

Management Options for Patients with Aspirin and Nonsteroidal Antiinflammatory Drug Sensitivity

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Aspirin and nonselective nonsteroidal antiinflammatory drugs (NSAIDs) are among the most widely used medications in the world. Aspirin is primarily used to treat and prevent heart disease, whereas NSAIDs are used as antipyretic, antiinflammatory, and analgesic therapy. While aspirin and the NSAIDs are generally well tolerated, common adverse effects associated with these medications include gastrointestinal toxicity and allergic-type reactions, often termed aspirin/NSAID sensitivity. Classically, 2 main types of aspirin sensitivity have been described: respiratory reactions and urticaria/angioedema.^{1,2} These are estimated to occur in 0.07–0.3% of the general population.^{3,4} More recent data indicate that patients may not always present with symptoms in one category but may have blended reactions.^{5,6} Blended reactions are characterized by the development of urticaria and shortness of breath. Although most aspirin/NSAID-induced reactions are dependent on the inhibition of the cyclooxygenase-1 (COX-1) pathway, some patients may experience true immunoglobulin E (IgE)-mediated reactions as well.

Since aspirin and nonselective NSAIDs are used therapeutically for the treatment of many conditions, a history of aspirin/

OBJECTIVE: To evaluate and provide management strategies for patients with aspirin or nonselective nonsteroidal antiinflammatory drug (NSAID) sensitivity.

DATA SOURCES: Literature retrieval was accessed through MEDLINE (1966–March 2007) using the terms acetaminophen, aspirin, antiinflammatory agents nonsteroidal, urticaria, angioedema, asthma, leukotriene antagonists, desensitization, and tacrolimus. Article references retrieved were hand-searched for other relevant articles.

STUDY SELECTION AND DATA EXTRACTION: All studies published in English were evaluated. Studies, review articles, and commentaries on aspirin-induced asthma and aspirin- or NSAID-induced urticaria/angioedema were included in the review.

DATA SYNTHESIS: Aspirin sensitivity is most often manifested as respiratory reactions (eg, bronchospasm, profuse rhinorrhea, conjunctival injection) or urticaria/angioedema. The primary mechanism is believed to be inhibition of the cyclooxygenase 1 (COX-1) enzyme; as such, patients with aspirin sensitivity often display cross-reactions to nonselective NSAIDs that inhibit the COX-1 enzyme. Management strategies include avoidance of aspirin and cross-reacting nonselective NSAIDs. However, desensitization to aspirin is a viable option for patients with aspirin-induced respiratory reactions, especially for those who require aspirin for thromboembolic prophylaxis. Aspirin desensitization is maintained indefinitely with a daily aspirin dose. There is limited evidence of the use of leukotriene modifiers in preventing aspirin-induced asthma. COX-2 selective NSAIDs, especially in patients with aspirin-induced asthma, have not been found to cross-react. However, approximately 4% of patients with a history of aspirin-induced skin reactions may experience a cutaneous reaction following a challenge to a COX-2 selective NSAID. Since acetaminophen is a weak inhibitor of the COX-1 enzyme, patients with aspirin-induced asthma should not take more than 1000 mg of acetaminophen in a single dose.

CONCLUSIONS: Management of patients with aspirin/NSAID sensitivity includes avoidance of aspirin/nonselective NSAIDs, use of COX-2 selective NSAIDs, acetaminophen in doses less than 1000 mg, and desensitization. The role of leukotriene modifiers requires further study before they can be recommended for patients.

KEY WORDS: aspirin, asthma, desensitization, urticaria.

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NSAID sensitivity restricts the use of these agents and may have a negative impact on patient care. The presentation, diagnosis, and epidemiology of cutaneous and respiratory aspirin/NSAID sensitivity are reviewed in this article. In addition, recent literature on management strategies for patients with aspirin/NSAID sensitivity are evaluated.

Data Sources

Literature retrieval was accessed through MEDLINE (1966–March 2007) using the terms aspirin, antiinflammatory agents nonsteroidal, acetaminophen, urticaria, angioedema, asthma, leukotriene antagonists, desensitization, and tacrolimus. In addition, retrieved article references were hand-searched for other relevant articles. All studies published in English were evaluated. Studies, review articles, and commentaries on aspirin-induced asthma and aspirin- or NSAID-induced urticaria/angioedema were appraised.

Clinical Presentation

A classification of allergic and pseudoallergic reactions to medications that inhibit the COX enzymes, based on clinical presentation and pathophysiological considerations, is presented in Table 1.⁶

RESPIRATORY REACTIONS

After ingestion of aspirin or other nonselective NSAIDs, patients with allergic reactions develop symptoms within 2–3 hours. Symptoms generally consist of bronchospasm, profuse rhinorrhea, conjunctival injection, periorbital edema, and generalized flushing.^{7,8} The prevalence of aspirin-induced respiratory reactions (also known as aspirin-exacerbated respiratory disease, aspirin-induced asthma, Samter's syndrome, aspirin triad) among asthma with adults is esti-

mated to be between 4.3% and 21%.^{4,9–11} Patients with aspirin-induced respiratory reactions tend to have more severe asthma than do those with aspirin-tolerant asthma.^{12–14} Aspirin sensitivity has been reported in 35–52% of patients with nasal polyps and in as many as 65% of patients who suffer from both bronchial asthma and nasal polyps.¹⁵

Patients with aspirin/NSAID-induced respiratory reactions often have an underlying history of asthma, nasal polyps, and/or rhinosinusitis,⁶ although some patients may not have any predisposing diseases. Individuals who develop the aspirin triad (asthma, nasal polyps, aspirin sensitivity) typically develop persistent rhinitis in their third or fourth decade of life that is often associated with a viral upper respiratory tract infection. Women are affected 2.5 times more often than men.

Approximately 2–5 years later, there is a progression to asthma, aspirin sensitivity, and nasal polyposis.¹⁶ Once aspirin sensitivity develops, it is usually present for life,¹⁷ although it has been reported to disappear spontaneously.¹⁷ Aspirin-induced respiratory reactions are thought to be very rare, if present at all, in children.^{3,18}

URTICARIA

Aspirin and other nonselective NSAIDs can either cause acute episodes of urticaria/angioedema in otherwise healthy individuals or aggravate pre-existing chronic idiopathic urticaria (CIU).¹⁹ In some patients, aspirin can act as a cofactor in urticarial reactions to food or exercise, and food-dependent, exercise-induced anaphylaxis may be augmented by aspirin ingestion.²⁰ Urticaria can occur within 15 minutes of aspirin ingestion or may be delayed for up to 24 hours, but most patients develop symptoms within 4 hours.²¹ Symptoms generally diminish within 24–48 hours, but urticaria may continue for up to 1–2 weeks after ingestion, even in patients without underlying CIU.¹⁹ Some

Table 1. Classification of Allergic and Pseudoallergic Reactions to COX Inhibitors⁶

Reaction	Underlying Risk Factor(s)	Cross-Reactions to Other COX-1 Inhibitors	Mechanism of Sensitivity	Desensitization Recommended
NSAID-induced rhinitis and asthma	asthma, nasal polyps, sinusitis	yes	COX-1 inhibition	yes
NSAID-induced urticaria and angioedema	chronic idiopathic urticaria	yes	COX-1 inhibition	no
Single drug-induced urticaria and angioedema	none	no	immunologic	yes
Multiple drug-induced urticaria and angioedema	none	yes	COX-1 inhibition	yes
Single drug anaphylaxis	none	no	immunologic	yes
NSAID-blended reaction	variable (risk factors such as asthma, rhinitis, or urticaria may be present in some individuals)	yes (not consistently)	unknown (COX-1 inhibition?)	data not available

COX-1 = cyclooxygenase 1; NSAID = nonsteroidal antiinflammatory drug.

predisposing factors for NSAID-induced urticaria and angioedema may include atopy, female sex, and intermittent NSAID use for relief of acute pain.²

Chronic urticaria (most often defined as daily or almost daily recurrences for at least 6 wk)¹⁹ is more likely to develop in individuals who have previously manifested aspirin or NSAID intolerance, and cutaneous reactions to nonselective NSAIDs may precede by years the development of chronic urticaria.²² In approximately 20–40% of patients with chronic idiopathic urticaria, aspirin will trigger or aggravate the disease.²³ In addition, the frequency of aspirin intolerance is over 20 times greater in patients with CIU than in the general population.³ Some familial predisposition to CIU has been found to stem from leukotriene-related genes,²⁴ but the observed inheritance patterns are not Mendelian and as such cannot be easily predicted along family lines.²³

ANAPHYLACTIC REACTIONS

Immediate-type hypersensitivity reactions (also known as IgE-mediated reactions) are characterized by the development of symptoms of anaphylaxis including urticaria, angioedema, bronchospasm, and/or hypotension.⁶ Previous exposure to the drug is required for the production of drug-specific IgE antibodies.² Although only limited clinical data exist, patients develop an IgE-mediated reaction to a specific NSAID and will not cross-react to other nonselective NSAIDs. The only exception to this is for nonselective NSAIDs that have molecular structures that are almost identical. For example, sulindac, tolmetin, and zomepirac are chemically similar and can be recognized by the same IgE antibodies.¹

Mechanisms of Pathogenesis

RESPIRATORY REACTIONS

Most available evidence points toward the inhibition of cyclooxygenase (COX) and/or lipoxygenase pathways by aspirin and other nonselective NSAIDs. The 2 major enzymes involved are COX-1, which is expressed constitutively in airway mucosa and considered the “housekeeping” enzyme responsible for physiological activities of prostaglandins, and COX-2, an enzyme that is induced with proinflammatory signals. Clinical studies show that inhibition of COX-1, but not COX-2, precipitates asthmatic attacks.²¹ COX-1 inhibitors accelerate depletion of prostaglandin E₂ (PGE₂), which would normally protect against the effects of bronchoconstriction and mast-cell mediator release.⁷ As well, expression of the COX-2 enzyme and its activity is reduced in patients with aspirin-induced asthma.²¹ The combination of diminished COX-2 activity in aspirin-sensitive individuals with the inhibition of COX-1 by aspirin and other nonselective NSAIDs may

contribute to reduced PGE₂ production, with the end result of aspirin-induced asthma.

Shunting of arachidonic acid metabolism away from prostanoid production and into leukotriene synthesis results in an increase in leukotriene production, with resultant bronchoconstriction and increased mucus production.¹⁶ Patients sensitive to aspirin also have upregulation of their 5-lipoxygenase pathway, which leads to increased synthesis of cysteinyl leukotrienes and release of histamine from mast cells.^{6,21} Cysteinyl leukotrienes induce bronchoconstriction, edema formation, and mucus production in airways and are considered mediators of asthma. Based on the proposed mechanism, patients who develop aspirin-induced asthma will cross-react to other nonselective NSAIDs that inhibit the COX-1 enzyme.

Other mechanisms that have been proposed to explain the pathogenesis of aspirin-induced asthma include chronic inflammation of the airways, possibly due to a chronic viral infection.^{16,25}

SKIN REACTIONS

The pathogenesis of aspirin-induced urticaria is unknown but appears to be related to the inhibition of the enzyme COX-1. Thus, patients who present with cutaneous symptoms after aspirin/NSAID therapy will generally cross-react with all nonselective NSAIDs that inhibit COX-1.^{6,19} Similar to aspirin-induced asthma, inhibition of the COX-1 enzyme leads to imbalances in the levels of leukotrienes and prostaglandins, thus provoking the inflammatory response observed in these patients. Excessive leukotriene production results in increased vasopermeability and subsequent urticaria.¹⁹ This is further supported by the use of leukotriene antagonists in the treatment of aspirin-induced urticaria.^{19,22,26} The rapid depletion of PGE₂ after COX-1 is inhibited triggers the skin eruptions by promoting mast cell discharge and cysteinyl leukotriene biosynthesis.²¹

Diagnosis

Definitive diagnosis of sensitivity to aspirin can only be obtained by using provocation challenges.²⁷ Oral, inhaled (bronchial), nasal, and intravenous provocation tests have been used, but only the first 3 are regularly used in clinical practice.²⁸ The oral route of administration is the most common challenge method and is generally the only one used in North America, as it best exemplifies natural exposure.²¹ In most patients, threshold doses that evoke positive respiratory reactions are 30–150 mg of aspirin (average 60).²⁹ Established protocols recommend a placebo challenge first to eliminate the possibility of spontaneous bronchospasm. Skin testing, though not typically performed in North America, is often negative and is not useful for diagnosis.³⁰

Before patients can undergo provocation tests, their underlying disease (eg, asthma, urticaria) must be stable. Oral provocation testing consists of administration of placebo and escalating doses of aspirin over 1–4 consecutive days.^{31,32} Protocols differ between various centers based on the dosage of aspirin used, intervals between successive doses (30 min to 2 h), cumulative doses (416–1165 mg), starting doses (usually 30–80 mg), and criteria for assessing a positive test. In general, a test is considered positive if a decrease in forced expiratory volume in one second (FEV₁) of more than 20% occurs, usually accompanied by bronchoconstriction and nasal symptoms.³³ Some of these oral challenge protocols are similar in dosing to desensitization protocols (ie, the protocols start with small doses and slowly increase the dose, similar to a desensitization protocol); as such, it is unclear whether a negative oral challenge simply means that a patient is “desensitized.” At the Drug Safety Clinic, our standard oral provocation protocol is a 2 dose challenge consisting of aspirin 80 mg and 325 mg administered one hour apart. Since oral provocation testing may cause serious reactions, the test should be performed by a highly experienced physician in a hospital environment with resuscitation resources readily available.

Management

Patients with underlying asthma or chronic idiopathic urticaria should have their disease managed according to published guidelines. Patients with aspirin-induced sensitivity must avoid aspirin and other cross-reacting nonselective NSAIDs, except when a desensitization approach is successful.^{19,21} Oral aspirin challenge to predict future reactions is not indicated since a negative challenge may be followed months or years later by a severe reaction to aspirin or an NSAID.³⁴ Since aspirin and nonselective NSAIDs are widely used in clinical practice for the management of inflammatory conditions, analgesia, and as antipyretics, patients with a history of aspirin-induced sensitivity require alternatives to this class of medication or should undergo a desensitization, if appropriate.

DESENSITIZATION

Avoidance of aspirin may not always be possible in some patients with aspirin sensitivity. In cases where aspirin is required, such as cardiovascular prophylaxis, desensitization may be a viable option, especially for patients with aspirin-induced asthma. Desensitization results in the elimination of pharmacologic and immunologic reactions by slowly increasing doses of oral aspirin.¹⁹ Desensitization also results in decreased leukotriene production, down-regulation of cysteinyl leukotriene receptors, and decreased extracellular histamine and tryptase levels after mast cell stimulation.^{19,35} Patients who successfully complete aspirin desensitization

should remain on the drug indefinitely.³⁶ Individual patient refractory periods range from less than 2 days to greater than 5 days, with most patients gradually returning to sensitivity between 2 and 4 days.

Desensitization in patients with aspirin-induced asthma not only allows the clinical use of aspirin but also improves the state of the patient's underlying disease including improved nasal and asthmatic symptom scores and decreased prednisone dose.^{37–42}

Several desensitization protocols have been successfully used in patients with aspirin-induced asthma.⁴³ Starting doses are smaller than those used in diagnostic challenge protocols, and the protocol requires aspirin to be administered over a longer period of time. Doses are administered every 2–24 hours in small incremental doses until 400–650 mg is tolerated.⁴⁴ Aspirin desensitization is maintained indefinitely with a daily dose of as little as 81 mg⁴⁵; therefore, desensitization is not recommended in patients who require intermittent use of aspirin or an NSAID. Alternatively, more rapid desensitization over a period of 2.5 or 3.5 hours has been used for patients with coronary artery disease in urgent need of aspirin therapy.^{46–48} Once desensitized to aspirin, patients are considered “cross-desensitized” to other nonselective NSAIDs.^{7,36}

Desensitization for aspirin-induced skin reactions is more controversial. Despite some reports to the contrary,^{47,49,50} some clinicians maintain that desensitization is not successful in patients with chronic idiopathic urticaria.^{6,45} A brief refractory period of tolerability following aspirin challenge has been observed, but continuation of aspirin may lead to exacerbation of the urticaria.⁵¹ However, desensitization may be successful in patients with single drug-induced urticaria/angioedema or in patients with single NSAID-induced anaphylaxis.⁴⁷

LEUKOTRIENE ANTAGONISTS

Since a proposed pathogenic mechanism for aspirin-induced asthma involves increased leukotriene levels that contribute to inflammatory mediator release, leukotriene-modifying drugs have been used in patients with aspirin-induced asthma. Available agents include those that inhibit cys-LT₁ synthesis by blocking either 5-lipoxygenase (zileuton) or the specific cys-LT₁ receptor (zafirlukast, montelukast, pranlukast). A review published in 2002 concluded that only 1 of 4 studies showed that leukotriene modifiers (specifically zileuton) had a statistically significant effect on preventing aspirin-induced respiratory reactions.⁵² The variability of the results may imply that there is inadequate inhibition of leukotriene activity or that there may be several mediators involved in aspirin-induced respiratory reactions. Although none of the studied leukotriene-modifying agents was able to significantly blunt aspirin-induced respiratory reactions, the dose–response

curve to aspirin challenge was shifted (eg, from 60 mg at baseline to 90 mg after montelukast pretreatment).⁵³ It should be noted that the studies reviewed had small sample sizes and used various aspirin challenge protocols.

There have been several studies conducted since that review. In a double-blind, placebo-controlled, crossover study,⁵⁴ 10 and 40 mg doses of montelukast led to a significant reduction in maximum peak nasal inspiratory flow drop 120 minutes after aspirin challenge (14% and 17%, respectively) compared with placebo (26%; $p < 0.05$). Another double-blind, placebo-controlled study investigated efficacy of montelukast in patients with aspirin-induced asthma when given for 4 weeks.⁵⁵ The nasal reaction remained unchanged following placebo but was completely minimized following montelukast 10 mg/day.

A nonrandomized study examined the effects of leukotriene receptor antagonists in patients with aspirin-induced asthma compared with a control group not receiving leukotriene modifiers.⁵⁶ All patients underwent an oral aspirin challenge beginning at 30 mg and increased to 650 mg. Thirty-nine percent of patients on leukotriene receptor antagonists had a bronchospastic reaction compared with 51% in the control group ($p = 0.05$). No significant differences were found in the percent changes in FEV₁ or in the mean provoking aspirin dose. Cys-LT modifiers shifted the response to aspirin from both upper and lower respiratory tract to upper tract alone. Another study showed similar results.⁵⁷

Leukotriene modifiers may have some role in the management of patients with aspirin-induced asthma.^{58,59} The evidence, albeit weak, supports their use as add-on therapy for patients with aspirin-induced asthma. Patients with aspirin-induced asthma who are on leukotriene modifiers should remain cautious when taking concomitant aspirin or nonselective NSAIDs.

There is limited evidence for the use of leukotriene modifiers to prevent NSAID-induced urticaria and angioedema.⁶⁰⁻⁶² One study reported complete or partial blockade of urticaria after an NSAID challenge in 90% of patients, when patients were pretreated with a single dose of montelukast 20 mg given 4 hours before the test.⁶⁰ Further studies are needed to assess the efficacy of leukotriene modifiers in patients with aspirin-induced urticaria/angioedema before they can be recommended.

TACROLIMUS

Tacrolimus is an immunosuppressant that inhibits the release of chemical mediators such as histamine and cys-LTs.⁶³ Since overproduction of cys-LTs is considered to be a major factor in the pathogenesis of aspirin-induced asthma, it has been postulated that tacrolimus may have therapeutic benefit for patients with aspirin-induced asthma. The results of 2 small studies have been conflicting.^{64,65} Based on these limited studies, tacrolimus' utility as a po-

tential treatment in patients with aspirin-induced asthma or as a means to conduct safer desensitization protocols is unclear and needs to be further investigated in larger patient populations before it can be recommended.

COX-2 SELECTIVE NSAIDS

Inhibition of the COX-1 enzyme by aspirin and nonselective NSAIDs is key in the development of reactions observed in patients sensitive to these medications. Based on this mechanism, NSAIDs that selectively inhibit the enzyme COX-2 may be safe in aspirin/NSAID-sensitive patients.⁶⁶ The COX-2 selective NSAIDs that are commercially available such as celecoxib, lumiracoxib (available in Canada but not in the US), and etoricoxib (not available in North America) do not lose their selectivity when the dose is increased. This is in contrast to the preferential NSAIDs, such as nimesulide (not available in North America) and meloxicam, which lose selectivity when the dose is increased^{67,68}; however, other studies have shown that meloxicam is often tolerated in aspirin-sensitive patients in doses up to 22.5 mg.⁶⁹

Aspirin-Induced Asthma

The safety of COX-2 selective NSAIDs in patients with aspirin-induced asthma has been reviewed.⁶⁸ A total of 172 patients were enrolled in the 4 studies, none of whom experienced any reaction to the COX-2 selective NSAIDs during challenge.⁷⁰⁻⁷³ The authors concluded that the specific COX-2 selective NSAIDs rofecoxib and celecoxib are safe antiinflammatory alternatives in patients with aspirin-induced asthma. There have been several studies that have been published since that time that confirm the results of the earlier trials (Table 2).⁷⁰⁻⁸⁰

The 8 published studies with a total sample size of 206 patients who had aspirin-induced asthma demonstrated that specific COX-2 selective NSAIDs could be used safely in this patient population.⁷⁴⁻⁸⁰ Despite these positive results, there have been isolated case reports documenting asthma in patients with aspirin-induced asthma after a celecoxib or rofecoxib challenge.^{81,82} Nevertheless, specific COX-2 selective NSAIDs can be used safely in the majority of patients with aspirin-induced asthma.

Urticaria/Angioedema

The literature on COX-2 selective NSAIDs in patients with aspirin-induced skin reactions is less conclusive than in patients with aspirin-induced asthma. A review in 2004 summarized published studies and abstracts using rofecoxib as the challenge agent.⁸³ Of 1101 patients challenged, 18 (1.6%) developed urticaria or angioedema. Additional studies using rofecoxib, celecoxib, or etoricoxib have shown similar results (Table 3).^{30,67,75,76,84-86} Four percent of patients with a history of aspirin/NSAID-induced skin reaction ex-

perienced a cutaneous reaction following a challenge to a COX-2 selective NSAID. It should be noted that the studies often used different inclusion criteria and various measures to determine a positive reaction, making comparisons between trials difficult. Specific COX-2 selective NSAIDs are often tolerated by patients with histories of urticaria/angioedema caused by aspirin or nonselective NSAIDs, but some patients may develop cutaneous reactions.

In the studies that challenged patients with aspirin-induced skin reactions to more than one COX-2 selective NSAID, patients with a positive reaction usually reacted only to a single COX-2 selective NSAID.^{30,75,87} In patients who develop cross-reactions to a COX-2 selective NSAID,

a challenge with a different agent from that class can be cautiously attempted.⁸⁵ However, only one of these—celecoxib—is currently available in the US. In Canada, both lumiracoxib and celecoxib are available. Based on the available literature, there are not enough data to conclude whether one COX-2 selective NSAID is safer than others. As well, limited data exist on the long-term tolerability of COX-2 selective NSAIDs in patients with cutaneous aspirin/NSAID sensitivity.⁸⁸

Based on published information, patients with aspirin-induced asthma should be able to use COX-2 selective NSAIDs such as celecoxib without risk of cross-reactions. In patients with cutaneous reactions to aspirin/nonselective

Table 2. Use of COX-2 Selective NSAIDs in Patients with Aspirin-Induced Asthma

Reference	Drug(s) and Dose, mg	Aspirin/NSAID Sensitivity Confirmed?	Protocol	Patients Reacting, n (%)
Szczeklik (2001) ^{70,a}	rofecoxib 25	yes	double-blind crossover challenge	0/12 (0)
Martin-Garcia (2002) ^{71,a}	rofecoxib 25	no	single-blind challenge	0/40 (0)
Woessner (2002) ^{72,a}	celecoxib 100 and 200	yes	double-blind challenge	0/60 (0)
Stevenson (2001) ^{73,a}	rofecoxib 12.5 and 25	yes	double-blind challenge	0/60 (0)
Perrone (2003) ⁷⁴	rofecoxib 25	no	single-blind challenge	0/23 (0) ^b
Senna (2004) ⁷⁵	meloxicam 15, rofecoxib 25, celecoxib 200	no	single-blind challenge	0/24 (0) ^b
Celik (2005) ⁷⁶	celecoxib 200	no	single-blind challenge	0/14 (0) ^b
Woessner (2004) ⁷⁷	rofecoxib 50	yes	double-blind challenge	0/60 (0)
Gyllfors (2003) ⁷⁸	celecoxib 10, 30, or 100	yes	double-blind, randomized, crossover challenge	0/33 (0)
Micheletto (2006) ⁷⁹	rofecoxib 50	yes	randomized, crossover oral challenge with rofecoxib and aspirin	0/19 (0)
Martin-Garcia (2003) ⁸⁰	celecoxib 200	no	single-blind challenge	0/33 (0)
TOTAL				0/378 (0)

COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal antiinflammatory drugs.
^aArticles reviewed by West et al.⁸⁸
^bRepresents a proportion of the total population studied.

Table 3. Use of COX-2 Selective NSAIDs in Patients with Aspirin-Induced Urticaria/Angioedema

Reference	Drug(s) and Dose, mg	Aspirin/NSAID Sensitivity Confirmed?	Protocol	Patients Reacting, n (%)
Zembowicz (2003) ³⁰	celecoxib 300, rofecoxib 37.5	yes	double-blind crossover challenge	0/18 (0)
Nettis (2005) ⁸⁴	etoricoxib 90	no	single-blind oral challenge	2/141 (1.4)
Sanchez-Borges (2005) ⁸⁵	etoricoxib 120, celecoxib 200	yes	double-blind challenge	E: 4/56 (7.1) C: 5/54 (9.3)
Bavbek (2004) ⁶⁷	rofecoxib 25	no	single-blind challenge	1/51 (2.0) ^a
Liccardi (2005) ⁸⁶	celecoxib 200	yes	single-blind challenge	1/29 (3)
Celik (2005) ⁷⁶	celecoxib 200	no	single-blind challenge	0/43 (0) ^a
Senna (2004) ⁷⁵	rofecoxib 25, celecoxib 200	no	single-blind challenge	5/52 (9.6) ^a
TOTAL				18/444 (4.1)

COX-2 = cyclooxygenase 2; E = etoricoxib; NSAIDs = nonsteroidal antiinflammatory drugs.
^aRepresents a proportion of the total population studied.

NSAIDs, specific COX-2 selective NSAIDs can be considered as alternative agents, although caution should be exercised, since approximately 4% of patients have developed cross-reactions.

WEAK INHIBITORS OF COX-1 ENZYME

Nonacetylated salicylates (eg, salsalate) and acetaminophen are weak inhibitors of the COX-1 enzyme and may cross-react with aspirin and nonselective NSAIDs when high doses of the nonacetylated salicylates and acetaminophen are used. Acetaminophen may also inhibit the enzyme COX-3, although this is controversial.⁸⁹

A study of 50 patients found that 34% of patients with aspirin-induced asthma will react to acetaminophen at doses of 1000–1500 mg.⁹⁰ In patients who reacted to acetaminophen, the reactions were generally mild. Therefore, it is recommended that patients with aspirin-induced asthma should not take more than 1000 mg of acetaminophen in a single dose.^{8,45}

Unfortunately, even though patients with aspirin-induced asthma can safely ingest therapeutic doses of nonacetylated salicylates, these agents are poor analgesics and have only mild antiinflammatory effects.⁷ Cross-reactivity with aspirin and nonselective NSAIDs can occur as well. A study of 10 patients with aspirin-induced asthma revealed a prevalence of 20% cross-reactivity with 2 g of salsalate (usual therapeutic dose is 1500 mg twice daily).⁹¹ In contrast, another study did not show cross-reactivity with choline magnesium trisalicylate in patients with aspirin-induced asthma.⁹²

MANAGEMENT STRATEGY

Table 4 lists management strategies for patients with aspirin/NSAID sensitivity and accompanying recommendations.

Summary

Although aspirin/NSAID sensitivity is a well-known clinical syndrome, investigations into its pathogenesis are only recently starting to provide insight for management of these patients. Currently, desensitization is a viable option, especially for patients with a history of aspirin-induced asthma who require the drug for thromboembolic prophylaxis. Desensitization requires continuous administration of aspirin or an NSAID; aspirin desensitization is not recommended in patients who require the use of these medications for intermittent indications, such as on an as-needed basis for management of various antiinflammatory conditions. COX-2 selective NSAIDs have not been shown to be cross-reacting in most patients and can usually be recommended as antiinflammatory alternatives to the nonselective NSAIDs, especially in those with aspirin-induced asthma. Patients with a history of aspirin-induced urticaria/angioedema may develop cutaneous reactions when challenged with a COX-2 selective NSAID. Acetaminophen in single doses less than 1000 mg and nonacetylated salicylates (salsalate <2000 mg) may also be used safely in patients with aspirin/NSAID sensitivity. The role of leukotriene antagonists has yet to be determined.

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Table 4. Management Strategy for Patients with Aspirin/NSAID Sensitivity

Management Strategy	Recommendations
Avoid aspirin and all cross-reacting nonselective NSAIDs	all patients, unless aspirin or other nonselective NSAIDs are required for the treatment of comorbid conditions
Desensitization	patients with aspirin-induced asthma who ⁷ : can only be controlled with unacceptably high doses of oral corticosteroids, require repeated polypectomy or sinus surgery, or need aspirin for the treatment of other diseases such as arthritis or thromboembolism desensitization can also be attempted in patients with aspirin/NSAID-induced urticaria/angioedema
COX-2 selective NSAIDs	these agents are well tolerated, especially in patients with aspirin-induced asthma; 4% of patients with histories of aspirin/NSAID-induced urticaria/angioedema may develop cutaneous reactions when challenged with a COX-2 selective NSAID
Leukotriene modifiers	as add-on therapy for the day-to-day treatment of aspirin-induced asthma
Weak inhibitors of COX-1 enzyme (acetaminophen, nonacetylated salicylates)	albeit weak antiinflammatory drugs, these agents can be used as alternatives to aspirin/nonselective NSAIDs; acetaminophen should be used in single doses of <1000 mg and salsalate in doses <2000 mg
COX-2 = cyclooxygenase 2; NSAIDs = nonsteroidal antiinflammatory drugs.	

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Alternativas de Manejo para Pacientes con Sensibilidad a Aspirina y a Antiinflamatorios No Esteroidales

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EXTRACTO

OBJETIVO: Evaluar y proveer estrategias de manejo a pacientes con sensibilidad a la aspirina o a antiinflamatorios no esteroidales.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda de la literatura utilizando la base de datos de MEDLINE (1966-marzo 2007) y los términos aspirina, agentes anti-inflamatorios no-esteroidales, urticaria, angioedema, asma, antagonistas de leucotrienos, y desensitización, y tacrolimus. Además se realizó una búsqueda manual de las referencias de los artículos identificados a través de MEDLINE para identificar otros artículos de relevancia.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE LA INFORMACIÓN: Se evaluaron todos los estudios publicados en el idioma inglés. En este repaso se incluyeron todos los estudios, artículos de revisión y comentarios sobre asma inducida por aspirina y urticaria o angioedema inducida por aspirina o antiinflamatorios no esteroidales.

SÍNTESIS: La sensibilidad a la aspirina se manifiesta comúnmente con una reacción respiratoria (por ej. broncoespasmo, rinorrea profusa, inyección conjuntival), o con urticaria/angioedema. El mecanismo primario se cree es la inhibición de la enzima ciclooxigenasa 1 (COX-1); los pacientes con sensibilidad a aspirina comúnmente exhiben reacción cruzada a los antiinflamatorios no esteroidales no selectivos que inhiben la enzima COX-1. Las estrategias de manejo incluyen evitar el uso de aspirina y de los antiinflamatorios no esteroidales no selectivos que tienen reactividad cruzada. Sin embargo, la desensitización de aspirina es una alternativa viable en pacientes con reacciones respiratorias inducidas por aspirina, especialmente aquellos que necesitan aspirina para profilaxis de eventos tromboembólicos. La desensitización con aspirina se mantiene indefinidamente con una dosis diaria de aspirina. Existe evidencia limitada sobre el uso de modificadores de leucotrienos para prevenir asma inducida por aspirina. No se ha encontrado que los antiinflamatorios no esteroidales selectivos para COX-2 exhiban reacción cruzada, especialmente en pacientes con asma inducida por aspirina. Sin embargo, aproximadamente 4% de los pacientes con historial de reacciones cutáneas inducidas por aspirina podrían experimentar reacciones cutáneas al recibir antiinflamatorios no esteroidales selectivos para COX-2. Siendo acetaminofen inhibidor débil de la enzima COX-1, los pacientes con asma inducida por aspirina no deben ingerir más de 1000 mg de acetaminofen en una dosis unitaria.

CONCLUSIONES: El manejo de pacientes con sensibilidad a aspirina o a antiinflamatorios no esteroidales incluye el evitar el consumo de aspirina y de los antiinflamatorios no esteroidales y el utilizar los antiinflamatorios no esteroidales selectivos para COX-2, acetaminofen en dosis menores a 1000 mg y la desensitización. El rol de los modificadores de leucotrienos requiere mayor estudio antes de poder ser recomendados para estos pacientes.

Traducido por Annette Pérez

Options de Traitement chez les Patients avec une Sensitivité à l'Aspirine et aux AINS

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RÉSUMÉ

OBJECTIF: Évaluer et étudier des stratégies de traitement pour les patients ayant une sensibilité à l'aspirine ou aux AINS.

SOURCE DES DONNÉES: Une revue de littérature dans MEDLINE (1966-mars 2007) en utilisant les mots-clés: aspirin, anti-inflammatory agents non steroïdal, urticaire, angioedema, asthma, leukotriene antagonist, desensitization, et tacrolimus. Les articles ont été utilisés pour retrouver des références croisées.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles publiés en langue anglaise ont été évalués. Les études, articles de revues, et les commentaires ont été inclus.

SYNTHÈSE DES DONNÉES: La sensibilité à l'aspirine se manifeste la plus souvent par des symptômes respiratoires (e.g. bronchospasmes, rhinorée profuse, yeux injectés de sang) ou par de l'angio-oedème et de l'urticaire. Le principal mécanisme impliqué semble être l'inhibition de la cyclooxygénase 1 (COX-1). De ce fait, les patients ayant une sensibilité à l'aspirine présentent souvent une réaction croisée avec les AINS non sélectifs qui inhibent aussi la COX-1. Les stratégies de traitement sont d'éviter la prise d'aspirine et des agents provoquant une réaction croisée. Cependant, la désensibilisation à l'aspirine est une option viable pour les patients ayant des réactions respiratoires, spécialement pour les patients qui nécessitent la prise d'aspirine pour la prévention de maladies thromboemboliques. La désensibilisation à l'aspirine peut être maintenue indéfiniment avec une dose quotidienne d'aspirine. Il y a peu d'évidence sur l'utilisation des anti-leucotriènes dans la prévention de l'asthme induit par l'aspirine. Les AINS sélectifs de la COX-2 ne semblent pas provoquer de réaction croisée, spécialement chez les patients souffrant d'asthme induit par l'aspirine. Par contre, environ 4% des patients avec une histoire de réactions cutanées avec l'aspirine pourraient présenter une réaction cutanée avec la prise d'agents sélectifs de la COX-2. Finalement, puisque l'acétaminophène est un faible inhibiteur de la COX-1, les patients avec un asthme induit par l'aspirine ne devraient pas prendre plus de 1000 mg d'acétaminophène par dose.

CONCLUSIONS: La gestion des patients avec une sensibilité à l'aspirine et aux AINS incluent l'évitement de ces agents, le recours aux agents sélectifs de la COX-2, l'utilisation de l'acétaminophène à des doses inférieures à 1000 mg et la désensibilisation. L'utilisation des anti-leucotriènes doit être étudiée davantage avant que leur emploi puisse être recommandé.

Traduit par Nicolas Paquette-Lamontagne