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Inhaled furosemide for dyspnoea relief in advanced heart failure

Submission date
19/03/2018

Recruitment status
No longer recruiting

Registration date
28/03/2018

Overall study status
Completed

Last Edited
20/09/2023

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
Patients with heart failure often feel breathless ('dyspnoea') which limit their daily activities. Furosemide is a prescription drug taken as a tablet or as an injection which makes kidneys produce more urine to remove fluid build-up in heart failure. Over time a third of patients will need more furosemide to get the same response from the kidneys but high level of furosemide can lead to kidney failure. If furosemide is inhaled instead this is known to stop coughing, protect the airways from collapsing, and can ease breathlessness by tricking the brain into thinking that more breathing is happening than is the case. This direct action may result in lower doses of furosemide which better protects the kidneys. This study will assess the effect of inhaled furosemide on breathlessness in patients with chronic advanced heart failure.

Who can participate?
Patients aged and over with advanced heart failure

What does the study involve?
Participants visit the hospital on five separate occasions and should complete their participation within 5 weeks. At each visit they are asked to do a breathing test and an exercise test before and after mist inhalation. The two treatments are mists containing either furosemide or placebo (dummy drug). Between visits participants are asked to inhale mist morning and evening at home. Each mist takes around 15 minutes to inhale. During Period 1 (days 1 to 8) participants are randomly allocated to one of the two mists. During Period 2 (days 15 to 22) participants use the other mist. Between Period 1 and Period 2 there is a break of at least 7 days. All participants are followed up at Day 8 (Visit 3), and for example, Day 15 (Visit 4) and Day 22 (Visit 5). The minimum total duration of treatment is 22 days.

What are the possible benefits and risks of participating?
Patients will not directly benefit from taking part in this study, although the results of this study may lead to improvements in the way in which heart failure is managed and treated so that patients with heart failure might experience fewer symptoms. It is possible that patients may experience a side effect to furosemide. It is currently unknown whether furosemide is safe

during pregnancy and no problems have been identified in women taking furosemide to date, but because experience is limited female participants of childbearing potential are required to use an effective form of contraception during the course of the study.

Where is the study run from?
Cardiovascular Clinical Research Facility, University of Oxford situated within John Radcliffe Hospital, Oxford University Hospitals NHS Trust (UK)

When is the study starting and how long is it expected to run for?
December 2017 to November 2020

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

Who is the main contact?
Dr Joanna Grogono

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2017-000124-95

Protocol serial number
36433

Study information

Scientific Title
Randomised controlled crossover trial of Inhaled Furosemide for Dyspnoea relief in advanced Heart Failure

Acronym

INFOD-HF V1.0

Study objectives
Patients with heart failure often feel breathless (dyspnoea) which limits their daily activities. Furosemide is a prescription drug taken as a tablet or as an injection which makes kidneys produce more urine to remove fluid build-up in heart failure. Over time a third of patients will need more furosemide to get the same response from the kidneys but high level of furosemide can lead to kidney failure. If furosemide is inhaled instead this is known to stop coughing, protect the airways from collapsing and can ease breathlessness by tricking the brain into thinking that more breathing is happening than is the case. This direct action may result in lower doses of furosemide which better protects the kidneys. This study will assess the effect of inhaled furosemide on breathlessness in patients with chronic advanced heart failure.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central – Oxford B Research Ethics Committee, 13/12/2017, ref: 17/SC/0580

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Dyspnoea in patients with heart failure

Interventions
All tests will be done at the Cardiovascular Clinical Research Facility, University of Oxford situated within John Radcliffe Hospital, Oxford University Hospitals NHS Trust. 40 patients with advanced heart failure will visit the hospital on five separate occasions and should complete their participation within 5 weeks. At each visit patients will be asked to do a breathing test and an exercise test before and after mist inhalation. The two treatments are Mist A and B (furosemide or placebo). Period 1 consists of administering IMP on days 1 to 8 where participants will receive either Mist A and B. Period 2 consists of administering IMP on, for example, days 15 to 22 where participants will receive the opposite mist to what they received in Period 1. Patients are asked to inhale the mist morning and evening at home, and each mist takes around 15 minutes to inhale. Between Period 1 and Period 2, there will be a washout period for a minimum of 7 days.

Both arms will start administering the IMP from Day 1 (Visit 2) and be followed up at Day 8 (Visit 3), and for example, Day 15 (Visit 4) and Day 22 (Visit 5). The minimum total duration of treatment is 22 days.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
'Air hunger (AH)' rated using a visual analogue scale (VAS) during experimentally induced breathlessness. The VAS is a 10cm line with one end marked as 'no breathlessness at all' and the other end marked as 'worst possible breathlessness.' The participant marks across the line to indicate the level of breathlessness experienced during a test that is designed to make participants feel breathless (air hunger); Timepoint(s): End of the study

Key secondary outcome(s)
1. Breathlessness measured using the Dyspnoea 12 questionnaire at visits 2-5
2. Breathlessness during exercise assessed during the CPET test or 6 minute walk test (observing peak workload, heart rate and oxygen consumption) and also measured using the VAS and/or Borg scale at Visits 2-5
3. Blood biomarkers of heart failure measured at visits 2-5
4. Health related quality of life measured using the MLHFQ questionnaire at Visits 2-5
5. Trait anxiety, depression and fatigue in correlation to breathlessness measured using the trait anxiety questionnaire and center for the epidemiological studies depression scale at Visit 1. The state anxiety questionnaire and fatigue severity score will be measured at Visits 1-5
6. Activity levels assessed using a wearable watch at Visits 2-5

Completion date
04/11/2020

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the trial
2. Male or female, aged 18 years or above (there is no upper age limit although the investigator will ensure they have the capacity to understand, consent and have the ability to perform the studies required)
3. Diagnosed with heart failure more than 3 months ago
4. Diagnosed with heart failure with a documented reduced ejection fraction <40%
5. Significant breathlessness that limits what they are able to do. MRC Dyspnoea Scale ≥2
6. In the Investigator’s opinion, is able and willing to comply with all trial requirements
7. Female participants of childbearing potential must be willing to ensure that they use effective contraception during the period they are taking the IMP/placebo and for 48 hours after Visit 5
8. Prescribed regular furosemide or bumetanide tablets for at least 1 month

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. Unplanned heart failure related hospital admission within the last month (unstable heart failure).
4. Patients diagnosed with heart failure within the last 3 months (unstable heart failure)
5. Individuals who are dehydrated or have significant symptomatic postural hypotension
6. Significant renal impairment (eGFR < 15) or anuric
7. Potassium < 3.0 or > 5.9 or Sodium < 130 or > 150 over the preceding month prior the screening visit.
8. Significant hepatic impairment/cirrhosis (Child-Pugh class C)
9. Addison's disease
10. Digitalis intoxication
11. Porphyria
12. Individuals who are immunocompromised
13. Patient with life expectancy < 6 months
14. Co-existent history of significant chronic obstructive pulmonary disease or asthma or interstitial lung disease or nasal polyps
15. Patients on inhaled B2 agonist therapy
16. 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
17. Have participated in another research trial involving investigational product in the past 4 weeks
18. Female patients who are pregnant, lactating or planning pregnancy over the course of trial

Date of first enrolment
09/04/2018

Date of final enrolment
31/08/2019

Locations

Countries of recruitment
United Kingdom

England

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

Study participating centre
Oxford Health Community Team
Oxford Health NHS Foundation Trust
Warneford Hospital
Warneford Lane
Headington
Oxford
United Kingdom
OX3 7JX

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF); Grant Codes: PG/13/84/30486

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 will be stored in a publically available repository called "Radar" (https://radar.brookes.ac.uk/radar). The data that will be shared will be the data that supports the publication. The data will be available once the data has been analysed and within 1 year of the end of the trial. It will be stored for a minimum of 10 years, and for 10 years since the last access. All data will be anonymised. The data will be open access with no restrictions. Consent was obtained for use of anonymised data collected during this study to be used in reports, publications and as part of an educational project and that the information collected may be used in an anonymous form to support other research in the future.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		29/03/2022	16/06/2022	No	No
HRA research summary			20/09/2023	No	No