

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: Evaluating the impact of single dose tiotropium on allergen-induced early asthmatic response

PRINCIPAL INVESTIGATOR: Dr. Brianne Philipenko, MD FRC(P)C
Department of Medicine
Division of Respiriology, Critical Care and Sleep Medicine
University of Saskatchewan

Co-Principal Investigator(S): Dr. Beth Davis, PhD
Department of Medicine
Division of Respiriology, Critical Care and Sleep Medicine
University of Saskatchewan
306-844-1444

Dr. Donald Cockcroft, MD, FRC(P)C
Department of Medicine
Division of Respiriology, Critical Care and Sleep Medicine
University of Saskatchewan
306-844-1446

24-hour Emergency Contact:
Dr. Beth Davis
306-229-8709 (text or call)
beth.davis@usask.ca (email)

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CONTACT PHONE NUMBER: 306-844-1444 (Dr. Beth Davis, Asthma Research Lab)

INTRODUCTION

You are invited to take part in this clinical research study because you have been diagnosed with allergic asthma and you are 18 years of age or older.

Your participation is entirely voluntary. If you decide to participate, you are still able to withdraw at any time. If you choose not to participate or choose to withdraw from the study, your access to health care, your employment and/or your academic status will not be affected.

Please take time to read the following information carefully. You may ask the study staff any questions you may have before, during and after the study. Please feel free to discuss this study with your family, friends and/or primary care physician before making a decision about participating.

WHO IS CONDUCTING THE STUDY?

The University of Saskatchewan (USask) College of Medicine has provided funding to conduct this clinical trial. The Investigators have no financial interest in the outcome of this study. The Investigators are not being paid beyond their regular salary to conduct this clinical trial. The study drug will be obtained from the manufacturer (Boehringer Ingelheim Canada).

WHY IS THIS STUDY BEING DONE?

Tiotropium (Spiriva Respimat®) is a medication used to treat respiratory conditions. Technically, tiotropium is referred to as a long-acting muscarinic antagonist or “LAMA”. The term long acting suggests the drug is used once a day. Muscarinic refers to a type of receptor on airway smooth muscle involved in causing bronchoconstriction or a tightening of the airway which makes breathing more difficult. Antagonist means it blocks or inhibits the effect. Therefore, tiotropium blocks muscarinic receptors on airway smooth muscle and prevents bronchoconstriction. Tiotropium was recently approved by Health Canada for use as add-on therapy in poorly controlled asthmatics. Although tiotropium is approved for use as an add-on therapy in poorly controlled asthma, the use of tiotropium is not approved for use in mild allergic asthma. The use of tiotropium in this study is therefore investigational or experimental. Recent research suggests tiotropium may also have anti-inflammatory effects. The potential anti-inflammatory effect of tiotropium is relevant to individuals with allergic asthma since allergen exposure not only causes acute bronchoconstriction (i.e. asthma symptoms) but also leads to airway inflammation.

The purpose of this study is to investigate the protective effects of tiotropium on the response to allergen exposure in individuals with mild allergic asthma.

WHAT DOES THE STUDY INVOLVE?

You are eligible to participate in this study if you are in general good health with no other medical conditions or lifestyle activities that would potentially alter the outcome of study procedures. You must be at least 18 years of age. Your asthma must be stable or well-controlled for the last 4 weeks. Your baseline lung function, measured as the amount of air that you can forcefully exhale in the first second of exhalation (FEV1), must be $\geq 65\%$ of what is predicted for a person of your age, height, and sex. You must have a positive skin prick test to one of the study allergens and you must demonstrate airway responsiveness to methacholine (i.e. respond with a decrease in lung function of at least 20% following inhalation of methacholine). Methacholine is an inhaled medication that causes slight narrowing of the airways and is used for testing people with asthma.

You may not participate in this study if you require medications other than occasional salbutamol (e.g. Ventolin®) or budesonide/formoterol (Symbicort®) to control your asthma or anti-histamines to treat allergy symptoms. If you are on as needed budesonide/formoterol therapy, no reported use within 3 weeks prior to allergen challenge. Salbutamol use may not exceed 4 times per week and anti-histamine use will need to be withheld prior to study visits. The duration to withhold the medication will depend on the anti-histamine used and this will be discussed with you.

You will be required to withhold salbutamol for six hours prior to any lab visit. However, should you

need to use salbutamol or an anti-histamine within the required washout timeframe, you should take the medication and then contact study personnel to reschedule your visit, which may mean repeating previous visits.

You will not be eligible to participate if any of the following apply:

- you are pregnant or breast-feeding
- you have another lung condition or medical condition that would put you at risk if you participate
- you are a current smoker of nicotine products (e.g. cigarettes) or you have a significant smoking history (e.g. pack a day for 10 years)
- you use cannabis or other inhaled recreational products (e.g. e-cigarettes or other vaping products) on a daily basis; occasional use will require a 24 hour withhold
- you have experienced a worsening of your asthma within 4 weeks of starting this study that required a change in how you treat your asthma (e.g. use of inhaled corticosteroids)
- you have been exposed to a trigger that worsens your asthma (e.g. cat) within the last 4 weeks
- you have experienced a respiratory infection within the last 4 weeks
- you have a diagnosis of narrow angle glaucoma
- you have a diagnosis of urinary retention
- you have a known hypersensitivity to tiotropium or components of tiotropium formulation (e.g. benzalkonium chloride)
- you have a history of anaphylaxis or angioedema
- you currently use any of the following medications:
 - inhaled corticosteroid including combination therapies
 - inhaled muscarinic antagonists – except study treatment (e.g. ipratropium bromide)
 - long-acting beta2-agonists (LABA; e.g. formoterol)
 - leukotriene receptor antagonists (e.g. montelukast)
 - biologics (e.g. benralizumab)
 - allergen immunotherapy
 - mast cell stabilizers (e.g. nedocromil sodium)

Visits, Procedures and Time Commitment:

If you decide to take part in this study, you will be required to attend the research lab (Room 346 Ellis Hall) on three occasions over the course of approximately 4 weeks. The study visits and procedures are summarized in Table 1. At Visit 1, which will require about 2.5 hours of your time, study staff will provide an overview of the study purpose and procedures and answer any questions you may have. If you choose to participate, you will be required to sign the consent form (i.e. this document). After consent is obtained, you will be required to undergo the following tests to determine your eligibility and to capture baseline measurements: spirometry, methacholine challenge, skin prick testing and skin titration endpoint testing. If you are eligible, you will be randomly assigned treatment 1. If you do not meet spirometry or methacholine challenge eligibility requirements at first attempt, one re-screen attempt will be allowed. At Visit 2, which will require about 6 hours of your time, you will be trained on the inhaler device use and after baseline spirometry 2 puffs of treatment one will be administered. Thirty minutes after dosing, blood pressure, and repeat spirometry will be performed followed by allergen inhalation challenge and then sputum induction. After Visit 2, there will be a washout period of at least three weeks before you return to the lab for Visit 3. The term “washout period” means you will not be receiving any treatment during this time. Visit 3 procedures are similar to Visit 2 procedures and will require about 6 hours of your time. You will do baseline spirometry, then will be given 2 puffs of treatment two followed by spirometry, allergen challenge and sputum induction. On one of the visits you will receive the treatment medication, inhaled tiotropium 2 puffs and on the other visit you will receive 2 puffs of a placebo inhaler. The placebo medication will have no therapeutic effect but will be designed to look like the intervention. This study is a “crossover” design which means you will receive both the study drug, tiotropium, as well as placebo on separate visits.

Table 1: Study Visits and Assessment Schedule

Visit 1	Visit 2	Washout	Visit 3
Consent	Spirometry	Minimum 3 weeks	Spirometry
Spirometry	2 puffs Tx1		2 puffs Tx2
MCh	Spirometry		Spirometry
SPT	AC		AC
STE	Sputum		Sputum

MCh = methacholine challenge; SPT = skin prick test; STE = skin titration endpoint; AC = allergen challenge; Tx = treatment

Study Assessments

Spirometry

Spirometry is a necessary component of bronchoprovocation testing. Spirometry will be performed according to current industry standards and used to assess your resting lung function for determining eligibility criteria and for monitoring the magnitude of airway narrowing induced during allergen and methacholine challenges. To perform spirometry, you will be required to breathe through a mouthpiece with your nose clipped. You will inhale as much air as you can and then exhale forcefully until your lungs are empty. The spirometer is connected to a computer and the computer software generates various lung function parameters. The parameters we are interested in are the forced expiratory volume during the first second of exhalation (FEV1) and the forced vital capacity (FVC). More simply put, FEV1 is the amount of air you are able to forcefully exhale in one second and the FVC is the total amount of air you are able to forcefully exhale after fully inhaling. Spirometry is performed at all visits, multiple times.

Skin Prick Testing

Skin prick testing will be used to determine what allergies you have and identify the allergen to be used in the allergen challenge. Drops of allergen extracts (including a positive and a negative control) will be placed on your forearm and introduced through the skin by pricking with a lancet. After 10-15 minutes, the skin reaction will then be evaluated based on size. The allergen chosen for your allergen challenges will depend on the largest skin reaction produced through skin prick testing as well as on your clinical history regarding exposure to that particular allergen. Skin prick testing will be performed once at Visit 1.

Skin Test Endpoint (STE) Titration

The STE Titration test is similar to skin prick testing but instead of applying several different allergen extracts, duplicate drops of increasing concentrations of the specific allergen chosen from the skin prick test will be applied to the forearm, pricked with a lancet, and assessed to determine the concentration that produces a particular sized skin reaction (i.e. reaction resembling a mosquito bite that is less than 2mm in diameter). Skin test endpoint testing is performed once at Visit 1.

Methacholine Challenge Testing (MCT)

Baseline spirometry will first be performed to obtain at least two reproducible measurements of your resting FEV1. Next, you will wear nose clips and inhale aerosolized saline through a mouthpiece while breathing normally until the nebulizer is empty (approximately 1.5-2.5 minutes). FEV1 measurements will be recorded at 30 and 90 seconds postinhalation, and the next inhalation will begin five minutes after the start of the previous inhalation. Each subsequent inhalation will entail doubling doses of methacholine, a compound that may cause your airways to narrow (i.e. make it harder to breathe).

The procedure will continue until your FEV1 has dropped at least 17% from the value obtained after inhaling saline. You will be required to undergo one methacholine challenge test at visit 1.

Allergen Challenge Testing

The early asthmatic response (EAR) allergen challenge will be performed per standard method. Following baseline spirometry, you will inhale doubling doses of allergen like was done with methacholine. Two FEV1 measurements, one minute apart, will be recorded ten minutes after you finish inhaling each dose. Twelve minutes will elapse between the start of one inhalation to the start of the next inhalation. The allergen challenge ends when your FEV1 drops at least 20% from the highest measurement obtained during baseline spirometry. You will be required to remain in the lab for the next 5 hours and perform FEV1 measurements at various time points. You will then self-administer 200mcg salbutamol and undergo a ten minute wait period before the process of sputum induction commences. Following sputum induction, you will self-administer an additional 200mcg salbutamol and 500mcg fluticasone propionate (or equivalent). A final spirometry measurement will be obtained to ensure lung function has returned to a safe level prior to leaving the lab. You will undergo two allergen challenges, one at Visit 2 and one at Visit 3.

Sputum Induction

Airway secretions (i.e. mucous or sputum) collected from your lungs are valuable samples for use in assessing airway inflammation. To help you produce sputum, you will be asked to inhale 3 different concentrations (3%, 5% and 7%) of “salty” water known as hypertonic saline, each for 7 minutes. Inhaling hypertonic saline creates an environment in your airways that draws sputum from your lungs into the airways where it can be expectorated (i.e. coughed, hacked, huffed up). After each inhalation you will be asked to blow your nose and rinse your mouth with water before trying to produce a sample. After each inhalation you will also perform an FEV1 measurement to ensure your lung function is stable. You will undergo the process of sputum induction at visit 2 and visit 3.

Sputum samples will be used to produce a layer of cells from your airway on microscope slides. These slides are then used to count the number of inflammatory cells on the slides which provides information about airway inflammation (i.e. the type of cells in the airway) and how the inflammation changes with exposure to allergen and following treatment with tiotropium. These data are required for the current study. Sputum samples will also be used to look at mediators or biomarkers involved in different cellular processes or pathways that are activated by allergen exposure or inhibited by treatment.

Optional Sub-study

Sputum samples will be used to produce a layer of cells from your airway on microscope slides. These slides are then used to count the number of inflammatory cells on the slides which provides information about airway inflammation (i.e. the type of cells in the airway) and how the inflammation changes with exposure to allergen and following treatment with tiotropium.

Sputum samples can also be used to look at mediators or biomarkers involved in different cellular processes or pathways that are activated by allergen exposure or inhibited by treatment. Although this is not the purpose of the current study, we would like to store part of your sputum sample for future research on mechanisms of airway inflammation specific to allergic asthma and how tiotropium may affect these events. Your samples will not contain identifiable information. Your samples will be stored in a freezer in the Asthma Research Lab for a period not exceeding 15 years. Your samples will not be shared. Any future research conducted on your samples will be reviewed and approved by the University of Saskatchewan Biomedical Research Ethics Board but your consent will not be sought.

If you change your mind about allowing your samples to be stored, contact the Investigators and let them know you would like your samples destroyed. Your samples will be removed from the freezer and destroyed. Any data already collected from the use of your samples will be retained, however no additional future research will be performed.

You will be able to indicate your willingness (or not) to store your sputum samples for future use by indicating yes or no on the signature page of this document.

Responsibilities of the Participant:

As a study participant, you will be expected to:

- a. Follow the directions of the study staff
- b. Report all medications (prescribed, over-the-counter, herbal etc.) currently being used
- c. Report any changes in your health or medications used during the study

The study investigator may remove you from the study early for non-compliance with the above responsibilities. Your health and wellbeing are most important and so, if faced with a situation where you must use a medication that will (or may) interfere with the study, we ask that you take the medication and contact us to reschedule your appointment.

Health records and use of data from secondary sources:

Your health record will **not** need to be accessed for the purposes of this study.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you choose to participate in this study, there will be no direct benefit to you. This study will provide information on whether or not tiotropium is useful for treating allergic asthma

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?**Spirometry**

There are no known risks associated with performing spirometry in individuals with mild allergic asthma.

Skin prick testing and skin titration endpoint testing

Skin prick testing and skin titration endpoint testing may cause itching and swelling where the allergens were administered. This usually subsides quickly. If symptoms persist, an antihistamine, topical corticosteroid cream, and/or an ice pack may be used to treat the reaction. Severe reactions from skin prick testing are very rare but may cause anaphylaxis which can be fatal. Such severe reactions typically occur shortly after testing during which time study staff will be monitoring you and ready to treat such a reaction immediately.

Methacholine Challenge Testing

Adverse reactions associated with inhaling methacholine may include headache, throat irritation, lightheadedness and itching. Additionally, chest tightness, cough or wheezing may occur. Adverse reactions are generally mild and quickly resolve without the use of treatment. Lung function is monitored throughout the test and bronchodilator (salbutamol/Ventolin®) is immediately available if necessary. Severe adverse reactions are extremely rare.

Allergen Challenge Testing

Allergen inhalation challenges are relatively safe when performed in centers with highly experienced personnel and with proper oversight. Allergen challenge testing may cause coughing, chest tightness, wheezing, and difficulty breathing. The testing method is designed to minimize the risk of causing a severe reaction but there is a risk of severe airway narrowing (i.e. anaphylaxis) developing. If such a situation occurs, you will be treated immediately. Symptoms induced by the allergen challenge usually resolve over time without treatment or may be reversed by use of a bronchodilator (e.g. Ventolin®) and/or inhaled corticosteroid (e.g. Flovent® or equivalent). You will self-administer these treatments prior to leaving the lab as is routine lab practice.

Sputum Induction

Inhalation of hypertonic saline may cause bronchoconstriction but this is not anticipated in individuals with mild allergic asthma. As a precaution, salbutamol (Ventolin®) is administered prior to undergoing sputum induction. In the event that severe bronchoconstriction occurs during the process of sputum induction, you will be treated with salbutamol (Ventolin®). In addition, FEV1 monitoring is performed during the process to monitor and detect any bronchoconstriction.

Tiotropium treatment

In the proposed study population (i.e. mild allergic asthma) adverse events associated with taking tiotropium are not anticipated. In theory, based on how the drug works, dry mouth may develop. The product monograph for tiotropium indicates adverse events occurred in 1.4-3.3% of individuals following use of tiotropium. Events included oral thrush (infection at back of mouth), dry mouth, gastroesophageal reflux, sinusitis (inflamed sinuses), cough, dysphonia (difficulty speaking) and rash. Less common events (occurring in <1%) were also observed and include: atrial fibrillation (abnormal heart beat), supraventricular tachycardia (increased heart rate), blurred vision, gingivitis (swelling of gums), joint swelling, dizziness, epistaxis (nose bleed), laryngitis and dry skin. These studies were conducted in individuals with severe asthma who were using additional medications such as inhaled corticosteroids and long acting beta agonists. Use of these types of medications are associated with some of the reported adverse events (e.g. oral thrush) In addition, these individuals were treated with tiotropium for a much longer duration (12 weeks to one year).

Placebo treatment

There are no anticipated adverse events associated with receiving placebo treatment.

WHAT HAPPENS IF I DECIDE TO WITHDRAW?

Participation in this study is entirely voluntary and you have the right to withdraw from the study at any time without providing a reason. The decision to withdraw will not affect your future health care, employment or academic standing. Data collected from you before your withdrawal may still be analyzed. You will be promptly notified if any new information regarding any aspect of this study becomes available that may affect your willingness to continue your participation.

WHAT HAPPENS IF SOMETHING GOES WRONG?

In the unlikely event of a medical emergency seek immediate medical attention and notify study staff as soon as possible. Necessary medical treatment will be made available to you at no cost. By signing this document, you do not waive any of your legal rights against the investigators or anyone else.

WILL I BE INFORMED OF THE RESULTS OF THE STUDY?

We plan to submit a manuscript (using the results we collected from your data) for publication. If you are interested, you can opt in to receive a summary of the results by providing your email or mailing address at the bottom of the consent form.

WHAT WILL THE STUDY COST ME?

If you choose to participate in this study, you will not be charged for the study drugs or any research related procedures. You will not be paid for your participation; however, you will be provided with an honorarium in the amount of \$500 in order to cover your time and out-of-pocket expenses. In the event all study visits are not completed, the honorarium will be prorated based on the study procedures/visits you were able to complete. The University of Saskatchewan will require your social insurance number (asked for on the signature page of this form) to provide the honorarium and a T4A will be sent to you at the appropriate time.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. Your name will not be attached to any information or mentioned in any study report or made available to anyone except the study staff and personnel of the University of Saskatchewan responsible for issuing the honorarium. Study records will identify you by a study code such as TIOAC01. All study related information will be stored in a locked room (e.g. asthma lab or investigator office) but no guarantee of complete confidentiality can be made. For quality assurance and/or monitoring reasons, the University of Saskatchewan Biomedical Research Ethics Board and/or Health Canada representatives have the right to

inspect research records in the presence of the principal investigator or designate and some records may contain identifying information. It is the intention of the Investigators to publish results of this research in scientific journals and to present the findings at related conferences, but your identity will not be revealed. Per Health Canada guidelines, your records will be stored for a period of 15 years. After storage, your records will be shredded in a confidential manner.

With your permission, your family physician may be informed of your participation in this study and may be consulted regarding your health and treatment.

A description of this clinical trial will be posted on <http://www.clinicaltrials.gov>, as required by Health Canada. This website will not include information that can identify you. You can search this website at any time.

Study results and your individual results will be available to you once all study data collection is complete.

If you are interested in receiving a copy of the results, please check the appropriate box(es) on the last page of this document.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

If you have any questions or desire further information about this study before or during participation, you can contact Dr. Davis at 306-844-1444.

If you have any concerns about your rights as a research participant and/or your experiences while participating in this study, contact the Chair of the University of Saskatchewan Biomedical Research Ethics Board, at 306-966-2975 (out of town calls 1-888-966-2975) or in writing at ethics.office@usask.ca. The Biomedical Research Ethics Board is a group of individuals (scientists, physicians, ethicists, lawyers, and members of the community) that provide an independent review of human research studies. This study has been reviewed and approved on ethical grounds by the University of Saskatchewan Biomedical Research Ethics Board.

CONSENT TO PARTICIPATE

Study Title: Evaluating the impact of single dose tiotropium on allergen-induced early asthmatic response

- I have read the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I understand that this study may not provide any benefits to me.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I understand that I am free to withdraw from this study at any time for any reason and I understand that the decision to stop taking part will not affect my future medical care/relationships.
- I give permission for the collection, use and disclosure of my personal health information for the research purposes, as described in this consent form.
- I understand that by signing this document I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.

My family physician can be informed about my participation in this study, and, if required, consulted regarding my health and treatment.

- Yes, you may contact my primary care physician
- No, please do not contact my primary care physician
- I do not have a primary care physician.

I consent to the storage of my sputum sample for future research on airway inflammation and how tiotropium alters airway inflammation specific to allergic asthma. YES NO

I am interested in receiving a summary of group study results: YES NO

My signature below indicates that I agree to participate in this study:

Name of participant:

Signature

Date

Name of person obtaining consent:

Signature

Date

Email or mailing address *(if you wish to receive results of the study)*

STATEMENT OF PERSON EXPLAINING CONSENT

I have explained to the participant and their parent/legal guardian/authorized representative the nature and purpose of the above study. The participant and their parent/legal guardian/authorized representative signing this form have been given enough time to review the information. There has been an opportunity to ask questions and receive answers regarding the nature, risks, and benefits of participation in this research study. The participant and their parent/legal guardian/authorized representative appear to understand the nature and purpose of the study and the demands required of participation.

Name of Person conducting consent discussion

Signature

Date