

Double-blind trial of a heated nasal aerosol in the treatment of perennial allergic rhinitis

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Background: The effect of heated, moisturized air, delivered at 40 L/min and 43° C, on allergic rhinitis was evaluated in two studies.

Methods: In the first study patients with chronic nasal symptoms and long-term exposure to a perennial allergen to which they were sensitive underwent 1 week of baseline observation and 1 week of treatment with either heated or room temperature moisturized air for 30 minutes twice daily. The effect of treatment was assessed by changes in nasal symptoms and nasal blockage index and by a global evaluation by the subjects at the end of the treatment period. In the second study subjects with a documented history of grass or weed pollen allergic rhinitis underwent titrated nasal pollen challenges immediately after treatment with either heated or room temperature moisturized air. The outcome was assessed by the end point of the nasal challenge and change in blockage index at the end point.

Results: In both models there was no significant difference in the response between those treated with heated and those treated with room temperature moisturized air.

Conclusion: This study did not demonstrate any evidence of a therapeutic effect of heated, moisturized air in the treatment of allergic rhinitis. (*J ALLERGY CLIN IMMUNOL* 1993;92:56-60.)

Key words: Allergic rhinitis, heated aerosol treatment

Delivery of a heated saline aerosol to the nasal mucosa has been reported to reduce symptoms of allergic rhinitis. The mechanism for this proposed beneficial effect of heated moisture is unknown; however, studies of the effect of heat on anaphylaxis in guinea pig tissues provide some rationale for this method of treatment.¹ In guinea pig lung and small bowel preparations, the allergen-induced release of histamine was inhibited as the temperature was raised to about 42.5° C; inhibition was rapid and persistent (for the 12 hours of the study) at 45° C. The inhibition was not due to alterations in surface-bound IgE but rather occurred through an effect on a heat-sensitive intracellular mechanism.

Several previous studies, in which a device that

produced a heated saline aerosol was used, reported a reduction in symptoms of allergic rhinitis,^{2, 3} and in one study, a reduction in nasal obstruction was observed.⁴

We performed research with the same device used in several of these studies (Rhinotherm, TwinMed Products, Inc., Santa Monica, Calif.) in the winter of 1990 (Nelson, unpublished data). In that study 40 subjects with allergic rhinitis and skin prick test results that were positive to cat or dog extract, who had a cat or dog living in their home, were treated with the Rhinotherm device in an unaltered state (airflow at 40 L/min, temperature projected to be 43° C) or in an altered state (airflow at 40 L/min at room temperature) for two 30-minute periods each day for 2 weeks. We found no significant difference in symptoms or nasal blockage index between subjects receiving heated therapy and those receiving room temperature therapy. Patients' global evaluation at the end of the study averaged 60.7 for the heated treatment and 63.1 for the room temperature treatment (0 = maximum deterioration, 50 = no change, 100 = maximum improvement in symptoms).

We noted that the devices were plagued by a number of technical problems. These included the

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reservoir leaking and the heating element cutting off during treatments. A post hoc assessment of the actual temperature output by the devices used in the study determined that the room temperature devices delivered vapor at approximately 27° C, whereas the heated devices delivered vapor at temperatures that often fluctuated over the course of the 30-minute treatment periods, with some devices never achieving temperatures above 41° C. Because the flawed performance of the Rhinotherm device had not permitted an adequate assessment of the effect of heated aerosol on symptoms of allergic rhinitis, we undertook a reexamination of this form of treatment with a device that avoided these technical problems.

METHODS

Subjects

Subjects with allergic rhinitis were recruited for the study. They were excluded if they had used nasally administered cromolyn, topical nasal decongestants, or an antibiotic in the past 2 weeks; nasal or systemic steroids during the previous month; or astemizole during the previous 3 months. Other antihistamines and anticholinergics were withheld for 3 days before beginning the study. Subjects were also excluded if they had a significant septal deviation, rhinitis medicamentosa, or large nasal polyps or if they had had a viral upper respiratory infection or acute sinusitis within 1 week before entry into the study.

Study design

Part I. In the first part of the study 20 subjects, aged 24 to 66 years, who had symptoms consistent with perennial allergic rhinitis and long-term exposure to an allergen to which they had positive skin prick test results (wheal at least 5 mm greater than negative control) were recruited. The implicated allergens were cat, dog, or indoor mold (*penicillium* or *Aspergillus* species). The patients recorded 1 week of twice daily symptom-medication scores (nasal pruritus, rhinorrhea, obstruction, and sneezing; 0 = no symptoms to 3 = severe symptoms and use of rescue medication [pseudoephedrine] up to 60 mg/day) and oral and nasal peak expiratory flows while undergoing no therapy. Subjects were then randomly assigned to one of two treatment groups; each group received saline aerosol delivered with an airflow of 40 L/min and a temperature of either 43° C or room temperature. Subjects used the device to which they were randomized (heated or room temperature aerosol) for two 30-minute periods each day for 1 week. During the week of therapy they continued to record symptom-medication scores twice daily and oral and nasal peak expiratory flow meter measurements twice daily.

At the end of their participation subjects completed a global evaluation using a 0 through 100 analog scale

(0 = maximum deterioration, 50 = no change, 100 = maximum improvement in symptoms).

Part II. In the second part of the study 10 subjects, aged 21 to 55 years, with a history of seasonal allergic rhinitis during the grass or weed pollen season and confirmatory positive skin prick tests and nasal challenge to timothy grass or Western ragweed (wheal at least 5 mm greater than negative control; symptom score of 5 with nasal pollen challenge) were recruited. The subjects underwent nasal pollen challenge immediately after treatment with aerosol at either 43° C or 27° C for 30 minutes. One week later the subjects were treated for 30 minutes with the alternative device (heated device for the group that received room temperature therapy and room temperature device for the group that received heated therapy); immediately after this treatment, they underwent a second nasal challenge.

Nasal challenges

Nasal challenges were performed by the method of Bousquet et al.⁵ Capsules that contained lactose or threefold increasing amounts of the clinically implicated pollen (timothy grass or Western ragweed [Miles Inc., Hollister-Stier Div., West Haven, Conn.]) from 50 to 36,450 pollen grains mixed with lactose were prepared. The contents of these capsules were insufflated into one nostril at 30-minute intervals with a nasal insufflator (Fisons Laboratories, Loughborough, England) with the patient refraining from inspiring during the insufflation. For each concentration the insufflator was actuated five times and the capsule opened to ensure that it was completely empty. Symptoms were recorded during the 30 minutes between insufflations in accordance with the method of Bousquet et al.⁵ The challenge was discontinued when a symptom score of 5 (out of a potential of 18) was attained, and this was termed the end point. Subjects also performed a nasal blockage index, before challenge and on achieving a symptom score of 5 or 30 minutes after the highest programmed dose of pollen was administered if a score of 5 was not reached.

Nasal blockage index

Nasal and oral peak expiratory flow readings were taken twice daily with a Mini-Wright Peak Flow Meter (Clement Clarke, Columbus, Ohio) in the first part of the study and before and on achieving a symptom score of 5 or 30 minutes after the highest programmed dose of pollen was given in the second part of the study. Nasal peak expiratory flow evaluations were performed by fitting an Artec mask (Artec, Indianapolis, Ind.) to the peak flow meter. Peak expiratory flows were converted to a nasal blockage index⁶ by subtracting the best nasal peak flow value from the best oral peak flow value, dividing the resultant number by the best oral peak flow value, and multiplying by 100 to convert to a percentage.

TABLE I. Symptom scores, blockage index, and global evaluation from part I

	Active (n = 10)	Placebo (n = 10)	p Value
Baseline symptom scores			
Mean	5.28	5.65	0.73
SD	0.90	0.56	
Treatment symptom scores			
Mean	5.39	5.35	0.97
SD	0.82	0.47	
Change in symptom scores			
Mean	0.09	-0.35	0.49
SD	0.50	0.39	
p Value	0.86	0.39	
Baseline blockage index	(n = 10)	(n = 9)	
Mean	57.76	37.96	0.004
SD	3.32	5.13	
Treatment blockage index			
Mean	60.11	36.34	0.002
SD	3.65	5.34	
Change in blockage index			
Mean	1.80	-1.61	0.31
SD	2.02	2.60	
p Value	0.40	0.55	
Global assessment			
Mean	61.67	67.52	0.56
SD	5.98	7.78	

Listed are the mean scores during a week of baseline observation and during a week of treatment with either heated (active) or room temperature (placebo) devices. The morning and evening blockage indices and symptoms scores have been combined to yield a single value. Although the mean blockage indices were lower for placebo both during baseline ($p < 0.004$) and during treatment ($p < 0.002$), there are no significant differences as a result of treatment.

Device

The device used in this study was a prototype. It has not been marketed in the United States. In the device an electrical heater transferred energy to water in a jarlike container and brought it to the boiling point. The steam produced within the device escaped under pressure through a tube and nozzle located toward the top of the unit. The escaping steam created a partial vacuum in the neck of a venturimeter located at the distal end of the nozzle. This vacuum not only drew up the water in the tube but also drew in ambient air in such manner that at ambient temperatures of 20° C with water vapor from the device at 100° C, the air was delivered at almost 100% saturation, at about 43° C, and at a flow rate of approximately 40 L/min. In addition to the escaping steam, some of the water from the jar at boiling point temperature, which was atomized into particles that ranged from 4 to 10 μ m in diameter, was delivered by a second tube. Thus the device delivered a combination of steam and spray, which was carried by a 1.5 cm tube with a nosepiece to the nostrils. The temperature was reduced in the room temperature devices by greatly increasing the input of side-stream air.

Subjects were unaware that the heated device was purported to be more effective than the device that produced aerosol at room temperature. Also, the investigator assisting in the device randomization was not involved in the nasal challenges and had no further patient contact during retrieval of the symptom-medication diaries.

Statistical analysis

In the first part of the study outcome variables examined were morning and evening blockage index, morning and evening symptom scores, and subjects' global evaluation at the end of therapy. As a preliminary step, a repeated measures analysis of variance was performed. This revealed no day of treatment effect for any of the outcome variables; therefore, mean scores were calculated for the week of baseline and the week of treatment. *T* tests were used to examine differences between means of the two treatment groups, and paired *t* tests were used to examine changes due to treatment within the treatment groups.

In the second part of the study, two outcome variables were measured: mean dose of pollen required to achieve the symptom score of 5 (expressed as mean

TABLE II. Mean nasal challenge end point and mean change in nasal blockage index

	Active (n = 8)	Placebo (n = 8)	p Value
Nasal challenge end point			
Mean	8.50	7.88	0.17
SD	0.38	0.44	
Change in blockage index			
Mean	11.88	11.13	0.92
SD	5.88	4.07	

Mean nasal challenge end point is expressed as the capsule number resulting in a nasal symptom score of 5, and mean change in the nasal blockage index is at the point of a positive challenge. There are no significant differences as a result of treatment.

capsule number) and change in the blockage index from baseline to the end-point challenge dose (after a symptom score of 5 was achieved or after the highest administered pollen dose if a score of 5 was not attained). An analysis of variance for crossover designs was used to examine treatment, period, and sequence (carryover) effects.

RESULTS

Part I

Twenty subjects successfully completed the home treatment phase. Blockage indices were available from 19. Data for the major outcome variables, blockage index, symptom scores during baseline and treatment periods, and the patients' global evaluations are included in Table I. There were no significant differences in symptom scores at baseline between the treatment groups. Blockage indices, however, were significantly lower in the placebo group. There were, however, no significant differences in the change in symptom scores, change in blockage index, or the patients' global evaluation between the group that used the heated device and the group that used room temperature device (Table I).

Part II

A total of nine subjects participated in the nasal challenge phase. One subject did not complete the challenge after room temperature treatment because urticaria developed before an end-point symptom score was reached. Therefore a total of eight subjects completed the challenges.

Two primary outcome variables were examined, mean dose (expressed as mean capsule number) required to produce the symptom score of 5 and change in the "blockage index" from baseline to end point (after a symptom score of 5 was achieved or 30 minutes after the highest programmed dose of pollen was given if a symptom score of 5 was not achieved).

The results of the nasal challenges are given in Table II. The differences between heated and room temperature devices in the end points of nasal pollen challenge and in the changes in blockage index were not significant.

DISCUSSION

To determine the efficacy of a heated nasal aerosol in reducing symptoms of allergic rhinitis we investigated a device that produced a saline aerosol delivered at 43° C with an airflow of 40 L/min. We compared these results with results of treatment with a similar device that was altered to deliver the aerosol at room temperature. This study consisted of two parts: in the first part efficacy was examined in subjects who had perennial allergic rhinitis caused by an environmental allergen to which they were sensitive and chronically exposed. There was no significant difference in morning or evening symptom scores, morning or evening nasal obstruction (as assessed by blockage index), or global assessment, when subjects who received heated therapy and those who received room temperature therapy were compared.

The second part of the study examined the effect of the device on nasal pollen challenges. Subjects with confirmed allergic rhinitis to timothy grass or Western ragweed underwent nasal challenges with the pollen to which they were allergic, with the use of a well-defined technique of graded challenges.⁵ The end point of the challenge was a symptom score of 5 or a dose of 36,450 pollen grains in subjects who did not have a score of 5. A nasal blockage index was obtained when the ceiling dose was reached or when a symptom score of 5 was reported. Again, no significant difference was observed between heated and room temperature therapy in either nasal challenge end point or change in blockage index.

There are a number of ways to assess nasal patency. We chose a method that used the difference between nasal and oral peak expiratory flow rates.⁶ Comparative studies in the same individuals have revealed, for resting readings in normal subjects, a correlation of 0.86 between the blockage index and measurement of nasal airway resistance by posterior rhinometry. Furthermore, serial measurements in normal individuals have revealed the coefficient of variation of the blockage index to be only 0.18, whereas it is 0.32 for posterior rhinometric measurement of nasal airway resistance.⁶

In this study, nasal challenges were performed with a method described by Bousquet et al.⁵ in which pollen grains were used. The results of this challenge technique have been shown to correlate with the occurrence of symptoms on natural exposure to the pollen. Bousquet et al.⁵ demonstrated that a symptom score end point of 5 was associated with the release of prostaglandin D₂ into the nasal secretions.

Although we were not able to demonstrate a reduction in symptoms of allergic rhinitis or nasal obstruction with a heated saline aerosol, several prior reports, in which an apparatus similar to the one used in this study was used, have reported efficacy. Warmed aerosol nasal treatment was first conceived of for the treatment of rhinovirus infections. It was later observed to have beneficial effects in the treatment of allergic rhinitis. Yerushalmi et al.,³ using the Rhinotherm device (a device with similar output characteristics to the one that we studied), demonstrated a 75% reduction in symptoms of perennial allergic rhinitis in subjects treated with this heated (43° C) aerosol device, whereas a control group treated with the same device producing room temperature aerosol experienced only a 28% reduction in symptoms. Ophir et al.² examined the efficacy of this device in patients who had perennial allergic rhinitis by assessing both reduction in symptoms and increase in nasal patency. They found that with heated treatment (40 L/min at a temperature of 42° C) there was a 37% reduction in symptoms and a 25% reduction in blockage index, whereas room temperature treatment (40 L/min, 27° C) resulted in a 14% reduction in symptoms and a 19% reduction in blockage index. In the study by

Ophir et al.² subjects noted improvement that lasted 5 days. Grossman et al.⁴ examined the efficacy of a similar device in subjects who had seasonal allergic rhinitis. Subjects received vapor either at 43° C and 20 L/min or 31° C and 6 L/min. Eighty-one percent of subjects treated with the high temperature and high flow rate experienced significant improvement, whereas only 36% of subjects treated with the low temperature and low flow rate noted a decrease in symptoms.⁴ The reason for the differences in results between these studies and ours is not apparent.

In conclusion, we have examined the efficacy of treatment with a heated humidified aerosol in subjects with allergic rhinitis; we measured its effect on symptoms of perennial allergy in patients who were sensitive to and chronically exposed to an allergen and its ability to ameliorate the effect of nasal challenge with timothy grass or Western ragweed. In both situations the device did not diminish symptoms of allergic rhinitis or result in a diminution of nasal obstruction as measured by the blockage index. Also, in the group with perennial allergic rhinitis, there was no significant difference between heated and room temperature treatment in the patients' global assessments.

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