Cardiovascular effects of apelin infusion in healthy male subjects

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39109

Source
ToetsingOnline

Brief title
Cardiovascular effects of apelin infusion

Condition

- Other condition

Synonym
heart- and bloodvessel diseases

Health condition

cardiovasculaire ziekten

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: apelin, cardiovascular effects

Outcome measures

Primary outcome

Pharmacodynamics: hemodynamic assessments, cardiac index, ATII pressor test, NE pressor test and Glomerular Filtration Rate (GFR)

Pharmacokinetics: plasma apelin and iohexol concentrations, pharmacokinetic parameters

Safety: adverse events, vital signs, ECG-parameters, laboratory parameters, physical examination

Secondary outcome

n/a

Study description

Background summary

Apelin is a protein that is made in the blood vessels of many parts of the body. Apelin increases the contraction of the heart, lowers blood pressure, and promotes the formation of new blood vessels. Apelin is not registered as a drug but has been given to humans before.

Study objective

The purpose of the study is to compare the hemodynamic effects (study of blood flow or circulation, such as blood pressure, heart rate, cardiac output (the volume of blood being pumped by the heart) and glomerular filtration rate (flow rate of filtered fluid through the kidney) of apelin to those of the registered

sodium nitroprusside (SNP; a drug that is used to lower blood pressure in people with severe hypertension) and control (placebo).
This study is not intended to improve the health of the subjects, but may help the further development of apelin. Furthermore, this study is being conducted to see if medications that are similar to apelin may be useful in people with heart or blood vessel diseases.

Study design

This is a six-period infusion study in fifteen healthy male subjects. In periods 1 and 2 the optimal dose, safety, and tolerability of apelin (APL) and sodium nitroprusside (SNP) infusions will be assessed.

Procedures and assessments:

Screening and follow-up: clinical laboratory, vital signs, weight, physical examination, ECG
At eligibility screening: medical history, height, drug screen, HBsAg, anti HCV, anti-HIV 1/2;
Drug screen to be repeated upon first admission

Observation period: 2 periods, first period in clinic from -17 h up to 24 h after start of APL infusion on Day 1 up to 4 h after start of APL infusion on Day 2 and second period in clinic from Day 8 for start of sodium stabilization up to 4 h after start of APL/SNP/placebo infusion on Day 12

Blood sampling:
For pharmacokinetics of APL in plasma: 5 minutes prior to the start of infusion on Day 1 of period 1, and 25, 55, 90, 95, 105 and 115 minutes after the start of infusion on Day 1 of period 1
5 minutes prior to the start of infusion on Day 2 of period 1, and 5, 10, 15, 25, 55, 115, 175, 235, 245, 255 and 270 minutes after the start of infusion on Day 2 of period 1
5 min prior to start of infusion in period 2, and 25, 55, 120, 180 and 240 minutes after the start of infusion in period 2
5 minutes prior to the start of infusion on Day 1 of period 7, and 5, 10, 15, 25, 55, 115, 175, 235, 245, 255 and 270 minutes after the start of infusion on Day 1 of period 3 (period 7 study protocol)

For pharmacokinetics of iohexol in plasma: 5 min prior to start of infusion in period 2, and 25, 55, 120, 180, 240 and 265 minutes after the start of infusion in period 2

Hemodynamic Assessments:
Upright blood pressure, heart rate and cardiac output: 5 minutes prior to the start of APL and SNP infusion on Day 1 of period 1, and 25, 55, 85 and 115 minutes after the start of APL and SNP infusion on Day 1 of period 1, and 5

minutes prior to the start of APL infusion on Day 2 of period 1, and 25, 145, 270 and 300 minutes after the start of APL infusion on Day 2 of period 1, and 5 minutes prior to the start of APL, SNP and placebo infusion in period 2, and 25, 145, 270 and 300 minutes after the start of APL, SNP and placebo infusion in period 2.
Supine blood pressure, heart rate and cardiac output: 55, 85, 115, 175, 210 and 235 minutes after the start of APL, SNP and placebo infusion in period 1 and 2.

ATII pressor test: 60 and 90 minutes after start of APL, SNP and placebo infusion in period 2

NE pressor test: 180 and 210 minutes after start of APL, SNP and placebo infusion in period 2

Glomerular Filtration Rate (GFR): 30 minutes prior to start of APL, SNP and placebo infusion in period 2

Safety assessments: adverse events and concomitant medications: throughout the study; ECG: 15 minutes prior to and 115 minutes after the start of APL infusion on Day 1 of period 1, and 15 minutes prior to and 300 minutes after the start of APL infusion on Day 2 of period 1.

Intervention

In the first period the subjects will receive 3 different infusions:
- Apelin will be administrated by infusion at 3 dose levels (0.3, 3.0 and 30 nmol/min) for 30 minutes each.
- SNP will be administrated by infusion at 3 dose levels (0.25, 0.625 and 1.5 ug/kg/min) for 30 minutes each.
- Apelin will be administrated by infusion at the maximum dose level for 4 hours.

In the second period the subjects will receive apelin, SNP and placebo infusions for 4 hours in a randomized (by chance) sequence.

In the third period (period 7 study protocol) the volunteers will receive a 4 hour infusion of apelin.

Study burden and risks

Registration of adverse effects: During the entire investigation all adverse effects will be documented.

Blood draw, indwelling cannula: During this study less than 500 ml of blood will be drawn. It is anticipated that for the blood draws at Day 1 and 2 of each period an indwelling cannula will be used as there are several blood

samples taken over these days. On the other days blood will be drawn by direct puncture of the vein.

IV dosing: For the iv administration an indwelling cannula will be inserted specifically for this purpose in addition to the indwelling cannula used for blood sampling.

Heart trace (ECG*s): ECG*s will be made regularly.

Systolic and diastolic blood pressure, and heart rate: Systolic and diastolic blood pressure and heart rate will be recorded twice over approximately 2 minutes at several time points during the study. Thereafter blood pressure and heart rate will be measured in upright position after 3 and 5 minutes.

Cardiac output: Electrodes will be placed on the chest to measure the volume of blood being pumped by the heart. This will be measured noninvasive with the Physioflow at many time points during each infusion.

Angiotensin II Pressor Test: Blood pressure and heart rate will be recorded twice over 2 minutes during the infusion of 2 and 6 ng/kg/min of intravenous angiotensin II (AT II), a naturally occurring hormone that increases blood pressure. Each dose will be infused for approximately 30 minutes in supine position. This test will be performed to study the effect of apelin on AT II-induced contraction of the blood vessels.

Noradrenaline Pressor Test: Blood pressure and heart rate will be recorded twice over 2 minutes during the infusion of 0.03 and 0.1 ug/kg/min of intravenous noradrenaline (NE), a naturally occurring hormone that increases blood pressure. Each dose will be infused for approximately 30 minutes each in supine position. This test will be performed to study the effect of apelin on noradrenaline-induced contraction of the blood vessels.

Glomerular filtration rate: Intravenous iohexol (an indicator of the blood flow in the kidney) will be administrated prior to the start of apelin infusion to calculate the flow rate of filtered fluid through the kidney. Blood samples to measure iohexol will be taken at several time points during the infusions.

Contacts

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Scientific
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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 subjects
18-55 yrs, inclusive
BMI: 18.5-30.0 kg/m2, inclusive
non-smoking or less than 10 cigarettes/day

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-07-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Apelin
Generic name:	(Pyr,1)-apelin-13
Product type:	Medicine
Brand name:	Nitroprusside Natrium
Generic name:	n/a

Ethics review

Approved WMO Date:	27-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	30-01-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012□001919□22-NL
CCMO	NL41086.056.12