Pharmacokinetics of Levosimendan in Children with Acute Heart Failure

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To describe the pharmacokinetic profile of a 24 hour infusion of levosimendan and its active metabolites in children with acute or chronic heart failure.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON37072

Source
ToetsingOnline

Brief title
LevoCorKids

Condition

- Heart failures

Synonym
Heartfailure

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Orion Pharma

Intervention

Keyword: children, heartfailure, Pharmacokinetics

Outcome measures

Primary outcome

The primary objective is to describe the pharmacokinetic profile of Levosimendan in children of different age groups (<6 months and > 6 months). With the knowledge of the pharmacokinetic profile of this useful drug we can come to a more rational and evidence based pharmacotherapy in children. When the pharmacokinetic profile is known, we can further assess the effectiveness of Levosimendan in future trials.

Secondary outcome

The secondary objective is to describe the pharmacodynamic profile of levosimendan by assessing the clinical effect of levosimendan therapy on heart rate, blood pressure, lactate, troponin, pro-BNP, venous saturation and cardiac function with echocardiography.

Acetylator status

Expected side effects: hypotension, arrhythmias

Serious Adverse Events (SAE)

Suspected Unexpected Serious Adverse Reactions (SUSARs)

Study description

Background summary

Levosimendan, a calcium-sensitizer, is a relatively new inotropic drug with the benefit over conventional inotropes that it does not increase myocardial oxygen

demand or lead to arrhythmias. Levosimendan has a relatively unique pharmacokinetic profile, after a 24 hour infusion its clinical effects remain for several days. This is achieved through the continuing haemodynamic effects of its active metabolites, which have a half life of approximately 80 hours compared to 1 hour of Levosimendan itself. Levosimendan has been extensively studied in adults and is used in ischemic heart disease, acute heart failure, chronic heart failure, following cardiac surgery, and in septic shock. Due to the inotropic properties and its strong pulmonary vasodilatory effect, Levosimendan could also be very useful as perioperative therapy in children with congenital heart disease, low cardiac output, or pulmonary artery hypertension.
Although experience with levosimendan in children is still scarce in the literature, initial reports have been promising and Levosimendan is used more and more often as a (rescue) therapy in children with heart failure. However, current dosing regimens in children are based on adult pharmacokinetic evidence. One pediatric report suggests that the pharmacokinetic profile of a single loading dose of Levosimendan is probably similar in children older than 6 months compared to adults. The pharmacokinetic profile of a 24-hour infusion of Levosimendan has not yet been studied in children. It is very important to study the pharmacokinetics of this useful drug in different age groups because of the diversity of the population due to age, volume of distribution, ontogeny of the metabolizing enzymes, and the influence of disease state on pharmacokinetics and pharmacodynamics.

Study objective

To describe the pharmacokinetic profile of a 24 hour infusion of levosimendan and its active metabolites in children with acute or chronic heart failure.

Study design

Observational study of Levosimendan levels in children treated with Levosimendan because of heart failure.

Study burden and risks

1. During the first 24 hours, 4 levosimendan samples (each 0,5 ml EDTA) will be taken using central or arterial lines already in situ. In, at least, 3 samples we can use restblood taken for blood gas analyses which are part of standard PICU-care. Furthermore we will take a small bloodsample for determining the acetylator status of each patient. During the second 24 hours another 5 samples will be taken (4 from restblood during standard blood gas analyses). After the first 48 hours, a sample will be taken on day 3, 5, 8 and 12 (from restblood). Therefore, a total of 13 samples will be taken from each patient with a total of 6.5 ml over the duration of 12 days, which is < 2% of the total bloodvolume in a 4 kg baby and therefore negligible. We estimate, based on our experience

with giving Levosimendan in 32 patients in two years, that 5-7 patients will not have a sampling line in situ anymore because of their clinical improvement and possible discharge to the ward. In these 5-7 children blood will be taken preferably during routine blood sampling or they will need to have their bloods taken especially for the study (we estimate 2-3 times), which is likely painful (although local sedatives are always used) and therefore a burden.
2. Other blood samples (lactate, troponin, and pro-BNP) are all part of standard ICU care in children with acute heart failure and therefore impose no extra burden.
3. Echocardiography will be done 4-6 times during 12 days, which in most cases is part of their routine care. Echocardiography is no burden for these children.
4. Known side-effects of Levosimendan are related to the vasodilating effect and include hypotension, nausea and headache. As the study is purely observational, taking part in the study does not increase this risk.
5. There will be no direct benefit for the patient by participating in this pharmacokinetic observational study. They will receive Levosimendan anyway as part of the treatment of heart failure.
6. The main endpoint of this study is to investigate the pharmacokinetic profile of Levosimendan and its metabolites in children of different ages. In our own experience of the last three years, more than 50% (12/22) of the patients receiving levosimendan are younger than 6 months of age. Which is an age group in which the pharmacokinetic profile of levosimendan is very likely to be different compared to older children and adults.It is therefore imperative to investigate the pharmacokinetics in these specific age groups.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children < 16 years of age with heartfailure admiited to the pediatric intensive care and who will recieve levosimendan as part of their treatment.
Informed consent from parents

Exclusion criteria

No informed consent.
Contraindications for levosimendan (arrhytmias, hypotension)
No sampling line

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-12-2012
Enrollment:	36

Type:	Actual

Ethics review

Approved WMO Date:	11-10-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	16-10-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-000588-26-NL
CCMO	NL40607.058.12
Other	volgt