The effects of atazanavir-induced hyperbilirubinemia during human endotoxemia.

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

Summary

ID

NL-OMON33311

Source
ToetsingOnline

Brief title
Atazanavir-induced hyperbilirubinemia during human endotoxemia.

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: Endotoxemia, Hyperbilirubinemia, Inflammation, Innate immune response

Outcome measures

Primary outcome

The main study parameter is the concentration of circulating cytokines after

LPS in the absence or presence of atazanavir-induced hyperbilirubinemia.

Secondary outcome

Secondary study parameters include:

- Endothelial function after LPS administration in the absence or presence of

atazanavir-induced hyperbilirubinemia

- Gastric perfusion after LPS administration in the absence or presence of

atazanavir-induced hyperbilirubinemia

- Subclinical renal impairment after LPS administration in the absence or

presence of atazanavir-induced hyperbilirubinemia

- HO-1 activity after LPS administration in the absence or presence of

atazanavir-induced hyperbilirubinemia

Study description

Background summary

Excessive inflammation, production of free radicals and vascular injury are considered the main contributors to the development of organ dysfunction during sepis. The endogenously produced unconjugated bilirubin is one of the most powerful anti-oxidants of the human body and the administration of bilirubin in animal experiments has been shown to protect from inflammation-induced death. However, bilirubin for human administration is not yet available. Therefore we wish to exploit one of the side effects of Atazanavir, which is currently used as a protease inhibitor in HIV-1 infected patients. Atazanavir inhibits UGT1A1

and therefore increases endogenously produced bilirubin levels moderately. We wish to study the anti-inflammatory and vascular effects of Atazanavir-induced hyperbilirubinemia using the human endotoxemia model. The human endotoxemia model permits elucidation 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 in a standardized setting.

Study objective

The primary objective of the study is to determine the effect of atazanavir-induced hyperbilirubinemia on systemic activation of the innate immune response induced by human endotoxemia.

Secondary objectives are:
- To determine if the vascular hyporeactive response to endothelium dependent vasodilators and vasoconstrictors can be prevented by atazanavir-induced hyperbilirubinemia.
- To determine whether gastric perfusion is reduced during humane endotoxemia and whether this effect can be reduced by atazanavir induced-hyperbilirubinemia.
- To determine if subclinical renal damage can be modulated by atazanavir-induced hyperbilirubinemia.
- To determine the effects of atazanavir-induced hyperbilirubinemia on HO-1 activity after endotoxemia.

Study design

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

Intervention

Subjects will receive atazanavir (four day treatment with 300 mg twice daily n=10) or placebo (n=10). Pre-hydration will be performed by infusion of 1.5 L 2.5% glucose/0.45% saline solution in 1 hour before LPS administration. LPS derived from E coli O:113 will be injected (2 ng/kg iv.).

Study burden and risks

A medical interview and physical examination are part of this study. Atazanavir will cause a mild and completely reversible hyperbilirubinemia. Other side effects tend to be mild (see for further information the SPC provided with the study protocol).
The administration of LPS induces flu-like symptoms for approximately 4 hrs. In total, approximately 350 ml blood will be drawn during each LPS experiment and urine will be collected.
To measure gastrointestinal perfusion a 16F nasogastric tube will be inserted.

This can cause mild discomfort at the time of insertion.
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 yrs
Male
Healthy

Exclusion criteria

- Use of any medication or anti-oxidant vitamin supplements
- History of allergic reaction to atazanavir
- 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 2nd degree atrioventricular block or a complex bundle branch block.
- Hypertension (defined as RR systolic > 160 or RR diastolic > 90 mmHg)
- 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 a total bilirubin level above 15 umol/l suggesting Gilbert Syndrome.
- 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

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):	11-05-2009
Enrollment:	20
Type:	Actual

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:	Nitroglycerine
Generic name:	Nitroglycerine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Noradrenaline
Generic name:	Noradrenaline
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Reyataz
Generic name:	Atazanavir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-03-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Application type:	First submission
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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	EUCTR2009-010705-36-NL
CCMO	NL27052.091.09
Other	volgt