

LETTER TO THE EDITOR

Acetaminophen-induced urticaria without aspirin intolerance

Dear Editor,

Acetaminophen is an analgesic-antipyretic drug, used world-wide, having a weak inhibitory effect on cyclooxygenase (COX).¹ Hypersensitivity to acetaminophen is seen mostly in patients with aspirin intolerance, and acetaminophen-specific hypersensitivity is rare.¹ We describe a case of acetaminophen-induced urticaria without aspirin intolerance confirmed by oral challenge test.

A 31-year-old woman had several prior episodes of acute urticaria. The first episode occurred approximately 5 months before the evaluation. She complained of itching, and several hives were present on her abdomen approximately 1 h after ingesting 1 g PL (150 mg acetaminophen) for a cold. The next episode occurred approximately 1 month before the evaluation. She was given one tablet of Cocarl (200 mg acetaminophen) for a treatment of toothache. Approximately 20 min later, she noticed itching on her eyes and ear canals. Approximately 30 min later, urticaria developed on her chest and arms, and she complained of dyspnea. She was taken to the emergency room of Shimane Prefectural Central Hospital, and treated with 20 ml Stronger Neo-Minophagen-C (glycyrrhizinate, glycine, and L-cystein hydrochloride) and 5 mg Polaramine (*d*-chlorpheniramine maleate) i.v. After several hours, she recovered from the symptoms. She had a history of acute urticaria after ingesting an analgesic-antipyretic drug when she was a child. She had no history of atopic diseases.

Aspirin intolerance was suspected and then she was referred to our hospital. Serum antigen-specific immunoglobulin (Ig)E were negative to foods or environmental allergens. Skin prick tests with 200 mg/ml solution (99.5% ethanol) of acetaminophen and of

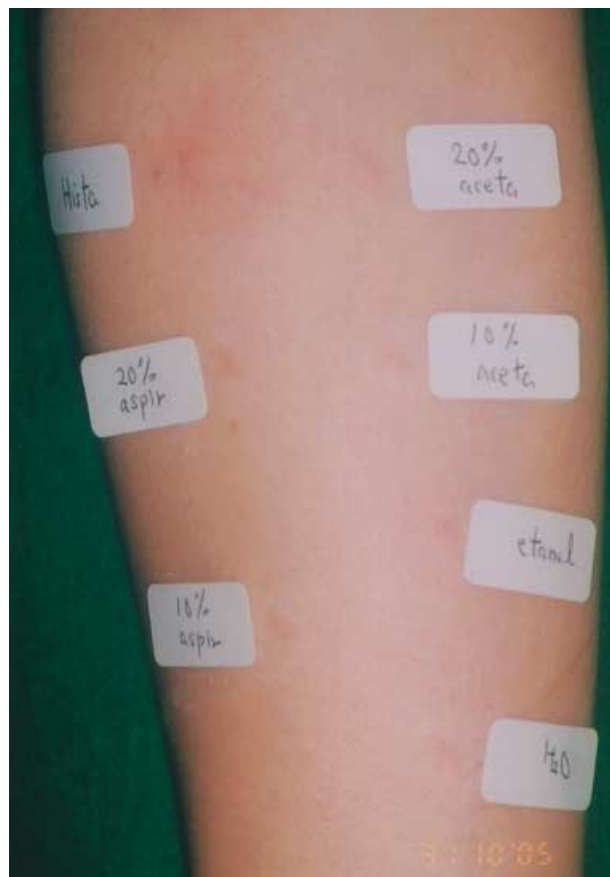


Figure 1. Prick tests showed negative reactions to 20% aspirin (aspir), 10% aspirin, 20% acetaminophen (aceta), 10% acetaminophen, ethanol (etanol), and distilled water (H₂O). hista, histamine.

aspirin were negative (Fig. 1). An oral challenge test with 200 mg pure acetaminophen elicited urticarial lesions developed on her abdomen and left thigh (Fig. 2). Oral challenge tests with 100, 300, 500 mg of

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Received 29 March 2006; accepted 6 October 2006.



Figure 2. Urticaria over abdomen which occurred 20 min after ingesting 200 mg acetaminophen.

aspirin were performed at 24-h intervals, as described in a previous study.² She was observed for 8 h after each ingestion, but symptoms were negative. Additional oral challenge test with one tablet of Solantal (100 mg tiaramide) was also negative. The patient was given a diagnosis of acetaminophen-induced urticaria without aspirin intolerance.

Aspirin and some non-steroidal anti-inflammatory drugs (NSAIDs) that block COX-1 sometimes induce urticaria, angioedema, rhinitis or asthma, and the reaction is called an intolerance. The hypersensitivity is usually seen to multiple NSAIDs and the mechanism of this allergy-like reaction has been explained by inhibition of COX-1 which is a key enzyme to synthesize prostaglandins. Cross-sensitivity between

aspirin and acetaminophen in aspirin-sensitive asthmatic patients has been reported, although the incidence is not high.³ In that report, the cross-reactivity to acetaminophen was well correlated with the provoking dose of aspirin, where none of the patients in whom the aspirin provoking dose was 150 mg or greater experienced reaction to acetaminophen.³ This finding was also supported by the report by Kivity *et al.* where four atopic patients with hypersensitivity to aspirin at doses below 126 mg were found to have hypersensitivity to acetaminophen.⁴

Cases with acetaminophen hypersensitivity without aspirin intolerance do exist, although the incidence is quite rare.^{5–9} Table 1 summarizes reported cases with acetaminophen hypersensitivity without aspirin intolerance. In these cases, hypersensitivity to acetaminophen was confirmed with oral challenge tests, and those with 500 mg aspirin were negative. The provocation doses of acetaminophen to induce positive reaction varied among the patients: the minimum dose was 75 mg and the maximum dose was 650 mg. Asero¹⁰ recommended an aspirin challenge test in order to diagnose single or multiple NSAID reactors in subjects with a history of urticaria induced by a single NSAID (other than aspirin). We performed the challenge test with up to 500 mg aspirin to evaluate single or multiple hypersensitivity to NSAIDs in our patient and found that she had hypersensitivity only to acetaminophen. The mechanism of the hypersensitivity to acetaminophen without aspirin intolerance is considered an IgE-mediated reaction; however, the diagnostic value

Table 1. Review of reported acetaminophen hypersensitive patients without aspirin intolerance

Author	Age/sex	Positive provocation doses of acetaminophen (mg)	Symptoms	Skin-prick test with acetaminophen
Martin <i>et al.</i> ⁵	–	75	Generalized urticaria	Positive
Vidal <i>et al.</i> ⁶	40/F	125	Generalized urticaria and angioedema	Not done
Mendizabal ⁷	48/F	60	Urticaria	Not done
	24/F	80	Urticaria	Negative
	48/F	160	Fixed eruption	Not done
	48/F	650	Urticaria	Not done
De Paramo <i>et al.</i> ⁸	21/F	75	Generalized urticaria and angioedema	Positive
	24/F	650	Anaphylaxis	Positive
	54/F	650	Generalized urticaria and angioedema	Negative
	65/F	650	Local urticaria	Negative
Bachmeyer <i>et al.</i> ⁹	28/F	200	Diffuse urticaria	Negative
Our case	31/F	200	Local urticaria	Negative

of the skin prick test is rather controversial as indicated in Table 1. Of the 12 patients, eight received a skin prick test with acetaminophen, and only three of the eight patients had a positive reaction. Our patient also had a negative skin-prick test, indicating that the diagnostic value of a skin prick test is limited, and that a provocation test is the only reliable method of diagnosis. Binding to protein might be necessary to react to corresponding IgE in case of low molecular weight chemicals such as acetaminophen, resulting in false-negative reaction in skin-prick test.

In recent years, a new classification system for allergic and pseudo-allergic reactions to NSAIDs has been proposed by Stevenson *et al.*¹¹ This classification divides hypersensitivity reactions to NSAIDs into six categories: (i) NSAID-induced rhinitis and asthma; (ii) NSAID-induced urticaria and/or angioedema; (iii) single drug-induced urticaria and/or angioedema; (iv) multiple drug-induced urticaria and/or angioedema; (v) single drug-induced anaphylaxis; and (vi) single drug or NSAID-induced blended reaction.¹¹ In this classification, our patient was classified as a single drug-induced urticaria and/or angioedema. It is now generally accepted that inhibition of COX-1 enzyme is the most likely pathogenic mechanism involved in hypersensitivity reactions to multiple NSAIDs, whereas reactions to single drugs are possibly IgE mediated.¹¹ It might be useful to classify patients who have hypersensitivity to NSAIDs using this new classification system, because we are able to advise the patients whether they can take aspirin or NSAIDs other than causative drugs.

ACKNOWLEDGEMENT

This work was partially supported by grant-in-aid for Scientific Research (18659534) from the Japan Society for the Promotion of Science.

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REFERENCES

- 1 Kvedariene V, Bencherioua AM, Messaad D, Godard P, Bousquet J, Demoly P. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial. *Clin Exp Allergy* 2002; **32**: 1366–1369.
- 2 Gamboa P, Sanz ML, Caballero MR *et al.* The flow-cytometric determination of basophil activation induced by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is useful for in vitro diagnosis of the NSAID hypersensitivity syndrome. *Clin Exp Allergy* 2004; **34**: 1448–1457.
- 3 Settipane RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol* 1995; **96**: 480–485.
- 4 Kivity S, Pawlik I, Katz Y. Acetaminophen hypersensitivity. *Allergy* 1999; **54**: 183–190.
- 5 Martin JA, Lazaro M, Cuevas M, Alvarez Cuesta E. Paracetamol anaphylaxis. *Clin Exp Allergy* 1993; **23**: 534.
- 6 Vidal C, Perez CC, Gonzalez QA. Paracetamol. Paracetamol (acetaminophen) hypersensitivity. *Ann Allergy Asthma Immunol* 1997; **79**: 320–321.
- 7 Mendizabal SL, Diez Gomez ML. Paracetamol sensitivity without aspirin intolerance. *Allergy* 1998; **53**: 457–458.
- 8 De Paramo BJ, Gancedo SQ, Cuevas M, Camo IP, Martin JA, Cosms EL. Paracetamol (acetaminophen) hypersensitivity. *Ann Allergy Asthma Immunol* 2000; **85**: 508–511.
- 9 Bachmeyer C, Vermeulen C, Habki R, Blay F, Leynadier F. Acetaminophen (paracetamol) – induced anaphylactic shock. *South Med J* 2002; **95**: 759–760.
- 10 Asero R. Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. *Clin Exp Allergy* 2005; **35**: 713–716.
- 11 Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase. *Ann Allergy Asthma Immunol* 2001; **87**: 177–180.