The effects of enoximone in acute exacerbation COPD: a pilot study

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Primary Objective: a reduction in bronchoconstriction, measured by auto-PEEP, in patients with AE-COPD. Secondary Objective(s): * To test for a dose-dependency. * Decrease in pulmonary artery pressures* Enhance cardiac output* Measure occurrence of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON49504

Source
ToetsingOnline

Brief title
The effects of enoximone in acute exacerbation COPD: a pilot study

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Acute pulmonary attack, Bronchospasm, Exacerbation COPD

Research involving
Human

Sponsors and support

Primary sponsor: Rijnstate Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W,De onderzoeker zal zelf de studie financieel ondersteunen;indien nodig

Intervention

Keyword: Bronchodilation, Enoximone, Exacerbation of COPD

Outcome measures

Primary outcome

Auto-PEEP

Secondary outcome

Respiratory parameters:

- Lungcompliance in L/cmH2O

- Airway resistance in cmH2O/L/s

- VCO2

- etCO2

- FiO2

Cardiac parameters:

- RVSP

- Cardiac output

- TAPSE

- MAPSE

- Ejection Fraction of the Left Ventricle

Arterial blood gas analysis (2 ml of blood, obtained through an arterial

cannula):

- pH, PaCO2, PaO2, saturation, lactate, base excess,

Vital Signs:

- Occurrence of adverse side effects such as (supraventricular) arrhythmics and

hypotension

Study description

Background summary

A severe acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) is a frequent occurring disorder in patients with COPD and may lead to respiratory failure despite treatment, consisting of corticosteroids, nebulized bronchodilators, magnesiumsulphate and non-invasive ventilation. If treatment fails, invasive mechanical ventilation may be necessary. Further treatment options in this situation are (es)ketamine, sevoflurane and enoximone. However, limited data is available to support all these treatment options. Since no other treatment options are available for these patients, research is necessary for this specific patient group.
Sevoflurane is an inhalation anaesthetic agent, which needs a special method for delivery in an ICU, thus limiting the availability. (es)Ketamine has the disadvantage of being an anaesthetic agent, for which intubation is necessary. Therefore, a patient is likely to have an increased duration of ventilation.
The level of evidence for these agents in AE-COPD is low. A third agent is enoximone, which has no sedative effects and is administered intravenously. Enoximone is a phosphodiesterase-3 inhibitor (PDE-3). Phosphodiesterase hydrolyses cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in the cell. Inhibitors of PDE results in the elevation of cAMP and cGMP which will lead to a number of various cell effects including the relaxation of smooth airway muscle cells. This pathway is believed to be beneficial in patients with an AECOPD.

Enoximone is commonly used in a ICU for patients with cardiac failure. A usual loading dose is 0.5 mg/kg after which further titration or a continuous infusion is started. However, in a study for bronchodilatory effects in AE-COPD, a dose of 3.0 mg/kg was administered, which led to ventricular tachycardia and limited the use of enoximone.
Recently, the use of low dose enoximone in acute asthma showed an remarkable bronchodilatory effect. Furthermore, other PDE-3 and PDE-4-inhibitors are developed for bronchodilatory therapy in COPD. Since extensive clinical experience with enoximone is available in ICU*s, low-dose enoximone may be an attractive treatment option.

A low-dose of enoximone is not yet studied for bronchodilatory properties.

Furthermore, a dose-dependent effect has not been investigated previously. This pilot study aims to answer these questions and may lead to a randomised controlled trial if proven beneficial.

Study objective

Primary Objective: a reduction in bronchoconstriction, measured by auto-PEEP, in patients with AE-COPD.

Secondary Objective(s):
* To test for a dose-dependency.
* Decrease in pulmonary artery pressures
* Enhance cardiac output
* Measure occurrence of side effects by enoximone administration

Study design

The study design is a prospective interventional randomized clinical study.

Intervention

Three doses of intravenous 0,5 mg/kg enoximone, leading to a total dose of 1.5 mg/kg enoximone

Study burden and risks

The participants will already be intubated and sedated when eligible for participation. Scientifically proven therapy, consisting of nebulized salbutamol/ipratropium, corticosteroids, magnesiumsulphate and neuromuscular blocking agents, will be continued throughout the study period. All outcome measures are non-invasively measured (e.g. echocardiography, ventilator measurements and arterial bloodgas analysis, obtained through a catheter already placed for clinical guidance). Therefore, the burden can be regarded as minimal.
The risks of enoximone are supraventricular arrhythmias, ventricular tachycardia and hypotension. These risks are minimally encountered in common practice. Furthermore, all patients will be treated in an ICU, where these side-effects can be treated and supported.
The benefit for a patient may be a reduction in time of ventilator-support and increased cardiac output, which may lead to less renal dysfunction.

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

Patients with an AE-COPD wherefore intubation occurred within 24 hours before enrollment.

Exclusion criteria

Patients with known asthma or interstitial lung disease (ILD)
Known neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Guillain-Barre and Dementia
Hypertrophic obstructive cardiomyopathy (HOCM)
Severe aortic stenosis with aortic valve area <1 cm2
Known ventricular arrhythmias
Severe kidney disorders with Glomerular Filtration Rate (GFR) < 30 ml/min
Severe liver insufficiency with spontaneous PT/INR > 1.5
Pregnancy

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Perfan
Generic name:	Enoximone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-01-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-02-2020
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-07-2020
Application type:	Amendment
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	EUCTR2019-002826-58-NL
CCMO	NL70865.091.19

Study results

Date completed:	21-12-2021
Actual enrolment:	4

Summary results
Trial is onging in other countries