

Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes

There continues to be considerable difficulty, and, not surprisingly, some controversy in classifying allergic and pseudoallergic reactions to aspirin and the other anti-inflammatory and analgesic drugs.¹⁻³ First, there is our inability to establish in vitro tests to identify patients who experience these reactions.^{3,4} We cannot consistently measure immunoglobulin (Ig)E antibodies directed against many NSAIDs, such as the use of routine skin testing with penicillin antigens. Asthmatic patients, who will react to aspirin (ASA) and the NSAIDs with respiratory reactions, cannot be identified with any known in vitro test. Because of these limitations, the only way to definitively make the diagnosis is through provocative challenge testing. Second, there is a spectrum of target organ responses to NSAIDs, and the same drug may induce different types of reactions in different organ systems in the same or different individuals.³⁻⁵ Third, other than a patient experiencing a similar reaction to a structurally dissimilar NSAID, there is no biochemical test to identify cross-reactions. Again, provocative challenge testing is the only way to establish or exclude cross-reac-

tions. Fourth, some reactions occur predominantly in individuals afflicted with marker diseases, such as asthmatic patients with nasal polyposis.⁶ However, if one searches the literature carefully, one can find rare exceptions to this rule. For example, some patients have respiratory reactions to aspirin first and then develop the identifying respiratory disease over the next several years.

The dilemma for the patient and physician is quite unsatisfactory. The advice the patient is seeking, after their reaction to ASA or an NSAID, is the answer to the question “What can I take now?” This question is even more compelling if the patient faces diseases in which one or more members of this class of drugs would be an important therapeutic intervention. Although it is convenient for the physician, and perhaps prudent from a medical-legal standpoint, to advise all patients to avoid all NSAIDs under any circumstances, this position is hardly enlightening and usually unnecessary.

Finally, the current literature is filled with descriptive terms, which mean one thing to one author and another to someone else. Such imprecis-

sion makes it difficult to draw useful conclusions from reading the medical literature. For example, “ASA sensitivity reaction” could mean that a patient had a respiratory reaction, urticaria/angioedema, anaphylaxis, a blended reaction or a variety of other single-drug reactions. We feel that the need for clarification is real. In an attempt to move us in the direction of precision, we are proposing the following classification of adverse reactions to NSAIDs (Table 1).

Our proposed classification system is divided into a new description of the reactions (*left-hand column*), the presence of an underlying disease (if known), whether or not cross-reactions with other cyclooxygenase (COX)-1 inhibitors occurs, and in the far right, a listing of some terms currently used to describe these reactions. Under “other reactions,” we have included all the other adverse reactions reported to occur as a result of taking one of these drugs. The pathogenesis of other reactions is largely unknown. However, previous exposures to the inciting drug are generally needed and reactions are to a single drug. This implicates immune sensitization and reaction. For example, there are data

Table 1. Editorial on NSAID Classification

Description of reactions	Underlying disease	Cross-reactions first exposure	Current terminology
NSAID-induced rhinitis and asthma	Asthma/nasalPolyps/sinusitis	Yes	Intolerance, ASA-induced, sensitivity
NSAID-induced urticaria/angioedema	Chronic idiopathic urticaria	Yes	Acute/chronic urticaria angioedema
Single drug-induced urticaria/angioedema	None	No	Acute urticaria/angioedema
Multiple drug-induced urticaria/angioedema	None	Yes	Acute urticaria
Single drug-induced anaphylaxis	None	No	Anaphylactoid
Single drug or NSAID-induced blended reaction	Asthma, rhinitis urticaria, or none	No or yes	Asthma & urticaria

suggesting that sensitized lymphocytes directed against a specific NSAID cause hypersensitivity pneumonitis and aseptic meningitis reactions.⁴

Other types of reactions which can occur with any of the COX-1 and probably the COX-2 inhibiting drugs are listed below. Because the reactions tend to be specific to a single drug, this suggests immune recognition and reaction.^{4,7}

- Interstitial nephritis
- Hepatocellular reactions
- Erythema multiforme
- Fixed drug eruptions
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Maculopapular eruptions
- Erythema nodosum
- Hypersensitivity pneumonitis
- Aseptic meningitis
- Bullous leukocytoclastic vasculitis

In looking at how reactions to NSAIDs might fit into our proposed classification system, we have elected to present typical case studies to better illustrate our points. This will allow the reader to focus on the clinical setting, previous history, and actual presentations of the different types of reactions listed in our classification system. After each clinical vignette, we have offered some comments, which relate to our proposed classification system and the management of the patient in this circumstance.

Case 1

A 44-year-old woman, who has had recurrent sinusitis and asthma for the last 2 years, takes two aspirin tablets. Forty minutes later, she experiences extreme nasal congestion and rhinorrhea. Fifty minutes later, she begins to wheeze and complains of significant dyspnea.

She uses her albuterol inhaler three times on the way to the hospital emergency room, where she is treated with seven treatments of nebulized albuterol over the course of 3 hours. She improves slowly but is well enough to be sent home after the 3 hours of treatment.

Comment: In our new system, this is classified as an *NSAID-induced rhinitis and asthma*. Older descriptive terms

are not as helpful. Intolerance is mostly used to describe gastrointestinal irritation that occurs after taking many medicines, including NSAIDs. ASA downplays the cross-reactivity with NSAIDs and the significant reactions occurring in the upper respiratory tract. ASA reaction again fails to recognize cross-reactivity with other NSAIDs, and sensitivity is such a broad term that it is used to describe many different types of reactions. To restrict the term to aspirin-induced does not recognize the fact that nearly half of the original reactions are induced by NSAIDs other than aspirin. We elected to use NSAID-induced rhinitis and asthma, although the COX-2 inhibiting NSAIDs do not cross-react^{8,9} Finally, the underlying respiratory disease, which these patients almost always have, might best be called *aspirin-exacerbated respiratory disease*. This leaves out the term "sensitivity" but does assign prime and historical association between ASA and the underlying respiratory inflammation. It also makes clear that aspirin does not induce the underlying respiratory disease.

If this woman came to an allergy or pulmonary specialist seeking advice about taking other NSAIDs, the specialist could tell her that the older COX-1 inhibiting NSAIDs would be expected to cross-react and she should avoid them.^{4,5} However, she could take rofecoxib or celecoxib without adverse effects.^{8,9} For conservative and medical-legal reasons, the first dose of a COX-2 inhibitor might best be given in the physician's office.

Case 2

A 35-year-old woman has had hives of unknown type for the past 6 months. Her allergy specialist has run tests and told her that he does not know the cause of her hives. Daily ingestion of loratadine, 10 mg, keeps the hives under control. However, every time she takes ibuprofen for menstrual cramps, her hives flare up for a day or so. The larger the dose of ibuprofen, the greater the flare-up of hives. She comes for advice as to what she can take for her menstrual cramps.

Comment: The patient has *chronic idiopathic urticaria* and her reaction is classified as *NSAID-induced urticaria/angioedema*. Cross-reactivity with COX-1-inhibiting NSAIDs occurs in approximately one-third of these patients when the hives are under control, and in up to two-thirds when the hives are active. Although not rigorously studied, preliminary observations are that most patients can take a selective COX-2 inhibitor without a cross-reaction.

Case 3

A 25-year-old male Olympic sprinter has always taken ibuprofen, 400 mg, before running. He has never had any problems with this drug in the past. One night, after a race, he broke out in hives. He took diphenhydramine and the hives cleared up completely. The coach said the hives were from the excitement of winning a gold medal, but the athlete was not convinced. To be sure that nerves, rather than ibuprofen, were the cause of the hives, he took 200 mg ibuprofen when not racing and again broke out in hives. The team trainer read the *Physician's Desk Reference* to him and told him not to take any aspirin or other NSAIDs. The team trainer knew about rofecoxib but the *Reference* indicated that it should not be taken after having had urticaria with another NSAID.

He was then referred to an allergy specialist to determine what to do. Additional history indicates that he has never had hives before, does not have any allergic diseases, and has ingested aspirin, acetaminophen, flurbiprofen, and naproxen in the past without any adverse effects.

Comment: This athlete carried out his own provocative testing by challenging himself with ibuprofen. (This is not a recommended approach). We would classify his reaction as a *single drug urticaria reaction*. This athlete does not have underlying chronic idiopathic urticaria, the underlying disease which predisposes patients to cross-reactions with other NSAIDs. He can be treated with any NSAID, including ASA or the new selective COX-2 inhibitors^{10,11} which have a molecular

structure dissimilar to ibuprofen. There are reports in the literature of a small number of patients, without underlying urticaria, who nevertheless experience cross-reactions between NSAID after first exposure to the second NSAID. Because of these rare instances of cross-reactivity in normal individuals, the first dose of the new NSAID should be given in the physician's office.

Case 4

A 56-year-old construction worker was taken to the emergency room (ER) because of acute back pain. The ER physician evaluated the patient, diagnosed acute back strain, and ordered ketorolac tromethamine 30 mg intramuscularly. Twenty minutes after the injection, the patient developed itching of his palms, a sense of impending doom, then angioedema of the lips, periorbital tissues, and the intramuscular injection site. His blood pressure dropped to 90/50 with a pulse of 130 beats/minute but neither wheezes nor respiratory distress was observed. The patient was treated appropriately and recovered. The ER physician told him to avoid aspirin and all older NSAIDs.

An allergy consult was requested because the ER physician wondered whether or not this patient could tolerate rofecoxib. During the allergy consult, the following additional information was elicited: the patient had never reacted to acetaminophen, aspirin, or ibuprofen in the past. He has previously received injections of ketorolac tromethamine with excellent pain relief and no adverse effects. The patient does not have chronic urticaria nor asthma and has never had an anaphylactic reaction previously. He was not hypertensive and was not taking β -blockers.

Comment: This patient was sensitized to ketorolac tromethamine in the past and with the current injection experienced an IgE-mediated *single drug anaphylaxis*. He does not have any of the cross-reacting underlying diseases. His chances of experiencing anaphylaxis after taking another NSAID are remote. Because he needs NSAIDs for his recurrent back pain, he should take the first full dose of another NSAID

orally in the allergist's office. The NSAID can be any NSAID that is structurally unrelated to ketorolac.

Case 5

A 56-year-old man has degenerative arthritis of the left knee, which resulted from a previous soccer injury. His orthopedic surgeon told him that a prosthetic knee would survive for 10 to 15 years, depending on how he abuses the artificial knee. He is an active tennis player and wishes to postpone knee replacement as long as possible. The orthopedic surgeon prescribes diclofenac, 100 mg. Sixty minutes after taking the first dose of diclofenac, the patient developed angioedema of the lips and face, wheezing, and respiratory distress. He borrowed his son's albuterol inhaler, took 2 capsules of diphenhydramine, 25 mg, and waited for the reaction to subside. He called the orthopedic surgeon, who referred him to an allergy specialist.

During the allergy consultation the following information was obtained: the patient had asthma as a child but outgrew it at age 14 and has not had any attacks of asthma until this episode. He has mild hay fever in the spring but only takes over-the-counter antihistamines. He has never had sinusitis and only one cold every other year. He has never had angioedema or urticaria in the past. Before this episode, he had taken aspirin, acetaminophen, ibuprofen, and naproxen with no reaction. The patient wants to take an anti-inflammatory drug before and after he plays tennis.

Comment: The difference between a "mild" anaphylactic (-toid) reaction, with respiratory and cutaneous shock organ responses and a *NSAID-blended reaction* may be difficult to distinguish. This case has all sorts of problems with respect to accurate classification. The patient had asthma as a child but none subsequently and he took aspirin 2 months ago without a reaction. Therefore, he does not have *ASA-exacerbated respiratory disease*. The diclofenac-induced reaction was

very mild and did not resemble typical *NSAID-induced rhinitis and asthma*. However, for this to be an IgE-mediated reaction, we would expect that previous exposure to diclofenac would have occurred. The patient denies this and we have no in vitro test to support or refute the possibility that IgE sensitization occurred. We are reluctant to call this anaphylaxis (-toid) because the reaction was so mild. In essence, this reaction does not fit into any of the previously described reactions and it is best to reserve a category for *NSAID-blended reactions*.

Management: We would be reluctant to give this man a COX-1 inhibiting NSAID, in view of his first dose reaction to diclofenac. Therefore, we would give him a COX-2 inhibitor.^{10,11} This is a drug with a different molecular structure, in case this was an IgE mediated reaction, but also does not inhibit COX-1, in case the reaction was triggered by depletion of prostaglandin E₂.

CONCLUSION

We hope that the above classification of reactions to NSAIDs makes sense to the reader of this editorial. It would be useful if investigators used this classification system when writing articles for medical journals. This would allow the reader to better understand which type of reactions constituted the subject of the publications.

DONALD D. STEVENSON, MD
Division of Allergy, Asthma, and
Immunology
Scripps Clinic and The Scripps
Research Institute
La Jolla, CA, USA

MARIO SANCHEZ-BORGES, MD
Department of Allergology and
Clinical Immunology
Centro Medico-Docente La Trinidad
and Clinica El Avila
Caracas, Venezuela

ANDREW SZCZEKLIK, MD, PhD
Department of Medicine
Jagellonian University School of
Medicine
Krakow, Poland

REFERENCES

1. Szczeklik A, Nizankowska E, Duplaga M., on behalf of the AIANE Investigators. Natural history of aspirin-induced asthma. *Eur Respir J* 2000;16: 432–436.
 2. Szczeklik A, Nizankowska E, Sanak M, Swierczynska M. Aspirin-induced asthma. *Curr Opin Allergy Clin Immunol* 2001;1:27–33.
 3. Stevenson DD. Systemic reactions to aspirin and non-steroidal anti-inflammatory drugs. In: Virant F, editor. *Immunology and Allergy Clinics of North America* Philadelphia: W. B. Saunders Company, 1995:529–552.
 4. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal anti-inflammatory drugs. In: Middleton E, Reed CE, Ellis EF, et al, editors. *Allergy: Principles and Practice*. Chap. 87. St Louis, C.V. Mosby Company, 1998:1225–1234.
 5. Stevenson DD. Adverse reactions to non-steroidal anti-inflammatory drugs. In: Tilles, S.A., editor. *Immunology and Allergy Clinics of North America*. Philadelphia: W. B. Saunders Company, 1998:773–798.
 6. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and treatment. *J Allergy Clin Immunol* 1999;104:5–13.
 7. Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. *J Am Acad Dermatol* 1985;12: 866–876.
 8. Szczeklik A, Nizankowska E, Bochenek G, et al. Safety of a specific Cox-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2000;31: 219–225.
 9. Dahlen B, Szczeklik A, Murray JJ. Celecoxib in patients with asthma and aspirin intolerance. *N Engl J Med* 2001;344:142.
 10. Sanchez-Borges M, Capriles-Hulett A, Caballero F, Perz C. Tolerance to COX-2 inhibitors in patients with NSAID-induced urticaria/angioedema. *J Allergy Clin Immunol* 2001;107: S134.
 11. Berges Gimeno MP, Camacho Garrido E, Garcia Rodriguez RM, et al. Rofecoxib, a selective high affinity COX-2 inhibitor, has proved to be safe in urticaria/angioedema associated with NSAIDs intolerance. *Allergy* 2001; 56:49.
-