Nasal hyperthermia and Simple Irrigation for Perennial Rhinitis*  
Changes in Inflammatory Mediators

John W. Georgitis, M.D.

Study objective: Local nasal hyperthermia or inhalation of heated water vapor is often recommended as a home remedy for various rhinitis disorders such as the common cold and allergic rhinitis. Inhaled heated vapor treatments and simple saline solution nasal irrigation were investigated for their effect on inflammatory mediator production in nasal secretions.

Design: Three treatments were given for nasal irrigation: heated water particles (large particle water vapor) at 43°C, heated molecular water vapor (molecular water vapor) at 41°C, and simple saline solution nasal irrigation. Nasal washes were done before each treatment (baseline), immediately after treatments, and at 30 min, 2, 4, and 6 h. Histamine, prostaglandin D₂, and leukotriene C₄ (LTC₄) concentrations were measured in nasal secretions and compared with baseline values.

Patients and participants: Thirty symptomatic patients with active perennial allergic rhinitis underwent three treatments at weekly intervals.

Measurements and results: Nasal histamine concentrations fell substantially with the nasal irrigation (p<0.01 immediately posttreatment and at 30 min; p<0.05 at 2, 4, and 6 h). Large particle vapor also reduced histamine concentrations for up to 4 h posttreatment compared with baseline values (p<0.05). Alternatively, molecular water vapor did not alter nasal histamine concentrations. Surprisingly, the three treatments did not alter prostaglandin D₂ concentrations over the 6 h. Leukotriene C₄ concentrations fell briefly after the large particle treatment but did not with the molecular water vapor. With saline solution irrigation, LTC₄ concentrations in nasal secretions were lower than baseline at 30 min to 4 h after a treatment (p<0.05).

Conclusions: This study demonstrated the usefulness of large particle vapor treatment and saline solution irrigation in reducing inflammatory mediators in nasal secretions and indirectly supports the clinical efficacy of these treatments for chronic rhinitis.

(Chest 1994; 106:1487-92)

Key words: local hyperthermia, nasal saline solution lavages, perennial rhinitis

Nasal hyperthermia or inhaled heated mist treatments have been proposed for years to treat severe congestion due to viral infections, the common cold, or allergic rhinitis.⁴,⁵ Anecdotal reports have suggested that there is a dramatic improvement in symptoms lasting up to weeks after a single treatment. This in turn has led physicians to recommend mist treatments for an extensive variety of nasal disorders, such as perennial rhinitis, allergic rhinitis, sinusitis, the common cold, and as part of postoperative care following nasal surgery or endoscopic sinus surgery.

Technologic advances in vapor generation have led to the development of a heated mist capable of delivering a large particle water vapor at 43°C for several minutes. A clinical trial with this heated mist has shown a reduction in allergic symptoms for several days following two 30-min treatments.⁶ Other studies have investigated the efficacy of heated mist treatments for acute sinusitis and the common cold.⁴,⁵ A molecular water vapor treatment has been developed recently that has a hydrophobic filter media that removes bacteria at an efficiency of 99.9 percent during flows of 50 L/min and delivers a vapor phase. However, none of the published reports have examined for any reduction of inflammatory mediators in these conditions.

This study evaluated two different heated vapor treatments compared with simple nasal lavage or irrigation since saline solution nasal sprays have been reported to be beneficial for rhinitis.⁵ The heated treatments were at 41°C for 20 min with a molecular water vapor, at 43°C for 20 min with a large particle water vapor (Rhinotherm), and simple nasal irrigation (using a Water Pik) at temperature of 39°C. The effect of the treatments was evaluated from changes in inflammatory mediators present in nasal secretions. The anticipated response was that since the heated vapor treatments reduce rhinitis symptoms, there would be a reduction in inflammatory mediators as a reflection of their clinical effect, whereas simple nasal irrigation would not alter

*From Department of Pediatrics, The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC. Manuscript received January 13; revision accepted March 16. Supported in part by NIH grant R29 AI 24598 and a grant from DeVilbiss Corporation.

Reprint requests: Dr. Georgitis, Bowman Gray School of Medicine, Dept. of Pediatrics, Medical Center Blvd., Winston-Salem, NC 27157
inflammatory mediator concentrations over any substantial time period.

METHODS AND MATERIALS

Study Design
This study was a crossover design involving 30 subjects aged 18 to 65 years with perennial allergies and was approved by the Clinical Research Practices Committee of Bowman Gray School of Medicine. At weekly intervals, patients underwent three baseline nasal lavages (1 ml lactated Ringer’s solution) followed by the heated mist treatments given for 20 mins. The molecular water vapor treatment consisted of the heating coils with a water reservoir capable of producing molecular water vapor at 41°C. The vapor output was connected to standard ventilator tubing with nasal adapters. Patients directly inhaled the heated mist by placing the nasal adapters inside the external nares (4 mm inside). The large particle heated treatment was given using a commercially available unit (Rhinotherm). Briefly, water is heated to 45°C and mixed with air at a rate of 28 L/min and delivered to the nasal cavity using a hand-held tube approximately 3 to 5 cm from the external nares. The saline solution lavage was given using a nasal adapter (Grossan) connected to a device (WaterPK) capable of delivering 400 ml of water or saline solution. Patients irrigated one nasal passage by placing the adapter directly inside the nares occluding any external airflow. Both passages were irrigated for a complete treatment lasting approximately 15 min in duration. Repeated nasal lavages for mediator collection (three 1-ml volume of lactated Ringer’s solution) were done at the following time intervals: immediately after each treatment and at 30 min and 2, 4, and 6 h.

Patient Criteria
Thirty subjects with allergy completed the three treatments. Patients signed an informed consent and were able to understand the procedures to be done and the study objectives. Patients were 18 years of age or older and had to have a diagnosis of active allergic rhinitis with a physical examination consistent with the diagnosis of active allergic rhinitis. Patients also had to have a known sensitivity to house dust mite or mold allergens. Skin testing was done by the prick method with a wheel diameter of at least 5 mm greater than the diluent control site. Significant nasal congestion, runny nose, and postnasal symptoms were present at baseline with a severity symptom score of at least moderate to severe degree. None of the patients had active asthma or were receiving immunotherapy.

Patients were excluded from the study if they had had a recent history of upper respiratory tract infections or significant surgery of the mucous membranes. Patients requiring corticosteroids, cromolyn, or other intranasal medications to control their rhinitis were excluded. Individuals who were taking a long-term antihypertensive medication or monoamine oxidase inhibitors were prohibited from enrolling into the study. In addition, all patients withheld treatment with all oral and intranasal decongestants for at least 48 h prior to the initial visit. All oral and intranasal decongestants were prohibited throughout the course of the study. If a patient was taking astemizole or terfenadine, treatment with this medication was withheld for 6 weeks or 4 weeks, respectively, before starting the study. Treatment with oral corticosteroids and nasal corticosteroids was discontinued at least 2 weeks prior to the screening and injected corticosteroids were not given for at least 40 days prior to screening. Subjects with severe septal deviations, nasal polyps, or active sinusitis were excluded.

Mediator Assays
Nasal washes were combined for each time interval and stored on ice. Washes were then centrifuged for 15 min at 1,500 rpm. The supernatant was removed and stored at –60°C until all the assays could be performed.

Histamine
Histamine concentrations were determined using a standard competitive radioimmunoassay. Briefly, acylation buffer was added to polypropylene tubes (AMAC Inc, Westbrook, Maine). Standards were then added to appropriately labeled tubes. 125I-histamine (1 ml) was added to each tube. From samples and standards, 500 μl was transferred to monoclonal-antihistamine-labeled tubes and incubated overnight at 4°C. Samples and standards were counted for 1 min using a gamma counter. Standards were plotted on semilogarithmic graphs. A standard curve was determined by the computer with subsequent calculation for the unknowns. The assay had a variability of <10 percent and was fairly reproducible. Histamine concentrations in samples were calculated from radioactive counts and corrected for dilution factor. The sensitivity of this assay was <0.5 nM histamine.

Leukotriene C4/D4/E4
A competitive radioimmunoassay was used to measure LTC4/D4/E4 (Amersham, Arlington Heights, Ill.). Aliquots (100 μl) of samples or standards were placed in polypropylene tubes. A radiolabeled tracer (14, 15 (n)=3H-leukotriene C4, 0.5 μCi in ethanol water-acetic acid, 60:40:0.1, pH 6.9) was added (100 μl), followed by antiserum (peptide-leukotrienes E4, 100 μl). Various samples included a known concentration of LTC4 in order to serve as internal standards. Buffer was added to samples, standards, and nonspecific binding tubes. Tubes were incubated overnight at 4°C, then dextran-coated charcoal was added to remove unbound (free) leukotrienes. This suspension was centrifuged at 2,000 g for 15 min at 5°C and supernatants placed into scintillation vials with 10 ml scintillant. Radioactivity was measured over 4 min in a counter. The antiserum had the following cross-reactivity characteristics: LTC4, 100 percent; LTD4, 64 percent; LTE4, 64 percent; 11-trans-LTE4, 24 percent; LTB4 <0.001 percent; PGE2 <0.001 percent; and PGD2 <0.001 percent. Sensitivity was 5 pg per tube.

Prostaglandin D2
Concentrations for prostaglandin D2 (PGD2) were performed using a competitive radioimmunoassay (Amersham, Arlington Heights, Ill.). Briefly, the same procedure used a modification of the previously described assay, and was performed in the same steps as the leukotriene assay described above, with the following exceptions. For the PGD2 assay, the tracer was 3H-prostaglandin D2, 1 mcCi in methanol:water:acetonitrile, 3:2:1. The antiserum was anti-PGD2 with 7 percent cross-reactivity with prostaglandin J2, and <0.5 percent cross-reactivity to thromboxane B2. The assay was sensitive to 3 pg per tube.

Statistical Analysis
Paired Student’s t scores were used for changes from baseline in histamine, leukotriene C4/D4/E4, and PGD2 concentrations.

RESULTS
The histamine concentrations fell over time with each treatment, but the greatest decline was observed with the saline solution irrigation (Fig 1). At each time interval, the change in histamine concentrations compared with baseline was significant following the nasal irrigation (p<0.05 and 0.01). The large particle treatment had a similar decline but not to the degree

Nasal Hyperthermia and Irrigation for Perennial Rhinitis (John W. Georgitis)
or duration (only 4 h) as the saline solution irrigation (p<0.05). The molecular water vapor treatment had only a minimal effect on the percent change from baseline (p>0.05).

The LTC4 concentrations did not demonstrate any obvious decline after the heated vapor treatments (Fig 2). Changes from baseline for the simple nasal irrigation did reach significance at 2, 4, and 6 h (p<0.05).

With the heated treatments, the PGD2 concentrations showed a similar response to the LTC4 response in that there was no significant change following the treatment (Fig 3). Surprisingly, the simple nasal lavage also did not reduce PGD2 concentrations from baseline unlike the observed response with histamine concentrations.
**DISCUSSION**

This study evaluated the physiologic responses of local hyperthermia compared with simple nasal irrigation. Local hyperthermia, ie, inhaled heated vapor treatments, appeared to have a beneficial effect for the patients, especially based on changes in histamine concentrations in the nasal secretions. Histamine concentrations in nasal secretions fell significantly after the saline solution irrigation and large particle treatments whereas molecular water vapor had no substantial effect on histamine. Since histamine is found in the highest concentrations in nasal secretions of patients with rhinitis, these two treatments clearly altered the mast cell or basophil releasability of histamine during active rhinitis.

In addition, simple nasal irrigation decreased LTC₄ production for several hours compared with baseline values but had a minimal effect on PGD₂. The heated treatments induced only a small decline in these two mediators. In this study population, the concentrations of PGD₂ and LTC₄ were found in much lower concentration in nasal secretions compared with histamine. This difference in mediator concentrations has been noted in other studies. However, mediator release into nasal secretions does occur during short-term antigen exposure and for several hours after the exposure. The actual source of these mediators, LTC₄ and histamine, during allergic reactions may be different cells such as leukocytes, platelets, endothelial cells, and epithelial cells. However, most investigators believe that PGD₂ is produced primarily by mast cells after antigen stimulation and histamine comes from mast cells and basophils, whereas LTC₄ is produced by other inflammatory cells, including the neutrophil and eosinophil.

The lack of demonstrable reduction in PGD₂ and LTC₄ concentrations by the heated water vapor treatments was surprising taken in context with the histamine response. Yet, the large particle heated treatment and nasal irrigation clearly affected the cellular source of histamine, a preformed, granule-associated mediator. Of note, these treatments did not alter the mediators of the arachidonate pathway that requires cell membrane stimulation and the release of arachidonic acid release. This difference in mediator production is difficult to explain but suggests that these nasal treatments alter basophil, neutrophil, and eosinophil release of histamine and LTC₄ but not the mast cell since PGD₂ production is not changed. Alternatively, this indicates that some of the histamine production during allergic nasal reactions may be contributed by basophils at the site.

In another study involving heated nasal insufflation therapy, Johnston and associates also found that prior treatment with local hyperthermia was effective in preventing nasal congestion and vascular leakage seen with nasal antigen challenge in allergic subjects. This implies that histamine release in nasal secretions can be altered by the addition of fluid during active allergic inflammation.

There are no reasonable explanations for the ben-
Of the heated treatments had a shorter duration of effect on nasal inflammatory mediators. Clinically, nasal irrigation may be considered as a useful therapy since it reduces nasal histamine for up to 6 h after a single 15-min treatment.

REFERENCES