The effect of the α7nACh receptor agonist GTS-21 on inflammation and end-organ dysfunction during human endotoxemia

Published: 11-12-2007
Last updated: 11-05-2024

to study the effect of pre-treatment with the specific a7nAChR agonist GTS-21 on cytokine production and the effects on the subsequent subclinical organ dysfunction in the human endotoxemia model. to measure the effect of LPS administration in the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Ancillary infectious topics
Study type	Interventional

Summary

ID

NL-OMON32321

Source
ToetsingOnline

Brief title
Anti-inflammatory effects of GTS-21 after LPS

Condition

- Ancillary infectious topics

Synonym
septic shock, systemic inflammation

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W,CoMentis, Inc., 280 Utah Avenue, Suite 275, South San Francisco, CA 94080

Intervention

Keyword: Cytokine, GTS-21, Inflammation, Sepsis

Outcome measures

Primary outcome

the concentration of TNF after the administration of LPS in the absence and

presence of GTS-21.

Secondary outcome

Concentration of pro- and anti-inflammatory cytokines, HMGB-1

AChR and TLR expression on circulating monocytes

Leucocyte number, C-reactive protein concentration

Severity of clinical symptoms, hemodynamic parameters

Ex-vivo TLR receptor stimulation assays on whole blood to measure cytokines,

AChR and TLR expression.

Circulating endothelial cells and markers of endothelial damage (adhesion

molecules).

Urine excretion of markers of proximal (GSTA1-1) and distal (GSTP1-1) renal

tubular damage.

Brain specific proteins S100β, NSE, GFAP

Vagal activity as measured by heart rate variability analysis

Study description

Background summary

The innate immune response is the first line of defense against invading pathogens. This tightly regulated system consists of a wide variety of chemokines, cytokines, cell associated receptors and other mediators orchestrating the initial response to infection. Experimental evidence in the past several years has demonstrated that activation of the efferent vagus nerve has an inhibitory effect on the innate immune response (the cholinergic anti-inflammatory pathway). Several in vitro studies have demonstrated that pretreatment of cultured human macrophages with the principal vagal neurotransmitter acetylcholine, significantly attenuates the LPS-induced release of pro-inflammatory mediators such as TNF-a, IL-6, IL-1b, IL-18 and HMGB1, while release of the anti-inflammatory cytokine IL-10 was unaffected. Moreover, vagal nerve electrical stimulation attenuates serum TNF-a and IL-6 levels in animals after endotoxin administration and prevents the development of shock. In contrast, vagotomized animals exhibited elevated levels of pro-inflammatory cytokines with aggravation of shock.
The anti-inflammatory effect of the vagal nerve is mediated by the a7 nicotinic acetylcholine receptor (a7nAChR) expressed on macrophages and other cytokine-producing cells. GTS-21 (E-3-(2,4)-dimethoxybenzylidene anabaseine) is a highly specific a7nAchR agonist, that has been developed for the treatment of Alzheimer*s disease that has been studied in a few inflammation-related models. Stimulation of the α7nAChR by GTS-21 in animal models of inflammation resulted in a profound anti-inflammatory shift of the pro-/anti-inflammatory balance. So far, no data are available on the anti-inflammatory effects of GTS-21 in humans in vivo.

Study objective

to study the effect of pre-treatment with the specific a7nAChR agonist GTS-21 on cytokine production and the effects on the subsequent subclinical organ dysfunction in the human endotoxemia model.

to measure the effect of LPS administration in the absence or presence of GTS-21 in human volunteers on vagal nerve activity measured by heart rate variability analysis.

Study design

Prospective double-blind placebo-controlled randomized cross-over study

Intervention

Subjects will be tested in a cross-over design in 2 separate sessions, 2-4 weeks apart. Subjects will receive 150 mg GTS-21 or placebo orally tid on the day before LPS injection and a single oral dose of 250 mg GTS-21 or placebo at 1 hour before LPS administration. Before LPS injection, prehydration will be

performed by infusion of 1.5 L 2.5% glucose/0.45% saline solution in 1 hour. One hour after the last dose of GTS-21 or placebo, LPS derived from E coli O:113 will be injected (2 ng/kg iv in 1 minute). A separate set of subjects will be subjected to an identical dose of LPS and placebo at two different moments 2-4 weeks apart to obtain time controls.

Study burden and risks

LPS infusion: The human endotoxemia model is widely used to study inflammation in humans in vivo. Systemic inflammation is induced by low-dose infusion of Escherichia coli lipopolysaccharide (LPS) in healthy volunteers, resulting in flu-like symptoms, increased production of C-reactive protein and increased concentrations of pro- and anti-inflammatory cytokines. The *human endotoxemia model* permits elucidation of key players in this proinflammatory response in humans in vivo and it serves as a useful tool to investigate potential novel therapeutic strategies in a standardized setting.

Oral GTS-21: Until date, 87 healthy male volunteers were enrolled in four Phase I studies that assessed the safety, tolerability, pharmacokinetics, and effects on cognitive function of oral administration of GTS-21 of which 77 subjects received GTS-21 and 10 subjects received placebo. GTS-21 was found to be well tolerated both up to a single dose of 250 mg/day, as well as up to a dose of 150 mg three times daily (450 mg/day) in healthy male subjects. The most common adverse event was headache, which occurred in 27% of subjects in the GTS-21 group compared to 21% of subjects in the placebo group. There were no serious adverse events, or severe adverse events reported during these studies. In one patient in the GTS-21 group transient mild elevation of liver enzymes was detected, without signs of hepatic dysfunction.
GTS-21 is currently being studied in a Phase II clinical trial assessing safety and cognitive improvement in patients with ADHD.

1 periferal intra-venous line and 1 intra arterial line: after removal pressure will be applied to avoid hematoma.

Total blood withdrawal: approximately 350 ml

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

healthy male volunteers (no medical history, no medication)
age 18-35 years
non-smokers

Exclusion criteria

Use of any medication
Smoking
History, signs or symptoms of cardiovascular disease
(Family) history of cerebrovascular disease
Previous vagal collaps
Hypertension (defined as RR systolic > 160 or RR diastolic > 90)
Hypotension (defined as RR systolic < 100 or RR diastolic < 50)
Renal impairement (defined as plasma creatinin >120 µmol/l)
Liver enzyme abnormalities or positive hepatitis serology
Positive HIV test

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:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GTS-21
Generic name:	E-3-(2,4)-dimethoxybenzylidene anabaseine
Product type:	Medicine
Brand name:	Standard Reference Endotoxin (SRE)
Generic name:	Lipopolysaccharide

Ethics review

Approved WMO

Date:	11-12-2007
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	EUCTR2007-006146-17-NL
CCMO	NL20388.091.07