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Allopurinol as a possible oxygen sparing agent during exercise in peripheral arterial disease

Submission date
02/09/2010

Recruitment status
No longer recruiting

Registration date
25/10/2010

Overall study status
Completed

Last Edited
24/03/2016

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Peripheral arterial disease refers to narrowing in the arteries supplying blood to the limbs. It is most commonly experienced by patients as a cramping pain in the legs that comes on whilst walking and rapidly settles when resting. Blood carries oxygen round the body and because of the narrowings in the arteries this means that that the leg muscles do not get as much oxygen as they need, causing the cramping pain. It has recently been found that a medication called allopurinol – a safe drug that has been used to treat gout for many years – has helped with another condition where oxygen demand outstrips oxygen supply, namely angina. Our theory is that this same medication may also help patients with peripheral arterial disease, by enabling them to walk further.

Who can participate?
Men and women aged 35-85 suffering from peripheral arterial disease.

What does the study involve?
To make sure you are suitable for the study we first ask you to undertake two exercise treadmill tests a week apart to ensure that your symptoms are stable. This test involves you walking on a treadmill. We are trying to find out how far you can walk before you experience leg pain. You will also be asked to walk for six minutes along a level corridor at your own pace to assess your overall exercise ability. We'll also take some blood tests. With your agreement we would also like to store the blood samples we take for a period of 5 years so we can use it to test any new blood markers that become available in the near future. You will be randomly allocated to take either a tablet which contains the medication we are testing (called allopurinol) or an inactive tablet (called a placebo). We will then follow you up regularly, with six hospital visits over six months and several telephone calls. We will use some questionnaires to ask you questions about your normal life and also your walking ability. At three of your visits we will measure blood vessel stiffness in your arm. A blood pressure cuff will be placed below your elbow. We will then take an ultrasound measurement of the artery above the elbow (this involves placing an ultrasound probe and some jelly gently on the skin above the elbow). We will then inflate the blood pressure cuff to block the circulation to the forearm for a period of five minutes. After

five minutes we will then release the cuff and take another scan to measure the artery above the elbow. We will then repeat this process this time before and after giving you a spray of GTN under the tongue (a drug that is also used to treat angina).

What are the possible benefits and risks of participating?
You will be monitored closely during the study and will be seen by a heart specialist at each of your study visits. Besides having tests that have already been mentioned, your medication will be reviewed on a regular basis. The tests will give us information about the function of your heart, kidneys and blood circulation. If any of these investigations reveal any new abnormality we will either discuss this with your GP or refer you to a specialist clinic at Ninewells Hospital (whichever seems most appropriate). The study may not immediately benefit you, but if the results of the study are positive this may change the practice of managing patients with peripheral arterial disease like you and potentially will have a great impact on thousands or even millions of patients in the future. If so, you may gain eventually from our discovering a new treatment for your condition. Allopurinol has been used for about 50 years, mainly for the treatment of gout. It has a good safety record and is generally well tolerated. However, like most medicines, allopurinol occasionally causes side effects. The most common side effect is nausea and some abdominal discomfort which affects less than one in ten of patients on allopurinol. This can be minimised by taking the tablets with food. Allopurinol causes a skin rash in one in a hundred or less of patients. This may be associated with fever, swollen glands, joint pains, unusual blistering or bleeding. Reports of other side effects of allopurinol are very rare (less than 1 in 10,000 people) and it is not always clear if they are truly related to the treatment. These include headache, stomach upset, drowsiness and anaemia. Having blood samples taken can cause some mild bruising. The GTN spray can cause a slight headache but this usually quickly passes. When the blood pressure cuff is inflated there can be some mild discomfort that goes away quickly once it is deflated.

Where is the study run from?
Ninewells Hospital & Medical School (UK).

When is the study starting and how long is it expected to run for?
From October 2010 to August 2012.

Who is funding the study?
British Heart Foundation (UK).

Who is the main contact?
Prof Allan Struthers

Contact information

Type(s)
Scientific

Contact name
Prof Allan Struthers

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Additional identifiers

EudraCT/CTIS number
2010-020662-23

IRAS number

ClinicalTrials.gov number
NCT01147705

Secondary identifying numbers
2009CV16

Study information

Scientific Title
Allopurinol as a possible oxygen sparing agent during exercise in peripheral arterial disease: a double-blind, placebo-controlled, parallel group study

Acronym
APOSA-PAD

Study objectives
Peripheral arterial disease (PAD) is a common condition that arises due to the build up of atheroma in the arteries supplying blood to the peripheral muscles and other tissues. This imbalance between oxygen supply and demand becomes particularly apparent when patients with the condition are walking. The pain and weakness they experience (mainly in the calf but less commonly in the thigh) is known as intermittent claudication and resolves upon cessation of exercise.

It is an important disease to study as it is (i) common (est. prevalence of symptomatic intermittent claudication in Scotland of 4.5%) and (ii) those with it have a 1.6 times higher relative risk of ischaemic heart disease. These patients also have a significantly higher mortality than age-matched controls at around 12% per year.

There are two main aims of therapy -
1. To reduce the risk of cardiovascular events by way of standard secondary prevention measures (smoking cessation, anti-platelet, anti-hypertensive and cholesterol-lowering therapy, diabetic control)
2. To treat symptoms

Supervised exercise therapy has been shown to be beneficial in improving walking time and distance in selected patients with leg pain from intermittent claudication with an overall increase in walking distance of approximately 150 metres at three months.

There are numerous drug treatments available for consideration in PAD patients (mainly cilostazol in the UK), but many of these have either undesirable side effects or no clear evidence of benefit. The range of increase in walking distance on cilostazol was reported to be a 50-76% increase over three months compared to 20% with placebo with some significant improvements in Quality of Life (QOL) indicators, although with a significant number of adverse effects (16% vs 8% on placebo) limiting therapy. The current cost (March 2010) is £35.31/month.

Other options for therapy include angioplasty and bypass surgery. At present these are only recommended for patients who fail to respond to medical therapy and have severely disabling symptoms (in the absence of significant exercise-limiting comorbidities).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A Research Ethics Committee, 19/07/2010, ref: 10/MRE00/51

Study design
Single-centre double-blind placebo-controlled parallel-group study

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Peripheral arterial disease

Interventions
Allopurinol vs placebo

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Allopurinol

Primary outcome measure
The distance to onset of claudication pain at 24 weeks but we will also measure total exercise distance.

Secondary outcome measures
1. To see if allopurinol improves quality of life in participants with PAD
2. To investigate the anti-oxidant effects of allopurinol of participants with PAD

Overall study start date
01/10/2010

Completion date
01/08/2012

Eligibility

Key inclusion criteria
1. Men and women age 35-85 years suffering from PAD. PAD will be defined as:
1.1. Claudication defined as leg pain on walking and disappearing within 10 minutes on standing and of presumed atherosclerotic origin
1.2. An ankle brachial pressure index (ABPI) of <0.90 on the worst leg at rest
2. Stable disease demonstrated by having a reproducible pain free walking distance on 2 consecutive treadmill tests, i.e. less than 25% variance. The reason for termination of the test must be claudication pain only. All treadmill tests will be done at a speed of 3.2 km/h (= 2 mph), as is standard practice in PAD trials. The incline will begin at 0% and increase in grade of 2% every 2 minutes. This is the standard Skinner-Gardner protocol (Angiology 1992, 43(8): 661-671).

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
50

Key exclusion criteria
1. Rest pain
2. Childbearing potential
3. Heart failure
4. Any other exercise limiting cardiac disease
5. BP >180/100 mHg
6. eGFR <60 ml/min
7. Liver disease
8. Malignancy
9. Already on allopurinol or had an adverse reaction to it.
10. Participants who have had a recent marked change in symptoms or recent (in the last six

months) intervention for PAD
11. Participants receiving treatment which is contraindicated with the study treatment
11.1. 6-mercaptopurine
11.2. Azathioprine
11.3. Warfarin
11.4. Theophylline

Date of first enrolment
14/01/2011

Date of final enrolment
13/01/2012

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Ninewells Hospital & Medical School
Dundee
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Sponsor information

Organisation
University of Dundee (UK)

Sponsor details
Tayside Academic Health Sciences Centre
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Sponsor type
University/education

Website
http://www.tahsc.org/

ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (UK) - Research Fellowship (ref: FS/10/014/28079)

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2016		Yes	No
HRA research summary			28/06/2023	No	No