Is Antihistamine associated with sinusitis? A Nationwide 10-year cohort study

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Abstract

Objective: Antihistamines are among the most prescribed medicines in otorhinolaryngology. This drug is excellent for rhinorrhea, sneezing and itching, however, it has a debatable effect in rhinosinusitis. At this point, it is useful to examine the relationship between antihistamine and the incidence of sinusitis based on large-cohort data analysis. Design: Retrospective study Setting: A Nationwide cohort study which used population-based insurance data (consisting of data from approximately 1 million patients). Participants: The antihistamine (AH) group consisted of patients who were diagnosed with allergic rhinitis (AR) between January 1, 2003 and December 31, 2003, taking at least one dose of antihistamine. Non-antihistamine (non-AH) group of patients who did not take antihistamines was obtained by 1:4 propensity score matching. Main outcome measures: Primary endpoint was the occurrence of sinusitis. Results: The adjusted hazard ratio for the sinusitis in the AH group was 1.53 [95% CI: 1.36-1.72] compared with the non-AH group. Sinusitis was more frequent in women (HR: 1.34), and less frequent the older the age (HR: 0.74, 0.58, 0.46, respectively) after exposure to antihistamine. In the subgroup analysis regarding the AH usage duration, there was no significant difference between the four subgroups. Conclusion: Antihistamines are probably the most prescribed medicines in the rhinologic area. But as all things have advantages and disadvantages, this large-scale longitudinal study shows that antihistamines are closely associated with sinusitis regardless of prescription duration and thus should be cautiously prescribed.

Introduction

Antihistamines are among the most prescribed medicines in otorhinolaryngology. This drug, which is excellent for rhinorrhea, sneezing and itching, is often prescribed in combination with upper respiratory infections such as colds and rhinitis. However, all drugs have side effects. Antihistamine has been reported to promote otitis media effusion,[1] and antihistamines such as dimetindene and azelastine have been shown to reduce ciliary beat frequency significantly.[2] This reduced ciliary beat frequency has been shown to reduce mucociliary clearance, a major defense mechanism in the respiratory mucosa, which ultimately lengthens the time that microorganisms or pollutants can contact nasal mucosa and increases the risk of sinusitis.[3] In particular, the reduced ciliary beat frequency is a characteristic of epithelial metaplasia.[3] In inflammatory conditions such as sinusitis, not only is the ciliary beat frequency reduced but mucociliary clearance function is decreased due to increased mucus production.[4]

Nevertheless, there are still many clinicians who prescribe antihistamines to patients with sinusitis.[5] This is because the ciliary beat frequency of patients who already have sinusitis does not differ significantly from controls who do not have sinusitis.[6] Antihistamine is one of the top three drugs prescribed by Asian pediatricians for the treatment of acute rhinosinusitis.[7] There is also a group who think that antihistamine is helpful in rhinosinusitis with allergic rhinitis.[8] In some animal studies, it is also reported that desloratadine inhibits allergic symptoms during allergen exposure and reduces the augmented bacterial response.[9]

Taken together, antihistamine has a debatable effect in rhinosinusitis. At this point, it is useful to examine the relationship between antihistamine and the incidence of sinusitis based on large-cohort data analysis.

Methods

Ethical consideration

All studies were conducted and designed in accordance with the Declaration of Helsinki using KNHIS-NSC data from Korea's health insurance service. This study also passed the Institutional Review Board of [removed for blind peer review] (IRB number 2019-04-010). Written informed consent was not required because of the nature of the study, as the KNHIS-NSC data are anonymized for research purposes.

Database

KNHIS is Korea's health insurance service, established by the Korean government in 1963, and since 1989, almost everyone in Korea has been enrolled. This database includes information such as the identification number of the individual, sex, age, residential area, and income quintiles, as well as diagnostic code, treatment history, prescription details including medication, and cost. KNHIS collects data by anonymizing it with the person-id to replace the 13-digit identification number of each individual. In KNHIS, the Korean Standard Classification of Disease (KCD) is used as the diagnostic code, similar to the WHO International Classification of Disease (ICD-10). The data used in this study consisted of approximately 1,025,340 individuals randomly selected from the total health insurance database in the period 2002 to 2013. The selected sample cohort of approximately 1 million individuals was divided into age (18 categories), sex (2 categories), income level (41 categories), and residential area (17 categories), and is representative of the approximately 50 million people in Korea.

Study cohort

We took the washout period for antihistamine in 2002 to be 1 year. In other words, patients who did not take antihistamine throughout 2002 were assigned to the patient group and the control group.

The antihistamine (AH) group consisted of patients who were diagnosed with allergic rhinitis (AR) between January 1, 2003 and December 31, 2003, taking at least three days of antihistamine medication. The inclusion criteria for the AH group were as follows: (1) patients diagnosed with KCD codes J301, J302, J303, J304, and (2) allergen skin test or multiple allergen simultaneous test (MAST), and (3) patients taking at least one days of antihistamine medication.

Exclusion criteria were as follows: (1) individuals who had been diagnosed with acute sinusitis or chronic sinusitis in 2002; or (2) who had undergone endoscopic sinus surgery, septoplasty, or turbinoplasty in 2002; or (3) who took antihistamines in 2002 or (4) who had died in 2002.

In order to wash out the effect of sinusitis on antihistamines, patients taking antihistamines in 2002 were excluded from the AH group, and patients with sinusitis in 2003 were included in the AH group.

In the control group (non-antihistamine; non-AH group) of patients who did not take antihistamines, their age, sex, residential area, and household income were not significantly different from the AH group. The 1:4 propensity score matching was performed to obtain the non-AH group in 2003.[10] As a result, the control group (non-AH) had 1988 individuals and the AH group had 497.

Outcome variables and operational definition of chronic rhinosinusitis (CRS) and antihistamine

Our study was largely divided into an antihistamine (AH) group and a non-antihistamine (non-AH) control group in AR patients, and the occurrence of sinusitis was checked. Antihistamine included the following drugs: 1st generation: chlorpheniramine, hydroxyzine hydrochloride, mequitazine, piprinhydrinate; 2nd generation: azelastine hydrochloride, bepotastine besilate, emedastine difumarate, ketotifen fumarate, olopatadine hydrochloride, desloratadine, fexofenadine hydrochloride, levocetirizine, ebastine. The detailed sex, age, residential area, and socioeconomic status of the study population were obtained from the database. Patients were divided into four groups: those younger than 20 years, those aged between 20 and 40, those aged 40 to

60, and those aged 60 or older. The residential areas were divided into urban (large cities – Seoul, Pusan, Daegu, Incheon, Daejeon, Gwangju, Ulsan) and rural (the rest of the region). Income level was divided into low (lower than 30th percentile), middle (30th to 70th percentile), and high (over 70th percentile). The definition of end point in this study was the occurrence of sinusitis. Thus, the elapsed time between the date of first visit to the hospital and the date of sinusitis during the follow-up period was calculated as naturally. Patients were censored after December 31, 2013 if no sinusitis occurred. The risk of developing sinusitis between the AH and non-AH groups was compared according to age, gender, residential area, and income level. As a subgroup analysis in the AH group, we defined as "1 week" if the consecutive duration of antihistamine usage is less than 1 week, "2 week" if the duration is less than 2 week, "1 month" if the duration is less than 4 week, and "over 1 month" if the duration is equal or more than 4 week .

Statistical analysis

Data analysis was conducted between January 2019 and March 2019. The Kaplan–Meier survival curve was used to examine the difference in survival function between the study groups.[11] We also used log-rank tests to compare the difference between the two groups. To determine whether antihistamine use increased sinusitis occurrence, we used Cox proportional hazard regression analysis which adjusted for other predictor variables to obtain the hazard ratio (HR) and 95% CI.[12] All statistical analyses were performed using R version 3.53 and Stata version 14.

Results

Baseline characteristics

The basic demographic information is summarized in Table 1. The total cohort was 2485, with 497 individuals in the AH group and 1988 in the non-AH group. Among them, there were 1186 men and 1299 women. There was no significant difference in sex (p = 0.976), age (p = 0.991), residential area (0.944), or socioeconomic status (p = 0.993) between the two groups. Therefore, we obtained the control group (non-AH) through appropriate propensity score matching from these statistics.

The HR was investigated for the occurrence of sinusitis during the follow-up period for 10 years using univariate and multivariate Cox regression models. Cumulative hazard ratio curve shows that there were significant differences between AH group and non-AH group. (Figure 1) In the subgroup analysis of the AH group, there was no significant difference between the four subgroup. ("1 week" if the consecutive duration of antihistamine usage is less than 1 week, "2 week" if the duration is less than 2 week, "1 month" if the duration is less than 4 week, and "over 1 month" if the duration is equal or more than 4 week) (p=0.70) (Figure 2)

After adjusting for factors such as sex, age, residential area, and socioeconomic status, sinusitis was more frequent in the AH group compared with the non-AH group (HR = 1.53; 95%CI: 1.36-1.72) (Table 2).

As for each factor, the occurrence of sinusitis was not related to a patient's income or residential area. Factors that influenced the occurrence of sinusitis were sex and age. Sinusitis was more frequent in women (HR: 1.34), and less frequent the older the age (HR: 0.74, 0.58, 0.46, respectively) (Table 2).

Discussion

There is a report that children with allergic rhinitis (AR) have significantly more sinusitis than those without AR.[13]It is also reported that the orbital complications of patients with acute bacterial sinusitis in the group with AR are more frequent than in the group without AR.[14] Of course, the mechanism for this has not been clarified; however, allergic rhinitis induces edema in the tissues of the nasal cavity, increases exudates, and causes symptoms such as nasal congestion and runny nose. This can block the ostiomeatal unit, which can lead to complications such as sinusitis.

We have divided AR patients into a patient group and control group. The reason for this is that people with AR frequently use antihistamines. However, because too many antihistamines are being prescribed in combination these days, it is necessary to discuss whether they are beneficial or detrimental to health.

In our study, antihistamine was shown to be approximately 1.53 times more likely to lead to sinusitis in AH group than in non-AH group. Non-AH group during the first year of 2003 had a sinusitis rate of about 61% over the next 10 years whereas patients in the AH group during the first year of 2003 had a sinusitis rate of about 74% over the next 10 years.

Histamine is actually an important mediator in causing symptoms such as runny nose, nasal congestion, and sneezing. The histamine-binding receptors include H1 receptors and H2 receptors, and antihistamine drugs have effects according to the location of each receptor attached to these receptors. The receptor that plays a major role in the nasal cavity is the H1 receptor, and H1 receptor antagonists are generally used as antihistamine drugs to improve symptoms such as rhinorrhea, sneezing and itching in the nose. Antihistamine drugs are divided into first-generation drugs developed earlier and second-generation drugs developed later. First-generation antihistamines are lipophilic and have a characteristic of passing through the blood-brain barrier (BBB), and with complications such as sedation, fatigue, attention disturbance, drowsiness, etc. These first-generation antihistamines have an anticholinergic effect that increases the viscosity of rhinorrhea, thus the ciliary beat frequency is reduced in dried nasal mucosa.[5] On the other hand, the second-generation antihistamines are lipophobic and do not pass through the BBB. However, these second-generation agents have no anticholinergic effect, and only have the effect of inhibiting histamine which is liberated from mast cells. Thus the second-generation antihistamines seem to have no beneficial effect on acute rhinosinusitis.[5]

Histamine also has a proinflammatory, immunomodulatory property.[15,16] Histamine itself increases TNF-α induced E selectin, ICAM-1 expression, and increases IL-6 and IL-8 in endothelial cells.[17,18] Indeed, H1 antihistamine reduces histamine-induced cytokine production and adhesion molecule expression in endothelial cells, and decreases ICAM expression. So antihistamines seem to play a beneficial role in chronic rhinosinusitis (CRS).[19]

When the mucociliary function is lowered, mucociliary clearance is delayed and movement of the mucus is disturbed. Unlike the lower airway, the upper airway, especially the sinus, can only be debrided by ciliary action.[20] In addition to the ciliary beat frequency, this ciliary transport is also affected by fluids around cilia, i.e. mucus.[21,22] This mucus is mainly secreted in goblet cells and consists of 1% NaCl, 0.5-1% free protein, 0.5-1% mucin (carbohydrate-rich glycoprotein) and the remainder water. Antihistamines alter the carbohydrate-water composition of mucus, resulting in ciliary stasis.[23]

We could not examine every single patient from a micro-perspective in the entire 1 million cohort, but we looked at it from a macro-perspective. In other words, we have confirmed that more sinusitis occurred in groups using antihistamines during a 10-year follow-up. Notably, in the subgroup analysis, the incidence of sinusitis according to the duration of antihistamine use was not significantly different.

The strength of this study is that it has a washout period of about 1 year (2002). First, we excluded patients with acute or chronic sinusitis complaints during the first year (2002). This is because antihistamine is an independent variable and sinusitis should be calculated as a dependent variable, thus eliminating possible interactions between the two variables. Second, all of the patients who used antihistamines for 1 year in 2002 were excluded. This was to prevent the residual effect of antihistamines. Finally, statistical validity was attained through a longitudinal study of about 10 years between AH patients who were recruited in 2003 and the control group obtained through propensity score matching.

The disadvantages of this study are: First, diagnosis of sinusitis and allergic rhinitis was made only by the diagnostic code without information such as CT or imaging tests. However, in this study, we tried to improve the diagnostic accuracy of allergic rhinitis by including patients who had had an allergic skin test or multiple allergen simultaneous test (MAST). Second, the results of this study did not consider family history, smoking history, drinking history, eating habits or other health-related indicators. Further research combining this information should be undertaken and would provide definitive results with regard to the effect of antihistamine on sinusitis.

Conclusion

Antihistamines are probably the most prescribed medicines in the rhinologic area. But as all things have advantages and disadvantages, this large-scale longitudinal study shows that antihistamines are closely associated with sinusitis regardless of prescription duration and thus should be cautiously prescribed.

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Figure legends

Figure 1. Survival curves of Patients in AH and non-AH group (AH; antihistamine, non-AH; non-antihistamine)

Figure 2. In the subgroup analysis of the AH group, there was no significant difference between the four subgroup. ("1 week" if the consecutive duration of antihistamine usage is less than 1 week, "2 week" if the duration is less than 2 week, "1 month" if the duration is less than 4 week, and "over 1 month" if the duration is equal or more than 4 week) (p=0.70)

Table 1. Characteristics of the study population

Variable	Control (non-AH) group (n=1988)	AH group (n=497)	Chi square	p value
Sex				
Male	948	238	0.0009	0.976
Female	1040	259		
Age (years)				
<20	395	98	0.1067	0.991
20-40	894	227		
40-60	504	123		
>60	195	49		
Residential area				
Urban	1006	253	0.0049	0.944
Rural	982	244		
Socioeconomic status (percentile)				
<30 (low)	971	243	0.0134	0.993
30-70 (middle)	193	49		
>70 (high)	824	205		

AH, antihistamine.

Table 2. Incidence per 1000 person-years and hazard ratios for sinusitis during 10-year follow-up period

	Study group			HR	
Variable	Total	Number of cases	Incidence per 100 person-years	Adjusted	U
Group					
Non-AH	1988	1220	95.7		
AH	497	368	150.1	1.53 (1.36-1.72)	1.
Sex					
Male	1186	697	90.4	1	1

	Study group			HR	
Female	1299	891	119.1	1.34 (1.21-1.48)	1.
Age (years)					
<20	493	356	151.9	1	1
20-40	1121	755	111.2	0.74 (0.65-0.85)	0.
40-60	627	355	84.7	0.58 (0.50-0.68)	0.
>60	244	122	65.2	0.46 (0.37-0.56)	0.
Residential area					
Urban	1259	803	103.8	1	1
Rural	1226	785	105.3	1.03 (0.93-1.13)	1.
Socioeconomic status (percentile)					
<30 (low)	242	150	92.1	1	1
30-70 (middle)	1029	649	102.8	1.19 (0.99-1.42)	1.
>70 (high)	1214	789	108.8	1.33 (1.11-1.59)	1.

AH, antihistamine; HR, hazard ratio.