates the effects of dobutamine on CI in this patient population. Furthermore, Lehtonen and Sundberg showed that 1 week of carvedilol administration had no effects on the contractility-enhancing properties of levosimendan in healthy volunteers.

In conclusion, levosimendan in combination with a β-adrenergic antagonist may have a beneficial role in patients with cardiogenic shock who exhibit significant tachycardia in response to catecholamine. However, a randomized controlled trial is required to substantiate this hypothesis.

References
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