

Case report

Drug-dependent exercise-induced anaphylaxis

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Exercise-induced anaphylaxis (EIA) is well known and may be food-dependent. We describe a patient with a history of anaphylaxis during exercise after taking nafylpropion acid (Naprosyne®), a nonsteroidal anti-inflammatory drug. An exercise-challenge test after Naprosyne intake induced bronchoconstriction. The combination of history and challenge tests suggests that intolerance or allergy to drugs may present as EIA.

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Exercise-induced anaphylaxis (EIA) is a well-known syndrome, characterized by the clinical features of systemic anaphylaxis such as collapse, urticaria, angioedema, upper respiratory obstruction, and bronchial constriction after exercise (1). Intake of food has been recognized as a precipitating factor of EIA (2). An early report on the syndrome described patients who took acetylsalicylic acid in advance of their exercise (1). An epidemiologic study has identified acetylsalicylic acid as a possible factor in EIA, suggesting that in some cases EIA might be drug dependent (3). However, exercise challenges have been performed to evaluate only the relation with food intake (4).

In this report, we describe a patient who experienced features of EIA, presumably precipitated by the use of nafylpropion acid (Naprosyne®), a nonsteroidal anti-inflammatory drug (NSAID).

Case report

Ms J.B., a 17-year-old girl, was referred to our clinic because she had experienced one episode of systemic anaphylaxis after exercise. About 8–10 min after a 20-min period of jogging, she had developed nausea, vomiting, dizziness, swelling of the face and eyelids, and dyspnea with wheezing; finally, she collapsed. She was treated by a general practitioner

with antihistamines and corticosteroid injections. Two and a half hours before exercise, she had taken a tablet of nafylpropion acid, which she had been taking twice daily for 3 weeks because of an injury of the wrist. Three hours before the onset of her symptoms, she had eaten a meal including avocado, tuna, and spaghetti. She had no history of rhinitis, bronchial asthma, or atopic eczema. She had no other illness and apart from nafylpropion acid, she did not use any medication. The family history revealed no evidence of allergic diseases.

In our department, intradermal skin tests were performed with inhalant allergens (ALK, Groningen, The Netherlands). Freshly prepared and then frozen food allergenic extracts (including tuna and avocado) were used in skin prick tests. Neither inhalant nor food allergens elicited positive skin reactions.

To evaluate the role of nafylpropion acid, we challenged the patient on three consecutive days with nafylpropion acid orally, exercise, and the combination of nafylpropion acid and exercise, respectively. Because she might have experienced a potentially severe reaction, this open-challenge protocol was chosen. Apart from physical examination, her peak expiratory flow (PEF) was monitored with a Mini-Wright peak-flow meter on the first day. The exercise challenge was similar to that for the diagnosis

of exercise-induced bronchoconstriction (5). For 7 min, she ran on a treadmill with a load such that her heart rate reached a level 20–30 min^{-1} below predicted measurements as determined by sex and age. Before and after the exercise challenges on the second and third day, her airway resistance was monitored from indices of maximal expiratory flow-volume curves (PEF, forced expiratory volume in 1 s, FEV_1).

On the first day, she was challenged with 10, 25, 250, and 500 mg nafylpropion acid every 30 min. A 17% drop in PEF was observed from 7.5 l/s (108% of predicted) before challenge to 6.3 l/s (91%) after challenge with 25 mg nafylpropion acid. PEF increased again up to 7.0 l/s. With 25 mg nafylpropion acid, she experienced subjective feelings of dizziness without any objective changes in heart rate or blood pressure. On the second day, FEV_1 was also measured, and no fluctuations in either PEF or FEV_1 (Fig. 1) were observed after exercise compared with baseline. On the third day, exercise challenge was performed 30 min after intake of 500 mg nafylpropion acid. FEV_1 dropped significantly from 3.52 l (113% of predicted) before exercise to 3.0 l (96%) 10 min after exercise (Fig. 1). A concomitant decrease in peak flow was seen from 6.74 l/s (97%) to 5.27 l/s (76%). Again, symptoms other than dizziness were not observed.

To estimate the daily fluctuation in PEF, we obtained PEF measurements on 3 other consecutive days at 8 a.m., 12 a.m., and 6 p.m. During the 3-day period, PEF ranged from 7.5 l/s (108%) to 8.6 l/s (125%). The maximal daily variation was 7%.

As it was concluded that nafylpropion acid elicited the episode of anaphylaxis, the patient was

instructed to stop taking NSAIDs. It was not possible to extend the challenge tests to other NSAIDs, as she went abroad immediately after the challenge procedure.

Discussion

In 1980, Sheffer & Austen described the clinical syndrome of EIA (1). In this first description of EIA, five out of 16 patients had ingested acetylsalicylic acid before exercise. In a Japanese study, 11 patients presented with food-dependent EIA (4). Two patients were reported to have more severe symptoms with acetylsalicylic acid ingestion before food intake preceding exercise as compared with symptoms without acetylsalicylic acid intake. Moreover, in an epidemiologic study comprising 199 individuals with EIA, 25 (13%) respondents identified medication as important in precipitating attacks of EIA, acetylsalicylic acid being important in 12 (6%) individuals (3). Nafylpropion acid has never been reported to induce EIA.

Exercise-challenge studies, however, have focused on the role of food ingestion, using protocols of exercising before and after meals or specific foods (4). In this case report, we tried to establish the role of drug intake in EIA. As a small drop in peak flow was observed after ingestion of nafylpropion acid without exercise, which exceeded the patient's 7% variation in peak flow and the daily variation of less than 10% reported in healthy subjects (6), we cannot exclude the possibility that nafylpropion acid itself leads to bronchial obstruction. However, both the history of the patient and the outcome of our challenge procedure strongly suggest that nafylpropion acid ingestion precipitated the EIA. The absence of an anaphylactic reaction after exercise challenge on the third day, apart from the slightly more severe bronchospasm we observed, may be explained by the shortness of the exercise period compared with the 20-min jogging period from the case history. Furthermore, it has been shown that the level of ventilation achieved and the environmental conditions determining heat and water loss from the airways are the main factors in the amount of exercise-induced asthma. A range of 20–100% of the maximum fall in PEF has been found by varying either exercise intensity (7) or heat loss in dependence on inspiratory air conditions (8). Both these stimuli may be enhanced in jogging. The episode of jogging and anaphylaxis took place in midwinter, whereas the exercise challenge was performed indoors in summer. Moreover, it is not known whether the combination of nafylpropion acid intake and food ingestion followed by exercise would have elicited more severe symptoms.

Our observation is in line with an earlier study (9),

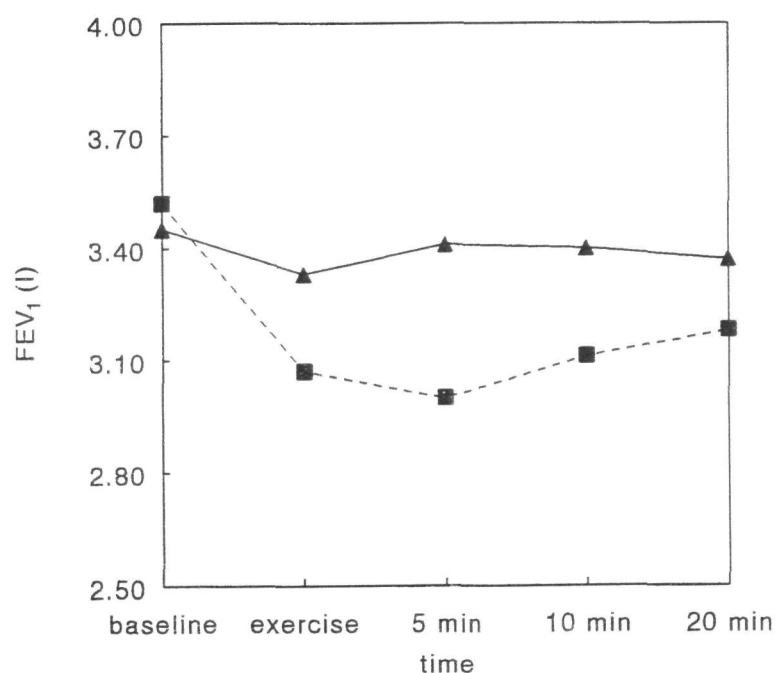


Fig. 1. FEV_1 (l) before; immediately after; and 5, 10, and 20 min after exercise without ($\blacktriangle$ — $\blacktriangle$) and with nafylpropion acid ($\blacksquare$ — $\blacksquare$).

in which exercise challenge gave rise to mild symptoms compared with the severity of natural attacks.

It is not known why the combination of exercise and nafylpropion acid intake induced anaphylaxis. It is known that leukotriene antagonists prevent exercise-induced bronchoconstriction (10), suggesting the activation of the leukotriene oxygenase pathway, whereas indomethacin can block refractoriness after asthma-producing exercise (11), pointing at the involvement of prostaglandin. Szczeklik suggested that, in aspirin-induced asthma, prostaglandin (PG) E_2 removal decreases the protection, which is achieved by suppression of mediator release from proinflammatory cells (12). By inhibiting the suppression of leukotriene release from eosinophils, bronchoconstriction will be generated. However, the presence of extrapulmonary symptoms in this case suggests that mast cells were involved. The difference between exercise-induced asthma and anaphylaxis precipitated by NSAIDs might be due to a more extensive involvement and different pattern of mediator cells in the latter case. In conclusion, it appears that intolerance or allergy to drugs may present as EIA.

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