The effect of endotoxin tolerance on ischemia-reperfusion injury in humans in vivo

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To demonstrate attenuated ischemia-reperfusion damage in subjects that have become tolerant due to repeated endotoxin administrations.

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON29815

Source
ToetsingOnline

Brief title
Endotoxin tolerance and ischemia-reperfusion injury

Condition

- Other condition

Synonym
ischemia-reperfusion injuy, tolerance against ischemia

Health condition

voorkomen van ischemie-reperfusieschade middels het induceren van endotoxine-tolerantie.

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: annexin A5, endotoxin, ischemia-reperfusion, tolerance

Outcome measures

Primary outcome

Ischemia-reperfusion damage in the thenar muscle using annexine A5

scintigraphy.

Secondary outcome

-

Study description

Background summary

Animal experiments demonstrate that induction of endotoxin tolerance results in protection from subsequent ischemia-reperfusion injury. For example, animals treated with endotoxin are protected from cardial or renal ischemic damage. Endotoxin-induced protection is more potent than any pharmacological form of protection studied up to now.

Study objective

To demonstrate attenuated ischemia-reperfusion damage in subjects that have become tolerant due to repeated endotoxin administrations.

Study design

In 10 subjects endotoxin tolerance will be induced by repeated infusions of increasing dosages of endotoxin (0.2-2.0 ng/kg/day) in 5 days.
Prior to and directly following the induction of endotoxine tolerance (day 6), ischemia-reperfusion damage is examined in the thenar muscle using annexine A5 scintigraphy.
In a second group of 10 subjects will serve as time-controls, in which

ischemia-reperfusion damage is examined in the thenar muscle using annexine A5 scintigraphy without the pretreatment with endotoxin.

Intervention

Endotoxin tolerance is induced by repeated infusions of endotoxine (E. coli O:113).
Ischemia-reperfusion damage is investigated using annexine A5 scintigraphy.
No additional drugs/agents are investigated in this project.

Study burden and risks

- Concerning the use of endotoxin.
The described protocol has been conducted many times before by our group. The subjects experience flue-like symptoms, but endotoxin administration is considered safe and it has never resulted in persistent damage.
Endotoxin administration is an accepted model of systemic inflammation, that is used in several European countries and the United States. Thousands of subjects have received endotoxin and apart from vagal collapse, no serious adverse events or prolonged hospitalisation have been reported. The dosage of endotoxin used is 2-4 ng/kg in the literature. In our project a maximal dose of 2 ng/kg is administered. Endotoxin is 'dead' material, there is no risk of infection.
The inflammatory response to endotoxin is predictable and reproducible. After the administration of 2 ng/kg, the volunteers experience flue-like symptoms like fever (max. 38.5 oC), chills, headache, muscleache, backache. These symptoms are qualified as 'mild' by the subjects. All subjects are closely monitored: symptoms, general appearance, heart rate, blood pressure. During the first 4 hours after the administration of the endotoxin, a medical docter is constantly present. It is important to notice that the described symptoms occur after the administration of 2 ng/kg endotoxin. During previously conducted endotoxin tolerance experiments, it was found that (due to the induction of tolerance) the subjects experienced no, or very mild symptoms.

- Concerning the repeated administrations of endotoxin.
In our previous study (CMO nr 2005-087), in which the subjects received 2 ng/kg endotoxin each day for 5 days, the flue-like symptoms occured the first 2 days and then faded. Subjects that are exposed to the increasing dosages of endotoxin (0.2-2.0 ng/kg/day), as in the present project, experience no or very mild symptoms.

- Concerning the 10 minutes of ischemic exercise and the administration of labeled annexine during the ischemia-reperfusion experiments.
In approximately 140 subjects this protocol was conducted without any side effects. In theory, an allergic reaction to annexine is possible. This never occured up to now, but it is mentioned in the information for the participants.
Also, the first 30 minutes and 1 hr and 4 hrs after the administration of

annexine, a medical doctor is with the subjects.

In view of the potential clinical implications we feel it justified to conduct the present project to confirm or reject the hypothesis of the study.

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

male
age 18-35 years
healthy

Exclusion criteria

cardiovascular and respiratory disease
hypertension
diabetes
history of syncope

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2006
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

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
ClinicalTrials.gov	NCT00246714
CCMO	NL12641.091.06