

Selective hypersensitivity reactions to acetaminophen: A 13-case series

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Clinical Implication

- Although acetaminophen usually is considered a safe drug, we emphasize that hypersensitivity reactions are possible, even in patients who tolerate nonsteroidal anti-inflammatory drugs.

TO THE EDITOR:

Although acetaminophen (N-acetyl-para-amino-phenol) is a well-known and widely used antipyretic and analgesic drug, rare hypersensitivity reactions, which range from urticaria to anaphylactic shock, can occur.¹⁻⁴ Across Europe, only 114 hypersensitivity reactions to acetaminophen were reported and transmitted to EudraVigilance⁵ during 2011 based on the following Medical Dictionary for Regulatory Activities terms for hypersensitivity: allergic conditions, anaphylactic shock, anaphylactic reaction, and angioedema (Table 1). To date, most epidemiologic studies classify these reactions as general adverse drug reactions rather than hypersensitivity to acetaminophen. The reported reactions usually involve intolerance to nonsteroidal anti-inflammatory drugs (NSAID) or even dose-dependent cross-intolerance to other NSAIDs. Although potential IgE-mediated hypersensitivity reactions to acetaminophen have been reported, these series are small in number, and *in vivo* and *in vitro* tests have unknown sensitivity and specificity. In most cases, diagnosis can only be confirmed by using a single-blind oral challenge test (SBOCT), which presents a certain level of risk for the patient.

Here, we describe a series of 13 cases with selective hypersensitivity reactions to acetaminophen diagnosed in our department between January 1999 and December 2012, excluding those with cross-intolerance to NSAIDs. The patients consisted of 7 women and 6 men ages 16-89 years old (mean, 39.46 years old). Clinical manifestations were as follows: immediate reactions (reactions <1 hour after acetaminophen intake) were recorded in 10 of 13 patients (76.92%), including urticaria (6 cases), urticaria with angioedema (1 case), grade 2 anaphylaxis (2 cases), and rhinitis without asthma (1 case). Regarding the 2 anaphylaxis cases, anaphylactic symptoms were classified according to severity⁶: one patient experienced abdominal pain, vomiting, and general pruritic erythema of the skin without wheal formation within 5 minutes; the other patient developed vomiting, hand swelling, and dysphagia within 10 minutes. Nonimmediate reactions (reaction onset >1 hour after acetaminophen intake) were recorded for the remaining 3 of 13 patients (23.07%),

including 1 case of generalized maculopapular rash and 2 cases of fixed drug eruptions: (1) a woman with a single erythematous papule on the hard palate, and (2) a man with sudden onset of individual, well-defined circular plaques on both the glans and distal shaft of the penis.

Before acetaminophen hypersensitivity was diagnosed by confirmatory tests 1 to 36 months after the observed initial acetaminophen reaction, the local ethics committee approved the study, and patients signed the written informed consent form. Acetaminophen-based skin tests were then performed according to the recommendations of the European Academy of Allergy and Clinical Immunology.⁷ Acetaminophen hypersensitivity was diagnosed in one or more of the following ways: a detailed history, including symptoms highly suggestive of drug hypersensitivity; skin prick tests (SPT); intradermal tests (IDT); patch tests (PT); and SBOCT, if necessary (Figure 1). Results of the SPTs (10 mg/mL in saline solution) and IDTs (10 and 1 mg/mL) with acetaminophen (Pro-Efferalgan, Actavis Group, Zug, Switzerland) were negative in all patients. The 3 patients with suspected nonimmediate reactions also tested negative by SPT and IDT (readings taken at 24 hours) as well as by PT with 1%, 5%, and 10% acetaminophen in petrolatum (readings taken at 48 and 96 hours). PT could not be performed in the 2 patients with fixed drug eruptions due to the location of the affected areas (palate mucosa or glans penis). Thus, all skin-based challenge tests were negative in our study.

The oral-based SBOCT was then performed in 10 of 13 patients, excluding 3 of the 13 patients due to the severity and/or location of their initial reactions (the 2 anaphylaxis cases and the genital fixed drug eruptions case). Oral challenges were performed with a single-blind placebo step followed by acetaminophen (250-, 500-, and 1000-mg doses increased at 1-hour intervals); the 3 of 10 patients with a history of nonimmediate reactions received subsequent therapeutic doses at home (500 mg every 8 hours for 3 days). All the patients tested positive for acetaminophen hypersensitivity by SBOCT (Figure 1). All the patients were treated with subcutaneous and oral antihistamines, and clinical manifestations disappeared within 24 hours of treatment. To definitively confirm or rule out intolerance to NSAIDs, all 13 patients received 1000 mg of aspirin orally. No reactions occurred, which confirmed tolerance to aspirin according to the European Academy of Allergy and Clinical Immunology protocol⁸ and ruled out cross-intolerance to NSAIDs.

TABLE 1. Number of case reports*

Reaction	No. of case reports		
	European Economic Area	Non-European Economic Area	Total
Anaphylactic reaction	13	8	21
Anaphylactic shock	10	7	17
Angioedema	20	27	47
Allergic conditions NEC	18	20	38
All reactions	58	56	114

NEC, Not elsewhere classified.

*Some reports may contain more than one of these reactions (consequently, the number of reports for all reactions may be lower than the total number of reports from each of the individual reactions).

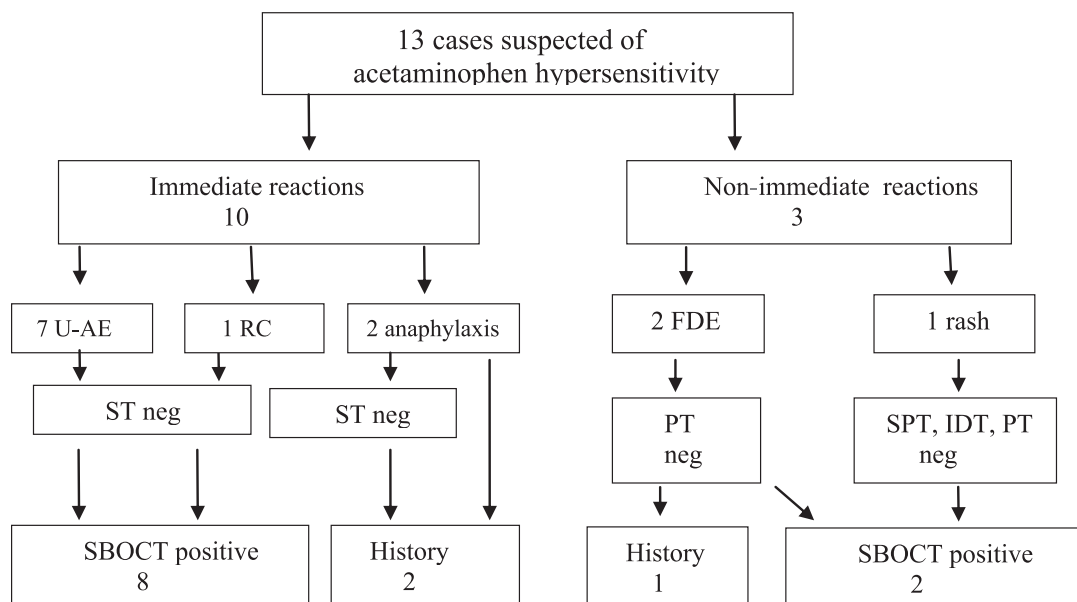


FIGURE 1. A diagnostic algorithm. *ST*, Skin tests (SPT, IDT); *RC*, rhinoconjunctivitis; *U*, urticaria; *AE*, angioedema; *neg*, negative; *history*, diagnosis based on a suggestive clinical history. (SBOCT: Immediate reactions: 7 positive cases of U [2 cases also with AE] and 1 case of RC; nonimmediate reactions: 2 cases of rash.)

We present a series of 13 cases with selective acetaminophen hypersensitivity diagnosed by either SBOCT (10/13 [76.92%]) or highly suggestive clinical history (3/13 [23.08%]). Based on our experience, skin tests were absolutely inconclusive for diagnosis. For some drugs (especially β -lactam antibiotics), the time interval between the initial observed reaction and the subsequent skin test is well known to influence the ability to diagnose hypersensitivity. However, this has not been formally determined for acetaminophen, and other studies that reported positive skin tests for acetaminophen have not provided the relevant timing data. We suspect that timing may have an effect on diagnosis, even though skin tests were negative in patients tested within 6 months of the initial reaction to acetaminophen in our study. Similar to what other researchers previously suggested, we think that the relevant immunogen (ie, an intermediate metabolite) for acetaminophen, as for most drugs, is unknown and that the predictive value of skin testing remains undetermined.⁹ A literature review revealed several studies that reported diagnosis of selective acetaminophen hypersensitivity by positive skin tests. Martín et al¹ described 1 case of generalized urticaria and labial angioedema to acetaminophen confirmed by SPT and specific anti-acetaminophen IgE by using a RAST. Galindo et al³ reported 1 case of anaphylaxis to acetaminophen confirmed by positive IDT (100 mg/mL). De Paramo et al⁴ performed SPT (but not IDT) in 4 patients and found that 2 were positive (1 anaphylaxis and 1 urticaria-angioedema). Rutkowski et al¹⁰ reported that 2 of 21 patients (9.5%) who presented with urticaria-angioedema with conjunctivitis and cough were positive by SPT and that 1 of 13 patients (7.7%) who presented with urticaria and dyspnea were positive by IDT but negative by SPT.

In cases with nonimmediate reactions, false negatives may occur with PT due to poor skin penetration by large drug molecules or low doses of the drug.¹¹ In immediate reactions, IgE detection is not part of routine clinical practice, and testing for specific IgE in serum is only available for a limited number of

drugs; moreover, these tests have unknown sensitivity and specificity because they require validation against sera from confirmed cases. De Paramo et al⁴ reported the largest series of cases with specific IgE against acetaminophen to date, in which 2 of 4 patients were positive when using RAST. Also, when using RAST, Martín et al¹ detected specific IgE to a protein conjugate of acetaminophen in 1 patient with an acute cutaneous reaction to acetaminophen in whom a positive skin test also was seen, which indicated the possible existence of specific IgE antibodies. The *in vitro* basophil activation test can also support the diagnosis of an IgE-mediated reaction, but results to date are inconclusive for NSAIDs, and more studies are necessary to determine its sensitivity and specificity.¹²

In summary, the 13-case series of selective acetaminophen hypersensitivity we describe here, to our knowledge, is the largest of its kind to be reported. The observed clinical manifestations suggest that both type I IgE (in 10 patients with immediate reactions) and type IV (in 3 patients with nonimmediate reactions) hypersensitivity mechanisms occurred in our patient population, although all 13 patients tested negative by skin tests. Because 76.92% of the cases were positive by SBOCT, analysis of our data suggests that oral challenge remains the criterion standard of diagnosing acetaminophen allergy. A COX-mediated NSAID cross-intolerance mechanism was ruled out in all the patients. We hypothesized that both immediate and nonimmediate reactions were true hypersensitivity reactions due to the clinical manifestations, onset period, and positive challenge tests. Although acetaminophen usually is considered a safe drug, we emphasize that hypersensitivity reactions are possible and should not be overlooked when evaluating patients with allergic manifestations. It is noteworthy that case reports of acetaminophen allergy are rare and that series are generally small. Therefore, further multicenter studies with larger numbers of patients are needed to identify ways to confirm the diagnosis without incurring the risks posed by SBOCT.

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