

Letter to the Editor

Acetaminophen anaphylaxis diagnosed by skin prick test



Dear Editor,

Acetaminophen (Paracetamol) is the most common medication for pain and fever. There are many case reports of severe cutaneous adverse reactions induced by acetaminophen such as anaphylaxis; however, only a few cases of IgE-mediated hypersensitivity proved by a skin prick test (SPT) have been reported.^{1–3} We described here the first case of acetaminophen anaphylaxis diagnosed by SPT in Japan, and reviewed 5 case reports of acetaminophen immediate-type reaction in Japanese patients.

A 20-year-old woman visited our department following a recent episode of anaphylaxis. Carbocysteine, acetaminophen, garenoxacin mesylate and tranexamic acid for tonsillitis were prescribed. A few minutes after administration of these drugs the patient developed urticaria and dyspnea. To identify the cause of the anaphylaxis, a SPT was performed. The results were positive for 100 mg/ml acetaminophen in saline (2+) within 15 min after application (Fig. 1a), whereas the results for the other drugs were negative. Additional SPTs later yielded positive results for 100 mg/ml acetaminophen (2+) and 10 mg/ml acetaminophen (2+), but the reaction to 1 mg/ml acetaminophen (1+) manifested as less than 50% of the wheals produced by histamine, and was therefore not considered clinically significant (Fig. 1b, c). Negative reactions to 100 mg/ml acetaminophen by SPT were confirmed in 5 healthy volunteers. Based on these SPT results, IgE-mediated anaphylaxis due to acetaminophen was diagnosed. Because of the severity of her clinical episode, intradermal and oral provocation tests (OPT) were not performed. The patient had no history of allergy to any food or medication. She had been working as a care taker for the aged for 3 years and often administered acetaminophen to the elderly. Consistently with the SPT results, she complained itchiness on the thumb and fingers after touching acetaminophen.

Following its introduction in 1893, acetaminophen has been prescribed as an antipyretic and analgesic worldwide.⁴ Although the safety and efficacy of acetaminophen are well established, several case reports exist of severe cutaneous adverse effects such as Stevens-Johnsons syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and anaphylaxis resulting from its use.³ In a recent report, 13 of 333 (3%) or 2 of 313 (0.6%)

paracetamol-sensitive patients was reported in the drug-induced anaphylaxis.^{2,5} Anaphylactic reactions to acetaminophen are thought to be immunologically or non-immunologically mediated.⁶ Non-immunologically, the drug functions as a weak inhibitor of cyclooxygenase-1 and thus a high-dose can induce aspirin-sensitive asthma and an anaphylactic reaction.⁷ On the other hand, IgE-mediated acetaminophen-induced hypersensitivity is extremely rare and SPT are usually negative.⁸ Our patient developed an urticarial rash and dyspnea a few minutes after taking the drug, and showed positive results for a low concentration of acetaminophen on the SPT (Fig. 1b, c). Her medical history revealed no allergy to NSAIDs such as Loxoprofen, suggesting the diagnosis of IgE-mediated anaphylaxis due to acetaminophen. Leung *et al.* first reported cases of acetaminophen anaphylaxis diagnosed by OPT without co-existing aspirin intolerance,⁹ and was followed by Martin *et al.*, who reported a similar case diagnosed by SPT.¹ In a recent report, 3 of 13 patients (23.0%) in one study and 2 of 16 patients (12.5%) in another study of acetaminophen hypersensitivity showed a positive reaction on SPT.^{2,3}

Five cases of acetaminophen hypersensitivity without aspirin intolerance, including the present case, have been reported during the past 15 years in the Japanese literature (Table 1). The gender distribution was 2 males and 3 females. The average age was 26.8 years. The youngest patient was a 6-year-old and the age range was wide. All patients demonstrated allergic symptoms after ingesting acetaminophen, with anaphylaxis occurring in 3 patients and urticaria occurring in 2 patients. The condition was diagnosed in 4 cases with aspirin tolerance by OPT. The positive provocation doses of acetaminophen in these cases were 30 mg, 100 mg, 200 mg, and 300 mg. To the best of our knowledge, the present case is the first report of acetaminophen-induced anaphylaxis diagnosed by SPT in Japan. Specific IgE determination by RAST to acetaminophen was not performed in any of the cases.

In a previous report, 100 mg/ml acetaminophen in saline produced a positive test result, whereas 10 mg/ml produced a positive result in our patient.⁴ Up to now, the optimal concentration of acetaminophen for SPT has not been established. However, based on the above findings, a 10 mg/ml solution of acetaminophen can be recommended for a SPT. More case reports are needed to determine the optimal concentration.

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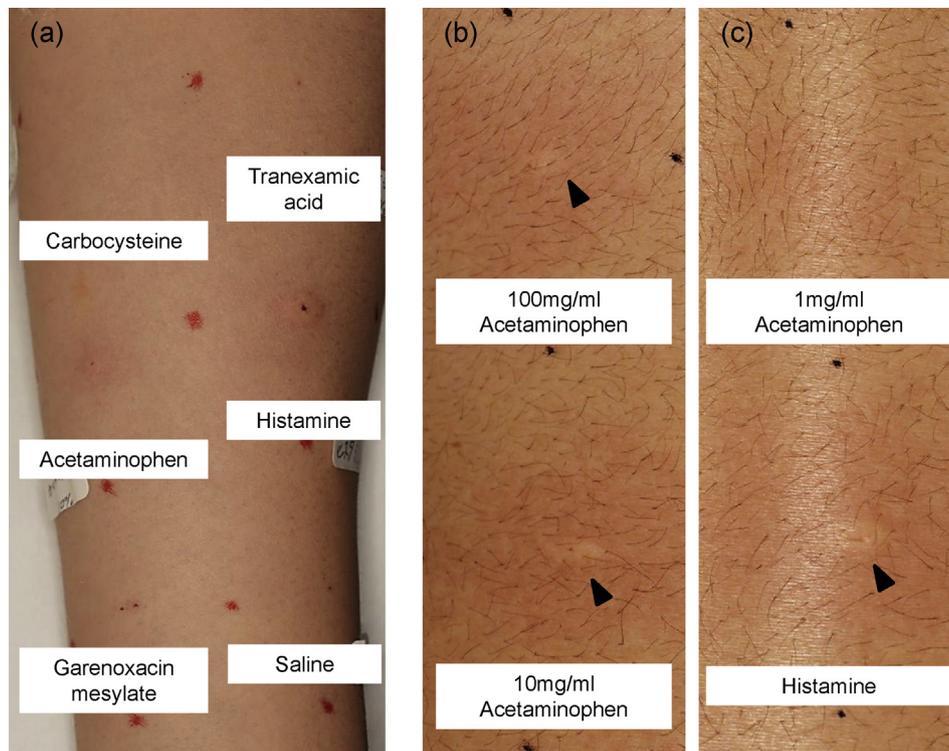


Fig. 1. (a) Results of skin prick test. A positive reaction to 100 mg/ml acetaminophen (2+). (b, c) Subsequent skin prick test. Positive reaction to 100 mg/ml acetaminophen (2+), 10 mg/ml acetaminophen (2+), and 1% histamine (arrow head). The reaction to 1 mg/ml acetaminophen was not considered clinically significant (1+).

Table 1

Review of reported cases of acetaminophen immediate-type reaction without aspirin intolerance in Japan.

Author	Age/Sex	Symptoms	Positive provocation doses of acetaminophen (mg)	Skin prick test with acetaminophen
Tsujino <i>et al.</i>	31/F	Urticaria	200	Negative
Sato <i>et al.</i>	58/M	Anaphylaxis	30	Negative
Nakamura <i>et al.</i>	6/M	Urticaria	100	ND
Kageyama <i>et al.</i>	19/F	Anaphylaxis	300	Negative
Our case	20/F	Anaphylaxis	ND	Positive

ND, not determined.

Conflict of interest

The authors have no conflict of interest to declare.

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