Effect of intrapulmonary recombinant human APC on coagulation and inflammation after LPS.

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What is the effect of locally administered rhAPC on LPS-induced lung inflammation and coagulation.

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON27608

Bron
NTR

Verkorte titel
LPS-APC study

Aandoening

pulmonary inflammation
gram negative pulmonary infections
recombinant activated protein C
pulmonary effects of lipopolysaccharide (LPS)
blood coagulation during pulmonary inflammation

longinflammatie
gramnegatieve longontstekingen
recombinant geactiveerd proteine C
pulmonale effecten van LPS
bloedstolling tijdens pulmonale inflammatie

Ondersteuning

Primaire sponsor: Prof. Dr. Tom van der Poll, principal investigator. Center of Experimental

Molecular Medicine, AMC-UvA, Amsterdam, The Netherlands
Overige ondersteuning: See initiator, ZonMW, stichting BEGETU

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To determine whether direct intrapulmonary delivery of rhAPC can inhibit LPS-induced lung inflammation, thereby avoiding systemic APC effects

Toelichting onderzoek

Achtergrond van het onderzoek

Recombinant human Activated Protein C (rhAPC) 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 rAPC into the lungs exerts local anti-inflammatory and anticoagulant effects. 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 in humans.

Doel van het onderzoek

What is the effect of locally administered rhAPC on LPS-induced lung inflammation and coagulation.

Onderzoeksopzet

t=0: first bronchoscopy

t=6: 6 hours after first bronchoscopy

Onderzoeksproduct en/of interventie

1. Dose-escalation study:
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.

The primary read-out of these dose-escalation studies will be the effect of rhAPC on coagulation. Specifically, we will seek to find an APC dose that inhibits the LPS-induced increase in TAT complexes by at least 30% without causing side effects. We will increase the rhAPC dose 5-fold after each cohort (4 per group) in this part of the project.

2. Follow-up study:
24 subjects 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).

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Male, 18-35 years of age

2. No clinically significant findings during physical examination and hematological and biochemical screening

3. Normal spirometry and ECG

4. Able to communicate well with the investigator and to comply with the requirements of the study

5. No medication

6. Written informed consent

7. No smoking

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Known diseases

2. A history of smoking within the last six months, or regular consumption of greater than three units of alcohol per day

3. Administration of any investigational drug within 30 days of study initiation

4. Donation of blood within 60 days, or loss of greater than 400 ml of blood within 12 weeks of study initiation

5. History of enhanced bleeding tendency

6. History of heparin-induced thrombocytopenia

7. History of serious drug-related reactions, including hypersensitivity

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Enkelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-09-2008
Aantal proefpersonen:	52
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	18-11-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1475

Register	ID
NTR-old	NTR1544
Ander register	METC AMC Amsterdam : CEMM-APC-01
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
Intrabronchial activated protein C enhances lipopolysaccharide-induced pulmonary responses.
European Respiratory Journal.