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Use of levosimendan in patients with heart failure in different settings: case reports and treatment guidance

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ABSTRACT

Introduction: The inodilator levosimendan was developed as a treatment for acutely decompensated severe chronic heart failure. In recent years, its use has broadened to treatment of heart failure in different settings. These include advanced chronic heart failure, and other scenarios where haemodynamic stability is sought, such as pre-operative treatment of patients at risk of low cardiac output syndrome or peri-operative heart failure. The aims of this presentation of four case reports were to compare the use of levosimendan in different settings, and to highlight differences and similarities in the effects obtained, with the purpose of defining common guidance on the use of levosimendan.

Methods: We retrospectively reviewed the records of patients with heart failure in the registries of our wards, identified and described four cases where levosimendan was received in four different settings. We provide here a systematic report on these four cases.

Results: One patient suffered from acutely worsened chronic heart failure, one from advanced chronic heart failure, with repetitive treatment needed, one experienced acute ventricular failure as a result of a perioperative myocardial infarction, and one with left-ventricular function impairment and planned surgery.

Conclusions: Heart failure arising from different aetiologies and occurring in different settings is amenable to successful treatment with levosimendan.

Keywords: *acute heart failure, advanced chronic heart failure, cardiac surgery, levosimendan.*

INTRODUCTION

Acute heart failure is a condition that is characterised by impaired myocardial function, whereby the heart cannot supply sufficient O_2 to the body tissues. The common causes of heart failure include hypertension, coronary artery disease (including previous myocardial infarction), atrial fibrillation, valvular heart disease, and cardiomyopathy (1, 2). Heart failure can also be triggered by surgical procedures, generally in the more elderly patients with limited cardiopulmonary reserve (3). All surgical procedures can lead to systemic inflammatory reactions, with the resultant increase in heart rate. Stress and inadequate postoperative analgesia can prompt elevated systemic blood pressure, tachycardia and increased afterload, thereby raising myocardial O_2 requirements. Treatment of heart failure has made substantial progress over recent years. The strategies commonly used focus not only on improvement of the symptoms, but also on prevention of the transition from asymptomatic to symptomatic heart failure, as well as on mortality reduction through slowing disease progression.

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However, once haemodynamic support is required, there is a relative scarcity of effective therapies. β-Adrenergic-receptor-stimulating drugs including dobutamine, dopamine and adrenaline are used in this setting. All of these act via the adrenergic receptors on the myocyte cell membranes, to intensify the production of the second messenger adenosine 3',5'-cyclic monophosphate, which leads to increases in Ca^{2+} influx and increased contraction force. However, this is achieved at the expense of enhanced O_2 requirements. In addition, these drugs tend to cause arrhythmia, which can further impair cardiac function.

More recently, the phosphodiesterase inhibitors drugs were developed, which reduce the degradation of adenosine 3',5'-cyclic monophosphate, thereby leading to increased influx of Ca^{2+}.

Also the phosphodiesterase inhibitors, hoverer, can increase the risk of arrhythmias.

The inodilator levosimendan is a Ca^{2+} sensitiser that has been approved for short-term treatment of acutely decompensated severe chronic heart failure when conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.

Levosimendan has a number of pharmacological effects, which include increased cardiac contractility mediated by Ca^{2+} sensitisation of troponin C (4-8), vasodilation based on the opening of K^+ channels in the vasculature (9-12), and cardioprotection due to the opening of mitochondrial K^+ channels in the cardiomyocytes (13-16).

Clinical data obtained in patients with heart failure has confirmed that these pharmacological effects translate into improved haemodynamics (17-19). Contrary to other inotropes, O_2 consumption is not increased to a significant extent during treatment with levosimendan (20, 21). Symptoms of acute heart failure have been shown to be diminished by levosimendan treatment (17, 18, 22, 23). Furthermore, beneficial effects have been noted on the level of the neurohormones (22-24). Levosimendan pre-treatment can decrease infarct size in an ischaemia–reperfusion model and improve recovery of cardiac function following global ischaemia (25). Levosimendan improves survival rate in rats with healed myocardial infarction.

This beneficial effect is not believed to be mediated through inhibition of ventricular hypertrophy, dilation or alterations in late-phase healing of the infarct, but primarily through Ca^{2+} sensitisation of contractile proteins (26). Levosimendan has an active metabolite, known as OR-1896, which ensures sustained efficacy for at least 7 days (24, 27).

In contrast to dobutamine, the effects of levosimendan are not attenuated by concomitant administration of β-blockers (28). Levosimendan also offers a predictable safety profile (17-19, 23), and no impairment of diastolic function has been demonstrated with levosimendan (29, 30). Also, there is no development of tolerance to levosimendan (25).

The most common adverse events of levosimendan treatment include hypotension, headache, atrial fibrillation, hypokalaemia and tachycardia (22, 23, 31).

In recent years, the use of levosimendan has broadened to treatment of heart failure in different settings.

These include advanced chronic heart failure, and other scenarios where haemodynamic stability is sought, such as pre-operative treatment of patients at risk of low cardiac output syndrome or peri-operative heart failure.

The aims of this presentation of four case reports were to compare the use of levosimendan in different settings, and to highlight differences and similarities in the effects obtained, with the purpose of defining common guidance on the use of levosimendan.

METHODS

We retrospectively reviewed the records of patients with heart failure in the registries of our wards, and identified four cases where the patients had received levosimendan in four different settings. We describe here the clinical management of these four cases.

According to the local laws and regulations, due to the retrospective nature of data collection we did not ask for ethical committee approval.

RESULTS

Case 1. In 2002, a 71-year-old, non-smoker male with a history of lymphoma, hypertension and long-standing diabetes was diagnosed with enlargement of the left ventricle and pronounced impairment of systolic function, with mitral insufficiency and pulmonary hypertension.

Treatment was initiated with angiotensin-converting enzyme inhibitors and diuretics. Over the course of the next 18 months, the patient was repeatedly hospitalised due to congestive heart failure, and his medication was adjusted several times.

Apart from treatments with angiotensin-converting enzyme inhibitors and diuretics, he also received an aldosterone antagonist, an angiotensin receptor blocker, and a β-blocker.

In April 2003, he had New York Heart Association (NYHA) class IIIB heart failure, coronary angiography showed no significant arterial stenosis and the findings suggested biventricular failure. Based on the electrocardiogram, the patient did not meet the criteria for cardiac resynchronisation therapy (failure) pacemaker implantation.

In the spring of 2004, medical treatment of this patient had effectively reached a dead end, and no further clinical improvement was seen. The decision was then taken to initiate treatment with levosimendan.

In late April 2004, the first dose of levosimendan was applied, followed by further levosimendan doses every 4 weeks. Since the start of this treatment, the patient has not needed any further emergency admissions.

In July 2004, echocardiographic improvements of his left-ventricular function were seen. Another echocardiograph that was performed in October 2004 showing only mildly impaired LV function with just minor MI and insignificant TI. Patient's condition was markedly improved with no symptoms, absence of oedema and improved quality of life. NYHA class now I-II. Simdax treatment was discontinued. At recheck to the cardiology clinic in March 2005, the patient remained asymptomatic and his quality of life had further improved with increased physical activity, such as dancing and 3-km long daily walks. Anticoagulants were replaced with ASA and the dosage of diuretics was reduced since there was no longer any fluid retention. At a follow up in September 2005 (three year after the first hospitalization) the patient was still asymptomatic.

Case 2. A 73-year-old male had myocardial infarction in 1994, which was followed by bypass surgery. He was suffering from paroxysmal atrial fibrillation and chronic heart failure. In spring 2005, the patient was hospitalised because of heart failure (NYHA class IIIB).

In August 2005, emergency admission became necessary because of increased shortness of breath and abdominal distension. The patient had orthopnoea and low blood pressure (85/60 mmHg). Echocardiography showed impaired left-ventricular systolic function with a left-ventricular ejection fraction (LVEF) of 10 % to 15 %. He also showed mild mitral and moderate tricuspid

insufficiency, with a maximum velocity of tricuspid regurgitation flow of 4.2 m/s. The patient was admitted to the Internal Medicine ward, and treatment with intravenous diuretics initiated. He experienced less dyspnoea, but was still dizzy, with blood pressure of 80/60 mmHg. After transfer to the Cardiology-Internal Medicine ward, levosimendan treatment was started at a loading dose of 12 µg/kg over 10 min, followed by continuous infusion with 0.2 µg/kg/min for 24 h.

The condition of the patient had already dramatically improved on the day after the levosimendan infusion. His blood pressure rose to 95/65 mmHg, his diuresis recovered, and the following day he was able to walk on the ward without dyspnoea. Laboratory results showed improved renal function with decreasing creatinine values, and normalised liver function tests. Coronary angiography revealed proximal occlusion of the left anterior descending artery, and proximal stenosis of the circumflex artery. The patient received a biventricular implantable cardioverter defibrillator pacemaker. He was completely symptom-free during surgery, and experienced no problems when lying flat on the operating table. He showed improved left-ventricular function, with LVEF of 20% to 25%. At the latest regular telephone follow up in 2008 (three year after the previous hospitalization) the patient was still alive.

Case 3. An 83-year-old male presented with severe lower abdominal pain. He had had a myocardial infarction approximately 7 years previously, had undergone coronary artery bypass surgery the same year, but had had no cardiac issues since that time. The abdominal computed tomography suggested an abscess at the level of the umbilicus. The patient soon developed localised peritonitis, and he was scheduled for emergency laparotomy. He showed an inflammatory response with vasodilation during the procedure, and required infusion of substantial amounts of both crystalloid and colloid fluids. Support with phenylephrine was needed to maintain his mean arterial pressure (MAP) > 65 mmHg. Surgery revealed a perforated diverticulum of the small intestine and an abscess that required small bowel resection. A couple of hours postoperatively, the patient developed atrial fibrillation. Successful cardioversion was performed after 6 h of fibrillation. On the morning of the first postoperative day, the patient showed normal sinus rhythm and heart rate, with MAP > 65 mmHg. However, he reported shortness of breath, and his O_2 saturation was 90% on 8 l/min supplemental O_2, using a mask. His O_2 requirement increased rapidly over the next few hours.

Laboratory results showed mild elevation of troponin T, but there were no electrocardiogram changes. Transthoracic echocardiography showed bilateral ventricular dilation and severely impaired mobility of the left ventricle. His LVEF was estimated at < 20%. Blood gas assessment showed desaturation of central venous blood, at 58%. This was interpreted as heart failure, which had perhaps been triggered by a small myocardial infarction.

Treatment with levosimendan was initiated with a loading dose for 10 min, which was followed by continuous infusion with 0.1 µg/kg/min. Norepinephrine was used to maintain his MAP levels > 65 mmHg. A couple of hours after the start of levosimendan treatment, the patient began to produce increasing amounts of urine. During the night, his O_2 supplementation was reduced. Serial analysis of his troponin levels suggested a small myocardial infarction. Repeated blood-gas evaluation showed a gradual increase in central venous O_2 saturation ($ScVO_2$), to 68%. After 24 h, the patient was discharged from the Intensive

Care Unit, and 10 days later he left for rehabilitation at another hospital. At one month after the operation the patient was asymptomatic.

Case 4. A 94-year-old male with known heart failure (LVEF, 15%-20%; mild elevation of pulmonary artery pressure with moderate tricuspid insufficiency; atrial fibrillation with normal heart rate) presented at the emergency room with a two-day history of abdominal pain. Following various radiographic investigations, he was referred for an emergency laparotomy with suspected intestinal perforation. Given his advanced age and cardiac status, attempts were made to preoperatively optimise his cardiovascular status. It was believed that the perioperative inflammatory response, the negative inotropic effects of anaesthesia, and the positive-pressure ventilation might tip the balance and trigger manifest heart failure. Transthoracic echocardiography showed that his LVEF was still barely 20%. His cardiac index was 1.7 l/min/m^2, and $ScVO_2$ was 59%. After treatment was begun with colloid administration, his cardiac index increased a little, to approximately 2 l/min/m^2, and his $ScVO_2$ to just over 60%. To further optimise treatment, the patient was started on levosimendan infusion (loading dose 12 μg/kg, followed by continuous infusion at 0.1 μg/kg/min). Norepinephrine was used to maintain his MAP levels > 65 mmHg.

After 4 h of levosimendan treatment, the heart function of the patient improved, with a cardiac index of 3 l/min/m^2, and $ScVO_2$ of almost 70%. The decision was taken to start the surgical procedure. Small bowel resection was performed because of a perforated diverticulum. During the entire procedure, the patient only required a small dose of norepinephrine to maintain acceptable MAP values. He was completely stable throughout the peri-operative course, and was extubated immediately after surgery. Then the patient was transferred to the postoperative ward for 24 h. Five days later, the patient was discharged from hospital. At one month after the operation the patient was asymptomatic.

DISCUSSION

In this case series, we have presented four patients who required haemodynamic support in various settings of a failing heart. Three patients (cases 1-3) experienced acute cardiac decompensation, while one patient (case 4) appeared stable at low LVEF, but needed to undergo abdominal surgery, which raised concerns as to probable cardiac failure during the course of the intervention.

The first patient developed persistent symptomatic heart failure on the basic of chronic ventricular dysfunction, with frequent emergency admissions to hospital. Customary heart-failure medication only temporarily relieved these symptoms. When it was felt that no further progress could be made, levosimendan treatment was administered over a total of four sessions, which produced a pronounced and rapid improvement at both the subjective and objective levels. No emergency hospitalisation occurred between the treatments.

The second patient showed signs of severe biventricular failure after chronic heart failure had been present for many years. He experienced hypotension, with signs of renal hypo-perfusion. In this patient with ischaemic heart disease and susceptibility to ventricular arrhythmia, levosimendan was the obvious choice. Biventricular pacing and levosimendan proved to be a well-chosen combination.

For the third patient, heart failure occurred after a relatively major surgical procedure. The patient developed atrial fibrillation.

Rhythm regularisation and diuretic therapy were not sufficiently effective, but the condition of the patient improved with levosimendan treatment. Dobutamine can be considered as an alternative inotropic in this setting, although it can increase myocardial O_2 consumption and the risk of arrhythmia.
As both a small myocardial infarction and atrial fibrillation were present in this patient, levosimendan was chosen.
The last case report describes the perioperative management of a 94 year old man with known impairment of left-ventricular function. Optimising his cardiac function prior to emergency surgery appeared to be necessary.
Levosimendan was deemed more appropriate than treatment with an adrenergic agonist, all the more so because the patient had chronic atrial fibrillation. The administration of levosimendan produced rapid improvements to cardiac function, thus enabling the surgery to go ahead.

Limitations

A large amount of data from many clinical trials has been published describing the effects of levosimendan in different clinical settings.
Our narrative should be considered as anecdotic as any set of case reports, but our aim was to collect cases in which the same inodilator was used in different settings. The description of the hemodynamic and symptomatic effects of the drug in parallel in such different patients may offer a new view point.
One clear limitation is that the patients undergoing surgery were followed up only for one month after operation. In our own clinical experience, the use of a loading dose could be harmful if:
1) the baseline pressure is too low;
2) the diuretic dose is too high;
3) the patient is hypokalemic.

In this case some episodes of hypotension and arrhythmias may be observed. Another point to be discussed is the cost of the drug: since at the moment no large mRCT are published to support the beneficial effect of levosimendan over comparator on long term outcome, it appears difficult to justify a premium price over cheap generic such as dobutamine.
Some pharmaco-economic studies, however, were published which justify the use of this drug in the settings which we described in our manuscript (32-34).

CONCLUSION

We have presented a case series that shows that the administration of the Ca^{2+} sensitiser levosimendan can greatly improve heart failure in different settings. The Ca^{2+}-sensitising effects of levosimendan are demonstrated here to remarkably improve cardiac output. Levosimendan, however, also has a pronounced vasodilatory effect, which contributes to lowering the pre-load and afterload. On the bases of our own experience, due to its vasodilatory effect, levosimendan should be given cautiously to patients with low blood pressure, especially in the case of hypovolaemia (35). The use of lower infusion rates without the loading bolus should be considered for such patients. Hypotension should be treated with fluid resuscitation and vasoconstrictors, as needed.
Finally, we present here three recommendations for dosing of levosimendan treatment based on our own experiences on the ward:
1) use a loading dose (6-12 μg/kg over 10 min) only if an immediate effect is needed and if systolic blood pressure is ≥100 mmHg;
2) use a maintenance infusion rate of < 0.2 μg/kg/min, with individualised dosing regimen;

3) avoid hypovolaemia before and during the treatment (fluid as needed; intravenous diuretics with caution). Guidance on the repetitive use of levosimendan in chronic advanced heart failure, and on the perioperative use of levosimendan was provided recently by Nieminen et al. (36) and Toller et al. (37, 38), respectively.

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