Effects of Sildenafil on pulmonary artery pressure in patients with heart failure with preserved ejection fraction and pulmonary hypertension

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Primary objectiveTo investigate wether Sildenafil treatment results in a reduction of pulmonary artery pressure without decrease of cardiac output in HFpEF patients with PHSecondary objectivesTo investigate wether Sildenafil treatment results in a...

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

Summary

ID

NL-OMON38270

Source
ToetsingOnline

Brief title
Sildenafil in HFpEF and PH

Condition

- Heart failures

Synonym
disturbed relaxation of the heart, heart failure with preserved ejection fraction

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: diastolic heart failure, heart failure with preserved ejection fraction, pulmonary hypertension, sildenafil

Outcome measures

Primary outcome

Reduction of pulmonary artery pressure (PAP) without decrease of cardiac

output.

Secondary outcome

reduction of wedge pressure

improvement of VO2max

Study description

Background summary

Isolated diastolic left heart failure, also called heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome with severe symptoms and high mortality. It counts for 40-60% of all patients with left heart failure. Nevertheless the level of evidence for medical treatment regiments is low compared to systolic left heart failure. Systolic left heart failure and also HFpEF can be associated with pulmonary hypertension (PH), and then belong to group 3 (PH due to left heart disease) of the current clinical classification of pulmonary hypertension from Dana point 2008. More recent studies suggest that PH is even more common in HFpEF than in systolic heart failure. The presence of PH in both conditions is associated with increased mortality .
The PDE/5 inhibitor Sildenafil , on the market as specific PAH medication targeting the pulmonary vascular tone is promising as new treatment option for this specific condition of HFpEF and PH . Next to dilation and antiproliferative impact on de pulmonary vascular system in PAH it also has potential favorable effects on the myocardium that may block adrenergic hypertrophic and proapoptotic signaling. For that reason Sildenfil might have an ideal profile for treatment of HFpEF and PH.
With the presented study we want to investigate the hemodynamic and clinical impact of Sildenafil in patients with HFpEF as an important step to possibly

establishing the first medical therapy for HFpEF and PH (see also page 4/5 of the protocol)

Study objective

Primary objective
To investigate wether Sildenafil treatment results in a reduction of pulmonary artery pressure without decrease of cardiac output in HFpEF patients with PH

Secondary objectives
To investigate wether Sildenafil treatment results in a reduction of wedge pressure in HFpEF patients with PH.
To investigate wether Sildenafil treatment results in improvement of exercise capacity in these patients (defined as change in VO2max).

Study design

multicenter, prospective, randomized, placebo controled study.
Recruitment in 2010 and inclusion continues until 52 patients have been randomized.

Intervention

Oral treatment with Sildenafil at initial dose of 20 mg 3 times daily, after 2 weeks increase dose to 60 mg 3 times daily. Administration period: 12 weeks. Changes of co-medication in this period only if heavily indicated (for instance cardial decompensation) and must be documented.

Study entry at the moment of right heart catheterisation evaluating the reason of pulmonary hypertension. When right heart catheterisation documents PH secondary th left heart failure and echocardiography or MUGA a systolic LV function with a left ventricular ejection fraction (LVEF) more than 45% patient can be asked for inclusion.

Study burden and risks

First burden of the study is that the patients will get oral treatment with Sildenafil at a maximum dosis of 3 times 60 mg. Sildenafil is already registered for two indications (PAH and erectile dysfunction) and it could be documented that the drug can be used safely. Side effects are scarce and mostly mild. Most important side effect is possible reduction of the artery pressure . Therefore the dose is increased gradually in the study and patients with hypotension are excluded. Also described interaction with other medication (for instance nitrates) is taken into consideration in de exclusion criteria.
Second burden of the study is one extra right heart catheterisation after 12 weeks of treatment with Sildenafil of placebo. Furthermore the patient has to

fill in two quality of life questionnaires. All other examinations are part of standard diagnostics for this condition.
A right heart catheterisation is a invasive examinanation with a puncture of the femoral vein. An arterial punctur is not neccessary. The right heart catheterisation has a low risk (1%) of bleeding in the groin where the vena femoralis has been punctured, a very low risk of infection and a very low risk of damage of cardiovascular structures by leading the swan ganz catheter to the pulmonay artery(<0.1%) For the right heart catheterisation the patient has to be admitted on the short stay ward for about 6 hours.
As the study population suffers from a disease with high mortality and mobidity with up to now no evidence based treatment options the possible benefit of th investigated treatment will strongly overweight the small risks of a right heart catheterisation and the time the patient would have to spend to come for a short stay in the hospital (6 hours).

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

PH secondary to HFpEF defined as mean PAP larger 25 mmHg, wedge larger 15, LVEF larger 45
NYHA II-IV

Exclusion criteria

other cause of PH
severe noncardiac limitation to exercise
coronary ischemia or recent myocardial infarction (<6 months)
hypotension , RR< 90/50
ongoing nitrate therapy
significant left sided valve disease
severe liver dysfunction
pregnancy
unable to read and comprehend Dutch language

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Health services research

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	27-10-2011
Enrollment:	52
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Revatio
Generic name:	Sildenafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2010-020153-14-NL
CCMO	NL32212.042.10