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Inhaled furosemide for dyspnoea relief

Submission date 09/09/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 09/09/2015	**Overall study status** Completed	
Last Edited 16/06/2022	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Heart failure is a serious condition caused by the heart failing to pump blood around the body properly. One of the most common symptoms of heart failure is shortness of breath (dyspnoea). This is because blood is not being pumped out of the heart at a high enough pressure, which leads to blood collecting in the blood vessels. This causes fluid to leak into the lungs (pulmonary oedema), making it more difficult to breathe. Furosemide is a loop diuretic (water pill) which helps the body to make more urine, allowing the body to get rid of excess water and salt. It is commonly used in the treatment of heart failure, as it helps to reduce the build-up of fluid in the lungs, making it easier to breathe. However, patients need to take more and more as time goes on to get the same effect, which can put a lot of strain on the kidneys, eventually leading to kidney failure. If furosemide is inhaled instead of swallowed, it is known to stop coughing, prevent the airways from collapsing, and reduce breathlessness, as it tricks the brain into thinking that the lungs are getting enough air. The aim of this study is to find out whether inhaling furosemide can help to ease the breathlessness of patients with heart failure.

Who can participate?
Medically stable adults with heart failure who have been treated with furosemide for at least three weeks.

What does the study involve?
Each participant attends the Cardiovascular Clinical Research Facility at John Radcliffe Hospital 4 times at weekly intervals. During each visit the participant is randomly allocated to receive four treatments in a random order. The treatments are inhaled as a mist over 15 minutes using one of two breathing patterns.
Treatment 1: furosemide using a slow, deep breathing pattern
Treatment 2: placebo (dummy drug) using a slow, deep breathing pattern
Treatment 3: furosemide using a fast, shallow breathing pattern
Treatment 4: placebo using a fast, shallow breathing pattern
Before and after each treatment, participants undertake a breathlessness test. Between tests, the patients are asked to comment on breathing sensations felt, and choose the best descriptions of breathing and non-breathing sensations from lists of phrases. Before and after each inhalation, the participants also undertake one of two exercise tests, which they are randomly allocated to at the start of the study. They either undertake a 6-minute walk test (6MWT) or a cardiopulmonary exercise test (CPET). They perform the same test on each of their

visits. If they are allocated to CPET and are unable to perform the test, then they are offered the 6MWT. During each visit, a cannula is inserted to allow multiple blood samples to be taken at various times before and after the treatment. The participants are also asked to visit the bathroom with a flask to measure their urine volume and are provided with an isotonic sports drink to replace the fluid volume excreted.

What are the possible benefits and risks of participating?
There are no direct benefits of participating in this study. There is a risk that participants will experience side effects from the furosemide used in this study.

Where is the study run from?
John Radcliffe Hospital, Oxford (UK)

When is the study starting and how long is it expected to run for?
September 2015 to January 2019

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

Who is the main contact?
Dr Jo Grogono

Contact information

Type(s)
Scientific

Contact name
Dr Jo Grogono

Contact details
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Additional identifiers

EudraCT/CTIS number
2015-001468-21

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

19570

Study information

Scientific Title
Inhaled furosemide for dyspnoea relief in advanced heart failure

Study objectives
The aim of this study is to determine the effect of inhaled furosemide on breathlessness in patients with chronic heart failure and to assess the amount of furosemide that is absorbed into the systemic circulation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Oxford C Research Ethics Committee, 11/09/2015, ref: 15/SC/0480

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Topic: Cardiovascular disease; Subtopic: Cardiovascular (all Subtopics); Disease: Heart Failure

Interventions
Each patient will attend the Cardiovascular Clinical Research Facility at John Radcliffe Hospital 4 times at weekly intervals. During each visit the patient will be randomly allocated to receive four treatments in a random order.

Treatment 1: Inhalation of 4ml of a 10mg/ml solution furosemide (nebulised as a mist) over 15 minutes using breathing pattern 1 (slow, deep breathing)
Treatment 2: Inhalation of 4ml of 0.9% sodium chloride (saline) (nebulised as a mist) over 15 minutes using breathing pattern 1 (slow, deep breathing)
Treatment 3: Inhalation of 4ml of a 10mg/ml solution furosemide (nebulised as a mist) over 15

minutes using breathing pattern 2 (fast, shallow breathing)
Treatment 4: Inhalation of 4ml of 0.9% sodium chloride (saline) (nebulised as a mist) over 15 minutes using breathing pattern 2 (fast, shallow breathing)

Air Hunger (AH) Breathlessness test: Before and after each inhalation of the furosemide or placebo, patients will undertake the AH form of breathlessness test. Please see section 8.5 (baseline assessments) section ‘vi’ for details of the AH test. The patients will rate their AH on a 10 cm VAS scale labelled 'none' (no sensation) at one end, and 'extreme' (an intolerable level) at the other end, at regular intervals.
Between tests, the patients will be asked to comment on breathing sensations felt during trials, and will choose the best descriptions of breathing and non–breathing sensations from lists of phrases.

Exercise tests: Before and after each inhalation, the patients will undertake the exercise test which they will be randomly allocated to at recruitment into trial. They will perform either a 6 minute walk test (6MWT) or cardiopulmonary exercise test (CPET). They will perform the same test on each of their visits and this will not be blinded. This is to assess the feasibility of the 6MWT and CPET in this patient population to guide a future clinical trial. If they were allocated to CPET and are unable to perform the test, then they will be offered the 6MWT.

Blood sampling & urine volume: During each visit, a cannula will be inserted to allow multiple blood samples will be taken at various times before and after inhalation to assay for BNP, NT-pro-BNP, troponin and furosemide. A blood sample will also be taken at Visit 1 to measure serum sodium and potassium and will be corrected prior to inclusion if needed. The patients will also be asked to visit the bathroom with a flask to measure urine volume and will be provided isotonic sports drink to replace the fluid volume excreted.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome measure
Breathlessness is measured using the visual analogue scale (VAS) before and after the air hunger breathing test (experimentally induced breathlessness.) This breathing test is done both before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4.

Secondary outcome measures
1. Breathlessness is measured Dyspnoea-12 questionnaire before and after the air hunger breathing test (experimentally induced breathlessness) before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4
2. Blood concentration of furosemide is directly measured from the blood before and after the mist inhalation (either furosemide or saline) before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4
3. Urine output is measured after the mist inhalation (either furosemide or saline) as an indirect measure of furosemide absorption on study visits 1, 2, 3 and 4
4. Breathlessness is measured using the visual analogue scale (VAS) and Borg scale for

breathlessness before and after the exercise test (cardiopulmonary exercise test, CPET or 6 minute walk test, 6MWT) before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4
5. Exercise tolerance/capacity is measured using the distance walked during the 6MWT or peak work rate, peak VO2 consumption and peak heart rate on CPET before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4
6. Blood concentration of cardiac biomarkers are measured directly before and after the exercise test (cardiopulmonary exercise test, CPET or 6 minute walk test, 6MWT) before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4
7. Breathlessness is measured using the VAS and Dyspnoea-12 before and after the mist inhalation (either furosemide or saline) on study visits 1, 2, 3 and 4

Overall study start date
25/09/2015

Completion date
31/01/2019

Eligibility

Key inclusion criteria
1. Aged 18 years or above
2. Diagnosed with NYHA stage III or IV heart failure
3. Treated with oral furosemide for at least 3 weeks
4. Ambulatory and clinically stable in the previous 3 months
5. Documented left ventricular ejection fraction (LVEF) of <35%.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 12; UK Sample Size: 12

Key exclusion criteria
1. Those unable to consent for themselves
2. History of allergic reaction (hypersensitive) to furosemide and/or any of the other ingredients of furosemide or amiloride, sulfonamides or sulphonamide derivatives, such as sulfadiazine or co¬trimoxazole
3. Individuals who are dehydrated or have significant symptomatic postural hypotension
4. Significant renal impairment (eGFR <15) or anuric
5. Significant hepatic impairment/cirrhosis (Child¬Pugh class C)

6. Addison's disease
7. Digitalis intoxication
8. Porphyria
9. Individuals who are immunocompromised
10. Patient with life expectancy <6 months
11. Patients who are inappropriate for saline
12. Co-existent history of significant chronic obstructive pulmonary disease or asthma or interstitial lung disease or nasal polyps
13. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the patients at risk because of participation in the trial, or may influence the result of the trial, or the patient's ability to participate in the trial
14. Have participated in another research trial involving investigational product in the past 4 weeks
15. Patients who have had an admission to hospital with heart failure within the last 3 months
16. Female patients who are pregnant, lactating or planning pregnancy over the course of trial

Date of first enrolment
27/01/2016

Date of final enrolment
31/07/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
John Radcliffe Hospital
Headley Way
Oxford
United Kingdom
OX3 9DU

Sponsor information

Organisation
Nuffield Dept of Obstetrics and Gynaecology, University of Oxford

Sponsor details
University of Oxford
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John Radcliffe Hospital

Oxford
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United Kingdom
OX3 9DU

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

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
Planned publication in a high impact peer reviewed journal.

Intention to publish date
31/01/2020

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Joanna Grogono (joanna.grogono@ouh.nhs.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		01/04/2022	16/06/2022	No	No
HRA research summary			28/06/2023	No	No