

Aspirin intolerance

II. A prospective study in an atopic and normal population

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In a prospective study 1,372 patients with asthma and rhinitis and 808 normal individuals were directly questioned about symptoms of intolerance to aspirin. The frequency of aspirin intolerance in our asthmatic group was significantly greater (3.8 per cent) than the frequency in the rhinitis alone group (1.4 per cent) or in our normal group (0.9 per cent). There was no statistical difference of aspirin intolerance between rhinitis alone and our normal individuals. The predominant symptom of aspirin intolerance in our asthmatic group was bronchospasm, while the predominant symptom in our rhinitis alone group was urticaria. In our normal individuals, manifestations of aspirin intolerance were about equally divided between bronchospasm and urticaria. It appears that at least two possible pathogenic mechanisms may be present in aspirin intolerance, one producing bronchospasm and the other resulting in angioedema/urticaria.

The vast amount of aspirin that is ingested is underscored by the fact that over 16,000 tons of aspirin is produced annually in the United States.¹ Because this drug is so commonly used, data on the frequency of adverse reactions to acetylsalicylic acid in various populations is important. In Part I of our study,² we attempted to determine the frequency and characteristics of aspirin intolerance in an allergic population. Our past population studies on asthma, allergic rhinitis, and allergy to Hymenoptera revealed significant information when both atopic and normal segments of a population were investigated and compared. In this report, we have attempted to investigate in a prospective manner the intolerance to aspirin in a population consisting of patients with demonstrable symptoms of allergy in addition to a normal population.

MATERIAL AND METHODS

Our population included patients from the Adult Allergy Clinic at Rhode Island Hospital and from three private allergy practices. For two months beginning November 15, 1972, consecutive allergy patients with asthma and/or rhinitis were specifically and actively asked in a face-to-face interview if they had any difficulty whatsoever with ingestion of aspirin or aspirin-containing compounds, and details of their symptoms, if any, were noted. A total of 1,372 individuals who comprised almost all our active patients 12 years of age or older with asthma and/or rhinitis were included in this study. All patients had been skin-tested to a battery of inhalant allergens* by the scratch technique. When the scratch test was negative for a particular allergen suspected by history, the intracutaneous test was also done. Allergens

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*Standard scratch tests extracts as purchased from Hollister-Stier or Greer Laboratories.

TABLE I. Prospective study of aspirin intolerance: Frequency in asthma, rhinitis alone, and nonallergic individuals

Diagnosis	Total No.	No. with aspirin intolerance	%	p value
Asthma	731	28	3.8*	< 0.001 N.S.†
Normal individuals	808	7	0.9	
Rhinitis alone	641	9	1.4*	

*The difference between aspirin intolerance in asthma (3.8 per cent) compared to rhinitis alone (1.4 per cent) is also statistically significant ($p < 0.01$).

†N.S. = not statistically significant.

included tree, grass, and ragweed pollens, animal danders, and molds. A positive reaction had to be definitely larger than the control, and all questionable reactions were considered to be negative. Patients were divided into three main categories: those with asthma alone, those with rhinitis alone, and those with both asthma and rhinitis. The three groups were further subdivided into those who had one or more definitely positive allergy skin tests and those who were negative reactors to these tests. The frequency of aspirin intolerance was determined in each of these groups.

A diagnosis of asthma was accepted if symptoms consisted of clinically reversible signs of wheezing, shortness of breath, and cough on a recurrent basis, not due to any other organic disease. A diagnosis of rhinitis was accepted if symptoms consisted of repeated nasal stuffiness, rhinorrhea, and frequent sneezing on a seasonal or nonseasonal basis. Cases of infectious rhinitis were excluded from this study. Vasomotor rhinitis was classified with those patients with rhinitis who had negative skin tests. Our criteria for intolerance to aspirin were acute bronchospasm, rhinorrhea, urticaria, angioedema, or shock occurring within 2 hours of ingestion. Angioedema was included in the category of urticaria.

Our nonallergic individuals were obtained from the Multi-Phase Health Testing Center at Rhode Island Hospital, and are called the "normal group" in this study. No attempt was made to match these individuals by sex or age to our group with asthma or rhinitis. Consecutive individuals tested at this Center at the same period were specifically questioned in a face-to-face interview about signs and symptoms of asthma, rhinitis, and aspirin intolerance using the same criteria for diagnosis as was done in the other group. Individuals with known or questionable asthma and rhinitis, even if symptoms were only suggestive, were excluded from this normal group, which totaled 808. The frequency of aspirin intolerance was then determined in these 808 individuals, and the results were compared to the frequency of aspirin intolerance found in our population with asthma and rhinitis. These 808 normal individuals did not undergo allergy skin tests.

All of our subjects admitted to ingesting aspirin at some time during their life. It was difficult to ascertain a definite age of onset of aspirin intolerance.

RESULTS

Our atopic population totaled 1,372 patients, 59 per cent females and 41 per cent males, with an age range from 12 to over 65 years of age. There were 359 patients or 26.2 per cent who had asthma alone, 372 or 27.1 per cent who had both asthma and rhinitis, and 641 or 46.7 per cent who had rhinitis alone. The frequency of intolerance to aspirin in our total population with asthma and rhinitis was 37 out of 1,372 or 2.7 per cent. The frequency of intolerance to aspirin in our asthmatic patients was 28 out of 731 or 3.8 per cent, and in our rhinitis alone group it was 9 out of 641 or 1.4 per cent (Table I). The difference between the latter two frequencies is statistically significant ($p < 0.01$). Patients with both rhinitis and asthma had a frequency of aspirin intolerance of 13 out

TABLE II. Prospective study of aspirin intolerance: Frequency in rhinitis alone versus rhinitis with asthma

Diagnosis	Total No.	No. with aspirin intolerance	%	p value
Rhinitis alone	641	9	1.4	< 0.05
Rhinitis and asthma	372	13	3.5	

TABLE III. Prospective study of aspirin intolerance: 37 aspirin intolerance patients with asthma and/or rhinitis

Clinical data	Number	%
Males	9	24
Females	28	76
Number with nasal polyps or x-ray evidence of sinusitis	18	49
Positive allergy skin tests	15	41
Symptoms of aspirin intolerance*		
Bronchospasm	20	54
Urticaria/angioedema	14	38
Rhinitis	4	11

*Includes one patient who had both bronchospasm and rhinitis.

of 372 or 3.5 per cent, which is statistically greater ($p < 0.05$) than the frequency found in patients with rhinitis alone (1.4 per cent) (Table II), but similar to the group with asthma alone (4.1 per cent). The frequency of aspirin intolerance in asthmatic patients with positive allergy skin tests, extrinsic asthma, was 18 out of 518 or 3.5 per cent, and in those asthmatics with negative skin tests, intrinsic asthma, it was 10 out of 213 or 4.7 per cent. This difference is not statistically significant.

The characteristics of these 37 patients with aspirin intolerance were: a predominance of females (76 per cent) and nasal polyps or x-ray evidence of sinusitis (49 per cent). Manifestations of their intolerance to aspirin were bronchospasm (54 per cent), urticaria/angioedema (38 per cent), and severe rhinitis (11 per cent) (Table III). None of our patients experienced shock. The age range was 12 to 75 years with an average age of 41 years. In general, the symptoms of aspirin intolerance were described as severe and occurred within 2 hours after ingestion. No statistically significant sex difference was found in any of our categories. Bronchospasm was the most frequent manifestation of intolerance in our patients with known asthma. However, urticaria was the most frequent manifestation in our patients with rhinitis alone. This difference, possibly because of small numbers, was not found to be statistically significant (Table IV). The frequency of positive allergy skin tests was about the same in those patients whose aspirin intolerance was manifested by either bronchospasm or by urticaria.

Our normal population numbered 808 individuals with 49 per cent males and 51 per cent females. The age range of this population was from 18 to 80 years of age with an average age of 45 years. The frequency of aspirin intolerance

TABLE IV. Prospective study of aspirin intolerance: Aspirin intolerance manifested by bronchospasm and urticaria in asthma, rhinitis alone, and normal individuals

Diagnosis	Total patients	No. with aspirin intolerance	No. with bronchospasm	%	No. with urticaria/angioedema	%
Asthma	731	28	18	2.5	10	1.4
Normal individuals	808	7	5*	0.6	3*	0.4
Rhinitis alone	641	9	2†	0.3	4†	0.6

*Includes one individual who had both bronchospasm and urticaria.

†Not including 3 patients whose symptom of aspirin intolerance was manifested by acute rhinorrhea only.

in these normal individuals was 7 out of 808 or 0.9 per cent. This difference is statistically highly significant ($p < 0.001$) when compared to the higher frequency of aspirin intolerance in our asthmatic group (3.8 per cent), but not significantly different from the frequency of aspirin intolerance in our group with rhinitis alone, (1.4 per cent) (Table I). The 7 individuals in our normal group who had aspirin intolerance included 5 females and 2 males who had an age range of 31 to 60 years, with an average age of 47 years. Their symptoms of aspirin intolerance were bronchospasm in 4 and urticaria in 2, and both of these conditions in one individual (Table IV).

DISCUSSION

Our frequency of aspirin intolerance in asthma (3.8 per cent) in this prospective study is quite similar to that found in asthma (4.3 per cent) in Part I of our report.² This similarity is important particularly since the same criteria were used for diagnosis in both studies. Also similar to our Part I report, the frequency of aspirin intolerance in rhinitis alone is significantly less than that found in asthma patients. When rhinitis and asthma coexist in the same individual, the frequency of aspirin intolerance resembles that of asthma alone. Other similarities between our two reports are that asthmatic patients with negative allergy skin tests, intrinsic asthma, appear to have a greater frequency of aspirin intolerance than asthmatic individuals with positive skin tests, extrinsic asthma. This difference is statistically significant in the part I study, but not in this prospective report. Both studies demonstrate that bronchospasm tends to be the predominant symptom of aspirin intolerance in asthmatic patients while urticaria tends to predominate in individuals with rhinitis alone.

Our data are in agreement with previous reports³⁻⁶ that the frequency of nasal polyps or x-ray evidence of sinusitis seems to be high (49 per cent) in our patients with asthma and rhinitis who have intolerance to aspirin. However, 15 out of 37 patients (41 per cent) did not have sinus x-rays and also did not have nasal polyps. Therefore, our combined frequency of sinusitis or nasal polyposis possibly would be higher than 49 per cent. A diagnosis of nasal polyps was made either by our physical examination or an ENT consultation. Individuals in this study were not challenged with aspirin, which might have resulted in higher frequencies of intolerance.⁷

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The frequency of aspirin intolerance in our normal group (0.9 per cent) is not statistically different than that found in our rhinitis alone group (1.4 per cent) or in the rhinitis alone group of our part I report (0.7 per cent).² It seems that aspirin intolerance has a peculiar propensity in asthmatic patients, especially in those with negative skin tests to allergens. This occurs perhaps in such a way as to aggravate an existing biochemical abnormality that results in bronchospasm. Our combined data also appears to support the hypothesis that at least two different mechanisms may exist for aspirin intolerance, one resulting in symptoms of bronchospasm and the other resulting in urticaria/angioedema.

Since antibodies to aspirin have not been found in sera of aspirin-intolerant individuals, most reports³⁻⁵ conclude that aspirin intolerance is not mediated through an antibody-antigen reaction. This theory is supported by the fact that chemically unrelated molecules such as indomethacin and tartrazine^{3, 4, 8} will cross-react with aspirin in aspirin-intolerant individuals and produce similar symptoms.

One possible mechanism of aspirin intolerance may be related to the prostaglandins system. An abnormal mechanism may exist in certain asthmatics where aspirin may unilaterally block the release of PGE_2 , a bronchodilator, without also blocking the release of a $\text{PGF}_2\alpha$, a bronchoconstrictor. This unequal inhibition may lead to dominance of a bronchoconstrictor effect. This explanation may account for the fact that a major symptom of aspirin intolerance is bronchospasm and not urticaria in asthmatic patients. It is evident that further investigations are needed to determine the exact mechanism of aspirin intolerance.

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