In vivo induction of heme oxygenase-1 (HO-1) in the metabolic syndrome (MetS).
Influence of heme arginate (Normosang) infusion on heme oxygenase-1 activity, endothelial dysfunction, insulin resistance and adipose tissue inflammation related to the metabolic syndrome

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON34409

Source
ToetsingOnline

Brief title
In vivo induction of HO in MetS.

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
atherosclerosis in the metabolic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: diabetes fonds

Intervention

Keyword: endothelial dysfunction, heme oxygenase, insulin resistance, metabolic syndrome

Outcome measures

Primary outcome

Insulin sensitivity assessed by an euglycemic hyperinsulinemic clamp expressed

as M-value. Vasodilation / forearm blood flow in response to acetylcholine,

assessed by venous occlusion strain gauge plethysmography.

Secondary outcome

Vasodilation / forearm blood flow in response to nitroprusside, assessed by

venous occlusion strain gauge plethysmography.Plasma biomarkers of oxidative

stress and vascular inflammation and markers of HO expression and activity.

Study description

Background summary

The metabolic syndrome (MetS) is characterized by a combination of
cardiovascular risk factors among which insulin resistance and can be seen as a

pre-stage of type 2 diabetes mellitus (T2DM). Cardiovascular complications are the leading cause of morbidity and mortality associated with both MetS and T2DM. Both MetS and T2DM are associated with a stage of low grade inflammatory activation of adipose tissue and the vascular system. Oxidative stress is thought to be a key phenomenon in the pathogenesis of this pro-inflammatory state. As pro-inflammatory cytokines reinforce insulin resistance, a vicious cycle of cumulating exposure to risk factors and inflammation of the vascular system and adipose tissue occurs. The cytoprotective enzyme heme oxygenase (HO-1), is well known for its powerful antioxidant and anti-inflammatory capacities. In vitro and animal studies convincingly show the beneficial effect of HO activity with regard to T2DM related insulin resistance and vascular dysfunction. We thus hypothesize that short term HO-1 induction by heme arginate infusion ameliorates insulin resistance and endothelial dysfunction in subjects with MetS.

Study objective

Our main objective is to determine the effect of HO-1 induction by heme arginate infusion on insulin resistance and endothelial dysfunction related to MetS. Secondary objectives are to determine the effect on adipose tissue, adiponectin plasma level, markers for oxidative stress and vascular inflammation and indicators of HO activity.

Study design

Single-centre, randomized, controlled, cross-over study.

Intervention

Three day treatment with heme arginate (3 mg/kg with a maximum of 250 mg, intravenously administered on day 1 and 3 of one treatment period) in a randomized and cross-over design with a washout period of two months. The control treatment will consist of a three day treatment with L-arginine (3,2 mg/kg with a maximum of 267 mg, intravenously administered on day 1 and 3 of the other treatment period).

Study burden and risks

Subjects will visit our department 7 times. The first visit relates to the medical screening, the next six visits include the administration of trial medication (either heme arginate or arginine) and/or the assessments among which plethysmography and clamps. Total burden of time will be 20 hours approximately. In daily clinical practice, heme arginate is used for the treatment of acute porphyria. The substance is hardly associated with side effects, but infusion may cause local irritation of the vene. Instructions given by the manufacturer to avoid these effects will be complied with

obviously. Side effects due to the euglycemic hyperinsulinemic clamp are infrequent. Plethysmography will cause temporary and completely reversible numbness and discomfort in both hands due to inflation of the wrist-cuffs. The adipose tissue biopsy is preceded by infiltration with local anaesthetics, but may induce a hematoma. The subjects will not benefit from participating in this study. A subject fee is to be provided.

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

At least 18 and not older than 70 years of age on the day of the first dosing.
Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
Metabolic syndrome defined by at least three out of five criteria:
Elevated waist circumference (women >= 88, men >= 102 cm).

Elevated triglycerides or drug treatment (>= 1.7 mmol/L).
Reduced HDL-cholesterol or drug treatment (women < 1.3 mmol/L, men < 1.0 mmol/L).
Elevated blood pressure (systolic >= 130 mm Hg and/or diastolic >= 85 mm Hg)
Elevated fasting glucose (>= 6.1 mmol/L)

Exclusion criteria

History of smoking within the past year.
History of or current abuse of drugs, alcohol or solvents.
Known diabetes mellitus
Repeated systolic blood pressure >= 180 mm Hg in all subjects, >= 160 mm Hg in women >= 65 yrs old and >= 140 mm Hg in men >= 65 yrs old
Fasting plasma glucose > 7.0 mmol/L or HbA1c > 6.2%
Pregnancy or breast feeding (contraception for at least 3 months before inclusion is required for fertile women)
Current use of antihypertensive, cardiac or other vasoactive medication
Current use of acetylsalicylic acid and/or statin
Use of antioxidant vitamin supplements
Clinical evidence of cardiac or pulmonary disease
Laboratory evidence of renal or hepatic abnormalities, defined as results exceeding twice the upper limit of normal range.
Unconjugated hyperbilirubinemia (total bilirubin level > 10 µmol/L and a normal direct bilirubin level) suggesting the Gilbert Syndrome.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-09-2010

Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	L-arginine
Generic name:	L-arginine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Normosang
Generic name:	heme arginate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-07-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2010
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	EUCTR2010-020875-22-NL
CCMO	NL32656.091.10