

# Inhaled furosemide for dyspnoea relief

<b>Submission date</b> 09/09/2015	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 09/09/2015	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 16/06/2022	<b>Condition category</b> Circulatory System	<input type="checkbox"/> Individual participant data

## 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**

Biological and Medical sciences  
Faculty of Health and Life Sciences  
Oxford Brookes University, Room S308c  
Gypsy Lane campus  
Oxford  
United Kingdom  
OX3 0BP

## Additional identifiers

**Clinical Trials Information System (CTIS)**

2015-001468-21

**Protocol serial number**

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

### **Study type(s)**

Treatment

### **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(s)**

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.

## **Key secondary outcome(s)**

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 VO<sub>2</sub> 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

## **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

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**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

United Kingdom

England

### 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

### ROR

<https://ror.org/052gg0110>

## Funder(s)

### Funder type

Charity

### Funder Name

British Heart Foundation

### Alternative Name(s)

The British Heart Foundation, the\_bhf, BHF

### Funding Body Type

Private sector organisation

### Funding Body Subtype

Trusts, charities, foundations (both public and private)

### Location

United Kingdom

## Results and Publications

### 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?
<a href="#">Basic results</a>		01/04/2022	16/06/2022	No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No