In vivo effects of C1-esterase inhibitor on innate immune response during endotoxemia in human - VECTOR II study

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- Primary objective: The effect of C1-INH prior to induction of a systemic inflammation by endotoxin (E. coli lipopolysaccharide), on the leukocyte phenotype, activation and mobilization. - Secondary objectives: - Determine the effect of C1-...

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

Summary

ID

NL-OMON39199

Source
ToetsingOnline

Brief title
VECTOR-II study

Condition

- Immune disorders NEC

Synonym
activated immuun system, Systemic inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Sanquin Bloedproducten, divisie plasmaproducten; Postbus 9190, 1006 AD, Amsterdam, The

Netherlands

Intervention

Keyword: C1-esterase inhibitor, Cytokines, Inflammation, Neutrophils

Outcome measures

Primary outcome

Main study endpoint is the phenotype of circulating neutrophils after LPS in the absence and presence of C1 INH substitution.

Secondary outcome

- Concentration of circulating cytokines after LPS in the absence and presence of C1 INH substitution.

- Study the possible differences between the circulatory and post-mitotic pool transit times of neutrophils in human blood in volunteers with and without C1-INH.

- Pharmacokinetic and pharmacodynamic data will be collected with respect to the anti-inflammatory effects of C1 INH.

- Effects on the PMN phenotype and function will be determined.

- C1 INH concentration and activity as well as anaphylatoxin concentrations will be measured and compared to baseline values.

Study description

Background summary

C1-esterase inhibitor (C1 INH) is a major inactivator of both the complement and contact system. C1 INH is an acute phase protein, which is normally excreted during inflammation. C1 INH substitution has shown to reduce complement and contact activation and, thereby, reducing oedema and

polymorphnuclear leukocyte (PMN) infiltration into tissue. Animal models have shown that C1 INH improves outcome both given before and shortly after induction of severe inflammation through sepsis or surgical trauma, but the underlying mechanism remains to be elucidated. In vitro C1 INH directly inhibits PMN functions. Since PMN*s are important effector cells in post-injury immunological pathology, inhibition of post-injury inflammation might be for a great part due to this entity.
A previous study from our laboratory showed that administration of the drug C1 INH has a significantly effect on the humoral response, by reducing the concentration of circulating pro-inflammatory cytokines during human experimental endotoxemia (Dorresteijn et al, Crit Med Care, Jan 2011).

In this study we will administer the C1 INH before LPS injection. We expect that this study will give us an insight in the pathophysiology of the cellular response caused by the LPS induced systemic inflammation, in volunteers with and without pre-treatment with C1-INH

Study objective

- Primary objective: The effect of C1-INH prior to induction of a systemic inflammation by endotoxin (E. coli lipopolysaccharide), on the leukocyte phenotype, activation and mobilization.
- Secondary objectives:
- Determine the effect of C1-esterase inhibition on the LPS induced pro-inflammatory response (IL-6, TNF-α and IL-1β) and increase of anti-inflammatory response (IL-10).
- Determination of neutrophil lifespans in blood, and post-mitotic pool transit times. These lifespans will be compared between healthy volunteers treated with or without C1-INH before LPS treatment.

Study design

Double-blind placebo-controlled randomized intervention pilot study in healthy human volunteers during experimental endotoxemia.

Intervention

Subjects will be tested in 2 separate sequential sessions. A total of 20 subjects will be randomly assigned to one of two dosing groups in a 1:1 ratio: C1 INH followed (n=10) or placebo (n=10). All subject will then receive a LPS injection.

Healthy volunteers will receive 100 U/kg U C1 INH or placebo half an hour before the induction of endotoxemia. Endotoxemia will be achieved by injection of LPS derived from E coli O:113 (2 ng/kg iv in 1 minute).

Before LPS injection, prehydration will be performed by infusion of 1.5 L 2.5% glucose/0.45% saline solution in 1 hour.

3 till 11 days (time points differ per subject) before the actual endotoxin experiment, the subject will be orally administered 1g of deuterated glucose per kilogram bodyweight in 12 doses over a period of 6 hours

Study burden and risks

A medical interview and physical examination are part of this study.
During endotoxemia, volunteers will be monitored on the research unit of the intensive care unit at the Radboud UMC. The participants will receive an arterial line to facilitate blood pressure monitoring and blood sampling. The arterial line will be placed under local anaesthesia using 2% lidocaine. Furthermore, a venous cannula will be placed for the administration of fluids and LPS.
There will be mild discomfort associated with participation in this study, as LPS induces flu-like symptoms for approximately 4-6 hours. This model of systemic inflammation has been applied for many years in various research centers in the world. Endotoxin administration is considered safe and no long-term effects have ever been documented. At the Radboud UMC, over 350 volunteers have received LPS. Therefore, there is sufficient experience with this model in this center.

Administration of C1 INH has been safely in high concentrations. C1 INH is a normal constituent of human blood. Side effects of C1 INH administration may include: injection site reaction (eg rash), allergic or anaphylactoid reactions. These side effects are rare (> 1/10.000 and <1/1000).

For the DNA 2H enrichment the subjects will need to drink 1 g of 2H-glucose per kg (dissolved in water at 0.4 mg/l) in twelve small portions during 6 hours, 3 to 11days (time points differ per volunteer) before the actual endotoxemia administration.
Intake of 2H-glucose has been performed in several other studies and it is considered safe, without side effects.

Approximately 350 ml blood will be drawn during each entire LPS experiment.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10

Nijmegen 6525HB
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
Nijmegen 6525HB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age >= 18 and <= 35 years
Male
Healthy

Exclusion criteria

Use of any medication
Congenital or acquired C1 inhibitory deficiency
Immune deficiency
Chronic inflammatory diseases
Smoking
History of allergic reaction to blood products
History, signs or symptoms of cardiovascular diseases
(Family) history of cerebrovasculair diseases under the age of 65 years
Previous vagal collaps
Hypertension (defined as RR systolic > 160 or RR diastolic > 90)
Hypotension (defined as RR systolic < 100 or RR diastolic < 50)
Renal impairment (defined as plasma creatinin > 120 µmol/l)

Liver enzyme abnormalities

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2013
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cetor
Generic name:	C1-esterase inhibitor
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-03-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-09-2013

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	EUCTR2011-002222-46-NL
ClinicalTrials.gov	NCT01766414
CCMO	NL36688.091.13