

Can NSAID-Induced Urticaria Be Treated?



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Urticarial reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) are common but can be confusing to categorize diagnostically. Reactions can be NSAID specific (likely IgE mediated) or cyclo-oxygenase -1 (COX-1) mediated (pharmacologic class effect). Confounding things further is the presence of respiratory symptoms, which can signal a diagnosis of aspirin-exacerbated respiratory disease or alternatively anaphylaxis. Because no diagnostic testing is available, thoughtful challenges must be performed to either rule in the offending drug as the cause, or perhaps more pragmatically, challenge with alternative NSAIDs the clinician suspects will be tolerated.

NSAID-exacerbated cutaneous disease (NECD) can be particularly challenging to diagnose. This condition, which is contingent on preexisting chronic urticaria, may occur in as many as 30% of patients with chronic urticaria.¹ The single criterion for diagnosis is a flare of the underlying disease with NSAID exposure. It is well known that many other variables can also be associated with worsening urticaria in chronic urticaria such as viral illness, physical factors, and hormonal changes. As such, the history may not always be accurate, or can be frustratingly vague, not allowing for a clear-cut diagnosis.

Therefore, an oral challenge is essential in a patient who needs an NSAID but has a history of possible NSAID reactions. The literature is mixed on what constitutes an adequate challenge in NECD. Many would feel that the challenge should be undertaken only when the baseline urticaria is adequately controlled, generally with the use of antihistamines. To completely withdraw all medications in a patient with chronic urticaria to perform a diagnostic oral challenge will make the results challenging to interpret. Is the flare of urticaria from the medication, or is the underlying disease process due to loss of control? An example of this problem is the widely variable reports of prevalence of additive-induced urticaria (between 1% and 68%).² Yet, with double-blinded placebo-controlled additive challenges, 0 of 100 consecutive subjects with chronic urticaria experienced an urticarial reaction. Importantly, in this study, antihistamines were

continued at a minimum effective dose. This study illustrates the importance of study design in chronic urticaria studies.

In NSAID-reactive subjects without baseline chronic urticaria, there is no need to maintain daily antihistamines; thus, the challenge can proceed without premedication interference, and the only questions are whether the challenge should be single- or double-blinded and what criteria are necessary to determine a positive challenge.

Once a diagnosis is secured in the NSAID-sensitive individual, it is not always clear what is the best approach to treatment. With the single exception of aspirin-exacerbated respiratory disease, where desensitization uniformly achieves tolerance, all other NSAID reactor categories suffer from limited data on effectiveness of desensitization. Thus, for many of these patients, the use of any NSAID other than a COX-2 inhibitor is no longer an option.

Trautmann et al³ in this issue present their experience with a series of challenges in this population. They present their clinical experience over the course of numerous NSAID-sensitive patients; thus, the study was unable to use a more rigorous design that could have included double-blinded challenges or antecedent challenges to establish drug hypersensitivity and allow the subjects to serve as their own control. And although their data are intriguing and of heuristic value, it is worth reviewing some of the methodologic limitations of their approach.

By definition, chronic urticaria was in "remission" for 1 week before the NSAID challenge. This included the absence of H1 receptor antagonists for 1 week. If the chronic urticaria is in remission, it is likely that the accompanying COX-1 sensitivity is also in remission.⁴ Thus, further challenges with antihistamine pretreatment are falsely interpreted as protective, when in fact the condition has resolved. The NSAID reactivity was confirmed only in 2 subjects. Although the history certainly suggests NSAID reactivity, ongoing hypersensitivity has not been demonstrated. The study design leads to concern that not all patients necessarily had ongoing NSAID hypersensitivity. Although it has been suggested that a history of 2 cutaneous reactions can sufficiently predict the diagnosis of NECD,⁴ it is clear that a history of a single reaction, even if recent, does not equal a diagnosis of NSAID hypersensitivity.⁵⁻⁷ In a similar study in which the goal was to suppress urticarial reactions, Nosbaum et al⁸ were able to find only 6 positive challenges in a group of 65 individuals with a history of multiple NSAID cutaneous reactivity.⁸ The results of the current study therefore need to be interpreted in light of the possibility that not all patients may have truly had NSAID hypersensitivity. Yet, despite these limitations, the authors present a series of patients with characteristics similar to those we see regularly in our allergy clinics: patients with a recent history of an urticarial reaction thought to be secondary to an NSAID and a question about what would be safe to take as an alternative.

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Conflicts of interest: R. A. Simon has provided expert testimony for various cases on various allergy/immunology cases; has received lecture fees from Merck, Novartis, Boehringer Ingelheim, and CSL Behring; and has stock/stock options in URXmobile. K. Woessner has disclosed receiving payment for lectures including service on speakers' bureaus from Shire (Teva) and Astra Zeneca. A. A. White declares no relevant conflicts of interest.

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Their results are surprising. They noted that after 30 minutes of a single dose of desloratidine 5 mg, most challenges were asymptomatic. This would seem to have significant ramifications both for diagnosis and for treatment in this patient population. Although this antihistaminic silencing of an urticarial reaction has been described previously,⁹ this was only in the context of weak COX-1 inhibitors where reactions would generally be considered mild and self-limited.

Desloratidine has an onset of action between 3 and 5 hours.^{10,11} Specifically, Meltzer and Gillman¹⁰ used a human skin test model, where desloratidine was only able to block histamine-induced wheal and flare more than placebo at 6 hours and no earlier. Antihistamine dosing 30 minutes before the NSAID administration should not be enough time to completely protect from an NSAID-induced reaction, unless, as the authors suggest, the oral dispersible formulation has a much faster onset of action.

It is important to point out that among the NSAID reactivity patterns, there exist subjects who have urticaria and angioedema specific to a single NSAID. Although difficult to prove, this is thought to be mediated by IgE. These patients may report only cutaneous reactions, but single NSAID reactions also can include life-threatening anaphylaxis. In a patient with a history of a single NSAID reaction, it would not be prudent to do a full-dose challenge with or without antihistamine pretreatment.

Finally, based on the data presented, it could be (perhaps falsely) concluded that antihistamine pretreatment before NSAID use could allow the asymptomatic administration of NSAIDs with impunity in this population. The authors point out that their study does not address the possibility of using antihistamines to cotreat in patients with NSAID urticaria. Yet this issue is worth reviewing. Starting with our own clinical practice, we have noted that those patients with NECD who require daily aspirin for antiplatelet effect present a challenging situation. These patients can be desensitized only rarely, and more frequently in our practice fail all attempts to suppress NSAID-induced urticaria, necessitating withdrawal of aspirin in favor of alternative antiplatelet agents. Simon¹² reported attempts to desensitize 25 patients to aspirin with a history of chronic urticaria and NECD. These patients developed marked worsening of urticaria, not responsive to antihistamines, and required prednisone. Rechallenge attempts were met with the same reaction.¹² Although there are several case reports of successful desensitization to aspirin in NECD,^{13,14} the very fact that these are rare suggests that attempts to desensitize or treat aspirin reactivity successfully with antihistamines are more often met with failure. This has been the clinical experience of these authors.

When one considers the typical need for NSAIDs for analgesic reasons, there would seem to be 2 patterns of utilization: those with brief and occasional NSAID use (migraine headache) and those with a more prolonged episode of use (sprained ankle). Given the data presented, perhaps the acute treatment of a headache with ibuprofen could be successful with desloratidine pretreatment, but what about the patient requiring high-dose, around-the-clock NSAID use? Would those patients still be suppressed with a single dose, or even a multiple high-dose antihistamine regimen? This study unfortunately does not address this question either. However, overall, the data are intriguing and suggest that this area should be explored in a rigorous study design.

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