The effects of acetylsalicylic acid on immunoparalysis following human endotoxemia

Published: 01-07-2016
Last updated: 16-04-2024

Primary objective:To determine whether endotoxin tolerance can be prevented by acetylsalicylic acid prophylaxis or can be reversed by acetylsalicylic acid treatment, expressed as an augmentation of pro-inflammatory cytokine levels during the second…

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

Summary

ID

NL-OMON43332

Source
ToetsingOnline

Brief title
SALYCENDO-study

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: acetylsalisylic acid, endotoxemia, immunoparalysis, immunostimulation

Outcome measures

Primary outcome

The primary study endpoint, endotoxin tolerance, is the decrease in the area under the curve (AUC) of the plasma TNF* concentration between the first and second endotoxin challenge in the control group compared to the treatment group.

Secondary outcome

- Plasma levels of other inflammatory mediators on the first and second endotoxemia day (including but not limited to TNF*, IL-6, IL-8, IL-10, IL-1RA)
- Ex vivo production of inflammatory mediators and reactive oxygen species (ROS) by whole blood and peripheral blood mononuclear cells (PBMCs) stimulated by LPS and several pathogens (including but not limited to S. aureus, M. tuberculosis, C. albicans)
- Monocyte surface antigen expression (including but not limited to mHLA-DR, Programmed Death Ligand (PDL)-1, Programmed cell Death protein (PD)-1, IL-7R)
- Plasma thromboxane B2 levels, as an expression of thromboxane A2
- Prostaglandin E2 urine metabolites (PGE-M)
- Kidney damage markers (including but not limited to NGAL, KIM-1, L-FABP)
- Transcriptional activity of leukocytes
- Symptom score
- Mean arterial pressure
- Heart rate

- Temperature

Study description

Background summary

Sepsis is a major health care burden with increasing incidence and high mortality rates. The immune response in sepsis is highly variable between patients and can comprise both a hyperinflammatory and immunosuppressive state (immunoparalysis). The field of sepsis research has seen many pharmacological trials, mainly aimed at inhibition of pro-inflammatory responses, fail to have any effect on sepsis outcome. This might be due to the fact that the majority of septic patients do not succumb to the early pro-inflammatory phase, but die at a later time-point in a protracted immunosuppressive state that renders them very vulnerable towards secondary infections. The last years, research focus has moved to immunostimulatory agents in order to restore/increase the functionality of the immune system during this sepsis-induced immunoparalysis. Epidemiologic data show that chronic use of ASA is associated with improved outcome during sepsis. Experimental data by our group and others indicates that ASA, perhaps counter-intuitively, exerts pro-inflammatory effects during systemic inflammation. Therefore, ASA may be an immunostimulatory agent that could reverse the immunosuppressive state in sepsis. To this end, it might be a promising, cheap, well-known, and globally available agent to reduce the incidence of secondary infections and improve patient outcome in sepsis. However, whether ASA is indeed capable of reversing immunoparalysis in vivo in humans is unknown.

Study objective

Primary objective:

To determine whether endotoxin tolerance can be prevented by acetylsalicylic acid prophylaxis or can be reversed by acetylsalicylic acid treatment, expressed as an augmentation of pro-inflammatory cytokine levels during the second endotoxemia one week after the first challenge.

Secondary objectives:

- To determine the effects of prophylaxis and treatment with acetylsalicylic acid on ex vivo responsiveness of monocytes and whole blood to various inflammatory stimuli.
- To determine the effects of prophylaxis and treatment with acetylsalicylic acid on cell surface expression of markers of immunoparalysis on circulating leukocytes, including but not limited to HLA-DR, PD-L1, PD-1, and IL-7R.

- To determine the effects of prophylaxis and treatment with acetylsalicylic acid on plasma and urine levels of prostaglandin E2.
- To determine the effects of prophylaxis and treatment with acetylsalicylic acid on inflammatory transcriptional pathways in monocytes.
- To determine the effects of prophylaxis and treatment with acetylsalicylic acid on LPS-induced clinical symptoms (symptom score), hemodynamic or temperature changes.

Study design

Double-blind randomized placebo-controlled pilot study in healthy male volunteers during repeated experimental endotoxemia. We will enrol 30 subjects which will be randomized in three study groups. Groups differ in allocated study medication (ASA or placebo) in the first and second treatment course (Table 1). The first course is the 7-day period before the first endotoxemia (also referred to as prophylaxis) and the second course is the 7-day period in-between first and second endotoxemia (also referred to as treatment). All subjects will undergo experimental endotoxemia twice, on day 7 and on day 14. For accurate resemblance of the clinical situation, we will conduct a continuous LPS administration model which is more similar to an ongoing inflammation as seen in patients. To this end, subjects will receive LPS in an initial bolus of 1ng/kg, followed by continuous infusion at 1ng/kg/hr during 3 hours, analogous to a previous study of our group.

Intervention

The subjects will be randomized in three groups (each n=10):

PA (placebo-ASA, treatment group): first course placebo, second course ASA
AA (ASA-ASA, prophylaxis group): first course ASA, second course ASA
PP (placebo-placebo, control group): first course placebo, second course placebo

In the ASA course, subjects receive low-dose ASA of 80 mg/day for the course of 7 days, they start with a loading dose of 160 mg.

Study burden and risks

Subjects will visit the research unit a total of six times; for screening, medication instruction, the first endotoxemia day, urine deposit, the second endotoxemia day and for follow-up. Volunteers will be recruited and are subjected to a medical examination (including interview, medical history and physical examination).

The use of ASA in this (low) dose is registered for patients and the risk on adverse events is low. The main potential side effects of ASA are

gastrointestinal complaints and a prolonged bleeding time. Many adverse effects of ASA are dose related, and are extremely rare at low dosages.

The administration of a lipopolysaccharide induces flu-like symptoms. This model of systemic inflammation has been applied for more than 10 years in our department and thousands of subjects worldwide have participated in endotoxemia trials. During the endotoxemia experiment day, subjects will be under constant supervision of an physician with continuous monitoring of blood pressure and heart rate. The endotoxemia protocol and associated risks are identical to earlier endotoxemia studies performed in our institute.

In total, a maximum of 450 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. The total risks to the subjects in this study is classified as a *negligible risk* (low risk on minor harms). A subject fee is provided.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein 10
Nijmegen 6500HB
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein 10
Nijmegen 6500HB
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 (as confirmed by medical history, examination, ECG, blood sampling)

Exclusion criteria

* Use of any medication
* Use of COX inhibitors within 6 weeks prior to the first endotoxemia day
* Smoking
* Known anaphylaxis or hypersensitivity to acetylsalicylic acid or non-investigational products
* History or signs of atopic syndrome (asthma, rhinitis with medication and/or eczema)
* History of peptic ulcer disease
* History or signs of hematological disease
* Thrombocytopenia (<150*10^9/ml) or anemia (hemoglobin < 8.0 mmol/L)
* History of glucose-6-phospate dehydrogenase deficiency
* History of intracranial hemorrhage
* History, signs or symptoms of cardiovascular disease, in particular:
* Previous spontaneous vagal collapse
* History of atrial or ventricular arrhythmia
* Cardiac conduction abnormalities on the ECG consisting of a 2nd degree atrioventricular block or a complete left 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 creatinine >120 *mol/l)
* Liver enzyme abnormalities (above 2x the upper limit of normal)
* Medical history of any disease associated with immune deficiency
* CRP > 20 mg/L, WBC > 12x109/L or < 4 x109/L or clinically significant acute illness, including infections, within 4 weeks before the first endotoxemia day
* Previous (participation in a study with) LPS administration
* Participation in a drug trial or donation of blood 3 months prior to first endotoxemia day
* Any vaccination within 3 months prior to first endotoxemia day until the end of the study
* Recent hospital admission or surgery with general anesthesia (<3 months to endotoxemia day)
* Use of recreational drugs within 21 days prior to the first endotoxemia day
* Inability to personally provide written informed consent (e.g. for linguistic or mental reasons) and/or take part in the study

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):	01-09-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Acetylsalicylic acid Cardio TEVA 80 mg
Generic name:	Acetylsalicylic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-07-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-08-2016
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	EUCTR2016-001971-61-NL
CCMO	NL57410.091.16