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Usefulness of oral macrogol challenge in anaphylaxis after intra-articular injection of corticosteroid preparation

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Key words: anaphylaxis; corticosteroid; macrogol; oral challenge.

Positive oral challenge with macrogol 4000 in a patient who experienced immediate hypersensitivity after intra-articular injection of corticosteroid.

Polyethylene glycols (or PEGs or macrogols) are polymers of ethylene oxide with molecular weight varying from 200 to $<10\,000$ daltons widely used as dispersing agents, solvents and excipients in the production of pharmaceutical preparations as well as in food and cosmetic industry. IgE-mediated anaphylaxis has been reported following shoulder infiltration with a corticosteroid solution containing macrogol 4000 (1). Other cases of anaphylaxis have been reported after ingestion of drug tablets containing macrogols of various molecular weights (i.e. 400, 1000, and 6000) (2, 3). An anaphylactic reaction has also been reported after ingestion of PEG solution (containing 50 g up to 200 g macrogol) before colonoscopy (4).

Although several cases of allergic reaction to macrogol have been reported, it is unclear whether the molecular weight and route of administration (parenteral *vs* oral) of macrogol could condition the allergic response in sensitized patients. Moreover, the use of macrogol oral challenge in patients with allergic response to parenteral preparation of macrogol has not been explored. Here, we report for the first time an immediate hypersensitivity reaction during an oral challenge with macrogol 4000 in a patient who experienced anaphylaxis after intra-articular injection of methylprednisolone acetas-lidocaini hydrochloridum (Depo-medrol lidocain®; Pfizer Manufacturing, Belgium).

A 44-year-old woman without previous history of allergy received an intra-articular infiltration of Depo-medrol lidocaine® (Pfizer Manufacturing Parrs, Belgium; 40 mg of methylprednisolone acetas and 10 mg of lidocaini hydrochloridum). Ten minutes later, she developed generalized urticaria, bronchospasm and systolic hypotension (arterial systolic blood pressure 75 mmHg). The patient was treated with volume loading, intravenous methylprednisolone (Solumedrol®), and oral H1-antihistamine. Her clinical condition improved and she was discharged from hospital 24 h after admission.

Three months later, skin tests were performed with various components of Depo-medrol lidocaine®. As shown in Table 1, the patient had a positive skin prick test with 0.4 mg/ml Depo-medrol lidocain and 0.1% preparation of macrogol 4000 while skin-prick tests with various macrogols gave negative results in seven non-allergic control volunteers. The patient had previously taken oral medications containing macrogol 4000 or 6000 as excipient without experiencing allergic manifestation. Therefore, a single blind placebo-controlled oral challenge test with macrogol 4000 was carried out with the patient's informed consent. After a negative labial test, the oral test was started with a dose of 1 mg of macrogol 4000 and the dose was increased at 30-min intervals. Thirty minutes after ingestion of a cumulative dose of 7.1 g (equivalent to the minimal dose contained in some osmotic laxatives) the patient developed palmo-plantar pruritus followed by edema of the lips, lids, feet, and hands. Hemodynamic parameters remained stable; she was administered an oral H1-antihistamine and i.v. corticosteroid.

The results of skin prick tests in our patient support an IgE-mediated allergic reaction induced by macrogol 4000. Cross-sensitization to macrogols with various molecular weights has been only occasionally investigated (3, 5). In the present case, skin prick testing with macrogols 400 and 1500/300 did not substantiate such a cross-sensitization phenomenon. In addition, the patient

Table 1. Results of skin tests

	Prick test	Intradermal test
Depo-medrol lidocain	+ (0.4 mg/ml)	ND
Methylprednisolone	–	–
Benzylic alcohol	–	–
Lidocaine†	ND	–
Macrogol 4000*	+ (0.1% solution)	ND
Macrogol 1500/300*	–	ND
Macrogol 400*	–	ND
Latex	–	ND

*Skin prick tests were performed using 0.01%, 0.1%, 1%, 10%, and 100% solutions of macrogol compounds (Pharminnova sa, Waregem, Belgium).
†S.c. lidocain provocation test was negative.

developed a hypersensitivity reaction during the oral challenge test with macrogol 4000 at a cumulative dose of 7 g. This raises the possibility that patients experiencing anaphylaxis after parenteral administration of macrogols may also develop allergic responses after ingestion of drugs containing these compounds. They should, therefore, be strongly advised to check systematically the composition of prescribed medications and they should avoid laxatives and colonoscopy preparations containing macrogol compounds. The findings in our patient also indicate that the amount of ingested macrogol is a critical factor for eliciting hypersensitivity reactions in sensitized patients. Accordingly, an oral challenge test should be considered for identifying the threshold reaction dose to recommend appropriate avoidance strategies to sensitized patients.

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Identification of vitellogenin as an allergen in Beluga caviar allergy

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Key words: allergy; beluga caviar; chicken egg; fish roes; vitellogenin.

Caviar is a valuable nutritious foodstuff taken from female sturgeon fish (*Acipenser* spp). Very little has been published on allergic reactions to caviar or other fish roe's species (1, 2). The aim of the study was to describe the first case reported of Iranian Beluga caviar allergy in Spain, identify allergens and study its cross-reactivity with other fish roes from salmon (*Salmo salar*), trout (*Salmo trutta*) and lumpfish (*Cyclopterus lumpus*), 'false' caviars from anchovy (*Engraulis mordax*) and salmon (*Salmo salar*) and chicken egg.

Iranian Beluga caviar allergy in Spain. Vitellogenin as the unique allergen involved in the allergic reaction.

We report the case of a 55-year-old woman who experienced two episodes of intense abdominal pain, followed by discomfort, nausea and diarrhoea within 10 min of intake of Beluga caviar. The patient had never had any food hypersensitivity before. She tolerates other allergenic foods.

Skin prick test (SPT) to the commercial battery of allergenic foods, including fish, shellfish, chicken egg and nuts (C.B.F. LETI, SA; Madrid, Spain) resulted negative. Skin prick test to aeroallergens were also negative (grass, trees and weeds pollen, mites, molds, cat and dog epithelia).

Skin prick–prick test were positive (5×10 mm wheal) to Iranian Beluga caviar extract (10% w/v), but negative to other fish roes (lumpfish, trout and salmon), 'false' caviars (anchovy and salmon), fish, shellfish, chicken egg and nuts. Because of the symptom's severity, the patient refused to undergo the oral challenge test with Beluga caviar.

Extracts from Iranian Beluga caviar, other fish roes, 'false' caviars and chicken egg were processed to obtain optimal *in vitro* diagnostic performance and to preserve antigens.

All extracts were fractionated by SDS-PAGE and used as antigens in immunoblot analysis (Fig. 1). A broad spectrum of IgE binding bands was detected ranging from 23 to 120 kDa (Fig. 1.1.B). IgE-binding bands were evaluated by Western blot (3). Serum from a nonallergic control individual was used as negative control (Fig. 1.1.C). Inhibition immunoblot with Beluga caviar extract and patient's serum demonstrated that the patient's serum indeed contained specific IgE to Iranian Beluga caviar (Fig. 1.1.D).

The IgE-binding bands from Iranian Beluga caviar were extracted from the gel, digested with trypsin, and the proteins were identified by mass spectrometry (MS) as previously described (4). Four out of six of these bands (marked with * in Fig. 1) were identified as vitellogenin by peptide mass fingerprinting (MALDI-TOF) when screened in the NCBI database. In addition three of the identified proteins were confirmed by MS/MS, obtaining the sequence of one peptide from each protein: FLQLTQLLR (m/z 1131 69) in C1 and C2 and LLINNNEIPLSQLPFTDSSGNIHIK (m/z = 2777.4) in C6 (Fig. 1). Thus, these protein bands are fragments of the same protein, vitellogenin (118 kDa) an egg yolk precursor protein expressed in female fish.

The IgE immunoblot of other fish roes, 'false' caviars and chicken egg showed no IgE-binding bands (Fig. 1.2.B). CAP-system to chicken egg was also negative (< 0.35 kU/l).

Allergy to fish roes has been reported (5, 6), even cross-reactivity among several of them (5). Vitellogenin has been described as allergen in chicken egg (Gal d vitellogenin); however, homology with caviar vitellogenin is low and cross-reactivity has not been found in this case report, as previously described (5, 6). Our patient eats eggs without any problem.