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Investigating the interaction between airway narrowing and cough in asthma

Submission date
12/03/2015

Recruitment status
No longer recruiting

Registration date
18/03/2015

Overall study status
Completed

Last Edited
14/11/2017

Condition category
Respiratory

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

Plain English summary of protocol

Background and study aims
Asthma is a common disorder of the small tubes that carry air in and out of the lungs (airways). The main problem in asthma is that these tubes can become inflamed, tight and narrowed. Patients with asthma occasionally have symptoms of wheeze, cough, shortness of breath, and chest tightness during attacks of asthma. It is not certain how narrowing of the tubes actually causes these symptoms. In a previous study the participants inhaled a chill pepper extract called capsaicin to induce coughing. It was found that people with asthma coughed more than healthy volunteers. This suggests that the nerves that cause cough might not be working properly. The majority of the patients in the study had good lung function, i.e. the airways were not narrowed. The next step is to find out whether people with asthma cough more to capsaicin if their airways are narrowed slightly. This will help to determine whether narrowing of the airways causes coughing, and whether excessive coughing makes it easier for the airways to become narrowed.

Who can participate?
People with asthma, aged 18 or over, who have taken part in the “Studying Cough in Asthma Phenotypes” (CoAst) study

What does the study involve?
The study involves six visits in total. Visit 1 involves taking consent and taking a medical history to ensure participants meet the eligibility criteria for the study. Thereafter all participants inhale capsaicin to induce coughing. This has been used extensively over the last 15 years to assess coughing. Visit 2 involves inhaling methacholine, which is a substance known cause narrowing of the airways. This is a commonly used test for the diagnosis of asthma. During all the visits, lung volumes are measured using a spirometer. Visits 3, 4, 5, and 6 involve inhaling a combination of capsaicin and methacholine along with a placebo (dummy) in different orders to assess how much coughing occurs after the airway become narrowed and vice versa. All participants are given salbutamol at the end of each visit to ensure that their lung function is normal.

What are the possible benefits and risks of participating?
Participants undergo a range of clinical tests to review their asthma symptoms and control and also have detailed physiological assessments of their lung function. As well as helping to advance our understanding of the mechanisms causing cough in asthma and to develop

improved treatments, the subject will benefit from being reviewed by a chest specialist. It is possible that participants may experience an increase in their asthma symptoms during the withdrawal of asthma medication before the methacholine and capsaicin challenge tests. Should this happen, patients are advised to re-start their medication and inform the chief investigator. There will be an on-call study doctor who is contactable outside of working hours should advice be needed. The main risk of performing a methacholine challenge is that of wheezing due to narrowing of the airways, but many patients do not develop any symptoms at all. Precautions will be taken for patient safety such as the availability of monitoring equipment and short-acting bronchodilators (salbutamol and ipratropium via inhaler/nebuliser), oxygen, and resuscitation equipment. Capsaicin can cause a burning/hot sensation at the back of the throat when inhaled. This can cause temporary discomfort, but wears off quickly. Capsaicin also makes people cough several times at the highest doses and this may be uncomfortable. Capsaicin can very rarely cause wheezing and this is easily treated. To minimise this risk, lung function is measured before and after all cough challenges. If necessary, participants receive rescue medications including oxygen and/or salbutamol inhalers. All participants are warned of these possible risks before they agree to take part and a medical doctor is available during all visits.

Where is the study run from?
NIHR Clinical Research Facility, South Manchester and NIHR/Wellcome Central Manchester Clinical Research Facility (UK)

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

Who is funding the study?
University of Manchester (UK)

Who is the main contact?
Dr Imran Satia

Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
14/BEA/003

Study information

Scientific Title
A randomised, single-blind, cross-over study investigating the interactions between bronchoconstriction and cough in asthma

Acronym
BEACH

Study objectives
The interaction between methacholine-induced bronchoconstriction and capsaicin-evoked coughing is unclear. Methacholine directly activates muscarinic receptors found on smooth muscle and capsaicin activates TRPV1 receptors found characteristically on vagal c-fibres. This study aims to investigate whether there is an interaction between neuronal activation via TRPV1 on vagal C-fibres and muscarinic receptors on airway smooth muscle. The hypothesis is that capsaicin-evoked coughing will be independent of airway calibre (the degree of bronchoconstriction). Secondly, if capsaicin-evoked coughing is truly independent then we would predict it would have no influence on airway hyper-responsiveness.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Liverpool East, North West, 28/01/2015, ref: 15/NW/0052

Study design
Randomised single-blinded cross-over study involving two centres

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Other

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

Mild atopic asthma

Interventions

VISIT 1: Consent, screening, and full dose capsaicin cough challenge
After taking consent and checking eligibility, a focused medical history and examination will take place to ensure the patient's asthma is currently stable. Participants will then undergo a full dose response capsaicin cough challenge. Spirometry will be performed pre and post challenge to detect any bronchoconstriction. If participants demonstrate a reduction of 20% in FEV1 or experience chest tightness or wheezing, then four puffs of 100 mcg of salbutamol (bronchodilator medication) will be administered via a spacer. Spirometry will be repeated to ensure values return to baseline.

VISIT 2: Methacholine challenge
Visit 2 will take place between 2-7 days after visit 1 and will involve an assessment of airway hyper-responsiveness (AHR) using a methacholine challenge test. The provocative concentration that causes a 20% drop in FEV1 (PC20) will be calculated. Four puffs of 100 mcg of salbutamol will be administered via a spacer after the last dose of methacholine.

VISIT 3: Methacholine inhalation followed by capsaicin inhalation
The objective of this visit is to assess cough responses to four inhalations of the ED50 capsaicin dose following a 15-25% induced fall in FEV1. The following will be performed:
1. Spirometry (FEV1)
2. Modified methacholine challenge
3. Spirometry (FEV1) at 30 seconds and 90 seconds thereafter
4. Four inhalations of a single dose of capsaicin (ED50 dose)
5. Spirometry (FEV1)
6. Four puffs of 100 mcg of salbutamol will be administered via a spacer
7. Spirometry (FEV1)

VISIT 4: Saline (placebo) inhalation followed by capsaicin inhalation
Visit 4 will last up to 45 minutes and will include:
1. Spirometry (FEV1)
2. Saline (0.9%) inhalation (2 minutes tidal breathing)
3. Spirometry (FEV1) at 30 seconds and 90 seconds thereafter
4. Four inhalations of a single dose of capsaicin (ED50 dose)
5. Spirometry (FEV1)
6. Four puffs of 100 mcg of salbutamol will be administered via a spacer
7. Spirometry (FEV1)

VISIT 5: Capsaicin inhalation followed by methacholine inhalation
This visit will last up to 45 minutes. The objective of this visit is to evoke coughing by inhaling capsaicin and then administer either one/two doses (for determination of these doses, see procedures section 5.6.4) of the methacholine concentrations for 2 minutes. This visit will involve:
1. Spirometry (FEV1)
2. Four inhalations of a single dose of capsaicin (ED50 dose)
3. Spirometry (FEV1) at 30 seconds after inhalation
4. Modified methacholine challenge
5. Spirometry (FEV1) at 30 seconds and 90 seconds thereafter
6. Four puffs of 100 mcg of salbutamol will be administered via a spacer
7. Spirometry (FEV1)

VISIT 6: Saline (placebo) inhalation followed by methacholine inhalation
This visit will last up to 45 minutes and the following will take place:
1. Spirometry (FEV1)
2. Four inhalations of saline (0.9%)
3. Spirometry (FEV1) 30 seconds after inhalation
4. Modified methacholine challenge
5. Spirometry (FEV1) at 30 seconds and 90 seconds thereafter
6. Four puffs of 100 mcg of salbutamol will be administered via a spacer
7. Spirometry (FEV1)

A telephone call will be made within 48 hours after completing visit 6 to ensure participants are safe and no adverse events have occurred after completing the study.

Intervention Type
Other

Primary outcome measure
1. The number of coughs evoked by an ED50 dose of capsaicin after methacholine-induced bronchoconstriction compared with saline inhalation
2. The % drop in FEV1 after inhaling methacholine immediately after coughing evoked by an ED50 dose of capsaicin compared to saline (0.9%)

Secondary outcome measures
The secondary outcome will be to explore the number of coughs throughout the duration of each visit, and in particular during methacholine challenges and the recovery periods after salbutamol is given

Overall study start date
01/01/2015

Completion date
01/09/2015

Eligibility

Key inclusion criteria
1. Aged ≥18
2. Have taken part in “Studying Cough in Asthma Phenotypes” (CoAst) study
3. Person with a diagnosis of atopic asthma (based on a positive skin prick test)
4. The subject is treated with:
4.1. Short acting Beta 2 Agonist PRN AND/OR
4.2. Inhaled corticosteroid (≤250 mcg fluticasone propionate daily or equivalent)
5. Controlled or has partial asthma control according to GINA classification

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
15

Key exclusion criteria
1. Subjects who have previously coughed less than a total of four coughs in one dose at the ED50 dose of capsaicin inhalation (assess after visit 1)
2. Subjects who bronchoconstrict by more than 10% at the end of the full dose capsaicin cough challenge (assess after visit 1)
3. Subjects who do not display evidence of airway hyper-responsiveness (PC20 >8 mg/ml) (assess after visit 2)
4. Symptoms of upper respiratory tract infection (URTI) in the last 1 month which have not resolved
5. Lower respiratory tract infection or pneumonia in the last 6 weeks
6. Current smoker or ex-smoker with ≥10 pack-year smoking history and abstinence of ≤6 months
7. Asthma exacerbation in the previous month requiring an increase or start of an ICS or OCS
8. Asthma medication which include theophylline or anti-cholinergic drugs
9. Subject has changed asthma medication within the past 4 weeks prior to screening
10. A previous asthma exacerbation requiring Intensive Care Unit (ICU) admission
11. Significant other primary pulmonary disorders, in particular: pulmonary embolism, pulmonary hypertension, interstitial lung disease, lung cancer, cystic fibrosis, emphysema or bronchiectasis
12. Pregnancy or breastfeeding
13. Use of ACE inhibitors
14. Any centrally acting medication which in the view of the investigator could alter the sensitivity of the cough reflex*
15. History of psychiatric illness, drug or alcohol abuse which may interfere in the participation of the trial
*Any participant who is taking tricyclic anti-depressants, pregabalin, gabapentin or opioids will not be eligible to take part in this study unless they are willing and medically able to withdraw from such medication for the duration of the study. The reason for this is that centrally acting medications may alter the sensitivity of the cough reflex

Date of first enrolment
12/04/2015

Date of final enrolment
01/09/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
NIHR Clinical Research Facility, South Manchester
University Hospital of South Manchester
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M23 9LT

Study participating centre
NIHR/Wellcome Central Manchester Clinical Research Facility
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Sponsor information

Organisation
University Hospital of South Manchester

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Sponsor type
University/education

ROR
https://ror.org/00he80998

Funder(s)

Funder type
University/education

Funder Name
University Of Manchester

Alternative Name(s)

The University of Manchester, University of Manchester UK, University of Manchester in United Kingdom, UoM

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/12/2017		Yes	No
HRA research summary			26/07/2023	No	No