Repetitive use of levosimendan in clinical practice: a case series
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Abstract
Levosimendan was developed as a treatment for acute decompen-sation of severe heart failure (HF). Its use has evolved during recent years, and new HF treatment strategies in different settings have been developed. This case series aimed to show indications for the use of levosimendan and to discuss the treatment response in various settings. Repetitive levosimendan infusions were found to be safe and effective. They seemed to prolong the time of clinical stability, although they did not alter the eventual natural history of HF, with increasing frequency of hospitalisations and rising natriuretic peptide levels.

Keywords: heart failure, advanced heart failure, drugs in cardiology, intensive care

Heart failure (HF) is a global problem affecting approximately 26 million people worldwide.1 Because of aging populations, the HF morbidity rate is expected to rise, thus generating more hospitalisations and costs for healthcare systems.1 Moreover, with the number of HF patients, the number of patients with advanced HF requiring therapy due to multiple HF decompensations is rising as well. HF treatment should focus on reduction in mortality and hospitalisation rates and improvement in the quality of life.2 Acute decompensated HF requires treatment with diuretics, vasodilators and inotropes.2 Levosimendan acts as a calcium (Ca2+) sensitiser and has a positive cardiac inotropic effect. It also shows a vasodilatory effect due to its mechanism of opening potassium channels in the vasculature and cardiomyocytes.3,4 These result in increased stroke volume and heart rate, consequently increasing the cardiac output.

According to the Lion-Heart trial, levosimendan significantly reduced N-terminal B-type natriuretic peptide (NT-proBNP) concentration in comparison with placebo.5 This effect translates into reduction in the risk of hospitalisation6 and death,7 and is explained by both the haemodynamic and cardioprotective properties of levosimendan.

The indications for levosimendan in HF have been changing throughout the years. Nowadays they include acute decompensated HF and repetitive use in chronic HF patients to prevent decompensation. However, the treatment strategy for repetitive use of levosimendan has not been clearly defined. This case series aimed to show indications for levosimendan use and to discuss the treatment response in various settings.

Case report 1
A 61-year-old man presented to the clinic (August 2018) due to decompensation of chronic HF, diagnosed 12 years earlier. His co-morbidities included ischaemic heart disease (IHD), acquired after an antero-lateral ST-segment elevation myocardial infarction (STEMI), treated with percutaneous coronary intervention (PCI) of the left anterior descending coronary artery (LAD) in 2008, and non-ST-segment elevation myocardial infarction (NSTEMI) treated with percutaneous balloon angioplasty (POBA) of the right coronary artery (RCA) in 2014. Since 2009 the patient has had an implantable cardioverter–defibrillator (ICD), which was upgraded to cardiac resynchronisation therapy (CRT-D) in 2019. Additionally, the patient suffers from chronic kidney disease (stage 3a).

At admission, he presented with severe dyspnoea, orthopnoea and abdominal pain. Echocardiography (echo) showed a general impairment of the left ventricular (LV) function with reduced LV ejection fraction (LVEF), estimated at 15%. The brain natriuretic peptide (BNP) value was 2 422 pg/ml. Due to a poor response to diuretics and standard inotropic treatment with dobutamine (7–15 mcg/kg/min), levosimendan was administered. After a 12.5-mg/24-hour infusion of levosimendan, LVEF improvement to 25% was observed, and the BNP value decreased to 1 779 pg/ml. After a spectacular improvement of the patient’s condition, he was discharged home in a stable state (New York Heart Association: NYHA class II).

Subsequent decompensation occurred after nine months from baseline (May 2019). The patient presented in NYHA class III and the LVEF was measured at 15%. At admission, the NT-proBNP value was 5 844 pg/ml. Despite intensification of the diuretic and inotropic treatment with dobutamine (7–15 mcg/kg/min), the NT-proBNP level continued increasing up to
Case report 2
A 40-year-old woman presented to the clinic (November 2018) with acute HF (severe dyspnoea at rest: NYHA class IV). She had a co-morbidity of breast cancer and a history of chemotherapy with doxorubicin, among others. During her control echo six weeks earlier, LVEF was within the normal range, but three weeks prior to hospitalisation, a worsening of her LVEF had been observed. Consequently, treatment with beta-blockers, angiotensin converting enzyme inhibitors, mineralocorticoid receptor antagonists and furosemide were started on an out-patient basis. The patient’s state was gradually worsening, with increasing dyspnoea, decreasing exercise tolerance, and fatigue, which eventually required hospitalisation. Additional tests revealed general hypokinesis with a LVEF of 15% and elevated BNP level (757 pg/ml).

Due to a poor response to intravenous diuretic, on the fifth day, a levosimendan (12.5 mg/24-hour infusion) was administered. The response and tolerance for treatment was satisfying. A follow-up echo showed a significant improvement in LVEF to 35%. Subsequently, during the course of the hospitalisation, the LVEF decreased. Afterwards, on the 12th day of hospitalisation, another dose of levosimendan 12.5 mg/24 hours was administered. The patient’s LVEF increased again to 35% and the BNP level decreased to 423 pg/ml. After obtaining a stable clinical state (NYHA class II), the patient was discharged.

Another decompensation event followed in February 2019. The patient presented with paroxysmal dyspnoea and nausea (NYHA class III). His LVEF was again at 20%. The GFR dropped to 31 ml/min and creatinine level increased to 178 μmol/l. The BNP level was 2 863 pg/ml at admission. Again, due to the poor response to the diuretic and catecholamine treatment, levosimendan was administered (12.5 mg/24-hour infusion). The patient’s response was not as good as during the previous hospitalisation. Nevertheless, it was satisfactory. The BNP value decreased to 2 781 pg/ml and LVEF increased to 25%. The GFR increased to 43 ml/ml and creatinine level decreased to 150 μmol/l. Despite only a moderate response of the BNP and LVEF, clinical symptoms were improved to NYHA class II.

This case is an example of the fact that even despite the lack of improvement in echocardiographic or biochemical parameters in the form of natriuretic peptides, after application of levsimendan, an improvement in terms of the clinical state can be achieved.

Case report 4
A 49-year-old man presented to the clinic (August 2019) with oedema of the lower limbs, ascites, severe dyspnoea at rest (NYHA class IV) and his body weight was increased by 13 kg. His co-morbidities included chronic atrial fibrillation, hypertension, type 2 diabetes, post minimally invasive aortic valve replacement (2018) and ICD implantation (2015). At admission, the LVEF was 20% and BNP level was 1 528 pg/ml.

The patient required furosemide and dobutamine infusions, which were continued up to the point when his body mass had dropped by approximately 10 kg. The attempts to discontinue dobutamine and furosemide resulted in worsening dyspnoea.
and increasing body weight. Levosimendan was administered at a dose of 12.5 mg/24 hours. The response and the tolerance of the treatment was satisfactory. LVEF increased to 25% and BNP level dropped to 1 43 pg/ml. The patient was discharged in a stable state in NYHA class II.

After 42 days, a deterioration in the clinical state occurred, with increasing exertional dyspnoea, orthopnoea and abdomen perimeter. At admission, the LVEF was 20% and BNP level was 2 787 pg/ml. Due to the previous satisfying response, levosimendan (12.5mg/24 hours) was administered. The patient’s condition improved, as well as the LVEF (25%). The BNP value dropped to 2 154 pg/ml. The patient was discharged from hospital in a stable condition in NYHA class II.

Another decompensation event followed after 52 days, in December 2019. The patient presented in NYHA class IV, with oedema of the lower limbs, ascites and an increase in body weight of about 9 kg. LVEF was at 20%. At admission, the BNP value was 2 991 pg/ml. Due to the severe state, the patient required an intensification of the diuretic and inotropic treatment with furosemide and dobutamine. Given the poor response to the treatment, the patient received a levosimendan infusion (12.5 mg/24 hours). His LVEF improved to 25% and the BNP value decreased to 1 803 pg/ml. The patient was discharged from hospital in a stable condition. His NYHA class improved from IV to III.

This case proves that levosimendan is very potent and more effective than intravenous diuretics, even if combined with dobutamine. Levosimendan infusions result in rapid clinical improvement.

**Discussion**

The prevalence of advanced HF is increasing, and is associated with high morbidity and mortality rates. According to the Heart Failure Association of the European Society of Cardiology, advanced HF is defined as a stage where conventionally used treatments are insufficient to control the patient’s symptoms, and advanced or palliative therapies are needed to obtain fluid volume control and end-of-life comfort care.

Solutions to improve the patients’ clinical state and to prevent hospitalisations and death are being investigated. Repetitive infusions of levosimendan may offer an advantage of a prolonged inotropic effect with the possibility of improving the clinical state. There are very limited data regarding the effectiveness of such a treatment. Use of levosimendan has gained popularity in intermittent use, since the haemodynamic effect may last more than seven days after infusion. Probably the reason is the long half-life of the pharmacoologically active metabolite. Nevertheless, the heterogeneity of the evidence seems to show potential.

The LevoRep study evaluated the effect of four injections of levosimendan (0.2 μg/kg/min) over six hours at two-week intervals in 120 advanced HF patients, and the results concerning event-free survival favoured the levosimendan group versus placebo. The Lion-Heart study, involving 69 patients with advanced HF, replicated the above methodology with a longer-duration study (12 weeks), showing a reduction in NT-proBNP level and readmission rate during the 12 months.

Based on the available data, the strategy of repetitive infusions can be considered in alleviation of the symptoms and improvement of the quality of life in patients with advanced HF. What is more, on the basis of the research results, levosimendan, as one of the inodilators, was included in the recommendations for the treatment of advanced HF. The questions of how many levosimendan doses can be administered and the interval length between the doses is still unknown.

**Conclusions**

Repetitive levosimendan infusions are safe and effective. They seem to prolong the time of clinical stability, even though they do not alter the eventual natural history of HF, with increasing frequency of hospitalisations and rising NT-proBNP level.

**References**

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