Effects of levosimendan on diaphragm function in mechanically ventilated patients

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To determine the effect of levosimendan on diaphragm function in mechanically ventilated patients.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON37368

Source
ToetsingOnline

Brief title
Levosimendan in mechanically ventilated patients

Condition

- Muscle disorders

Synonym
diaphragm dysfunction, respiratory muscle weakness

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,Orion Pharma

Intervention

Keyword: diaphragm, levosimendan, mechanical ventilation

Outcome measures

Primary outcome

The primary outcome measure is the difference in neuro-mechanical efficiency of the diaphragm (i.e. the ratio of diaphragm electrical activity [Edi] and transdiaphragmatic pressure [Pdi]) before and after levosimendan administration during a CPAP trial.

Secondary outcome

• Neuro-ventilatory efficiency of the diaphragm (i.e. the ratio of diaphragm electrical activity [Edi] and tidal volume [Vt]).

• Oxygen consumption (VO2).

• Carbon dioxide production (VCO2).

• Oxygen level in blood (PaO2).

• Carbon dioxide level in blood (PaCO2).

• Accessory muscle recruitment (also in response to various pressure support level)

i. electrical activity of the sternocleidomastoid muscle

ii. electrical activity of the scalene muscles

iii. electrical activity of the intercostal muscles

iv. electrical activity of the genioglossal muscles

Study description

Background summary

Mechanical ventilation offers essential ventilatory support during acute respiratory failure. Unfortunately, mechanical ventilation is associated with risks and complications and therefore, physicians aim to wean patients from the ventilator as soon as the underlying reason for respiratory failure has resolved. However, 20 - 30 % of intubated patients are difficult to wean from mechanical ventilation, resulting in increased morbidity, mortality and health care costs. The respiratory muscles drive ventilation, with the diaphragm as the most important inspiratory muscle. The capacity of the diaphragm of critically ill patients is impaired by ICU-acquired muscle weakness. No specific intervention is available to improve strength of the respiratory muscles in critically ill patients.

Levosimendan is a relatively new drug that improves cardiac contractility in patients with heart failure. Its main mechanism of action is enhanced binding of calcium to the myocardial contractile proteins. Recent data from our lab showed that levosimendan improves contractility of human diaphragm in vitro (muscle fibers from COPD patient diaphragm) and in vivo (healthy subjects). Accordingly, levosimendan may appear of value in the treatment of disorders associated with impaired respiratory muscle function, such as mechanically ventilated patients.

Study objective

To determine the effect of levosimendan on diaphragm function in mechanically ventilated patients.

Study design

A double-blind randomized placebo-controlled trial.

Intervention

Subjects are treated with either levosimendan (continuous levosimendan infusion of 0.2 µg/kg/min) or placebo for 6 hours. Before treatment and after treatment patients perform a 30 minute weaning trial.

Study burden and risks

A specifically designed naso-gastric tube will be inserted for measurement of the primary outcome parameter. No complications have been reported with the introduction / use of the dedicated naso-gastric tube. From our clinical experience, we consider the risks of naso-gastric tube placement minimal, especially when *high risk patients* are excluded (upper airway / esophageal pathology, bleeding disorders, hepatic failure) and insertion performed by

well-trained nurses.

A known side effect of levosimendan in patients with cardiogenic shock and acute heart failure is hypotension due to vasodilation. In the current study patients with cardiac diseases are excluded, thereby minimizing the risks of side effects following administration of levosimendan. In our previous study, that included healthy subjects, no cardiac side effects of levosimendan administration were reported, despite a high loading dose (40 µg/kg compared to no bolus in the current study).

A weaning trial is a commonly used method to determine readiness for extubation and is frequently used on our ICU. The weaning trial will be terminated if patients have any signs of distress, as acknowledged in clinical protocols.

Blood will be withdrawn from an indwelling arterial catheter already present as part of routine clinical care. Therefore, no adverse events are anticipated from blood withdrawal.

The study proposed in the current application will be carried out in mechanically ventilated patients. Effects of levosimendan on diaphragm function in vitro and in healthy subjects have been studied and published in high impact (IF > 10) peer-reviewed medical journals by applicants. Ultimately, we want to perform a multi-center trial to test whether levosimendan decreases the duration of mechanical ventilation in critically ill patients. However, first it should be confirmed that levosimendan indeed improves diaphragm function in mechanically ventilated patients. Data obtained from this study are an important step towards innovative pharmacological intervention in patients failing to wean from mechanical ventilation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• age >18 year
• mechanical ventilation for at least 3 days
• PaO2/FiO2 ratio >200 mmHg
• Ventilatory settings: Positive End Expiratory Pressure <=10 cmH2O, Pressure Support <= 10 cmH2O.

Exclusion criteria

• pre-existent muscle disease (congenital or acquired) or diseases / disorders know to be associated with myopathy including auto-immune diseases.
• pre-existent cardiac disease (based on history, electrocardiography and transthoracic echocardiography)
• upper airway / esophageal pathology (i.e. recent surgery, esophageal varices, diaphragmatic hernia)
• phrenic nerve lesions
• pregnancy, breast feeding
• severe renal failure (serum creatinine > 450 µmol/L)
• severe hepatic failure
• recent (within 5 days) nasal bleeding

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2012
Enrollment:	42
Type:	Actual

Medical products/devices used

Generic name:	Mechanical ventilator
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Simdax
Generic name:	Levosimendan

Ethics review

Approved WMO Date:	29-05-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-06-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-005093-29-NL
CCMO	NL40137.091.12