The effects of different vasopressors on the innate immune response during experimental human endotoxemia, a pilot proof-of-principle study

Published: 28-10-2015
Last updated: 19-04-2024

Our primary objective is to investigate whether noradrenaline exerts immunomodulatory effects in humans in vivo during experimental human endotoxemia. This will be determined by comparing plasma levels of various pro- and anti-inflammatory cytokines...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON42684

Source
ToetsingOnline

Brief title
Effects of vasopressors on immune response

Condition

- Immune disorders NEC
- Bacterial infectious disorders

Synonym
bacterial bloodstream infection, Sepsis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Human endotoxemia model, Immunoparalysis, Sepsis, vasopressors

Outcome measures

Primary outcome

Our primary objective is to investigate whether noradrenaline exerts immunomodulatory effects in humans in vivo during experimental human endotoxemia. This will be determined by comparing plasma levels of various pro- and anti-inflammatory cytokines between the group that receives noradrenaline infusion and the group that receives placebo (0.9% NaCl) infusion.

Secondary outcome

1. To determine the extent of immunomodulatory effects of phenylephrine and vasopressin in humans in vivo during experimental human endotoxemia. Therefore, plasma cytokines will be compared between the phenylephrine and vasopressin groups and the placebo group, but head-to-head comparisons between the different vasopressors will also be made.

2. To determine the effects of the different vasopressors on responsiveness of leukocytes to various inflammatory stimuli ex vivo.

3. To determine the effects of the different vasopressors on the phenotype of circulating leukocytes (e.g. expression pattern of cell-surface receptors by use of flow cytometry).

4. To determine the effects of the different vasopressors on inflammatory

transcriptional pathways (by use of qPCR/microarrays/RNA sequencing).

5. To determine the effects of the different vasopressors on LPS-induced

clinical symptoms (illness score) and hemodynamic/temperature changes.

Study description

Background summary

Septic shock is a major medical challenge associated with a high mortality rate and increasing incidence. Massive release of pro-inflammatory mediators result in hemodynamic instability, coagulation disorders and multiple organ dysfunction. Previous strategies have aimed to treat sepsis by inhibition of pro-inflammatory mediators, however, most of these approaches have failed. This might be due to the fact that the majority of septic patients do not succumb to the initial pro-inflammatory *hit*, but die at a later time-point in a pronounced immunosuppressive state. This so-called *immunoparalysis*, which renders patients extremely vulnerable to secondary infections, results from the triggering of counter-regulatory anti-inflammatory pathways along with the pro-inflammatory response. Immunoparalysis is increasingly being recognized as the overriding immune dysfunction during sepsis. As a consequence, preservation of immune function should be a pillar in current treatment strategies for septic patients.

Noradrenaline is a catecholamine and is the cornerstone treatment for the improvement of hemodynamic parameters and organ perfusion in septic shock. However, catecholamines exert profound immunomodulatory effects which have mainly been studied for adrenaline. It has been shown that adrenaline profoundly inhibits LPS-induced production of TNF-α, and enhances production of anti-inflammatory IL-10 in vitro, as well as in animal and human models of inflammation. Furthermore, we have recently shown that endogenously increased production of adrenalin in humans potently dampens the inflammatory response, again through increased production of the anti-inflammatory cytokine IL-10. The effects of noradrenaline, a potent α-adrenergic agonist which has β affinity as well, on the immune system are far less studied: no in vivo (animal or human) studies have been performed to date. Nevertheless, in vitro studies have shown that noradrenaline inhibits LPS-induced pro-inflammatory cytokine production as potently as adrenaline.

Considering the important role of immunoparalysis in patients with septic shock and the anti-inflammatory effects of catecholamines, it is vital to review current vasopressor management. Therefore the immunomodulatory effects of noradrenaline in humans in vivo warrantinvestigation. Furthermore, effects on

the immune system of viable vasopressor alternatives for the treatment of septic patients, namely phenylephrine and vasopressin, need to be established in humans in vivo to evaluate whether they could represent non- or less immunosuppressive alternatives.

Study objective

Our primary objective is to investigate whether noradrenaline exerts immunomodulatory effects in humans in vivo during experimental human endotoxemia. This will be determined by comparing plasma levels of various pro- and anti-inflammatory cytokines between the group that receives noradrenaline infusion and the group that receives placebo (0.9% NaCl) infusion.

Study design

A randomized single-blind placebo-controlled study in healthy human volunteers during experimental endotoxemia.
In this study we will enrol 40 subjects. There will be four groups, all will undergo experimental endotoxemia combined with infusion of noradrenaline, phenylephrine, vasopressin, or placebo.

Study groups:
1. The noradrenaline group: a group of 10 subjects that will receive noradrenaline 0.05 µg/kg/min infusion for 5 hours, starting 60 minutes before the endotoxemia experiment.

2. The phenylephrine group: a group of 10 subjects that will receive phenylephrine 0.5 µg/kg/min infusion for 5 hours, starting 60 minutes before the endotoxemia experiment.

3. The vasopressin group: a group of 10 subjects that will receive vasopressin 0.04 IU/min infusion for 5 hours, starting 60 minutes before the endotoxemia experiment

4. The placebo group: a group of 10 subjects that will receive NaCL 0.9% infusion for 5 hours, starting 60 minutes before the endotoxemia experiment.

Intervention

Two hours before LPS administration, subjects will be admitted to the research unit of the Intensive Care department. A venous cathether (fossa cubiti) will be placed. Furthermore, an arterial catheter (brachial artery) will be inserted after local anaesthesia using lidocaïne 2%. One hour prior to LPS administration, subjects will receive a continuous infusion of noradrenaline, phenylephrine, vasopressin, or placebo (for dosages, see study design) for 5 hours. At T=0, 2 ng/kg LPS will be administered intravenously. Subjects will be

monitored for 8 hours after LPS administration, after which catheters will be removed and subjects can return home.

Study burden and risks

All subjects will visit the hospital for an initial screening visit in which a medical interview and physical examination will be carried out (60 minutes). At the screening visit blood will be collected.

Subjects will undergo experimental endotoxemia. Volunteers will be admitted and monitored on the research unit of our intensive care unit for 10 hours and receive an arterial line to facilitate blood pressure monitoring and blood sampling. Furthermore, a venous cannula will be placed for the administration of vasopressors, fluids and LPS.
Noradrenaline, phenylephrine and vasopressin can in theory induce hypertension when administered to normotensive subjects (ie. healthy volunteers). However, extensive research has been performed administering these drugs in healthy volunteers showing no serious adverse events, no malignant hypertension and no long term effects. Furthermore, vasopressors have been administered in numerous trials to healthy volunteers in low dosages for short periodes of time over normal venous canulas, showing nog local side effects.

The administration of LPS induces flu-like symptoms for approximately 4-6 hrs. This model of systemic inflammation has been applied for 10 years in our department and thousands of subjects in various research centres in the world have participated in experimental endotoxemia trials. During the endotoxemia experiment day, subjects will be under constant supervision of an experienced intensivist with continuous monitoring of blood pressure (intra-arterially) and heart rate (ECG). The endotoxemia protocol and associated risks are identical to earlier endotoxemia studies performed in our institute. Furthermore, randomization will be carried out in a manner guaranteeing that LPS will not be administered to more than one person with the same intervention on one day. In total, a maximum of 350 ml blood will be drawn during the study, which is comparable to previous studies and never resulted in adverse events. Subjects will not benefit directly from participation to the study. A subject fee is provided

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein 10
Nijmegen 6500 HB

NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein 10
Nijmegen 6500 HB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Written informed consent;- Age >=18 and <=35 yrs;- Male;- Healthy

Exclusion criteria

- Use of any medication;- Smoking;- Previous spontaneous vagal collapse;- History of atrial or ventricular arrhythmia;- (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);- 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;- Medical history of any disease associated with immune deficiency;- CRP > 20 mg/L, WBC > 12x109/L, or clinically significant acute illness, including infections, within 4 weeks before endotoxin administration;- Participation in a drug trial or donation of blood 3 months prior to the LPS challenge;- Use of recreational drugs within 7 days prior to experiment day;- Recent hospital admission or surgery with general anaesthesia (<3 months)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-02-2016
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Argipressin
Generic name:	Vasopressin
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:	Phenylefrine
Generic name:	Phenylefrine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-10-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-01-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2016
Application type:	Amendment
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	EUCTR2015-002706-36-NL
CCMO	NL53411.091.15