

Challenge procedures in detection of reactions to aspirin and nonsteroidal anti-inflammatory drugs

There are four different and well recognized types of reactions to aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAID). In the first two types of reaction susceptible patients have specific risk factors that predispose them to react adversely to ASA/NSAID. Asthmatic patients, particularly those who simultaneously form nasal polyps and develop chronic sinusitis, are at risk to develop respiratory reactions to ASA and NSAID. These reactions consist of various combinations of rhinorrhea, nasal congestion, ocular injection and bronchospasm. In a small percentage of patients, extrapulmonary reactions (flushing, gastrointestinal cramping, and even hives) occur simultaneously but are clearly secondary events.¹

Patients with chronic urticaria are at risk to experience mild to profound flares of urticaria and/or angioedema following ingestion of either ASA or nonsteroidal anti-inflammatory drugs. Some reactions are also characterized by flushing and/or angioedema of the soft tissues, including the larynx.

In seemingly normal individuals ASA or NSAID alone, or in cross-combination, can induce anaphylactoid reactions which include combinations of cutaneous flush, pruritus, or urticaria with hypotension (anaphylactoid reaction). Since risk factors for anaphylactoid reactions to ASA/NSAID do not exist, sudden onset of unexpected anaphylaxis is the usual presentation. Since some patients only react to a specific NSAID or to ASA itself,

there is speculative assumption that some of these reactions are immune recognized and mediated.

Finally, a handful of case reports have accumulated over the years in which ingestion of a specific NSAID (but not ASA itself) has produced hypersensitivity pneumonitis (allergic alveolitis). Most patients had underlying arthritis and ingested ASA both before and even after the reaction without adverse effect. NSAID-induced hypersensitivity alveolitis was specifically associated with only one NSAID.² The reaction occurred over hours to days, resolved more rapidly with systemic corticosteroid therapy and did not leave residual lung damage.

To complicate further our understanding of these reactions to ASA and the NSAIDs, blended reactions occasionally occur in which features of bronchospasm, urticaria, flush, shock, laryngoedema and/or pruritus may predominate or occur simultaneously. In fact, some reactions do not lend themselves to classification and are best described in detail. Finally and equally perplexing are phantom reactions in which a "reaction" appears during one or even two exposures to ASA or NSAID. But upon rechallenge with the same drug at another time an adverse effect does not occur.

There are three circumstances where phantom reactions are likely to occur. First, in the initial "reaction" typical allergic symptoms occurred but were the consequence of something other than ASA or NSAID, such as an unsuspected food allergen (false assignment of

blame). In the second type of phantom reaction, the natural disease activates spontaneously (bronchospasm or hives for example) but blame is assigned to ASA or an NSAID which happens to have been taken simultaneously. This is equivalent to the physician conducting an oral drug challenge but failing to use appropriate control challenges with placebos and, therefore, ending up measuring spontaneous asthma activity or urticaria rather than a specific effect from the drug.

In the third type of phantom reaction the patient has a tendency toward hysteria and because of anticipatory stress develops symptoms that are interpreted as a respiratory, cutaneous or even systemic reaction. The use of placebo control challenges at another time, or mixed with a challenge substance, tends to expose such reactors.

In this issue of the *Annals of Allergy* a case of flurbiprofen sensitivity followed by "desensitization" is reported.³ This report illustrates many of the difficulties in judging whether or not sensitivity actually exists, an essential exercise before judging that "desensitization" has been achieved. In this patient the history of prior reactions to a spectrum of NSAIDs (tolmetin, zomepirac, and ibuprofen) and ASA consisted of periorbital edema, generalized itching with hives, associated with throat tightness, dysphagia, cough, and wheezing. Based on the history, hypotension did not occur during these prior reactions. Furthermore, the authors did not elicit any known risk factors of asthma/

nasal polyps/sinusitis or chronic urticaria to give us historical confidence that the reactions were occurring within the framework of respiratory or cutaneous cross reactivity syndromes. The closest we can come to a classification is a variant of cross-reactive anaphylactoid reaction, since a systemic reaction was reported to have occurred involving the skin and respiratory tract.

In the challenge experiment, the choice of flurbiprofen as the challenge NSAID was curious because prior reactions/exposure to flurbiprofen had never occurred. Although the challenge with flurbiprofen was conducted in the correct location (intensive care unit) and by a conscientious physician observer, several important components of proper challenge procedure were omitted. First, lung function studies were not performed during the challenge. Second, placebo control challenges were not conducted. The "reaction" described in the article was macular rash, throat itchiness, and cough. Did she experience bronchospasm, laryngospasm, laryngoe-dema, or none of the above? Only by using spirometry measurements, including inspiratory and expiratory flow/volume curves, could one interpret the meaning of the above respiratory symptoms. If the lung function studies were normal, the reaction might have been due to anxiety or even faked. Did the patient have a true reaction to 25 mg of flurbiprofen?

This brings up the issue of open versus placebo blinded challenges. Anytime a suggestible patient is told he or she might react to a medication (informed consent), the possibility of an anxiety reaction can occur and be a significant confounding problem in the interpretation of subsequent events. Since the only objective evidence in this

reaction was a macular rash, it is possible that psychic vasodilation of the skin occurred. In a single blind challenge, placebo capsules can be interspersed with a study drug during the challenge. Furthermore, if patients are told that they will not know which capsules contain placebo and which the study drug, anticipatory anxiety is at least diminished if not eliminated. Only a double-blind challenge helps with the problem of psychic transfer from the observer into anticipatory reactions by the patient.

In this case report it would have been useful to establish a threshold dose of provocation of a reaction (25 mg of flurbiprofen), wait seven days and repeat the challenge with two placebo doses and one (in this case 25 mg. of flurbiprofen) double-blind. Such measures would have been reassuring to the reader that a specific cutaneous, respiratory reaction to flurbiprofen actually occurred.

Assuming that a reaction to flurbiprofen occurred, did continued administration of flurbiprofen lead to "desensitization"? The only prior documented challenge reaction to flurbiprofen occurred in a patient with asthma and sinusitis who experienced a bronchospastic reaction to 10 mg of oral flurbiprofen. Attempts to desensitize this individual were unsuccessful.⁴ Similarly, all attempts to desensitize with NSAID or ASA after induced urticarial reactions have also been unsuccessful.⁵ Anaphylactic reactions have not been studied with respect to whether or not desensitization with the inciting NSAID could then be engineered.

This case report in the *Annals* is, therefore, of considerable interest because the prior reactions to other NSAIDs represented either a form of anaphylactoid reaction or some

type of hybrid reactions. For this reason, the authors may have described the first report of anaphylaxis to a NSAID (flurbiprofen) followed by successful desensitization. However, because of confounding variables, particularly the open challenge, the lack of PFT measurements and the lack of confirmation with a second double blind challenge or even single blind challenge, we cannot be reasonably assured that a reaction to flurbiprofen actually occurred. Such a fact would need to be established unequivocally before claims of successful desensitization could be made.

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