Effect of an H1 receptor antagonist on exercise performance in hypoxia

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1.0 Background

It is well established that exercise tolerance is strongly dependent on and limited by the ability to deliver oxygen to skeletal muscle. Thus, it is often inferred that the reduced exercise tolerance commonly seen in extreme environments, including altitude, is a result of a frank limitation in skeletal muscle oxygen delivery. At altitude, the mechanism behind reduced oxygen delivery to exercising muscle is traditionally believed to be a reduced blood content of oxygen (Chapman and Levine, 1999). The primary barrier to adequately oxygenating the arterial blood is the alveolar – capillary interface in the lung, where oxygen must diffuse across the alveolar wall, through the interstitial space, across the pulmonary capillary wall, and ultimately bind with hemoglobin (Dempsey and Wagner, 1999). Any thickening of these tissues or fluid spaces will slow oxygen diffusion and ultimately impair blood oxygenation.

During heavy exercise in many trained individuals, a rise in histamine release from mast cells in the airways is commonly seen, due to the natural irritation of the airways from high levels of ventilation (Youness and Kivinen, 1984) (Figure 1). This causes an inflammatory response in the alveolar wall, increasing the diffusion distance oxygen must travel from the alveoli to arterial blood (Anselme et al., 1994). While during exercise at sea level, a reduced rate of pulmonary oxygen diffusion may not be a limiting factor, at altitude, diffusion of oxygen is already slowed substantially (West, 2012). Therefore, any intervention which could minimize a histamine-mediated inflammatory response could help to maximize arterial blood oxygenation at altitude and defend exercise performance. Cetirizine (Zyrtec®) is a selective H1 receptor antagonist, which blocks histamine binding, thereby minimizing any inflammatory response in the airways (Togias, 2003). Unlike other selective H1 receptor antagonists, like Diphenhydramine (Benadryl®), Cetirizine does not cross the blood-brain barrier as readily, and therefore has minimal side effects (e.g. drowsiness) which could negatively affect exercise performance.

Whether a simple, single intervention of Cetirizine / Zyrtec® use can improve exercise performance of active individuals when acutely exposed to altitude is completely unknown.

2.0 Rationale and Specific Aims

Specific Aim #1 – Determine the effect of Cetirizine (Zyrtec®) on exercise performance and arterial oxygenation with acute exposure to a simulated altitude

For this project, healthy subjects will perform steady state and progressive work rate exercise, endurance performance time trials, and repeated sprint performance time trials in the laboratory at a simulated altitude of 3000m (9900ft) after dosing with 10 mg of Cetirizine or a placebo in a repeated measures design. Non-invasive techniques (pulse oximetry, near-infrared spectroscopy [NIRS]) will be utilized to measure changes in arterial oxyhemoglobin saturation and skeletal muscle oxygenation at the level of the microvasculature during exercise.

It is expected that after Cetirizine, blood and muscle microvascular oxygenation during heavy exercise will improve compared to placebo, ultimately improving exercise performance at altitude.

3.0 Inclusion/Exclusion Criteria

Inclusion criteria:

- Physically active a minimum of 120 minutes a week, as determined by questionnaire
- 18-35 years of age
- Classified as low risk, based on the modified PAR-Q questionnaire, BMI, and non-smoking status
- No history of pulmonary disease and pulmonary function classified as normal, as defined by the following measurements being 80% of predicted values: forced vital capacity (FVC), forced expired volume in one second (FEV1) and FEV1/FVC, according to the American Thoracic Society standards.

Exclusion criteria:

- Current smoker
- Women who are pregnant or could possibly be pregnant
- BMI > 25 kg/m^2
- A 'yes' answer to any of the 14 questions on the PAR-Q pre-participation questionnaire
- History of pulmonary disease or <80% of predicted FCV, FEV1 and/or FEV1/FVC.
- A history of renal or liver disease, due to possible interaction effect with Cetirizine
- Currently taking any prescription or over the counter medications for the treatment of allergies, or taking any of the below listed drugs known to have a moderate or higher interaction effect with Cetirizine:

isocarboxazid
tranylcypromine
bosutinib
clobazam
crizotinib
daclatasvir
eliglustat
hyaluronidase
lomitapide
lurasidone
ombitasvir/paritaprevir/ritonavir
phenelzine
ponatinib
ritonavir
vemurafenib

4.0 Enrollment/Randomization

Subjects will be recruited by flyers posted in the School of Public Health building and local cycle shops. Subjects will also be recruited by direct email to known cyclists and endurance athletes who are either a) contacts of the PI and co-I, or b) members of club or fraternity cycling teams.

5.0 Study Procedures

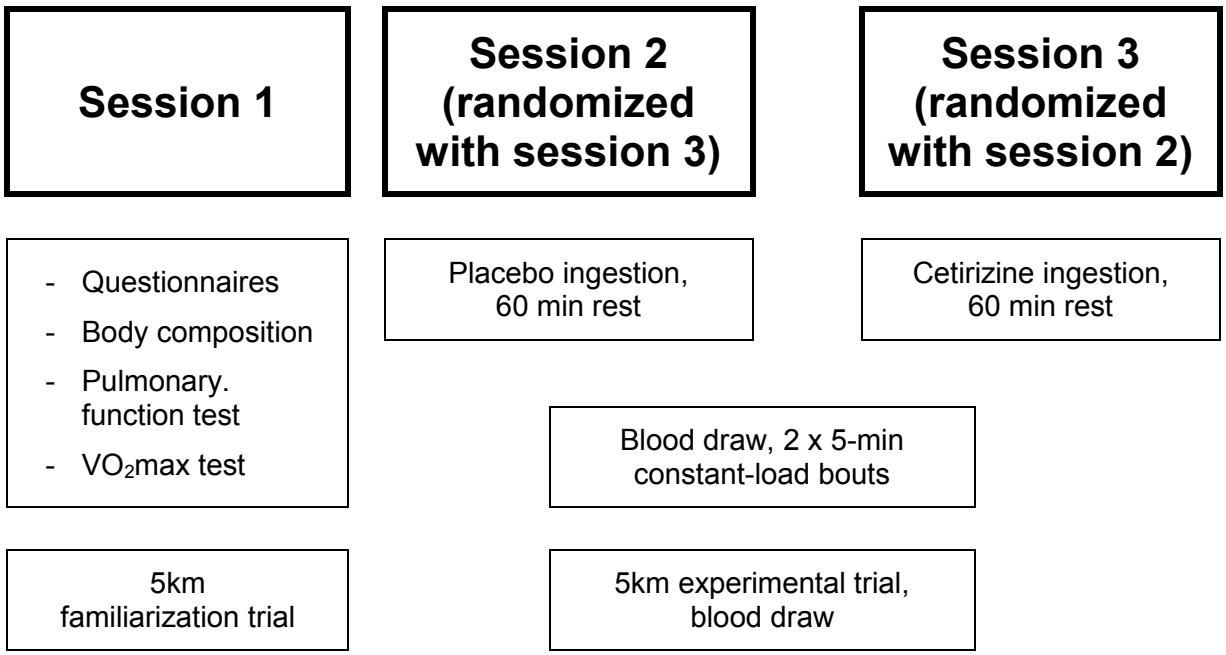
Study design: Subjects will be asked to report to the laboratory on a three occasions, separated by a minimum of 48 hours and a maximum of 14 days. For each subject, all testing sessions will be performed at the same time of day. Prior to each testing session, subjects will be asked to abstain from caffeine consumption for 12 hours. Subjects will also be asked to avoid alcohol consumption for 24 hours before testing, be at least 3-hour post prandial and avoid high-intensity exercise during the 24 hours leading to the exercise testing. Finally, subjects will be asked to consume a similar diet the night before, and the morning of, Sessions 2 and 3.

The first session of testing includes: informed consent completion, completion of a general questionnaire, completion of a standard medical questionnaire, measures of height and weight, measures of body composition, resting pulmonary function testing, completion of a maximal oxygen uptake test on a cycle ergometer (in normoxia) with measures of respiratory flow-volume characteristics, and familiarization with the 5km cycle ergometry time trial (TT) in hypoxia (14.3% O_2, simulating 3000m). This session is expected to take approximately 60-90 minutes.

The 2nd and 3rd sessions will include Cetirizine (10 mg) or placebo ingestion, 60 minutes of rest (time required to reach peak Cetirizine plasma levels), a blood draw to measure plasma histamine levels, a brief warm-up, two 5-miniute constant-load cycle ergometry exercise bouts at moderate intensity in hypoxia with 5-minute of passive recovery following each exercise bout, a 5km cycle ergometry TT in hypoxia, and a post-exercise blood draw to measure plasma histamine levels. These sessions are expected to take approximately 120 minutes each.

During the hour between Cetirizine / placebo ingestion and the beginning of the testing trial, subjects will be allowed to rest comfortably in the lab. Sessions 2 and 3 will be randomized and counterbalanced.

A graphical timeline is below:



Study procedures: (Session 1) after completion of informed consent documents and questionnaires, height and weight will be measured. Body composition will be measured by bioelectrical impedance. Resting pulmonary function will then be performed as described by the American Thoracic Society (specific procedures and measurements are detailed under "*Resting Pulmonary Function Testing*" below). Following these measurements, subjects will be allowed to warm up on the cycle ergometer at a self-selected speed for 10 minutes. Subjects will then be fitted with a chest strap heart rate monitor and an oro-nasal face mask. A pulse oximeter sensor will also be placed on the subject's forehead to non-invasively measure arterial oxyhemoglobin saturation. Optodes from a near-infrared spectroscopy device will be placed on the subject's thigh and secured with a Velcro strap, in order to non-invasively measure oxygenated and deoxygenated heme-O_2 carriers in the skeletal muscle.

The maximal oxygen uptake test will begin with subjects pedaling at 50W, with subjects instructed to keep RPMs between 80 and 110. The workload will increase by 25W each minute until volitional exhaustion or until RPMs fall below 70 for more than five seconds. After completion of the maximal oxygen uptake test and following a 15-minute rest period, subjects will be asked to complete a familiarization 5km time trial on the cycle ergometer breathing a hypoxic inspirate (14.3% O_2, simulating 3000m) in as short of a time as possible (most subjects require between 8 and 12 minutes). Subjects will be able to self-select cadence and resistance on the ergometer.

(Session 2 and 3) Upon arrival at the lab, subject will be given either 10 mg of Cetirizine in pill form or a placebo (10 mg of gelatin in capsule form). Subjects will be allowed to sit comfortably or lie down for 60 minutes. Following this rest period, approximately 5 ml of blood will be drawn from an antecubital vein. Subjects will then be allowed to warm up

on the cycle ergometer at a self-selected speed for 10 minutes. Following the warm-up, subjects will be fitted with a chest strap heart rate monitor, an oro-nasal face mask, a pulse oximeter sensor, and near-infrared spectroscopy optodes. Subjects will then be asked to complete two 5-minute cycling bouts at a constant, moderate intensity (as will be determined individually according to each subject's maximal oxygen uptake test performed on Session 1, details below). Subjects will be allowed 5 minutes of passive recovery after each of the 5-minute cycling bouts. Following the second recovery period, subjects will be asked to ride 5km, completing the distance in as short of a time as possible. Subjects will be allowed to shift gears on the bike at will and pedal at any RPM desired. Feedback on distance completed will be shown on a video monitor and verbally announced every 1km. During the TT, respiratory flow-volume measures will be completed by having the subjects complete two inspiratory capacity (IC) maneuvers near the end of each kilometer of the TT. Immediately following the TT, approximately 5 ml of blood will be drawn from an antecubital vein.

Demographic and screening variables: Age, height, weight, sex, body mass index, body composition (estimated percent lean body mass and fat mass), pulmonary function measures (total lung capacity, vital capacity, forced expiratory volume in one second, lung diffusing capacity, and maximal voluntary ventilation).

Dependent variables: exercise metabolic measures (VO_2, VCO_2, ventilation, heart rate), dyspnea and rating of perceived exertion during the 5km TT, time to completion of the 5km TT, power output during the 5km TT, muscle oxygenation, plasma histamine levels.

Specific Measures:

Height and weight: Height will be measured using a standard wall mounted, sliding height measuring board (stadiometer). Weight will be measured by an electronic scale.

Body composition: Subject stands in bare feet on an electrode imbedded scale (Tanita) and holds on to electrode imbedded handles. An unnoticeable electrical current is passed through the subject for 2 seconds, from which resistance to electrical flow is measured and body composition is estimated.

Resting Pulmonary Function Testing: Subjects will be asked to sit in a comfortable chair for approximately 10 minutes of rest. Tests of breathing function are performed as described by the American Thoracic Society. These tests include the measurement of total lung capacity (the volume of air the lungs can hold), vital capacity (the volume of air that can pushed out with one maximal breath), FEV1 (the volume of air that can be forcefully breathed out in one second), maximal inspiratory and expiratory flow rates (used to generate maximal flow-volume loops), lung diffusing capacity and maximal voluntary ventilation (MVV; the maximal volume of air that can breathed in 12 seconds). For all of these procedures, the subject will then be fitted with a rubber mouthpiece and noseclip.

Respiratory flow-volume measures: At a number of time points during the exercise trials subjects will be asked to complete two inspiratory capacity (IC) maneuvers by inspiring maximally once and then continuing to breathe normally. For the maximal oxygen uptake test the IC maneuver will be performed near the end of each minute of exercise, and for the TT near the end of every 1km.

Near-infrared spectroscopy (NIRS) measures: Near-infrared Spectroscopy (NIRS): Frequency domain NIRS will be used in vivo to non-invasively determine the volume of heme-O_2 carriers in the exercising muscle microcirculation. During the constant-load and 5km TT, the device probe will be placed on the surface of the right vastus lateralis. The device probe will be secured with a Velcro strap and wrapped with a cloth bandage to prevent movement and light leakage. Position of the device probe will be marked with indelible marker and photographed to match placement between trials.

Rating of perceived effort: At the completion of each km during the 5km TT subject will be shown a chart and asked to point to a rating of perceived breathlessness (dyspnea) on a scale of 0-10 (modified Borg scale). Subjects will be familiarized with this scale prior to the TT and will be told that 0 implies no "noticeable breathing effort above what occurs at rest" and 10 indicates "maximal ventilatory effort". Additionally, at the end of each km, subjects will be asked to point to a chart to indicate their overall rating of perceived exertion (RPE; 0-10 modified Borg scale where 0 in implies "no effort" and 10 indicates "maximal effort").

Cetirizine and placebo.
Upon arrival at the laboratory for Sessions 2 and 3, subjects will be asked to ingest a pill containing 10mg of Cetirizine or a gelatin placebo. Black colored (e.g. non-opaque) size 1 gelatin capsules will be purchased commercially. For placebo, the capsules will be filled with 10 mg of sugar-free gelatin, purchased from a local grocery store. Cetirizine will be purchased over-the-counter, and the 10mg pill will be encapsulated within the same black colored size 1 gelatin capsule as the placebo. The treatment will be double-blinded and the order will be randomized and counter-balanced. Pharmacokinetics of Cetirizine indicate peak plasma levels are achieved within 60 min, and as subjects will be at least 3 hours post-prandial, will not be delayed by recent diet.

Maximal oxygen uptake: The subject will be asked to warm up on the cycle ergometer for 10 minutes at a comfortable, self-selected pace. Subjects will be fitted with a) an oro-nasal face mask which covers the nose and mouth, b) a chest strap heart rate monitor, and c) a pulse oximeter sensor will also be placed on the subject's forehead to non-invasively measure arterial oxygen content. The subject will then be asked to pedal at a cadence between 80 and 110 rpm at a workload of 50W. The workload will be increased by 25W every minute until volitional exhaustion or until RPMs fall below 70 for 3 seconds. Expired air from the face mask is collected in a tube for the determination of oxygen content, CO_2 content, and expired ventilatory volumes.

Constant-load cycling: In sessions #2 and #3, subjects will be asked to complete five minutes of cycling at submaximal workloads equal to 60% and 75% of VO_2max, as determined in session #1. Subjects will have five minutes of passive rest after each 5-minute exercise bout.

5km cycle performance trial: Subject will be asked to complete 5km on the cycle ergometer in as short a time as possible (fit individuals typically take between 8 and 12 minutes). Subjects will be free to shift gears on the cycle and pedal at any cadence desired. Subjects will be given visual feedback on distance travelled and verbal feedback every 1km.

Hypoxic inspirate: Altitude will be simulated by breathing a hypoxic inspirate. A commercially available, portable nitrogen generator (Colorado Altitude Training Systems) will be used to generate nitrogen rich air, in order to decrease the O_2 content to the specified level. The nitrogen generator will be set to produce an outflow of 14.3% O_2, equivalent to an altitude of 3000m / 9900 ft. Note that the mechanical design limits of the nitrogen generator only allows for a minimal O_2 level of 14.3%. Additionally, our laboratory O_2 analyzer will constantly monitor and record inspired oxygen levels. Hypoxic gas from the generator will be collected in two large meteorological balloons, to serve as the inspired air reservoir.

Blood sampling: In each of Sessions 2 and 3, subjects will be asked to give two blood samples of ~ 2-5 ml each: one prior to beginning cycle exercise, and one after completing the 5km time trial. Blood will be taken via routine venipuncture procedure from an antecubital vein using a 22g or smaller needle and a sodium EDTA treated (lavender top) vacutainer. Standard precautions will be used, and an experienced investigator will perform the venipuncture. Subjects will be free to choose the arm used for each venipuncture.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The primary investigator will report the frequency of monitoring and dates, summary of adverse events, assessment of external factors that impact safety of subjects, summary of subject privacy and research data confidentiality, and changes to the risk-benefit ratio. Adverse events include death, an injury requiring hospitalization, loss of information containing identifiable records, an unanticipated experience associated with intensive exercise, and other related events. Our intention is that the data from this study may be used in characterizing the athletic population, and may be used in longitudinal comparisons.

In the event of an adverse event, the PI will report immediately to and cooperate with the IRB in any necessary investigation. After two adverse events, the protocol will be evaluated for possible modification.

The primary investigator is responsible for the data and safety monitoring. In addition, Dr. Timothy Mickleborough, a faculty member within the Department of Kinesiology, will serve as an independent data safety monitor for the study. Data will be analyzed by subject number. Thus, analysis of data will be done without any identifying features to individuals. Statistical software will be used to analyze data for significance. Results will be reported through traditional scientific outlets such as journals and presentations. Communication with the IRB regarding safety will be reported directly by the primary investigator.

7.0 Study Withdrawal/Discontinuation

Subjects can voluntarily withdraw from the study at any time by contacting any of the researchers on the study via any available means (personal contact, email, phone, etc.). If a researcher on the project wishes to withdraw a subject from the study, they will

contact the subject directly (personal contact, phone, email, etc.). Possible indications for withdrawal by a researcher include: concern that a subject could injure himself performing one of the exercise tasks in the study (perhaps due to poor coordination), results that do not meet the criteria for inclusion in the study, an abnormal response to exercise or hypoxic exposure, an abnormal response to Cetirizine, an inability to complete the exercise tests, inability of a subject to complete a task properly to obtain valid measures, etc.

8.0 Statistical Considerations

Paired t-tests will be used to determine differences between Cetirizine and Placebo trials for select dependent variables (e.g. mass, percent fat). A 2 x 2 (condition by time) repeated measures ANOVA will be used to determine pre- vs. post-test differences across conditions with select dependent variables (e.g. plasma histamine). A 2 x 5 (condition by time) repeated measures ANOVA with a priori simple main effects and a Bonferroni correction for multiple pairwise comparisons will be used to determine differences between conditions for select dependent variables (e.g. ventilation, VO_2, SpO_2) obtained at each km of the 5km time trials.

A power analysis was completed using previous literature (Prefaut et al., *Med Sci Sports Exerc*, 1997). Their data examined the change in arterial PO_2 levels pre- and post-antihistamine, which relates to our outcome variable of arterial oyhemoglobin saturation. From their data, we were able to calculate an interventional treatment effect (Cohen's d) of 0.61. Using a one tailed test to match our directional hypothesis, a power analysis with that treatment effect indicates that approximately 9 subjects will provide adequate statistical power (i.e. $1 - \beta > 0.80$) to show significant differences at the $p < 0.05$ level (experiment-wise error rate). With the potential for drop-outs and non-qualifiers after the initial VO_{2max} screening, we anticipate testing a total of 15 subjects.

9.0 Privacy/Confidentiality Issues

Data will be coded to help preserve confidentiality. Data will be stored on computers in locked rooms or in password protected files. Paper will be stored in locked rooms. Informed consent will be obtained and the testing procedures will be completed in a closed, private laboratory setting at the School of Public Health, with only the subjects and investigators present.

10.0 Follow-up and Record Retention

The intention is to maintain the data indefinitely. Once data are to be deleted, paper will be shredded and data permanently deleted from computers and portable storage mediums.