

Aspirin Intolerance and Recurrent Urticaria in Normal Adults and Children

Epidemiology and Review

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The frequency of aspirin intolerance by history in 2,592 normal individuals was 0.3%. Although the frequency of aspirin intolerance was similar in adults and children, the bronchospastic type predominated in adults, and only the urticarial type was found in normal children. The frequency of recurrent urticaria, regardless of etiology, was significantly greater in adults than in children (3.8% vs. 0.3, $P < 0.001$). In adults the frequency of aspirin intolerance was over 20 times greater in individuals with recurrent urticaria than in normal individuals (6.5% vs. 0.3%, $P < 0.001$).

Key words: aspirin intolerance; aspiryl antibodies; bronchospasm; chronic urticaria; normal adult population; normal pediatric population.

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Acetylsalicylic acid (aspirin) is probably the most frequently used drug. Over 16,000 tons of aspirin are produced annually in the United States and over 200 drugs on the commercial market contain this ingredient (11, 33). Although salicylates in the form of willow bark (*Salix alba*) were used in Hippocrates time, salicylates in the form of acetylsalicylic acid were introduced into medicine in 1899 by Dreser (8). Three years later, the first adverse reaction to aspirin in the form of acute angioedema was reported in the literature (10).

Adverse reactions to aspirin have been well studied in asthma and chronic urticaria. However, little is known about adverse reactions to aspirin in a normal population, especially in normal children. The purpose of this study was to determine the frequency and type of aspirin intolerance in a normal adult and pediatric population as well as in a population with recurrent urticaria.

MATERIAL AND METHODS

Our normal adult population was obtained from the Multiphasic Health Testing Center at Rhode Island Hospital. Consecutive individuals tested at this Center from Dec. 1972 to June 1974 were specifically questioned in a direct interview about signs and symptoms of aspirin intolerance. Our criteria for intolerance to aspirin were the same as in our previous studies (5, 22, 24) and consisted of a history of definite acute bronchospasm, urticaria/angioedema, severe rhinorrhea or shock occurring within about 2 h after aspirin ingestion. Individuals with a history of asthma, chronic bronchitis, emphysema, hay fever, recurrent rhinitis and recurrent urticaria were excluded from our normal population when determining the frequency of aspirin intolerance. In addition, we determined the frequency of recurrent urticaria among those

Table 1
Aspirin intolerance in normal adult and pediatric population

Population Type		Aspirin intolerance								
		<i>P</i> value			Subtypes					
					Urticaria		Bronchospastic		Both	
Total	<i>n</i>	%		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Adult	1974	6	0.30	N.S.	2	0.10	3	0.15	1	0.05
Children	618	2	0.32		2	0.32	0	0		
Total	2592*	8	0.31							

*79 Individuals with recurrent urticaria were excluded.

individuals without a history of pulmonary or recurrent rhinitis disorders. The frequency and type of aspirin intolerance in recurrent urticaria were also determined.

Our normal pediatric population was obtained through a mobile pediatric medical unit from Rhode Island Hospital that provided medical care in medically underserved areas of the state. Most of the children evaluated in this mobile unit were provided with routine examinations as part of a preventive medicine and screening program. Similar to our adult population, children with pulmonary diseases, recurrent rhinitis and recurrent urticaria were excluded from our normal pediatric population when determining the frequency of aspirin intolerance. Our data on children were obtained from Oct. 1974 to March 1976. The procedures were similar to those in our adult population. Answers to specific questions on signs and symptoms of aspirin intolerance were obtained by direct interviews.

RESULTS

Our normal population without pulmonary or rhinitis disorders, or recurrent urticaria totalled 2,592 individuals of which 1,974 were adults and 618 were children (Table 1). Of the 1,974 normal adults, 52% were males and 48% were females. The age range was 18–84 years with an average age of 46 years. The frequency of aspirin intolerance among adults was 0.3%,

(6/1974). The six individuals in our normal adult population with aspirin intolerance included four females and two males, with an age range of 31–60 years, and an average age of 45 years. Their symptoms of aspirin intolerance were bronchospasm in three, urticaria in two and both of these conditions in one individual.

Of the 618 normal children, 49% were males and 51% were females. The age range was 2–16 years with an average age of 7.6 years. The frequency of aspirin intolerance among these children was 0.32% (2/618). The two children with aspirin intolerance comprised one male and one female, both were 5 years of age, and both had the urticaria type of intolerance.

In addition to the 2,592 normal individuals, there were 79 subjects with recurrent urticaria (regardless of etiology) and no past history of pulmonary or rhinitis disorders. The frequency of recurrent urticaria in individuals without pulmonary or rhinitis disorders was significantly greater in adults than in children, 3.8% (77/2051) vs. 0.3% (2/620), $P < 0.001$ (Table 2). In adults, the frequency of aspirin intolerance in recurrent urticaria was significantly greater than that found in our normal population, 6.5% vs. 0.3%, $P < 0.001$. The type of intolerance in the individuals with recurrent urticaria was hives in four subjects and bronchospasm in one subject. Neither of the two children with recurrent urticaria in our pediatric group had aspirin intolerance.

Table 2
Frequency of recurrent urticaria and aspirin intolerance

Population		Recurrent urticaria		<i>P</i> value	Aspirin intolerance in urticaria		Subtype of aspirin intolerance	
		<i>n</i>	%		<i>n</i>	%	Urticaria	Bronchospastic
Type	Total							
Adult	2051	77	3.8	<0.001	5	6.5	4	1
Children	620	2	0.3		0	0	0	0
Total	2671	79						

DISCUSSION

The frequency of aspirin intolerance in our normal population was lower than we reported previously (22). One reason for this lower rate is that in our present study we excluded not only individuals with pulmonary and rhinitis disorders, but also those individuals with recurrent urticaria, from our normal population. Our previous study excluded only those with pulmonary and rhinitis disorders. It has become increasingly apparent that the frequency of aspirin intolerance in patients with urticaria is significantly increased compared to that found in normal individuals (6, 13, 16, 23). The removal of the recurrent urticaria segment from our normal population may account for our present lower frequency rate than in our past study. As expected, the frequency of aspirin intolerance in the recurrent urticaria segment of our adult population (6.5%) was more than 20 times the frequency observed in our normal adult population (0.3%) (Tables 1, 2). This finding is statistically significant ($P < 0.001$) and is consistent with past reports on this subject (6, 13, 16, 23).

The frequency of aspirin intolerance in the adult and pediatric segments of our normal population was essentially the same. However, the type of manifestation of aspirin intolerance was different in adults compared to children. Four of the six adults with aspirin intolerance had a bronchospastic manifestation while none

of the children with aspirin intolerance had a bronchospastic component. These results are consistent with our previous findings which demonstrated that the frequency of the bronchospastic type of aspirin intolerance increases with age while the urticaria type does not (5).

The frequency of aspirin intolerance in a normal population is significantly lower than that found in asthma or chronic urticaria (22). The type of aspirin intolerance found in asthma is predominantly the bronchospastic type while that found in chronic urticaria is predominantly the urticaria type (5, 22, 24). In a normal population, a mixture of both types of aspirin intolerance is present (22).

In this study, we relied on a history of aspirin intolerance to determine our frequency. In studies where aspirin oral challenges were used, the frequency of aspirin intolerance may be increased by the inclusion of some patients who may not be aware of the mild symptoms produced by aspirin. Pulmonary function tests before and after aspirin challenge may objectively measure mild subjective symptoms (12, 19, 26).

The mechanism of aspirin intolerance is still unknown. No specific immunoglobulin E (IgE) or other relevant antibodies for aspirin have been found in the sera of intolerant patients despite the fact that these individuals usually have an elevated total eosinophil count (15, 32). However, elevated eosinophil counts may be non-specific and may not be

Table 3
Characteristics of the major subtypes of aspirin intolerance

	Subtypes	
	Bronchospastic	Urticaria/ Angioedema
Increased frequency in chronic urticaria	no	yes
Increased frequency in asthma	yes	no
Correlated with nasal polyposis	yes	no
Similar age onset as asthma	yes	no
Increased frequency in older age groups	yes	no
Familial occurrence	yes	yes
Elevated total eosinophil count	yes	yes
Tartrazine cross- reaction	yes	yes
Specific IgE (anti-aspiryl)	no	no
Increased total IgE	no	no
Mediated by prostaglandins	yes	no

related to an immunological reaction. For example, increased eosinophil counts are frequently found in most immune deficiency syndromes (2). Other characteristics of the bronchospastic and urticarial types of aspirin intolerance are listed in Table 3.

Besides the color additive, (tartrazine (4, 23, 24)) other drugs which may result in the same adverse symptoms as aspirin in intolerant individuals are as follows: Indomethacin, Ibuprofen, Sodium benzoate, Aminopyrine, Mefenamic acid, Phenylbutazone and Sulindac. These drugs have molecular structures that are vastly different from aspirin. Sodium salicylate which has a molecular structure similar to aspirin does not produce similar adverse reactions in intolerant individuals (20, 21). If aspirin intolerance is mediated by an antibody-antigen reaction, one would expect that only antigens with similar molecular configuration as aspirin would cause similar reactions. This apparently does not occur. In

addition, aspiryl antibodies induced by aspirin in mice do not react with tartrazine (32).

The pathological physiology of aspirin-induced asthma appears to have many characteristics common to other types of asthma. Histamine, Mecholyl and prostaglandin F ($\text{PGF}_2\alpha$) produced acute bronchospasm in asthmatics with aspirin intolerance (3, 17, 20, 21). Atropine prevents bronchospasm produced by an aerosolized $\text{PGF}_2\alpha$ and probably also prevents acute bronchospasm produced by aspirin challenge (17). Samter & Beers (20) reported that atropine fails to control aspirin-induced bronchospasm but a recent elegant experiment by Mielens & Rosenberg (14) demonstrated that in guinea-pigs, atropine prevented aspirin-induced bronchoconstriction. In addition, these authors reported that propranolol (a blocker of beta-2 adrenoreceptors) caused aspirin to produce bronchoconstriction and that phenoxybenzamine (a blocker of alpha-adrenoreceptors) had no effect on aspirin-

induced bronchospasm. There is also disagreement about the effect of aspirin on blood histamine. Stevenson et al. (27) found an increase in plasma histamine after aspirin challenge while Wasserman et al. (31) reported normal levels of blood histamine. Basomba et al. (1) reported that prior administration of sodium cromolyn prevented aspirin-induced bronchospasm. Cromolyn has been known also to prevent the degranulation and release of histamine and slow-reacting substance of anaphylaxis (SRS-A) caused by compound 48/80, a potent histamine liberator. Cromolyn's inhibitory effect on challenges with aspirin and compound 48/80 is considered to be on a non-immunological basis.

A prevailing pathogenic hypothesis for the abnormal mechanism in the bronchospastic type of aspirin intolerance is that aspirin may affect the ratio of prostaglandin F (PGF)—a bronchoconstrictor to prostaglandin E, a bronchodilator—through its inhibiting effect on prostaglandin synthetase (22, 28). A predominance of PGF₂α may occur, resulting in bronchoconstriction. This hypothesis is supported by the fact that atropine not only inhibits the bronchoconstrictor effect of PGF₂α but also inhibits the bronchoconstrictor effect of aspirin (17). There is an association between prostaglandin and SRS-A in that both are formed from the same precursor—arachidonic acid (18). The mediation of bronchospastic type of aspirin intolerance may involve both the prostaglandin system and SRS-A.

No prevailing pathogenic mechanism is apparent for the urticarial type of aspirin intolerance. Specific IgE or other specific antibodies have not been found in the sera of the urticarial or bronchospastic type of aspirin intolerance (32). The positive skin tests to aspiryl-polylysine are probably due to non-specific urticarial reactions. Symptoms of generalized urticaria/angioedema are not always mediated by an antibody-antigen reaction and may be non-immunologic (23). Therefore, the association of urticaria with

aspirin intolerance does not imply an antibody-antigen reaction.

Szczeklik et al. (29) have hypothesized that both the bronchospastic and urticarial type of aspirin intolerance are mediated by the prostaglandin system. In support of this speculation, they stated that some patients with aspirin intolerance have both the bronchospastic type and urticarial type occurring at the same time. However, only a few aspirin-intolerant patients have both types of intolerance. Most patients with aspirin intolerance have only one type of intolerance. In addition, the other characteristics of the different types of aspirin intolerance are vastly different and distinctive (Table 3). For these reasons, it seems unlikely that the two major types of aspirin intolerance are mediated by the same mechanism.

The frequency of urticaria in a population varies according to the types of patients studied and the type of urticaria considered (30). Sheldon et al. (25) reported that in a survey of 1,424 college students, 15.7% had a "... history of having at least one bout of hives". Hellgren & Hersle (9) reported a frequency of 1.9% in a dermatology division in Sweden. We considered recurrent urticaria only, regardless of etiology, and found a frequency of 3.8% in adults and only 0.3% in children ($P < 0.001$). Other investigators (6, 7, 13, 25) have also observed that children have a lower frequency of urticaria than adults.

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REFERENCES

1. Basomba, A., Romar, A., Pelaez, A., Vallalmanzo, I. G. & Campos, A.: The effect of sodium cromoglycate in preventing the aspirin induced bronchospasm. *Clin. Allergy* 6, 269-275, 1976.
2. Beeson, P. B. & Bass, D. A.: The eosinophil. p. 197, W. B. Saunders, Co., Philadelphia, 1977.

3. Casterline, C. L. & Evans, R., III: Further studies on the mechanism of human histamine-induced asthma: The effect of an aerosolized H_1 receptor antagonist (diphenhydramine). *J. Allergy Clin. Immunol.* **59**, 420-424, 1977.
4. Chafee, F. H. & Settipane, G. A.: Asthma caused by FD&C approved dyes. *J. Allergy* **40**, 65-72, 1967.
5. Chafee, F. H. & Settipane, G. A.: Aspirin intolerance. I. Frequency in an allergic population. *J. Allergy Clin. Immunol.* **53**, 193-199, 1974.
6. Champion, R. H., Roberts, S. O., Carpenter, R. G. & Roger, J. H.: Urticaria and angioedema. A review of 554 patients. *Br. J. Dermatol.* **81**, 588-597, 1969.
7. Fink, A. I. & Gay, L. N.: A critical review of 170 cases of urticaria and angioneurotic edema followed for a period of from two to ten years. *J. Allergy* **5**, 615-616, 1934.
8. Goodman, L. S. & Gilman, A.: The pharmacological basis of therapeutics, 5th ed. The Macmillan Co., New York, 1975.
9. Hellgren, L. & Hersle, K.: Acute and chronic urticaria. A statistical investigation on clinical and laboratory data in 1,204 patients and matched healthy controls. *Acta Allergol.* **19**, 406-420, 1964.
10. Hirschberg, Dr.: Mitteilung über einen fall von nebenwirkung des aspirin. *Dtsch. Med. Wochenschr.* **28**, 416-417, 1902.
11. Leist, E. R. & Banwell, J. G.: Products containing aspirin, New Eng. *J. Med.* **291**, 710-712, 1974.
12. McDonald, J. R., Mathison, D. A. & Stevenson, D. D.: Aspirin intolerance in asthma. *J. Allergy Clin. Immunol.* **50**, 198-207, 1972.
13. Michaelsson G.: Chronic urticaria: A clinical study with special reference to vascular reactions mediated by the kallikrein-kinin system. *Acta Dermatovenerolog. (Stockh.)* **49**, 404-416, 1969.
14. Mielen, Z. E. & Rosenberg, F. J.: Dual effects of aspirin in guinea pig lungs. *Br. J. Pharmacol.* **57**, 495-500, 1976.
15. Minden, P. & Farr, R. S.: Human antibodies against acetylsalicylic acid-altered human serum albumin. *Arthritis Rheum.* **10**, 299-300, 1967.
16. Moore-Robinson, M. & Warin, R. P.: Effect of salicylates in urticaria. *Br. Med. J.* **4**, 262-264, 1967.
17. Orehek, J., Gayraud, P., Grimaud, C. & Charpin, J.: Bronchial response to inhaled prostaglandin $F_{2\alpha}$ in patients with common or aspirin-sensitive asthma. *J. Allergy Clin. Immunol.* **59**, 414-419, 1977.
18. Parker, C. W.: Prostaglandins and slow-reacting substance. *J. Allergy Clin. Immunol.* **63**, 1-14, 1979.
19. Rachelefsky, G. S., Coulson, A., Siegel, S. C. & Stiehm, E. R.: Aspirin intolerance in chronic childhood asthma: Detected by oral challenge. *Pediatrics* **56**, 443-448, 1975.
20. Samter, M. & Beers, R. F., Jr.: Concerning the nature of intolerance to aspirin. *J. Allergy* **40**, 281-293, 1967.
21. Samter, M. & Beers, R. F., Jr.: Intolerance to aspirin: Clinical studies and considerations of its pathogenesis. *Ann. Intern. Med.* **68**, 975-983, 1968.
22. Settipane, G. A., Chafee, F. H. & Klein, D. E.: Aspirin intolerance. II. A prospective study in an atopic and normal population. *J. Allergy Clin. Immunol.* **53**, 200-204, 1974.
23. Settipane, G. A., Chafee, F. H., Postman, I. M., et al.: Significance of tartrazine sensitivity in chronic urticaria of unknown etiology. *J. Allergy Clin. Immunol.* **57**, 541-546, 1976.
24. Settipane, G. A. & Pudupakkam, R. K.: Aspirin intolerance. III. Subtypes, familial occurrence and cross-reactivity with tartrazine. *J. Allergy Clin. Immunol.* **56**, 215-221, 1975.
25. Sheldon, J. M., Mathews, K. P. & Lovell, R. G.: The vexing urticaria problem: Present concepts of etiology and management. *J. Allergy* **25**, 525-560, 1954.
26. Stenius, B. S. & Lemola, M.: Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. *Clin. Allergy* **6**, 119-129, 1976.
27. Stevenson, D. D., Arroyave, C. M., Bhat, K. N. & Tan, E. M.: Oral aspirin challenges in asthmatic patients: A study of plasma histamine. *Clin. Allergy* **6**, 493-505, 1976.
28. Szczeklik, A., Gryglewski, R. J., Czerniawska-Mysik, G.: Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin sensitive patients. *Br. Med. J.* **1**, 67-69, 1975.
29. Szczeklik, A., Gryglewski, R. J. & Czerniawska-Mysik, G.: Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J. Allergy Clin. Immunol.* **60**, 276-284, 1977.
30. Warin, R. P. & Champion, R. H.: Urticaria, p. 11. W. B. Saunders, Co., London, 1974.
31. Wasserman, S. I., Sheffer, A. L., Soter, N. A., Austen, K. F. & McFadden, E. R.: Assessment of mast cell mediators and pulmonary function in aspirin (ASA)-induced bronchospasm. *J. Allergy Clin. Immunol.* **61**, 139, 1978, (abstract).
32. Weltman, J. K., Szaro, R. P. & Settipane, G. A.: An analysis of the role of IgE in intolerance to aspirin and tartrazine. *Allergy* **33**, 273-281, 1978.
33. U.S. Bureau of the Census Statistical Abstract of the United States (96th edn.) Washington, D.C., 1975.

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