The effects of oral dipyridamole treatment on the innate immune response during human endotoxemia.

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Primary objective: The primary objective of the study is to determine the effect of oral dipyridamole treatment on the innate immune response induced by a lipopolysaccharide (LPS) challenge. Various pro- and anti-inflammatory cytokines will be...

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

Summary

ID

NL-OMON34679

Source
ToetsingOnline

Brief title
Effects of dipyridamole on innate immune response 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: Adenosine, Endotoxemia, Inflammation, Innate immune response

Outcome measures

Primary outcome

The main study parameter is the concentration of circulating cytokines

following LPS administration in the absence or presence of dipyridamole.

Secondary outcome

Secondary study parameters include endothelial dysfunction, vascular

reactivity, subclinical renal injury and the endogenous adenosine concentration

after LPS administration in the absence or presence of dipyridamole.

Study description

Background summary

During sepsis and septic shock the immune response can be overwhelming leading to excessive tissue damage. Ideally, the inflammatory response is modulated leading to both adequate protection to invading pathogens as well as limitation of an exuberant immune response. In the last few years adenosine is opposed to have a central role in the modulation of inflammation. In unfavorable conditions such as hypoxia, ischemia or inflammation adenosine is quickly up-regulated; with concentrations up to tenfold in septic patients. Many animal studies have shown that adenosine is able to attenuate the inflammatory response and decrease mortality rates. Therefore, pharmacological elevation of the adenosine concentration is an attractive target to attenuate inflammation and limit organ injury. Dipyridamole, an adenosine re-uptake inhibitor is able to increase the adenosine concentration and limit ischemia-reperfusion injury. In order to study the effects of dipyridamole on the inflammatory response we use the so called human endotoxemia model. This 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

Primary objective: The primary objective of the study is to determine the effect of oral dipyridamole treatment on the innate immune response induced by a lipopolysaccharide (LPS) challenge. Various pro- and anti-inflammatory cytokines will be measured for this purpose.

Secondary Objective(s): There are three secondary objectives:
1. To determine if the attenuated vascular response to endothelium dependent vasodilators and vasoconstrictors during endotoxemia can be prevented by oral dipyridamole treatment.
2. To determine if dipyridamole can attenuate (subclinical) renal damage known to occur during human endotoxemia, markers of proximal and distal tubular damage will be measured at various time points.
3. To measure the dipyridamole-induced increase of adenosine after LPS challenge.

Study design

Randomized double-blind placebo-controlled parallel intervention study in healthy human volunteers during experimental endotoxemia.

Intervention

Subjects will receive dipyridamole (five day treatment with 200 mg twice daily n=15) or placebo (n=15). The day of the experiment, prehydration will be performed by infusion of 1.5 L 2.5% glucose/0.45% saline (moeten we niet naar een 0,9% NaCL oplossing toe?) solution in 1 hour before LPS administration. LPS derived from E coli O:113 will be injected (2 ng/kg i.v., infusion rate; 1 minute).

Study burden and risks

A medical interview and physical examination are part of this study. Dipyridamole can cause a headache after ingestion of the first dosages. Other side effects are mild and are described in the investigators brochure. The day of the experiment, volunteers will be monitored on the research unit of our intensive care and receive an arterial line (a. brachialis) to facilitate blood pressure monitoring, drug infusion during venous occlusion plethysmography 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 saline/glucose.
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 Nijmegen Medical Centre, over 150 volunteers have received over 250 injections of lipopolysaccharide. Therefore, there is

sufficient experience with this model at this centre.
In total, approximately 350 ml blood will be drawn during the experiment and urine will be collected.

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.
History of allergic reaction to dipyridamole
Bleeding disorder.
Smoking.
Previous spontaneous vagal collapse.
History, signs or symptoms of cardiovascular disease.
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).
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.
Positive HIV serology or any other obvious disease associated with 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):	12-04-2010
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Acetylcholine
Generic name:	Acetylcholine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Norepinephrine
Generic name:	Norepinephrine
Product type:	Medicine
Brand name:	Persantin
Generic name:	Dipyridamole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sodium Nitroprusside
Generic name:	Sodium Nitroprusside
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-12-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-03-2010
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	EUCTR2009-016963-12-NL
CCMO	NL30625.091.09
Other	volgt