The effect of rosiglitazone on ischemia-reperfusion-injury using annexin A5 scintigraphy.
A double blind placebo- controlled cross-over study in subjects with the metabolic syndrome

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To estimate the effect of rosiglitazone compared to placebo on ischemia-reperfusion injury as assessed by annexin A5 scintigraphy in the human forearm in subjects with the metabolic syndrome.

Ethical review	Approved WMO
Status	Pending
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON30227

Source
ToetsingOnline

Brief title
Rosiglitazone and ischemia-reperfusion-injury in humans

Condition

- Myocardial disorders
- Diabetic complications

Synonym
insulin resistance syndrome, Metabolic syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Annexin A5 scintigraphy, human, ischemia-reperfusion injury, rosiglitazone

Outcome measures

Primary outcome

Annexin targeting in the thenar muscle after ischemic exercise. The primary

analysis is the difference in annexin targeting following 8 weeks of treatment

with rosiglitazone 4 mg bd or placebo.

Secondary outcome

The effect of rosiglitazone as compared to placebo on the HOMA-index.

Study description

Background summary

Cardiovascular disease is the leading cause of death in diabetic patients due to both a high event rate and a worse outcome. A pharmacological intervention that reduces ischemia-reperfusion-injury would improve the outcome of diabetic patients after a cardiovascular event. The thiazolidinedione derivatives are peroxisome proliferator-activated receptor-γ (PPARγ) ligands that are approved for the treatment of hyperglycemia in type 2 diabetes mellitus. Animal data suggest that PPARγ ligands can protect against ischemia-reperfusion-injuryby improving insulin responsiveness. However, no human data on these beneficial effects are available. Recently, our group developed a human in vivo model to quantify ischemia-reperfusion-injury. In this model annexin A5 scintigraphy is used to visualize early and reversible cellular membrane changes that occur in the forearm skeletal muscle vascular bed after ischemic exercise. In the present study, we will use this approach to address the following hypothesis: Rosiglitazone reduces ischemia-reperfusion-injury in humans with insulin

resistance, selected by using the criteria for the metabolic syndrome.

Study objective

To estimate the effect of rosiglitazone compared to placebo on ischemia-reperfusion injury as assessed by annexin A5 scintigraphy in the human forearm in subjects with the metabolic syndrome.

Study design

This is a single-center randomized, double blind, placebo-controlled crossover study comparing 8 weeks of treatment with rosiglitazone 4mg bd and placebo bd. In between the treatment periods there is a washout period of 6 weeks.

Intervention

Every subject uses during 8 weeks rosiglitazone 4 mg bd and placebo bd. Week 8 and 22: assessment of ischemic-reperfusion injury with Technetium Annexin A5 Scintigraphy. Ischemic intervention: 10 minutes ischemia of the non-dominant arm with at the same time rhythmic contractions of the forearm and hand muscles.

Study burden and risks

Drug intervention: Rosiglitazone 4 mg bd and placebo bd both during 8 weeks. Ambulant clinic visits: During at maximum 30 weeks, 5 visits (screening visit 1.5 hour, other visits 45 minutes). During all these visits anamnesis, physical examination, blood measurements (fasting at screening and two other visits). Ischemic exercise protocol: In week 8 and 22. The subject has to come to the hospital after an overnight fast and refrain of using caffeine for the last 24 hours. During this day one venous catheter will be inserted. Then ischemia will be applied to the non-dominant forearm of the subject for 10 minutes, while the subject is asked to do hand gripping with half maximum strength. Directly following this ischemic exercise, the Annexin will be injected. After having made a scintigraphic picture 4 hours later the subject may go home. Blood drawing: During the whole study protocol 131 ml of blood will be drawn. Risks: Rosiglitazone has been used worldwide for several years already and does not seem to induce severe adverse events in a high frequency, especially not when used in subjects without diabetes and exogenous use of insulin. Adverse events most frequently reported are weight increase and fluid retention. Theoretically, Annexin could induce an allergic reaction, but this was not described before. The amount of radioactivity is within the range that is allowed for use in volunteers.

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

1). At least 3 features of the metabolic syndrome (AHA/NHLBI) (10)
2). Willing and able to provide a signed and dated written informed consent.
3). Male and postmenopausal female subjects aged between 20 and 70 years

Exclusion criteria

1). Fasting glucose > 7,0 mmol/L or the use of hypoglycaemic agents. If fasting plasma glucose is between 6.1 and 7,0 mmol/L,an oral 75 g glucose test will be performed to exclude diabetes mellitus.
2). Exposure to a PPAR-g agonist during the last 4 months or a documented significant hypersensitivity to a PPAR-g agonist.

3). Participant in another study.
4). Angina or heart failure (NYHA I-IV).
5). Clinically significant liver disease (3 times the upper normal limit of ALAT, ASAT, AF, γGT or LDH)
6). Clinically significant anaemia (male Hb < 6,9 mmol/L, female < 6,25 mmol/L)
7). Creatinin clearance < 40 mL/min
8). Alcohol or drug abuse.
9). Any physical inability to perform the exercise protocol.
10). Administration of any radiotracer for research purposes during the previous 5 years.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-12-2006
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avandia
Generic name:	Rosiglitazone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-12-2006
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	EUCTR2006-006208-13-NL
ClinicalTrials.gov	NCT00405015
CCMO	NL15030.091.06