In vivo effects of the selective a7nAChR agonist GTS-21 on inflammation

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

Summary

ID

NL-OMON31411

Source
ToetsingOnline

Brief title
Anti-inflammatory effects of GTS-21

Condition

- Ancillary infectious topics

Synonym
Inflammation, 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,CoMentis, Inc., 280 Utah Avenue, Suite 275, South San Francisco, CA 94080

Intervention

Keyword: Cytokine, GTS-21, Inflammation

Outcome measures

Primary outcome

The concentration of TNF after in vitro whole blood stimulation with the TLR-2 agonist pepticoglycan and TLR-4 agonist lipopolysaccharide.

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

Aim of this study is to investigate the effects of oral administration of GTS-21 in healthy volunteers on cytokine release in ex-vivo TLR agonists stimulated whole blood .

Pharmacokinetic and pharmacodynamic data will be collected with respect to the anti-inflammatory effects of GTS-21 and its effects on the expression of TLR2, TLR4 and α7nAChR.

Study design

Interventional study

Intervention

Oral administration of GTS-21

Study burden and risks

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: after removal ligth pressure 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:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	10

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GTS-21
Generic name:	E-3-(2,4)-dimethoxybenzylidene anabaseine

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	EUCTR2007-002596-14-NL
CCMO	NL17847.091.07