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Pre-treatment with misoprostol prevents food-dependent exercise-induced anaphylaxis (FDEIA)

Recently, wheat omega-5 gliadin and high molecular weight glutenin have been known to be major allergens in wheat-dependent exercise-induced anaphylaxis.¹ As wheat is a very common cooking ingredient and an important resource of carbohydrate and protein, it is difficult to avoid the wheat allergens from daily diets. We sought to determine any prophylactic drug which could prevent wheat-dependent exercise-induced anaphylaxis. For this purpose, we measured serum gliadin levels as an indicator of potential allergic protein ingestion.

A 47-year-old Japanese man presented with a several year history of frequent episodes for urticaria, periocular edema, and dyspnea when he exercised after eating bread. As he took aspirin with bread before exercising, the symptoms were often exacerbated.

At the first visit, serum IgE level and the antigen-specific IgE level of radioallergosorbent testing (RAST) for wheat, rye, peanut, milk, egg white, shrimp, cuttlefish, octopus, pork, beef, chicken, and tomato were not increased. On the other hand, mild increased RAST scores for gluten, crab, and barleycorn were demonstrated. After hospitalization, he fasted for 12 hours before the provocation tests, which were composed of challenging of (i) bread intake, (ii) exercise (stepping exercise for 15 min), (iii) bread intake followed by exercise, and (iv) bread and aspirin (500 mg) intake followed by exercise. The tests of bread and/or the combination with exercise did not affect any of his physical conditions. Notably, aspirin intake, at a dose of 500 mg, together with bread and stepping exercise reproduced the anaphylactic symptoms including urticaria, ocular itching, eyelid swelling, conjunctival injection, nasal discharge, wheezing, coughing, and dyspnea within five minutes (Table 1). He was diagnosed as having wheat-dependent exercise-induced anaphylaxis. As the patient desired to prevent anaphylactic symptoms, we tried to find useful drug for food-dependent exercise-induced anaphylaxis (FDEIA). We chose sodium cromoglicate, a mast cell stabilizer, and misoprostol, a synthetic prostaglandin E₁ (PGE₁) analog. Despite taking 100 mg of sodium cromoglicate an hour before eating bread only once, serum gliadin levels were increased, and anaphylactic symptoms were induced a

Table 1 Results of provocation tests

Loads	Symptoms
Bread	—
Stepping exercise	—
Bread + stepping exercise	—
Aspirin + bread + stepping exercise	Urticaria, ocular itching, eyelid swelling, conjunctival injection, nasal discharge, wheezing, coughing and dyspnea

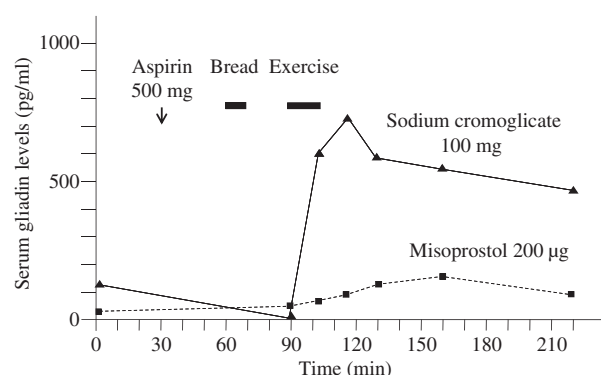


Figure 1 Serum gliadin levels during the provocation test after the treatment with sodium cromoglicate or misoprostol

few minutes after starting the exercise (Fig. 1). However, taking 200 µg of misoprostol in the same way effectively prevented the serum gliadin increment. Misoprostol also completely prevented the anaphylactic symptoms.

Although the pathophysiology of FDEIA remains elusive, several hypotheses have been proposed. Physical exercise increases blood flow in the muscles but decreases that in the stomach. As a result, digestion in the stomach is impaired, resulting in an insufficient degradation of the food antigens. This may contribute to the elevation of hazardous antigens in the blood through intestinal absorption. It was shown that serum gliadin levels were elevated after exercise in wheat-dependent exercise-induced anaphylaxis patients.² In addition, physical exercise is revealed to accelerate the degranulation of mast cells.³

Misoprostol is a PGE₁ derivative that is used for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers. It is reported that PGE₁ increases

thickness of the mucous layer of small intestines, resulting in the inhibition of small intestinal absorption.⁴ In addition, PGE₁ increases blood flow in the stomach and upregulates the digestion in the stomach. During the provocation test in our case, serum gliadin levels were not increased by administering misoprostol. However, sodium cromoglicate, a mast cell stabilizer commonly used to treat allergic rhinitis, allergic conjunctivitis, and asthma, could not affect serum gliadin levels in the provocation test, and therefore allowed the symptoms to occur. We consider that the effects of misoprostol on the alimentary tract are crucial for the prevention of FDEIA. Our observation indicates that the exacerbating effect of aspirin in FDEIA comes from the inhibitory effects of aspirin on PGE₁ in the gastrointestinal milieu. Thus, misoprostol would be a promising prophylactic drug for FDEIA.

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Type XVII collagen ELISA indices significantly decreased after bullous pemphigoid remission

The major pathogenic epitope of bullous pemphigoid (BP) is known to be the noncollagenous extracellular domain (NC16A) of type XVII collagen (COL17).¹ Here we investigated indirect immunofluorescence (IIF) and COL17 NC16A domain enzyme-linked immunosorbent assay (ELISA)^{2–5} data before treatment and after remission to evaluate the usefulness of ELISA analyses as indicators for BP disease activity.

We included ten consecutive BP patients [eight women and two men: between 33 and 80 years old (mean; 59 years old)] who showed typical clinical features before treatment and were successfully treated, resulting in complete or partial remission at our institute. The first day of each patient visit was within the last three years. In all patients, the diagnosis was confirmed by histopathological observation and immunofluorescence study, i.e. histopathological subepidermal blister formation was observed and direct and IIF studies revealed the presence of autoantibodies along the dermal–epidermal junction. All patients were successfully treated with oral prednisolone therapy of 30–50 mg/d with or without azathioprine or a combination therapy using tetracycline and nicotinamide. Treatment periods from initial diagnosis to remission ran-

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ged from four months to 35 months (mean; 14.6 ± 10.8 months). Serum samples were obtained for ELISA and IIF at least twice during the disease course for each patient.

Concentration of autoantibodies in the patients' sera directed against the NC16A domain of COL17 was measured using the COL17 NC16A ELISA kit following the kit's instructions.⁶ IIF staining and evaluation were performed as previously described using normal human skin as a substrate.⁷

In all the cases, the ELISA indices showed a decrease during the successful treatment course. ELISA indices after remission were significantly reduced compared with those before treatment ($P < 0.0001$) (Fig. 1a). IIF titers also decreased after remission in six cases, but the titers were not apparently reduced in the other four cases, although a statistically significant reduction in combined IIF titer was observed after remission compared with those before treatment ($P < 0.05$) (Fig. 1b).

Positive correlation between ELISA indices and BP disease activity has been reported previously in the literature. Di Zenzo *et al.*⁸ demonstrated that disease severity before treatment was well correlated with ELISA indices in BP patients. Izumi *et al.*⁹ described ELISA indices and alteration of disease activity of five BP patients during various treatments. In this study, we compared the ELISA