

Recurrent Angioedema Due to Lysozyme Allergy

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■ Abstract

A 54-year-old woman suffered an episode of dyspnea and edema affecting her eyelids, tongue, and lips a few minutes after intake of Lizipaina (bacitracin, papain, and lysozyme). She was treated with intravenous drugs and her symptoms improved within 2 hours. She had experienced 3 to 4 bouts of similar symptoms related to the ingestion of cured cheeses or raw egg. Specific serum immunoglobulin (Ig) E against lysozyme was present at a concentration of 0.45 kU/L, and no specific IgE was found against egg white and yolk, ovalbumin, or ovomucoid. Skin prick tests were positive with commercial extracts of egg white and lysozyme but doubtful with yolk, ovalbumin, and ovomucoid. Prick-to-prick tests with raw egg white and yolk gave positive results, but negative results were obtained with cooked egg white and yolk and 5 brands of cheese (3 of them containing lysozyme and the other 2 without lysozyme). Controlled oral administration of papain, bacitracin, and cheeses without lysozyme was well tolerated. We suggest that the presence of lysozyme in a pharmaceutical preparation, cured cheese, and raw egg was responsible for the symptoms suffered by our patient, probably through an IgE-mediated mechanism.

Key words: Additives. Drug allergy. Food allergy. Hypersensitivity. Lysozyme.

■ Resumen

Mujer de 54 años de edad, que presentó un cuadro de disnea y edema de párpados, lengua y labios a los pocos minutos de tomar un comprimido de Lizipaina (bacitracina, papaína y lisozima). Fue tratada con medicación intravenosa, con mejoría en 2 horas. Refería 3-4 episodios similares previos asociados a la ingesta de queso curado o de huevo crudo. IgE específica para lisozima: 0.45 kU/L; negativa para clara, yema, ovoalbúmina y ovomucoide. Pricks con extractos comerciales de clara y lisozima positivos; dudosos con yema de huevo, ovoalbúmina y ovomucoide. Prick-prick positivo con yema y clara crudas y negativo con yema y clara cocidas y 5 marcas de quesos (3 sin lisozima y 2 con lisozima). La administración controlada de papaína, bacitracina y los quesos curados sin lisozima fue bien tolerada. Sugerimos que la lisozima incluida en el huevo, quesos curados y en un fármaco ha sido responsable de los síntomas sufridos por nuestra paciente y que el mecanismo responsable sería IgE mediado.

Palabras clave: Aditivos. Alergia a alimentos. Alergia a fármacos. Hipersensibilidad. Lisozima.

Introduction

Lysozyme (also known as muramidase) is an enzyme obtained from egg white. It is a polypeptide consisting of 129 amino acids and has a molecular weight of about 14 kilodaltons. Its lytic activity on the cell wall of gram-positive microorganisms has led to it being used for many years in pharmaceutical products (to increase the natural defenses of the body, to treat sore throats, for decontamination of contact lenses, in infant formulae, etc)

and in food applications (cheese and wine industry) [1,2]. However, hypersensitivity reactions to lysozyme have rarely been reported.

Case Description

A 54-year-old woman was referred to our department having suffered 5 months earlier an episode of dyspnea and edema affecting her eyelids, tongue, and lips a few minutes

after intake of a tablet of Lizipaina (3 mg bacitracin, 2 mg papain, and 5 mg lysozyme) for the first time. She was treated in the emergency department with unspecified intravenous drugs and symptoms improved within 2 hours. The patient denied previous administration of Lizipaina and stated that she had experienced 3 to 4 bouts of similar symptoms related to the ingestion of cured cheese or raw egg, in each case treated with parenteral drugs. She had avoided these foods, but tolerated cooked egg, fresh cheese, milk, and other dairy products. Other possible circumstances responsible for the reactions, such as physical exercise, simultaneous administration of other drugs, or infections were ruled out by the patient's history. The only difference in the composition of cheeses that were not tolerated by the patient was the presence of lysozyme (declared in the manufacturer's list of ingredients); the remaining ingredients had been ingested with no reactions.

Total immunoglobulin (Ig) E was normal (45 IU/mL). Serum specific IgE (CAP System, Pharmacia, Uppsala, Sweden) was found against lysozyme (0.45 kU/L) but was absent against egg white and yolk, ovalbumin, and ovomucoid. Skin prick tests with aeroallergens (pollens, mites, moulds, latex, cockroach, and cat and dog dander) and food allergens (cow's milk, cereal grains, nuts, fish, meat, crustaceans, molluscs, and fruits) were negative. The results of skin prick tests with commercially available extracts of egg white and lysozyme (10 mg/mL) were positive, while they were doubtful with egg yolk, ovalbumin, and ovomucoid (see table). Interestingly, 1 hour after the skin prick test with lysozyme the patient developed eyelid edema lasting 3 hours. Prick-to-prick tests with raw egg white and yolk gave positive results, but the results were negative with cooked egg white and yolk and with 5 brands of cheese (a mixture of goat, sheep, and cow's milk), 3 of them containing lysozyme and the other 2 without (see table). As lysozyme was included in egg, cured cheeses, and Lizipaina,

it seemed likely to have been responsible for the reaction. Therefore, we decided to perform controlled oral challenge with papain, bacitracin, and cheeses without lysozyme in the hospital after obtaining written informed consent. Only 1 challenge was carried out per day. We used commercial preparations containing papain (Digestomen Complex, containing papain, lipase, pancreatin, and pepsin; Menarini, Barcelona, Spain) and bacitracin (Phonal, containing bacitracin, benzocaine, neomycin and polymyxin b; Reig Jofre, Barcelona, Spain). The starting dose was a quarter of the therapeutic dose and then 2 more doses of a quarter and a half were administered at intervals of 30 minutes; all were well tolerated. Single-blind challenges with cheeses that did not contain lysozyme were performed with an initial dose of 100 mg, followed by 200 mg and 400 mg every 30 minutes. After that, an open challenge test was carried out: The patient ingested 1, 5, 10, 15, and 20 g every 30 minutes with no reactions. We did not perform challenge tests with cheeses containing lysozyme due to the severity of the reactions suffered by our patient.

Discussion

Hen egg-white proteins have traditionally been implicated in the development of food allergy. The major allergens reside in the egg white fraction, and ovomucoid (Gal d 1), ovalbumin (Gal d 2), conalbumin (Gal d 3), and lysozyme (Gal d 4) are responsible for the majority of the reactions [3]. Although some *in vitro* studies show that lysozyme binds significant amounts of IgE in the sera of egg-allergic patients, clinical reactions to lysozyme have rarely been reported [3,4]. A few case reports have described clinical reactions to lysozyme as a result of egg or cheese ingestion [2,4], aerosol inhalation (bakery or cheese workers, confectioners, pharmaceutical plant workers, and homemakers) [2,4-6], or medicinal preparations [7-9]. We report the case of an IgE-mediated hypersensitivity reaction to lysozyme. A diagnosis was established based on the patient's history and the results of prick tests and IgE measurement. Since diagnosis, the patient has avoided consumption of lysozyme and has not experienced angioedema. Since lysozyme was the common ingredient in a pharmaceutical preparation (Lizipaina), cured cheeses, and raw egg, it is likely to have been responsible for the episodes of severe edema suffered by our patient. As prick-to-prick testing with cheeses was negative, the evidence supporting the presence of lysozyme in the cheeses as having provoked the symptoms is only indirect (negative challenge with the cheeses without lysozyme and positive history with the cheeses with lysozyme). However, in our opinion it is highly likely to have been the cause, since lysozyme was the only difference between cheeses that were tolerated and those that were not tolerated.

It is noteworthy that the patient developed a systemic reaction after skin prick testing with lysozyme, a very rare complication of this procedure. The concentration used for skin prick tests (10 mg/mL) had been used previously in other studies without adverse reactions [6]. It has been demonstrated that even very small amounts of lysozyme can provoke allergic reactions (oral test with 3 mg or labial test with 1 mg/mL) [4]. The amount of lysozyme used in

Results of Prick Tests in a Patient With Suspected Lysozyme Allergy

	Wheal, mm	Erythema, mm
Histamine	7	12
Saline	0	0
Commercial extracts		
Ovalbumin	3	3
Ovomucoid	3	3
Egg white	10	16
Yolk	3	3
Lysozyme	20	27
Prick-to-prick		
Raw egg white	6	10
Raw yolk	6	9
Cooked egg white	0	0
Cooked yolk	0	0
3 cheeses with lysozyme	0	0
2 cheeses without lysozyme	0	0

foods varies from 250 to 400 mg/kg in cheese and 100 to 500 mg/kg in wine [2]. Such quantities are not negligible in patients sensitized to lysozyme. The proportion of lysozyme-specific IgE, among other egg protein-specific IgE, varies considerably from one individual to another, making the risk of allergy to these products unpredictable [4]. It is therefore of interest to identify sensitivity to lysozyme among individuals allergic to eggs in order to specify protective measures to prevent recurrent reactions. Patients must be advised to carefully read the list of food and drug ingredients looking for the presence of this enzyme, taking into account that lysozyme is sometimes identified as E1105 on food labels.

References

1. Lysozyme. [cited 2006 Sep 12] Available from: <http://www.greatvistachemicals.com/proteins-sugars-nucleotides/lysozyme.html>
2. Opinion of the scientific panel on dietetic products, nutrition and allergies on a request from the commission related to a notification from AMAFE on egg lysozyme used as additive in food pursuant to Article 6 paragraph 11 of Directive 2000/13/EC. [cited 2006 Sep 12]. Available from: http://www.efsa.eu.int/science/nda/nda_opinions/catindex_en.html
3. Walsh BJ, Hill DJ, Macoun P, Cairns D, Howden ME. Detection of four distinct groups of hen egg allergens binding IgE in the sera of children with egg allergy. *Allergol Immunopathol (Madr)*. 2005;33:183-91.
4. Fremont S, Kanny G, Nicolas JP, Moneret-Vautrin DA. Prevalence of lysozyme sensitization in an egg-allergic population. *Allergy*. 1997;52:224-8.
5. Anibarro Bausela B, Fontela JL. Occupational asthma in a cheese worker. *Allergy*. 1996;51:960-1.
6. Escudero C, Quirce S, Fernandez-Nieto M, Miguel J, Cuesta J, Sastre J. Egg white proteins as inhalant allergens associated with baker's asthma. *Allergy*. 2003;58:616-20.
7. Luvoni R. Two fatal cases caused by the first intramuscular injection of lysozyme [in Italian] *Minerva Medicoleg*. 1963;83:130-4.
8. Pichler WJ, Campi P. Allergy to lysozyme/egg white-containing vaginal suppositories. *Ann Allergy*. 1992;69:521-5.
9. Kobayashi M, Yamamoto O, Yasuda H, Asahi M. A case of toxic epidermal necrolysis-type drug eruption induced by oral lysozyme chloride. *J Dermatol*. 2000;27:401-4.

■ *Manuscript received September 25, 2006; accepted for publication January 17, 2007*

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