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STUDY ON ASPIRIN-INDUCED BRONCHIAL OBSTRUCTION IN CHILDREN WITH BRONCHIAL ASTHMA*

*Yıldız Saraçlar MD**, *Ayfer Tuncer MD****

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Anaphylactic-like reactions to aspirin were reported within a few years of its introduction as a therapeutic[1]. "Triad of aspirin", consisting of aspirin-induced urticaria-angioedema, rhinitis-nasal polyposis and bronchial asthma, aroused much interest when it was first described by Samter and Beers[2,3]. The pathogenesis of this triad is unknown. Since there is no convincing evidence that the problem is mediated by an immune mechanism, the term "aspirin intolerance" is preferred to "aspirin allergies" when referring to these reactions. In addition, some authors suggest that "idiosyncrasy" is the most appropriate term for the pulmonary symptoms caused by very low doses of aspirin[4].

The three symptoms of the "aspirin triad" are rarely seen together, but the incidence of a single symptom is not very uncommon. For this reason, it has been suggested that the term "triad" not be used[5].

The results of studies on the incidence of aspirin intolerance vary according to the population studied and the method used[1,6-13]. In general, oral aspirin challenge studies reveal a significantly higher incidence than those studies that examine historical data alone. In order to prove real aspirin intolerance, patients should be observed for bronchial obstruction during the 4 hours following the oral administration of aspirin; but brnonchial obstruction may not always be severe enough to produce clinical symptoms. The subclinical bronchial obstruction can be shown by pulmonary function tests. Studies on the incidence of aspirin intolerance, using pulmonary function tests before and after aspirin ingestion, have dealt largely with adult populations[5,11,14,15]. Only a few reports concerning this matter in children have been published, moreover, with conflicting results[8,9,12].

* From the Pediatric Allergy Unit, Hacettepe University Institute of Child Health, Ankara.
** Professor of Pediatrics, Pediatric Allergy Unit, Hacettepe University Institute of Child Health.
*** Instructor in Pediatrics, Fellow in Allergy, Pediatric Allergy Unit, Hacettepe University Institute of Child Health.

It is generally assumed that aspirin-induced asthma is very uncommon in children. Most patients and their parents are not aware that aspirin and certain food additives cross reacting with aspirin can provoke an asthma attack. If such patients could be identified, they could be protected from excessive aspirin ingestion. With this purpose in mind, bronchial asthmatic children with no history of clinical aspirin intolerance were investigated by pulmonary function tests before and after oral challenge with aspirin.

Material and Methods

Fifty-two asthmatic children who had been attending the pediatric allergy clinic for hyposensitization treatment for at least two years were studied. Thirty were boys and 22 girls (Table I). The mean age was 12.6 years, with a range from 8 to 18. Fifty children had bronchial asthma plus perennial allergic rhinitis and two had bronchial asthma only. None of the patients had a personal or family history of aspirin intolerance or nasal polyps. They were not steroid-dependent.

TABLE I

DATA ON THE STUDY POPULATION

— No of cases	52 (30 male; 22 female)
— Age (years)	8-18 (mean: 12.6)
— Diagnosis:	
Br. asthma	2
Br. asthma + perennial allergic rhinitis	50
— Nasal polyposis	None
— Severity	Mild to moderate
— Steroid usage	None

The diagnosis of bronchial asthma and perennial allergic rhinitis had been previously established by personal and family histories, physical examination, improvement of bronchial obstruction by sympathomimetics, peripheral and nasal eosinophilia and positive immediate skin tests to allergens.

Among the pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and maximal mid-expiratory flow (MMEF) were measured using a standard 9-liter Colin's spirometer.

Antihistaminics and all other medicines were withdrawn 72 and 24 hours prior to the tests, respectively.

The tests were conducted in a double-blind manner. Each subject ingested 500 mg of aspirin one day and 100 mg of lactose as a placebo another day. The aspirin and lactose were administered in identical capsules and at the same time of day on both days. Prior to challenge, baseline physical examination and pulmonary function

tests were performed. There was little difference in the baseline values on the two challenge days. Following challenge, physical examination and pulmonary function tests were repeated after one-half, one, two, three and four hours.

Our criteria for aspirin intolerance are as follows:

1. A 20% fall in FEV_1 and/or MMEF volumes compared to baseline after aspirin administration,
2. Duration of this fall for at least two hours,
3. Either no fall with the placebo, or a 20% greater fall with aspirin.

The mean values of the changes in percentage, obtained from all patients for each of the tests, were compared using Student's t test.

Results

None of the patients had clinical symptoms following aspirin challenge, and statistical analysis of the mean values for the group showed no significant differences between their pulmonary function test results following ingestion of aspirin or placebo (Table II).

TABLE II

MEAN PERCENT OF CHANGE FROM BASELINE FOR EACH PULMONARY FUNCTION TEST AT EACH TIME PERIOD (all 52 asthmatic patients)

Percent of Change From Baseline

Time of observation	Aspirin		Placebo		
	Mean	± SD	Mean	± SD	
FVC:					
30 min	2.29	1.16	1.71	0.59	$p > 0.05$
1 hr	3.21	1.30	2.08	0.79	"
2 hr	3.85	1.39	2.05	0.82	"
3 hr	4.02	1.43	2.63	1.04	"
4 hr	3.62	1.40	3.10	1.12	"
FEV_1:					
30 min	3.29	1.21	0.76	0.67	$p > 0.05$
1 hr	4.03	1.51	3.29	1.12	"
2 hr	5.38	1.55	2.55	1.20	"
3 hr	5.47	0.76	4.72	1.55	"
4 hr	5.54	1.87	4.20	1.67	"
MMEF:					
30 min	4.04	1.35	2.69	1.11	$p > 0.05$
1 hr	4.39	1.93	5.94	1.71	"
2 hr	9.34	2.63	4.49	0.14	"
3 hr	9.35	2.65	7.21	2.09	"
4 hr	8.83	2.66	8.88	1.99	"

On the other hand, when each of the cases was evaluated separately, 4 of the patients showed a fall greater than 20% in FEV_1 values and 6 of them showed a similar fall in MMEF values following aspirin ingestion. This fall continued for at least two hours in each case. Three of the 6 patients showing a fall in MMEF also showed a fall in FEV_1 (Tables III, IV).

Since these findings met our criteria for aspirin intolerance, these 7 cases were accepted as aspirin-intolerant.

This represents about 14% of all our cases. Some data for the 7 aspirin-intolerant cases compared with data for the 45 aspirin-tolerant patients are shown in Table V. Occurrences of abnormal chest and sinus x-rays were higher in the intolerant group. Other findings were similar in both groups.

Discussion

Aspirin-induced reactions are thought to increase with chronological age. Bronchial obstruction may begin subclinically and appear with severe clinical symptoms in later ages[12]. Aspirin intolerance in children is not as rare as assumed, because aspirin and dyes cross reacting with aspirin are consumed in large quantities by children as well as by adults. The benefits of taking preventive and therapeutic measures before the appearance of more severe symptoms are therefore considerable.

There are only three studies in the literature on the use of provocation and pulmonary function tests on asthmatic children. The first, reported by Rachelefsky et al[8] in 1975, included 50 intractable asthmatic children with no history of aspirin intolerance; 28% were shown to have aspirin-induced bronchial obstruction. The results of the other two reports, by Vedanthan et al[12] and Schull and Pepeyra[9], were that 13% and 0% of the cases respectively had bronchial obstruction. Our results of 14% bronchial obstruction in the cases studied are in accordance with those of Vedanthan et al.

Although like certain other authors[1,5,11] we accepted a 20% fall as a positive criterion whereas Rachelefsky et al accepted a 30% fall, the percentage of bronchial obstruction reported by the latter group was twice that of ours. Their results, as the authors themselves pointed out, should be interpreted with caution because antiasthmatics were withheld during the study and this by itself can cause bronchial obstruction in intractable cases. Our cases were mild to moderate asthmatic cases and therefore we faced no such problems. Only three of the cases studied showed placebo intolerance. This was explained by lack of cooperation, and these cases were excluded.

TABLE III

PERCENT OF CHANGE FROM BASELINE FOR FEV_1* SHOWN BY FOUR PATIENTS FOLLOWING ADMINISTRATION OF ASPIRIN AND PLACEBO

Case No.	Name	Age (yrs)	Sex	Percent of change** at various time intervals (hrs)									
				Aspirin					Placebo				
				1/2	1	2	3	4	1/2	1	2	3	4
30	S.B.	18	M	22	31.6	40	22	22	0	13.5	18.3	4.2	0
32	U.K.	9	M	49.4	49.4	42.1	46.5	51.1	0	0	0	9.6	34.6
40	A.G.	9	M	6	20.3	27.3	5.9	0	0	5.8	−18.4	−28.7	−21.3
43	O.A.	15	F	4	25	19.7	19.7	36.5	0	0	0	− 4.5	−15.4

* FEV_1 = Forced expiratory volume in one second.

** Negative number represents improvement.

TABLE IV

PERCENT OF CHANGE FROM BASELINE FOR MMEF* SHOWN BY SIX PATIENTS FOLLOWING ADMINISTRATION OF ASPIRIN AND PLACEBO

Case No.	Name	Age (yrs)	Sex	Percent of change** at various time intervals (hrs)									
				Aspirin					Placebo				
				1/2	1	2	3	4	1/2	1	2	3	4
3	E.U.	9	M	8.9	10.1	26.6	26.6	21.9	6.7	1.5	1.5	1.5	6.7
8	D.M.	14	F	37.1	38.7	39	41.7	31.7	0	0	– 0.4	0	1.6
19	A.K.	11	M	23.9	26.2	34.8	19	21.3	1.1	13.1	11.7	– 5.3	– 3.5
30	S.B.	18	M	0	39.8	38	– 2.3	2.3	0	5.3	5.3	6.3	6.3
32	U.K.	9	M	25.8	25.8	23.4	34.4	31.2	0	0	0.9	0.9	0.9
43	O.A.	15	F	4.7	29.3	25	45.3	57	0	0	0	0	0

* Maximal mid-expiratory flow.

** Negative number represents improvement.

TABLE V

COMPARISON OF ASA-TOLERANT AND ASA-INTOLERANT ASTHMATIC CHILDREN TESTED

Patient Data	Asthmatic Children	
	ASA Tolerant	ASA Intolerant
Number	45	7
Mean age	12.7	12.1
Female	19 (42%)	2 (28.5%)
Sinusitis	11 (24%)	3 (43%)
Eosinophils (cells/mm)	444	500
Nasal eosinophilia	45 (100%)	7 (100%)
Abnormal chest x-ray	8 (17.7%)	5 (71%)

On the other hand, Schull and Pepeyra demonstrated a significant increase in PEFR (Peak Expiratory Flow Rate) due to aspirin. A slight decrease (8%) was observed in only 3 of their cases. Since the possible therapeutic effect of aspirin can be accepted to be as low as 1% [16], it may be more appropriate to explain these results by the age of the cases studied (very young: mean age 9.6) and by their lack of cooperation.

In conclusion, we can suggest that aspirin intolerance is not rare among asthmatic children and that it can be detected by pulmonary function tests before clinical symptoms appear. It may therefore be possible to prevent a severe ashmatic condition in these children by avoiding excessive intake of aspirin or food additives (for example dyes and some preservatives) which might cross react with aspirin.

Summary

It is well known that aspirin may cause bronchial obstruction. It is generally assumed that aspirin-induced bronchial obstruction starts at a subclinical level and develops severe symptoms at older ages. It is possible to demonstrate asymptomatic bronchial obstruction by spirometric studies.

Only a few reports concerning this matter in children have been published. In order to detect bronchial obstruction due to aspirin, pulmonary function tests were applied to fifty-two children with mild to moderate asthma. The results indicated 14% intolerance and were compared with those in the literature.

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