Successful Prophylaxis of Wheat-Dependent Exercise-Induced Anaphylaxis with Terfenadine

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A 20-year-old female was brought to our emergency unit with generalized erythema and discomfort induced by running after having eaten wheat bread. The laboratory examinations, including eosinophils, total IgE, RAST score to wheat, heat challenge test and methacholine inhalation test were within normal limits. No anaphylactoid responses occurred after provocation tests of wheat bread intake or exercise alone. However, on provocation exercise test after eating pancakes, she developed hypotension, generalized itching and urticaria associated with an elevation of plasma histamine levels. These findings suggested wheat-dependent exercise-induced anaphylaxis. This was completely prevented by daily administration of terfenadine 120 mg p.o. without side effects such as fatigue or drowsiness.

(Key words: exercise, anaphylaxis, plasma histamine level, urticaria, anti-allergic drug)

Introduction

Exercise-induced anaphylaxis is characterized by a unique syndrome consisting of generalized itching, urticaria and erythema, which progresses and continues on to include angioedema, gastrointestinal symptoms, headache and occasional episodes of unconsciousness (1–3). These symptoms of anaphylaxis, which occur only when exercise is followed by the ingestion of certain foods, can be prevented by fasting for a few hours before exercise (4). We report here the patient in whom wheat-dependent exercise-induced anaphylaxis (EIA n) was inhibited by the administration of terfenadine.

Case Report

A 20-year-old female was brought to our emergency unit with generalized erythema and discomfort induced by running after having eaten fried shrimp, roast meat and wheat bread for lunch. On physical examination, her blood pressure was 110/88 mmHg and heart rate was 160 beats/min with regular rhythm. Generalized urticaria was noted over the entire body, the conjunctivae bulbi were injected, and the patient was drowsy. These symptoms in addition to the patient’s hypotension and tachycardia were remitted following anti-histamine and steroid injection. At the age of 19 years, she had had an episode of itching and erythema over her entire body and discomfort during running after having eaten pancakes for breakfast. Those symptoms had remitted spontaneously with about one hour of rest. She had no history of bronchial asthma, or of drug or food allergy including that to wheat. There was no family history of epilepsy.

Laboratory findings included the following: white blood cell count was 6,300/mm³ with 4% eosinophils. Total serum IgE was 53.2 U/ml, and specific IgE antibodies by RAST to milk, cheese, meat, shellfish, shrimp, crab, salmon, tuna, rice, soybean and wheat were all negative. Initial spirometry disclosed a vital capacity of 3.16 l (97% of expected value), forced expiratory volume in one second (FEV1.0) of 2.97 l (105%), and maximal voluntary ventilation of 92.3 l/min (95%). On a methacholine inhalation test, PC20 was above 10 mg/ml, suggesting that the patient had no bronchial hypersensitivity. A food provocation test with bread alone induced no symptoms. The heat challenge test with warm water immersion induced no urticaria.

We performed three types of exercise challenge tests in our clinical evaluation of the patient. Exercise testing was conducted by having the patient run on a treadmill, the workload for which was a speed of 5 mile/h and an incline of 12% maintained for 8 minutes.

On the first trial, the patient underwent the simple exercise challenge test described above after having fasted for 8 hours.
Wheat-Dependent EIAn with Terfenadine

No symptoms and signs, such as itching, urticaria, erythema, syncopal attack or hypotension, were induced by the exercise. The FEV1.0 after exercise was 104% of the baseline value and thus provided no evidence of exercise-induced bronchoconstriction.

For the second trial, the patient ate some wheat flour pancakes 1 hour before an exercise challenge test with a protocol identical to that described above. Minute ventilation increased to 75.1 l/min and heart rate to 181 beats/min at the cessation of exercise. Systolic blood pressure increased to 250 mmHg during exercise, but fell to 170 mmHg on cessation of exercise. Diastolic blood pressure gradually decreased from 76 mmHg at rest to 47 mmHg on cessation of exercise. A few minutes after cessation of exercise, an itching urticaria consisting of small red bumps that were most prominent over her upper extremities and trunk was noted. She began to feel discomfort and had an episode of hypotension (BP 102/72 mmHg) at 20 minutes after cessation of exercise. The plasma histamine levels at rest, during exercise and 20 minutes after exercise were respectively 1.5, 13.0 and 50.0 nmol/1 (Fig. 1). These findings suggested the diagnosis of wheat-dependent EIAn (1, 2, 4).

On the third trial, the patient underwent an exercise challenge test with the same protocol after eating the same amount of pancakes as prior to the second trial and having received terfenadine 120 mg p.o. daily for 5 days. Minute ventilation increased to 71.3 l/min and heart rate to 162 beats/min during exercise. Blood pressure had increased to 220/80 mmHg at cessation of exercise from 142/74 mmHg at rest. No symptoms or signs, such as urticaria, discomfort or syncope appeared following exercise. Serum histamine levels were respectively 1.3, 1.3 and 1.8 nmol/l at rest, during exercise and 20 minutes after exercise.

Discussion

In the wheat-dependent EIAn patient described here, pretreatment with terfenadine prevented the abnormal response. In this case, exercise following the ingestion of wheat had induced symptoms of anaphylaxis and increased serum histamine levels. Provocation tests with exercise alone or with wheat bread alone precipitated no notable symptoms. A passive heat challenge test employing warm water immersion induced no urti-
cari. These findings excluded the diagnosis of cholinergic urticaria (2, 4). This patient, therefore, could be diagnosed as having wheat-dependent EIAn in accordance with the description by various authors (1–3).

The mechanisms responsible for EIAn have been thought to involve numerous vasoactive mediators that can be released from activated mast cells (5). Histamine is released from such cells following the binding of antigen by IgE antibody. Other vasoactive factors released from cutaneous mast cells include prostaglandin D2, leukotrienes C and D, platelet activating factor and bradykinin (6).

Since the EIAn episodes of the present patient were closely related to increases in the plasma histamine levels, prevention of EIAn in this case could be achieved with the administration of anti-histamine drugs preceding exercise. Akutsu et al reported inhibition of the development of anaphylaxis by diphenhydramine in the treatment of wheat-dependent EIAn (7). In many cases, however, there does not appear to be a potent prophylactic medication, the use of which successfully reduces the severity or intensity of symptoms of EIAn. Furthermore, the doses of anti-histamine required may induce symptoms of sedation (8).

Terfenadine has been found to have some pharmacological effects of peripheral H1-receptor antagonists, but it does not compete for cerebral H1-receptors (9). Other effects of terfenadine include inhibition of the release of histamine and certain other chemical mediators from mast cells, and competition with released histamine, PAF and leukotriene (10). Correspondingly, it is administered to patients with bronchial asthma, allergic rhinitis, urticaria or itching eczema. However, there has been no report discussing the prophylactic effect of terfenadine on EIAn. In the present patient with wheat-dependent EIAn, terfenadine completely prevented the occurrence of symptoms following exercise. Prevention of the increase in serum histamine levels on exercise after eating wheat bread might provide evidence for the inhibition of degranulation of skin mast cells. These findings suggested that terfenadine might have an effect of stabilizing skin mast cells following exercise and the ingestion of wheat bread.

It has been reported that other anti-allergic drugs, cromolyn sodium (8) and ketotifen (11), inhibit degranulation of mast cells and the release of inflammatory mediators.

Ketotifen, which inhibits the release of mediators by mast cells and also acts as an H1 receptor antagonist, has been found to reduce histamine levels and symptoms of EIAn (11). In some cases of ketotifen use, however, general fatigue and drowsiness have been noted.

Since cromolyn sodium is administered by inhalation, it may be helpful in the prevention of allergic reactions due to inhaled allergens. However, it is doubtful whether generalized anaphylactic reactions similar to those of EIAn can be prevented by inhaled cromolyn. Briner and Bruno reported a case of wheat-dependent EIAn in which symptoms were effectively controlled with inhaled cromolyn (12). Since it appears only a few percent of cromolyn is absorbed via the lung (13), cromolyn may afford little protection from the development of whole-body anaphylactic reactions (13).

On the other hand, it has been found that metabolic acidosis accompanied by exercise with a severe work load induces degranulation of mast cells. Notably, the optimal pH for degranulation of mast cells has been reported to be about 7.0 (14). Garcia et al found that pretreatment with sodium bicarbonate administration prior to exercise inhibits the appearance of the symptoms of EIAn (15). One of the reasons for the efficacy of sodium bicarbonate in treatment of patients with EIAn may be its prevention of the blood pH decrease during exercise and its inhibition of the increase in plasma histamine levels (16). However, patients with EIAn sometimes develop symptoms with low work load exercise, during which metabolic acidosis is not present. These findings indicate that the mechanism of EIAn involves factors other than acidosis.

In conclusion, we reported a case in which terfenadine prevented wheat-dependent EIAn without side effects such as fatigue or drowsiness.

References