

Dobutamine Kills Good Hearts! Levosimendan May Not

S Kumar

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Abstract

Levosimendan (Simdax®- Abbott) is a calcium sensitizer that can be administered intravenously (IV) to patients with acute decompensated congestive heart failure (CHF).

At therapeutic dosages levosimendan enhances myocardial contractility without increasing oxygen requirements and causes coronary and systemic vasodilation. So, like the phosphodiesterase inhibitors it is also an 'Inodilator'.

In clinical trials, levosimendan has been shown to reduce the risk of worsening CHF or death compared with dobutamine and placebo in patients with decompensated CHF. The drug is well tolerated, does not appear to be proarrhythmic, has minimal potential for interactions with other drugs and does not reduce short-or long-term (30-day) survival.

Thus, unlike some other agents administered to improve contractility in decompensated heart failure, IV levosimendan appears to offer therapeutic benefits without risk of arrhythmogenesis or uncertain impacts on survival.

INTRODUCTION

One strategy used in the management of CHF is to increase myocardial contractility. Established positive inotropic agents achieve this by increasing intracellular concentrations of free calcium. However, this action markedly increases myocardial energy consumption, which may contribute to the risk of arrhythmias seen with some inotropic agents.¹

Levosimendan, like pimobendan is one of a new class of heterogeneous agents, the calcium sensitizers. The drug works via a dual mechanism of action which enhances cardiac contractility and vasodilatation without affecting intracellular free calcium, and so should have reduced proarrhythmic potential. It can be administered intravenously (IV) which makes it a therapeutic option for acute decompensated CHF.

Decompensated CHF has been defined as sustained deterioration of at least one New York Heart Association functional class, usually associated with objective evidence of volume overload (e.g. neck vein distension, rales, oedema).²

FEATURES OF LEVOSIMENDAN

LEVOSIMENDAN BOOSTS CONTRACTILITY

Levosimendan increases myocardial contractility in a dose-dependent fashion in healthy subjects, patients with left

ventricular dysfunction, and patients who have undergone coronary artery bypass surgery.^{3,4,5} (in single doses dose-dependently)

The drug acts by increasing the sensitivity of the cardiac myofilament to calcium, rather than increasing intracellular concentrations of free calcium. By binding to cardiac troponin C in a calcium-dependent manner, levosimendan stabilises troponin C and the kinetics of actin-myosin cross-bridges without increasing myocardial consumption of adenosine triphosphate (ATP).¹

NO EFFECT ON MYOCARDIAL ENERGETICS

Administration of levosimendan 8 or 24 µg/kg IV in 23 patients undergoing elective cardiac surgery significantly increased cardiac output, heart rate and stroke volume without significantly increasing myocardial oxygen consumption or changing utilization of myocardial substrates.⁵ A similar 'neutral' effect of levosimendan on myocardial energetics has also been demonstrated in healthy volunteers, whereas dobutamine increased oxygen consumption in addition to contractility.⁶

POTENT VASODILATORY EFFECTS

Levosimendan also causes venous, arterial and coronary vasodilation, probably by opening ATP-sensitive potassium channels in smooth muscle.¹ Continuous 24-hour infusion of

levosimendan decreased pulmonary capillary wedge pressure (PCWP), systemic vascular resistance, pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) in patients with moderate to severe stable CHF.^{7, 8} Dobutamine had no significant effect on PVR or PAP in one of these studies.⁷

NO EVIDENCE OF ARRHYTHMOGENESIS

Levosimendan is not expected to be proarrhythmic because of its lack of effect on potentially arrhythmogenic intracellular calcium concentrations.¹

There was no increase in the frequency of nonsustained ventricular tachycardia or development of new supraventricular or ventricular tachyarrhythmias in 386 patients with heart failure treated with IV levosimendan in pooled data from 10 short term studies.⁹

FAVOURABLE PHARMACOKINETICS

The main pharmacokinetic parameters of levosimendan in patients with CHF are as follows:

- Linearity
- 98% binding to plasma proteins
- Elimination half-life ($t_{1/2\beta}$) of about 1 hour
- Complete metabolism, with some active metabolites possibly extending the drug's haemodynamic effects.¹

BEST RESULTS IN DECOMPENSATED CHF

In patients with decompensated CHF, levosimendan significantly reduced the incidence of worsening CHF or death, and improved cardiac indices.

BETTER THAN DOBUTAMINE

In the randomized Levosimendan Infusion versus Dobutamine (LIDO) trial in 203 patients with severe, low-output decompensated CHF¹⁰ significantly 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 PCWP $\geq 25\%$ than in the dobutamine group (5 to 10 $\mu\text{g}/\text{kg}/\text{min}$ for 24 hours) [28 and 15%, respectively].

Furthermore, more patients treated with dobutamine than levosimendan experienced worsening heart failure or died by the 30-day follow-up point (17 vs 6.8%).^[10] Levosimendan

was given as a 24 $\mu\text{g}/\text{kg}$ loading dose followed by 0.1 to 0.2 $\mu\text{g}/\text{kg}/\text{min}$ for 24 hours.

WORKS AFTER ACUTE-MI TOO

A significant dose-related decrease in worsening heart failure or death over the first 24 hours was observed in patients treated with levosimendan (1 of 4 different dosages) compared with placebo (4.0 vs 8.8%); this was shown in the Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct (RUSSLAN) trial in 504 patients with decompensated CHF after acute myocardial infarction (MI).¹¹ Furthermore, at 14 days, significantly fewer levosimendan recipients had died (11.4%) than placebo recipients (19.6%).¹¹

May Be Useful In Stable CHF...

At least 50% of levosimendan recipients in all of 5 different dosage groups had a favorable haemodynamic response in a study of 151 patients. The response rates at all doses of levosimendan were significantly superior to placebo but similar to that with dobutamine.⁷

...And After Cardiac Surgery

When 18 patients were randomized to receive low or high dose levosimendan or placebo 15 minutes prior to cardiopulmonary bypass and then for 6 hours after surgery, both doses of levosimendan significantly increased cardiac output 15 and 60 minutes post-surgery compared with placebo.¹²

Levosimendan improved the function of stunned myocardium following successful percutaneous transluminal coronary angioplasty.¹³

GOOD TOLERABILITY PROFILE

Levosimendan is well tolerated, with most adverse events (e.g. headache, hypotension) being dose-related and arising from the vasodilatory actions of the drug.^{1, 14}

Other important features of the adverse events profile of levosimendan are as follows:

in the LIDO trial, levosimendan was associated with fewer serious adverse events than dobutamine (6.7 vs 18.4%)¹⁰

- No clinically relevant changes in any laboratory parameters were observed in pooled data from 3 large clinical trials of levosimendan in heart failure

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- Levosimendan was found to have no important electrophysiological effects at the ventricular level in patients with subtherapeutic plasma concentrations of levosimendan.¹⁵

NO IMPORTANT INTERACTIONS TO DATE

Levosimendan does not have clinically important pharmacokinetic interactions with captopril, β-blockers, felodipine, digoxin, warfarin, isosorbide mononitrate, carvedilol, ethanol or itraconazole.¹

DOSAGE AND ADMINISTRATION

The usual dosage of IV levosimendan used in clinical trials of patients with heart failure is RUSSLAN6 to 12 µg/kg loading dose over 10 minutes followed by 0.05 to 0.2 µg/kg/min as a continuous infusion. (The dosing used in the LIDO trial was 0.1 µg/kg/min for first 2 hours, whereafter the dose was increased to 0.2 µg/kg/min according to the response.) It is pretty safe and effective to reduce pulmonary congestion. Haemodynamic responses are generally observed within 5 minutes of commencement of infusion of the loading dose. Peak effects are observed within 10 to 30 minutes of infusion; the duration of action of levosimendan is about 1 to 2 hours.^[1] No dosage adjustments are required in patients with mild to moderate renal failure. Similarly, loading doses do not require adjustment in patients with mild to moderate hepatic impairment.¹

PRESCRIBING AND FORMULARY CONSIDERATIONS

Use of IV inotropes for the short term treatment of decompensated CHF is well established. Currently available IV drugs are vasodilators [e.g. nitroprusside, glyceryl trinitrate], catecholamine inotropes (e.g. dobutamine) and inodilators (e.g. milrinone).² When administered over longer periods, however, oral inotropes have proved less successful. Digoxin, for example, decreases morbidity but not mortality in patients in sinus rhythm,¹⁶ whereas the phosphodiesterase inhibitor milrinone has been reported to increase morbidity and mortality, presumably as a result of arrhythmogenesis.¹⁷

IV levosimendan increases myocardial contractility without increasing myocardial oxygen demand, and as a consequence appears to be free of serious arrhythmogenic effects in patients with cardiac failure. The Differential features table compares various features of levosimendan and other agents used in this clinical setting.

Levosimendan is a promising agent for the treatment of CHF requiring IV treatment, and an oral formulation is also under development.²² However, the role of levosimendan will become more clearly defined with more extensive clinical use of the drug. Levosimendan received its first marketing approval in Sweden, but is not yet available in most countries.²³

Figure 1

| Key points in the overall evaluation of levosimendan for the treatment of decompensated CHF | |
|---|---|
| CLINICAL BENEFITS | |
| • | Enhances cardiac contractility without increasing myocardial oxygen demand, and causes vasodilation |
| • | Significantly reduces the incidence of worsening CHF or death in patients with decompensated CHF |
| • | No evidence of arrhythmogenesis to date |
| POTENTIAL LIMITATIONS | |
| • | Vasodilatory properties can cause adverse effects (headache, hypotension) |
| • | Must be administered intravenously |
| • | Limited clinical experience at present |

DIFFERENTIAL FEATURES

Comparison of selected features of representative drugs used to increase cardiac contractility in patients with decompensated congestive heart failure (CHF)^{1, 2, 18, 19, 20, 21}

Figure 2

| Feature | Levosimendan | Milrinone | Dobutamine |
|---|---|---|---|
| Class | Calcium sensitizer | Phosphodiesterase inhibitor | Catecholamine |
| Increases intracellular calcium concentrations? | No | Yes | Yes |
| Increases cardiac contractility? | Yes | Yes | Yes |
| Vasodilator? | Coronary and systemic | Peripheral | Mild peripheral |
| Increase myocardial oxygen demand? | No | No | Yes |
| Arrhythmogenic potential | No evidence of arrhythmogenesis to date | Ventricular (12.1%) and supraventricular arrhythmias (3.8%) | Ventricular ectopic activity (5%); less arrhythmogenic than milrinone |
| Available formulations | IV* | IV, PO | IV |
| Drug interactions? | No clinically important interactions reported | Few clinically important interactions | No clinically important interactions reported |
| Can be given with β-blockers? | Yes | Yes | Yes |
| Adverse events | Headache, hypotension | Ventricular irregularities, hypotension, headache | Tachycardia and increased SBP on overdosage |

* An oral formulation is under development
 IV = intravenously; PO = orally; SBP = systolic blood pressure.

ADDRESS FOR CORESPONDANCE

Dr. Satish Kumar; Qr. No. - 1134, Sector 4 / C; Bokaro Steel

City; Jharkhand, India. PIN -827004. e-mail :
dr_satish_kumar@hotmail.com Phone: (91)06542-31273
Fax (Office): (91)06542-32911

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Author Information

Satish Kumar, MD

Cardiology Unit, Department of Medicine, Bokaro General Hospital, BSL (SAIL)