Title: The Effect of Oral Guaifenesin on Pediatric Chronic Rhinitis: A Pilot Study

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The Effect of Oral Guaifenesin on Pediatric Chronic Rhinitis: A Pilot Study

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Introduction

Rhinosinusitis accounts for over 2 billion dollars in over the counter medication sales[1] and is one of the most common infections in the United States. In children, rhinosinusitis is estimated to account for 4.2% of all visits to pediatricians' offices during the winter months, and 17.3% of visits related to cough or cold symptoms[2]. Many factors such as atopy, anatomic obstruction and immunodeficiency predispose patients to developing rhinitis. Chronic rhinosinusitis (CRS), defined as a constellation of symptoms involving nasal congestion and obstruction, drainage, and thickened tenacious nasal secretions lasting for a period longer than 3 months[3], is an especially troubling entity in children.

Therapies for chronic rhinitis are aimed at alleviating these symptoms and frequently include the use of antihistamines, decongestants, and topical nasal sprays. Guaifenesin, a mucus expectorant derived from guaiac resin of the wood *Guajacum officinale* Linne[4], has been used for many years in the treatment of both acute and chronic rhinitis in an over-the-counter preparation. Other indications for its use include the treatment of cough and in cold formulations for adults and children. The mechanism of guaifenesin's action has been theorized to result from enhancement in mucus secretion from lower airway submucosal glands, with subsequent increase in total mucus volume and diminished mucus viscosity[4]. A number of reports have shown subjective improvements in nasal symptom scores using guaifenesin[5,6,7,8]; however, to date no randomized, controlled studies have been conducted to show clear, objectively determined benefit in pediatric patients[7]. We propose to investigate the effectiveness of guaifenesin in the relief of nasal symptoms in children with CRS using the sinonasal 5 survey (SN-5). We will also measure nasal airway volume using acoustic rhinometry, and nasal secretion mucociliary clearability and dynamic viscoelasticity.

In this pilot study we will test the hypothesis that:

1) Guaifenesin use over a period of 14 days improves subjective nasal complaints in pediatric patients with chronic rhinitis and nasal congestion, as measured by the SN-5 survey compared to use of placebo.

2) There will be an observed improvement in nasal volume and cross-sectional area following use of guaifenesin, measured objectively using acoustic rhinometry compared to use of placebo.

3) Following treatment with guaifenesin, nasal secretions will have more favorable mucociliary and sneeze clearability compared to use of placebo.

4.) Children that respond and those that do not respond to guaifenesin therapy will show significant differences in mucus characteristics and mucociliary clearance.

Materials and Methods

Study Design

This is a 14-day, randomized, placebo-controlled, parallel group, masked clinical trial of oral guaifenesin for the therapy of CRS in 36 children between the ages of 7 and 18 years. A 2:1 ratio of subjects on active medication to placebo will be used. Before starting the study, this study will be approved by the Virginia Commonwealth University Institutional Review Board for human research. Study subjects will be assigned a unique coded identifier and all information will be entered into an Excel database in a password-protected computer, to which only the investigators have access. There is minimal risk to the child in acoustic rhinometry measurements, collecting nasal secretions, and completing the SN-5 surveys.

Subject Recruitment

We will enroll 36 subjects from the pediatric otolaryngology clinic at the Virginia Commonwealth University Medical Center in a 2:1 ratio of active medication to placebo. The subjects will be between the ages of 7 and 18 years at the time of the study. They will be identified during routine clinical evaluation for CRS as defined as chronic rhinitis and nasal stuffiness of at least 3 months duration. Informed consent will be obtained from the subject's parent or legal guardian and assent will be obtained from the study subjects. Given our clinic volume we anticipate that it will take 12 months to complete subject enrollment.

Children with immunodeficiency, cystic fibrosis, acute or subacute symptoms, signs of bacterial infection, and/or those who are unable to cooperate with testing will be excluded. Children with documented use of the study medication in the month before evaluation and during period of symptoms will also be excluded.

Parents of the subjects will complete the SN-5 questionnaire as described below, at initial evaluation and again during a lead-in phase three days later to ensure stability of symptoms. Patients with an improved score will be excluded.

The Sinus and Nasal Quality of Life Survey (SN-5)

The Sinus and Nasal Quality of Life Survey (SN-5) is a validated and reliable questionnaire designed to score five areas of impact from sinonasal dysfunction (SN-5) in patients 1 year to 18 years of age[9,10]. Parents assess the impact of infection on nasal symptoms, emotion, and activity on a scale of worsening symptoms scored 1 through 7 to provide a quantifiable score capable of comparing both disease severity and the impact of interventions on subjective complaints. It has been shown as a responsive measure of health-related quality of life

for children with persistent sinonasal symptoms, suitable for use in outcomes studies and routine clinical care. Kay et al showed SN-5 test-retest reliability with an R value of 0.70[9]. Terrell et all demonstrated that the SN-5 correlated to disease severity as measured by the Lung-MacKay CT scan score[11].

Acoustic rhinometry

Acoustic rhinometry is used to measure cross-sectional volume of the nasal cavity allowing the calculation of nasal volume. Audible reflected sound waves are painlessly introduced through nasal adaptors into the nasal passages allowing the production of area-distance graphs. As the acoustic rhinometer is calibrated to a standard nose, accurate results can be obtained with good test-retest reliability[12,13].

Analysis of nasal secretions
Secretion collection

Collection and analysis of nasal secretions will be performed under direct vision at the time of rhinologic assessment. These will be collected using the Jun-Tymp-Tap (Xomed, Jacksonville, FL) as previously described[14].

Mucociliary clearability

A mature leopard frog (*Rana pipiens*) is pithed and rapidly decapitated. The lower jaw is then disarticulated and the palate removed by cutting through from the junction of the posterior pharynx and esophagus out to the skin of the back. The excised palate is placed on a piece of gauze saturated with amphibian Ringer's solution and the palate is allowed to rest in a

refrigerator at 4°C for 12 hours to deplete of mucus. The palate is then placed in a Plexiglas box

with a fitted top where humidity is maintained at 95-100% and temperature is kept at 24°C. The

palate is focused under a microscope so that a 5 mm micrometer scale runs between the optic

bulges to the opening of the esophagus. The movement of a 4μL mucus specimen is timed as the

trailing edge moves across a 3 mm segment. Three measurements of mucu transport rate are

taken to minimize variability[15].

Dynamic viscoelasticity

Dynamic viscoelasticity measures the strain response of mucus to an applied stress.

Because mucus is subjected to both low stress (ciliary beat) and high stress (sneeze) conditions,

we measure the strain developed in response to a dynamic stress. Viscosity (loss modulus) is the

loss of energy from a rheologic probe (stress) moving through a substance and thus the resistance

to flow. Elasticity (storage modulus) is the recoil energy transmitted back to the probe.

Viscoelasticity is a property of non-Newtonian fluids (gels). In the AR1500ex rheometer (TA

Instruments, New Castle, DE), a parallel plate geometry is used to assess the dynamic frequency

range of stress-strain of a 20μL nasal mucus sample over driving frequencies of 1 to 100 rad/sec.

The viscosity G" and the elasticity G' of the specimen are determined from these curves after

non-destructive creep transformation. Rheologic data can also be presented using vectorial

notation as tangent δ which is the ratio of viscosity to elasticity and G*, the vector sum of

viscosity and elasticity (mechanical impedance). The viscoelastic properties of a gel can be

plotted using Cartesian coordinates (G', G") or vector notation (G*, δ)[16].

Study Protocol

After informed consent is obtained, a medical history will be obtained, including demographic data of personal or family history of allergies, asthma, nasal or sinus disease, exposure to tobacco smoke, prior medication history and other associated conditions. A head and neck physical examination will be performed, including a thorough rhinoscopic examination. We will determine nasal patency both by direct visualization and scoring and by acoustic rhinometry pretreatment and at post treatment follow-up, using the mean of three consecutive measurements. Secretions will be collected from the middle meatus pre and post treatment using the Jun-Tym-Tap. The SN-5 questionnaire will be completed at two baseline visits and after completion of the study.

The subject will be given a 14- day course of either guaifenesin or matched placebo to be taken orally three times daily according to following age-matched dosages: children aged 7-11 years old will receive guaifenesin 200 mg TID, while children older than 12 will receive guaifenesin 400 mg TID. Randomization of medication use will be carried out by a study participant not involved in the direct care of the patient. A 2:1 ratio of subjects on active medication to placebo will be used. After two weeks, the subject will return for data collection including nasal examination, SN-5, acoustic rhinometry, and collection of nasal secretions. Subjects that do not return for their follow up visit will be contacted to schedule repeat examination.

Data Analysis

Power calculation

The primary outcome variable will be changes in the SN-5 questionnaire score. It has been reported that the mean score in children with CRS is 3.8 with a standard deviation of 1.0 and a temporal effect size of standard therapy equal to 0.88[11]. Thus assuming a normal distribution of results, using a paired 2-tail test to evaluate pre and post treatment outcome with an α error probability of 0.05 and a β (power) to detect a change of 0.88 at 80%, the critical t is 2.1788 yielding a sample size of 13 subjects per group[17].

We will also compare pre and post treatment nasal patency scores based upon subjective direct visualization score of % obstruction by a single investigator and objective mean acoustic rhinometry values, and pre- and post treatment mucus biophysical properties. Collected data will be used to evaluate the outcome measures most predictive of therapeutic response. We will compare responders to non-responders to see if there are factors in the history, physical examination, demographics (e.g. tobacco smoke exposure), or baseline measurement that predict response to guaifenesin. These pilot data will be used to develop a focused controlled prospective study of children and adults most likely to respond to oral guaifenesin.

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