

## Levosimendan

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One of the strategies used in the management of congestive heart failure (CHF) is to increase myocardial contractility without increasing the afterload. "Inodilators", as their name suggest, are a group of drugs that achieve this dual goal by increasing the contractility and causing vasodilatation(1). This group includes dobutamine ( $\beta$ -adrenergic agent) and milrinone (phosphodiesterase III inhibitor). These agents achieve these effects by increasing intracellular concentrations of free calcium. However, this action markedly increases myocardial energy consumption, which may contribute to the risk of arrhythmias. Levosimendan is one of a new class of inodilators, the calcium sensitizers. The present review highlights the clinical pharmacology, indications and therapeutic efficacy of this drug in clinical practice.

### MECHANISM OF ACTION

Levosimendan is a pyridazone-dinitrile derivative. It has two important actions. Its primary action is to enhance cardiac contractility. This is achieved by a pharmacological mechanism known as calcium sensitization. It does not increase intracellular concentrations of free calcium. It binds to cardiac troponin C in a calcium-dependent manner and stabilises troponin C. This causes actin-myosin cross-bridges, without increasing myocardial consumption of adenosine triphosphate (ATP). The cardiac performance and contractility are significantly improved with no increase in the total myocardial energy demand and oxygen consumption. The potential for arrhythmia is also reduced as total intracellular calcium levels are not raised. An additional benefit is that the stabilization

effect is calcium dependant and levosimendan exerts its effects during systole; it does not effect the duration of diastole and so ventricular relaxation is not impaired. Consequently adequate ventricular filling and optimal coronary perfusion still occurs.

Levosimendan also causes venous, arterial and coronary vasodilation, probably by opening ATP-sensitive potassium channels in smooth muscle. Dose-dependant hypotension may occur. Levosimendan is also of benefit in the setting of pulmonary vasoconstriction and right ventricular dysfunction and reduces pulmonary vascular resistance.

Levosimendan is 98% bound to plasma proteins and completely metabolized prior to excretion. Approximately 5% of a dose is converted in the intestines, and then to a highly-active metabolite with an elimination half-life of 75–80 h (compared to 1 hour elimination half-life for levosimendan itself). This metabolite reaches a peak plasma concentration about 2 days after the termination of the infusion and exhibits haemodynamic effects similar to those of levosimendan. Because of the long half-life of the active metabolite, these effects last for up to 7 to 9 days after discontinuation of a 24-hour infusion of levosimendan.

Through its non- $\beta$ -adrenergic actions, it allows for interruption of catecholamine infusions, which may mitigate the tolerance or tachyphylaxis associated with these drugs, an approach that has been reported in adult patients. Finally, its inotropic properties may be particularly desirable in children who are receiving  $\alpha$ -blockers, for whom catecholamines may provide only limited benefit.

**DOSE**

The usual dosage of intravenous levosimendan used in clinical trials of patients with heart failure is 6 to 12 µg/kg loading dose over 10 minutes followed by 0.05 to 0.2 µg/kg/min as a continuous infusion. Hemodynamic response is generally observed within 5 minutes of commencement of infusion of the loading dose. Peak effects are observed within 10 to 30 minutes of infusion; duration of action of levosimendan is about 75-78 hours to 1 week due to active metabolites. No dosage adjustments are required in patients with mild to moderate renal failure and hepatic impairment. Efficacy with once a week administration makes it a promising drug. The published trials so far have utilized intravenous levosimendan. However, the agent is also well absorbed orally and oral preparation is now available. Comparison of levosimendan with dobutamine and milrinone is given below in **Table I**.

Levosimendan is currently licensed in 10 European countries (Simdax, Abbot Pharmaceuticals) for the treatment of acute heart failure. The drug is not licensed to be marketed in India. It needs to be procured by obtaining a special license. Levosimendan is available in the strength of 2.5 mg per 5 mL per ampoule and 10mL per ampoule. The cost of each vial accounts to approximately 75,000 to 1,00,000 INR depending upon the country it is imported.

**SIDE EFFECTS**

Levosimendan is well tolerated, with most adverse events (e.g., headache, hypotension) being dose-related and arising from the vasodilatory actions of the drug. In order to avoid undue hypotension it may be prudent to temporarily stop milrinone and other vasodilators when administering this drug(2,3). The other side effects that are forthcoming from trials include prolongation of corrected QT interval and rarely, ventricular tachycardia. Nevertheless, it should be avoided in patients with Torsades or any other abnormal rhythm.

**EVIDENCE SUPPORTING USE OF LEVOSIMENDAN**

A study in a pediatric cohort of children with severe heart failure who were inotrope dependent demonstrated that levosimendan can be safely administered to infants and children with severe heart failure(4). In this study, amongst children with acute onset cardiac failure, levosimendan allowed for substantial reduction in catecholamine infusions and produced an objective improvement in myocardial performance. The effects of levosimendan was less favourable in patients with end stage chronic heart failure. In another study from Australia, when levosimendan was administered during cardiopulmonary bypass in children with anticipated low cardiac output, it demonstrated low arterial lactate levels, trends toward improved hemodynamics, heart rate reduction, an increase in mean blood pressure, and reduced conventional inotrope use(5).

**TABLE I** COMPARISON BETWEEN LEVOSIMENDAN, MILRINONE AND DOBUTAMINE

Feature	Levosimendan	Milrinone	Dobutamine
Class	Calcium channel sensitizer	Phosphodiesterase-III inhibitor	Catecholamine ( $\beta$ -adrenergic agent)
Increases intracellular calcium concentrations	No	Yes	Yes
Vasodilator	Coronary and systemic	Peripheral	Mild peripheral
Increase myocardial oxygen demand	No	No	Yes
Arrhythmogenic potential	Rare and may be due to QTc prolongation	Ventricular and supraventricular arrhythmias	Ventricular ectopic activity; less arrhythmogenic than milrinone
Adverse events	Headache, hypotension	Ventricular irregularities, hypotension, headache	Tachycardia and increased SBP on overdosage

**KEY MESSAGES**

- Levosimendan, a new inodilator, may be useful in refractory cardiac failure, refractory pulmonary hypertension and dilated cardiomyopathy.
- Levosimendan may help in decreasing the need for long term inotropic support and may thus act as a bridge to heart transport.
- Levosimendan with its long half-life appears to be a promising “once a week” inotrope.

A similar pharmacokinetic profile of Levosimendan was demonstrated in children with congenital heart disease, comparable to adults(6). Case reports of Levosimendan in myocardial stunning have been documented(7). Levosimendan seems to improve medium term survival in patients failing to wean off cardiopulmonary bypass and requiring cardiac assist devices as a bridge to recovery(8). Two large prospective trials- REVIVE II (randomized multicenter evaluation of intravenous levosimendan efficacy-II) and SURVIVE (survival of patients with acute heart failure in need of intravenous inotropic support) evaluated the efficacy of levosimendan in patients hospitalized for acute decompensated heart failure (ADHF) have concluded that this novel inotropic agent does confer early additional benefit in addition to standard therapy(9,10). In the LIDO(Levosimendan versus Dobutamine) study, Levosimendan improved hemodynamic performance and survival, compared with dobutamine, in adults with severe heart failure(11). In the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct (RUSSLAN), the drug showed outcome benefits in comparison with dobutamine and placebo, respectively(12). A comparative study, Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure (CASINO), suggested mortality benefits with levosimendan over placebo and dobutamine(13). A prospective randomized pilot study demonstrated improved right ventricular performance in patients with acute respiratory distress syndrome(ARDS) and septic shock(14). The role of levosimendan in septic myocardial dysfunction has been studied and found to be beneficial(15). Levosimendan also finds a place in the management of septic shock in the latest pediatric septic shock guidelines(16). It has been recommended by the guidelines to use levosimendan

in refractory cold septic shock.

It has been also been reported that oral levosimendan has favorable cardiac and hemodynamic effects in patients with severe congestive heart failure; these effects are similar to those seen after intravenous dosing with levosimendan(17). The 4-8 mg daily doses of oral levosimendan showed moderate inotropic effects(18). Both 6-h infusion and a 2-mg single dose of levosimendan showed that it has moderate inotropic and vasodilatory effects in patient with severe congestive heart failure(19). Thus, oral levosimendan may be used as substitute for intravenous inotropic support in end-stage heart failure, as pilot results on the use of oral levosimendan are encouraging.

**CONCLUSION**

Levosimendan has been found to be a safe and useful drug when given to the sickest children with acute heart failure refractory to standard anti-failure medications. The pharmacokinetics of levosimendan underpins the prolonged beneficial hemodynamic effects that result from single dose infusion regime. It is an appealing and promising alternative or an intermittent adjunct to current therapies for heart failure, as well as in refractory septic shock in children.

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