Systemic effects in patients with COPD; training or treatment

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To study the possible relation between systemic inflammation and oxidative stress and muscle breakdown using pharmacological interventions.

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON30383

Source
ToetsingOnline

Brief title
Systemic effects in patients with COPD

Condition

- Respiratory disorders NEC

Synonym
Chronic obstructive pulmonary disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Astra Zeneca

Intervention

Keyword: (anti)inflammatic, (anti)oxidative stress, COPD, exercise, immune response

Outcome measures

Primary outcome

Differences in parameters of systemic inflammation (concentrations of leukocyts, CRP, IL-6, IL-8, IL-1ra, TNFa) after intervention. Differences in parameters of oxidative stress (ROS-production, plasma antioxidant capacity, protein oxidation, lipid peroxidation, GSSG/GSH-ratio) after intervention.

Differences in parameters of muscle damage (troponin I) after intervention.

Differences in parameters of muscle breakdown (ubiquitin-proteasome system).

Differences in pulmonary parameters and exercise capacity.

Secondary outcome

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Study description

Background summary

Systemic effects of COPD (Chronic Obstructive Pulmonary Disease) are now recognized as important features of the disease. The most extensively studied features are cachexia and muscle wasting. Several aspects may contribute to these features including inactivity, systemic inflammation and oxidative stress. For example, in stable COPD patients increased levels of circulating neutrophils are present in an activated status. Furthermore, increased levels of tumour necrosis factor (TNF-α) and its receptors (TNFR-55 and TNFR75), interleukin(IL)-6, IL-8, Fas and Fas Ligand, and elevated levels of acute phase proteins C-reactive protein and lipopolysaccharide-binding protein are found. Systemic inflammation and enhanced production of reactive oxygen species (ROS) are closely related. This increase in ROS production may lead to an imbalance in oxidant and antioxidant production, resulting in local as well as systemic oxidative stress.
In response to physical activity, all the above mentioned is further increased, especially in muscle wasted COPD patients. The actual mechanism between oxidative stress, systemic inflammation and muscle wasting is unknown. Because fat-free mass is an independent predictor of mortality in COPD patients, it is important to investigate the relationship between muscle wasting, oxidative

stress and systemic inflammation in order to explore new possible pharmacological interventions. We hypothesize that muscle damage in patients with COPD is related to systemic inflammation and oxidative stress and can be decreased by reduction of these systemic effects with anti-inflammatory and anti-oxidative therapy.

Study objective

To study the possible relation between systemic inflammation and oxidative stress and muscle breakdown using pharmacological interventions.

Study design

First, a pilot study will be conducted. Two muscle wasted COPD patients will subsequently visit the clinic 9 times. One patient will receive n-acetylcysteine 600 mg and placebo 3-times daily and the other will receive rosuvastatin 20 mg and placebo 1 time daily. This pilot study will consist of three pairs of treatment periods. Each period consists of treatment with placebo and active substance, both for 7 days. After each pair of treatment, there is a washout period of one week. During each visit, blood samples will be taken to be analyzed for markers of muscle damage (skeletal muscle troponin I) and muscle breakdown (activity of the ubiquitin-proteasome system).

This study is a double-blind randomized placebo-controlled cross-over trail. Before the start of the protocol, subjects will be subjected to complete lungfunctiontesting and a maximal incremental exercisetest to characterize their condition. At the start of the protocol subjects will be subjected to complete lungfunction testing after which an exercise test on a bicyle ergometer is preformed. After the exercise test, subjects are instructed to take 1 tablet (600 mg) fluimucil or placebo three times daily for 7 days. After 7 days subjects will return to the hospital and the complete lungfunction testing and the exercise test are repeated. The next 7 days will serve as a wash-out period and no additional treatment is prescribed. After the wash-out period of 7 days subjects again will visit the hospital and complete lungfunction testing and the exercise test are repeated. After the exercise test subjects are instructed to take 1 tablet (600 mg) placebo or fluimucil three times daily for 7 days. After 7 days subjects will return to the hospital for the last time and again complete pulmonary function testing and the exercise test are repeated.
Before, during and after each bicylce ergometry test arterial blood samples will be taken. Bloodsamples will be analysed for markers of oxidative stress; Thiobarbituric acid reactive substance (TBARs), Malondialdehyde (MDA), oxidized versus reduced glutathione (GSSG/GSH) and antioxidant capacity (ferric reducing ability of plasma (FRAP)). Furthermore ROS-production by neutrophils will be determined. Also, leukocyt concentration, high sensitivity C-reactive protein

(HS CRP), interleukin (IL)-6, IL-8, IL-1ra and TNFα will be determined.
Finally, blood will be analysed for markers of muscle damage (troponin I) and muscle breakdown (activity of the ubiquitin-proteasome system).

The same protocol will be applied for rosuvastatin. Subjects will take 1 tablet (20 mg) per day for 7 days. During the protocol the investigator and laboratories will be blinded for treatment groups.

Intervention

We study the influence of n-acetylcysteine and rosuvastatin on the parameters of systemic inflammation, oxidative stress and muscle breakdown in bloodsamples of muscle depleted COPD patients, before and after bicycle ergometry.
Rosuvastatin has antiinflammatory properties by reducing the number of adhesion molecules on endothelial cells, through a proces which involves endothelial nitric oxide synthase and nitric oxide. Eventually it prevents the adhesion of the leukocytes to the endothelial cells. Furthermore, in vitro crestor induced hemeoxygenase, an enzyme that catalyzes the degradation of heme to form biliverdin and its metabolic product bilirubin. Both products are strong antioxidants.
N-acetylcysteine acts as a precursor of cysteine. The availibility of cysteine is the rate limiting step in the synthesis of glutathione, which plays an important role in the prevention of oxidative damage.

Pilot study
One patient will receive n-acetylcysteine 600 mg and placebo 3-times daily and the other will receive rosuvastatin 20 mg and placebo 1 time daily according to the design shown in figure 1. This pilot study will consist of three pairs of treatment periods. Each period consists of treatment with placebo and active substance, both for 7 days. After each pair of treatment, there is a washout period of one week.

Main experiment
After inclusion, one group of patients and one group of healthy subjects receives 3 times daily 600 mg n-acetylcysteine or placebo (randomized, dubbel blind) for one week. After this week a wash-out period of one week is included in the protocol. After the wash-out the groups receive the other treatment (placebo or n-acetylcysteine) for one week.
The same protocol will be applied for rosuvastatin. Subjects will take 1 tablet (20 mg) per day for 7 days.

Study burden and risks

Measurements involving bicycle ergometry including the obtainment of blood samples are part of the regular controle, treatment and rehabilitation program of COPD patients and are generally beared well. During exercise testing vital

functions are constantly monitored. The test is immediatly aborted when abnormalities occur. Blood is obtained by placing an arterial cannula in the arteria radialis. Placement of the cannula will be done under locale anesthesia and can cause a little discomfort. This rarely leads to hematoma, flebitis, thrombosis, sepsis or local stimulation of the nerve. These complications have not occured last decade at our department.

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

clinically stable COPD patients (GOLD II, III, IV) with a low fat-free mass (<16 kg/m2 in men and <15 kg/m2 in women) and healthy volunteers

Exclusion criteria

Exacerbation less than 2 months before the start of the experiment
Smoking
Oral corticosteroids
Long-term oxygen therapy
Respiratory insufficiency (PaO2 < 8 kPa or PaCO2 > 6,3 kPa)
Other chronic exercise limiting disorders

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2006
Enrollment:	42
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Crestor
Generic name:	rosuvastatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fluimucil
Generic name:	acetylcysteine

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-12-2006
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	EUCTR2006-000978-68-NL
CCMO	NL11142.091.06