Levosimendan: Guide to use in Critical Care [Unlicensed Drug]

Levosimendan is Consultant Intensivist Prescription Only

Background

Levosimendan is a calcium sensitising agent, which increases cardiac contractility by enhancing the sensitivity of the myocardium to calcium. As a result this produces positive inotropic effects that are independent of beta-receptors or cyclic AMP. It also has a vasodilator effect, by opening ATP- sensitive potassium channels in vascular smooth muscles, which results in smooth muscle relaxation. The combination of inotropic and vasodilator actions results in an increased force of contraction with decreased preload and afterload in the myocardium.[1]

Indications

Levosimendan may be considered as an **alternative or addition** to dobutamine in patients with acute decompensated heart failure.

It has been used in the following situations:

- Acute decompensation of severe chronic heart failure (NYHA III / IV) despite standard oral therapy (ACEI / A2RA / β-blocker / aldosterone antagonist) as tolerated + IV vasodilators / diuretics
- Left ventricular failure post acute MI necessitating inotropic therapy despite optimal therapy
- Low cardiac output syndrome or cardiogenic shock post coronary artery bypass grafting or heart valve repair / replacement
- Cardiogenic shock refractory to dobutamine (≥ 5mcg/kg/min for > 24 hours)
- Undesirable adverse effects as a result of dobutamine therapy e.g. arrhythmias

All patients must:

- Have had a recent ECHO (within 5 days) and
- Undergo advanced haemodynamic monitoring e.g. PiCCO®

Cautions[2]

Hypotensive patients or those at risk of hypotension.
Patients with tachycardia, atrial fibrillation or life threatening arrhythmias.
Correct severe hypokalaemia prior to commencing levosimendan infusion.
Patients with ischaemic heart disease or anaemia due to the risk of haemoglobin drop.
Patients with mild to moderate renal failure or mild to moderate hepatic failure. No dose adjustment is required in mild to moderate renal failure or during renal replacement therapy.

Contraindications[2]

- Severe hypotension and tachycardia.
- Significant mechanical obstructions affecting ventricular filling or outflow or both.
- Severe renal impairment (creatinine clearance <30 mL/min).
- Severe hepatic impairment.
- History of Torsades de Pointes.

Adverse events[2]

The most frequent adverse events with Levosimendan are ventricular tachycardia, atrial fibrillation, hypotension, ventricular extra systoles, tachycardia, hypokalaemia, haemoglobin drop and headache. A reduction in the infusion rate or discontinuation of the infusion may be required if adverse events are severe.

Preparation and administration

One 5 mL vial (12.5mg) of levosimendan should be diluted to 250 mL with dextrose 5% giving a concentration of 0.05 mg in 1mL (50micrograms in 1mL).
Due to the low pH (3.5 – 4) of the solution, if the central route is available, this is preferred. [3]
If a central venous access device is unavailable, administer via a large peripheral vein monitoring insertion site closely and resite cannula at first signs of inflammation. Administer via a dedicated line.[3]

Infusion rate

A loading dose is not required

Run infusion at 0.1 micrograms /kg /min and continue for 24 hours.
0.05micrograms/kg/min should be considered if a more cautious dosing regimen is preferred to assess tolerability, or if the patient develops severe adverse effects with 0.1micrograms/kg/min.

Example Calculation

To administer a dose of 0.1 micrograms/kg/minute of levosimendan to a 70kg patient using a standard solution of 12.5mg in 250mL (50 micrograms in 1mL):

$$\text{Levosimendan infusion rate (mL/hour)} = \frac{0.1\text{micrograms/kg/min} \times 60\text{mins} \times 70\text{kg}}{50 \text{ micrograms in 1mL}} = 8.4 \text{ mL/hour}$$

The following specifies the infusion rate (mL per hour) required for different patient weights:

Patient weight (kg)	Infusion rate of Levosimendan 12.5mg in 250mL (50micrograms in 1ml)		How long one 12.5mg vial of Levosimendan will last at each infusion rate	
	0.05 mcg/kg/minute	0.1mcg/kg/minute	0.05 mcg/kg/minute	0.1mcg/kg/minute
40	2.4mL/hour	4.8 mL/hour	104 hours	52 hours
50	3 mL/hour	6 mL/hour	83 hours	41 hours
60	3.6mL/hour	7.2 mL/hour	69 hours	34 hours
70	4.2mL/hour	8.4 mL/hour	59 hours	29 hours
80	4.8mL/hour	9.6 mL/hour	52 hours	26 hours
90	5.4mL/hour	10.8 mL/hour	46 hours	23 hours
100	6 mL/hour	12 mL/hour	41 hours	21 hours
110	6.6 mL/hour	13.2 mL/hour	37 hours	19 hours
120	7.2mL/hour	14.4 mL/hour	34 hours	17 hours

Use of levosimendan for longer than 24 hours is unnecessary.
The haemodynamic effects persist for 7 – 10 days after the end of infusion.
ONE vial of levosimendan is adequate for treatment in the majority of cases.
Patients >90kg may require a second vial in order to complete the 24 hour infusion.
It is a consultant decision whether a second vial is required to complete the 24 hour infusion.

References

1. Follath F *et al*. Dose ranging study and safety with iv levosimendan in low output heart failure: Experience in three pilot studies and outline of the levosimendan infusion versus dobutamine (LIDO) trial. *Am J Cardiol* 1999; **83**: 211 – 251.
2. Summary of product characteristics, Simdax, Orion Pharma. Last updated 03/10/2016 accessed via www.simdax.com on 26/04/2018
3. Injectable Medicines Guide Levosimendan monograph accessed via http://www.injguide.nhs.uk 26/04/2018