

Intersection of Drug Allergy and Food Allergy



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In contrast to acute urticaria or anaphylaxis that occurs in people allergic to foods or medications or when triggered by exercise, food-dependent exercise-induced anaphylaxis (FDEIA) occurs in susceptible people when there are 2 triggers in place (food consumed within 6 hours of exercise).¹ For some people, any food will suffice, whereas in others, the triggering food can be shown to have induced anti-food IgE antibodies. In FDEIA, in the absence of exercise, the ingested food does not produce any allergic signs or symptoms; however, the ingested food serves as a cofactor to trigger anaphylaxis when the susceptible person subsequently engages in exercise, even brisk walking. In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Romano et al² make the case that the clinical guidelines/classification of reactions to nonselective, nonsteroidal anti-inflammatory drugs (NSAIDs) be extended to include NSAID-induced or -aggravated allergic reactions to foods. The data extend previously reported cases from Cardona et al in 2012.³ NSAID-induced allergic reactions to foods describe patients who tolerate a particular food, but when a nonselective NSAID has been taken, the patient experiences allergic reactivity such as acute urticaria or acute urticaria with angioedema or anaphylaxis. The authors propose the acronym NIFA for NSAID-induced food allergy, in which the NSAID serves as the cofactor.² The purposeful challenge with the NSAID confirmed that the NSAID was tolerated in the absence of the food. The second type of reaction is NSAID-aggravated or -exacerbated food allergy to describe the more severe signs and symptoms of the reaction to a known food allergen.² In this reaction, even a patient who is known to have oral allergy syndrome or mild urticaria from a food would develop more severe acute urticaria if the NSAID had been taken before the culprit food was ingested. The authors propose the acronym NEFA for NSAID-exacerbated food allergy. The data were obtained from a review of 414 patients aged 18 to 86 years evaluated from 2011 to 2016 at 2 centers for what I would call a provisional diagnosis of an NSAID hypersensitivity reaction.² Approximately 162 (39.1%) patients tolerated the

NSAID so were excluded. Positive reactions to NSAIDs were reported to have occurred within 1 hour after ingestion of the NSAID in 66 occasions and from >1 to 4 hours in 33 others.² Because the NSAID or food may have been ingested before or after 4 hours of each other, further workup was performed. From the remaining patients, who underwent skin prick testing, prick by prick testing, blood testing for IgE antibodies, and some provocation challenges, 66 patients were classified as having NIFA and 9 as NEFA.² In both the earlier report³ and current series,² patients were often sensitized and allergic to peach and its major allergen Pru p 3. This finding contrasts with typical adult, food allergy patients who are allergic to nuts or legumes.

When aspirin or nonselective NSAIDs are ingested, there is an increase in absorption of food antigens because of increased permeability of the intestines.⁴ For example, in healthy volunteers, who were fed noodles made from wheat flour, serial blood samples were obtained, and concentrations of serum gliadin were determined.⁴ Aspirin doses of 100 mg, 200 mg, 500 mg, and 1000 mg were administered 30 minutes before the challenge with the wheat noodles.⁴ There was a little change with aspirin 100 mg, but beginning with 200 mg, there were dose-response increases with the maximum concentrations of serum gliadin occurring with aspirin 1000 mg.⁴ Similarly, whereas there were little changes in serum gliadin concentrations after pretreating with the selective cyclooxygenase-2 inhibitor, meloxicam 15 mg, the preferential cyclooxygenase-1 inhibitors, diclofenac 50 mg and loxoprofen 120 mg, caused increased absorption of gliadin by 60 minutes.⁴ These observations may well help explain the pathophysiology of NSAID as a critical cofactor or inducer in food allergy and FDEIA, but they may be an epiphenomenon too, until our understanding is more certain. This statement implies undertaking careful challenges with the NSAID and food and monitoring for a clinical reaction with laboratory evidence of mast cell activation.

Another important takeaway from the current publication is that physicians and health care professionals need to consider the diagnosis of allergy or hypersensitivity reaction provisional when a food has been ingested within 4 hours of the NSAID use. Although virtually all IgE-mediated allergic reactions to foods occur within 2 hours of ingestion of the food, the ingestion of an NSAID that within 4 hours leads to the onset of hypersensitivity signs and symptoms may be attributed to the NSAID. This conclusion would be accurate in many cases. However, the “intersection” between the NSAID followed by food in susceptible people requires astute clinical expertise and effort (skin testing or *in vitro* testing and purposeful challenge) to confirm the patterns of NIFA and NEFA. The American Academy of Allergy Asthma and Immunology’s 2022 work group report on making electronic health records and documentation more accurate describes recommendations for how information about

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reactions to drugs and biologicals can be improved.⁵ Although most initial entries of a new drug allergy are made by non—allergist-immunologists, we can help by editing the information such as after delabeling patients with a listed allergy to penicillin. In the case of hypersensitivity reactions to NSAIDs, some such reactions also can be delabeled after noneventful provocation challenges.

Lastly, the classification system for hypersensitivity reactions to nonselective NSAIDs includes (1) aspirin- or NSAID-exacerbated respiratory disease, (2) NSAID-exacerbated cutaneous disease (in a patient with chronic spontaneous urticaria), (3) NSAID-induced acute urticaria and/or angioedema (in people without chronic spontaneous urticaria), and (4) single NSAID-induced hypersensitivity reactions.^{6,7} The publication² in this issue should encourage us to consider modifying this classification system and our diagnosis of a new drug allergy to an NSAID to include the effects of nonselective NSAIDs when the NSAID acts as an aggravator of existing allergy to food or cofactor in people who otherwise would tolerate the food if the NSAID had not been taken.

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