

Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin

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In order to determine the types of respiratory responses observed during aspirin-induced reactions, 50 consecutive asthmatic patients with a history of aspirin sensitivity underwent prospective oral aspirin challenges between 1979 and 1981. Oral aspirin challenges produced 36 asthmatic responses (33 combined with rhinitis and three purely asthmatic) and six acute rhinoconjunctivitis responses (three combined with mild asthma and three purely rhinoconjunctivitis) but failed to stimulate any reaction in eight patients. The results produced by these challenges were then compared with results recorded during additional aspirin challenges in 28 of these patients, performed after the index challenge in 1979-1981 in 26 patients and in the case of two patients before 1979. The type of respiratory response to aspirin varied significantly in 11 (39%) of the 28 patients and included disappearance of aspirin reactivity in four patients. (J ALLERGY CLIN IMMUNOL 71:574, 1983.)

Adverse reactions to therapeutic dosages of aspirin (acetylsalicylic acid) have been documented since 1902.¹ These reactions have included a variety of responses such as asthma, rhinitis, urticaria, angioedema, purpura, and anaphylaxis.¹⁻⁵ The occurrence of asthma after ingestion of aspirin is of importance because of its prevalence⁶⁻¹⁰ and potential severity.^{1, 5, 7, 11-13} Patients who have adverse reactions to aspirin often have additional findings such as nasal polyps and sinusitis.^{4, 5, 14-16} In fact, the association of asthma, nasal polyps, and aspirin sensitivity is recognized as a distinct clinical entity, commonly referred to as the "aspirin triad."⁵ Although symptoms of this respiratory response to aspirin are consistent with or even suggestive of an underlying allergic etiology, an IgE-mediated mechanism of inflammation has never been identified.^{4, 5, 15, 17-20} Furthermore, the recognition of cross-sensitivity in these pa-

tients to a variety of structurally unrelated compounds such as indomethacin and ibuprofen^{19, 21, 22} has suggested some alternative mechanism, possibly related to arachidonic acid metabolism.^{19, 22-26}

During a continuing effort to understand the pathogenesis of this syndrome, oral aspirin challenges have been performed with asthmatic patients at our institution for over 10 yr. This experience provided us with the expertise to safely and accurately identify aspirin-sensitive patients, to observe their reactions, and then to rechallenge them with aspirin at another point in time in order to determine whether or not each aspirin-sensitive patient experienced the same type of respiratory tract reaction with each exposure to aspirin. This report describes the spectrum of adverse responses observed during an index aspirin challenge performed between 1979 and 1981 in 50 consecutive asthmatic patients with a history of aspirin sensitivity. The responses observed during these index challenges were compared with the responses recorded during prior and/or subsequent oral aspirin challenges performed in 28 of these patients.

PATIENTS AND METHODS

Patient population

Asthmatic patients, ages 16 to 65, were selected from the Divisions of Allergy and Immunology of Scripps Clinic and Research Foundation and Kaiser Permanente Medical Center, San Diego. All patients gave a history of a prior asth-

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Abbreviation used

FEV₁: Forced expiratory volume in 1 sec

matic reaction to aspirin. Four patients had previously been documented to have aspirin sensitivity during oral aspirin challenges at Scripps Clinic.

Materials

Capsules containing varying amounts of acetylsalicylic acid (3, 30, 60, 100, 150, and 300 mg) combined with lactose and lactose placebo tablets were prepared by the Scripps Clinic pharmacy. Ascriptin tablets (acetylsalicylic acid, 325 mg) were provided by William H. Rorer, Inc., Fort Washington, Pa.

Flow-volume spirometry values were obtained on a Model 570 wedge spirometer, with results displayed on a Model 585 pulmodigitizer and recorded on a Model 562 X-Y-T recorder (Medsience Electronics, Inc., St. Louis, Mo.).

Aspirin challenge procedure

Patients were admitted to the General Clinical Research Center at Scripps Clinic and Research Foundation where they underwent oral aspirin challenges. Informed consent was obtained for procedures, which were approved by the Human Research Committee.

The minimum spirometric measurements that were required for each patient before proceeding with oral aspirin challenges were an FEV₁ ≥ 1.50 L and $\geq 70\%$ of prior recorded best value. All patients continued their regular medications, except that antihistamines, cromolyn sodium, and inhaled sympathomimetics were discontinued 24 hr prior to the procedure. All challenges were started in the morning. Emergency resuscitative equipment was present.

Single-blind placebo challenges with serial spirometric measurements were conducted in all patients (FEV₁ varied 0 to 15%). After placebo challenges, aspirin challenges were then performed by progressive, incremental oral administration of aspirin as described in our prior publications.^{19, 25} Sequential dosages of aspirin were individualized for each patient. In the four patients studied prior to 1979, two were challenged with an initial single dose of 650 mg of aspirin and two with an initial single dose of 325 mg. This was our customary challenge procedure at that time. Baseline flow-volume spirometry was performed prior to the challenge and every 30 min thereafter until completion of the study. Spirometry was performed more frequently and dosages of aspirin were modified when symptoms or signs of aspirin reaction appeared. After 1979, the incremental challenge procedure started with 30 mg of aspirin and progressed to a maximum single dosage of 650 mg aspirin except in patients in whom the FEV₁ decreased $\geq 25\%$ from baseline (positive asthmatic response) as a consequence of smaller dosages of aspirin. In the latter cases challenges were temporarily suspended and each patient was treated with nebulized isoetharine (0.25 ml) diluted in normal saline by inhalation. Oxymetazoline hydrochloride (Afrin; Schering-Plough

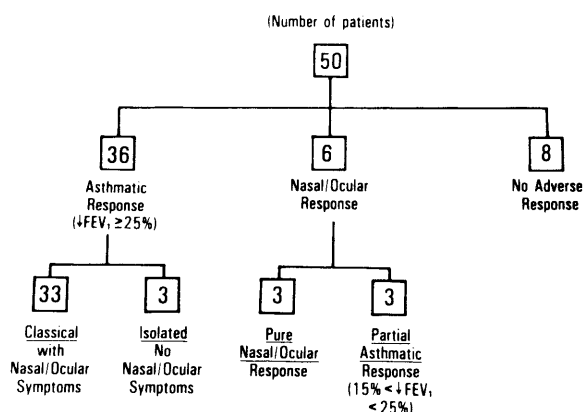


FIG. 1. Spectrum of respiratory responses to oral aspirin challenges in 50 patients during the index challenge, 1979-1981. Numbers of patients are noted in squares.

Corp., Kenilworth, N. J.) spray was used by patients who developed nasal congestion and naphazoline hydrochloride (Vasocon-A; Cooper Vision Pharmaceuticals, Inc., San German, Puerto Rico) eye drops were used in those patients developing conjunctivitis.

Identification of respiratory responses to aspirin

1. *Positive asthmatic response*, defined as a decline in FEV₁ values $\geq 25\%$ below baseline.
2. *Partial asthmatic response*, defined as a decline in FEV₁ values of $\geq 15\%$ but $< 25\%$ from baseline values.
3. *Naso-ocular response*, defined as profound nasal congestion, rhinorrhea, and/or ocular injection.
4. *"Classic" response*, defined as the simultaneous occurrence of both an asthmatic and naso-ocular response.
5. *No response*, defined as the absence of any upper or lower respiratory tract signs or symptoms in conjunction with less than a 15% variation in FEV₁ from baseline values, after ingestion of 650 mg of aspirin.

RESULTS

Spectrum of respiratory responses

Fifty consecutive asthmatic patients with a history of aspirin sensitivity underwent an oral aspirin challenge during the index period, 1979-1981. The types of respiratory responses that these patients experienced are outlined in Fig. 1. Thirty-six patients responded with an asthmatic reaction, 33 of whom also developed naso-ocular symptoms (classic response). Three patients experienced pure asthmatic responses: Six patients exhibited primarily upper respiratory responses without a concomitant fall in FEV₁ values of 25% and were classified as naso-ocular responders. Three of these six naso-ocular responders demonstrated partial declines in FEV₁ values (between 15% and 25% from the baseline values). Eight patients did

TABLE I. Results of repeated aspirin challenges in 28 patients

No. of patients (28)	%	Variation in response*
No variation		
17	61	
Variation		
11	39	
1 (Pt. A)		Asthmatic/nasal → no response
1 (Pt. B)		Asthmatic/nasal → asthmatic/nasal → no response → nasal
1 (Pt. C)		Asthmatic/nasal → no response → asthmatic/nasal
1 (Pt. D)		Nasal → asthmatic/nasal → no response
2		Asthmatic/nasal → nasal
1		Asthmatic/nasal → partial asthmatic/ nasal
3		Isolated asthmatic → asthmatic/ nasal
1		Partial asthmatic/nasal → nasal

*Dotted line with an arrow connects each aspirin challenge reaction response to the next chronological aspirin challenge reaction response.

not react to aspirin despite giving an excellent history suggestive of aspirin sensitivity. In fact, two of these eight asthmatic patients had previously experienced classic responses during oral aspirin challenges at Scripps Clinic, performed prior to 1979.

A review of our 36 subjects who developed asthmatic response to aspirin revealed that 20 were concurrently taking oral corticosteroids and 21 were receiving theophylline compounds, suggesting that a bronchial response to aspirin regularly occurred in the presence of these drugs. Six of these patients were receiving high daily doses of prednisone (≥ 20 mg/day). One patient who had normal FEV₁ values and was not taking corticosteroids experienced a classic reaction during oral aspirin challenge. Later, he was rechallenged with aspirin after receiving pretreatment with 40 mg/day prednisone for 4 days and experienced the same classic reaction to aspirin. Three of the patients with negative challenges but aspirin sensitive by history were rechallenged at a later time after corticosteroids had been discontinued for 3 days, and again did not react to aspirin. These observations strongly suggest that corticosteroid pretreatment does not influence the capacity of the respiratory tract to respond to aspirin nor do changes in the dosages of these drugs account for the variability in responsiveness encountered in this study. From a practical standpoint, it also appears advisable to continue corti-

costeroids and theophylline during aspirin challenges in order to maintain control of asthma.

Urticaria or angioedema did not occur during any of these challenges. Some patients who experienced profound reactions had flushing and abdominal pain but not urticaria.

Results of repeated challenges

Twenty-four of the 50 asthmatic patients studied have subsequently undergone two or more aspirin challenges at Scripps Clinic at intervals varying from 4 mo to 2 yr after the index challenge. In the case of an additional four patients, studies were performed as much as 6 yr prior to the index challenge. Seventeen (61%) of these 28 patients demonstrated the same type of response during each challenge, whereas 11 patients (39%) showed some significant variation in their responses during the additional challenges (Table I).

For example, patients A and B, listed in Table I, failed to respond to aspirin during 1979-1981 index challenges. However, both had previously experienced one or even two classic reactions to aspirin at Scripps Clinic as far back as 1973. Patient B was subsequently rechallenged 2 yr after the negative index challenge and exhibited a naso-ocular response without asthma. In patient C, the reaction to aspirin varied from asthmatic/nasal (100 mg of aspirin) to no response (650 mg of aspirin) and then back to asthmatic/nasal response (100 mg of aspirin). This variation occurred within 1 yr. Patient D experienced aspirin reactions, also within 1 yr, that varied from pure nasal to asthmatic/nasal and later to no response. Also, in Table I are listed all three patients who manifested isolated asthmatic responses and later experienced combined asthmatic and naso-ocular responses to aspirin.

In these 11 patients, the careful examination of their supporting medications, including theophylline, prednisone, and inhaled beclomethasone, did not reveal any pattern that might theoretically suppress the responsiveness of the upper or lower respiratory tract from one challenge to another. In fact, the opposite was observed. Those patients whose responses changed from asthmatic to naso-ocular or who lost their reactions were all taking less total medications, particularly corticosteroids, than when they responded to aspirin with an asthmatic reaction. Theophylline dosages remained constant for all challenges. For example, patient A in Table I was taking 20 mg/day prednisone in 1976 when he had a naso-ocular/asthmatic response. Three years later when he did not respond to aspirin he had discontinued predni-

sone. Similarly, patient B was taking 7.5 mg/day prednisone in 1973 and 1974 when he experienced a classic reaction to aspirin. In 1979 and 1981 when he experienced no reaction on one challenge and a naso-ocular reaction on the other challenge, he was taking 10 mg of prednisone every other day and was challenged on the off day. Similar trends were observed in all 11 patients reported in Table I.

DISCUSSION

Provocative oral aspirin challenge can produce a spectrum of responses in the respiratory tract, ranging from purely asthmatic to asthmatic/naso-ocular (classic response) to purely naso-ocular. Furthermore, when studied longitudinally over a number of years with repeated aspirin challenges, approximately one third of aspirin-sensitive patients experienced variations in the response of their target organs to aspirin. Most interesting were the few patients who were documented to have become unresponsive to aspirin.

Traditionally the diagnosis of respiratory aspirin sensitivity has been reserved for patients who experienced an asthmatic response during a provocative aspirin challenge, as documented by a significant fall in spirometric parameters. Controversy exists with respect to the type of lung function parameter that should be used to measure such responses as well as the percent change required to confirm such a response. Declines in FEV₁ values ranging from 20% to 50% below baseline have been previously reported by separate authors as objective criteria in documenting lower respiratory tract reactions.⁷⁻¹⁰ Since 1978, our group has used 25% decline in FEV₁ values as objective evidence for lower respiratory reactions because such changes provide evidence for asthmatic responses that are not easily confused with spontaneous changes in FEV₁ values.¹⁹ This is particularly true because placebo challenges are routinely employed in our challenges (0 to 15%) to provide a baseline for comparison to the results of aspirin challenge.

In this present study we found that during aspirin challenges, aspirin sensitivity may be manifested not only by an asthmatic reaction but also by objective nasal and/or ocular symptoms and signs in the absence of an asthmatic reaction or with "partial" asthmatic responses (FEV₁ 15% to 25%). In some patients with documented aspirin-sensitive asthma, aspirin reactions selectively occurred in the upper respiratory tract only. Thus we would propose that the definition of respiratory aspirin sensitivity should be broadened to include the naso-ocular as well as asthmatic responses.

The prevalence of aspirin sensitivity in asthmatic

populations has been estimated to be from 4% to 25%, depending on patient selection and whether or not aspirin challenges were performed.⁷⁻¹⁰ In one such study, Spector et al.²⁷ found 14 of 41 patients (35%) with excellent histories suggestive of aspirin sensitivity who did not react to aspirin during oral challenges. However, 15 of 171 patients (8.8%) with no suspicion of aspirin sensitivity by history had positive oral aspirin challenges. Other authors have reported similar perplexing findings.^{6, 9, 26, 28} These apparently contradictory observations can be better understood by recognizing the spectrum and variability of the respiratory responses to aspirin. Some patients giving a history of a prior aspirin reaction may in fact, have been sensitive to aspirin in the past despite a negative provocative challenge at this time. Conversely, it is widely recognized that all aspirin-sensitive patients have been able to tolerate aspirin at some time in their past.^{4, 5} Our study shows that the response to aspirin at the time of challenge establishes only the presence or absence of aspirin sensitivity at that specific time. If the oral aspirin challenge is negative, this does not necessarily exclude the presence of the ongoing disease associated with aspirin sensitivity (asthma, rhinosinusitis, nasal polyps) or that the disease has not or will not be associated with aspirin-induced reactions at another time. Since the focus of prevalence studies in aspirin sensitivity has been directed at populations of asthmatics, it seems likely that subpopulations of patients with eosinophilic rhinosinusitis *without* asthma may also be aspirin sensitive (naso-ocular responders). In fact, the true prevalence of aspirin-sensitive respiratory diseases may be very elusive.

The variability and/or loss of aspirin sensitivity in some patients is difficult to reconcile or understand. One might suspect that antiasthmatic drugs used before and during the aspirin challenges produced false negative reactions in some patients by protecting the tracheobronchial tree, since pretreatment with both cromolyn sodium²⁹⁻³² and antihistamines³³ have been reported to block or at least blunt the aspirin response. In this study, however, all antihistamines, cromolyn, and inhaled sympathomimetics were withheld prior to challenge. Furthermore, as outlined in Results, neither theophylline nor corticosteroids appeared to exert a masking effect on the respiratory response to aspirin. Aspirin reactions in both the upper and lower respiratory tract regularly occurred in the presence of these drugs. From a practical standpoint, it will be difficult to study this issue further, since withdrawal of theophylline and corticosteroids in the majority of these patients may produce exacerbations of dis-

ease activity (asthma) and prevent safe and accurate challenges.

With respect to the 28 patients who underwent repeated challenges, 17 showed no variation in the type of response. Another 11 showed some variation in response. In none of these patients could we show that they were taking more medications when their challenge results reverted from asthmatic reactions to naso-ocular or no response during repeated challenges. It seems unlikely that these changes in target organ susceptibility to aspirin can be explained by the effects of antiasthmatic medications.

The dosage of aspirin used to provoke aspirin reactions might be an important variable in whether or not a respiratory tract reaction occurred as a consequence of aspirin challenge. However, careful attention to this point in analyzing the provoking aspirin dosages in the 28 patients who underwent repeat challenges showed that when aspirin challenges produced nasal reactions or no reactions, dosages of aspirin always exceeded 650 mg and were consistently larger than the dosages that provoked asthma during prior challenges.

In some patients, the degree of aspirin sensitivity seemed to reflect the activity of the underlying disease process. Six patients were clearly improved clinically at the same time that their reduced aspirin sensitivity was documented during repeated oral aspirin challenges. As a result, all six were taking less medication because of this improvement in their course. In addition, all six patients who experienced primarily naso-ocular responses ($FEV_1 < 25\%$) complained of rhinosinusitis/polyp symptoms in excess of their asthmatic complaints. Such observations suggest that in an individual patient, remissions in upper and/or lower respiratory tract disease activity seemed to roughly correlate with reduced aspirin sensitivity. However, beyond this rough correlation between severity of disease and susceptibility to aspirin in an aspirin-sensitive patient, additional diagnostic clarity may not be possible until in vitro studies of target organ cells are accomplished and the underlying biochemical defects of this disorder are identified.

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