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PROTOCOL TITLE

Alleviation of Acute Sore Throat Pain and Inflammation

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INTRODUCTION/BACKGROUND INFORMATION

The nasopharynx (located between the nose and throat) is the main site of viral replication during upper respiratory infection (URI) (Winther et al 1986). Infections often start in the nose and are carried down to the nasopharynx. The nasopharynx is also the main site of bradykinin release, which would in turn stimulate nociceptive nerves in the throat, hence the feeling of a sore throat following a nasal infection,and a sore throat being among the most common and earliest indicators of an upper respiratory infection such as the common cold or influenza (Eccles 2005).

Despite the plethora of over the counter (OTC) products and supplements available to the US consumer, almost none have shown efficacy for common cold symptoms in clinical studies. A Cochrane meta-analysis found that non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin when taken orally are “somewhat effective” in relieving discomfort caused by a cold (Kim et al 2015). We have developed three possible treatments with and without aspirin, each containing a mix of several natural compounds which act synergistically to resolve inflammation and prevent damage to the respiratory lining in an effort to treat common cold symptoms.

Bradykinin is a naturally occurring peptide molecule that is one of the first chemical signals generated by pharyngial cells that will ultimately result in common cold symptoms (Eccles 2005). At least three prior clinical studies have used bradykinin to induce common cold symptoms in healthy subjects (Rees and Eccles, 1994; Doyle, Boehm, and Skoner, 1990; Proud et al., 1988). According to these studies, bradykinin release from the nasopharynx causes inflammation and pain. Each of these studies cites prior *in vitro* research that outlines the biochemical pathways and mechanism of action for this.

Our previous research as well as that of others has shown that bradykinin induces arachidonic acid which then releases COX-1 and COX-2 to increase levels of PGE2, a downstream

inflammatory signal (ref), and that PGE 2 may induce Il-8 has well as other inflammatory chemokines and cytokines.

Acetyl salicylic acid (aspirin) is a COX inhibitor and therefore, a logical option for treating COX-induced inflammation locally. Aspirin is commonly used as a symptomatic treatment for occasional pain, but according to several clinical and laboratory studies, aspirin has strong anti-viral as well as anti-inflammatory properties that can affect cold symptoms and cold duration (Glatthaar-Saalmuler et al 2017; Eccles et al., 2003; Sessa et al., 2017) .

AIMS & OBJECTIVES

We aim to test various treatments against placebo for clinical efficacy against sore throat pain as our primary endpoint and common cold symptoms as our secondary endpoint. Subjects who are affected by mild to severe sore throat pain lasting less than 2 days will be seen virtually by a physician and randomly assigned to receive either placebo or one of three different treatments. Treatment groups will contain placebo and/or a combination of aspirin-based tablets and throat sprays. The study will be conducted in a double-blind format. Only subjects who are unlikely to have a bacterial infection (such as strep throat) based on comorbid symptoms and presence of fever will be enrolled.

The dependent variable will be a visual analog score (VAS) of sore throat pain on a 100mm scale (Sore Throat Pain Intensity Score described below). The visual analog scales used in these studies have been well-validated for sore throat and other types of pain studies (Schactel et al., 2014 and references therin). Secondary endpoints will include changes to the modified Jackson Score.

HYPOTHESES

We hypothesize that subjects receiving spray treatment will report an average sore throat score that is one-half as high as those not receiving treatment and that their sore throat pain will be alleviated significantly faster than subjects receiving placebo. We hypothesize that the aspirin tablet combined with the aspirin and/or wintergreen throat spray will decrease sore throat pain as well as improve Jackson scores for common cold symptoms. This hypothesis is based on our own data using human biopsy tissue showing that Treatment decreases inflammatory prostaglandin production by at least 50% without damaging respiratory tissue and is also based on studies of aspirin treatment for the common cold (Glatthaar-Saalmuller et al., 2017). The Treatment will consist of a formulation of active and inactive ingredients listed in the “Additional Information” section of this protocol. The placebo will consist of vehicle buffer, a sub-therapeutic dose of menthol, and a sweetener. The sub-therapeutic dose of menthol is included so the placebo will taste and smell similar to treatment. Since a multitude of mechanisms contribute to the placebo effect, such as expectations, learning, memory, and motivation (Gupta and Verma 2013), we aim to remove as many stimuli as possible from the placebo group to control for these effects.

METHODS

OVERVIEW OF THE STUDY DESIGN

Subjects will be recruited via targeted social media advertisements (Facebook). Subjects interested in enrolling in the study will call a number listed in the ad or fill out an online form and be called back by the Clinical Trial Manager (CTM).

The CTM will ask potential participants a series of questions on the phone to determine their initial eligibility and enter responses on a digital form (CTM Intake Form) contained on a HIPAA-compliant platform.

The CTM will arrange an in-person visit by the Clinical Trial Administrator (CTA) to the participant's home for that evening as well as a virtual visit by the physician (PI) also for that evening. In addition, the CTM will email participants a copy of the Informed Consent (IC) for them to look over. The CTA will collect a signed physical copy of the IC during their visit as well as baseline sore throat assessments.

The CTA will collect vital signs from each participant during the in-person visit and fill out digital forms (CTA Intake Form). The CTA will also provide the participants with study materials and randomly assigned and double-blinded interventions or placebo.

Subjects will be randomized with respect to which treatment or placebo they receive, and whether they get the placebo or treatment spray or lozenge. The spray will be applied every hour during waking hours and the tablet will be taken every four hours during waking hours. Subjects will be asked not to eat or drink anything for a few minutes after administration.

Subjects will be asked at four-hour intervals during waking hours to rate their sore throat pain on a validated, paper-based sore throat pain scale, Sore Throat Pain Intensity Scale (STPIS) consisting of a 100mm line along which participants mark their pain intensity (Schactel et al., 2014 and references therin).

The study will end when participants complete their second day of treatment and surveys.

The study will be conducted in a double-blind format, neither the participant nor the CTA, CTM, or PI will know whether the participants are getting treatment or placebo. Participants will be coded and randomized by a third party as the treatments are bottled.

The study will only be unblinded at the end of the study after the data analysis has been completed and by the Adverse Events Specialist (AES) in the case of adverse events.

STUDY POPULATION

Healthy adults, half male, half female, aged 18-65 with no history within the past 30 days of serious allergy, asthma, nasal or otologic disease, and no symptoms of upper respiratory infection (URI). After age 65 many of the exclusion criteria listed below become more common. We feel it is important to enroll an equal number of males and females to control for gender bias in the data.

This will be controlled for in the recruitment process and adjusted if needed by controlling social media targeting criteria. Initially the target population will be: age 18-65, living in the Washington DC/northern Virginia area, retired, government employee, teacher, non-activee duty military personnel, or college student.

INCLUSION AND EXCLUSION CRITERIA

Inclusion

Healthy adults between the ages of 18-65 that do not meet any of the exclusion criteria listed below, and who rate their sore throat at least a 3 on a 10 point scale, and who have had a sore throat for less than 48 hours by the time they complete the CTM assessment.

Exclusion

Sore throat for more than 2 full days at the time of CTM assessment

Fever or development of fever during the course of the trial

Positive COVID-19 test or influenza test at CTA visit

Likelihood of strep throat (to be determined by PI to the best of their ability)

Less than 2 doses of the COVID vaccine

Any allergies to eggs, milk, or aspirin

Females who are pregnant or test positive for pregnancy at the CTA visit

Any chronic disease such as asthma, hypertension, post-nasal drip, gastroesophogeal reflux disease (GERD), cadiopulmonary obstructive disorder (COPD), diabetes, cancer, HIV

Any history of allergy in the last 14 days for which they took medication

Anyone with fever above 101 or who has taken medication other than birth control in the last 30 days

Anyone taking an ACE inhibitor

Participation in another clinical trial within the last 6 months or during this trial

Anyone who smokes

STATISTICAL CONSIDERATIONS

ANALYSIS PLAN

The design of this study will be a between patient, non-crossover, randomized controlled trial. The primary endpoint of this study is a time-weighted summed difference in pain intensity on the sore throat pain intensity scale over 36 hours after the first dose of medication (STPIS 1st entry Day 1 compared to STPIS 4th entry Day 2). For the study to have 80% power and 20% effect size, we believe we will need at least 100 participants per condition. Our hypothesis is that Biovanta will decrease STPIS score by 25-50%. Our assumptions and our hypothesis are based on a previous study utilizing this endpoint with an average baseline STPIS score of 79.1 (+/- 8.2) (Schachtel et al., 2014). Assuming a 50% drop-out or exclusion rate, we aim to enroll a total of 400 participants across all four conditions.

Efficacy will be determined by t-test comparing time-weighted summed differences in STPIS scores for placebo and Biovanta treatment groups. Secondary endpoints will include changes in STPIS at different time points and changes in Modified Jackson Score over the course of the study.

SAMPLE SIZE JUSTIFICATION

Based on a similar prior study of an NSAID containing lozenge for sore throat (Schachtel et al., 2014) a 59% decrease in time weighted summed difference for STPIS over 24 hours was seen with a p-value less than 0.01 with a sample size of 198 participants.

PROCEDURES AND DATA COLLECTION

Paper-based Patient Forms will be mailed to a PO Box monitored by the PI and the DA, located in Rockville MD. Survey assessments will be measured in mm from the beginning of the line and recorded on an Excel spreadsheet according to kit number (Participants will not be identified by name).

FOLLOW-UP

Participants will be able to contact thee PI, CTA, and CTM at any point during the trial. They will be encouraged to contact the trial staff should they suspect any adverse events including fever above 101 at which point a determination will be made by the PI or AES if they should continue. Participants will not be followed after the study ends. Other serious adverse events that the PI will discuss with participants include nausea or vomiting, difficulty breathing, and/or breaking out in a rash or hives.

If anyone else should require information gathered from this study, they will only receive the participant's code number, age, sex, ethnicity, but no other identifying information.

DATA AND SAFETY MONITORING

Participants will self monitor at home and fill out the survey questionnaire at the required time points. Participants will be encouraged to call 911 in case of emergencies such as anaphalactic shock and high fever. The PI and CTM will be available for questions and non-urgent matters.

The AES will be available to address serious adverse events and will unblind the study in cases such as high fever where the participant may be harmed by being in the placebo group, or for any other medically necessary reason.

DISCONTINUATION OF RESEARCH PARTICIPANTS/WITHDRAWAL

Participants will be able to voluntarily discontinue at any point in the study by calling the CTM.

RECORD RETENTION

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

REPORTABLE EVENTS

As required by Policy IRB-01, all reportable events will be reported to the IRB within the specified deadlines. Additional information is provided in the IRB Guidance on "Reportable Events." Events are defined in the IRB Guidance on "Acronyms and Definitions." For additional information see: http://research.downstate.edu/irb/irb-policies.html

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