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Pharmacological modulation of the urge to cough: the effects of morphine sulphate

Submission date
30/03/2015

Recruitment status
No longer recruiting

Registration date
06/05/2015

Overall study status
Completed

Last Edited
15/05/2018

Condition category
Signs and Symptoms

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Coughing is a reflex action which in healthy people stops food and irritating substances getting into the airways. Some people develop persistent (chronic) coughing which can last for many years, the cause of which is unknown. Most people with chronic cough have a very sensitive cough reflex and often describe throat sensations such as a 'tickle' before they cough. It is possible that chronic cough patients may be very sensitive to all throat sensations. Some patients with chronic cough are successfully treated with low dose morphine, yet it is not known exactly how morphine works in these patients. In this study we aim to compare the sensations of coughing experienced by both healthy people and patients with chronic cough.

Who can participate?
Phase 1: healthy nonsmokers aged over 18
Phase 2: male or female patients aged over 18 with chronic cough, treated with low dose morphine sulphate twice daily and willing to temporarily withdraw morphine treatment

What does the study involve?
In order to investigate this, the study will be conducted in two phases. In phase 1 we will investigate the throat sensations healthy people feel when they have an urge to cough. In order to measure this we will need to induce coughing by asking healthy people to perform a cough challenge and simple breathing tests, and complete some questionnaires. Participation in this phase will require one visit to the research unit. In phase 2 we will assess the effect of morphine sulphate on sensations experienced prior to coughing, the urge to cough and objective cough counts in patients with chronic cough. In order to measure this, we will require patients to visit the research unit on nine separate occasions. Participants will be treated with either morphine sulphate or a placebo (dummy) treatment (participants will receive both treatments over the course of the study).We will ask patients to perform cough challenges, breathing challenges, 24-hr cough monitoring, provide urine samples (for morphine clearance and a pregnancy test), complete several questionnaires and record the sensations they experience.

What are the possible benefits and risks of participating?
There will be no direct benefit to the participants for taking part in the study. The main risk in the study is worsening of the participants' cough prior to random allocation and during placebo treatment.

Where is the study run from?
North West Lung Centre, Wythenshawe Hospital (UK).

When is the study starting and how long is it expected to run for?
March 2015 to March 2016.

Who is funding the study?
Moulton Charitable Foundation (UK).

Who is the main contact?
Dr Basma Issa

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
12/MEM/006

Study information

Scientific Title
Pharmacological modulation of the urge to cough: the effects of morphine sulphate

Study objectives
Patients with chronic cough complain of a variety of sensations that they perceive as provoking coughing. These most commonly include sensations of airway irritation, usually localised to the throat, and an urge-to-cough (UTC). These sensations are reported to occur with trivial exposures to environmental irritants, use of the voice, with certain foods or even without obvious provocation. Similar sensations can be evoked experimentally in healthy volunteers by the inhalation of irritants such as capsaicin or citric acid. A number of recent studies have focussed on the UTC, finding it is perceived at concentrations of irritant lower than those evoking cough, is enhanced during an upper respiratory tract infection, and enhanced in females compared with males. However, studies to date have largely ignored the sensation of airway irritation which, based on patient reports, is intimately associated with the UTC. We hypothesise that sensations of airway irritation are a pre-requisite to experiencing an UTC and ultimately coughing; this sequence is analogous to itching leading to an urge to scratch and scratching. It is well established that patients with chronic cough have heightened cough responses when challenged with inhaled irritants, but the sensations that precede coughing have rarely been studied. Therefore it is not known whether sensations of airway irritation and UTC occur at lower levels than in healthy volunteers or whether the relationships suggested in Figure 2 are altered in any way. Furthermore, effective therapies for chronic cough such has low dose morphine and gabapentin have failed to reduce experimentally evoked cough responses, but their effect on the sensations associated with coughing is unknown.

We hypothesise that chronic coughing occurs as a result of a disturbance of the sensory pathways responsible for mediating the sensation of airway irritation. The excessive coughing observed in these patients is in response to the heightened sensations experienced, and the resulting urge to cough, rather than a disturbance of the cough reflex per se. Effective therapies such as low dose morphine may therefore improve coughing by reducing the airway irritation experienced and therefore also the UTC.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The research ethics committee (NRES North West, Greater Manchester Central) gave a favourable opinion of the research subject to receiving a complete response for further information. The meeting was held on 09/03/2015, REC ref: 15/NW/0153, IRAS project ID: 160119

Study design
Phase 1 (healthy volunteers): pilot study
Phase 2 (chronic cough patients): randomised double-blind placebo-controlled two-way crossover single-site study

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 to request a patient information sheet

Health condition(s) or problem(s) studied
Chronic cough

Interventions
Phase 1 (healthy volunteers):
A pilot study to identify in healthy individuals the threshold concentration of inhaled citric acid that induces somatic sensations such as irritation, and then the subsequent threshold associated with an urge to cough.

The following procedures will be carried out:
1. Written informed consent
2. Assessment of inclusion/exclusion criteria
3. Recording of demographics
4. Medical history and medications
5. Spirometry
6. Questionnaires
7. Single inhalation citric acid cough challenge

Phase 2 (chronic cough patients):
A randomised, double-blind, placebo-controlled, two-way crossover, single-site study to assess the physiological effect of controlled release Morphine Sulphate (MST) in subjects with idiopathic chronic cough, already known to respond clinically to morphine. This study will also verify the change in cough frequency with morphine vs placebo to understand whether this relates to the sensory changes. Compared with placebo, low dose (5 to 10 mg) controlled release Morphine Sulphate will reduce:
1. Sensations of airway irritation and urge to cough induced by inhalation of low dose citric acid compared with placebo, single inhalations breathing
2. The number of coughs recorded during a 24-hr period
3. The change in airway irritation will be correlated with the changes in cough frequency.

Up to 50 patients with chronic cough will be recruited from the cough research clinic at the host site in order to collect complete data on 30 subjects. In order to be eligible for participation in the study, patients will need to be currently prescribed morphine sulphate for treatment of their cough, and be willing to temporarily withdraw from treatment prior
to enrolment in the study. Participation in this phase of the study involves nine separate visits to the NIHR South Manchester Respiratory and Allergy Clinical Research Facility.

Patients will attend the NIHR South Manchester Respiratory and Allergy Clinical Research Facility (RACRF) and undergo the following:
1. Consent obtained and eligibility determined
2. Weight and vital signs recorded

3. Physical examination by a medical doctor
4. Urine pregnancy test for women of childbearing potential
5. Complete a series of questionnaires
6. Rate perceived cough severity on a visual analogue scale
7. Undergo spirometry (breathing test)
8. Fitted with a cough monitor to be worn for a period of 24 hours

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Morphine sulphate

Primary outcome measure
Phase 1 (healthy volunteers):
To evaluate the differences in citric acid threshold at which initial throat sensations and the urge to cough are reported

Phase 2 (chronic cough patients):
To evaluate the within-subject differences in urge-to-cough (UTC) ratings with citric acid inhalation with morphine compared with placebo therapy

Secondary outcome measures
Phase 1 (healthy volunteers):
1. To investigate the relationship between citric acid dose for first detectable throat sensation and somatosensory amplification scale
2. To investigate the relationship between citric acid dose for first detectable throat sensation and state/trait anxiety

Phase 2 (chronic cough patients):
1. To evaluate the differences in citric acid threshold at which initial throat sensations and the urge to cough are reported
2. To compare with healthy controls the differences in citric acid threshold at which initial throat sensations and the urge to cough are reported
3. To evaluate the within subject differences in respiratory rate with morphine compared with placebo therapy
4. To evaluate the within subject differences in objective cough frequency with morphine compared with placebo therapy
5. To evaluate the within subject differences in intensity and unpleasantness rating of UTC with morphine compared with placebo therapy
6. To explore the relationships between state anxiety, somatosensory amplification and citric acid thresholds and the response to morphine

Overall study start date
01/03/2015

Completion date
01/03/2016

Eligibility

Key inclusion criteria
Phase 1 (healthy volunteers):
1. Healthy male or female aged over 18 years
2. Nonsmoker
3. Normal spirometry
4. No history of asthma

Phase 2 (chronic cough patients):
1. Male or female age over 18 years
2. Diagnosed with idiopathic chronic cough (greater than 8 weeks duration)
3. Normal spirometry
4. Treated with low dose (5 to 10 mg) Morphine Sulphate twice daily and willing to temporarily withdraw morphine treatment for study purposes

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
10 healthy volunteers and up to 50 patients with chronic cough

Key exclusion criteria
Phase 1 (healthy volunteers):
1. Male or female <18 years old
2. Current smoker
3. History of asthma or other chronic respiratory disease

Phase 2 (chronic cough patients):
1. Current use of medications potentially modifying cough reflex sensitivity e.g. Amitriptyline, Pregabalin, Codeine, etc
2. History of medical conditions potentially modifying cough reflex sensitivity e.g. Diabetes Mellitus with autonomic neuropathy, neurological conditions e.g. cerebrovascular disease, Parkinson’s disease etc
3. Recent upper respiratory tract infection (<4 weeks)
4. Pregnancy/breastfeeding. Women of childbearing potential (not >2 years postmenopausal and /or not surgically sterilised) must have a negative urine pregnancy test, performed at visit 1 prior to administration of study medication
5. Current smokers or exsmokers with <6 months abstinence or cumulative history of >10 pack years
6. Current treatment with ACE inhibitors

7. Drug or alcohol abuse
8. Uncontrolled hypertension (i.e., >160/90 mmHg despite adequate medical therapy)
9. Recent myocardial infarction, or history of congestive cardiac failure
10. Any clinically significant neurological disorder
11. Any clinically significant or unstable medical or psychiatric condition that would interfere with the patient's ability to participate in the study

Date of first enrolment
15/04/2015

Date of final enrolment
01/03/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
North West Lung Centre, Wythenshawe Hospital
University Hospital of South Manchester
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Sponsor information

Organisation
University Hospital of South Manchester NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.uhsm.nhs.uk/research

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Charity

Funder Name
Moulton Charitable Foundation (UK)

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No