The effects of bilirubin infusion on the innate immune response during human endotoxemia.;A parallel open label placebo controlled pilot study.

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Primary objective: To determine the effect of hyperbilirubinemia on systemic activation of the innate immune response induced by a lipopolysaccharide (LPS) challenge. Secondary Objective(s): - To determine if hyperbilirubinemia shifts the pro-anti...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON35603

Source
ToetsingOnline

Brief title
LPSBILI

Condition

- Bacterial infectious disorders
- Decreased and nonspecific blood pressure disorders and shock

Synonym
Blood poisoning, 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: Bilirubin, Inflammation, Lipopolysaccharide, Vascular hyporeactivity

Outcome measures

Primary outcome

The main study parameter is the concentration of circulating cytokines at different time points following LPS administration in the absence or presence of hyperbilirubinemia.

Secondary outcome

- pro-anti oxidant balance during human endotoxemia in the absence or presence of hyperbilirubinemia
- endothelial dysfunction during human endotoxemia in the absence or presence of hyperbilirubinemia as assessed by the measurement of the response to vasodilators acetylcholine and nitroglycerin. Furthermore, the release of vascular adhesion molecules indicating activation of the endothelium will be measured
- subclinical renal damage known to occur during human endotoxemia in the absence or presence of hyperbilirubinemia
- the interplay between HO-1, NO and bilirubin during human endotoxemia

Study description

Background summary

Excessive inflammation, production of free radicals and vascular injury are considered main contributors to the development of organ dysfunction in patients with sepsis. Bilirubin is one of the most powerful anti-oxidants of the human body and the administration of bilirubin in animal models for sepsis reduces inflammation and mortality. Recent experiments of our research group have demonstrated beneficial effects of increased concentrations of endogenously produced bilirubin, induced by atazanavir (CMO numbers 2008/028 and 2009/047). These studies demonstrated an increase in anti-oxidant potential and, an improved vascular response to acetylcholine in diabetes patients and healthy volunteers during human endotoxemia. Furthermore, immunomodulatory effects were observed after infusion with LPS.
However, direct effects of atazanavir (not related to the increase in bilirubin) could not be excluded. Recently, the departments of clinical pharmacy and pharmacology-toxicology of the Radboud University Nijmegen Medical Centre have developed a bilirubin formulation that is suitable for infusion in humans. Safety and kinetics have been studied recently (CMO 2009/170). Bilirubin infusion appears to be safe and without side effects.
In the present study, we aim to determine the effects of parenteral treatment with bilirubin on the innate immune response and end organ damage as assessed by vascular response and subclinical kidney damage using the human endotoxemia model. The human endotoxemia model permits the study of key players in the immune response to a gram negative stimulus in vivo, therefore serving as a useful tool to investigate potential novel therapeutic strategies for inflammation/sepsis in a standardized setting in humans in vivo.

Study objective

Primary objective:
To determine the effect of hyperbilirubinemia on systemic activation of the innate immune response induced by a lipopolysaccharide (LPS) challenge.

Secondary Objective(s):
- To determine if hyperbilirubinemia shifts the pro-anti oxidant balance during human endotoxemia
- To determine if hyperbilirubinemia attenuates vascular injury as assessed by the measurement of the response to vasodilators acetylcholine and nitroglycerin . Furthermore, the release of vascular adhesion molecules indicating activation of the endothelium will be measured
- To determine if hyperbilirubinemia can attenuate subclinical renal damage known to occur during human endotoxemia
- To investigate the interplay between HO-1, NO and bilirubin during human endotoxemia

Study design

Randomized open label placebo controlled parallel intervention study in healthy

human volunteers using human experimental endotoxemia

Intervention

Subjects will be included in one of three different protocols:
1. In this arm, 2 subjects will be infused with 2.9 mg/kg bilirubin (diluted in albumin 200 mg/ml).
2. Subjects in this group (n=10) will be infused with 387 mg/kg albumin (200 mg/ml) intravenously serving as placebo. This dosage is the exact amount needed to dilute the bilirubin in arm 1 and 3 normalized for body weight. Infusion will be performed over 10 minutes. At 15 minutes after the start of the albumin infusion, a dose of 2 ng/kg LPS derived from E coli O:113 will be administered.
3. Subjects in this group (n=10) receive 2.9 mg/kg bilirubin (diluted in albumin 200 mg/ml) intravenously over 10 minutes. At 15 minutes after the start of the bilirubin infusion, a dose of 2 ng/kg LPS derived from E coli O:113 will be administered.

Study burden and risks

A medical interview and physical examination are part of this study. Bilirubin will be administered by continuous infusion and concentrations will be checked in blood at several time points. In the previously performed safety and kinetics study no side effects of intravenous bilirubin were observed. Volunteers will be monitored on the research unit of our intensive care. Subjects in Arm 1 will receive two intravenous lines (one for blood sampling and one for bilirubin administration). Blood pressure will be monitored using non-invasive blood pressure measurements every 30 minutes.
Subjects in arm 2 and 3 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 in these subjects.
The administration of LPS induces flu-like symptoms for approximately 4 hrs. This model of systemic inflammation has been applied for many years in research centres all over the world. Endotoxin administration is considered safe and no long term effects have ever been documented.
At the Radboud University Medical Centre, over 250 volunteers have received more than 350 injections of lipopolysaccharide. Therefore, there is sufficient experience with this model at this centre.
In total, a maximum of 400 ml blood will be drawn during the experiment and urine will be collected.
The subjects will not benefit directly from participation to the study. A subject fee is provided.

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

-Age >= 18 and <= 35 years
-Male
-Healthy

Exclusion criteria

-Use of any medication or anti-oxidant vitamin supplements.
-History of allergic reaction to albumin or any other drug used in the study.
-Smoking.
-Previous spontaneous 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 (or higher degree) atrioventricular block or a complex bundle branch block.
- Hypertension (defined as a repeated measurement of RR systolic > 160 or RR diastolic > 90 mmHg).
- Hypotension (defined as RR systolic < 100 or RR diastolic < 50 mmHg).
- Renal impairment (defined as plasma creatinin >120 µmol/l).
- Liver enzyme abnormalities or positive hepatitis B serology.
- Subjects with a total bilirubin level above 15 µmol/L and a normal direct bilirubin level suggesting Gilbert Syndrome.
- Positive HIV serology or any other obvious disease associated with immune deficiency.
- Febrile illness in the week before the experiment.
- Participation in a drug trial or donation of blood 3 months prior to the LPS challenge.
- Inability to understand the nature and extent of the trial and the procedures required.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	22
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Albuman
Generic name:	albumin
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	Bilirubin for infusion 6 mg/ml
Generic name:	Bilirubin for infusion 6 mg/ml
Product type:	Medicine
Brand name:	Miochol-E
Generic name:	Acetylcholine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nitroglycerin
Generic name:	Nitroglycerin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-10-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-02-2012
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	EUCTR2011-004969-32-NL
CCMO	NL38438.091.11
Other	Volgt