Levosimendan

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7.1 General Principles

Cardiac dysfunction, with hemodynamic compromise and need for inotropic support, may complicate cardiac surgery as well as general surgery, leading to unfavorable outcomes [1].

Levosimendan is an inodilator with specific properties, belonging to the class of calcium sensitizers. Levosimendan improves heart contractility without increasing calcium concentration or affecting lusitropy, nor increasing myocardial oxygen consumption [2]. Due to these favorable features, levosimendan is gaining more and more prominence in acute or chronic heart failure, or cardiac complication after surgery, and in critically ill patients [3, 4]. In 2012 the first international consensus conference on perioperative medicine identified levosimendan as one of the drugs that can increase survival after surgery [5]. Recently, a new and updated consensus conference was conducted to include all the new randomized evidence produced since. The new consensus confirmed that levosimendan is 1 of the 11 drugs/techniques that have been proved, with high-quality evidence, to reduce mortality in the perioperative period [6].

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7.2 Main Evidences

Levosimendan has been extensively studied in cardiac anesthesia, intensive care, and in the heart failure setting. Its positive action on critically ill patients was recently supported by results from a meta-analysis by Landoni et al. [4] reporting a significant reduction in mortality for levosimendan with a number needed to treat as low as 17. In the perioperative setting, most of the high-quality evidence derives from cardiac surgery. The first meta-analysis of randomized controlled studies to suggest that levosimendan reduces 30-day mortality (odds ratio 0.35 [95 % CI 0.18–0.71]) when compared to classic inotropes or placebo was published in 2010 [3]. Levin et al. conducted a randomized controlled study confirming that levosimendan was superior to dobutamine to treat postoperative low cardiac output syndrome [7]. In patients undergoing coronary revascularization, levosimendan was found to be superior to any other comparator, with a 60 % [95 % CI 0.21–0.76] reduction in odds ratio for mortality, and improvements in several ancillary perioperative outcomes [8]. In a meta-analysis of RCT by Harrison et al., levosimendan reduced cardiac surgery mortality in high-risk patients with low ejection fraction (7 % [3–11 %] risk difference for mortality) [9].

These studies confirm the results of the first International Consensus Conference in cardiac anesthesia, which enthroned levosimendan among the drugs that might reduce mortality in this perioperative setting [10]. The superiority of levosimendan in cardiac surgery is evident not only versus classic inotropes but also when confronted to intra-aortic balloon pump [11].

In noncardiac surgery, the effect of levosimendan on mortality has not yet been cleared. However, given its prolonged action and its effects in cardiac surgery and in heart failure patients, a preoperative administration of levosimendan has been proposed as a possible technique to optimize cardiac function in patients with heart failure undergoing noncardiac surgery [12].

Levosimendan has been first and thoroughly investigated in patients with decompensated heart failure. In the RUSSLAN study, patients with cardiac insufficiency randomized to levosimendan showed an increased survival when compared to placebo (hazard ratio 0.56 [95 % CI 0.33–0.95]) [13]. In the LIDO study, severe low-output heart failure patients receiving levosimendan achieved the composite endpoint of improvement in hemodynamic values (30 % increase in cardiac output and 5 % decrease in pulmonary capillary wedge pressure) significantly more than patients receiving dobutamine [14]. The CASINO trial confirmed these results against dobutamine and placebo, with the study interrupted prematurely by the ethical committee due to the clear survival advantage for levosimendan [15], similarly to REVIVE I and II trials where dobutamine was confirmed to reduce symptoms, hospital stay, and levels of brain natriuretic peptide (BNP) [16]. The reduction in BNP levels was confirmed in the SURVIVE study, although a similar rate of mortality was found at 6 months between cases and controls [17].

7.3 Pharmacologic Properties

Classic inotropic drugs function through stimulation of beta-receptors, increasing intracellular cyclic adenosine monophosphate (cAMP) levels, leading to sarcoplasmic reticulum calcium release. The elevation in plasmatic calcium concentration enhances contractility and improves stroke volume. Phosphodiesterase 3 inhibitors (PDE-3 inhibitors) exert a similar action that directly increases cAMP levels through inhibition of the enzyme catalyzing its breakdown, leading to an increased intracellular calcium concentration.

Both beta-receptor agonists and PDE-3 inhibitors increase cardiac stroke volume at the expenses of higher myocardial oxygen demand and jeopardize cardiac relaxation (lusitropy) and diastolic function. These side effects are directly related to cytoplasmic calcium content, and they are considered the origin of the detrimental effects of PDE-3 inhibitors and beta-adrenergic inotropes [18].

On the contrary, levosimendan uniquely increases troponin C affinity for calcium stabilizing its conformation, without increase in intracellular calcium concentration. Cardiac contractility thus improves without increasing oxygen consumption [19]. Moreover, the binding of levosimendan to troponin C is dependent on cytosolic calcium content, and it consistently reduces during diastole, when cytoplasmic calcium content is low (Fig. 7.1). This action avoids the detrimental effects of traditional inotropes: lusitropy reduction and increase in arrhythmias [2]. As other inodilators, levosimendan induces vasodilation in the peripheral smooth musculature but exerts its action through binding of potassium channels.

Levosimendan has anti-apoptotic and anti-inflammatory properties that have been recently demonstrated and that may further improve long-term outcomes in the failing heart [20]. The beneficial effect of levosimendan on mortality is probably due to the sum of these unique actions.

7.4 Therapeutic Use

Levosimendan is administered through continuous infusion with or without an initial bolus. It has a 60-min half-life, with steady-state concentration reached within 4 h and active metabolite plasma concentration peaking at 2 days after infusion. Levosimendan clearance is about 3 mL/kg/h, largely through liver metabolism and with a smaller proportion metabolized through the intestine, and it is eliminated through renal and fecal excretion. Its main metabolites are OR-1855 and OR-1986. The former is an intermediate compound, extracted in the bowel through the biliary route. The latter is formed by N-acetylation of OR-1855 and is the most clinical relevant metabolite, with an 80-h half-life that is probably responsible for the prolonged effect of drug, which persists for many days after administration.

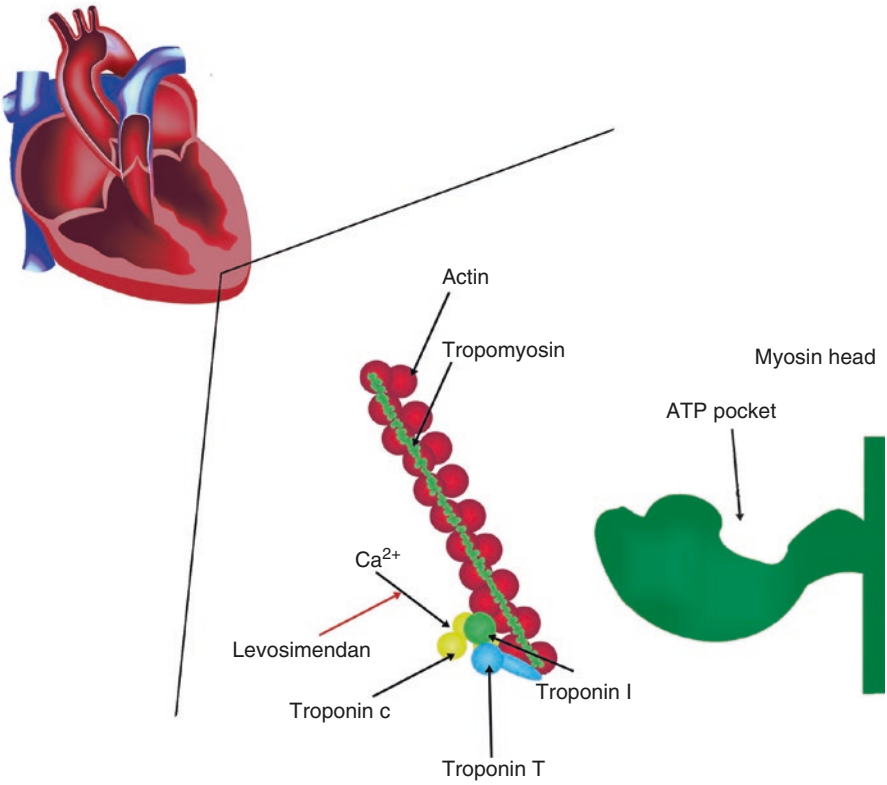

Fig. 7.1 Levosimendan myocardial mechanism of action

Levosimendan dosage should be cautious in patients with end-stage renal disease, as data on patients with renal dysfunction suggest that the elimination half-life of OR-1986 (but not levosimendan half-life) is prolonged in these patients. Hepatic insufficiency directly increases levosimendan concentration, and dosing should be reduced in patients with liver failure. Other relative contraindications are left ventricular outlet obstruction that may be worsened by levosimendan, severe hypotension and tachycardia, or history of torsades de pointes.

No risk of tolerance or rebound has been documented after prolonged infusion. Due to its distinct action, levosimendan can be safely used with other cardioactive drugs, including beta-adrenergic inotropes and PDE-3 inhibitors. Moreover, beta-blockers do not reduce levosimendan action, leading to new potential therapeutic synergism in heart failure patients [21].

Levosimendan is administered through continuous infusion ranging from 0.05 to 0.2 μg/kg/min. A loading dose of 6–12 μg/kg was suggested to anticipate the target

concentration, but a significant increase in rate of hypotension has been demonstrated for bolus doses. Thus, bolus administration of this drug should be probably avoided [4].

7.4.1 Intermittent Administration

Promising results have also been achieved in outpatients with end-stage heart failure, using an intermittent monthly intravenous administration of levosimendan. A trial documented an increased survival as well as hemodynamic improvements for levosimendan intermittent administration when confronted to dobutamine or other controls [22]. This positive action is probably related with the long-lasting effects of levosimendan metabolites.

Outpatients with chronic severe heart failure will be the target of this treatment, probably reducing hospitalization, morbidity, and mortality and reducing healthcare costs.

7.4.2 Possible Future Targets

Diaphragm muscle weakness is a prominent finding in critically ill patients, and it is due to various conditions, such as mechanical ventilation, chronic obstructive pulmonary disease (COPD), and cachexia. In these patients, specifically in COPD patients, a higher level of intracellular calcium concentration is needed to obtain normal muscular contraction [23]. Moreover, results from animal studies document impaired contractility and reduced efficiency of the diaphragm in congestive heart failure and prolonged mechanical ventilation animal models. No therapeutic options are available to improve diaphragm function. However, levosimendan showed a beneficial effect in isolated diaphragm test, enhancing contractility, possibly suggesting a new therapeutic approach in patients with respiratory failure and difficult weaning from mechanical ventilation.

Conclusion

Levosimendan has been introduced in clinical practice a decade ago and has been proven to be superior to other inodilators in various clinical settings. Its beneficial effect is probably due to its peculiar mechanism of action. Levosimendan should be preferred in perioperative medicine in patients with cardiac dysfunction, after cardiac and noncardiac surgery. Further trials in critically ill patients with sepsis or septic shock or in ambulatory patients with chronic heart failure are ongoing and may lead to further application of levosimendan in new settings.

Summary Table

Clinical summary					
Drug	Indications	Cautions	Side effects	Dose	Notes
Levosimendan	Acutely decompensated heart failure Low output syndrome in cardiac surgery Critically ill patients (evidence mostly from above reported settings) Sepsis-related cardiac dysfunction (unconclusive but promising results) Intermittent levosimendan administration in chronic heart failure	Monitor for hypotension and tachycardia Loading dose has been associated with adverse effects and hypotension and should be avoided whenever possible Should be used with caution in patients with renal or hepatic impairment	Hypotension (dose dependant) Tachycardia Headache Atrial/ventricular arrhythmias	[Loading dose: 6–12 μg/kg, see cautions] Continuous infusion of 0.05–0.1 μg/kg/min, if tolerated can be increased up to 0.2 μg/kg/min	Hemodynamic effect persist for at least 24 h, and has been reported to last for 7–10 days No adjustment is required for age Can be used in patients receiving β-blocking agents without loss of efficacy. Synergistic effects with classic inotropes

New indications like prevention of decompensation in chronic heart failure through oral or intermittent intravenous administration are currently under investigation and are showing promising results in preliminary data

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