

Adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs

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Nonsteroidal anti-inflammatory drugs (NSAID) are among the most frequent causes of adverse drug reactions. The clinical symptoms often resemble allergy and consist of anaphylactic shock, bronchospasm, urticaria, angioedema, and various skin eruptions. Patients with asthma or urticaria are particularly prone to these reactions. In about 10% of adult asthmatics, aspirin and several other NSAID precipitate open asthmatic attacks, most likely through inhibition of cyclooxygenase. This distinct clinical syndrome has a characteristic sequence of symptoms and clinical course. In 20% to 40% of patients with active urticaria, aspirin increases wheals and swelling. Pyrazolones might provoke two different types of clinical reactions, acting as allergens or interfering pharmacologically with cyclooxygenation of arachidonic acid. Other mechanisms might operate in some of the remaining adverse reactions to NSAID. Emerging clinical syndromes help to guide the clinicians through the maze of symptoms and often provide a unique insight into the mechanism of basic disease.

INTRODUCTION

The first idiosyncratic reactions to aspirin were recognized soon after its introduction. Contemporary surveys list aspirin among the drugs most frequently involved in adverse symptoms.¹ According to the recent report² by the US Food and Drug Administration (FDA), nonsteroidal anti-inflammatory drugs (NSAID) accounted for 21% of the adverse reactions registered in 1984. In this respect, aspirin occupied the first place of all therapeutic classes of drugs. In certain diseases (eg, asthma or urticaria) intolerance to NSAID is high and constitutes a major clinical problem. It presents itself as anaphylactic shock, bronchospasm, angioedema, and various skin eruptions. These symptoms suggest an allergic background which, indeed, is the case in some patients. In others, we are faced with pseudoallergy.³ Fortunately, out of the maze of symptoms, certain clinical and pharmacologic patterns have emerged.⁴ Here we present manifestations of allergic and pseudo-allergic reactions to NSAID, describe distinct clinical syndromes, discuss their background as well as

prevention and therapy. The rare injuries to certain organs or tissues associated with NSAID administration, such as Reye's syndrome,⁵ agranulocytosis and aplastic anemia,^{6,7} and nephropathy^{8,9} were recently reviewed and will not be discussed here.

ANAPHYLACTIC SHOCK

A number of anaphylactic reactions, including shock, were reported following recently marketed zomepirac (a pyrolic acid) and its close congener, tolmetin.² Diclofenac, at an oral dose of 25 mg, was also reported to produce shock accompanied by a high-grade fever in an elderly man.¹⁰ In patients with lupus erythematosus or with aspirin-induced asthma, severe reactions to analgesics may take the form of an anaphylactic shock.

Pyrazolones are a relatively common cause of anaphylaxis. Shock is just one extreme of a whole range of symptoms which include urticaria, maculopapular rashes, angioedema, and bronchospasm. The reactions to pyrazolones can be grouped into two categories: allergic and pseudo-allergic.¹¹⁻¹⁴ The two groups differ distinctly in clinical presentation and intolerance to other analgesics.

In the first group, comprising true

allergic reactions, anaphylactic shock and urticaria are leading symptoms, while asthmatic attacks occur only in 5% of patients. Intradermal skin tests with 0.01% noramidopyrine or aminophenazone, performed 2 to 24 months after the acute reaction, are positive. Skin tests with phenylbutazone and sulfinpyrazone are negative. Oral challenge tests with therapeutic doses of aspirin, indomethacin, fenoprofen, ibuprofen, mefenamic acid, paracetamol, phenylbutazone, and sulfinpyrazone are all negative and the patients can take these drugs with impunity.

Patients of the second, pseudo-allergic group, present usually with an asthmatic attack, while symptoms of shock appear only in sporadic cases with most severe attacks of asthma. Skin tests with noramidopyrine and aminophenazone are negative. Patients are intolerant to aspirin, indomethacin, noramidopyrine, aminophenazone, and several other anti-cyclooxygenase agents that, when given orally in minute amounts, precipitate acute asthmatic attacks. All of these patients are running asthma with aspirin-intolerance. In contrast to the first group, the mechanism involved in the second one does not appear

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to be truly allergic but involves inhibition of cyclooxygenase.¹³

Anaphylactic shock requires prompt, energetic treatment. Adrenaline is given intramuscularly in a dose of 0.5 to 1.0 mg, repeated every 15 minutes until improvement occurs. Antihistamines, eg, 10 mg chlorpheniramine administered by a slow intravenous injection, are a useful adjunctive treatment. Intravenous steroids are of secondary value as their onset of action is delayed for several hours, but they should be used to prevent further deterioration in severely affected patients. Treatment of aspirin-precipitated asthmatic attacks is presented below.

ASPIRIN-INDUCED ASTHMA

Definition and Clinical Symptoms

In about 10% of adults with asthma, but rarely in asthmatic children, aspirin and other NSAID precipitate asthma attacks. This distinct clinical syndrome is called aspirin-induced asthma (AIA). The majority of patients afflicted with AIA give a negative family history. When HLA typing was performed, no change in either frequency of class I HLA-A, B and C antigens or HLA-DR antigens were found.^{15,16} There was however a significant increase in HLA-DQw2 in aspirin-sensitive asthmatics as compared with asthmatic patients with good tolerance of aspirin.¹⁶

The course of the disease and its clinical picture are very characteristic.^{4,17-19} In individual cases, the onset of symptoms before puberty or after the age of 60 have been well documented. In a majority of patients, however, first symptoms appear during the third or fourth decade of life. The typical patient starts to experience intense vasomotor rhinitis characterized by intermittent and profuse watery rhinorrhea. Over a period of months, chronic nasal congestion appears and physical examination reveals nasal polyps. Bronchial asthma and intolerance to aspirin develop during sub-

sequent stages of the illness. The intolerance presents itself as a unique picture: within an hour following ingestion of aspirin, acute asthmatic attacks develop, often accompanied by rhinorrhea, conjunctival irritation, and a scarlet flush of the head and neck. These reactions are dangerous. A single therapeutic dose of aspirin or another anticyclooxygenase agent can provoke a violent bronchospasm, shock, unconsciousness, and respiratory arrest. Asthma runs a protracted course despite the avoidance of aspirin and cross-reactive drugs. The eosinophil count is elevated. Skin tests with common aeroallergens are often negative and those with aspirin are always negative.

Intolerance to Anti-inflammatory Drugs and Chemicals

In patients with AIA, not only aspirin but several other NSAID precipitate bronchoconstriction.²⁰ These drugs include indomethacin, mefenamic acid, flufenamic acid, cyclofenamic acid, ibuprofen, fenoprofen, ketoprofen, naproxen, diclofenac sodium, piroxicam, sulindac, tiaprofenic acid, amidopyrine, dipyrone, sulfapyrazone, phenylbutazone, zomepirac, tolmetin, fenflumizole, and ditazole. All these drugs are contraindicated in patients with AIA. If necessary, these patients can safely take salicylamide, dextropropoxyphene, benzydamine, guacetal (guaiacol ester of acetylsalicylic acid), sodium salicylate, choline salicylate, and chloroquine. Paracetamol can also be taken with impunity by the majority of patients; however, it is safer to give half a tablet first and then to observe patients for two to three hours for symptoms. We have found symptoms with paracetamol in (4%) of our patients. The rare patients in whom paracetamol produced obstruction to airflow experienced the same effects following ingestion of phenacetin, which is metabolized to paracetamol. These reactions should be distinguished from acute hypersensitivity to par-

acetamol, presumably mediated immunologically.²¹

Tartrazine, a yellow azo-dye (FD&C no. 5) is used for coloring foods, drinks, drugs, and cosmetics. Contrary to aspirin-like drugs, tartrazine does not inhibit cyclooxygenase activity.²² In some aspirin-sensitive subjects a bronchoconstriction similar to that caused by aspirin has been observed following tartrazine ingestion. Older reports suggested that such reactions could be quite common, affecting up to 40% of aspirin-intolerant asthmatics. The critical evaluation of the studies reporting high incidence of tartrazine intolerance was published by Simon.²³ He pointed out that these studies were either totally non-placebo controlled or the criteria for positive reactions were subjective and vaguely defined. Furthermore,²³ many of the reactions considered positive were merely a product of clinical liability in these patients in whom all symptomatic treatment was usually withheld at the beginning of the tests.

In a multicenter, international study,²⁴ we have found tartrazine hypersensitivity to be rare. Of 168 Italian, Polish, and Swiss patients with well documented AIA, only four had positive reactions when challenged with tartrazine.²⁴ Similarly, Weber et al²⁵ was unable to confirm a single case of tartrazine intolerance among 44 patients. Morales et al²⁶ observed one questionable case in 47 patients, and Simon²⁵ found none among 125 patients.

Intravenous hydrocortisone may sporadically provoke bronchoconstriction in patients with AIA. In 31 such patients the mean FEV₁ fell significantly five minutes after an intravenous bolus of 300 mg of hydrocortisone, but not after the solvent, and returned to the initial values one hour later.²⁷ At this time, only 3 of 31 patients displayed clinical signs of increased impairment of airflow, which resolved spontaneously. Such reactions, however,

might sometimes be of great clinical concern.²⁷ It is therefore advisable to use other than hydrocortisone parenteral steroids (eg, dexamethasone, bethamethasone, or methylprednisone) in patients with AIA.

Eicosanoids and Pathogenesis of Aspirin-Induced Asthma

Allergic mechanisms for AIA have been excluded by numerous extensive immunologic studies (see references 4, 18, and 19). Furthermore, in aspirin-sensitive patients, asthma attacks may be precipitated by several other analgesics with differing chemical structures, which makes immunologic cross-reactivity unlikely.

Recent studies point to mast cell degranulation in asthma attacks provoked by aspirin. Indeed, blood neutrophil chemotactic activity increases during the attacks and roughly parallels bronchoconstriction.^{28,29} This event, however, appears to be secondary, prolonging or amplifying, but not initiating, the reaction.²⁸ An increase in blood histamine levels might also occur during the reaction but this is not a consistent finding.³⁰

We have put forward a hypothesis³¹ that in sensitive patients, precipitation of asthma attacks by certain analgesics results from inhibition of cyclooxygenase, leading to an imbalance of prostanoids in the respiratory tract. Nine points of evidence that have been accumulated in favor of this hypothesis^{4,19,20} are as follows.

(1) Analgesics with anticyclooxygenase activity invariably precipitate bronchoconstriction in aspirin-sensitive asthma patients.

(2) Analgesics not affecting cyclooxygenase are devoid of bronchospastic properties in these patients.

(3) There is a positive correlation between the potency of analgesics in inhibiting cyclooxygenase *in vitro* and their potency in inducing asthma attacks in sensitive patients.

(4) The degree of enzymatic inhibition that is sufficient to precipi-

tate bronchoconstriction is an individual hallmark (thus, if the threshold dose for any anticyclooxygenase drug in a particular patient is known, one can predict the threshold doses for other analgesics in that patient).

(5) The cyclooxygenase in nasal polyps of aspirin-sensitive patients has an increased susceptibility to the inhibitory action of aspirin.³² On the other hand, PGE₂ formation by nasal polyps of aspirin-intolerant patients is within the range of the control group.^{32,33}

(6) *In vitro*, aspirin has a greater inhibitory effect on cyclooxygenase of blood basophil-enriched leukocytes in aspirin-sensitive patients compared with aspirin-tolerant patients with asthma and normal subjects.³⁴

(7) *In vitro*, cyclooxygenase inhibitors activate platelets to release cytotoxic mediators in aspirin-sensitive asthmatics but not in the atopic asthmatics or healthy subjects.^{35,36}

(8) Stimulated alveolar macrophages from aspirin-intolerant asthma patients release smaller quantities of PGE₂, PGF_{2α}, and TXB₂ than do alveolar macrophages from normal subjects.³⁷ Attempts were also made to measure circulating primary prostaglandins in blood.³⁸⁻⁴⁰ This approach, however, might be misleading⁴¹ because of the very short half-life of PGE₂ and PGF_{2α} in the blood-stream, and because handling of the blood samples generally leads to the artifactual production of prostaglandins.

(9) In aspirin-intolerant patients, pharmacologic inhibition of thromboxane A₂ synthetase neither precipitates asthmatic attacks nor alters pulmonary function.⁴²

The inhibition of bronchial cyclooxygenase by aspirin-like drugs thus appears to set off a chain of reactions leading to asthma attacks in aspirin-intolerant patients. What follows at the biochemical level is a matter of speculation. Various biochemical possibilities have been dis-

cussed elsewhere.⁴³ We do not favor the widely held concept that aspirin-like drugs, by blocking the cyclooxygenase pathway, divert arachidonic acid metabolism towards leukotrienes C₄ and D₄, potent bronchoconstrictors and mucous secretagogues. This concept lacks experimental evidence and is hard to accept in view of likely compartmentalization of arachidonic acid in the lung.^{44,45} Alternatively, the cyclooxygenase products such as PGE₂ or PGI₂ may interact with alveolar macrophages, infiltrating leukocytes and mastocytes and leading to suppression of the release of leukotrienes by these cells.^{45,46} Furthermore, PGE₂ and PGI₂ decrease the responsiveness of specific receptors to leukotrienes in the lung.⁴⁵ Based on these observations, Kuehl et al⁴⁶ reasoned that aspirin-like drugs cause a local deficiency of PGI₂ and PGE₂ and thereby may remove a damping mechanism controlling leukotriene production, which results in asthma attacks. In the clinical setting, infusion of prostacyclin does not prevent attacks of asthma precipitated by aspirin.⁴⁷ This result, however, does not exclude the possibility that Kuehl's concept might be correct. The protective mechanism in bronchi can be, perhaps, provided by PGE₂, the actions of which were too often assumed to be exactly the same as those of prostacyclin.

Diagnosis, Prevention and Therapy

There are no *in vitro* tests suitable for routine clinical diagnosis of aspirin intolerance, which can be established with certainty only by careful aspirin challenge.^{4,11}

Patients with aspirin-induced asthma should avoid aspirin and other anti-cyclooxygenase agents listed above. If necessary, they can take safely, even for prolonged periods, salicylamide, dextropropoxyphene, or benzydamine. Most patients will also tolerate paracetamol well.

Another option is desensitization. This can be achieved by giving four

to eight incremental doses of aspirin every two to three hours with careful observation. State of aspirin tolerance (refractory period) lasts two to five days but in most patients it can be extended over months if aspirin is administered regularly at a daily dose of 600 mg. At the same time patients can ingest other anti-cyclooxygenase drugs without any adverse effects. Long-term maintenance of tolerance has no effect on asthma, but often leads to improvement in rhinosinusitis.^{48,49} An interesting explanation for the phenomenon of desensitization has been recently proposed by Kowalski et al.⁵⁰

Therapy of aspirin-induced asthma does not differ from other types of asthma. Long-term treatment with steroids is necessary in at least half of the patients.

URTICARIA AND ANGIOEDEMA

Many patients with chronic urticaria develop an obvious increase in the wheals and swellings after taking aspirin. These exacerbations occur only while urticaria is active, but not in the symptomless period.⁵¹ The proportion of patients with chronic urticaria who develop an exacerbation after taking aspirin and other salicylates ranges from 20% to 40%.^{52,53} A high level of salicylates in the blood of patients with chronic urticaria has been found.⁵³ It appears that aspirin precipitates wheals and swelling in patients with idiopathic urticaria, delayed pressure urticaria, and cholinergic urticaria but not in patients with cold urticaria.⁵⁴

It seems clear that all patients with urticaria should avoid aspirin in any form. Care should be taken also to exclude from the diet drug additives and colorants (eg, benzoates or tartrazine) to which some patients are intolerant.⁵³ Intolerance to tartrazine amounts to 13%⁵⁵ among patients with chronic urticaria.

The reactions to tartrazine seem to have many common features

with more frequent reactions to salicylates. Both occur when urticaria is active. When patients have been clear for some time, they are able to take salicylates and tartrazine without producing wheals. This suggests that the reactions are probably not due to an allergic mechanism but to some pharmacologic action.⁵⁵ A simple diet free of aspirin, azo dyes, and preservatives might bring improvement in some patients with chronic urticaria.⁵³

There is a distinct group of patients who can be distinguished from all the others linking their cutaneous reactions to aspirin ingestion. In these patients skin reactions are evoked by all NSAID that are cyclooxygenase inhibitors. This is the type B hypersensitivity to cyclooxygenase inhibitors¹¹ as opposed to type A (aspirin-induced asthma). The same aspirin-like drugs that induce bronchoconstriction in type A patients also produce angioedema associated with urticaria or rhinitis in type B patients.

In other patients, impurities contaminating commercial aspirin preparations could be responsible for appearance of urticaria and angioedema.^{56,57} These contaminants include acetylsalicylic anhydride, acetylsalicylic salicylic acid, and cis-disalicylide. In these cases, an immunologic basis (formation of anti-aspirin antibodies) of aspirin hypersensitivity appears very likely.⁵⁶

In sporadic cases, laryngeal edema might be the only symptom of hypersensitivity to aspirin and salicylates.⁵⁸

OTHER CUTANEOUS REACTIONS TO NSAID

According to the recently published⁵⁹ survey by the Adverse Drug Reaction Reporting System of the American Academy of Dermatology, piroxicam was the most frequent causative agent of skin reactions produced by NSAID. The majority of reactions to this drug were vesicobullous and occurred in sun-exposed areas. Other reactions to

NSAID, not previously recognized, included serum sickness, exfoliative erythroderma, and photosensitivity associated with sulindac; toxic epidermal necrolysis was reported with tolemin, zomepirac, and piroxicam. Other sources⁶⁰ point to pyrazolones and salicylates as possible causes of toxic epidermal necrolysis. Nine cases of Stevens-Johnson syndrome have been associated with diflunisal.⁶¹ The cutaneous manifestations of drug allergy with special reference to NSAID has been reviewed in detail by Schulz.⁶⁰

INTOLERANCE TO NSAID IN LUPUS ERYTHEMATOSUS

In eight patients with systemic lupus erythematosus who developed adverse reactions to ibuprofen^{11,62,63} sudden appearance of high fever, abdominal pain and rash were reported. Some transaminases were raised in some patients. Perhaps, like many other clinical manifestations of lupus erythematosus, these reactions were due to formation of antigen-antibody complexes.

NSAID AND MASTOCYTOSIS

Some patients with mastocytosis have a severe hypotensive response to initial ingestion of aspirin, and other cyclooxygenase blockers, even to the point of frank shock or, rarely, death.⁶⁴ On the other hand, in patients with severe course of systemic mastocytosis, the addition of aspirin to the anti-histamine regimen might be warranted, although under strictly controlled circumstances.⁶⁵ The therapeutic value of aspirin in these cases appears to be linked to blockade of PGD₂ synthesis in mast cells.⁶⁶ The warning that other NSAIDs should be considered as potentially dangerous (and just as potentially therapeutic) as aspirin should be strongly heeded.

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