

Hypersensitivity to nonsteroidal antiinflammatory drugs: Indications and methods for oral challenges

David A. Mathison, M.D., and Donald D. Stevenson, M.D. *La Jolla, Calif.*

Almost 60 yr ago Dr. Robert Cooke¹ reported asthmatic reaction following ingestion of aspirin. More than 10 yr ago Vanselow and Smith² demonstrated that indomethacin provoked an acute asthmatic attack in a patient with asthma, nasal polyps, and aspirin sensitivity. Samter and Beers³ reported that cross-intolerance to aspirin and other antigenically dissimilar drugs is common. In the intervening years there have been additional reports of hypersensitivity reactions to the aspirin-like drugs.^{4, 5}

There are 2 major types of clinical manifestations of aspirin hypersensitivity, rhinosinusitis-asthma and urticaria-angioedema. The respiratory reaction to aspirin has also been called an "intolerance" or "idiosyncrasy." In accordance with a major pharmacology text⁶ "hypersensitivity" appears to be the appropriate descriptor. Only a few cases of simultaneous manifestation of both rhinosinusitis-asthma and urticaria-angioedema have been reported.^{3, 5}

In the typical patient with rhinosinusitis-asthma and aspirin sensitivity there are consecutive stages of disease covering years or decades. These include vasomotor rhinosinusitis complicated by polyp formation, asthma which usually requires corticosteroid treatment for adequate control, and a unique hypersensitivity response to aspirin characterized by an acute flush, rhinorrhea, and severe asthmatic attack within an hour or so of ingesting ordinary dosages of aspirin or an aspirin-like drug. Although aspirin exacerbates the respiratory disease, the rhinosinusitis-asthma occur and continue without ingestion of aspirin or aspirin-like drugs. Approximately 25% of patients with rhinosinusitis, nasal polyps, and asthma

and 8% to 14% of all asthmatic patients are hypersensitive to aspirin.^{3, 7, 8}

Hypersensitivity to aspirin, which is manifested by exacerbation of urticaria and angioedema, was found in 55% of patients with recurrent urticaria or angioedema reported by Ros, Juhlin, and Michaëlsson.⁹ They reported that angioedema appeared within the first few hours and urticaria appeared up to 6 to 14 hr after oral provocation with aspirin.¹⁰ Other symptoms included erythema of the neck and face, rhinorrhea, and nasal congestion. As is true for patients with rhinosinusitis-asthma, aspirin hypersensitivity in the urticaria-angioedema patient is probably a marker rather than the cause of the disease.

There have been isolated reports of other reactions to nonsteroidal antiinflammatory drugs. Fever and skin rash following aspirin, mefenamic acid, and ibuprofen have been reported in patients with systemic lupus erythematosus.^{5, 11} Anaphylactic shock and perhaps, on an immunologic basis, angioedema, rash, fever, and transitory arthritis have followed aminopyrine (Pyramidon, Amidopyrazoline).^{5, 12} Since aminopyrine tends to cause agranulocytosis, over-the-counter sale in the United States has been prohibited.

POTENTIAL MECHANISMS OF HYPERSENSITIVITY TO ASPIRIN-LIKE COMPOUNDS

In 1971, Vane¹³ found that indomethacin and aspirin inhibit prostaglandin biosynthesis and postulated that aspirin-like drugs exert their antiinflammatory effects through this mechanism of action. Subsequently, Vane¹⁴ and Szczeklik et al.¹⁵ attributed the acute asthmatic attack in aspirin-sensitive patients to the inhibition of prostaglandin biosynthesis.

Fig. 1 summarizes the metabolism of arachidonic acid in the lungs. Indomethacin, aspirin, and several other chemically dissimilar nonsteroidal, antiinflammatory agents (Table I) interfere with the cyclooxy-

From the Department of Clinical Research, Research Institute of Scripps Clinic.

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Reprint requests to: David A. Mathison, M.D., 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

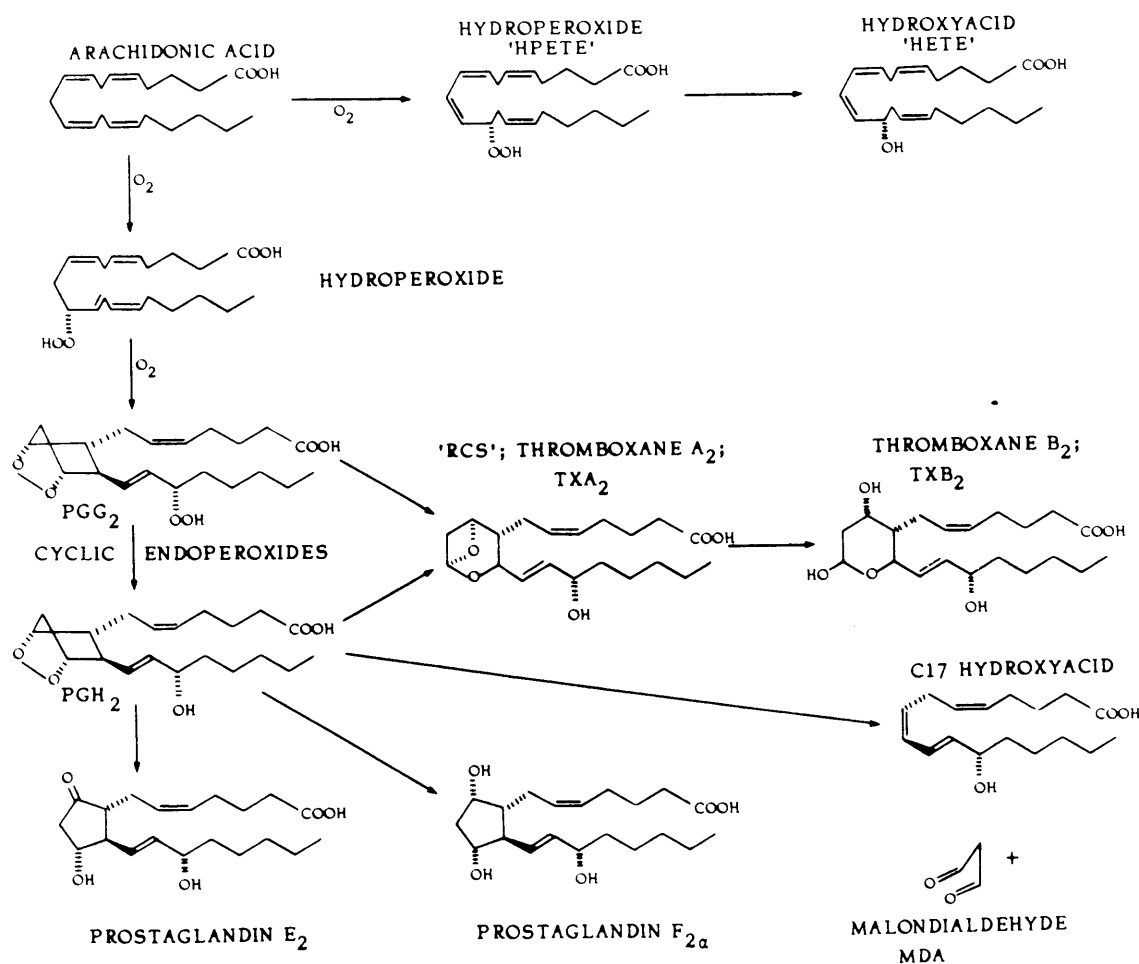


FIG. 1. Pathways of prostaglandin metabolism in lungs. (From Vane JR: J ALLERGY CLIN IMMUNOL 58:694, 1976.)

genase enzyme complex that generates the cyclic endoperoxides, the thromboxanes, and prostaglandins from arachidonic acid. The E prostaglandins are bronchodilators and prostaglandin F_{2α} (PGF_{2α}) is a bronchoconstrictor. The bronchoconstrictive response to inhaled PGF_{2α} is markedly increased in patients with asthma, both those with and without aspirin hypersensitivity.¹⁶

One theory⁵ to explain aspirin hypersensitivity postulates that the prostaglandin synthesis in susceptible individuals is predominantly into the E prostaglandins. Prostaglandin E (PGE) also inhibits the release of histamine and slow-reacting substance of anaphylaxis (SRS-A) from mast cells in the lung.¹⁷ A role for these latter mediators in aspirin-sensitive asthma is suggested by the findings of a rise in peripheral venous plasma histamine during acute asthma provoked by oral aspirin challenge¹⁸ and the inhibition of aspirin-provoked bronchoconstriction by inhaled cromol-

yn sodium in some patients.^{19, 20} The observations might also be interpreted to reflect a direct effect of aspirin on mast cells, leading to mediator release. Inhibition of prostaglandin synthesis in the susceptible individual with asthma would be expected to result in bronchoconstriction due to a decrease of direct PGE bronchodilating effect, or decrease of inhibition of histamine and SRS-A release, or both mechanisms. In the aspirin-sensitive individual with urticaria-angioedema the latter mechanisms may also operate, with the target tissue being the skin.

Another mechanism that might, in part, account for the hypersensitivity in aspirin-sensitive patients is enhancement of the metabolism of arachidonic acid under the influence of the lipoxygenase enzyme complex through the pathway leading to hydroxyacid (HETE, Fig. 1) since this pathway may also lead to generation of a slow-reacting substance.²¹

In a very occasional asthmatic patient aspirin ap-

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TABLE I. Reported prevalence of hypersensitivity to other nonsteroidal anti-inflammatory drugs in aspirin-hypersensitive patients

	% of Aspirin-sensitive asthma patients*	% of Aspirin-sensitive urticaria-angioedema patients ⁵
<i>Prostaglandin synthetase inhibitors:</i>		
Indomethacin (Indocin)	100 ⁵	100
Fenoprofen (Nalfon)	100 ⁵	80
Naproxen (Naprosyn)	100 ⁵	
Tolmetin (Tolectin)	100 ²³	
Ibuprofen (Motrin)	97 ⁵	75
Mefenamic acid (Ponstel)	60 ⁵	
Sulindac (Clinoril)	?†	
<i>Possible prostaglandin synthetase inhibitors:</i>		
Phenylbutazone (Butazolidin)	42 ⁵	
Acetaminophen	<5 ^{3, 24†}	
<i>Non-prostaglandin synthetase inhibitors:</i>		
Sodium salicylate	0 ³	
Choline salicylate	0 ³	
Salicylamide	0 ³	
Propoxyphene	<5 ^{3, 24†}	

*Reference numbers listed.

†Isolated case report.

pears to improve asthma²² and this finding may be attributed to inhibition of lung prostaglandin synthesis, which is assumed to be predominantly that of the bronchoconstricting PGF_{2α}. Since most asthmatic patients do not experience either harm or benefit from aspirin-like drugs, it seems unlikely that the prostaglandins are important mediators of asthma in the majority of patients.

CROSS-HYPERSENSITIVITY TO ASPIRIN

Table I summarizes the extent of cross-hypersensitivity between aspirin-like, nonsteroidal, antiinflammatory agents and aspirin among patients with hypersensitivity manifested by rhinosinusitis-asthma or by urticaria-angioedema. The table lists those agents that have been approved for prescription use in the United States. Overall there is a high degree of cross-reactivity among the nonsteroidal antiinflammatory drugs that inhibit prostaglandin synthetase. Szczeklik et al.^{5, 15} noted the prevalence of cross-sensitivity to roughly correlate with the drug's potency as a prostaglandin synthetase inhibitor and that individual patients show similar degrees of hypersensitivity to multiple drugs in this group when tested by oral challenges.

Except for mefenamic acid and phenylbutazone, the product information for each of these drugs lists aspirin sensitivity as a contraindication to use. Sixty percent of aspirin-sensitive asthmatic patients challenged with mefenamic acid and 42% challenged with

phenylbutazone were reported by Szczeklik et al.⁵ to have asthmatic reactions. The details of these challenges with respect to changes in symptoms and bronchopulmonary function before and after challenge are not included in the report. The case of one asthmatic patient who improved with aspirin and indomethacin but who suffered asthma relapse following phenylbutazone has been reported.²²

Reports of cross-sensitivity to prostaglandin synthetase inhibitors in aspirin-sensitive patients with urticaria-angioedema are limited. In small numbers of patients Szczeklik et al. found 100% cutaneous reactivity to indomethacin, 80% reactivity to fenoprofen, and 75% reactivity to ibuprofen.

In contrast to the prostaglandin synthetase inhibitors, other analgesic and antiinflammatory agents have most often not been found to produce reaction in aspirin-hypersensitive patients. In the few instances in which reactions to acetaminophen or propoxyphene have been reported,^{4, 24} lesser declines in bronchopulmonary function have been found than those ordinarily noted following reaction to aspirin or indomethacin.

INDICATIONS FOR CHALLENGE

Since approximately 10% of all asthmatic patients have developed or will develop hypersensitivity to the prostaglandin synthetase inhibitors, and less than 1% of asthmatic patients appear to benefit from aspirin-

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like drugs,²⁵ the prudent approach to the management of most asthmatic patients is to counsel them to avoid this family of drugs. Oral aspirin challenge as a predictor of future reactions is not indicated for such patients since a negative challenge may be followed months or years later by a severe reaction to aspirin or an aspirin-like drug.

Oral challenge with aspirin, indomethacin, or other drugs in this family may be indicated for the occasional rhinosinusitis-asthmatic patient for whom there is negative, unknown, or equivocal history of hypersensitivity to aspirin or aspirin-like drugs, who also has vascular disease requiring an inhibitor of platelet aggregation or musculoskeletal disease that is unresponsive to non-aspirin-like drugs.

Oral challenge with aspirin-like drugs for investigative purposes requires consent of a fully informed subject. Asthmatic patients known to be hypersensitive to aspirin who participate in investigative studies of nonsteroidal antiinflammatory agents need be warned of potential for severe asthmatic reaction to these agents.

CHALLENGE METHOD

Thus far there has been no organized attempt to standardize the methodology for oral challenges with nonsteroidal antiinflammatory drugs. There is no clinically useful *in vitro* test to detect hypersensitivity to these agents.

Zeiss and Lockey²⁶ described a patient with rhinosinusitis, nasal polyps, and asthma in whom repeated double-blind challenges with aspirin or placebo on consecutive days led to the serendipitous discovery of a 72-hr refractory period to the adverse effect of aspirin after initial ingestion of 300 mg aspirin resulted in respiratory and systemic symptoms. Bianco, Robuschi, and Petrigli²⁷ reported detection of aspirin hypersensitivity in 6 patients by inhalations of minute amounts of lysine acetylsalicylate; they also found a 6 to 7-day relative insensitivity following the challenge and this insensitivity could be maintained by ingestion of 500 mg aspirin daily or on alternate days. These observations raise concern that the "safety" of starting challenge with small doses, administered on one or several days, may actually allow for "desensitization" resulting in subclinical reactions and false interpretation of the challenge test as being negative.

Until the nature and mechanisms of aspirin hypersensitivity reactions, including the refractory or insensitive period, are better understood, it will be difficult to make definite recommendations regarding the appropriate doses and timing of oral challenges.

The following methods are those currently in use at Scripps Clinic.

Rhinosinusitis-asthma

Asthmatic patients for whom aspirin or aspirin-like drug challenge is an indicated diagnostic test are studied when their asthma is in remission as a result of a stable regimen of medications. Most of these patients have moderate to severe asthma necessitating regular use of medications including methylxanthine and systemic or inhaled corticosteroids. The patient is told to continue his usual medications and we recognize that these medications may counter a mild reaction and thereby lead to a false negative test result. The alternative of withholding medications prior to challenge allows spontaneous deterioration of the asthma during the hours of challenge which may lead to reduction of bronchopulmonary function and false conclusion of reaction to the drug.

To allow challenge the baseline (best of 3) 1-sec forced expiratory volume (FEV_1) must be greater than 70% of predicted normal or 70% of best previously recorded for an individual patient. We have not challenged any adult whose best FEV_1 has been less than 1.5 l. Challenge is begun early in the morning in the clinic allergy laboratory where intravenous fluids and medications and aerosolized medications are readily available; this laboratory is within the hospital, and emergency resuscitative equipment, medications, and personnel are immediately available.

At ½-hr intervals 3, 30, 300, and 600 mg aspirin or 1%, 10%, 100%, and 200% of the usual therapeutic dose of the other indicated, nonsteroidal, antiinflammatory drug are administered by mouth. Spirometry is performed at 30-min intervals or sooner if the patient develops nasal or ocular congestion or watering, chest tightness, dyspnea, or wheezing. After the largest dose, spirometric measurements are continued at 1-hr intervals for 3 hr. If the fall in FEV_1 exceeds 30%, and ocular-respiratory symptoms appear, no additional doses are administered and the patient is treated with intravenous aminophylline and corticosteroid and inhalations of isoetharine delivered by aerosol via a positive pressure breathing device.

A challenge is interpreted to be "positive" if the fall in FEV_1 exceeds 30% and, if on another day (at least 7 days later), similar challenge with placebo or acetaminophen produces a fall in FEV_1 of less than 20%. A challenge is interpreted to be "equivocal" if there is a 20% to 30% fall of FEV_1 or if there are ocular, nasal, or bronchial symptoms with an FEV_1 decline of less than 20%. Patients with an "equivocal"

result are rechallenged a week or more later with a dose larger than that which produced the "equivocal" result. A challenge is interpreted to be "negative" if no respiratory symptoms and a $>20\%$ fall in FEV₁ occur during the 4½ hr of observation.

Patients with a definite history of asthmatic reaction following spontaneous ingestion of aspirin or "positive" aspirin challenge, who have agreed to receive aspirin for the purpose of investigating the hypersensitivity reaction, are challenged under the same precautions as noted previously and by the same method, except that doses are modified to 25%, 50%, or 100% of the usual therapeutic dose as to produce a mild or moderate reaction.

Urticaria-angioedema

Patients with chronic unexplained urticaria are studied when their symptoms and signs are stable, preferably at a time when they are not taking anti-mediator drugs. Doses and timing of administration are the same as for the asthmatic patient. In addition, the patient is seen 24 hr following the initiation of challenge to report late reactions. The challenge is interpreted as "positive" for the individual if multiple new welts or giant swellings appear and if, on another day (at least 7 days later), similar challenge with placebo or acetaminophen produces no reaction. Differentiation of urticaria-angioedema response to aspirin from exacerbation due to another ongoing mechanism can be difficult; repeated blind challenges are indicated when there is doubt. For investigative purposes a double-blind crossover method with placebo is used.

CONCLUSION

Hypersensitivity to nonsteroidal antiinflammatory drugs presents a life-threatening hazard to some patients with asthma and an opportunity to further unravel the primary mechanisms underlying respiratory and cutaneous diseases. With our present state of knowledge, the practitioner should counsel patients with rhinosinusitis/nasal polyps/asthma to avoid aspirin and aspirin-like drugs. Only occasionally will it be necessary to perform oral challenge with these drugs for the purpose of patient management. If there is to be progress in the clinical investigation of hypersensitivity to nonsteroidal antiinflammatory drugs, investigators will need to report the details of clinical findings in their populations of asthma and urticaria patients undergoing challenges, especially concerning whether or not their patients are taking other drugs, the doses and timing of the aspirin or aspirin-like drug used in challenges, and the measurements of bron-

chopulmonary function and other parameters following oral challenge.

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