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Comparison of the response to histamine challenge of the nose and the maxillary sinus: effect of loratadine

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Baroody, Fuad M., Anil Gungor, Marcy deTineo, Lauran Haney, Christopher Blair, and Robert M. Naclerio. Comparison of the response to histamine challenge of the nose and the maxillary sinus: effect of loratadine. *J. Appl. Physiol.* 87(3): 1038–1047, 1999.—To study the response of the maxillary sinus to histamine provocation, we performed a double-blind, randomized, crossover trial during which nonallergic subjects without symptoms of rhinitis ($n = 25$) received either 10 mg loratadine or placebo once daily for a week and then underwent nasal challenge with histamine (3, 10, and 30 mg/ml) followed, 24 h later, by a maxillary sinus challenge while still receiving the medication. Nasal challenge with histamine led to significant increases in vascular permeability, reflex nasal secretions, sneezing, and other nasal symptoms. Sinus challenge resulted in significant increases in vascular permeability within the sinus cavity ($P < 0.01$) and some nasal symptoms but no significant change in reflex nasal secretions. The response of the sinus mucosa to histamine was lower in magnitude than that of the nose. Treatment with loratadine resulted in a significant inhibition of the histamine-induced changes in both nasal and sinus cavities. Our data suggest the lack of a sinonasal reflex response to histamine provocation of the maxillary sinus of nonallergic individuals.

sinonasal reflex; antihistamine; challenge; secretory response

THE SINUSES are air-filled cavities within the skull named after the bones in which they are located: frontal, ethmoid, maxillary, and sphenoid. There is no consensus as to the physiological role of the sinuses, but acute and chronic sinus inflammations are increasingly being recognized as important health concerns (11, 18). Acute sinusitis is a bacterial infection that often follows an upper respiratory viral infection and is responsive to antimicrobial treatment. Chronic sinusitis, on the other hand, is characterized by prolonged symptoms (>3 mo) that are unresponsive to medical treatment and that are accompanied by evidence of mucosal thickening of one or more paranasal sinuses on imaging studies. Bacterial infection can accompany chronic sinusitis. The sinus mucosa obtained from patients with chronic sinusitis shows a preponderance of eosinophils and helper T cells (15, 17).

Because sinusitis almost always occurs with concurrent rhinitis, an international task force of rhinologists has recommended the term "sinusitis" be replaced by "rhinosinusitis" (14, 20). Like the nasal cavity, the paranasal sinuses are lined by pseudostratified columnar ciliated epithelium, but, unlike the nasal cavity, they have fewer glands and vessels and they lack cavernous sinusoids, the large vascular channels that contribute to nasal congestion by causing enlargement of the turbinates when they are engorged with blood. The sinuses are in close proximity to the nasal cavity, and secretions generated within these cavities drain into the nose. Symptoms of rhinosinusitis include purulent nasal drainage, nasal congestion, facial pain and fullness, headache, halitosis, and cough, and the diagnosis is usually made by history, physical examination, and radiological evaluation.

The existence of a nasonasal reflex is well known, and it has been shown in nasal challenge studies using histamine, capsaicin, cold, dry air, and allergen. When one nasal cavity is challenged with one of these stimulants, a secretory response is generated not only in the challenged cavity but also in the contralateral nasal cavity (5, 7, 22, 24–26). The secretory reflex response has been shown to be generated by glands and has been inhibited by premedicating the contralateral nostril with atropine, an anticholinergic (5, 7). Although studying the nasonasal reflex is relatively simple, investigating the presence of sinonasal or nasosinal reflexes is more complex because of technical difficulty in accessing nonoperated sinus cavities. The ostia connecting the sinuses to the nasal cavity are located in the middle meatal area of the nose and are small (<3 mm) and protected by bones such as the uncinate process.

SinoJect is a clinically available tool that has been used for maxillary sinus irrigations in subjects with acute and chronic sinusitis (8). It positions a catheter in the maxillary sinus that can be used to deliver and retrieve fluids to and from the sinus cavity. In this study, we used this tool to repetitively sample the maxillary sinus and to challenge the sinus with histamine. The purpose of this study was *1*) to compare the sinus and nasal responses to histamine; *2*) to investigate the existence of a sinonasal reflex; and *3*) to evaluate the efficacy of loratadine, a nonsedating H_1 antihistamine, on the histamine-induced responses in both the nasal and sinus cavities.

MATERIALS AND METHODS

Pilot and experimental study design. An initial pilot study was performed to assess the feasibility of the challenges. This involved eight healthy nonallergic subjects who were randomized to undergo a nasal histamine challenge, a histamine challenge of the maxillary sinus, and a control sinus challenge with repeated administrations of lactated Ringer (LR) solution. The challenges were separated by at least 48 h. This

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was followed by a double-blind, randomized, crossover trial in 25 healthy nonallergic volunteers. During this study, subjects received loratadine (10 mg) or placebo per os once daily for 7 days and then underwent a nasal challenge with histamine followed 24 h later, and while they were still on medication, with a maxillary sinus challenge with histamine. After a 1-wk washout period, subjects were crossed over to the alternate treatment. Nasal and sinus challenges with histamine were performed 1.5–3 h after administration of the study medication. Both protocols were approved by the Institutional Review Board of the University of Chicago, and all participants read and signed an informed consent form before their participation in each study.

Subjects. A total of 25 subjects were included in the studies. There were 11 women and 14 men with a median age of 23 yr and an age range between 19 and 31 yr. All subjects were healthy with no nasal symptoms and a negative skin-prick test to common aeroallergens in the Chicago area. Subjects with active respiratory infection within the previous 2 wk, nasal polyps or nasal malformation, significant medical conditions, or a history of allergic rhinitis, sinusitis, asthma, or multiple drug allergies were excluded.

Nasal challenges. All challenges were performed in the right, ipsilateral nasal cavity, and collection of reflex generated nasal secretions after each challenge was performed in the left, contralateral nostril (Fig. 1). Secretion weights were measured by placing a preweighed filter paper disk on the anterior portion of the nasal septum posterior to the mucocutaneous junction for 30 s by using a headlight, nasal speculum, and duckbill forceps. After removal, the disk was placed in an Eppendorf tube, which was then sealed and weighed as previously described (7). The difference between the pre- and postcollection weights represented the amount of nasal secretions produced during the collection interval. A rubber plug fitted with a catheter was used to occlude the right nasal cavity, thus providing a watertight seal of the nostril. A syringe fitted to the catheter allowed us to lavage the nasal cavity with various solutions with the subjects' head bent slightly forward to prevent lavage fluid from reaching the nasopharynx.

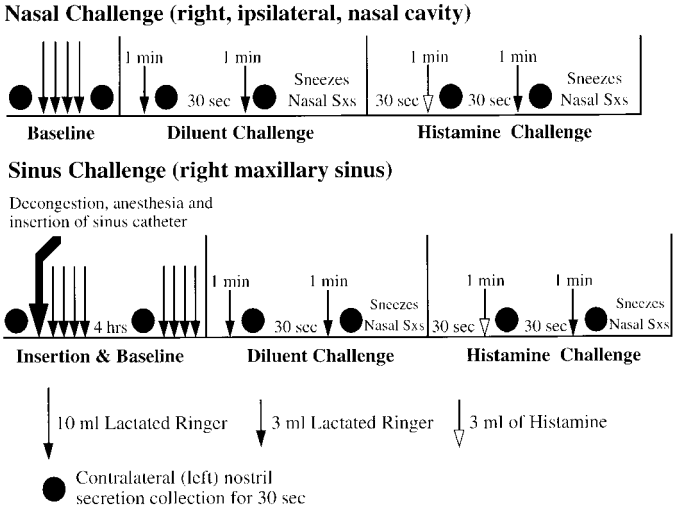

Fig. 1. Protocol of nasal and sinus challenges. Different challenges and measurements are depicted in this schematic. As detailed in MATERIALS AND METHODS, each of the histamine challenges is followed by 2 identical histamine challenges utilizing increasing concentrations. Doses of histamine used for sinus and nasal challenge were 0.1, 1, and 10 mg/ml during pilot study and 3, 10, and 30 mg/ml during experimental double-blind, placebo-controlled study. Sxs, symptoms.

Each challenge started by obtaining a baseline secretion weight measurement from the left nostril. This was followed by four 10-ml lavages with warm (37°C) LR solution in the right nostril to bring albumin levels to a stable baseline. Secretion weights were collected a second time in the left nostril. A sham challenge was then performed by instilling 3 ml of LR in the right nostril for 1 min. Immediately after instillation of the LR, left nostril secretion weights were collected for 30 s. One minute after withdrawal of the LR aliquot, another 3-ml aliquot of LR was used to lavage the right nasal cavity for 1 min. Secretion weights were again collected for 30 s from the left nostril immediately after insertion of the second LR aliquot. The number of sneezes and nasal symptoms during and immediately after each challenge were recorded by the subjects after both sham challenges. One minute after withdrawal of the second sham challenge, 3 ml of a histamine solution were used to lavage the right nostril for 1 min. After removal of this aliquot, a 3-ml aliquot of LR was used to lavage the right nostril for 1 min. Secretions were collected from the left nostril by placing disks for 30 s immediately after the histamine and LR solutions were inserted into the right nostril. Sneezes were recorded by the subjects after each of the lavages. Nasal symptoms were recorded by the subjects after each of the sham LR lavages and once at the end of each series of histamine-LR lavages. Identical challenges were performed with two histamine solutions of increasing concentrations, each followed by a LR lavage. The nasal plug was then removed, and the challenge ended. The doses of histamine used for nasal challenge were 0.1, 1, and 10 mg/ml during the pilot study and 3, 10, and 30 mg/ml during the experimental double-blind, placebo-controlled study.

Maxillary sinus challenges. These challenges were started by collecting secretions from the left nasal cavity for 30 s as described in *Nasal challenges* (Fig. 1). The right nostril was then prepared for insertion of the maxillary sinus catheter by inserting cotton pledgets soaked with oxymetazoline hydrochloride (0.05%; Pennex Laboratories, Verona, PA) and lidocaine hydrochloride (4%; Roxane Laboratories, Columbus, OH) in the inferior meatus, the space between the inferior turbinate and the lateral nasal wall. SinoJect (Atos Medical, distributed by Bivona Medical Technologies, Gary, IN) was then used to puncture the medial wall of the right maxillary sinus and introduce a plastic catheter that remained in the sinus cavity for the duration of each experiment. By using a special adapter, the sinus catheter was connected to a syringe that was used to lavage the antrum of the maxillary sinus. Immediately after catheter insertion, the sinus cavity was lavaged with four 10-ml aliquots of warm (37°C) LR, and the subject was asked to remain in the laboratory for the next 4 h with the sinus catheter in place to allow the body to seal the site of puncture. Left nasal secretions were then collected, and the right sinus cavity was lavaged with another four 10-ml aliquots of LR. A sham challenge was then performed by instilling 3 ml of LR in the right maxillary sinus for 1 min. One minute after withdrawal of the first LR aliquot, another 3 ml of LR were used to lavage the sinus cavity for 1 min. Secretions were collected from the left nasal cavity immediately after the instillation of each of the LR aliquots. Sneezes and nasal symptoms were recorded by the subjects for the period during and immediately after the sham challenges. One minute after the withdrawal of the second LR lavage, 3 ml of the first concentration of histamine were instilled into the right maxillary sinus cavity for 1 min followed 1 min later by a 3-ml aliquot of LR. Secretion weights were collected from the left nasal cavity immediately after instillation of each of the histamine and LR lavages into the sinus. Sneezes were

recorded by the subjects after each of the lavages. Nasal symptoms were recorded after each of the sham LR lavages and once at the end of each series of histamine-LR lavages. This was followed by identical lavages using two more solutions of increasing histamine concentration. After the last secretion collection was performed and sneezes and nasal symptoms were recorded, the maxillary sinus catheter was removed and the challenge ended. The doses of histamine used for sinus challenge were 0.1, 1, and 10 mg/ml during the pilot study and 3, 10, and 30 mg/ml during the experimental double-blind, placebo-controlled study.

Nasal symptoms. The number of sneezes was recorded after each challenge. Symptoms of runny and stuffy nose were recorded for the left nostril during the nasal challenges and for both nostrils during the sinus challenges. Symptoms of nasal itch, throat/palate itch, as well as eye itch were recorded for both challenges. The subjects ranked their nasal symptoms on a scale from 0 = no symptoms to 3 = severe symptoms.

Albumin assay. Lavages obtained during the challenges were centrifuged (3,500 *g* for 15 min at 4°C), cells were discarded, and the supernatants were stored at −20°C until assayed. Levels of human serum albumin, an index of vascular permeability, were measured in each of the lavages after the sham and histamine challenges by using an ELISA sensitive to 1 ng/ml of albumin (10). Lavages from the same patient during all visits were measured in the same assay to reduce interassay variability. Levels below the detection limit were arbitrarily assigned a value of 0.5 ng/ml.

Statistical analysis. On the basis of power calculations using the data obtained from the pilot study, we needed 20 subjects to complete the double-blind, placebo-controlled experimental study. It was estimated that, with this sample size, there would be an 80% power to detect significant differences between the two treatments with a significance level of 0.05 (2 tailed). Thus we recruited subjects until a total of 20 completed the study. The sum of the two time points after each challenge was used to analyze and plot the data, and nonparametric statistical tests were used. Friedman's ANOVA was first performed within each treatment group to compare the different time points during each challenge. If statistical significance was established ($P < 0.05$), a post hoc analysis was performed comparing the diluent challenge to each of the histamine challenges by using the Wilcoxon signed-rank test. To compare the effect of the two treatments on each of the measured parameters, we calculated the net change over the diluent challenge by subtracting the diluent response from each histamine response and then summing the resultant values. We then compared the net changes after each of the treatments by using a paired analysis with the Wilcoxon signed-rank test. To compare the nasal responses with those of the sinus to histamine provocation, we used data obtained during the placebo limb of the drug study and compared the net change from diluent for all these parameters between the nose and the sinus by using the Wilcoxon signed-rank test. The statistical tests were performed using a Macintosh computer (Apple Computer, Cupertino, CA) and Statview II statistical software (Abacus concepts).

RESULTS

Pilot experiment. Eight nonallergic volunteers were randomized to nasal challenge with histamine, sinus challenge with histamine, and sinus challenge with LR solution. The results are summarized in Table 1. During nasal challenge with histamine, only three of eight subjects had a sneezing response after at least one of the doses of histamine compared with sham challenge (ANOVA: $P = 0.09$). There was a reflex increase in left nostril secretion weights (ANOVA: $P = 0.004$) and an increase in the levels of human serum albumin (HSA) in the challenged right nasal cavity (ANOVA: $P < 0.001$) after increasing doses of histamine compared with the sham challenge with LR.

After right maxillary sinus challenge with histamine, only two of eight subjects had a sneezing response after at least one of the doses of histamine (ANOVA: $P = 0.1$). There were no significant increases in either left nasal secretions (ANOVA: $P = 0.14$) or right sinus lavage levels of HSA (ANOVA: $P > 0.999$) (Table 1). The control sinus challenge with repeated lavages of LR yielded no increase in sneezes (ANOVA: $P > 0.999$) in any of the subjects and no significant increase in sinus-lavage HSA levels after challenge (ANOVA: $P = 0.7$). Secretion weights in the left nasal cavity showed significant reductions from baseline with repeated LR challenges (ANOVA: $P = 0.02$) (Table 1).

To compare the response of the maxillary sinus after histamine to that after LR, we calculated the net change from sham challenge for all three parameters. There were no significant differences in the net change from sham challenge in the number of sneezes [0 (0–0) after LR vs. 0 (0–6) after histamine; $P = 0.2$], left

Table 1. *Nasal and sinus responses during the pilot experiment*

		Histamine, mg/ml		
	Lactated Ringer	0.1	1	10
Histamine nasal challenge				
Sneezes, no.	0 (0–0)	0 (0–2)	0 (0–3)	0 (0–4)
Contralateral SW, mg	7.6 (1.6–29.4)	11.2 (2.4–71.4)	14.5 (1.8–96.2)	42.6 (3.3–110.1)*
HSA, μg/ml	23 (3.1–104.2)	19.3 (4.1–92.9)	54.6 (4.5–251.1)	124.6 (13.2–1,051.2)*
Histamine sinus challenge				
Sneezes, no.	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–6)
Contralateral SW, mg	7.0 (5.2–32.4)	4.7 (2.5–66.9)	4.0 (1.7–23)	4 (2.1–31)
HSA, μg/ml	7.6 (2.1–54.7)	6.5 (1.0–40.2)	6.8 (1.7–23.3)	9.6 (2.9–41.5)
Sham sinus challenge				
Sneezes, no.	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Contralateral SW, mg	11.7 (3.8–47.6)	6.5 (1.8–29.2)*	6.7 (1.8–45.5)*	8.0 (1.8–46.2)
HSA, μg/ml	6.7 (1.5–57.9)	7.0 (1.0–36.8)	4.6 (2.4–29.3)	7.6 (2.4–23.3)

Values are medians with range in parentheses for 8 subjects. Contralateral, left nostril; SW, secretion weight; HSA, human serum albumin. *$P < 0.05$ vs. respective lactated Ringer challenges.

nostril secretion weights [−10.4 (−38.7–1.4 mg) after LR vs. −7.4 (−25.3–27.8 mg) after histamine; $P = 0.09$] or HSA levels [−2.5 (−84.3–8.2 μg/ml) after LR vs. 1.9 (−77.2–41.1 μg/ml) after histamine; $P = 0.4$]. These pilot experiments served the purpose of providing us with a negative control (LR challenge of the maxillary sinus) that showed that manipulation (introduction of the sinus catheter) and repeated sinus lavages with LR did not lead to any significant increases in the measured parameters. They also demonstrated a very mild, although nonsignificant, increase in some parameters after histamine challenge of the sinuses. Because of these results, we decided to increase the concentrations of histamine used for challenge and thus used 3, 10, and 30 mg/ml to perform the challenges in the next set of experiments during which the efficacy of loratadine was examined.

Double-blind, randomized trial using placebo or loratadine. Of 57 subjects screened for the drug study, 25 were enrolled. Five subjects dropped out: two for catheter malfunction, one for improper placement of the catheter, and two for noncompliance with the protocol. Six adverse events were reported during the study: three were related to catheter insertion (two vagovagal episodes and one facial swelling), two were headaches, and one was facial pain.

Nasal challenge. The median data (range) for all parameters monitored after nasal challenge with the subjects on placebo and loratadine are summarized in Table 2. After pretreatment with placebo, there were significant dose-dependent increases in the following parameters after nasal histamine challenge compared with sham challenge: sneezes, left nasal secretion weights, albumin levels in right nasal lavages, left nostril rhinorrhea symptom scores, left nasal congestion, nasal itch, throat/palate itch, and eye itch symptoms.

When the net change from sham challenge was compared between the two treatments, treatment with loratadine significantly inhibited the histamine-induced increase in sneezes, left nostril secretion weights, albumin levels in right nasal lavages, left nostril rhinorrhea, left nasal congestion, and throat/palate itch (see Table 4; Figs 2–6). Pretreatment with loratadine had no significant inhibitory effect on nasal itch and eye itch after histamine challenge.

Maxillary sinus challenge. The median data (range) for all parameters monitored after sinus challenge with the subjects on placebo and loratadine are summarized in Table 3. After pretreatment with placebo, there were significant dose dependent increases in the following parameters after histamine challenge compared with sham challenge of the right maxillary sinus: albumin levels in right sinus lavages, left nostril rhinorrhea, left nasal congestion, throat/palate itch, eye itch, right nostril rhinorrhea, and right nasal congestion.

To ensure that we were not missing a subgroup of subjects with a sinonasal reflex, we identified nine subjects who had a positive sneezing response to nasal histamine challenge when pretreated with placebo as defined by two or more sneezes after any of the histamine nasal challenges, and we performed post hoc analysis. These subjects had a significant increase in sneezes (ANOVA: $P = 0.004$) and left nostril secretion weight (ANOVA: $P = 0.001$) after right nostril histamine challenge but still failed to show a significant

Table 2. *Effect of loratadine on nasal challenge parameters*

Parameter	Lactated Ringer	Histamine, mg/ml			ANOVA (*P* Value)
		3	10	30	
Sneezes, no.					
Placebo	0 (0–0)	0 (0–5)*	0 (0–6)*	1 (0–7)†	0.001
Loratadine	0 (0–0)	0 (0–0)	0 (0–4)	0 (0–0)	NS
Con SW, mg					
Placebo	9.2 (2.3–82.4)	37.6 (4.9–102.8)†	45.6 (4.6–106.2)†	73.2 (14.9–113.8)†	<0.001
Loratadine	10.5 (2–47.1)	10 (1.1–84.4)	10.5 (1.4–99.8)	11.8 (1.4–71.4)	NS
HSA, μg/ml					
Placebo	10.3 (1–46.9)	38.1 (1.6–250.4)†	135.1 (3.3–763.6)†	378.8 (4–2,815.9)†	<0.001
Loratadine	12.4 (4.3–224.9)	9.8 (1–221.4)	10.1 (1–410.8)	7.9 (1–432.4)	NS
Con rhinorrhea, score					
Placebo	0 (0–2)	0 (0–3)*	1 (0–3)†	2 (0–3)†	<0.001
Loratadine	0 (0–3)	0 (0–2)	0 (0–3)	0 (0–3)*	0.03
Con congestion, score					
Placebo	0 (0–1)	0 (0–2)	1 (0–3)†	1.5 (0–3)†	<0.001
Loratadine	0 (0–2)	0 (0–3)*	0 (0–2)*	0 (0–2)*	0.004
Nose itch, score					
Placebo	0 (0–2)	0.5 (0–2)	1 (0–2)	1 (0–3)*	<0.001
Loratadine	0 (0–1)	0 (0–3)	0 (0–3)*	0 (0–3)	<0.001
Throat/palate itch, score					
Placebo	0 (0–0)	0 (0–2)	0 (0–2)	0 (0–3)†	<0.001
Loratadine	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–2)*	<0.001
Eye itch, score					
Placebo	0 (0–1)	0 (0–2)	0 (0–2)	0 (0–3)*	<0.001
Loratadine	0 (0–1)	0 (0–1)*	0 (0–1)	0 (0–2)	0.02

Values are medians with range in parentheses for 20 subjects. Con, contralateral (left nostril); NS, nonsignificant. *$P < 0.05$; †$P < 0.01$ vs. respective lactated Ringer challenges (obtained by Wilcoxon signed rank test). When ANOVA yielded no significant differences between the different points, no post hoc analysis was performed.

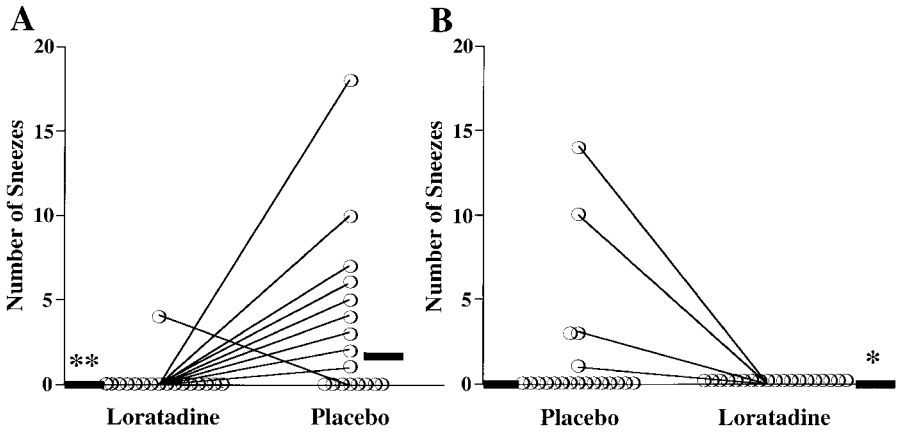

Fig. 2. Net change over sham challenge in number of sneezes after histamine provocation. Individual data for all 20 subjects are shown for nasal responses (*A*) and sinus responses (*B*). Solid bars, median values. Compared with placebo, pretreatment with loratadine resulted in a significant decrease in sneezes after histamine challenge of nose (**$P < 0.01$) and sinus (*$P < 0.05$) cavities. There was no significant difference in net change over sham challenge for sneezes between nasal and sinus responses with subjects on placebo treatment.

increase in sneezes or left nostril secretion weights after histamine challenge of the right maxillary sinus. We also identified a subgroup of 11 subjects who had a twofold rise in sinus lavage albumin levels over sham challenge after at least two of the three sinus histamine challenges during the placebo limb of the trial, and we performed post hoc analysis. When the response to challenge of the right maxillary sinus was analyzed in these subjects, there was a significant increase in albumin levels in sinus lavages after histamine challenge (ANOVA: $P = 0.0001$) but no significant increase in sneezing or reflex left nasal secretion weights.

When the net change from sham challenge of the maxillary sinus was compared between the two treatments, pretreatment with loratadine significantly inhibited the histamine-induced increase in sneezes, albumin levels in right sinus lavages, left nasal congestion, throat/palate itch, eye itch, and right nasal congestion (Table 4, Figs. 2–6). Pretreatment with loratadine had no significant inhibitory effect on left nostril secretion weight, left nostril rhinorrhea, nasal itch, and right nostril rhinorrhea after histamine challenge.

Comparison of nasal and sinus responses. To assess differences in the magnitude of the nasal and sinus responses, we compared the net changes in all measured parameters after histamine challenge when the subjects were premedicated with placebo. In general, the responses measured after nasal histamine challenge were greater in magnitude than those observed after sinus challenge with the following parameters showing significant differences: left nostril secretion weights, albumin levels in lavages of the cavities, left nostril rhinorrhea score, and left nasal congestion score (Table 5).

DISCUSSION

To our knowledge, this is the first study examining the response of the maxillary sinus cavity to challenge with histamine and investigating the existence of a sinonasal reflex. The pilot experiments helped us determine the appropriate dose of histamine to be used for the challenges and established the lack of a significant effect of introduction of the sinus catheter and repeated irrigation of the sinus cavity on the measured parameters. The placebo limb of the drug study allowed us to compare the responses of the sinus with that of the nasal cavity to histamine as well as to investigate whether a sinonasal reflex exists. As predicted, nasal challenge with histamine led to significant, dose-dependent increases in sneezing, vascular permeability, and other nasal symptoms as well as a reflex, contralateral increase in secretions. This provided a positive control for our studies of the sinus. Histamine challenge of the maxillary sinus resulted in significant, dose-dependent increases in vascular permeability but

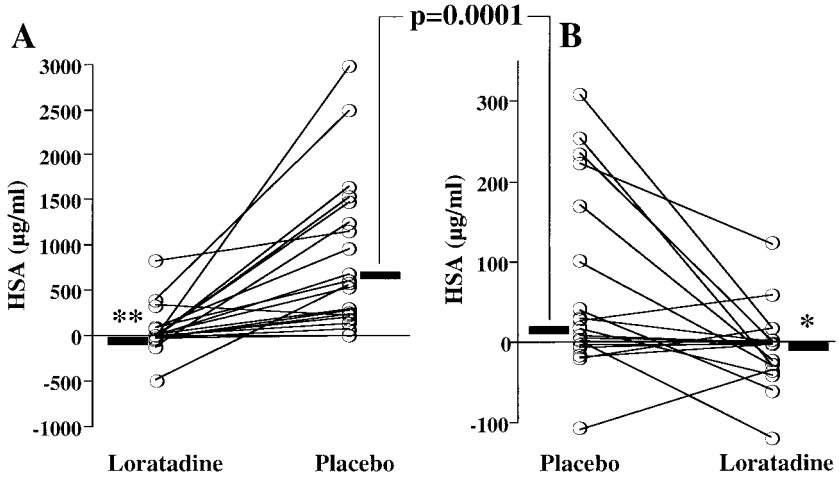

Fig. 3. Net change over sham challenge in levels of albumin in nasal and sinus lavages after histamine provocation. Individual data for all 20 subjects are shown for nasal responses (*A*) and sinus responses (*B*). Solid bars, median values. Compared with placebo, pretreatment with loratadine resulted in a significant decrease in albumin levels after histamine challenge of the nose (**$P < 0.01$) and sinus (*$P < 0.05$) cavities. When change over sham challenge of albumin levels was compared between nasal and sinus responses with subjects on placebo treatment, nasal challenge resulted in significantly higher levels of albumin compared with the sinus challenge ($P = 0.0001$). Note that there is a 10-fold difference in the scales depicted on *y*-axis between levels of albumin obtained after nasal challenge compared with those obtained after sinus challenge. HSA, human serum albumin.

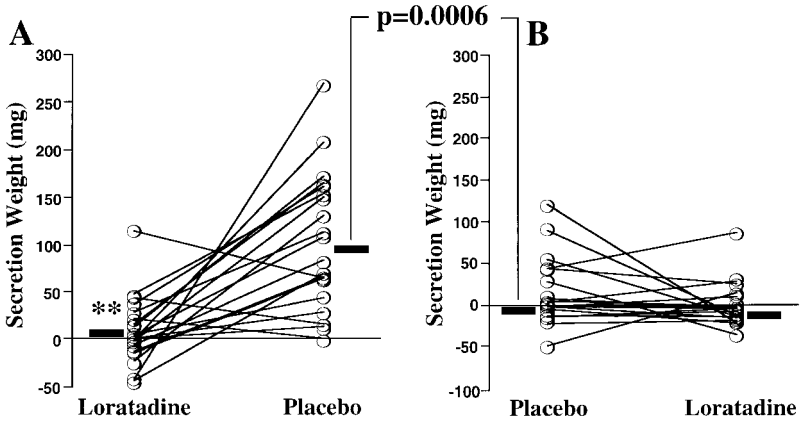

Fig. 4. Net change over sham challenge in contralateral (left) nasal secretion weights after histamine provocation. Individual data for all 20 subjects are shown for nasal responses (*A*) and sinus responses (*B*). Solid bars, median values. Compared with placebo, pretreatment with loratadine resulted in a significant decrease in contralateral nasal secretion weights after histamine challenge of the nose (**$P < 0.01$). Histamine did not lead to significant increases in contralateral (left) nasal secretion weights after sinus challenge with subjects on placebo, and loratadine had no effect on this parameter. When net change over sham challenge was compared between nasal and sinus responses with subjects on placebo treatment, nasal challenge resulted in significantly higher contralateral (left) nasal secretion weights compared with sinus challenge ($P = 0.0006$).

no contralateral secretory response. This part of the study demonstrated the active effect of histamine in the sinus and showed that the magnitude of this effect was less than that on the nasal mucosa with use of the same dose, concentration, and volume of histamine. The specificity of the response was demonstrated by inhibition with a receptor antagonist and appropriate controls. The absence of a contralateral response differed dramatically from the reflex secretory response seen after nasal stimulation with histamine. This was true even when subgroups with increased nasal and sinus responsiveness to histamine were considered.

The blood supply of the maxillary sinus is via branches of the maxillary arteries, which include the infraorbital, greater palatine, posterosuperior, and anterosuperior alveolar arteries and the lateral nasal branches of the sphenopalatine arteries. The blood vessels to the maxillary sinuses are considered to reach the mucosa both through their natural ostia and through the bone, but there is no recent histological description of the blood supply to the mucosa (13). Presumably, the vessels are like those present in the superficial portion of the nasal submucosa with absence of the cavernous sinusoids that are present in the deeper parts of the submucosa. We have previously noted that vessels are much less abundant in mucosa obtained from normal sphenoid sinuses compared with nasal mucosal biopsies obtained from healthy subjects (unpublished observations). Because histamine increases vascular permeability by interacting with H_1 receptors on blood vessels and because albumin in recovered sinus and nasal lavages is an index of changes in the vascular permeability of the respective tissues, our data suggest that there are probably fewer vessels in the sinus cavity than in the nasal cavity available for histamine stimulation, thus leading to almost 10-fold-lower albumin levels in response to identical doses, concentrations, and volumes of histamine. Another explanation for this finding is that the nasal mucosal surface area in contact with the histamine challenge solution was greater than the area of contact of that solution with sinus mucosa. Although identical volumes of the solution were utilized for both challenges, the nasal cavity has convolutions (the inferior and middle turbinates as well as

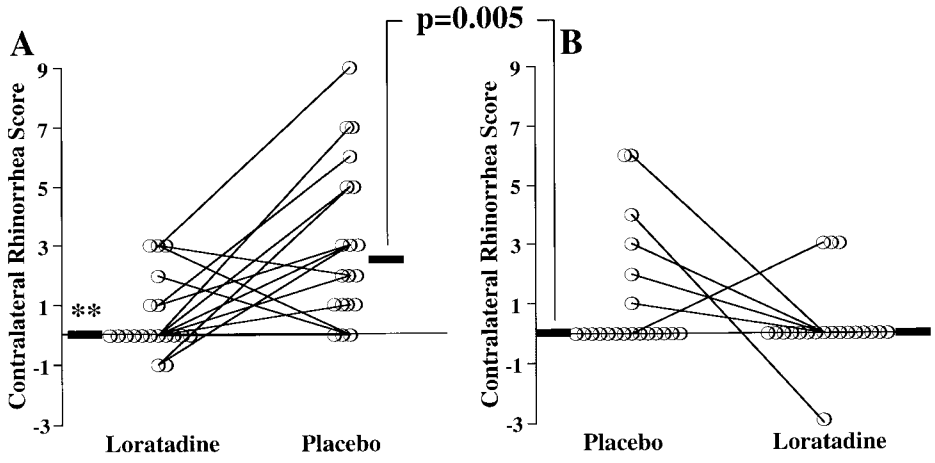

Fig. 5. Net change over sham challenge in contralateral (left) nasal rhinorrhea scores after histamine provocation. Individual data for all 20 subjects are shown for nasal responses (*A*) and sinus responses (*B*). Solid bars, median values. Compared with placebo, pretreatment with loratadine resulted in a significant decrease in contralateral (left) nasal rhinorrhea scores after histamine challenge of the nose (**$P < 0.01$). Histamine did not lead to significant increases in contralateral (left) nasal rhinorrhea scores after sinus challenge with subjects on placebo, and loratadine had no effect on this parameter. When net change over sham challenge was compared between nasal and sinus responses with subjects on placebo treatment, nasal challenge resulted in significantly higher contralateral nasal rhinorrhea scores compared with sinus challenge ($P = 0.005$).

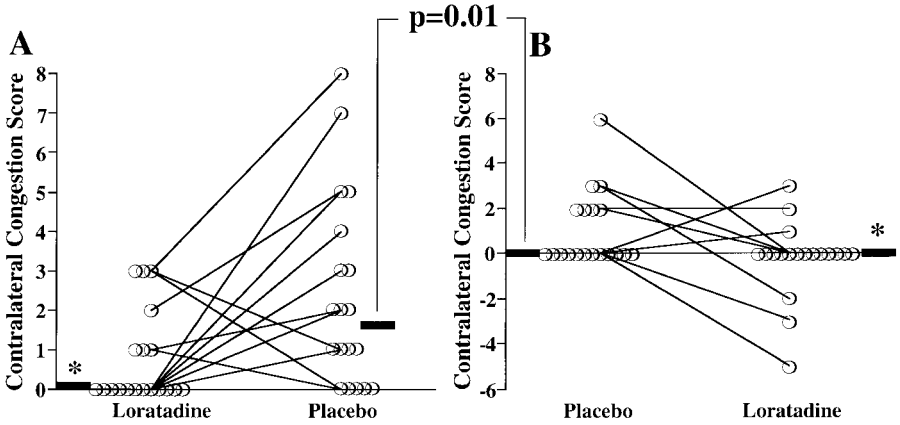

Fig. 6. Net change over sham challenge in contralateral (left) nasal congestion scores after histamine provocation. Individual data for all 20 subjects for nasal responses (*A*) and sinus responses (*B*). Solid bars, median values. Compared with placebo, pretreatment with loratadine resulted in a significant decrease in contralateral nasal congestion scores after histamine challenge of nose and sinus (*$P < 0.05$). When net change over sham challenge was compared between nasal and sinus responses with subjects on placebo treatment, nasal challenge resulted in significantly higher contralateral nasal congestion scores compared with sinus challenge ($P = 0.01$).

their respective meati) that the sinus cavity does not have, accounting for a larger surface area of contact and potentially more vessels with increased permeability in response to histamine with subsequent higher levels of albumin in recovered nasal lavages. Differences in H_1-receptor numbers, possibly related to decreased exposure to environmental stimuli, could also explain these differences.

The maxillary sinus mucosa is innervated by several branches of the maxillary nerve, a branch of the trigeminal nerve, which carries sensory input from the sinus mucosa to the central nervous system. The glands of the sinus mucosa are also innervated by secretomotor postganglionic parasympathetic fibers that originate in the superior salivary nucleus and travel within the facial nerve to the sphenopalatine ganglion where they synapse. A similar pattern of innervation supplies the nasal cavity. Neuropeptides, the presence of which has been established using immunohistochemistry in the nasal cavity (1–3, 19), probably also exist in the sinuses on the basis of findings in animal studies (21, 23). These are secreted by unmyelinated nociceptive C fibers (tachykinins, calcitonin gene-related peptide, neurokinin A, and gastrin-releasing peptide), parasym-

Table 3. *Effect of loratadine on sinus challenge parameters*

Parameter	Lactated Ringer	Histamine, mg/ml			ANOVA (*P* Value)
		3	10	30	
Sneezes, no.					
Placebo	0 (0–0)	0 (0–7)	0 (0–1)	0 (0–10)	NS
Loratadine	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	NS
Con SW, mg					
Placebo	10.2 (4–31.4)	6.6 (2.8–81.1)	8.5 (2.4–51.3)	10.1 (1.4–58.6)	NS
Loratadine	11.1 (4.8–29.9)	8.4 (3.3–29.9)†	8.4 (2–42.1)	11.2 (2.4–64.7)	0.027
HSA, μg/ml					
Placebo	11.6 (1–65.6)	20.1 (1–68.1)	25.8 (1–113.8)*	22.8 (1–270.1)†	0.006
Loratadine	17.1 (1–49.1)	12.3 (1–51.8)	8.8 (1–40.4)	8.6 (1–106.4)	NS
Con rhinorrhea, score					
Placebo	0 (0–0)	0 (0–3)	0 (0–3)	0.5 (0–3)*	0.005
Loratadine	0 (0–0)	0 (0–3)	0 (0–3)	0 (0–3)	NS
Con congestion, score					
Placebo	0 (0–2)	0 (0–2)	0 (0–3)†	0 (0–3)†	<0.001
Loratadine	0 (0–3)	0 (0–2)	0 (0–2)	0 (0–3)	NS
Nose itch, score					
Placebo	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–2)	NS
Loratadine	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	NS
Throat/palate itch, score					
Placebo	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–3)*	0.02
Loratadine	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)	NS
Eye itch, score					
Placebo	0 (0–0)	0 (0–1)	0 (0–2)	0 (0–3)*	0.006
Loratadine	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	NS
Ipsi rhinorrhea, score					
Placebo	1 (0–2)	1 (0–3)*	1 (0–3)	1 (0–3)†	0.009
Loratadine	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)*	0.04
Ipsi congestion, score					
Placebo	0 (0–1)	0 (0–2)	0 (0–3)*	0.5 (0–3)*	<0.001
Loratadine	0 (0–3)	0 (0–2)	0 (0–2)	0 (0–2)	NS

Values are medians with range in parentheses for 20 subjects. Ipsi, ipsilateral (right nostril). *$P < 0.05$; †$P \leq 0.01$ vs. respective lactated Ringer challenges (obtained by Wilcoxon signed-rank test). When ANOVA yielded no significant differences between the different points, no post hoc analysis was performed.

Table 4. *Effect of loratadine on nasal and sinus responses to histamine challenge*

Parameter	Nasal		Sinus	
	Placebo	Loratadine	Placebo	Loratadine
Sneezes, no.	1.5 (0–18)	0 (0–4)†	0 (0–14)	0 (0–0)*
Contralateral SW, mg	95.3 (−0.2–269)	2.6 (−44–114)†	−1.1 (−52–120)	−7.8 (−38–84)
HSA, μg/ml	601.8 (6–2,975)	−7.5 (−503–844)†	11.6 (−108–308)	−2.8 (−120–121)*
Contralateral rhinorrhea	2.5 (0–9)	0 (−1–3)†	0 (0–6)	0 (−3–3)
Contralateral congestion	1.5 (0–8)	0 (0–3)*	0 (0–6)	0 (−5–3)*
Nose itch	2 (−5–7)	0 (−2–6)	0 (−2–3)	0 (−2–3)
Throat/palate itch	0 (0–7)	0 (0–2)*	0 (0–5)	0 (0–1)*
Eye itch	0 (−1–7)	0 (0–4)	0 (0–5)	0 (0–2)*
Ipsilateral rhinorrhea	ND	ND	0 (−2–5)	0 (0–3)
Ipsilateral congestion	ND	ND	0 (0–8)	0 (−3–2)*

Values are medians with range in parentheses. Nos. represent net change over diluent challenge for all parameters. Ipsilateral, right nostril; ND, no data because these parameters were not measured after the nasal challenge. *$P < 0.05$; †$P < 0.01$ loratadine vs. placebo.

pathetic nerve endings (vasointestinal inhibitory peptide, peptide histidine methionine), and sympathetic nerve endings (neuropeptide Y) (1–3, 19). Our data suggest that, in contrast to the nasal cavity, stimulation of the maxillary sinus with histamine did not lead to a secretory response in the contralateral nasal cavity when assessed by objective measures (secretion weights). In support of the presence of sensory nerves within the maxillary sinuses is the clinical observation that many patients with acute maxillary sinusitis complain of pain and pressure during these episodes and that some of our patients did exhibit a sneezing response to histamine stimulation. Of interest is the significant increases in both contralateral rhinorrhea and congestion scores in response to histamine stimulation of the sinus. The fact that these subjective measures were not paralleled by an increase in the objective parameter, and that they were modest in magnitude, tends to discount the importance of these observations. The reason for the lack of this central reflex involving sensory stimulation followed by a parasympathetic efferent limb in response to sinus stimulation is not clear and might be related to differences in the innervation of the nose and the sinus not yet investigated. In support of that speculation is that challenge of the sinus mucosa with histamine did not generate as vigorous a sneezing response as did a similar challenge of the nasal cavity. Because the sneezing response is neurally mediated, this observation supports a possible difference between the innervation of the nose and the sinus. These observations can also be explained by a lower number of histamine receptors in the maxillary sinus mucosa or by the fact that the dose of histamine used was not high enough to stimulate sensory nerves and generate a measurable response.

Table 5. *Comparison of the net change in nasal and sinus responses to histamine during placebo pretreatment*

Parameter	Net Change	*P* Value
Sneezes, no.		
Nose	1.5 (0–18)	NS
Sinus	0 (0–14)	
Con SW, mg		
Nose	95.3 (−0.2–268.8)	0.0006
Sinus	−1.1 (−51.6–119.6)	
HSA, μg/ml		
Nose	601.8 (5.9–2,974.9)	0.0001
Sinus	11.6 (−108–308.1)	
Con rhinorrhea, score		
Nose	2.5 (0–9)	0.005
Sinus	0 (0–6)	
Con congestion, score		
Nose	1.5 (0–8)	0.01
Sinus	0 (0–6)	
Nose itch, score		
Nose	2 (−5–7)	NS
Sinus	0 (−2–3)	
Throat/palate itch, score		
Nose	0 (0–7)	NS
Sinus	0 (0–5)	
Eye itch, score		
Nose	0 (−1–7)	NS
Sinus	0 (0–5)	

Values are medians with range in parentheses. Net change = net change over diluent. *P* values are obtained from Wilcoxon signed-rank test comparing the responses after nasal and sinus challenge.

In the active treatment limb of this study, we examined the effect of loratadine, a nonsedating H_1 antihistamine without significant anticholinergic properties (4, 27), on the nasal and sinus responses to histamine stimulation. Loratadine is effective in relieving and preventing nasal and nonnasal symptoms of seasonal allergic rhinitis and has been used extensively in the treatment of this disease (12, 16). Our results show that pretreatment with loratadine resulted in significant reduction in histamine-induced nasal sneezing, increased vascular permeability, throat/palate itch, as well as the reflex-induced secretory response. This is in accordance with previous reports utilizing terfenadine, another nonsedating antihistamine (7), and parallels the observed effects of loratadine on antigen-induced changes in the nasal mucosa, another positive control for our experiments (6, 9). Loratadine also significantly reduced the sinus responses to histamine, including sneezing; and increased vascular permeability; throat, palate, and eye itch; as well as ipsilateral nasal congestion. This supports the belief that histamine's effects on the sinus were mediated via stimulation of H_1 receptors in the sinus mucosa and supports adequate penetration of the antihistamine into the sinus cavity.

Like all techniques available to study humans, the technique of sinus puncture used in our experiments

has advantages and disadvantages. After the sinus catheter is inserted, there is slight bleeding from the puncture site, which is self-limited and stopped at the end of the 4-h observation period before the initiation of the challenges. The lack of significant elevations in levels of albumin during the repeated LR lavages in the pilot experiments attests to the lack of bleeding into the sinus cavity during the challenge. There is always some concern that the stimulant solution applied to the sinus might overflow through the natural ostium of the sinus into the nasal cavity and lead to nasal stimulation. The volume of stimulant solution used (3 ml) was chosen to be smaller than the maximal capacity of the maxillary sinus (10–15 ml) to try to avoid this problem. Furthermore, the LR lavage used after the histamine challenge lavage also serves to wash the histamine solution out of the sinus to prevent mucociliary clearance from carrying part of the solution into the nasal cavity. When the patients were on placebo and the sinus was challenged with histamine (as seen from Table 3), there were significant increases in contralateral rhinorrhea, congestion, throat/palate itch, eye itch, as well as ipsilateral rhinorrhea and congestion. Although these changes are significant, their magnitudes are very small, and, for many of the parameters, the median values show no change from baseline, suggesting that these changes are not very important. Furthermore, the contralateral increase in subjective rhinorrhea was not paralleled by an objective increase in the weight of nasal secretions, which diminishes the importance of this finding. Thus it does not seem that overflow of histamine from the maxillary sinus into the nasal cavity is a major contributor to contralateral or ipsilateral nasal symptomatology.

The technique has several advantages that include its safety and ease of introduction of the sinus catheter without the risk of injury to the eye. As the present experiments show, it is easy to study maxillary sinus responses by using this technique, which enables the delivery of stimulants and the recording of resultant responses within the sinus by repeated lavages. When the limitations of the technique are acknowledged and appropriate control experiments performed, it is likely to be useful in helping us to better understand the sinus responses to different stimuli and the interaction between the nose and the maxillary sinus.

In conclusion, this study investigated responses of the nose and maxillary sinuses to histamine stimulation by adapting an existing method of maxillary sinus irrigation. In our population of healthy, nonallergic subjects, the results demonstrate a difference between the nasal and sinus responses to the same secretagogue, namely, a reduced response in the sinus compared with the nose and the lack of a contralateral reflex secretory response after stimulation of the sinus with histamine. Premedication with loratadine resulted in inhibition of both nasal and sinus histamine-induced responses, indicating that the sinus response was secondary to H_1-receptor stimulation and ensuring penetration of the antihistamine into the sinus mucosa after oral administration. Whether the response of the sinus to histamine and the generation of a sinonasal reflex response would differ in other study populations, such as subjects with perennial allergic or nonallergic rhinitis, chronic sinusitis, or asthma, remains to be investigated.

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