Insulin-induced microvascular activity in patients with essential hypertension: a possible role for angiotensin II AT1-receptor blockers-Amendement 26-03-2008.

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Main study:1. Does blockade of the angiotensin II AT1-receptor improve the insulin-induced microvascular effects in hypertensive patients.2. Does blockade of the angiotensin II AT1-receptor impair the insulin-induced mi-crovascular effects in...

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

Summary

ID

NL-OMON31747

Source
ToetsingOnline

Brief title
AT1-receptor blockade in insulin-induced dilation-Amendement 26-03-08

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Vascular hypertensive disorders

Synonym
high blood pressure, hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Amendement:, Angiotensin II AT1-receptor blockade, Angiotensin II receptor blocker, Hypertension, Insulin resistance, Main study:, Microcirculation

Outcome measures

Primary outcome

Main Study:

- functional recruitment of capillaries in the skin.

Amendement:

- the angiotensin II AT1-recptor blockade with a single oral dose of 600mg

irbesartan.

Secondary outcome

Main Study:

- perfused capillary density in the nailfold.

- Endothelium- (in)dependent vasodilatation of finger skin microcirculation

- Density of arterioloes, capillaries and venules in the bulbar conjunctiva.

- Diameter of arterioles and venules in the bulbar conjunctiva.

Amendement:

- Time-course of angiotensin II AT1-recptor blockade after 600 mg irbesartan

- plasma angiotensin II and active plasma renin concentrations (APRC)

- Blood pressure drop after intake irbesartan (600mg) and felodipien ER (20mg)

Study description

Background summary

Title: Insulin-induced microvascular activity in patients with essential hypertension: a possible role for angiotensin II AT1-receptor blockers.

There is a relation between hypertension and insulin resistance, both associated with increased cardiovascular risk. Hypertension and insulin resistance are characterized by dysfunctions in microcirculation, however it is unclear if microcirculation is the link between these two abnormalities. In addition to its actions in mediating glucose uptake, insulin knows several vascular effects. Insulin induces a vasodilatory response by resis-tance vessels and preterminal arterioles leading to an overall increase in blood flow (glucose) to the muscles.
The local activity of the vasoconstrictor angiotensin II is elevated in patients with hypertension. Previous studies show a possible role for angiotensin II in the hypertensive, insulin resistant phenotype, however a mechanism remains unexplained. In this study we hypothesize that blocking the angiotensin II AT1-receptor improves the insulin-induced microvascular dilatation.

Study objective

Main study:
1. Does blockade of the angiotensin II AT1-receptor improve the insulin-induced microvascular effects in hypertensive patients.
2. Does blockade of the angiotensin II AT1-receptor impair the insulin-induced mi-crovascular effects in normotensive control subjects?

Amendement:
The objective of the amendement is to test the angiotensin II AT1-recptor blockade with a single oral dose of 600mg irbesartan. Furtheremore, we would likte to investigate the time-course of this blockade and we would like to examine if the blood presure drop with this dose of irbesartan is similar to the blood pressure drop achieved with the ingestion of a single dose of Felodipien ER (20mg).

Study design

Main study:
All subjects will bring 3 visits to the AZM. The following interventions will

be applied:
- hyperinsulinemic euglycemic clamp (HEC) + placebo
- HEC + irbesartan (600 mg)
- HEC + felodipine ER (20 mg)

During all visits 2 catheters will be inserted in the antecubital vein of the lower arms. On one study day (randomly assigned)
a set of microcirculation measurements will be performed on t=-90 minutes. On all three study days insulin and glucose will be infused on t=0 min. After 90 minutes of HEC a set microcirculation measurements will be done, and after these measurements placebo, irbesartan or felodipine will be taken in a single oral dose. 210 minutes after intake (t=300 min.) another set of microcirculation measurements will be done. During the study days the heart rate and blood pressure will be monitored and blood samples will be taken. The interventions will be randomly assigned. One week is scheduled between each visit.

Amendement:
All subjects will bring two visits to the AZM.
On the study day with intake of irbesartan the measure and time-course of angiotensin II AT1-receptor blockade will be measured. Two catheters will be inserted in the antecubital vein of the lower arms (Venflon; B-D, Helingborg, Zweden). Three bloodsamples of 5 ml will be taken to measure basal subject characteristics, the plasma angiotensin II and active plasma renin concentrations (APRC). After 30 minutes, blood presure and heart rate will be measured. Next, the dose response-curve to Angiotensin II will be measured. Angiotensin II will be infused intravenously in increasing dose steps (angiotensin II is previously incjected intravenously in MEC 06-2-074). Next, irbesartan will be ingested in a single oral dose of 600 mg. 120 and 180 minutes after ingestion the dose-response curves to Angiotensin II will be measured again. Blood pressure and heart rate will be measured 30, 60, 90, 120, 150 and 180 minutes after intake of irbesartan. 60, 120 and 180 minutes after intake 2 bloodsamples of 5 ml will be taken from the katheter in the dominant arm. The total amount of blood taken is 45 ml. This studyday will take approximaltely 4,5 hours.

On the studyday with intake of felodipine blood pressure and heart rate will be measured on the same timepoints as in the studyday with irbesartan (before the intake of felodipine and 30, 60, 90, 120, 150, and 180 min. after intake). No dose-response curves will be measured. This study day will take approx. 4 hours.

At least 24 hours will be scheduled these two study days. The intake of irbesartan and felodipine will be randomised. All subjects fasted from 10pm the night before each study day.

Intervention

Main study:
Hypertensive subjects will be asked to discontinue the intake of antihypertensive medi-cation three weeks before the start of the study. All subjects will be asked to start a low salt diet (100mmol/day) 7 days prior to the first study day and to collect urine during 24hrs prior to the first study day. Microcirculation measurements: 1) perfused capillary density and functional capillary recruitment in the nailfold, visualized by a capillary mi-croscope, 2) endothelium- (in)dependent vasodilation of finger skin microcirculation, evaluated with laser Doppler measurements in combination with iontophoresis of acetylcholine and sodium nitroprusside, and 3) densities and diameter of arterioles, capillaries and venules in the bulbar conjunctiva, measured with conjunctival microscopy. Placebo, irbesartan (600mg) and felodipine (20mg) will be ingested orally in a single dose. Insulin is infused in a primed continuous manner at a rate of 50mU·kg-1·hr-1. Euglycemia will be maintained by adjusting the rate of a 20% D-glucose infusion based on plasma glucose measurements performed at 5 min intervals. During the visit several blood samples will be taken, blood pressure and heart rate will be monitored.

Amendement:
Angiotensin II will be intravenously infused to measure the dose-response curve. During a study day 45 ml of blood will be taken (sampled at 4 timepoints in the day). Blood pressure and heart rate will be monitored. Irbesartan (600mg) and felodipine ER (20mg) will be taken orally. All subjects will be asked to start a low salt diet (100mmol/day) 7 days prior to the first study day and to collect urine during 24hrs prior to the first study day.

Study burden and risks

Main Study:
No risks are involved in discontinuing the medication of the hypertensive subjects. All methods used for measuring microcirculation are non-invasive. The burden of these measurements is therefore negligible. Inserting the catheters can be a little bit painful and after removal sometimes bruises can appear. There is a small chance (<1.0%) hypoglycemia will occur during the infusion of insulin and glucose. This can feel slightly unpleasant for the subject, however hypoglycemia is not harmful. Irbesartan and felodipine will be taken orally in a single dose. The dosages are not toxic and the expected reduction in blood pressure will not induce problems concerning hypotension. Due to the intake of a single dose of irbesartan and felodipine there is only a very small chance for side effects to occur. The used dose of acetylcholine and sodium nitroprusside is very low and appeared to have side effects only in very rare cases (for example during an allergic reaction). The effect is only local in the skin an whenever a side effect will occur, the study will be immediately stopped. There will be taken

84 ml of blood during one study day. No burden or risk is involved with this amount. De subject will be sober during the whole study day. Previous studies showed that this isn't a big burden for a subject.

Amendement:
Inserting the catheters can be a little bit painful and after removal sometimes bruises can appear. There are no expected risks involved to the infusion of Angiotnsin II, the blood pressure will be monitored continuously. Irbesartan and felodipine will be taken orally in a single dose. The dosages are not toxic and the expected reduction in blood pressure will not induce problems concerning hypotension. Due to the intake of a single dose of irbesartan and felodipine there is only a very small chance for side effects to occur. There will be taken 40 ml of blood during one study day. No burden or risk is involved with this amount. De subject will be sober during the whole study day. Previous studies showed that this isn't a big burden for a subject.

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

Main study:
Inclusion criteria hypertensive subjects: 18-60 years, Caucasian, untreated hypertension>140/90mmHg.
Inclusion criteria normotensive subjects : 18-60 years, Caucasian, blood pressure <140/90 mmHg.;Amendement:
18-60 years, Caucasian, blood pressure <140/90 mmHg.

Exclusion criteria

Obesity (BMI>27kg/m2), cardiovascular disease (stroke, coronary artery disease, peripheral vascular disease, heart failure), impaired glucose tolerance or diabetes mellitus according to the criteria of the ADA, smoking, alcohol use >4U/day, use of medication (antihypertensive drugs, lipid lowering drugs, corticosteroids, NNSAIDs), and pregnancy.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-03-2008
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Actrapid Penfill 100IE/ml
Generic name:	Human insulin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Aprovel
Generic name:	Irbesartan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Miochol E
Generic name:	Acetylcholine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Plendil
Generic name:	Felodipine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sodium Nitroprusside
Generic name:	Sodium Nitroprusside
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-01-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-02-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	16-04-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2007-007654-57-NL
ClinicalTrials.gov	NCTTC-1202
CCMO	NL21113.068.07