

Rhinitis therapy and the prevention of hospital care for asthma: A case-control study

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Background: Although clinical trials have demonstrated that rhinitis therapy improves subjective and objective measures of asthma, it is uncertain whether treatment of allergic rhinitis significantly affects the frequency of asthma exacerbations. **Objective:** The objective of this study was to determine whether treatment with intranasal corticosteroids and/or second-generation antihistamines is associated with changes in rates of asthma exacerbations resulting in emergency room visits and/or hospitalizations in patients with asthma and allergic rhinitis.

Methods: This was a nested, case-control study.

Results: Treatment with either nasal corticosteroids or second-generation antihistamines was associated with a lower risk of asthma-related emergency room treatment and hospitalization (adjusted odds ratio [OR], 0.51; 95% CI, 0.34 to 0.77 and 0.34, 0.18 to 0.62, respectively). Patients who used nasal corticosteroids had a significantly lower risk of both asthma-related emergency room treatment and hospitalization (adjusted OR, 0.75; 95% CI, 0.62 to 0.91 and 0.56, 0.42 to 0.76, respectively), whereas there was a trend toward lower risk of emergency room treatment and hospitalization in patients who used second-generation antihistamines (adjusted OR, 0.88; 95% CI, 0.62 to 1.26 and 0.68, 0.40 to 1.14, respectively). Combined treatment with both medications was associated with a further lowering of the risk of both emergency room treatment and hospitalization (adjusted OR, 0.37; 95% CI, 0.19 to 0.73 and 0.22, 0.07 to 0.63).

Conclusions: In patients with asthma, treatment of concomitant allergic rhinitis was associated with significant reductions in risk of emergency room treatment and hospitalization for asthma. (*J Allergy Clin Immunol* 2004;113:415-9.)

Key words: Allergic rhinitis, asthma, emergency room, hospitalization, corticosteroid, antihistamine

Recent epidemiologic studies have demonstrated that allergic rhinitis is a ubiquitous disorder in patients with bronchial asthma. Cross-sectional population surveys have estimated that the vast majority of patients with asthma also have rhinitis.¹ Laboratory studies have shown that experimentally induced nasal dysfunction may result in acute bronchospasm² and increased bronchial hyperresponsiveness to methacholine³ and exercise,⁴ suggesting that the upper airway may contribute to asthma severity. Clinical trials of intranasal corticosteroids in patients with allergic rhinitis and mild asthma have consistently demonstrated improvements in bronchial hyperresponsiveness to methacholine⁵⁻⁷ and exercise⁸ and to a lesser extent, asthma symptoms.^{5-7,9} Recent clinical trials of other nasal therapies, including antihistamines alone and antihistamines plus decongestants, have demonstrated small but statistically significant improvements in asthma symptoms^{10,11} and pulmonary function.¹¹ Based on our growing understanding of this relation, recent practice guidelines for asthma care have reinforced the importance of identifying and treating allergic rhinitis in patients with asthma.^{1,12}

Although nasal disease appears to play a role in modulating lower airway symptoms and function, it is unclear whether treatment of allergic rhinitis has a significant effect on the frequency of asthma exacerbations. To assess the possible association between rhinitis therapy and asthma exacerbations resulting in hospital care, we conducted a population-based, case-control study in patients with asthma and allergic rhinitis.

METHODS

Data source

The study population of patients with both allergic rhinitis and asthma was selected from a northeastern United States, commercial, managed-care organization with approximately 215,000 enrollees. The plan maintains extensive and comprehensive computerized records containing administrative, medical, and pharmacy claims for their membership. Diagnoses (recorded with the use of ICD-9 codes), procedures, laboratory tests, physician visits, emergency room visits, hospitalizations, and pharmacy records (recorded using National Drug Codes) are routinely entered into the managed-care organization's administrative claims records.

Selection of study subjects

Patients included in this analysis were identified as having both asthma and allergic rhinitis between 1996 and 1997; were at least 6 years of age; and had fewer than 2 claims for chronic obstructive pul-

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monary disease (ICD-9 codes 491, 492, 495, 496). Asthma was defined as having (a) 2 or more claims with a diagnostic code for asthma (ICD-9 codes 493.xx or 519.8x); (b) 1 claim with a diagnostic code for asthma and a prescription for an asthma-related drug (β -adrenergic agonist, inhaled corticosteroid, oral corticosteroid, theophylline, or cromolyn); or (c) filling 2 or more prescriptions for an asthma-related drug. Allergic rhinitis was defined as (a) having 2 or more claims with a diagnostic code for allergic rhinitis (ICD-9 code 477.xx); (b) filling 2 or more prescriptions for a second-generation antihistamine (cetirizine, fexofenadine, or loratadine); (c) filling 2 or more prescriptions for a nasal corticosteroid (INS); (d) filling 1 prescription for a second-generation antihistamine and 1 prescription for a nasal corticosteroid; or (e) having at least 1 claim with a diagnostic code for allergic rhinitis and filling at least 1 prescription for a second-generation antihistamine and nasal corticosteroid.

To be included, the diagnostic criteria for both asthma and allergic rhinitis had to be fulfilled during a 12-month period and the patient enrolled in the plan for a minimum of 12 months.

Patients with chronic obstructive pulmonary disease were excluded because of their chronically compromised lung function. Patients below the age of 6 years were excluded because the allergy medications studied are not indicated and seldom prescribed for this group.

Data collection

Information for calendar years 1996 through 1998 inclusive was extracted from the claims records of the cohort of patients identified above. The data included patient age, sex, prescriptions for nasal corticosteroids, second-generation antihistamines, β -adrenergic agonists, inhaled corticosteroids, oral corticosteroids, theophylline, and cromolyn; primary care and subspecialist (allergist and pulmonologist) visits for asthma, claims for serious comorbid conditions (congestive heart failure, cancers [nonskin], diabetes, HIV, bronchiectasis, idiopathic pulmonary fibrosis, sarcoidosis and cystic fibrosis), and enrollment based on Medicaid status.

Study design

We used a case-control study nested within the cohort of patients identified with asthma and allergy. Once patients met the criteria for asthma and allergic rhinitis during a 12-month period of time and had completed at least 1 year of eligibility in the health plan, their claims were searched forward from that date for asthma-related emergency room visits and/or hospitalizations (defined as the index date). The earliest that a patient could qualify, meeting both diagnostic and membership criteria, was January 1997, and the latest was December 1997. As an example, if a patient entered the plan in February 1996 and met both asthma and rhinitis diagnostic criteria by June 1996, they would then enter the study in February 1997. Once the patient qualified, they would then remain in the study until either an asthma event occurred, they disenrolled from membership, or they continued without an event until the end of December 1998. Emergency room visits and hospitalizations for asthma were defined as having a primary code for asthma and no additional codes for serious comorbid conditions (congestive heart failure, cancers [nonskin], diabetes, HIV, bronchiectasis, idiopathic pulmonary fibrosis, sarcoidosis, and cystic fibrosis). Each patient case was randomly matched with 4 control patients on the basis of sex and age (by decade). Control patients were drawn from the remaining patient pool, who met the asthma and allergy requirements and had been a plan member for at least 1 year before the month in which the event occurred for their matching case (index date). Control patients were used only once in the analysis.

The study was approved by the University of Pennsylvania Committee on Studies Involving Human Beings.

Statistical analysis

Conditional logistic regression (with the PHREG procedure used in SAS version 8.2) was used to calculate odds ratios (ORs) with 95% confidence intervals, comparing use of intranasal corticosteroid and/or second-generation antihistamine use in cases (first asthma-related emergency room visit and/or hospitalization) versus control patients (no hospital or emergency room event) during the 12 months before the index date. If patients had both an emergency room visit and hospitalization for asthma, the patient was included as a case in each database analysis. In the analysis, we tested the effects of any treatment (either nasal corticosteroids or second-generation antihistamines); nasal corticosteroids alone; second-generation antihistamines alone; and combined treatment with both medications. After calculating the crude OR, each of the other variables was considered as a possible confounder. Data on all potential confounders were gathered for the 12-month period before the month in which the index date was established. Variables affecting any of the ORs by 10% or more were included in a final model.¹³

To test for a dose-response relation, we calculated the adjusted OR for second-generation antihistamine and nasal corticosteroid use as continuous variables, excluding subjects with no usage. The same approach to identify potential confounders was used as described above.

We performed formal sensitivity analyses to quantify the effect of potential unmeasured confounding.¹⁴ Because this method requires a 2×2 table, we first imputed an adjusted 2×2 table from the crude data along with the adjusted odds ratio.^{15,16} We then calculated the OR and 95% CI, adjusting for an unmeasured hypothetical binary confounder assumed to be present in 10% to 50% of users of intranasal corticosteroids and/or second-generation antihistamines and in 5% to 40% of nonusers. We further assumed that the unmeasured confounder reduced the relative odds of asthma hospitalization and emergency room treatment by 10% to 50%.

RESULTS

Demographics

Three hundred sixty-one patients were treated in the emergency room and/or hospitalized for exacerbations of asthma and were matched to 1444 control patients (Tables I and II). Case patients used more antiasthma medications and had received more hospital care for asthma exacerbations during the year before the index month than did the control group.

Asthma-related emergency room visits

The results of the crude and multivariate analyses for asthma-related emergency room visits and hospitalizations are shown in Table III. Use of β -adrenergic agonists, inhaled corticosteroids, oral corticosteroids, prior emergency room visits for asthma, prior hospitalizations for asthma, and Medicaid enrollment status were the only variables that materially affected the crude OR. The effect of each of the remaining variables was tested, and none changed the OR by 10% or more. After adjusting for the above factors, use of either a nasal corticosteroid or second-generation antihistamine was associated with a reduction in emergency room utilization (adjusted OR, 0.51; 95% CI, 0.34 to 0.77). In the sensitivity analysis, this finding was robust in all scenarios examined (data not shown). For example, even if an unmeasured factor

TABLE I. Patient characteristics for emergency room analysis (mean and standard deviation)

	Case patients (n = 234)	Control patients (n = 936)
Age (y)	29.87 ± 15.62	30.03 ± 15.69
Male sex	32.48%	32.48%
Scripts for β-adrenergic agonists*	6.20 ± 7.55	2.91 ± 4.60
Scripts for cromolyn	0.21 ± 0.89	0.24 ± 1.10
Scripts for nasal corticosteroids	1.01 ± 1.93	1.16 ± 2.08
Scripts for 2nd-generation antihistamines	2.18 ± 2.96	1.89 ± 2.64
Scripts for inhaled corticosteroids*	2.19 ± 3.06	1.36 ± 2.60
Scripts for oral corticosteroids*	1.41 ± 2.44	0.38 ± 0.98
Scripts for theophylline*	1.14 ± 3.36	0.39 ± 1.95
Primary care visits*	8.46 ± 7.65	7.14 ± 9.31
Specialist visits*	3.33 ± 7.46	3.45 ± 7.74
Emergency room visits*	0.41 ± 0.96	0.04 ± 0.28
In-patient hospitalizations*	0.29 ± 1.29	0.03 ± 0.39

*P < .05.

TABLE II. Patient characteristics for inpatient analysis (mean and standard deviation)

	Case patients (n = 127)	Control patients (n = 508)
Age (y)	41.42 ± 17.95	40.95 ± 18.37
Male sex	35.43%	35.43%
Scripts for β-adrenergic agonists*	7.43 ± 9.24	3.45 ± 4.47
Scripts for cromolyn	0.08 ± 0.57	0.23 ± 1.02
Scripts for nasal corticosteroids*	0.81 ± 1.51	1.33 ± 2.23
Scripts for 2nd-generation antihistamines	2.61 ± 3.28	2.36 ± 3.15
Scripts for inhaled corticosteroids*	2.65 ± 3.55	1.91 ± 3.27
Scripts for oral corticosteroids*	2.28 ± 3.49	0.49 ± 1.36
Scripts for theophylline*	1.76 ± 3.89	0.75 ± 2.87
Primary care visits*	12.87 ± 11.31	7.71 ± 9.31
Specialist visits	2.96 ± 6.48	3.53 ± 8.96
Emergency room visits*	0.46 ± 1.00	0.02 ± 0.17
In-patient hospitalizations*	0.70 ± 1.70	0.02 ± 0.19

*P < .05.

TABLE III. Adjusted odds ratios for asthma-related hospital care in relation to intranasal corticosteroid and second-generation antihistamine use during 1-year period before the index date

Outcome	Crude OR (95% CI)	Adjusted OR* (95% CI)
Emergency room visits		
Either nasal corticosteroid or 2nd-generation antihistamine	0.86 (0.62-1.20)	0.51 (0.34-0.77)
Nasal corticosteroid	0.90 (0.77-1.05)	0.75 (0.62-0.91)
2nd-Generation antihistamine	1.18 (0.88-1.60)	0.88 (0.62-1.26)
Combination	0.88 (0.56-1.37)	0.37 (0.19-0.73)
Hospitalization		
Either nasal corticosteroid or 2nd-generation antihistamine	0.71 (0.45-1.11)	0.34 (0.18-0.62)
Nasal corticosteroid	0.78 (0.64-0.96)	0.56 (0.42-0.76)
2nd-Generation antihistamine	0.94 (0.63-1.39)	0.68 (0.40-1.14)
Combination	0.59 (0.30-1.15)	0.22 (0.07-0.63)

The index date for case patients is the date of the first hospital use (ER or IP) after meeting the criteria of having both asthma and allergic rhinitis and being a plan member for the 12 months before the event. The index date for control patients matches that for case patients. Control patients must also have been a plan member for the 12 months before the index date and have met the criteria for having both asthma and allergic rhinitis before the index date.

*Multivariate analysis controls for amount of use of β-agonists, oral inhaled steroids, oral steroids, asthma hospital admissions that occurred before the index date, asthma ER use before the index date, and Medicaid enrollment status. Control and case patients are matched for age group (by decade) and sex.

reduced the relative odds of emergency room utilization by 50% and was present in 50% of treated subjects and 5% of untreated subjects, the true adjusted OR would still be 0.66 (95% CI, 0.47 to 0.93). When the effects of rhinitis therapies were tested separately, patients who

used nasal corticosteroids had a significantly lower risk of emergency room visits (adjusted OR, 0.75; 95% CI, 0.62 to 0.91), whereas second-generation antihistamine usage showed a similar trend that did not reach statistical significance (adjusted OR, 0.88; 95% CI, 0.62 to 1.26).

The use of both medications together was associated with the greatest reduction in emergency room visits (adjusted OR, 0.37; 95% CI, 0.19 to 0.73). No significant relation was noted between the dose of either medication and alterations in the risk of emergency room utilization.

Asthma-related hospitalization

Treatment with either nasal corticosteroids or second-generation antihistamines was associated with a significant reduction in the risk of hospitalization for asthma (adjusted OR, 0.34; 95% CI, 0.18 to 0.62). This finding was also robust in all confounding scenarios examined (data not shown). For example, even if an unmeasured factor reduced the relative odds of emergency room utilization by 50% and was present in 50% of treated subjects and 5% of untreated subjects, the true adjusted odds ratio would still be 0.44 (95% CI, 0.28 to 0.68). Separate analyses for each class of medication revealed that users of nasal corticosteroids had a lower risk for asthma hospitalization (adjusted OR, 0.56; 95% CI, 0.42 to 0.76), whereas second-generation antihistamines demonstrated a trend toward reduced risk (adjusted OR, 0.68; 95% CI, 0.40 to 1.14). The combined use of both medications achieved the greatest reduction in risk of hospitalization (adjusted OR, 0.22; 95% CI, 0.07 to 0.63). The dose-response analysis showed a nonsignificant trend toward a relation of dose of intranasal corticosteroids only (data not shown).

DISCUSSION

These results suggest that treatment of allergic rhinitis reduces the risk of emergency room visits and hospitalizations for asthma. To our knowledge, this is the first case-control study to show such a relation.

A recently published cohort study reported that composite exposure of nasal corticosteroids or second-generation antihistamines was associated with a reduction in the composite outcome of hospitalization or emergency room use for asthma.¹⁷ Their study differed from ours in three important regards. First, the effects of nasal corticosteroids and second-generation antihistamines were not tested separately in the earlier study, nor was the effect of combined medication use. Second, their analysis did not distinguish between emergency room use and inpatient admissions. In addition, that study did not control for the effects of concomitant asthma medications. Finally, assessment of both exposure and outcomes during the same time interval may have overestimated drug exposure. By clarifying each of these issues, our study strengthens the previously observed association between rhinitis treatment and asthma exacerbations.

The relation between allergy medications and asthma-related hospital care may relate to a number of pharmacologic effects of nasal corticosteroids and oral antihistamines. In clinical trials of nasal corticosteroids in patients with rhinitis and asthma, the most pronounced effect in the lower airways has been reduction in nonspecific bronchial hyperresponsiveness.⁵⁻⁷ A number of theories has been offered to explain how nasal anti-inflammatory

therapy might affect lower airway reactivity, including (1) reduction in the systemic spread of inflammatory cells or mediators from the nose to the lung¹⁸; (2) downregulation of nasal-bronchial reflexes,² (3) improvements in chronic mouth-breathing, resulting in reduced deposition of inflammatory stimuli to the lower airways,⁸ and (4) direct effects on circulating or bronchial inflammatory cells secondary to systemic availability of the corticosteroid.⁶ As measures of lower airway reactivity are among the best clinical predictors of asthma exacerbations,¹⁹ these salutary effects of nasal corticosteroids might explain the findings observed in our study.

Clinical trials of H1-antihistamines have yielded variable results in asthma,²⁰ and, to date, no long-term, randomized studies have evaluated the effects on asthma exacerbations. The most recent large-scale study of an oral antihistamine (cetirizine) in patients with allergic rhinitis and mild asthma demonstrated small but statistically significant reductions in asthma symptoms.¹⁰ These improvements in asthma probably relate to histamine antagonism in the lower airways, resulting in both prevention of allergen-induced bronchoconstriction²¹ and in mild bronchodilation.²² The addition of pseudoephedrine appears to enhance the effects of the antihistamines alone, probably as the result of improvements in nasal patency and function. However, direct effects of oral decongestants on the lower airway cannot be ruled out.¹¹

Epidemiologic studies such as these are susceptible to a number of potential limitations that might affect the results. There are well-recognized problems with the validity and completeness of diagnosis data in claims data.²³ For that reason, we required two appearances of each diagnosis and/or a diagnosis and treatment. We could not measure use of over-the-counter, first-generation antihistamines because of the limitations of administrative data. However, since over-the-counter antihistamines use should be less common in users of second-generation antihistamines, lack of ability to identify these agents should bias the results against second-generation antihistamines rather than making them appear more effective. Similarly, although one might expect that patients with more severe asthma would be more likely to receive treatment for allergic rhinitis, this could not explain our findings of better outcomes in treated patients. In addition, when we adjusted for measures of asthma severity (including excessive use of short-acting β -adrenergic agonists, use of oral corticosteroids, and prior hospitalizations), the strength of these associations increased. Furthermore, formal sensitivity analyses showed that our results were robust even to relatively extreme degrees of unmeasured confounding (ie, an unmeasured factor that reduced the relative odds of the outcome by 50% and was present in 50% of treated patients and 5% of untreated patients).

Thus, these data suggest that treatment of allergic rhinitis with nasal corticosteroids or second-generation antihistamines may reduce the frequency of asthma exacerbations. Future randomized, prospective studies will be critical in confirming the significant improvements in asthma outcomes observed in this study.

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