



Letters

Anaphylaxis to nimesulide

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) that specifically inhibits cyclooxygenase 2 (COX-2), which is the inducible form of the cyclooxygenase enzyme. When administered at high doses, it is also known to inhibit COX-1. Nimesulide (N-[4-Nitro-2-phenoxyphenyl]-methanesulfonamide) has a unique chemical structure among the NSAIDs and belongs to the sulfonanilide class. It is often used as a reliable alternative for NSAID-sensitive patients; but, to date, the molecular mechanisms that confer its uniqueness have not yet been defined. Because of hepatotoxicity, nimesulide has not been approved in several countries including the United States and Canada. In 2012, a full assessment committed by the European Medicines Agency confirmed that benefits exceeded risks for a time- and dose-limited therapy.¹

NSAID hypersensitivity reactions are classified as either nonimmunologic or immunologic. Inhibition of COX-1 is the main cause of nonimmunologic reactions, thus, explaining the cross-reactive hypersensitivity among chemically unrelated groups of NSAIDs. Immunologic reactions include both immunoglobulin E (IgE)-mediated and IgE-independent responses such as mast cell degranulation by means of the activation of the Mas-related G protein-coupled receptor X2 (MRGPRX2).²

According to the European Academy of Allergy and Clinical Immunology classification of phenotypes in hypersensitivity drug reactions to NSAIDs, 5 major clinical syndromes can be distinguished.³ Anaphylactic reactions to many NSAIDs have been reported, including to most of the COX-1-inhibiting agents such as ibuprofen, diclofenac, and pyrazole NSAIDs, and to COX-2 inhibitor and paracetamol.⁴ Literature reports of putative immunologic reactions to nimesulide are limited to few cases, such as fixed drug eruption, induced-vasculitis,⁵ and acute urticaria, or exacerbation of the cutaneous disease.⁶

Here, we present the case of a 43-year-old woman, with no history of allergic and autoimmune diseases, asthma, and previous anaphylactic episodes. The patient presented to our facility to investigate an episode of anaphylaxis after taking a 100-mg tablet of nimesulide for a mild headache. She had previously tolerated nimesulide on several occasions, and the dose the patient took is known to selectively inhibit COX-2 with weak and reversible effect on COX-1.¹ She had not eaten any food in the previous 3 hours, had not exercised, and had not been exposed to venom stings, cold, or any other medications. The symptoms started with flushing and generalized pruritus, and within 20 minutes she reported weakness, abdominal pain, diarrhea, and shortness of breath; on presentation, we also observed hypotension (systolic blood pressure 60 mm Hg). Intramuscular epinephrine, a short-acting bronchodilator associated with endovenous hydrocortisone, and intramuscular chlorphenamine were

administered. Respiratory and cutaneous symptoms improved within minutes and blood pressure was restored during fluid infusion. The total tryptase levels (Phadia AB, Uppsala, Sweden) were 16 ng/mL after 2 hours, compared with 5 ng/mL at baseline.

At present, no effective tools for diagnosing NSAID allergies are available. We resorted to a basophil activation test (BAT), which returned a positive result for nimesulide but negative for other NSAIDs tested—that is, paracetamol, acetylsalicylic acid (ASA), etoricoxib, and celecoxib. The BAT was performed immediately after blood sampling. The CD63 expression was 6.5% and the stimulation index was 2.5. The expression of CD63 was evaluated with flow cytometry.⁷

Basophil activation test is generally considered to be highly specific despite the lack of sensitivity,⁸ and most importantly for our study, the recent literature has proved BAT to have a specificity nearing 100% when challenged with NSAIDs.⁷ We, therefore, considered the result obtained through BAT as highly valuable and assumed that a challenge test with nimesulide would be too risky, given both the severity of the reaction and the availability of alternative effective NSAIDs.

To study the cross-reactivity with other COX inhibitors and find alternative NSAIDs, we performed single-blind, placebo-controlled tolerability tests with weak (paracetamol 500 mg) and strong (ASA 500 mg) COX-1 inhibitors, and with a highly selective (etoricoxib 60 mg) COX-2 inhibitor. We performed basal spirometry (Vitalograph, Buckingham, UK) before and after the tests. All the challenge tests had negative results and the patient had used both paracetamol and etoricoxib as a pain reliever at home, with no observed reactions.

In our case, the patient's history and BAT positivity enabled us to diagnose her with hypersensitivity to nimesulide. We were, however, unable to establish the exact pathogenic mechanism: we hypothesize that nimesulide elicited a reaction resulting from either a direct mast cell and basophil activation, similarly to those reported for opiates,² or an IgE-mediated anaphylactic reaction. Mast cell degranulation and basophil activation play a major role in the pathogenesis of anaphylaxis. Direct mast cell/basophil activation can present clinically identical symptoms to those of IgE-mediated reactions. At present, no skin tests and serum-specific IgE assays are available to exhibit an IgE-mediated mechanism.⁹ We do not support the hypothesis that the manifestations were due to cyclooxygenase inhibition, given the ability of the patient to tolerate NSAIDs other than nimesulide, including selective COX-1 inhibitors. More importantly, immediate reactions by COX inhibition are usually induced by mediators generated by COX-1 inhibition, whereas nimesulide is a relatively selective COX-2 inhibitor.

Recent evidence indicates that mast cell degranulation by means of MRGPRX2 constitutes a novel endotype of immediate drug hypersensitivity independent of IgE cross-linking. Neuromuscular blocking

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agents, icatibant, quinolones antibiotics, and morphine are examples of drugs acting by means of MRGPRX2. Many of these drugs harbor a tetrahydroisoquinoline motif, which is not present in the nimesulide's chemical structure, and we cannot currently predict a direct activation of MRGPRX2 by nimesulide.²

According to the European Academy of Allergy and Clinical Immunology classification of phenotypes in drug hypersensitivity reactions to NSAIDs, our case is a selective drug responder belonging to the single NSAID reactions.³ Despite the advised strict avoidance to nimesulide, we were able to give the patient safe alternative drugs without extending avoidance to all NSAIDs.

Considering the difficulties involved in the chemical synthesis of appropriate conjugates for skin testing, BAT has proven a useful tool, especially to study severe reactions. We believe BAT to be a valuable alternative to assess immunologic responses in patients with severe reactions and who may develop symptoms after skin testing. More broadly, the concordance of anamnesis and in vitro tests could reduce the need for challenge tests, thus, limiting the latter to selected cases.^{7,10}

Although some cases of hypersensitivity to nimesulide without cross-reactivity with ASA have been previously described, this is the first report in the literature of nimesulide-induced anaphylaxis confirmed by BAT.

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References

1. Caiazzo E, Ialenti A, Cicala C. The relatively selective cyclooxygenase-2 inhibitor nimesulide: what's going on? *Eur J Pharmacol*. 2019;848:105–111.
2. Elst J, Sabato V, Faber MA, et al. MRGPRX2 and immediate drug hypersensitivity: insights from cultured human mast cells [e-pub ahead of print]. *J Invest Allergol Clin Immunol*. doi:10.18176/jiaci.0557, accessed February 6, 2021.
3. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68(10):1219–1232.
4. Dhopeswarkar N, Sheikh A, Doan R, et al. Drug-induced anaphylaxis documented in electronic health records. *J Allergy Clin Immunol Pract*. 2019;7(1):103–111.
5. Marques LP, Villarinho ALCF, Melo MDGM, Torre MGS. Fixed drug eruption to nimesulide: an exuberant presentation confirmed by patch testing. *An Bras Dermatol*. 2018;93(3):470–472.
6. Viola M, Maietta G, Quarantino D, Rumi G, Gaeta F, Romano A. Selective hypersensitivity to nimesulide. *Allergy*. 2008;63(5):624–626.
7. Marraccini P, Pignatti P, D'Apos Alcamo A, Salimbeni R, Consonni D, Consonni D. Basophil activation test application in drug hypersensitivity diagnosis: an empirical approach. *Int Arch Allergy Immunol*. 2018;177(2):160–166.
8. Mayorga C, Ebo DG, Lang DM, et al. Controversies in drug allergy: in vitro testing. *J Allergy Clin Immunol*. 2019;143(1):56–65.
9. Chen CB, Abe R, Pan RY, et al. An updated review of the molecular mechanisms in drug hypersensitivity. *J Immunol Res*. 2018;2018: 6431694.
10. Mayorga C, Doña I, Perez-Inestrosa E, Fernández TD, Torres MJ. The value of in vitro tests to diminish drug challenges. *Int J Mol Sci*. 2017;18(6):1222.