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Therapeutic options

FOCUS ON ASA/NSAID SENSITIVITY REACTIONS

Acetylsalicylic acid (ASA; "aspirin") and nonsteroidal anti-inflammatory drugs (NSAIDs) are used very commonly worldwide.[1,2] While these agents are well tolerated by most individuals, they are associated with sensitivity reactions that occur in substantial proportions of patients with specific comorbid conditions.[1] In addition, cross-sensitivity has been documented among NSAIDs for certain types of reactions.

Given the widespread use of ASA and NSAIDs, often for indications where few, if any, reasonable alternatives exist, treatment of patients with a history of sensitivity to these agents is a common therapeutic issue. This article discusses the most frequently encountered sensitivity reactions to ASA/NSAIDs, including their appropriate management.

CLINICAL PRESENTATION & EPIDEMIOLOGY

The primary ASA sensitivity reactions described in the literature include respiratory reactions, urticaria/angioedema, and anaphylaxis.[1,3] Such reactions are estimated to occur in 0.2% to 0.6% of the general population,[3] but are much more common in certain patient populations, as noted below. Data indicate that a minority of patients present with both dermatological and respiratory symptoms ("blended" reactions).[1,4]

A classification of sensitivity reactions to ASA and NSAIDs, including details regarding risk factors, cross-reactivity, mechanism of sensitivity, and potential for desensitization, is provided in Table 1.

Table 1 – Summary of ASA/NSAID sensitivity reactions[1,2,5]

Reaction	Underlying risk factor(s)	Cross-reactions to other COX-1 inhibitors	Mechanism of sensitivity	Able to undergo desensitization
NSAID-induced rhinitis and asthma*	Asthma, nasal polyps, sinusitis	Yes	COX-1 inhibition	Yes
NSAID-induced urticaria/angioedema	Chronic idiopathic urticaria	Yes	COX-1 inhibition	No
Single drug-induced urticaria/angioedema	None	No	Immunologic†	Yes
Multiple drug-induced urticaria/angioedema	None	Yes	COX-1 inhibition	Yes
Single drug anaphylaxis	None	No	Immunologic (IgE-mediated)	Yes
NSAID blended reaction	Variable (risk factors such as asthma, rhinitis, or urticaria may be present)	Yes or No	Unknown‡	Unknown§

ASA = acetylsalicylic acid; COX-1 = cyclooxygenase 1; IgE = immunoglobulin E; NSAID = nonsteroidal anti-inflammatory drug

* Often referred to as aspirin-exacerbated respiratory disease (AERD).[6]

† Presumed to be mediated by drug-specific IgE.

‡ Possibly related to COX-1 inhibition.

§ Data not available.

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Respiratory Reactions

Respiratory reactions related to ASA and other nonselective NSAIDs (i.e., agents that inhibit both cyclooxygenase [COX]-1 and COX-2; see Box 1) often present with asthma attacks/bronchospasm (which may be severe), laryngeal spasm, rhinorrhea, nasal congestion, ocular itching and tearing, periorbital edema, and generalized flushing.[1,6,7] The onset of symptoms after ingesting full therapeutic doses of an offending agent typically occurs within 30 minutes to 3 hours.[1,4,6]

Although various terms have been used to refer to ASA/NSAID-induced respiratory reactions, including aspirin-induced asthma, Samter's triad, and aspirin triad, current preferred terminology appears to be aspirin-exacerbated respiratory disease (AERD).[1,6] The prevalence of AERD in adults with asthma is estimated to be as high as 21%, and even higher among those with nasal polyps (up to 52%) or asthma and nasal polyps (up to 65%).[1,3]

Urticaria/Angioedema

ASA/NSAID-induced urticaria/angioedema can occur in otherwise healthy individuals and in those with a history of chronic idiopathic urticaria (CIU). Urticarial reactions occur as quickly as 15 minutes after ASA/NSAID ingestion, but may be delayed for up to 24 hours; the majority of patients develop symptoms within 4 hours. Resolution typically occurs within 24 to 48 hours, but may take as long as 1 to 2 weeks.[1]

Between 20% and 40% of patients with CIU experience a flare of hives following ingestion of ASA or chemically unrelated NSAIDs.[1-3]

Anaphylaxis

Anaphylaxis generally manifests with an array of signs and symptoms, including pruritis, urticaria, angioedema, laryngeal edema, shortness of breath, wheezing, bronchospasm, nausea, vomiting, diarrhea, and hypotension.[1,7,8] In severe cases, cardiac and respiratory arrest can occur.[4] Anaphylactic reactions to ASA/NSAIDs are rare.[4]

DIAGNOSIS

A definitive diagnosis of any of the ASA/NSAID-induced sensitivity reactions described above can only be established through *in vivo* provocation challenges.[1,4,6] While different routes of administration have been used, oral provocation challenges are employed most commonly in North America.[1,6,9] Generally, such challenges involve giving patients increasing doses of the drug under consideration (sometimes preceded by placebo) until a therapeutic dose is reached.[2,6] Specific protocols for ASA provocation challenges differ among institutions based on doses used, intervals between doses, and the number of days over which the challenge is carried out.[1] A 2-dose challenge consisting of ASA 80 mg and 325 mg administered 1 hour apart is the standard protocol at a leading Canadian medical centre.[1] If a substance other than ASA is used, a similar 2-dose challenge (utilizing doses corresponding to one-quarter and three-quarters of a therapeutic dose) has been advocated.[2] Lower starting doses (e.g., ASA 3–10 mg) are often used in patients with a history of anaphylaxis.[5,10]

Prior to undergoing provocation challenges, patients' underlying disease states (e.g., asthma, urticaria) should be stable and under control.[1,3] Asthmatic patients should continue taking oral, inhaled, and intranasal corticosteroids, long-acting bronchodilators, and leukotriene modifiers, since stopping these medications could lead to hyperirritable airways.[6] Medications that should be discontinued 24 hours before challenge include antihistamines and short-acting inhaled beta agonists and anticholinergics.[6]

A challenge is generally considered positive (i.e., indicating the presence of ASA/NSAID sensitivity) for AERD if there is a decrease in forced expiratory volume in one second (FEV_1) of more than 20%, although naso-ocular symptoms, laryngeal spasm, and other reactions (urticaria/angioedema, flushing, gastric pain, hypotension) may also be considered diagnostic, depending on the initial reaction for which the provocation test is being conducted.[1,2,6]

Given the potential for serious adverse events, it has been recommended that provocation challenges be carried out by an experienced physician in a hospital setting where resuscitation resources are readily available.[1,3]

MECHANISM OF REACTIONS & CROSS-REACTIVITY

The exact pathogenesis of ASA/NSAID sensitivity remains unclear;[4,11] however, proposed mechanisms (see Table 1) include inhibition of COX-1 and immunoglobulin E (IgE)-mediated immunologic reactions.

COX-1 Inhibition

Under normal circumstances, arachadonic acid can be metabolized via the COX pathway or the lipoxygenase pathway (see Figure 1). ASA and NSAIDs inhibit the COX pathway, diverting arachadonic acid metabolism to the lipoxygenase pathway, resulting in:

- a decrease in levels of anti-inflammatory prostaglandins (particularly prostaglandin E_2, a substance that protects against bronchoconstriction and mast cell mediator release); and
- an increase in levels of inflammatory cysteinyl leukotrienes, which induce bronchoconstriction and increase mucus production and vascular permeability/edema formation (with subsequent urticaria) in sensitive individuals.[1,4,11]

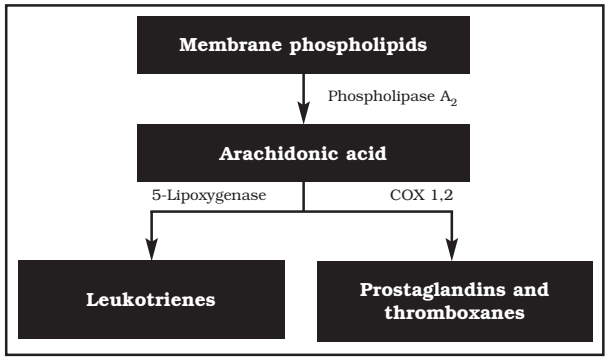
It appears that inhibition of COX-1, but not COX-2, is responsible for most ASA/NSAID-induced respi-

ratory reactions and urticaria/angioedema. As such, patients who experience these reactions often display cross-reactivity to other nonselective NSAIDs, but not to selective COX-2 inhibitors.[1,6,7] A classification of drugs based on COX inhibition and likelihood of cross-reactivity is provided in Box 1.

IgE-Mediated Immunologic Reactions

For IgE-mediated immunologic reactions (e.g., anaphylaxis*), antigen-specific IgE bound to mast cells and basophils is cross-linked by an allergen, triggering the release of preformed chemical mediators such as histamine and tryptase.[10] These mediators can result in multi-organ symptoms.[10] Based on the mechanism of reaction, previous exposure to a particular drug or a chemically related agent is required for anaphylaxis to occur.[1] Also based on this mechanism, a patient with a history of reaction to a specific NSAID will not cross-react to ASA or other NSAIDs, except for agents with nearly identical chemical structures (e.g., a patient with a history of anaphylaxis to sulindac may also react to tolmetin).[1,3]

Figure 1 – Simplified overview of the arachadonic acid metabolic pathway[5,11]



MANAGEMENT & PREVENTION

Most ASA/NSAID-induced sensitivity reactions can be appropriately managed by avoidance, desensitization, and/or use of alternative medications, as outlined below. In addition, patients with underlying asthma or CIU should be managed according to current standards of care for these diseases.[1]

Avoidance

In general, patients with ASA/NSAID-induced sensitivity reactions should avoid ASA and all cross-reacting nonselective NSAIDs where possible[1,4] (see Table 1 and Box 1).

Desensitization

In instances where avoidance isn't feasible (e.g., where ASA is required for cardiovascular protection or NSAIDs are necessary for rheumatologic/pain conditions), desensitization may be an option, particularly for patients with uncontrolled or difficult-to-control AERD.[1,4] In those with AERD, desensitization not only improves upper and lower respiratory symptoms for most patients, but also

Box 1 – Classification of COX inhibitors[2,6,11]

Strong COX-1 inhibitors* (traditional nonselective NSAIDs)

Acetylsalicylic acid
Diclofenac
Diflunisal
Etodolac
Fenoprofen†
Flurbiprofen
Ibuprofen
Indomethacin
Ketoprofen
Ketorolac
Mefenamic acid
Nabumetone
Naproxen
Oxaprozin
Piroxicam
Sulindac
Tolmetin†

Weak COX-1 inhibitors‡

Acetaminophen
Salsalate†

Preferential COX-2 inhibitors§

Nimesulide†
Meloxicam

Selective COX-2 inhibitors||

Celecoxib
Etoricoxib†
Parecoxib†
Lumiracoxib†

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug

* These agents also inhibit COX-2 at high concentrations. There is a very high potential for cross-reactivity among strong COX-1 inhibitors.[6]

† Not available/no longer available in Canada.

‡ At higher doses, these agents can induce mild respiratory reactions in patients with AERD. Acetaminophen doses ≤650 mg and salsalate doses <2000 mg can usually be given safely.[6]

§ These agents also inhibit COX-1 at high concentrations. Mild respiratory reactions can occur in a minority of AERD patients.[6]

|| In therapeutic doses, these agents do not cross-react with ASA or other NSAIDs in patients with AERD. Case reports of COX-2 inhibitors causing respiratory reactions are likely related to IgE or unknown mechanisms.[6] A small proportion (4%) of patients with a history of ASA/NSAID-induced urticaria/angioedema may develop cutaneous reactions with COX-2 selective agents.[1]

* Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions, but are not mediated by IgE. Since anaphylactoid reactions to NSAIDs are presumed to be related to COX-1 inhibition, cross-reactivity may occur among chemically unrelated agents.[10]

permits the use of NSAIDs typically considered to be cross-reactive.[3,4,6] Desensitization is often unsuccessful in patients with ASA/NSAID-induced skin reactions who have underlying CIU, although it can be used in those with single drug-induced urticaria/angioedema or anaphylaxis.[1,3]

Desensitization, like oral provocation challenges (see Diagnosis, above), involves administering escalating doses of ASA until 325–650 mg is tolerated.[1,4,6] However, starting doses are usually smaller (e.g., 0.1–20 mg) than those employed in provocation challenges and doses are administered over a longer period of time (e.g., 2–3 days).[1,3,4,6] Once completed, patients can ingest ASA or other typically cross-reactive NSAIDs, but must continue daily use to maintain desensitization.[1] It has been suggested that maintenance ASA doses as low as 81 mg daily are effective, although some experts recommend higher doses (e.g., 325–650 mg twice daily).[1,6] If therapy is interrupted, most patients become re-sensitized over 2 to 4 days;[1] after such time, another course of desensitization may be warranted.

Desensitization is not recommended for patients requiring intermittent ASA/NSAID therapy.[1]

Use of Alternative/Concomitant Medications

As previously noted, most patients with AERD, or angioedema/urticaria induced by ASA or nonselective NSAIDs, can safely receive selective COX-2 inhibitors (e.g., celecoxib). Nonetheless, patients with AERD, or asthmatics with unknown sensitivities, should probably receive the first full dose of a selective COX-2 inhibitor under physician supervision.[6] Acetaminophen (≤650 mg/dose), opioid analgesics, or other medications (e.g., corticosteroids) may also be options, depending on the indication.

In patients with a history of anaphylaxis to ASA who require antiplatelet therapy for cardiovascular protection, some experts suggest that use of an alternative agent (e.g., a thienopyridine such as clopidogrel, prasugrel, or ticlopidine) is the safest option.[2]

As some reactions are postulated to be caused by increased leukotriene levels, leukotriene receptor antagonists (e.g., montelukast, zafirlukast) have been used in an attempt to prevent sensitivity.[1] Based on available evidence, these agents cannot be relied upon to prevent respiratory or skin reactions to ASA/NSAIDs, but they may be used as add-on therapy to enhance underlying disease control in patients with AERD.[1,6]

References

1. Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. Ann Pharmacother. 2007 Jul;41(7):1191-1200.
2. Asero R. Clinical management of adult patients with a history of nonsteroidal anti-inflammatory drug-induced urticaria/angioedema: Update. Allergy Asthma Clin Immunol. 2007;3(1):24-30.
3. Kong JSW, Teuber SS, Gershwin ME. Aspirin and nonsteroidal anti-inflammatory drug hypersensitivity. Clin Rev Allergy Immunol. 2007;32(1):97-109.
4. Jenneck C, Juergens U, Buecheler M, Novak N. Pathogenesis, diagnosis, and treatment of aspirin intolerance. Ann Allergy Asthma Immunol. 2007;99(1):13-21.
5. Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. JAMA. 2004 Dec 22;292(24):3017-23. Available from: http://jama.ama-assn.org/cgi/reprint/292/24/3017
6. Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. Curr Allergy Asthma Rep. 2009;9(2):155-63.
7. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol. 2010 Feb;125(2 Suppl 2):S126-37.
8. Castells M. Desensitization for drug allergy. Curr Opin Allergy Clin Immunol. 2006 Dec;6(6):476-81.
9. Simon RA. Adverse respiratory reactions to aspirin and nonsteroidal anti-inflammatory drugs. Curr Allergy Asthma Rep. 2004 Jan;4(1): 17-24.
10. Berkes EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. Clin Rev Allergy Immunol. 2003 Apr;24(2):137-48.
11. Pfaar O, Klimek L. Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements. Curr Opin Allergy Clin Immunol. 2006 Jun;6(3):161-6.

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