The effects of iron loading and iron chelation during human endotoxemia.

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The primary objective of the study is to determine concentration of circulation cytokines na administration of LPS in the presence of iron sucrose (Venofer®), Deferasirox (Exjade®) of placebo.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ancillary infectious topics
Study type	Interventional

Summary

ID

NL-OMON33343

Source
ToetsingOnline

Brief title
iron loading and iron chelation during human endotoxemia.

Condition

- Ancillary infectious topics
- Decreased and nonspecific blood pressure disorders and shock

Synonym
Blood poisening, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: endotoxemia, inflammation, Iron, Iron chelation

Outcome measures

Primary outcome

The primary objective of the study is the concentraion of circulation cytokines after administraion of LPS in the presence of iron sucrose (Venofer®), Deferasirox (Exjade®) or placebo.

Secondary outcome

Secondary objectives are:

Markers of iron homeastasis:

- plasma levels of hepcidin, transferrin, soluable transferrin receptor, serum iron, total ironbindingcapacity, GDF15.
- expression of these same proteins in isolated monocytes on mRNA and protein level.

Markers of oxidative stress in whole blood/plasma:

- neutrofil burst, concentration of thiols, TBARS, carbonyls, superoxide dysmutase, glutathion peroxidase, hemoxygenase-1 mRNA and protein.

Subclinical organ damage:

- Endothelial dysfunction measured as the change in forearm blood flow in reaction to intra-arterially administration of vasoactive mediaction (acetylcholine, nitroglycerine en norepinephrine)

- Subclinical kidneydamage (measured as excrestion of tubular proteins

GST-alpha and pi in the urine)

Study description

Background summary

Iron homeostatis affects the immune system, and inflammation affects iron homeostasis.
Iron acts as a catalytic molecule in the formation of oxygen radicals, needed for effective killing of pathogens, but also enhances the inflammatory response that is associated with organ dysfunction. Iron can modulate immune effector mechanisms, such as cytokine activity, nitric oxide (NO) formation or immune cell proliferation. Effects of iron overload include decreased antibody-mediated phagocytosis, alterations in T-lymfocyte subsets, and modification of lymphocyte distribution in different compartments of the immune system. Furthermore, iron treatment has been associated with acute exacerbations of infection. For example, in African children, iron supplementation resulted in an increased rate of malaria and death, and in children with cerebral malaria, the addition of the iron chelator deferoxamine to a standard anti-malarial treatment resulted in an improved clinical course. Therefore, gaining control over iron homeostasis is one of the central battlefields in deciding the fate of an infection. This is of importance for the development of future therapeutic targets for the treatment of sepsis. Moreover, vascular injury is considered one of the main contributors to the development of organ dysfunction during sepsis. Among other factors this is caused by oxidative stress. The reduction of oxidative stress by an iron chelator may represent a therapy to reduce endothelial damage during sepsis.

On the other hand, inflammatory stimuly enhance the production of hepcidin, a key regulator of iron homeostasis that reduces iron uptake from te gut, and abrogates the release of iron from macrophages. In this way continuous stimulation of hepcidin production by inflammatory processes leads to 'anemia of inflammation'. Anemia of inflammation is a frequently encoutered clinical problem during chronic as well as acute systemic inflammation or infection. Studying the pathofysiology of the disturbed iron balance during systemic inflammation may lead to the development of future therapies.

However, human data on the effects of iron on innate immunity are lacking. The human endotoxemia model permits elucidation of key players in the immune response to a gram negative stimulus in vivo and serves as a useful tool to investigate potential novel therapeutic strategies in a standardized setting.

We wish exploid the human endotoxemia model to study the immunomodulatory and vascular effects of iron. This may lead to new therapies for patients with systemic infection or inflammation, and for patients with inflammation associated anemia. Also this study will contribute to our understanding or iron homeostasis and hepcidin regulation.

Study objective

The primary objective of the study is to determine concentration of circulation cytokines na administration of LPS in the presence of iron sucrose (Venofer®), Deferasirox (Exjade®) of placebo.

Study design

Double blinded placebo controlled parallel intervention study in healthy human volunteers during expermental endotoxemia.

Intervention

The volunteers will be randomized to 5 intervention groups.

1. iron loading + placebo prio to endotoxemia (N=12):
T=-2: Placebo orally
T=-1: iron sucrose (Venofer®) 1.25 mg/kg i.v.
T= 0: 2ng/kg LPS i.v.

2. Placebo + iron chelation prior to endotoxemia (N=12)
T=-2: Deferasirox (Exjade®) 30mg/kg orally
T=-1: Placebo i.v.
T= 0: 2ng/kg LPS i.v.

3. Placebo + Placebo prior to endotoxemia(N=12)
T=-2: Placebo orally
T=-1: Placebo i.v.
T= 0: 2ng/kg LPS i.v.

4. IJzer chelation prior to placebo (N=8)
T=-2: Deferasirox (Exjade®) 30mg/kg orally
T=-1: Placebo i.v.
T= 0: Placebo i.v.

5. Iron loading prior to placebo (N=8)
T=-2: Placebo oraal
T=-1: Ferrioxidesaccharaat (Venofer®) 1.25 mg/kg i.v.
T= 0: Placebo

Pre-hydration will be administered by infusion of 1.5 Liter 2.5% glucose/0.45% NaCl solution in one hours, one hour prior to endotoxin administration.
Pre-hydratie zal worden gegeven door infusie van 1.5 liter 2.5% glucose/0.45% NaCl oplossing in één uur, één uur voor de LPS toediening. (gelijktijdig gestart met Ferrioxidesaccharaat (Venofer®) toediening)

Study burden and risks

A medical interview and physical examintaion are part of this study.
Venofer causes a reversible hyperferremia and deferasirox causses a reversible hypoferremia.
Other side effects are described in the adjunctive SPC's

The administration of LPS induces flu-like sylptoms during approximately 4 hours. In total, approximately 350-400 ml blood will be drawn during each LPS experiment and all urine will be be colleted.

The subjects have no direct benefit from participation in the study. A subject fee is provided.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-zuid 10
6525 GA Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-zuid 10
6525 GA Nijmegen
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 yrs
Male
Healthy

Exclusion criteria

- Use of any medication or anti-oxidant vitamin supplements
- History of allergic reaction to iron preparations or iron chelators.
- Smoking
- History of frequent vaso-vagal collapse
- History, signs or symptoms of cardiovascular disease
- (Family) history of myocardial infarction or stroke under the age of 65 years
- Cardiac conduction abnormalities on the ECG consisting of a 1st degree atrioventricular block or a complex bundle branch block.
- 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 or positive hepatitis serology
- Subjects with elevated bilirubin levels >20 umol/l
- Dyslipidemia or elevated glucose level
- Positive HIV serology
- Immune deficiency
- Febrile illness in the week before the LPS challenge
- Participation in a drug trial or donation of blood 3 months prior to the LPS challenge
- Participation in a previous study in which LPS was administered.

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2009
Enrollment:	54
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Acetylcholine
Generic name:	Acetylcholine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Exjade
Generic name:	Deferasirox
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nitroglycerine
Generic name:	Nitroglycerine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Norepinephrine
Generic name:	Norepinephrine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Venofer
Generic name:	iron sucrose

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-01-2010
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	EUCTR2009-014639-19-NL
CCMO	NL29171.091.09
Other	volgt