



Challenging Clinical Cases

An unusual case of immediate hypersensitivity reaction to a common medication

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Introduction

A 31-year-old, white woman with a history of migraines was referred by an outside allergist to our allergy-immunology clinic for evaluation of urticaria and possible medication allergy. Her hives began approximately 3 months before presentation when she first noted hives on awakening. Since then, she reported having 7 to 10 outbreaks of hives, which usually occurred around the time of her menses. The patient described her hives as raised red welts, very pruritic, and lasting fewer than 24 hours.

In the 1 month before presentation, the patient developed hives all over her body approximately 15 minutes after taking acetaminophen (Tylenol) for menstrual symptoms. She discontinued use of all analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs]), and she was hive free for several weeks. The week before her clinic visit, the patient had a migraine headache and took an aspirin, acetaminophen, and caffeine tablet (Excedrin), subsequently developing coalescing hives all over her body. She also experienced swelling of the face, dizziness, and vomiting within 1 hour of taking this medication. Her symptoms improved within 24 hours. The patient denied having any tongue or throat swelling and did not have any dyspnea with this episode. Since her hives began, the patient had been taking loratadine every morning and cetirizine every night with continued breakthrough symptoms. She denied having any recent viral or gastrointestinal illness and had not been taking any new medications or antibiotics before the onset of her hives. Her physical examination findings on the initial visit were notable for several flat erythematous lesions on her back consistent with resolving urticaria, as well as facial and neck flushing, which appeared and resolved during the interview.

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Of note, during this clinic visit she was nearing the end of her monthly menstrual cycle.

Since NSAIDs, aspirin, acetaminophen, and the combination of aspirin, acetaminophen, and caffeine could not be ruled out as potential causes of the patient's urticaria, a cyclooxygenase (COX) 2 inhibitor was recommended as an alternative medication for the management of the patient's migraines. An outpatient celecoxib oral graded challenge was suggested to the patient. However, given the chronicity of the patient's migraines and the expense associated with celecoxib, she preferred to undergo an oral drug challenge with an alternative analgesic. Because acetaminophen hypersensitivity was thought to be the least likely cause of the patient's urticaria, cautious oral graded challenge to acetaminophen was discussed and offered to the patient. In addition, because menses was thought to be a possible exacerbating factor for the hives, it was decided that the patient would undergo acetaminophen oral graded challenge when she was hive free and not menstruating.

The patient returned at the agreed time, and informed consent for an acetaminophen drug challenge was obtained before conducting the procedure. She had discontinued use of antihistamines 72 hours before the office visit. The patient's total goal dose of acetaminophen was 360.75 mg orally. The stepwise plan to administer acetaminophen was 3.25-, 32.5-, and 325-mg doses, each 30 minutes apart. The patient's vital signs were stable at the start of the oral drug challenge, and she was administered 3.25 mg of acetaminophen without an adverse reaction.

Thirty minutes after the initial dose, the patient was given 32.5 mg of acetaminophen. She experienced generalized pruritus soon after receiving this dose, although no rash or other cutaneous symptoms were noted. The physicians were not notified about these symptoms, and the nursing staff proceeded with the challenge because the symptoms did not progress and the pruritus resolved. Forty minutes after the second dose of acetaminophen, the patient was given 325 mg of acetaminophen. Twenty minutes after this dose was administered, the patient developed a single

urticarial lesion on her right upper arm, bilateral conjunctival injection, and diffuse pruritus. She stated that, in the past, all her hives episodes began with a single hive in the same location. The patient was immediately given 1 dose of 0.3 mL of 1:1,000 intramuscular epinephrine and 10 mg of cetirizine by mouth. Her blood pressure at this time was 119/71 mm Hg, and her heart rate was 101/min. Five minutes after epinephrine was administered, the patient experienced abdominal discomfort. Symptoms stabilized but did not resolve. Thirty-five minutes after the onset of her initial symptoms, an oral dose of 30 mg of prednisone was administered. Fifteen minutes after prednisone was given, the symptoms returned and progressed, with an increase in urticarial lesions that began to coalesce (Fig 1). The patient denied having dyspnea, wheezing, or nausea. Her blood pressure at this point was recorded as 109/60 mm Hg, heart rate was 84/min, and oxygen saturation was 100% on room air. A second dose of 0.3 mL of 1:1,000 intramuscular epinephrine was administered. On physical examination, there was no angioedema, and her lungs were clear to auscultation bilaterally without any wheezing. She was given another dose of prednisone, 30 mg orally, followed by an additional cetirizine dose, 10 mg, 20 minutes later. Symptoms stabilized, and no further medications were administered.

Two hours after her symptoms initially started, the patient's blood pressure was 101/72 mm Hg, heart rate was 72/min, and oxygen saturation was 100% on room air. Three hours after the onset of her initial symptoms, the patient's urticaria significantly improved. She was comfortable and tolerating solid food and liquids. She was monitored for a total of 5 hours 30 minutes after her reaction. Before being discharged from the clinic, her vital signs were stable, and her urticaria had completely resolved. She was diagnosed as having an immediate hypersensitivity reaction to acetaminophen and discharged home with 1 additional dose of 30 mg of prednisone. The patient was advised to avoid all medications that contained acetaminophen. She was also instructed to avoid all NSAIDs, including selective COX-2 inhibitor medications, such as celecoxib, until her drug allergies were further clarified.

At a follow-up clinic visit 2 weeks later, the patient reiterated her need for analgesics for her migraine headaches. Risks and benefits of a celecoxib oral drug challenge were discussed, and the patient opted to proceed with a celecoxib oral drug challenge with a goal dose of 100 mg. The patient was administered 1, 10, 50, and 100 mg of celecoxib, each at 30-minute intervals. She successfully tolerated celecoxib and did not report any adverse events. Given the cost of celecoxib and concern for increased cardiovascular risk associated with COX-2 inhibitors, the patient was evaluated for her possible NSAID allergy 1 month after the celecoxib challenge. She was informed that a nonselective COX-1 and COX-2 inhibitor could potentially cause an immediate reaction, including hives or anaphylaxis. After explanation of the risks and benefits of the procedure, the patient wished to proceed with an ibuprofen challenge. She was administered 2-, 20-, and 200-mg doses of ibuprofen, each at 30-minute intervals. The patient completed the ibuprofen oral drug challenge without a reaction. She takes NSAIDs and celecoxib without any incident and is continuing to strictly avoid acetaminophen.

Discussion

Acetaminophen, also referred to as paracetamol, is a commonly used analgesic and antipyretic.¹ This medication was discovered in 1878 but became a popular drug in the 1950s.^{1,2} Acetaminophen is often used as an alternative drug of choice to treat pain in patients with aspirin or NSAID sensitivity. Despite its widespread use, only a limited number of case reports of hypersensitivity reactions to acetaminophen have been published.³



Figure 1. Urticaria and erythroderma on left upper extremity and chest.

Although acetaminophen has a relatively safe drug profile, adverse effects of this drug can cause hypersensitivity reactions, such as urticaria, angioedema, pruritus, dyspnea, abdominal pain, fixed-drug eruption, Stevens-Johnson syndrome, and anaphylaxis.^{1,3–7} A higher prevalence of allergic reactions to acetaminophen has also been reported in females than males.^{5,8} Some of the reported reactions that occur soon after ingestion of acetaminophen have been described as anaphylactoid reactions (ie, pseudoallergic) or anaphylaxis. Cases of liver toxic effects from acetaminophen overdose are still routinely encountered; however, the cause of liver injury attributable to acetaminophen is not immunologically mediated and is a result of impaired clearance of its toxic metabolites.²

We describe a case of a woman who developed an immediate hypersensitivity reaction after an acetaminophen oral drug challenge. Our differential diagnosis for this patient included idiopathic urticaria controlled with twice-daily antihistamines with breakthrough from exacerbating factors, such as menses, migraine, or medications (ibuprofen, aspirin) vs drug allergy from NSAIDs, aspirin, acetaminophen, or the combination of aspirin, acetaminophen, and caffeine. Idiopathic urticaria was thought to be the likely diagnosis for the patient because she initially awoke with urticaria without having had a reaction to a medication. In addition, the patient had resolving hives despite avoiding all pain medications for 1 week before her initial clinic visit. She also described exacerbations during her menses, which is not uncommon with idiopathic urticaria.

In retrospect, the patient was indeed allergic to one of the drugs that she was taking as demonstrated by her last reaction to the combination of aspirin, acetaminophen, and caffeine. Because allergy to any of the drugs was a possibility, a COX-2 inhibitor, such as

celecoxib, was the best and safest alternative that was recommended to the patient. This option was unfortunately limiting and costly for the patient. As a result, an alternative medication was necessary to manage the patient's migraine headaches. Because hypersensitivity to acetaminophen is rare, this was the drug chosen for the oral drug challenge for the patient.

Diagnostic tests to evaluate suspected IgE-mediated hypersensitivity reaction to acetaminophen include skin testing⁴ and checking serum specific IgE levels to the acetaminophen molecule.¹ Epicutaneous and intradermal skin testing with acetaminophen can be performed; however, the results are not always accurate.⁴ Similarly, the results of specific IgE testing to acetaminophen may not necessarily be positive in a patient with an immediate reaction to acetaminophen, and this test is not reliable.⁴ As a result, these tests were not performed in our patient. Oral drug challenge is therefore the preferred modality to evaluate a patient with suspected immediate hypersensitivity reaction to acetaminophen because of the poor predictability of skin testing and serum specific IgE.

Overall, oral drug challenges are useful in broadening therapeutic options in patients and can be safely performed in a trained allergist's office. This case highlights that early signs of an allergic reaction are important to recognize, particularly conjunctival injection and pruritus. In addition, as practitioners, we should not hesitate to administer epinephrine, especially in young, healthy individuals, because an immediate hypersensitivity reaction can progress rapidly and likely be curtailed by early administration of intramuscular epinephrine. As noted in this case report, despite very early intervention with epinephrine, our patient had progression of symptoms and required additional epinephrine. Our experienced nurse did not think the pruritus was significant because the symptoms resolved and the medication was acetaminophen. In retrospect, the nurse realized this mistake and informed us about the reaction. If we had been notified about the patient's symptoms with

the 32.5-mg dose of acetaminophen, we would have likely repeated this dose and extended the waiting period.

Conclusion

We describe a case of a woman with immediate hypersensitivity to acetaminophen, presumably IgE mediated, that only became apparent after a drug challenge. This case demonstrates hypersensitivity to acetaminophen presenting as urticaria and developing into a more severe systemic reaction. Overall, given the widespread use of acetaminophen, health care professionals should be vigilant of hypersensitivity reactions to acetaminophen and consider acetaminophen as a potential cause of drug allergy.

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