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# Use of Rhinitis Antihistamines Induces Hypersensitive Bronchitis

**Rajan Pradhan[1]* and Sachin Pradhan[2]**

[1]*Project Hospital, NMDC, Kirandul, India*
[2]*DFSL, Mumbai, India*

## Abstract

**Background:** Antihistamine medicines are used in variety of allergic disorders including rhinitis of infectious as well as non-infectious origin. There lacks an extensive study suggesting the increased incidence of Bronchitis on exposure to antihistamine medication. From our experience we noticed increased incidence of Bronchitis in patients using anti allergic medication for rhinitis and this motivated us to undertake a retrospective study on the previous patients' management data.

**Method:** We collected and documented the clinical data during last 10 years of approximately 7650 patients treated in our clinic out of which we took 3101 patients for study. Antihistamine medicines Cetrizine and Fexofenadin were used in 2009 patients and these antihistamine medicines were not received by 1092 patients, which were termed as control.

**Results:** There was significant increase in the incidence of Bronchitis in the patients who were given antihistamine medicines in regular doses in the initial stage of disease.

**Conclusion:** The patients treated with antihistamines were more prone to develop bronchitis than the control group. There is compelling evidence that antihistamines have this side effect. Additionally, albumin bound structure of Cetrizine that is present in Protein Data Bank suggests that Cetrizine could be circulated in the blood stream to its target through albumin and so it might be possible for it to have distributed to other tissues and so its side reactions. Detailed molecular structural analysis and Ingenuity Pathway Analysis further suggest that cetirizine can bind proteins involved in infectious diseases (such as Bronchitis).

**Keywords:** Rhinitis; Antihistamines; Allergic disorders

## Introduction

Acute bronchitis is the inflammation of the bronchial mucous membranes that usually results from a viral infection; however non-infectious agents too have been shown to cause bronchitis. It is one of the most common medical conditions for which patients seek medical attention from physicians [1].

It is ironical that there is no single universally accepted definition of actual bronchitis despite the medical condition being routinely diagnosed in patients. This results in variable treatments being prescribed by physicians. According to webmd and a recent article, though, bronchitis is often treated with antibiotics; this pharmacological treatment is not very incisive in patients with uncomplicated acute bronchitis [2]. The problem is further complicated due to the associated side effects and the potential for antibiotic resistance in future. Bronchitis has been shown to have huge socioeconomic burden on society. Therefore due to the complexity associated with bronchitis diagnosis and treatment, it should be evaded at all cost.

After remaining in clinical practice for long time, we observe that patients treated with antihistamines for running of nose seen in upper respiratory tract infections are developing dry hacking cough with signs of Bronchitis [3, 4]. These patients got relieved of their cough with the use of bronchodilators. There are isolated reports in the literature regarding the development of Bronchitis [5, 6]. Few studies are available but don't appear to be exhaustive. Hence we studied previous data of patients available with us during last 8 years to have similar patients in the study. In summary, we have identified a new cause of bronchitis for the first time in the form a side reaction to rhinitis treatment by oral antihistamines.

In contrast to bronchitis, a relatively well accepted definition exists for allergic rhinitis; characterized as "a symptomatic disorder of the nose induced after exposure to allergens *via* IgE-mediated hypersensitivity reactions". 4 key symptoms signifiy rhinitis: (1) watery rhinorrhea (2) nasal obstruction (3) nasal itching and (4) sneezing [7-9].

The 2008 ARIA guidelines suggest 3 classes of treating rhinitis: (1) leukotriene receptor antagonists (2) first generation antihistamines and second generation antihistamines (3) topical steroids. Oral antihistamines are routinely prescribed by physicians [10]. Side effects like sedation, memory impairment and psychomotor dysfunction have been associated with the first generation antihistamines (like clemastine, diphenhydramine, brompheniramine and chlorpheniramine) and that limits their use in clinics. However, the second generation antihistamines (like cetrizine and fexofenadin) are more lipophobic and so deficient in penetrating the blood-brain barrier and so have much milder side effects, leading ARIA to recommend the later class of antihistamines over the former. It is important to note that oral antihistamines have been reported to be safe for children [7,8,11].

This study for the first time identifies a non-infectious/non allergic cause of bronchitis. The statistics might help the physician make a rationale choice of a particular antihistamine if it needs to be administered in a patient depending on the symptoms.

## Methodology

### Systematic statistical survey in patients with rhinitis

This study presents systematic documented results and observations of 3101 Rhinitis patients treated according to the FDA approved guidelines over a period of 8 years. This is not a clinical study. 1430 patients were selected in the group of 20-40 years and 1671 patients were selected in the age group of 40-60 years. Out of 1430 patients in the

***Corresponding author:** Pradhan R, Chief Medical Officer, Project Hospital, NMDC, Kirandul, India, Tel: (+91) 9425266471; E-mail: ddhsnmc@gmail.com

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age group of 20-40 years, 680 patients were males and 750 patients were females, and 483 patients (166 male patients and 317 female patients) in the group who did not receive antihistamines were taken as control and 947 patients were taken as those patients who received anti histamine medication which include Cetrizine 10 mg OD to 670 patients (329 males and 341 females), and Fexofenadine 120 mg OD to 277 patients (185 males and 92 females). In the age group of 40-60 years 703 patients (399 males and 304 females) received Tablet Cetrizine 10 mg OD and 359 patients (213 males and 146 females) received Tablet Fexofenadine 120 mg OD, while 609 patients (333 male and 276 female) who did not receive antihistamines were taken as control. The patient selection was made on the basis of age, sex, symptoms, signs, and investigations. Only those patients were selected who had no previous history of Asthamatic Bronchitis. Patients were grouped according to age (20-40 years and 40-60 years) and sex (M/F). Patients with similar symptoms were selected for study. Only those patients with fever in the range of 39 degree C to 41 degree C were considered in the study. Patients with throat irritation, running of nose, dry/wet cough, head ache and body ache were included in the study. Patients having these 5 symptoms were only considered. Patients reporting to hospital on 2nd day of the onset of symptoms were considered. Patients with throat congestion, nasal congestion and no ascultatory findings in the chest were considered for study. Patients with detailed investigations available with record like basic investigations, biochemical investigations, chest X-ray were taken for comparison. Patients with all investigations within normal limits except polymorphonuclear leukocytosis were considered in the study. Other parameters that could influence treatment outcomes were regulated to be as invariant as possible; these include diet, environmental variations, family history, etc.

Treated patients were grouped in 3 groups for the purpose of standardizing treatment modality statistics. First group of patients received Cetrizine 10 mg daily, 2nd group of patients received Fexofenadin 120 mg OD along with other medication like paracetamol, antibiotics and antacid. The 3rd group, the control group of patients received only Antibiotics, paracetamol, antacid and were never found to have received antihistamin medication.

## Results

### Increased incidence of hypersensitive bronchitis in rhinitis patient treated with anti-histaminics

Surprisingly, in 21 patients (14 female and 7 male patients) in the age group of 40-60 years were found to develop a patch of pneumonitis on 5th day of treatment with anti- allergic medicines, which was detected on X-ray chest. No development of pneumonitis was seen in controlled patients (Figure 1).

It is seen that there is remarkable increase in the incidence of bronchitis after use of antihistaminic. Female patients in all age group demonstrate more incidence of bronchitis. Except in the female with the age group of 20-40, all groups showed more number of patients develop bronchitis after use of fexofenadine. Cetrizine is associated with less number of patients developing bronchitis. Female patients have more preponderance for bronchitis.

We also compared the development of bronchitis symptoms across more commonly used rhinitis drugs- Cetirizine, and Fexofenadine. It can also be seen from Figure 2 that patients receiving Fexofenadin are more likely to develop bronchitis as compared to patients receiving cetirizine.

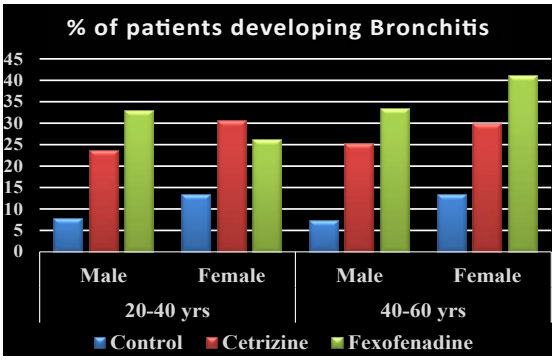


**Figure 1:** patients receiving Fexofenadine are more likely to develop bronchitis as compared to patients receiving cetirizine.

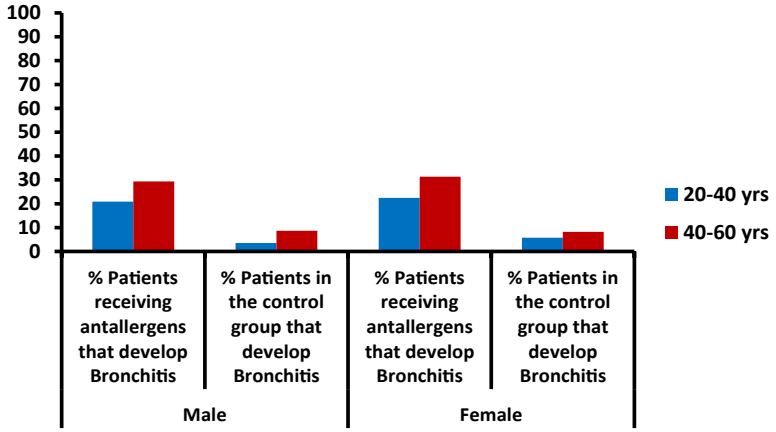


**Figure 2:** Statistics showing the susceptibility of different groups to Bronchitis. Control group don't receive antallergens.

## Discussion

It is a common observation that the patients suffering with upper respiratory tract are invariably treated with anti-allergic medications like Cetirizine, Phenylpropalamine, Chlorpheniramin and Fexofenadine. It is noticed that patients initially have no clinical manifestations of bronchitis, but on 4$^{th}$ or 5$^{th}$ day, many of the patients developed dry hacking cough with signs of bronchitis. Thus, this initial observation suggested that rhinitis patients were more susceptible to bronchitis when treated with Antallergens. A retrospective study was done in 3101 patients from the records available with us. It is obvious that there is remarkable difference in the number of cases developing Bronchitis in the group of patients treated with anti-allergic medicines. Patients treated with antallergens are three to four times more prone to develop Bronchitis than patients in the control group. Out of the 2 antihistamine groups used in the study, patients treated with Fexofenadine are significantly more susceptible to Bronchitis as compared to patients treated with Cetrizine. Similarly, the developement of Pneumonitis is seen more in fexofenadine group.

It is likely that in the patients treated with antihistamine medication, watery discharge of nasal mucosa is suppressed and thereby the viral / bacterial shedding is also suppressed. This leads to more viral / bacterial penetration in the cells and the mucus becoming more viscid.

To make study comprehensive, we tried to include maximum number of patients whose complete health record is available with us. The patient's selection was made on the basis of similar complaints and signs. Only those patients having symptoms of dry/wet cough, mild to moderate fever, headache, body ache, throat irritation and running of nose without any symptom of breathlessness since one day were included in the study. Similarly those patients are having nasal and throat congestion (without tonsilar enlargement), dry hacking cough and on examination scattered sibilant rhonchi in the chest were considered as developed bronchitis. The patients having their complete workup done like complete hierogram, Urine routine test, Blood sugar estimation, Renal function tests, Liver function tests, Electrocardiogram, X-ray chest were considered in the study. Only those patients having all investigations studies normal on the initial presentation were included in the study. Majority patients had normal blood counts with the exception of few (8%) who demonstrated increased in the leucocytic count. X-ray chest was normal except in the patients who developed pneumonitis. Pneumonitis was mainly seen in the basal portion of the lower lobes (right sided in 13 patients and left sided in 7 patients) and 1 patient developed pneumonitis in Right middle lobe. Final outcome in all patients of bronchitis was satisfactory with all patients of bronchitis being treated with bronchodilators and steroid inhalation therapy along with antibiotics.

It has been observed that the median time for recovery is shorter in patients who were treated without anti allergic medication.

## Conclusion

Anti-allergic medicines are routinely used to treat upper respiratory tract infections (URI), particularly running nose. Though, these drugs typically provide symptomatic relief in about a day, side effects manifests as Bronchitis and prolonged illness in a sizable number of patients. The anticipated pathophysiology is that these anti allergic medicines diminish the secretions of nasal mucosa but increase bronchial hypersensitivity. Therefore, one solution could be to modulate the drug such that it decreases nasal mucosal secretion and causes bronchial dilation. Alternatively, a multidrug approach could be explored. Also, given that patients in the control group (did not receive ant allergens or any other medicines) recovered from URI in at most 2 days and were remarkably less susceptible to post nasal drip bronchitis, probably makes the need and use of these ant allergens obsolete.

These findings made us to postulate that anti allergic medication may be altering the ciliary movements of nasal mucosal cells and result in the stasis of secretions. Secondly we have also observed that the secretions of the patients treated with anti-allergic medication became more viscid than patients without receiving anti allergic medicines. These two factors probably increase the bronchial hypersensitivity. Viscid secretions likely prolong the illness and few of the patients develop pneumonitis.

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