

Short Communication

Safety of barley starch syrup in patients with allergy to cereals

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It is not known whether trace amounts of proteins that may remain in cereal-starch-derived food ingredients even after food processing can trigger allergic symptoms in cereal-allergic individuals. The aim of this study was to find out if barley starch syrup causes allergic reactions in patients with allergy to wheat, barley, rye or oats. Fifteen children with allergy to these cereals, confirmed by double-blind placebo-controlled food challenge (DBPCFC), were selected for the study. When exposed to cereals, seven of the children (47 %) showed immediate type reactions, such as urticaria, rash or anaphylaxis. Eight of the children (53 %) showed delayed type reactions, such as deterioration of atopic dermatitis or diarrhoea. The fifteen children with allergy to cereals were exposed to barley starch syrup in DBPCFC and none of them showed any objective signs of allergy. On skin-prick tests (SPT), five of the children (33.3 %) showed a positive (≥ 3 mm) reaction to at least one of the cereals but none of them to barley starch syrup. This study confirmed with 98 % confidence that at least 90 % of the patients with verified allergy to cereals will not react with allergic symptoms to barley starch syrup.

Barley starch syrup: Safety: Allergy to cereals

In contrast to coeliac disease where ingested gluten levels lower than 50 mg/d have been shown to be tolerated⁽¹⁾, no safety thresholds of exposure to cereal proteins have been established in allergy to cereals. Therefore, concern has arisen whether potential trace amounts of proteins in products derived from cereal starch could induce allergic symptoms in cereal-allergic subjects.

The prevalence of true food allergy and self-perceived adverse reactions to food show large discrepancies^(2–4). Epidemiological studies indicate that only about one third of perceived food reactions in children and 10 % of those in adults are due to food allergy, i.e. abnormal immunological reactions to food proteins⁽⁵⁾. Food allergy can manifest as immediate hypersensitivity responses, usually mediated by specific IgE antibodies to food proteins, or delayed type hypersensitivity reactions, mediated by T cells directed against food-derived peptides. In the worst case, food allergic reaction may generalise to several organs, leading to anaphylaxis.

Food allergies are most common among young children, affecting about 8 % of them⁽⁶⁾. Many food allergies disappear over time, as tolerance to the offending allergens develops⁽⁷⁾. Wheat is among the most common food items causing allergic reactions in early childhood⁽⁸⁾, and immune cross-reactivity has been shown between wheat, barley and rye⁽⁹⁾. In general,

wheat-allergic children react to lesser amounts of allergen than do adults⁽¹⁰⁾.

The aim of this study was to find out, using double-blind placebo-controlled food challenge (DBPCFC), which is the gold standard of food-allergy diagnosis, whether glucose syrup produced from barley (barley starch syrup) can cause allergic reactions in individuals with allergy to wheat, barley, rye or oats.

Materials and methods

Patients

Fifteen patients with allergy to at least one of the cereals wheat, rye, barley or oats, confirmed by DBPCFC, were enrolled in DBPCFC testing with barley starch syrup. The patients were recruited from the paediatric outpatient clinics in the catchment area of the Turku University Central Hospital. If allergy to the above cereals was proved by DBPCFC within 3 months before the first study visit, the patient was directly eligible for DBPCFC with barley starch syrup. Otherwise, the presence of allergy to wheat, barley, rye or oats was studied in DBPCFC before the subject underwent DBPCFC with barley starch syrup.

Clinical examination of the patient was carried out at each study visit. The diagnostic criteria of Hanifin & Rajka⁽¹¹⁾ were

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; SCORAD, scoring atopic dermatitis; SPT, skin-prick test.

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used to determine the possible presence of atopic dermatitis, and scoring atopic dermatitis (SCORAD) assessment⁽¹²⁾ to determine its severity.

The permission of the Ethics Committee of the Hospital District of South-western Finland was obtained for the study and informed, written consent was received from the participants and/or parents.

Double-blind placebo-controlled food challenge with wheat, barley, rye and oats

Water-based gruel prepared of a flour mixture containing wheat, barley, rye and oats (four-cereal gruel) in equal amounts was used in DBPCFC to detect the presence of cereal allergy. Water-based placebo gruel containing rice and buckwheat was mixed with the four-cereal gruel (1:1) in order to mask the appearance and taste of the latter. If the patient was known or suspected to be allergic to buckwheat, placebo gruel made of corn was used instead.

DBPCFC with the four-cereal gruel, masked with the placebo, was carried out after the cereals had been eliminated from the diet for at least 1 week. In DBPCFC, gruel containing four cereals and mere placebo gruel were served in randomised order. Increasing doses of 3 g, 15 g and 30 g of cereal in gruel were given at 20 min intervals, provided that no objective allergic symptoms appeared with the lower dose. The doses of 3 g, 15 g and 30 g of the four-cereal gruel contained 0.17 g, 0.85 g and 1.70 g protein, respectively. The subjects were monitored for immediate reactions in the study unit for at least 1 h after the last challenge dose, and if symptoms appeared, for as long as their clinical status required. If no immediate symptoms occurred, administration of gruel made with 30 g flour was continued at home twice daily, for a maximum of 5 d, to monitor the development of delayed type reactions. If any symptoms developed during the home-consumption period, the patient was advised to attend the study unit for a clinical assessment, and, if objective allergic symptoms were seen, the challenge testing was discontinued. If allergic symptoms developed with exposure to four-cereal gruel but not to placebo, the patient was judged as having cereal allergy to wheat, rye, barley or oats.

Double-blind placebo-controlled food challenge with barley starch syrup

DBPCFC with barley starch hydrolysate (isoglucose), Neste 70 FSS (Finnsugar Ltd, Jokioinen, Finland) and saccharose solution, Neste 67 S (Finnsugar Ltd, Kantvik, Finland) used as placebo, was conducted according to the regimens described earlier. Fresh test solutions were provided every 2 weeks, since the shelf life of the solutions was about 3 weeks. The test solutions came from the normal manufacturing line and represented the typical commercially available solutions. The N content of barley starch hydrolysate was regularly analysed by the Kjeldahl method. Ten lots were used for the study.

Three increasing doses of barley starch hydrolysate and saccharose solution, 5 g, 10 g and 15 g of both, were used in the challenges. Unless objective allergic symptoms occurred, administration of test solutions was continued at home, with 15 g twice daily, for a maximum of 5 d.

Skin-prick tests

To study IgE-mediated sensitisation, skin-prick tests (SPT) were carried out with wheat, barley, rye, oats (each as 10 % (w/v) in physiological saline), barley starch hydrolysate as undiluted standard foodstuff (Finnsugar, Kantvik, Finland) and 1 mg/ml gliadin, which is the major allergen of wheat⁽¹³⁾. Commercial cereal grains were milled to produce cereal flour for the allergen extract. Histamine dihydrochloride (10 mg/ml; ALK, Copenhagen, Denmark) was used as a positive control and physiological saline as a negative control. The perpendicular diameters of each SPT reaction were recorded after 15 min, and the results were expressed as mean wheal diameter. Mean wheal diameters ≥ 3 mm were considered positive.

Statistics

The data were analysed using SPSS 13.0 statistical software (SPSS Inc., Chicago, USA). In subjects with atopic dermatitis, the Friedman test was used to compare the mean of SCORAD indices during the barley starch syrup and placebo challenges, and the Wilcoxon signed ranks test was used to compare changes in SCORAD indices during the challenges.

Results

The age range of the study subjects allergic to wheat, barley, rye or oats was 0.9–13.8 years (median 2.1 years). Nine of them were boys. Table 1 shows the symptoms of the allergic patients induced by cereals, but not by placebo, in DBPCFC as well as the SPT results to cereals and gliadin. The diluent of the allergen solutions, saccharose and barley starch syrup gave negative results on SPT in all patients. Seven (47 %) of the patients showed immediate allergic reactions (within 1 h after the last dose at the study unit) in DBPCFC with cereals, and eight of them had delayed type reactions (later than 1 h after the last dose at the study unit). One patient experienced an anaphylactic reaction (generalised urticaria, abdominal pain and vomiting) after the first challenge dose of four-cereal gruel. He was treated with intramuscular epinephrine, oral prednisolone and antihistamine and recovered in a few hours.

After normal refining process the N content of barley starch hydrolysate was 1–30 mg N in 1 kg fresh-weight barley starch hydrolysate⁽¹⁴⁾. In DBPCFC with barley starch hydrolysate, none of the fifteen patients with allergy to cereals developed allergic symptoms. Regarding atopic dermatitis, the mean values of SCORAD indices showed no significant differences between barley starch syrup and placebo challenges. Neither did changes in SCORAD indices during the two challenge periods show any significant differences. The result of the study provided statistical power of 98 % certainty that at least 90 % of cereal allergic patients will not have any allergic reaction when exposed to barley starch syrup.

Discussion

In the present study, none of the cereal-allergic patients showed objectively detectable symptoms when exposed to barley starch syrup in a double-blind placebo-controlled manner. Notably, even the patient showing the most intense IgE-mediated

Table 1. Characteristics of the patients with allergy to cereals and their skin-prick test results with wheat, barley, rye, oats and gliadin*

Patient no.	Sex	Age (years)	Symptoms in DBPCFC with cereals	Skin-prick tests (wheal diameter (mm))					
				Histamine (10 mg/ml; positive control)	Wheat	Barley	Rye	Oats	Gliadin
1	F	4.5	Diarrhoea†, angioedema†	3.0	0	0	0	0	0
2	M	11.2	Itching and scratching of the lips and mouth†	4.5	5.5	4.5	6.0	2.0	2.0
3	M	1.1	Worsening of AD†	3.0	0	0	0	0	0
4	F	13.8	Abdominal pain†, diarrhoea†	4.0	0	0	0	0	0
5	M	2.0	Worsening of AD†, diarrhoea†	3.5	0	0	0	0	0
6	M	4.0	Anaphylaxis†	5.5	7.0	5.5	7.0	5.0	6.5
7	M	5.4	Worsening of AD†	4.0	0	0	0	0	0
8	M	2.1	Worsening of AD†, diarrhoea†	11.0	0	0	0	0	0
9	F	4.3	Rhinoconjunctivitis†, rash†	4.5	5.5	5.5	3.5	5.0	4.5
10	M	0.9	Worsening of AD†	4.0	0	0	0	0	0
11	F	1.4	Worsening of AD†	6.0	1.0	0	0	0	2.0
12	F	1.1	Urticaria†	6.0	5.5	6.0	9.5	0	6.0
13	M	3.7	Urticaria†	4.0	0	0	0	0	0
14	M	1.2	Rash†, vomiting†	4.0	6.5	9.0	7.0	2.0	1.5
15	F	1.5	Rash†	4.0	0	0	0	0	0

M, male; F, female; DBPCFC, double-blind placebo-controlled food challenge; AD, atopic dermatitis.

*For details see Materials and methods.

†Delayed-type allergic reaction, i.e. emerging after 1 h after the last challenge dose.

‡Immediate allergic reaction, i.e. emerging within 1 h after the last challenge dose.

sensitisation to cereals on SPT and having the most severe form of allergic reaction, anaphylaxis, when exposed to cereals, had no symptoms on the barley starch syrup challenge.

Barley starch syrup is a commercial product mainly used as a sweetener in non-alcoholic or alcoholic beverages, confectionery, bakery products and food sauces such as mustard and ketchup. In our study, the daily challenge dose of 30 g barley starch syrup was estimated to correspond to maximal daily consumption⁽¹⁴⁾. According to the laboratory assessments, this amount of barley starch syrup contains a maximum of 0.9 mg N, possibly as degradation products of lysophospholipids or derived from some unknown non-protein source⁽¹⁴⁾. However, using the generally accepted conversion factor of 6.25 for dietary N⁽¹⁵⁾, it can be calculated that 0.9 mg N equals 5.6 mg of protein. On this basis, it could be concluded that barley starch syrup is tolerated by coeliac patients, but its safety in cereal-allergic patients could not be determined without a clinical trial. The fact that none of the study patients showed positive SPT results with barley starch hydrolysate further confirmed the suggestion that barley starch hydrolysate does not contain any intact proteins or peptides, and the results of DBPCFC finally confirmed the safety aspect.

To our knowledge, NESTE 70 FSS is the only barley-starch based glucose syrup on the market. Instead, due to the higher starch content e.g. wheat is frequently used as a source of glucose syrup in the areas where climate conditions favour the growth of wheat. Low amounts of residual gluten and peptides (0.3–1.4 mg/kg) have been reported in wheat-starch based glucose syrup⁽¹⁶⁾.

Peanut oil is the most thoroughly studied among the processed food stuffs that may contain residual allergenicity. In the study of Olszewski *et al.*⁽¹⁷⁾ the residual proteins of peanut oil showed immunologic activity *in vitro* and positive SPT results in some individuals, but the implication of these proteins in clinical allergic reactions was not completely established in the absence of DBPCFC. In general, it is now concluded on the basis of several other well-defined studies that refined peanut oil can be safely consumed by peanut-allergic individuals, whereas unrefined oil can provoke reactions in some of the same individuals⁽¹⁸⁾.

In conclusion, this clinical study of ours confirmed the safety of barley starch syrup in at least the vast majority of cereal-allergic patients. Further studies are needed to address the same issue for several other foodstuffs derived from potentially allergenic sources.

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