Effect of intrapulmonary administration of recombinant human activated protein C on local coagulation and inflammation after bronchial instillation of lipopolysaccharide in humans

Published: 10-09-2008
Last updated: 06-05-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON31950

Source
ToetsingOnline

Brief title
Effect of intrapulmonary rhAPC on coagulation and inflammation after LPS

Condition

- Bacterial infectious disorders
- Respiratory tract infections

Synonym
pulmonary inflammation and coagulation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,ZonMw;stichting BEGETU

Intervention

Keyword: coagulation, human recombinant activated protein C, lipopolysaccharide (LPS), pulmonary inflammation

Outcome measures

Primary outcome

To determine the effect of rhAPC on the following LPS-induced responses (by

using measurements on cells harvested from BAL-fluid and in BAL-fluid

supernatant):

1. Neutrophil responses

2. Response of alveolar macrophages

3. Activation of the cytokine network

4. Activation of the chemokine network

5. Activation of coagulation and fibrinolysis

Secondary outcome

See primary study parameters.

Study description

Background summary

Recombinant human Activated Protein C (rhAPC; drotrecogin alfa (activated)) has been shown to reduce the mortality of patients with severe sepsis. The biological effects of APC are pleiotropic, and can be roughly divided in

anticoagulant and cytoprotective effects. Lung infection and inflammation are associated with reduced bronchoalveolar levels of endogenous APC. Recent evidence derived from animal studies indicates that local administration of rhAPC into the lungs exerts anti-inflammatory and anticoagulant effects in the pulmonary compartment. In this study we propose to study the potential of locally administered APC, within a lung subsegment, to inhibit lipopolysaccharide (LPS) induced lung inflammation and coagulation, thereby avoiding systemic APC effects, in humans. Inhaled APC could be a new therapeutic approach in inflammatory lung diseases such as asthma and acute lung injury/acute respiratory distress syndrome, disorders in which systemic effects of APC are not required and/or desired.

Study objective

The primary objective is to determine the effect of locally administered rhAPC on LPS-induced lung inflammation and coagulation. By using measurements on cells harvested from bronchoalveolar lavage (BAL)-fluid and in BAL-fluid supernatants, we will seek to obtain insight into neutrophil responses, the response of alveolar macrophages, activation of the cytokine network, activation of the chemokine network and activation of coagulation and fibrinolysis.

Study design

First a dose-escalation study will be performed (N=4-16): healthy volunteers will be challenged with LPS (4 ng/kg) into a subsegment of both lungs; in one lung segment LPS will be combined with rhAPC, whereas in the contralateral lung segment LPS will be combined with normal saline. Six hours later a bilateral bronchoalveolar lavage (BAL) will be done in order to obtain BAL-fluid and cells. Since rhAPC has not been administered into the lungs of humans before we will conduct a dose-escalation study with rhAPC administered in a lung subsegment by bronchoscope (N = 4 per dose, 5-fold escalation after each dose).

Thereafter a follow-up study will be performed (N=36): This will be done in 24 subjects who will be challenged with LPS in one lung subsegment and with normal saline in a contralateral lung subsegment; in 12 of these subjects LPS will be combined with rhAPC (dose determined in the dose-escalation study), in the other 12 subjects LPS will be combined with saline. In addition, 12 subjects will receive saline in both lung subsegments (not LPS), combined on one side with either rhAPC (N=6) or saline (N=6).

Intervention

Local intrabronchial administration of rhAPC after challenge with intrabronchial LPS.

Study burden and risks

Bronchoscopy, segmental instillation and BAL:
The protocol for segmental instillation by bronchoscopy followed by a second bronchoscopy has been described extensively in the international scientific literature. This protocol has been mainly used to study local effects of purified allergens, and more recently also to study local inflammation on purified bacterial antigens, such as LPS (references 12, 21, 22). Both bronchoscopies will be done by experienced pulmonologsts. The first bronchoscopy (for segmental instillation) will take less than one minute. The second (for bronchoalveolar lavage) takes about five minutes. The most important discomfort experienced during a bronchoscopy is a dry cough and pain in the nose on introduction of the scope. This can be prevented by local anaesthetics of the mucosa with lidocaine. In our two recent studies in healthy subjects, volunteers shortly experienced the complaints described above and recovered quickly and completely within minutes. Hence, in our own experience the procedure of both the bronchoscopy and BAL is tolerated very well by healthy non-smoking subjects.

Signs and symptoms induced by LPS:
LPS at the dose given in this study has been administered into a lung segment by bronchoscope previously in other centers (references 12, 21) and in the Academic Medical Center (reference 22). This procedure did not induce clinicals signs or symptoms besides a modest rise in body temperature not exceeding 37.3 degrees Celcius. However, this LPS-dosage did induce detectable inflammatory and procoagulant reactions in the instilled lung subsegment, especially influx of neutophiles, cytokine release, coagulation activation and inhibitiion of fibrinolysis (references 12, 21, 22). This study will be the first to administer LPS in two contralateral lung subsegments of the same individual. Considering the total absence of clinical findings after LPS administration in a single lung subsegment and considering that only a subsegment of each lung is challenged, significant clinical symptoms are not expected.

Intrapulmonary administration of rhAPC
RhAPC has not been administered directly in the human lung before. Animal studies, discussed above (see research protocol pages 3 and 4) have revealed that APC exerts anticoagulant and anti-inflammatory effects in the bronchoalveolar space upon intrapulmonary delivery. If rhAPC is to be used for direct intrapulmonary delivery in humans in the future, it is likely that this compound will be administered by inhalation of nebulized product. In the current study we seek to obtain proof of concept that direct administration of rhAPC into the lung inhibits coagulation and inflammation in the human lung after challenge with LPS. We chose not to conduct studies using inhalation of nebulized APC since this would expose both (entire) lungs of patients to a compound that has thus far not been used for nebulisation or inhalation in humans. By administering APC via a bronchoscope only a subsegment of a lung

will be exposed. The study will start with a dose-escalation study, using an initial APC based on our previous study in which the same drug was infused intravenously in healthy humans (references 12 and 13). The risks regarding local administration of recombinant human APC are thereby minimized.

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

Male subjects between 18 and 35 years of age
No clinically significant findings during physical examination and hematological and biochemical screening
Normal spirometry
Able to communicate well with the investigator and to comply with the requirements of the study

No medication
Written informed consent
No smoking

Exclusion criteria

Known diseases
A history of smoking within the last six months, or regular consumption of greater than three units of alcohol per day
Administration of any investigational drug within 30 days of study initiation
Donation of blood within 60 days, or loss of greater than 400 ml of blood within 12 weeks of study initiation
History of enhanced bleeding tendency
History of heparin-induced thrombocytopenia
History of serious drug-related reactions, including hypersensitivity

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2008
Enrollment:	52
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	lipopolysaccharide
Generic name:	lipopolysaccharide
Product type:	Medicine
Brand name:	Xigris
Generic name:	drotrecogin alpha
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-10-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2008-003981-25-NL
CCMO	NL23413.018.08