Review Article

Levosimendan

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Abstract. We designed this review to examine the mechanism of action of levosimendan (Simdax®, Orion Pharma, Espoo, Finland) and its current clinical application in critically ill adults and children with acutely decompensated severe congestive heart failure and who require inotropic support. We applied Pubmed (primarily) and Google search engines for English-language papers whose main topic was the use of levosimendan in the general population and those that concentrated on pediatric cohorts aged 0 to 18-year-old. Levosimendan increases contractile force of the heart and improves vasodilation. It increases the heart's sensitivity to calcium, thereby increasing cardiac contractility. Its mechanism of action is via the increased calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner. Its opening of adenosine triphosphate-sensitive potassium channels in vascular smooth muscle leads to a vasodilatory effect and smooth muscle relaxation. Levosimendan was shown to be effective in the treatment of acute decompensated heart failure, rescue therapy for septic shock, weaning patients from assisted devices and weaning patients from inotropic therapy. Neonates with hypoplastic left heart syndrome who were treated by levosimendan showed improvement in systemic perfusion following cardiac surgery. Cost-effectiveness of this new drug is discussed.

Keywords: Levosimendan, low cardiac output syndrome, mechanical circulatory support, acutely ill children, inotropic therapy, cost efficiency, cardiac surgery

1. Introduction

Levosimendan (Simdax®, Orion Pharma, Espoo, Finland) is a novel drug indicated for providing inotropic support for patients with acutely decompensated heart failure (HF), the leading cause of death worldwide. New surgical and medical approaches and treatments are constantly being tested in the attempt to reduce mortality and morbidity, as well as to improve the quality of life and general prognosis of patients with cardiomyopathy. Pharmacological treatments include the use of inotropes (adrenalin, noradrenalin, dopamine, dobutamine,

phosphodiesterase [PDE] inhibitor, levosimendan and others), angiotensin-converting enzyme inhibitors to reduce afterload, diuretics to reduce preload and various other drugs. The need for newer drugs and therapies arises from the undesired effects of the current drugs. For example, inotropes are known to increase the oxygen demand of the myocytes, which may evoke or worsen ischemia. They are also known to cause hypotension, arrhythmias, vision disturbances, headache, diarrhea and other untoward sequelae [1,2].

The purpose of this review is to summarize the mechanism of action and clinical application of levosimendan, its effect on septic shock, its role in the setting of cardiopulmonary resuscitation (CPR) and cardiopulmonary bypass (CPB), its cost efficiency and its use specifically in pediatric medicine.

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2. Data sources

Our main search engine was Pubmed using the key word “levosimendan”, and we retrieved only English-language publications for which there were complete texts on human subjects. Relevant reports on children (birth to 18-years-old) were reviewed separately. We also searched Google with the key words “levosimendan + pediatrics”. Uptodate.com yielded no relevant results. Table 1 lists a summary of the articles used in this paper with some general information about the populations studied.

3. Mechanism of action

Levosimendan is a pyridazone-dinitrile derivative and the first of a new class of drugs termed “calcium sensitizers”. It was recently introduced into clinical practice in the treatment of acutely decompensated HF. About 5% of levosimendan (which has 98% affinity to its binding protein) is converted in the small intestine and then acetylated in the liver to form the active OR-1896 (with 40% affinity to its binding protein). Levosimendan has a half-life of 1 to 1.5 h while OR-1896 has a half-life of 75 to 80 h. The drug binds to saturated cardiac troponin C at a hydrophobic region of its N-domain near the so-called D/E linker region, stabilizes the calcium (Ca) to it, and thus stabilizes and prolongs the binding of troponin C to troponin I. This action increases the force of contraction. The higher affinity of Ca to cardiac troponin C reduces adenosine triphosphate consumption by cardiac myocytes, thereby reducing oxygen consumption. This reduction in oxygen consumption protects the heart in the presence of ischemia. Intracellular Ca^{2+} levels are tightly regulated in a healthy cell since impaired calcium balance has many potentially deleterious effects, including the generation of arrhythmias. It has an on-off property, which affects systole but not diastole. In addition, PDE inhibition has been proposed to contribute to levosimendan-induced vasodilatation because of cyclic adenosine monophosphate inhibition in vascular smooth muscle [3–6].

Variable types of potassium channels are activated by levosimendan, thus hyperpolarizing the membrane, inhibiting inward Ca^{2+} current and activating the sodium- Ca^{2+} exchanger to extrude Ca^{2+} . Both effects act to lower intracellular Ca^{2+} and thereby promote vasorelaxation by vascular smooth muscle relaxation [7]. This process affects the arteries, veins and coronary

vessels, reducing preload and afterload, although it also may cause hypotension.

4. Clinical use in adults and children

The usual dosage of levosimendan in both research and clinical practice is 6–12 $\mu\text{g/kg}$ body weight for 12 minutes as a loading dose, followed by 0.05–0.2 $\mu\text{g/kg}$ body weight in a 24 hour continuous intravenous infusion. Both the loading dose and the maintenance dose should be diluted in a 5% glucose solution. A hemodynamic effect is expected after five minutes, while a maximal effect is expected after 10 to 30 minutes if a loading dose had been administered and 2–3 hours after the initiation of treatment in the absence of a loading dose. The drug’s effect lasts for 1–2 hours if it is administered as a single dose, but its effects have been observed up to 9 days after a 24 hour infusion due to its high affinity to plasma proteins and long metabolite half-life. Neither renal and nor hepatic failure has any bearing on the choice of dosage [3–6].

Data on levosimendan’s pharmacokinetics in children are available in a recent report by Turanlahti et al. [8]. Their phase II study enrolled 16 children between three-months and 12-year-old who presented with congenital heart disease (New York Heart Association functional class I or II) and underwent cardiac catheterization prior to undergoing cardiac surgery. Eleven children had an uncorrected left-to-right shunt. Following a 10-minute infusion of 12 $\mu\text{g/kg}$ levosimendan, the mean maximum concentration based on the open one- or two-compartment model-fitting curve was $59 \pm 23 \text{ ng/mL}$ in children older than six-months-old. The concentrations of levosimendan in plasma declined rapidly, and the mean concentration was $6.0 \pm 3.5 \text{ ng/mL}$ at 2 h after administration. Four hours after administration, the concentration was below detection level ($<2.0 \text{ ng/mL}$) in seven subjects. The mean terminal half-life was $1.6 \pm 0.80 \text{ h}$, while the terminal half-life in children aged 3–6 months was slower than in the older children, i.e., 2.3 h vs. 1.6 h, respectively.

5. The levosimendan infusion versus dobutamine trial

The results of the randomized levosimendan infusion versus dobutamine trial on 203 adult patients with severe, low-output chronic HF showed that significantly

Table 1
Number of patients, ages, pathologies and drug dosages in the reviewed papers

Reference number	Total number of patients	Mean age	Pathologies	Trial end-point	Loading dose	Maintenance dose
3			Summary of the available evidence on the mechanism and use of levosimendan in different clinical situations			
4	16	Not provided	Mild congestive heart failure	Evaluation of the pharmacokinetics of levosimendan	2 doses of 0.5 mg each	None used
5				Literature review		
6				Consensus paper		
7				In vitro experiment		
8	13	1.7 yr	Congenital heart diseases	No data provided in the article	12 µg/kg over 10 min	None used
9	199	59 yr	Low output heart failure	Comparison between levosimendan and dobutamine after 24 h infusion	24 µg/kg over 10 min	0.1 µg/kg/min over 24 h
10	6	Not provided	Refractory septic shock	Not provided	Not provided	0.1–0.2 µg/kg/min over 24 h
11	42	66.1 yr	Sepsis and severe heart dysfunction	Not provided	Not provided	0.1 µg/kg/min over 24 h
12	25	71.5 yr	Acute heart failure or septic shock	Not provided	Not provided	0.1–0.15 µg/kg/min up to 12.5 mg over 24 h
13				Not provided		
14	1	16 yr	Septic shock	Not provided	Not provided	0.1 µg/kg/min over 24 h
15				Editorial letter		
16	40	67 yr	Septic shock	Investigation of the microcirculatory blood flow in patients with septic shock treated with levosimendan compared to an active comparator drug	Not provided	0.2 µg/kg/min over 24 h
17	42	Not provided	Sepsis and septic shock	True mixed venous oxygen saturation >70%	Not provided	Up to 0.2 µg/kg/min in increasing doses for 24 h
18	9	57 yr	Patients undergoing implantation of a centrifugal assist device as a bridge to recovery	Mixed venous oxygen saturation of 70% or more, and mean arterial pressure of 70 mmHg	20 µg/kg over 10 min	0.1–0.2 µg/kg/min up to 48 h
19	7	7.7 yr	Potential candidates for mechanical circulatory support	Not provided	Variable	None used
20	63	>30 d	Patients undergoing risk-adjusted classification for congenital heart surgery	Not provided	Not provided	0.1 µg/kg/min over 72 h
21	26	68.6 yr	High-risk acute coronary syndrome after cardiopulmonary resuscitation due to cardiogenic shock	Analysis of short-term and long-term effects of levosimendan on cardiac functions and on survival of cardiogenic shock and post-cardiopulmonary resuscitation patients	Not provided	0.1 µg/kg/min over 6 h

(continued)

Table 1. Number of patients, ages, pathologies and drug dosages in the reviewed papers (Continued)

Reference number	Total number of patients	Mean age	Pathologies	Trial end-point	Loading dose	Maintenance dose
22	15	3 yr	Severe myocardial dysfunction secondary to end stage heart failure, or acute heart failure	Not provided	6-12 µg/kg over 10 min	0.1 µg/kg/min for 24 h or 0.05 µg/kg/min for 48 h
23	9	34 mo	Decompensated congestive heart failure	Investigation of rotating inotropic regimen, including levosimendan	No loading dose was used.	Not provided
24	1	3 yr	Heart failure during cardiopulmonary bypass removal period	Not provided	12 µg/kg over 10 min	0.1 µg/kg/min over 24 h
25	1	32 wk	Transposition of the great arteries	Not provided	Not provided	0.05-0.1 µg/kg/min for 24 h
26	1	3.5 mo	Idiopathic infantile arterial calcification	Not provided	Not provided	Not provided
27	203	The levosimendan infusion versus dobutamine trial patients	Severe low-output heart failure	Estimation of the cost-effectiveness of intravenous treatment with levosimendan compared with dobutamine in patients with severe low-output heart failure	According to the levosimendan infusion versus dobutamine trial	Not provided
28	5480	Various	Various	Determination of the impact of levosimendan on mortality and hospital stay	Various	Not provided
29				Conference		
30	292	66 yr	Patients with ejection fraction less than 40%	Estimation of the effects of levosimendan versus standard dobutamine in acute heart failure	No loading dose was used	0.05-0.1 µg/kg/min for 24 h
31	600	Not provided	Acute decompensated heart failure	Economic analysis of the randomized evaluation of intravenous levosimendan efficacy II study	Not provided	Not provided

more patients in the levosimendan group achieved the primary efficacy end-point of an increase from baseline in cardiac index $\geq 30\%$ and a decrease in pulmonary capillary wedge pressure $\geq 25\%$ than in the dobutamine group (28% and 15%, respectively) [9]. Furthermore, more patients treated with dobutamine experienced worsening HF or died by the 30-day follow-up point (17% vs. 6.8% in the levosimendan group).

6. Septic shock

Powell and De Keulenaer [10] used 0.1-0.2 $\mu\text{g/kg/min}$ over 24 hours as rescue therapy in six adult patients with refractory septic shock. Their results showed a trend towards increased mean arterial pressure, improved arterial oxygen partial pressure, fractional inspired oxygen ratio, increased cardiac index, reduced base excess, improved pH and reduced lactate. Reductions in heart rate, pulmonary vascular resistance index and systemic vascular resistance index were also noted. Inotropic usage was reduced in all patients. Vaitis et al. [11] described 42 adult patients who met the criteria of sepsis and displayed severe heart dysfunction. In addition to standard treatment, 23 of them received levosimendan without a loading dose, while the remaining 19 received dobutamine. Those authors' results revealed that the cardiac index of the levosimendan group improved by 1.79 ± 0.16 compared to 1.4 ± 0.12 in the dobutamine group ($P = 0.027$), as did the ejection fraction ($4.8 \pm 0.2\%$ vs. $3.5 \pm 0.7\%$, respectively, $P = 0.04$). Hasslacher et al. [12] reported on the use of levosimendan in the setting of septic shock and HF and their results demonstrated positive effects of the medication in those patients. There is additional literature regarding levosimendan use in both pediatric and adult sepsis [12,15–17].

7. CPB and mechanical circulatory support (MCS)

Braun et al. [18] described their experience with levosimendan and its effect on adult patients who were on centrifugal assist devices. Of the 29 patients who were not treated with levosimendan, 20 could be weaned from the device, and nine survived to be released from the intensive care unit (ICU). Seven of the nine survivors were released from the hospital, but only three survived for 180 d. Nine other patients were treated with levosimendan and they all could be weaned from the assist device. Eight were released

from the ICU and from the hospital, and seven survived for at least 180 days after the operation.

In their search for new ways to avoid the need for MCS, Schweigmann et al. [19] combined milrinone, nesiritide and levosimendan in different combinations with each other and with inotropes. Their seven reported pediatric patients included four toddlers (three with fulminant myocarditis and one with dilated cardiomyopathy associated with spongy myocardium) and three adolescents (two with post-myocarditis cardiomyopathy and one with hypertrophic cardiomyopathy and severe restrictive dysfunction after an ischemic event with CPR [stunned heart]). Six of these children responded well to therapy and could be spared the use of MCS. Those authors also noted that the levosimendan-milrinone combination was more effective than the others were. Ricci et al. [20] recently reported their results on a study designed to explore whether the addition of levosimendan to vasoactive support after CPB would help reduce postoperative low cardiac output syndrome in 63 neonates (32 cases and 31 controls). Although levosimendan did not significantly affect low cardiac output syndrome, it was well tolerated and significantly improved postoperative parameters.

8. CPR

Soos et al. [21] reported their a 3 year study on 3852 adult patients with high-risk acute coronary syndrome who underwent percutaneous coronary intervention. CPR was required in 26 of those procedures due to cardiogenic shock. Levosimendan was administered in 39 out of the 106 study patients who had impaired left ventricular function. There were no significant differences in short-term and long-term survival between patients who received levosimendan post-CPR and those who did not.

9. Comparison with milrinone

Most researchers on levosimendan compared it with dobutamine. One exception is Salmenperä and Eriksson [5] who compared the effects of levosimendan to those of milrinone, a PDE-III inhibitor. Those authors found that the effect of levosimendan was more sustained than that of milrinone, and suggested that the difference was probably due to the buildup of an active, poorly protein-bound metabolite of levosimendan. They also noted that the ratio between

power output and energy utilization was much more favorable with levosimendan.

10. Levosimendan in pediatrics

Namachivayam et al. [22] studied 15 children (median age 38-month-old, range 7 days to 18 years) who were already receiving intravenous inotropic therapy from which they could not be safely weaned. They were all receiving intravenous or oral vasodilators, and three were receiving an oral beta-blocker. Seven children had longstanding end-stage HF, and the remaining eight children had acute HF. All 15 patients received levosimendan as a loading dose followed by continuous infusion. Their heart rate, systolic pressure, diastolic pressure, mean blood pressure and central venous pressure remained unchanged during and after the administration of levosimendan. The drug enabled the discontinuation of inotropes in 10 patients and a dose reduction in three (i.e., from 6.4 $\mu\text{g/kg/min}$ to 1.8 $\mu\text{g/kg/min}$ on day 5). The ejection fraction for the group as a whole improved from 29.8% to 40.5%, and did not increase significantly in the patients with end-stage HF, but increased by 63% in the children with acute HF. The mean arterial lactate concentrations tended to decrease over the first 48 hours. Eleven of the 15 children were discharged from the ICU after the primary admission (during which levosimendan was given), and seven were still alive at the time of publication. Ryerson et al. [23] tried a regimen of rotating inotropes (levosimendan, dobutamine and milrinone) in search of a solution to the tachyphylaxis and reduced sensitivity of the cardiac cells to inotropes in prolonged inotropic therapy for decompensated cardiac failure in nine children. The inotropes were administered in the following

order: dobutamine 5 $\mu\text{g/kg/min}$ for 3 days followed by a bolus of 12 $\mu\text{g/kg}$ levosimendan and a 24 hour infusion of 0.2 $\mu\text{g/kg/min}$ levosimendan. A 4 day course of 0.5-0.75 $\mu\text{g/kg/min}$ (according to age and renal function) milrinone followed the levosimendan and then dobutamine, levosimendan and milrinone were reinstated. Eight of the nine children survived to ICU discharge and seven (78%) to hospital discharge. Two of the children died, one of severe sepsis and the other from in-hospital cardiac arrest. Six of the eight mechanically ventilated patients were successfully weaned from the ventilator (Fig. 1). There was no significant change in ejection fraction at the end of the therapy. Two patients became hypotensive, one under milrinone treatment and one after the first loading dose of levosimendan, and both were resolved, one by ceasing milrinone and the other spontaneously. No other adverse effects were noted.

As noted earlier, Schweigmann et al. [19] reported that the levosimendan-milrinone combination succeeded in avoiding mechanical circulatory support in five of their seven pediatric patients. Turanlahti et al. [8] examined 16 children between 3 months and 12 years of age with congenital heart disease who were referred to cardiac catheterization for evaluation prior to cardiac surgery. Hemodynamic effects were measured at the initiation and 10 and 25 minutes after the administration of levosimendan at a dose of 12 $\mu\text{g/kg}$ over 10 minutes. The results are provided in detail in Fig. 2.

Aksun et al. [24] described a 3-year-old girl who underwent repair of a progressive aneurysm detected during an evaluation 4 months after the repair of tetralogy of Fallot. At the end of CPB, she developed hypotension and suboptimal diuresis, which could not be corrected with dopamine (15 $\mu\text{g/kg/min}$), dobutamine (15 $\mu\text{g/kg/min}$) and adrenalin (1 mg/h) infusions.

Fig. 1. The outcome of nine children with decompensated cardiac failure following a regimen of rotating inotropes (levosimendan, dobutamine and milrinone) (data from [23]). ICU = Intensive care unit.

Fig. 2. Hemodynamic effects at the initiation, 10 and 25 min after the administration of levosimendan in 16 children with congenital heart disease who were referred to cardiac catheterization for evaluation prior to cardiac surgery (data from [8]). Group 1 = Children between 3-month and 1-year-old; group 2 = Children between 1 and 7-year-old. PAP = Pulmonary artery pressure; PAOP = Pulmonary artery occlusion pressure; LVEDP = Left ventricular end-diastolic pressure; PVRI = Pulmonary vascular resistance index; SVRI = Systemic vascular resistance index.

A levosimendan infusion was administered with a loading dose of 12 $\mu\text{g/kg}$ over 10 min, and a 0.2 $\mu\text{g/kg/min}$ maintenance dose was given over 24 hours. Her vital signs were normalized within one hour and a 200 cc diuresis was observed. The inotropes were gradually reduced until they were completely withdrawn after 48 hours, and the patient was discharged from the hospital 10 days after the operation.

Lechner et al. [25] reported their experience with the use of levosimendan in a neonate male twin with a gestational age of 32 weeks who was diagnosed as having simple transposition of the greater arteries. Post-operative bypass weaning was achieved by dopamine (4 $\mu\text{g/kg/min}$), milrinone (0.5 $\mu\text{g/kg/min}$), nitroglycerin (5 $\mu\text{g/kg/min}$) and epinephrine (0.05 $\mu\text{g/kg/min}$). Following surgery, the infant showed signs of low cardiac output syndrome. Since no pathologies were discovered, the nitroglycerine and milrinone were discontinued, the epinephrine dose was increased to 0.1 $\mu\text{g/kg/min}$ and 10 mL/h albumin was administered, all with no effect. At this point, 0.05 $\mu\text{g/kg/min}$ levosimendan was initiated and increased to 0.1 $\mu\text{g/kg/min}$ after two hours. The infusion was discontinued after 24 hours. Within six hours, left arterial pressure decreased to 7 mmHg, systolic pulmonary arterial pressure decreased to 25 mmHg, systolic arterial pressure increased to 60 mmHg and right atrial pressure decreased to 7 to 10 mmHg. The PO_2 and PCO_2 levels were stable

(according to arterial blood gases), serum lactate steadily decreased, and mixed venous saturation increased within 24 hours, accompanied by an almost normalized fractional shortening. The inotropic support was stopped altogether on the second postoperative day. There were no further signs of hemodynamic instability. On the 12th postoperative day, the patient was weaned from the ventilator despite a left diaphragmatic paralysis. At the age of one year, the patient's neurodevelopment was normal for gestational age. Finally, Ryerson et al. [26] reported a child with idiopathic infantile arterial calcification who was administered levosimendan to no avail.

11. Cost-efficiency of levosimendan

There was a consensus among all of the articles that we retrieved for conducting this review that levosimendan increases life expectancy. Unlike other chronic patients who create a greater burden on the healthcare system due to frequent hospitalizations, however, patients who benefit from levosimendan do not. Cleland et al. [27] examined the survival rate and the hospitalizations of the patients who participated in the levosimendan infusion versus dobutamine trial three years after that trial had closed: the six month survival rates were 74% for patients who received levosimendan

and 63% for those who received dobutamine. The mortality risk was reduced by 41% in relative terms with levosimendan treatment, and the absolute difference in mortality was 11% at six months in favor of levosimendan. This means that levosimendan saved 0.37-life year/patient more than dobutamine. Importantly, despite the increased survival in the levosimendan group, there was no difference in the number of hospital admissions or the number of hospital days per patient between the groups. The absolute difference in drug costs was relatively high, i.e., 1024 euro for one treatment of levosimendan vs. 41 euro for one treatment of dobutamine. The cost per life a year saved with levosimendan, however, was only 3205 euro, which is superior to other cardiovascular therapies. Furthermore, Landoni et al.'s [28] meta-analysis of 45 randomized controlled studies on adults who were treated with levosimendan showed that the effects of the drug on mortality and hospital length of stay improved in survival in comparison to other inotropes and to placebo. Specifically, mortality was reduced in both the long- and short-term studies. The mortality rate was 17.4% with levosimendan when compared to 18.7% with placebo, and 15% with levosimendan vs. 27.7% when compared with dobutamine. There were similar results for patients in a cardiology environment, cardiac surgery environment and in patients undergoing revascularization. A significant reduction in mortality for levosimendan-treated patients was found when only studies on patients on mechanical ventilation, only studies with mortality as a primary endpoint, both single and double blind studies, or only studies with over 100 patients were considered. The length of hospital stay was reduced in the levosimendan group by -1.59 weighted mean differences in the cardiology settings, although not in the cardiosurgery settings. Fedele et al. [29] and de Lissovoy et al. [30] addressed issues of cost effectiveness in detail.

Finally, Landoni et al. [31] reported an international consensus conference that included cardiac anesthesiologists, cardiac surgeons and cardiologists in Milan, June 2010. Several surgical and non-surgical methods were evaluated in terms of mortality after cardiac surgery, and 77% of the participants agreed that levosimendan is effective in reducing 30 day mortality.

12. Conclusion

In conclusions, levosimendan produces good results in weaning patients from assist devices and from inotropic therapy as well as in their overall survival rate.

The reduction in the arterio-venous oxygen gradient, normalization of the temperature gradient, improvement in urine output, and fall of lactate levels and pulmonary-to-systemic blood flow ratio values demonstrate the improvement in systemic perfusion under levosimendan treatment in neonates with hypoplastic left heart syndrome and following cardiac surgery in general. Rotating inotrope treatment that includes levosimendan shows promise since levosimendan acts independently from androgenic receptors and so under-regulation of the receptor does not affect its action. Little clinical data are available about this relatively new drug, and more research is warranted both on adults and children.

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