Drug Guideline Title: Simdax (levosimendan)

Summary:
Levosimendan is a cardiac inotrope and vasodilator with calcium sensitising properties. It is used in ICU for the management of acute heart failure.

Approved by: ICU Director A/Prof M. Parr
Publication (Issue) Date: December 2014
Next Review Date: December 2017

Replaces Existing Drug Guideline: levosimendan_2014

Background Information:
Levosimendan is an inotrope agent with a unique mode of action. It is a calcium sensitizer, which increase cardiac contractility by enhancing the sensitivity of the myocardium to calcium. As a result, levosimendan 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. Introduction contains:
The risk addressed by this policy:

Patient Safety

The Aims / Expected Outcome of this policy:

Levosimendan will be administered safely and without adverse side effects.

Related Policies
- C3.00 Drug prescribing
- C3.01 Drug administration
- C3.012 Administration of IV medications

2. Policy Statement:
- All care provided within Liverpool Hospital will be in accordance with infection prevention/control, manual handling and minimisation and management of aggression guidelines.
- Medications are to be prescribed and signed by a medical officer/authorised nurse practitioner unless required during an emergency.
- Medications are to be given at the time prescribed (as close to the time as is possible when multiple drugs require ‘same time’ administration and, when the nurse is caring for more than one patient, recognition is given to a possible short delay to
administration – antibiotics and other lifesaving drugs are to be prioritised) and are to be signed by the administering nurse.

- Parenteral medication prescriptions and the drug are to be checked with a second nurse prior to administration.
- All drugs administered during an emergency (under the direction of a medical officer/authorised nurse practitioner) are to be documented during the event, then prescribed and signed following the event.
- Adverse drug reactions are to be documented and reported to a medical officer.
- Medication errors are to be reported using the hospital electronic reporting system: IIMS.
- Guidelines are for adult patients unless otherwise stated.
- Levosimendan is not TGA (Therapeutic Goods Administration) approved in Australia. Medical Officers wishing to prescribe this drug must do so using the SAS (Special Access Scheme) and must complete the Category A form.

3. Principles / Guidelines

**Actions**

Levosimendan enhances the calcium sensitivity of contractile proteins by binding to cardiac troponin C in a calcium-dependent manner. Levosimendan increases the contraction force but does not impair ventricular relaxation. In addition, levosimendan opens ATP-sensitive potassium channels in vascular smooth muscle, thus inducing vasodilatation of systemic and coronary arterial vessels and systemic venous vessels.

In patients with heart failure, the positive calcium-dependent inotropic and vasodilatory actions of levosimendan result in an increased contractile force and a reduction in both preload and after load, without adversely affecting diastolic function. Levosimendan activates stunned myocardium in patients after percutaneous transluminal coronary angioplasty (PTCA) or thrombolysis.

**Indications**

- As this drug is not TGA approved (in Australia), the Liverpool Hospital Drug Committee advises that it is approved for the purpose of assisting weaning of ventilator-dependent patients with impaired cardiac function in ICU
- Its use in other patients requires individual patient approval from Medical Administration

- **Cardiogenic shock**
  - Efficacy: Adult, Evidence is inconclusive
  - May improve haemodynamics in patients with cardiogenic shock
  - Continuous infusion of levosimendan improved haemodynamics in a small series of critically ill patients with cardiogenic shock. No bolus dose was given.
  - Levosimendan significantly increased cardiac index and decreased systemic vascular resistance

- **Congestive cardiac failure**
  - Efficacy: Adult, Evidence favours efficacy
  - Levosimendan reduced the incidence of worsening heart failure and death in myocardial infarction patients without inducing hypotension or ischemia
  - Possible treatment option for the management of left ventricular failure due to acute myocardial infarction

- **Cardiac Surgery**
  - Efficacy: Adult, Evidence is inconclusive
  - Provides hemodynamic improvement during low cardiac output states after cardiopulmonary bypass
  - Did not, however, improve coronary perfusion pressure
Contraindications

- Hypersensitivity to levosimendan or to racemic simendan
- Levosimendan should not be used in either severe renal (creatinine clearance <30mL/min) or severe hepatic impairment.
- Severe hypotension and tachycardia
- Significant mechanical obstructions affecting ventricular filling or outflow or both
- History of Torsades de Pointes

Precautions

- Should be used cautiously in patients with tachycardia, atrial fibrillation with rapid ventricular response or potentially life-threatening arrhythmias
- Should be used cautiously and under close ECG monitoring in patients with ongoing coronary ischaemia, long QTc interval regardless of aetiology, or when given concomitantly with medicinal products that prolong the QTc interval
- Hypotension
- As excessive decrease in cardiac filling pressure may limit the response to levosimendan, severe hypovolaemia should be corrected
- If excessive changes in blood pressure or heart rate are observed, the rate of infusion should be reduced or the infusion discontinued
- Effects on blood pressure generally last for 3-4 days and the effects on heart rate for 7-9 days. Non-invasive monitoring for at least 3 days after the end of infusion or until the patient is clinically stable is recommended.
- Hepatic dysfunction (reduced clearance) may lead to increased concentrations of the metabolite, which may result in more pronounced and prolonged haemodynamic effects
- May cause a decrease in serum potassium concentration.
- Levosimendan infusions of may be accompanied by decreases in haemoglobin and haematocrit and caution should be exercised in patients with ischaemic cardiovascular disease and concurrent anaemia.
- Levosimendan undergoes extensive hepatic metabolism but there is no evidence yet to support the need for dose adjustment – evaluate patient history and LFTs.

Significant interactions

- Co-administration of isosorbide mononitrate and levosimendan in healthy volunteers resulted in significant potentiation of the orthostatic hypotensive response.

Adverse effects

- Headache, hypotension
- Increased heart rate (dose-dependent), due to peripheral vasodilation
- Hypokalaemia
- Nausea
- Decreased haemoglobin

Presentation

- Levosimendan 12.5 mg in 5mL (2.5mg/1mL)
- Inactive ingredients include: povidone, anhydrous citric acid and anhydrous ethanol.
- The concentrate is a clear, yellow or orange solution for dilution prior to administration. (normal for solution to be yellow).
- ONE VIAL OF THE DRUG IS ADEQUATE FOR A 24 HOUR ADMINISTRATION, if the dose finishes in under 24hours, there is no need to top up the dose to make the 24 hour time period except in patients weighing > 100kg.
- Each vial of levosimendan costs $1200. Please read the administration guidelines carefully before opening a vial.
**Administrations Guidelines**

1, 2, 3, 9

- Initial IV bolus of 12 micrograms/kg delivered **over 10 minutes** (please check box below for rate and volume for loading dose), followed by
- Continuous IV infusion of levosimendan 0.1micrograms/kg/minute.
  - If hypotension and tachycardia occur, decrease the infusion rate to 0.05 micrograms/kg/min or discontinue.
  - Duration of the infusion is recommended for 24 hours only.

**Infusion**

- Levosimendan 2.5mg/1mL: Draw up 5mL (12.5mg = 1 vial) of the drug and dilute in a bag of sterile 5% glucose 495mL – to total 500mL fluid.
- This will give you levosimendan 0.025mg/mL or 25micrograms/mL

- **CAUTION with Loading dose** –this runs over 10 minutes ONLY: (Optional at the discretion of ICU Staff Specialist / Senior registrar) There is some evidence in literature that a loading dose is unnecessary 4, 3

- Initial IV bolus of 12 micrograms/kg delivered over 10 minutes, followed by
- Continuous IV infusion of levosimendan 0.1micrograms/kg/minute.
  - If hypotension and tachycardia occur, decrease the infusion rate to 0.05 micrograms/kg/min or discontinue.
  - Duration of the infusion is recommended for 24 hours only

**Infusion rate for both Loading and Maintenance Infusion using levosimendan 25micrograms/mL**

<table>
<thead>
<tr>
<th>Patient’s weight (kg)</th>
<th>LOADING dose at 12 micrograms/kg</th>
<th>LOADNG dose TOTAL VOLUME to be infused for 10 minute loading dose</th>
<th>MAINTENANCE Dose Maintenance Infusion Infusion rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RATE of 10 minute loading dose</td>
<td>Run this infusion for 10 minutes ONLY</td>
<td>0.1/mcg/kg/min</td>
</tr>
<tr>
<td>12micrograms/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>115mL/hr for 10 minutes</td>
<td>19 mL</td>
<td>10 mL/hr</td>
</tr>
<tr>
<td>50</td>
<td>144mL/hr for 10 minutes</td>
<td>24 mL</td>
<td>12 mL/hr</td>
</tr>
<tr>
<td>60</td>
<td>173 mL/hr for 10 minutes</td>
<td>29 mL</td>
<td>14 mL/hr</td>
</tr>
<tr>
<td>70</td>
<td>202 mL/hr for 10 minutes</td>
<td>34 mL</td>
<td>17 mL/hr</td>
</tr>
<tr>
<td>80</td>
<td>230 mL/hr for 10 minutes</td>
<td>38 mL</td>
<td>19 mL/hr</td>
</tr>
<tr>
<td>90</td>
<td>259 mL/hr for 10 minutes</td>
<td>43 mL</td>
<td>22 mL/hr</td>
</tr>
<tr>
<td>100</td>
<td>288 mL/hr for 10 minutes</td>
<td>48 mL</td>
<td>24 mL/hr</td>
</tr>
<tr>
<td>110</td>
<td>317 mL/hr for 10 minutes</td>
<td>53 mL</td>
<td>26 mL/hr</td>
</tr>
<tr>
<td>120</td>
<td>346 mL/hr for 10 minutes</td>
<td>58 mL</td>
<td>29 mL/hr</td>
</tr>
</tbody>
</table>
Clinical Considerations\textsuperscript{1,3}
\begin{itemize}
    \item The drug is preferably administered via a CVAD
    \item The infusion is currently recommended for a maximum period of 24 hours only. If there were interruptions to the infusion, the bag of fluid containing levosimendan must be changed at 24 hours.
    \item Monitoring should continue for 72 hours after cessation of the drug due to long-half life of its metabolites.
    \item Monitor serum electrolytes, renal, hepatic function, ABGs, continuous ECG, ABP and vitals.
\end{itemize}

4. Performance Measures
All incidents are documented using the hospital electronic reporting system: IIMS and managed appropriately by the NUM and staff as directed.

5. References / Links
1. \url{www.medsafe.govt.nz.Simdax Data Sheet.pdf.2009}
2. Inotropic agents in heart failure due to systolic dysfunction. Wilson S Colucci MD. \url{www.uptodate.com 2014}
3. \url{www.micromedexsolutions.com Levosimendan.2014}
4. Levosimendan: A retrospective single center case series. Berry, William T: Hewson,Russell W et al. Journal of Critical Care 28.6 (Dec2013); 1075-8

Author: ICU – CNE (P. Nekic)
Reviewers: ICU Director, ICU – CNC, NUM, CNE, Pharmacist.
Endorsed by: Dr Michael Parr, Medical Director ICU