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Abstract

Levosimendan is a “Ca\(^{2+}\) sensitizer,” which exerts its inotropic effect by increasing the affinity of troponin C for Ca\(^{2+}\), directly stabilising the Ca\(^{2+}\)-induced conformation of troponin C. It leads to a positive inotropic effect without impairing diastolic relaxation and causing cytosolic Ca\(^{2+}\) ion overload, which might result in cardiac myocyte dysfunction, arrhythmias and cell death. Levosimendan may also have significant anti-inflammatory properties. Data from various studies suggest that levosimendan might have antiarrhythmic effects, although the outcome of clinical trials on the effect of this agent in (for example) atrial fibrillation remain controversial. Currently, on the basis of available data, it is especially worth emphasizing the potential role of this drug in the termination of AF after cardiac surgery, which significantly influences early and long term morbidity and mortality. This review, considers the putative antiarrhythmic properties of levosimendan, and discusses the potential clinical application of such a drug.

**Key words:** atrial fibrillation, heart failure, levosimendan, OR-1896, OR-1855.
Introduction

Levosimendan is a “Ca^{2+} sensitizer,” (1-3) that binds to troponin C (2,3). Levosimendan may also have significant anti-inflammatory (2-4) and antiarrhythmic effects (5-7).

In this review, we consider the putative antiarrhythmic properties of levosimendan, and discuss the potential clinical application of such a drug.

Search strategy

We searched using the electronic databases [MEDLINE (1966 - September 2009), EMBASE and SCOPUS (1965 – September 2009), DARE (1966 – September 2009)]. Additionally, abstracts from national and international cardiovascular meetings were searched. Where necessary, the relevant authors of these studies were contacted to obtain further data. The main data search terms were: atrial fibrillation, heart failure, levosimendan, OR-1896, OR-1855 and treatment.

Levosimendan

Mechanism of action and pharmacological effects

Levosimendan is a “Ca^{2+} sensitizer,” with several mechanisms of action. It exerts its inotropic effect by increasing the affinity of troponin C for Ca^{2+}, directly stabilising the Ca^{2+}-induced conformation of troponin C, or by acting distally to the troponin C molecule (1,2). This drug binds in a Ca^{2+}-dependent manner to the N-terminal domain of troponin C, thus magnifying the extent of the contraction produced by troponin C when it is Ca^{2+}-activated. This results in a positive inotropic effect without impairing diastolic
relaxation and causing cytosolic $\text{Ca}^{2+}$ ion overload, which might provoke cardiac myocyte dysfunction, arrhythmias and cell death (2).

In contrast to other myofilament $\text{Ca}^{2+}$ sensitizers that are bound to the troponin C-$\text{Ca}^{2+}$ complex during both systole and diastole, impairing diastolic function (2,3), levosimendan binding to troponin C is dependent on cytosolic $\text{Ca}^{2+}$, and is significantly weaker (causing minimal $\text{Ca}^{2+}$ sensitization) during diastole (i.e. when intracellular $\text{Ca}^{2+}$ levels are low) (2,4). Hence, levosimendan enhances myocardial contractility and increases left ventricular diastolic function with relatively low arrhythmogenesis and oxygen demand in the human myocardium.

Levosimendan also has vasodilatory properties and anti-ischemic effects due to its facilitation of an adenosine triphosphate-dependent potassium channel opening (8-13). Some studies have suggested that this drug increases cardiac output and lowers cardiac filling pressures, leading to a reduction in cardiac symptoms, risk of death and hospitalization (10-13). Unlike other positive inotropic agents, the primary actions of levosimendan are independent of interactions with $\beta$-adrenergic receptors (13-15); furthermore the use of $\beta$-blockers enhances its hemodynamic effects but reduces the hemodynamic effect of dobutamine (16). Levosimendan and its active metabolite OR-1896 have structural similarities with a family of phosphodiesterase (PDE) inhibitors and therefore both may exert part of their action via inhibition of PDE III (2). The main data on the pharmacokinetics and metabolism of levosimendan are summarised in Table 1 (2, 17-23).
Therapeutic applications/indications of levosimendan

Levosimendan has marketing authorization in 48 countries (22,23). The main indications of levosimendan include the inotropic support in acutely decompensated severe congestive heart failure (23-25).

Results from clinical trials such as LIDO (Levosimendan Infusion versus DObutamine) (22), RUSSLAN (Randomised study on safety and effectiveness in patients with left ventricular failure after an acute myocardial infarction) (24), and REVIVE-II (The second Randomised multicentre Evaluation of Intravenous levosimendan Efficacy) (25) studies show well documented benefits of levosimendan in patients with acute heart failure syndrome (AHFS). The PERSIST study (Oral levosimendan in patients with severe chronic heart failure) evaluated the effects of oral levosimendan in severe chronic heart failure (CHF) (26). 307 CHF patients with NYHA (New York Heart Association) class IIIB - IV were randomly assigned, double-blind, to levosimendan 1 mg once or twice daily or placebo for at least 180 days. An exploratory primary end-point, the Patient Journey, a composite consisting of repeated symptom assessments, worsening heart failure (HF) and mortality during 60 days was used. Minnesota Living with Heart Failure quality of life score (MLHFQoL) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were also assessed. The patients assigned to a lower dose of levosimendan had more severe CHF at baseline. No differences in symptoms emerged and worsening HF events and death were similar resulting in a similar Patient Journey score with levosimendan and placebo (p=0.567). Compared with placebo, a net improvement of 3-4 points in MLHFQoL at several time-points in favour of the combined levosimendan groups was observed (p<0.001), which was accompanied by a substantial and persistent
reduction in NT-proBNP (by 30-40%) (p<0.001). The authors conclude that levosimendan improves quality of life and decreases NT-proBNP but does not improve the Patient Journey composite in patients with severe CHF (26).

Decompensated low-output CHF is the best therapeutic indication for levosimendan administration. Compared with other agents for AHFS, the main advantages of levosimendan are improved myocardial contractility without increased oxygen demand, reduction of ventricular preload, rapid increase in cardiac index with simultaneous reduction of pulmonary capillary wedge pressure (PCWP) and reduced peripheral vascular resistance without a proarrhythmic effect (27). Furthermore, positive effects on long-term survival up to 6 months were also observed (12,27) as well as improved dyspnoea and fatigue (28). The treatment of CHF with levosimendan resulted in significant reduction in BNP (brain natriuretic peptide) levels, which may be useful to monitor treatment and as a prognostic marker (28,29).

Levosimendan alone is not the first drug of choice in cardiogenic shock, but there are several recent clinical observations indicating that it can improve hemodynamics, even in patients with cardiogenic shock, if it is combined with norepinephrine to maintain adequate perfusion pressures (28,30).

Levosimendan may also be used in a perioperative treatment in patients undergoing cardiac surgery. It improves hemodynamics in patients after coronary artery bypass grafting (CABG) (30-32). On the other hand, a decrease in systemic arterial pressure that occurs during its intravenous (i.v.) administration could actually be dangerous, particularly with associated coronary artery disease where in the presence of critical coronary stenosis, coronary perfusion is pressure-dependent, so that i.v. levosimendan
administration can affect the regional kinesis (33). In the experimental rabbit heart model it was also shown that it may exacerbate myocardial stunning and thus impair cardiac output (34).

However, animal models show that intracoronary administration of levosimendan does not cause a decrease in arterial pressure and it might be useful during cardiac ischemia or in end-stage CHF (33). In addition, its antiischemic effect has been investigated in an isolated rabbit heart subjected to circumflex artery ligation. Levosimendan infusion continuously 30-120 min after ischemia results in dose-dependent increases in coronary flow and a reduction in ischemic zone size at 60 and 120 min (35,36). Kaptan et al., in an in vitro model, also showed that levosimendan, at clinically relevant doses, might have a significant inhibitory effect on platelets (37).

**Contraindications of levosimendan**

The use of levosimendan is contraindicated in patients with: moderate-to-severe renal impairment, severe hepatic impairment, severe ventricular filling or outflow obstruction, severe hypotension and tachycardia, and/or history of torsades de pointes (2,21).

**Side effects of levosimendan**

In general, levosimendan is well tolerated by patients and the most common side effect observed is hypotension, especially at higher doses (2,38). When levosimendan is administered orally, headache is the most common adverse effect - 40% compared with only 10% after i.v. dosing (38).
The **anti-inflammatory** effects of levosimendan and its potential role in arrhythmogenesis

Levosimendan might provoke cardiac myocyte dysfunction and arrhythmogenesis (2,38). However, by decreasing oxygen demand and improving heart muscle contraction in heart failure patients, levosimendan may be indirectly responsible for decreasing AF episodes due to its action on CHF (39-42).

Recently more clinical data suggest that levosimendan drug has anti-inflammatory and antioxidant properties. The roles of inflammation and oxidative stress have been evaluated in the pathogenesis of AF (43-45). Levosimendan administration in contrast to dobutamine has been shown, by means of malondialdehyde (MDA) levels, to decrease oxidative stress 5 days after the administration to patients hospitalized for CHF exacerbation (44).

This effect may be due to the active metabolite of levosimendan OR-1896, which has a long elimination half-life and preserves the biologic action of the parent drug several days after infusion. Parissis et al. (43) found that during acute exacerbation of CHF, MDA concentration remained stable in levosimendan-treated patients in contrast with the placebo-treated group, which exhibited an increase in MDA levels 48 h post-treatment. This observation confirms the antioxidant effectiveness of levosimendan in the prevention of lipid peroxidation and possible AF (43). Moreover, levosimendan suppressed protein oxidative damage, as evidenced by stable levels of protein carbonyl content after administration of the drug, in contrast with the placebo-treated patients whereby higher levels of this oxidative marker were found (43). Levosimendan also acts as a mitochondrial KATP channel opening agent that stimulates K⁺ flux through
mitochondrial K\textsubscript{ATP} channels, maintaining cellular energy homeostasis and protects mitochondria from oxidative injury (43,45).

Furthermore, levosimendan can reduce proinflammatory cytokine interleukin-6 (46) and CRP (C-reactive protein) levels (47). The decreased expression of proinflammatory cytokine could be explained partially by improved hemodynamics and partially by levosimendan and its inhibition of the stimuli for myocardial cytokine production and spillover into the circulation (48). By improving systolic function and inducing peripheral vasorelaxation, it is responsible for attenuating peripheral tissue hypoperfusion, leading to downregulation of cytokine extracardiac production by transcripational factors such as nuclear factor kappa B (NF-κB) (2,49,50). The possible mechanism of antiarrhythmic properties of levosimendan is presented in figure 1.

In a randomised trial (47), levosimendan started before cardiopulmonary bypass was associated with a lower risk of postoperative AF (POAF). This observation was confirmed in recent reports (51,52). Zangrillo et al. performed a meta-analysis to investigate the effects of levosimendan in cardiac surgery patients, whereby a total of 139 patients from 5 randomized controlled studies were included. They showed that levosimendan was associated with a significant reduction in cardiac troponin peak release (weighted mean difference = 2.5 ng/dL, p=0.0003) and in time to hospital discharge (weighted mean difference = -1.38 days, p=0.05). This meta-analysis suggested that the drug had cardioprotective effects, resulting in reduced postoperative cardiac troponin release. They also noticed a nonsignificant trend to decrease the risk of POAF (52). In a recent meta-analysis (53), the authors included 440 patients from 10 randomized controlled studies. Inclusion criteria were random allocation to treatment, comparison of
levosimendan versus control, and cardiac surgery patients. Levosimendan was associated with a significant reduction in postoperative mortality (4.7% in the levosimendan group vs 12.7% in the control arm, odds ratio [OR] =0.35, p=0.003), cardiac troponin release (p=0.0003), rate of myocardial infarction (1.1% vs 5.9%, respectively, OR=0.26, p=0.04), rate of acute renal failure (6.7% vs 23.9%, respectively, OR=0.26, p=0.002) and AF (22.9% vs 31.4% respectively, OR=0.48, p=0.003). They concluded that levosimendan had cardioprotective effects that could result in reduced postoperative complications and mortality (53).

Furthermore, levosimendan had no proarrythmic effects and no significant increase in AF in the Portland (54), LIDO (22) and RUSSLAN studies (24). The aim of the RUSSLAN trial was to evaluate the safety and efficacy of levosimendan in patients with left ventricular failure complicating acute myocardial infarction (24). Levosimendan at different doses (0.1-0.4 µg x kg(-1) x min(-1)) or placebo were administered intravenously for 6h to 504 patients in a randomised, placebo-controlled, double-blind study. The primary endpoint was hypotension or myocardial ischaemia of clinical significance, and secondary endpoints included risk of death and worsening heart failure, symptoms of heart failure and all-cause mortality. The only significant differences between levosimendan and placebo were observed in the prevalence of sinus tachycardia and myocardial rupture (24) (table 2). Also, the haemodynamic benefits of a 6h infusion of the drug in patients with CHF were not at the expense of increased sympathomimetic stimulation or autonomic imbalance which is known to be associated with an increased proarrythmic risk (24,55,56). In contrast, both the REVIVE-II (25) and the SURVIVE (The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic
Support) studies (55,57) found that infusion of levosimendan was clearly associated with an increased risk for AF.

The SURVIVE study is the first prospective, randomized trial to monitor long-term survival in patients with acute decompensated heart failure (ADHF). The results revealed no significant difference between levosimendan and dobutamine in all-cause mortality at 31 and 180 days after study drug infusion (55). The SURVIVE study showed that patients who received levosimendan were more likely to experience AF (9.1% vs 6.1%, p=0.05) compared with dobutamine-treated patients (55). In the REVIVE-II randomized placebo-controlled trial, examining the effect of the drug (initial bolus, 12 µg/kg followed by a stepped dose regimen of levosimendan, 0.1-0.2 µg/kg/min for 24 h), the prevalence of AF was increased (8% vs 2%) in levosimendan-treated patients compared with placebo (25).

Taking all above results together, the outcome of clinical trials regarding the effect of levosimendan on AF is still controversial. The conflicting results of these trials reflect a few issues. First, interpretation is particularly difficult, since in some of these trials, patients with documented AF and sustained ventricular arrhythmia were excluded, like in the SURVIVE trial where exclusion criteria were: sustained ventricular tachycardia or frequent ventricular non-sustained tachycardia not related to thrombolysis and AF with a rapid ventricular response (55). Secondly, most of the trials were designed to assess levosimendan in the treatment of CHF and its effect on mortality (table 3).

Another important issue is a dose-effect relationship between levosimendan and AF. Increased frequency of ventricular arrhythmias was observed when high-dose of the drug was used in patients with stable ischemic cardiomyopathy (10). Further safety studies
should therefore assess whether or not the incidence of AF may be related to the high
doses of levosimendan.

The relation of levosimendan and arrhythmias occurrence could also have been caused by
the co-administration of the drug with preparations that can induce arrhythmia disorders
(56,57). This may be proved by observation that arrhythmias were not increased when
levosimendan was compared with placebo in patients with acute myocardial infarction
(24) or when it was administered perioperatively in patients having coronary artery
bypass grafting (47,58).

PDE inhibitors or other classic dobutamine-like inotropic agents are limited by their
arrhythmogenic effect (59). In particular, PDE inhibition induces nonsustained
ventricular tachycardias (VT), and increases overall mortality (59). However, in recent
animal studies of ischemia, levosimendan proved to be clearly superior to the PDE
inhibitor milrinone, since it was associated with fewer ventricular premature beats and
smaller incidence of tachycardia or ventricular fibrillation (57).

We await the results of ongoing studies which might confirm the antiarrhythmic
properties of levosimendan. One of them - *Effects of Oral Levosimendan on Ambulatory
Electrocardiographic Variables* started in August 2008 and aims to evaluate of
proarrhythmic potential of the different dose regimens of levosimendan (60). This is a
prospective, multicentre, phase II, randomized, double-blind, placebo-controlled 2-arm
parallel group study with five escalating dose-levels of oral levosimendan, each given for
13-18 days. The study population - male and female patients 50 to 80 years of age with
ischaemic stroke or TIA within 1 to 9 months before the screening visit - will be
randomly allocated either to levosimendan or to a placebo group. The study consists of 9
visits (screening visit, 7 visits during the treatment period and an end-of-study visit). Each subject will be on study treatment for 78-108 days and the duration of the study for each subject, including the screening and the end of study visit, is approximately 17 weeks (60).

Other effects of levosimendan on cardiac rhythm

Levosimendan may increase sinus rate, shorten sinus node recovery time, decrease atrioventricular nodal conduction interval (56), and prolong the rate-corrected QT interval. Most clinical studies have showed no evidence of increased life threatening ventricular tachyarrhythmias due to its administration (28).

Conclusions

As we currently practice evidence-based medicine, any new therapy can only be adopted for routine clinical practice after rigorous scrutiny of the evidence. We should therefore wait for the results of further randomized clinical trials to evaluate if levosimendan induces dangerous arrhythmias like AF in CHF patients or if it acts as an antiarrhythmic drug to decrease the risk of AF. To find the answer it is necessary to design large studies where AF (and other arrhythmias) will be the primary endpoint. Currently, in connection with recent published meta-analyses, it is worth emphasizing the potential role of this drug in the termination of AF after cardiac surgery – the most common complication in cardiosurgical patients, which significantly influences early and long term morbidity and mortality (31,36,47,53,61-63).
Declaration of interest

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Table 1. Pharmacokinetics and metabolism of levosimendan (2,17-23).

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bioavailability</strong></td>
<td>high oral bioavailability, but in clinical practice it has only been developed for intravenous administration</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>approximately 1 h</td>
</tr>
<tr>
<td><strong>Body clearance</strong></td>
<td>~300 mL/min</td>
</tr>
<tr>
<td><strong>Binding to albumin</strong></td>
<td>&gt;90%</td>
</tr>
<tr>
<td><strong>Free in plasma</strong></td>
<td>~4%</td>
</tr>
<tr>
<td><strong>Main active metabolites of LV</strong></td>
<td>OR-1896 and OR-1855</td>
</tr>
<tr>
<td><strong>Elimination half-life of the metabolites</strong></td>
<td>~1 week; a maximum concentration after 24 h infusion is reached after 2 days with prolonged effect</td>
</tr>
<tr>
<td><strong>Recommended dosage of LV</strong></td>
<td>6-24 µg/kg of bolus administration followed by a 24-h infusion of 0.05-0.2 µg/kg/min</td>
</tr>
<tr>
<td><strong>Pharmacokinetics in renal failure</strong></td>
<td>the elimination half-life of OR-1896 is prolonged, but it has little effect on the plasma concentration of levosimendan</td>
</tr>
<tr>
<td><strong>Pharmacokinetics in liver failure</strong></td>
<td>the elimination half-life of levosimendan is prolonged, although its effects on production or metabolism of OR-1896 are unknown</td>
</tr>
</tbody>
</table>
Table 2. Baseline characteristics in the RUSSLAN study (24).

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Placebo (n=102)</th>
<th>Levosimendan 6µg. kg⁻¹ + 0.1µg. kg⁻¹.min⁻¹ (n = 103)</th>
<th>Levosimendan 12µg. kg⁻¹ + 0.2µg. kg⁻¹.min⁻¹ (n = 100)</th>
<th>Levosimendan 24µg. kg⁻¹ + 0.2µg. kg⁻¹.min⁻¹ (n = 99)</th>
<th>Levosimendan 24µg. kg⁻¹ + 0.4µg. kg⁻¹.min⁻¹ (n = 99)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation (%)</td>
<td>2.9</td>
<td>6.8</td>
<td>2.0</td>
<td>7.2</td>
<td>10.0</td>
<td>0.097</td>
</tr>
<tr>
<td>Antiarrhythmics (%)**</td>
<td>30.1</td>
<td>22.5</td>
<td>29.0</td>
<td>20.2</td>
<td>26.3</td>
<td>0.385</td>
</tr>
<tr>
<td>Beta-blockers (%)**</td>
<td>40.8</td>
<td>42.2</td>
<td>38.0</td>
<td>32.3</td>
<td>42.4</td>
<td>0.520</td>
</tr>
<tr>
<td>Calcium channel blockers (%)**</td>
<td>14.6</td>
<td>10.8</td>
<td>12.0</td>
<td>14.1</td>
<td>14.1</td>
<td>0.881</td>
</tr>
</tbody>
</table>

* Comparison of levosimendan groups versus placebo based on Cochran-Mantel-Haenszel test.
** Baseline and concomitant medication during the 24 h after start of infusion.
Table 3. The influence of levosimendan on arrhythmias in the available studies.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POSITIVE EFFECT</strong></td>
<td></td>
</tr>
<tr>
<td>LIDO Study [2002] (22)</td>
<td>Significant reduction of rhythm disorders* (4% vs 13% respectively, p = 0.023).</td>
</tr>
<tr>
<td>Portland Study [2004] (54)</td>
<td>No increase in HR (p = 0.150 at 24h, p = 0.086 at 5 days), and the incidences of supraventricular arrhythmias or nonsustained ventricular tachycardias.</td>
</tr>
<tr>
<td>Metaanalysis of Zangrillo et al. [2009] (52)</td>
<td>Nonsignificant trend to decrease the risk of POAF.</td>
</tr>
<tr>
<td>Meta-analysis of Landoni et al. [2009] (53)</td>
<td>Significant AF reduction (22.9% vs 31.4% respectively, p = 0.003).</td>
</tr>
<tr>
<td><strong>NEGATIVE EFFECT</strong></td>
<td></td>
</tr>
<tr>
<td>REVIVE-II study [2006] (25)</td>
<td>The higher incidence of AF (8% vs 2%) and VT (25% vs 17%).</td>
</tr>
<tr>
<td>SURVIVE Trial [2007] (55)</td>
<td>The higher incidence of AF (9.1% vs 6.1%, p = 0.05).</td>
</tr>
</tbody>
</table>

*Rhythm disorders defined as atrial fibrillation, extrasystoles, tachycardia, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, and bradycardia.

ABBREVIATIONS: AF, atrial fibrillation; HR, heart rate; POAF, postoperative AF; VT, ventricular tachycardia.
Figure 1. The possible mechanisms of levosimendan (L) properties in the pathogenesis of atrial fibrillation.