Randomized, double blind, placebo-controlled trial of ubiquinol in a statin-induced mitochondrial dysfunction model in healthy volunteers.

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Primary Objectives-To evaluate if mitochondrial dysfunction can be induced in healthy, middle aged subjects, through the use of simvastatin, and whether it can be reversed by oral ubiquinol supplementation. -To validate the techniques NIRS, PpIX-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON41941

Source
ToetsingOnline

Brief title
Ubiquinol in statin-induced mitochondrial dysfunction

Condition

- Other condition

Synonym
energy metabolism defects, mitochondrial respiratory chain defects

Health condition

mitochondrial dysfunction

Research involving

Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR Foundation

Intervention

Keyword: 31P-MRS, mitochondrial dysfunction, statin, ubiquinol

Outcome measures

Primary outcome

-PCr recovery time (in seconds) 8 weeks after the start of simvastatin

administration.

-PCr recovery time (in seconds) after 4 weeks of simvastatin administration.

Secondary outcome

-mVO2 (in ml/min/100 ml) measured by NIRS.

-mitoPO2 (in mmHg) measured by PpIX-TSLT.

-MMP in WBCs (in ratio of aggregated and monomeric JC-1) measured by the JC-1

assay.

-Serum FGF-21 concentration (in pg/ml).

-Hand grip strength (in kg) measured by the Jamar dynamometer and the pinch

gauge.

-hand grip strength (in kg) measured by the POWERjar©.

-Serum creatine kinase concentration.

Study description

Background summary

Age related diseases pose a burden for both the elderly and society as a whole. In recent years, evidence has shown that dysfunction of mitochondria plays an important role in age related diseases, such as Alzheimer*s Disease, diabetes mellitus type 2 and sarcopenia. The mitochondrion is therefore becoming increasingly important as a drug target. As mitochondrial function is already optimal in healthy subjects, there is no way to show drug induced enhancement of mitochondrial function early in clinical drug development other than using patients with a mitochondrial disease. There are, however, many disadvantages of doing early phase drug studies in patients with a rare disease. In this study we aim to set up and validate a model for statin-induced mitochondrial dysfunction in healthy subjects, which can be used to evaluate the pharmacological effects of drugs that potentially enhance mitochondrial function.

Prolonged administration of statins to middle aged, otherwise healthy subjects has previously been shown to cause reversible mitochondrial dysfunction, which is thought to be mainly due to a depletion of coenzyme Q10, an electron carrier in complex I of the electron transport chain. Concurrent replenishment of Q10, in the form of ubiquinol, during statin therapy is therefore expected to reverse the statin-induced mitochondrial dysfunction. It has been successfully demonstrated using dynamic 31P-MRS, that statins can induce a slight, yet not clinically relevant, mitochondrial dysfunction. Treatment with statins for a period of 4 weeks led to a prolongation of the phosphocreatine (PCr) recovery time after muscle exertion induced PCr depletion using MR spectroscopy of the muscle. However, whether oral Q10 supplementation can successfully reverse the statin-induced prolongation in PCr recovery time has not yet been demonstrated. It is considered essential to establish this prior to the use of statin-induced mitochondrial dysfunction in healthy subjects as a model that can be applied in early phase clinical drug development.

In conjunction, four techniques to measure mitochondrial function will be compared in this study: near infrared spectroscopy (NIRS, a cheap, non-invasive and portable method to measure mitochondrial function via muscle oxygen consumption (mVO2)), Protoporphyrin IX - Triplet State Lifetime Technique (PpIX-TSLT, a novel method to locally measure mitochondrial function through the skin) and the mitochondrial membrane potential (MMP) in white blood cells (WBCs). These new techniques will be validated against dynamic phosphorous Magnetic Resonance Spectroscopy (31P-MRS). Dynamic 31P-MRS is an established method to measure mitochondrial function and can be considered to be the gold standard for in vivo mitochondrial function measurement. The PpIX-TSLT method can potentially be used in low dose toxicology studies and the MMP in WBCs for ex vivo dose response studies.

Hand muscle strength measurements, using the Jamar dynamometer and pinch gauge (both validated methods widely used in the clinical setting), will be performed to measure muscular strength and to determine whether a decrease in mitochondrial function is associated with a decline in muscle strength. These hand strength measurements will be compared to the POWERjar©, a novel method to measure hand strength by opening a jar-like device. This hand strength measurement is expected to correlate better with ADL functioning.

A rise in serum creatine kinase (CK) can result from statin use, which is hypothesized to be due to muscle damage caused by mitochondrial dysfunction of muscle cells. Therefore, serum CK measurements will be used as a safety outcome variable.
Fibroblast growth factor 21 (FGF-21) in plasma has recently been shown to correlate with mitochondrial disease as a biomarker. We hypothesise that it yields potential as a plasma biomarker for mitochondrial dysfunction as a whole.
In the current study healthy subjects will use statins for 8 weeks to induce mild mitochondrial dysfunction. After mild mitochondrial dysfunction has been established, i.e. after a 4 week open-label treatment with simvastatin, subjects will be randomized to receive either ubiquinol or placebo in a double blind fashion. The three additional techniques that are used to quantify mitochondrial dysfunction are non-invasive, cheaper to use, and less burdensome for subjects than dynamic 31P-MRS. These techniques will be used in parallel for comparison and validation to gold standard dynamic 31P-MRS. Healthy subjects will be included to keep the variability as low as possible.

Study objective

Primary Objectives
-To evaluate if mitochondrial dysfunction can be induced in healthy, middle aged subjects, through the use of simvastatin, and whether it can be reversed by oral ubiquinol supplementation.
-To validate the techniques NIRS, PpIX-TSLT and MMP in WBCs to measure mitochondrial function and compare to dynamic 31P-MRS of the muscle in the statin-induced mitochondrial dysfunction model.

Secondary Objectives
-To determine the safety of the statin-induced mitochondrial dysfunction model in healthy, middle aged subjects.
-To determine the correlation between various states of mitochondrial function and serum CK concentration.
-To determine the correlation between various states of mitochondrial function and serum FGF-21 concentration.
-To determine the correlation between mitochondrial function and muscle strength using the hand grip strength test (Jamar dynamometer) and pinch strength test (pinch gauge).
-To determine the correlation in hand strength between Jamar dynamometry test and pinch gauge test and the POWERjar© test.

Study design

The study consists of a screening (maximal 28 days before start of study period), a statin part of 8 weeks, in which the subject will be asked to self-administer simvastatin 40 mg orally once daily and an ubiquinol or placebo

part of 4 weeks, in which the subject will be asked to take solubilised ubiquinol (Q10) 300 mg orally once daily or placebo orally once daily in parallel to the statins. The ubiquinol or placebo part starts after 4 weeks of simvastatin administration. Measurements (dynamic 31P-MRS, NIRS, PpIX-TSLT and MMP) and blood sampling (mitochondrial function biomarker) will be done 4 times in a period of 8 weeks: once before the start of the statin part (baseline), once after 2 weeks of statin administration, once before the ubiquinol or placebo part (baseline ubiquinol) and after the both parts (end of study). One follow-up telephone call is scheduled no longer than 10 days after the last occasion.

Study burden and risks

Simvastatin is a registered drug, which is widely used in the clinic as cholesterol lowering drug. The safety profile of this compound is well known. The risk of myopathy/rhabdomyolysis of daily administration of simvastatin 40 mg is 0,08% and simvastatin 80 mg is 0.61%. However, to induce mild mitochondrial dysfunction the dose of simvastatin needs to be high enough. The risk of taking ubiquinol 300 mg is excpected to be minimal. The use of the 5-aminolevulinic acid patch is needed to validate the PpIX-TSLT and local adverse events in the skin are reported. The most common side effects (seen in more than 1 patient in 10) are reactions at the site of application, including irritation, erythema (reddening of the skin), pain, pruritus (itching), oedema (swelling), exfoliation (skin peeling), scab formation and induration (hardening of the skin) The benefit of this measurement is the later use as a cheap and non-invasive device to measure mitochondrial function. The main benefit is to find a model for mitochondrial dysfunction in healthy volunteers, so that early drug research does not hasve to be performed in patients with mitochondrial dysfunction and to validate cheap and non-invasive to do this. There is no direct benefit in participating for the subject, but there might be a beneficial effect on the cardiovascular system due to simvastatin.

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. Signed informed consent prior to any study-mandated procedure.;2. Males or females aged 40-70 years (inclusive).;3. BMI between: 18-32 kg/m2, minimal weight 50 kg.;4. Expected compliance to the protocol especially with respect to administering simvastatin 40 mg orally once daily for 56 days and ubiquinol 300 mg orally once daily for 28 days.;5. Having a normal day and night rhythm.

Exclusion criteria

1. Clinically relevant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, rheumatic/joint, psychiatric, renal, and/or other major disease.;2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In case of uncertain or questionable results, tests performed during screening may be repeated before the first occasion to confirm eligibility or judged to be clinically irrelevant.;3. Creatine Kinase (CK) > 145 U/L (females) or > 170 U/L (males) in laboratory test results.;4. Presence of any contraindication to have MRI scans performed (e.g. pacemaker, intracranial clips etc.).;5. Having diabetes mellitus or lower extremity peripheral vascular disease, as these conditions may interfere with interpretation of the dynamic 31P-MRS and NIRS of the lower extremity.;6. Recent (within 14 days) or current use of interfering medications: paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), statins and gluco- and/or mineralocorticoid drugs with exception of contraceptives. Usage of other medications will have to be reviewed for interference with the study by the study physician.;7. Participation in a clinical trial within 90 days of screening or more than 4 times in the previous year.;8. Positive test for drugs of

abuse at screening or pre-dose.;9. If female, pregnancy (defined as a positive bHCG urine test) or breast-feeding.;10. A history (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol). ;11. History or symptoms of any significant disease including (but not limited to) neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.;12. History or symptoms of any myopathy.;13. A history or presence of porphyria or any other skin disease that is caused by exposure to light. ;14. A history or presence of allergy to 5-aminolevulinic acid or porphyrins.;15. Positive hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.;16. Donation of blood or loss of over 500 mL within 3 months prior to screening.;17. Unwillingness or inability to refrain from consuming aldosterone increasing food or supplements during the study period: bananas, liquorice, glucosamine and palm oil. ;18. Unwillingness or inability to refrain from consuming grapefruit or grapefruit juice.;19. Unwillingness or inability to refrain from consuming alcohol within 48 hours before each visit until the end of that visit.;20. Unwillingness or inability to refrain from tobacco usage within 12 hours before each visit until the end of that visit.;21. Unwillingness or inability to refrain from moderate to strenuous physical activity (e.g. fitness classes, weight lifting, marathon-running etc.) from the screening until the last study visit. ;22. Having a type of lifestyle with no physical activity.;23. Unwillingness or inability to refrain from consuming xanthine containing beverages and foods within 12 hours before each visit and during the study visits.;24. Unwillingness or inability to use contraception if female with child bearing potential.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-08-2014
Enrollment:	28

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALACARE
Generic name:	5-aminolevulinic acid
Product type:	Medicine
Brand name:	simvastatin
Generic name:	simvastatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-04-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-07-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2014-001289-91-NL
CCMO	NL48758.058.14