Effects of levosimendan on diaphragm contractility in healthy subjects

Published: 30-11-2009
Last updated: 04-05-2024

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

Summary

ID

NL-OMON35071

Source
ToetsingOnline

Brief title
Effects of levosimendan on the diaphragm

Condition

- Muscle disorders
- Neuromuscular disorders

Synonym
respiratory muscle weakness and fatigue, weaning

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Contractiliteit, Diaphragm, EMG, Levosimendan

Outcome measures

Primary outcome

The main study parameters are the transdiaphragmatic pressure, diaphragm efficiency, maximal inspiratory pressure and tenson time index before and after levosimendan infusion.

Secondary outcome

Not applicable

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. The combination of an increased load imposed on the respiratory muscles and a reduced capacity to generate pressure results in weaning failure. 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 also improves in vitro contractility of human respiratory muscle fibers. The effect of levosimendan on respiratory muscle in vivo has not been studied. If levosimendan indeed does improve respiratory muscle contractility in vivo, it may be useful in patients with impaired contractility of the respiratory muscles, such as weaning failure patients.

Study objective

The primary objective of this proof of principle study is to determine the effect of levosimendan on the strength and endurance of the diaphragm in healthy subjects. The secondary objective is to gain insight in the neural activation and efficiency of contraction of the diaphragm during unloaded and loaded breathing.

Study design

A double blind randomized parallel trial in healthy subjects.

Intervention

Subjects are treated with either levosimendan or placebo. Diaphragm strength and endurance is determined by measuring transdiaphragmatic pressure (Pdi) during magnetic stimulation of the phrenic nerves. Electrical activity of the diaphragm (Edi) is measured by esophageal electromyography. Diaphragm muscle contractile efficiency is expressed as the Edi / Pdi ratio. Diaphragm efficiency is measured before and after a loading dose of levosimendan (or placebo), and subsequently, before and after loaded inspiratory breathing in the presence of levosimendan (or placebo).

Study burden and risks

Subjects will visit our ICU research unit once for approximately 6 hours. After informed consent, physical examination, electrocardiography and echocardiography are performed by an experienced clinician. Several studies have shown the safety of levosimendan in healthy subjects. No severe adverse events were reported in any study. Positioning of the esophageal catheter is associated with temporary discomfort, but is not painful. The presence of the catheter during the experiment may result in mild discomfort. No complications have been reported with the introduction / use of this soft small bore catheter. Magnetic stimulation of the phrenic nerve is not painful, but co-contraction could be encountered as uncomfortable. Therefore, stimulation intensity is gradually increased to let the subject get acquinted with the stimulus intensity. No adverse affects of magnetic stimualtion have been reported by other researchers. Subjects have no clinical benefits in participating in this study. A modest financial compensation is available

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
- informed consent

Exclusion criteria

- use of any prescript medication
- chronic hiccups (defined as hiccups longer than 15 minutes in the past 6 months)
- pre-existent muscle disease (congenital or acquired) or diseases / disorders know to be associated with myopathy including diabetes and auto-immune diseases.
- pre-existent lung disease
- pre-existent cardiac disease- pregnancy, breast feeding
- innability to obtain adequate view of the heart with transthoracic echocardiography
- upper airway / esophageal pathology
- recent (< 1 month) nasal bleeding
- phrenic nerve lesions
- any metals in body (pacemaker, splinters, metal stiches)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-04-2010
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Simdax
Generic name:	Levosimendan

Ethics review

Approved WMO Date:	30-11-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-01-2010
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	EUCTR2009-017190-37-NL
CCMO	NL30316.091.09