

Induction of Oral Tolerance to Peanut: A Successful Home-Based Protocol

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■ Abstract

In Spain, peanut allergy is increasingly prevalent. Successful protocols for the induction of oral tolerance (IOT) with several foods have been reported. We aimed to induce clinical tolerance to peanut in a child with severe peanut allergy (age 4 years, facial urticaria and lip angioedema upon licking a peanut; peanut skin prick test, 13×10 mm; specific immunoglobulin (Ig) E > 100 kU_A/L). At age 6, the threshold oral challenge dose was 62.5 mg. Several peanut solutions were prepared and sequentially administered at the patient's home. Over 138 days, the dose was increased from 0.625 to 5500 mg. There were 43 mild-to-moderate reactions (28% of the doses administered). Pre-IOT and post-IOT peanut IgE and IgG4 values were 265 vs 487 kU_A/L, and 6.11 vs 14.8 mg/L. This is the first report of successful IOT to peanut in Spain. This home-based regimen is safe under permanent and close medical supervision by an allergist.

Key words: Induction of oral tolerance. Peanut allergy. Desensitization. Home-based.

■ Resumen

En España, la alergia al cacahuete es cada vez más importante. Se han notificado protocolos de ITO con diversos alimentos con éxito. Nos propusimos inducir tolerancia clínica al cacahuete en un niño muy alérgico al cacahuete (a los 4 años urticaria facial y angioedema de labios al chupar un cacahuete; PC 13×10 mm; IgE específica > 100 kU/L). A los 6 años, la dosis umbral de provocación fue de 62,5 mg de cacahuete. Se prepararon varias soluciones de cacahuete que se administraron secuencialmente en el domicilio del paciente. Durante 138 días se aumentó la dosis de 0,625 a 5500 mg de cacahuete. Hubo 43 reacciones leves-moderadas (28% de las dosis administradas). Valores de IgE e IgG4 específicas pre y post-ITO: 265 vs. 487 kU/L y 6.11 vs. 14.8 mg/L. Esta es la primera notificación en España de ITO al cacahuete con éxito. Esta pauta domiciliaria es segura bajo la supervisión médica continua de un alergólogo.

Palabras clave: Inducción de tolerancia oral. Alergia a cacahuete. Desensibilización. Domiciliaria.

Introduction

Although not so marked as in the USA, allergy to nuts ranks fourth among food-induced allergies in the pediatric population in Spain [1]. Since the first publication in 1998 by Patriarca et al [2] on successful desensitization in children with allergy to cow's milk, there have been several reports (mainly with milk and egg), including a report by our group on milk allergy [3,4]. However, few protocols have been designed for induction of oral tolerance (IOT) to peanut [5-7]. We describe our experience with IOT to peanut in an extremely peanut-allergic child. To our knowledge, this is the first case of this type in Spain.

Case Description

In June 2004, a 4-year-old child presented at our clinic. Two months previously, he had experienced immediate swelling of the lips and facial urticaria, with no associated signs or symptoms, upon licking half a peanut (without chewing or swallowing). The reaction subsided spontaneously within a few hours. Prior to this reaction, the patient tolerated other legumes and nuts; however, hazelnut was forbidden in his diet after positive results in specific immunoglobulin (Ig) E determination performed at another clinic. There were no other allergic conditions and the family history only revealed that his mother was allergic to pollen. The results of the initial

Table 1. Initial Skin Prick Tests With Foods and Food Challenge Tests

Tested Food Allergens	SPT, mm	Specific IgE (kU _A /L)	Results of OOFc (Date Performed)	MTD
Peanut	13×10	> 100	Initially ND	
Chickpea	6×9	9.79	ST	
Lentil	3×3	4.48	ST	
Hazelnut	4×4	0.88	Neg (06/2006)	34 nuts
Sesame	ND	4.13	Neg (10/2006)	1½ teaspoonfuls
Lupine	ND	1.53	Neg (05/2007)	10 nuts
Cashew nut	ND	1.10	Neg (06/2008)	9 nuts
Macadamia walnut	ND	3.29	Neg (07/2008)	9 nuts
Other nuts and legumes	Negative		ST	

Abbreviation: Ig, immunoglobulin; MTD, maximum tolerated dose; Neg, negative; ND, not done; OOFc, open oral food challenge; RC, rhinoconjunctivitis; SPT, skin prick tests; ST, spontaneous tolerance.

Table 2. Summary of the Patient's Clinical Course Before and After IOT

	Apr/06	Jun/06	May/07	May/08	Sept/08	Feb/09
Clinical reactivity	Lip swelling and facial urticaria upon licking half a peanut					Perfect tolerance to 7 nuts daily
Eos/mm ³ , %			408 (6.3%)	490 (9.2%)		340 (3.5%)
SPT	13×10		20×7		12×6	
Total IgE, IU/L		877	550	612		2819
Specific IgE, kU _A /L		>100	>100	265		487
IgG4, mg/L		ND		6.11		14.8
Oral food challenge					Moderate-to-severe abdominal pain, plus nausea and vomiting 20 minutes after taking 62.5 mg of peanut	Perfect tolerance to 7 peanuts
IOT to peanut					Start (25/09/08) 0.625 mg of peanut	End (21/02/09) (5500 mg; Δ 88-fold)

Abbreviations: Eos, eosinophils; Ig, immunoglobulin; IOT, induction of oral tolerance; ND, not done

allergy workup for inhalant allergens showed positive results for olive, grass, and *Cupressus arizonica* pollen, as well as for dog and cat dander, although the patient had no related symptoms other than grass pollen allergy during the spring of 2007. The results of skin prick testing (SPT) for foods (ALK-Abello Laboratories, Madrid, Spain) and specific IgE and IgG4 (Phadia Diagnostics, Uppsala, Sweden) and subsequent open oral challenge tests performed with nuts during June 2006-July 2008 are summarized in Table 1. The results of follow-up are summarized in Table 2.

In view of the 4-year experience and good results our group had obtained with IOT to cow's milk, the parents asked us to induce tolerance to peanut in their son. After reviewing the literature [5] and obtaining written informed consent, we decided to initiate IOT to peanut in June 2008.

For the purpose of the oral challenge test and potential IOT, an initial peanut solution (solution A) was prepared by whisking 500 g of roasted peanuts (Aperitivos Medina S.L., Madrid, Spain; 29.7 g of peanut protein/100 g of peanut, according to the nutritional information provided by the

manufacturer) and mixing them in 100 mL of water (500 mg/mL). Solution A was diluted by half and 1/40 to obtain solutions B and C (250 mg/mL and 12.5 mg/mL, respectively).

In September 2008, an open challenge test was performed in the intensive care unit with solution C, which was positive at 5 mL (62.5 mg of peanut; Table 2). The reaction resolved after administration of 3 mL of dexchlorpheniramine maleate syrup. Three days later, IOT was administered following a regimen starting with a 0.625-mg dose and reaching a maximum 50 000-mg dose within 54 days. The regimen was based on our clinical and home-based protocol with cow's milk, which provided good efficacy and safety results, namely, complete tolerance in 25/30 subjects with no severe reactions. Cetirizine syrup (5 mL/d) was administered concomitantly, and peanut doses were given daily once the patient had returned from school and was resting at home. The parents had been trained in identifying and managing potential adverse reactions. A 24-hour telephone line was available to contact an allergist from our team whenever necessary. The initial dose of every peanut dilution and any other problematic doses were administered at our clinic, where the patient remained under observation for 2 hours.

The IOT course is shown in the Figure. Briefly, the maximum dose of peanut administered was 5500 mg (11 mL of solution A), because the parents found this amount sufficient to prevent adverse reactions upon inadvertent peanut ingestion in situations such as birthday parties or restaurants. Therapy was extended to 138 days. A new open challenge was performed

with whole nuts, until day 139, when the patient was able to tolerate 7 nuts (approximately 5000 mg of peanut). From days 140 to 152, concomitant medication was progressively withdrawn, and, since then, the patient has tolerated 7 nuts daily. The immunological data are shown in Table 2.

With regards to the safety of the regimen, 43 reactions (28% of the doses administered) were recorded. According to the classification of Malling et al [8], 74.4% of the reactions were grade 1 (unspecific or mild symptoms) and 25.6% were grade 2 (moderate symptoms such as abdominal pain or vomiting). We did not encounter anaphylactic reactions (grade 3) or anaphylactic shock (grade 4). The symptoms were headache (13 occasions), abdominal pain (26), nausea (3), vomiting (8), and red eye (1). All the reactions occurred 20-90 minutes after receiving the dose. During the IOT course, the cetirizine dose was doubled (5 mL bid; day 106), and metoclopramide hydrochloride (2 mg 1 hour prior to the IOT dose; day 120) was added to prevent abdominal symptoms. The parents managed all the reactions properly by consulting with the allergist by telephone and did not have to attend the emergency room.

Discussion

To date, there have been 3 publications on IOT to peanut [5-7]. The first, by Patriarca et al [5] in 2006, reported the case of a 38-year-old woman with a 10-year history

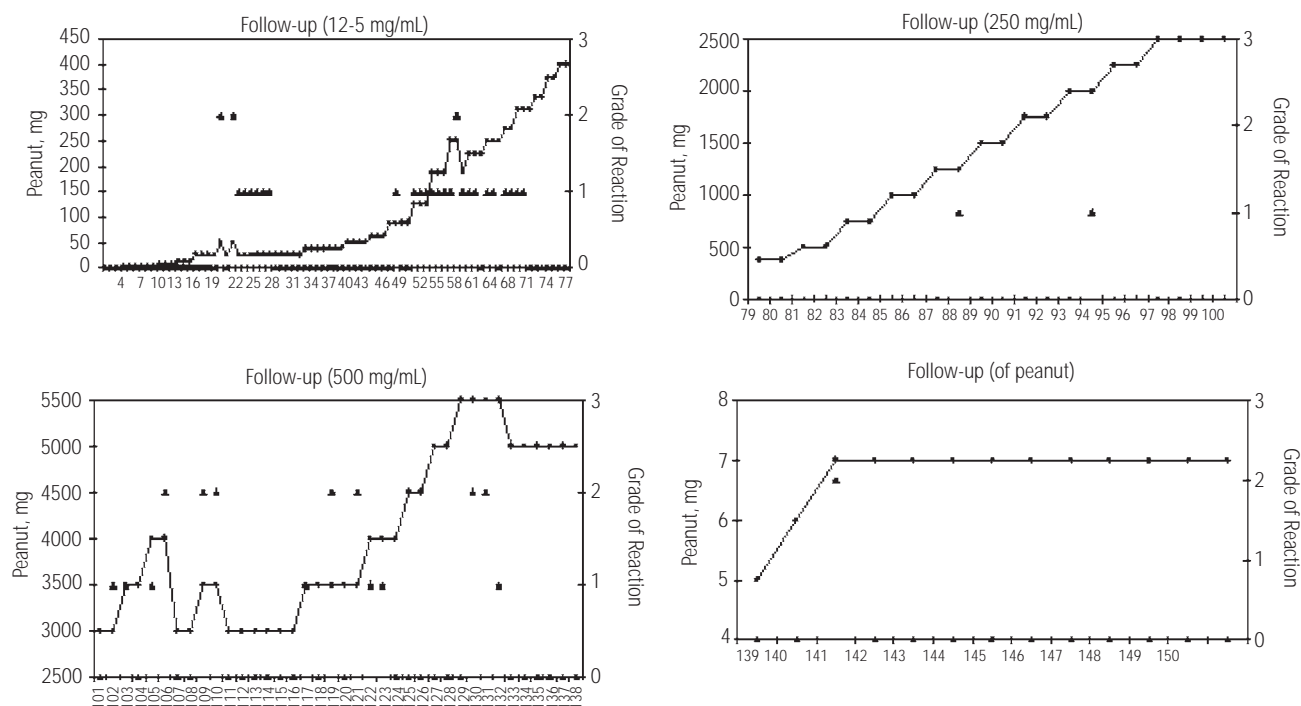


Figure. Follow-up of the updosing regimen with the different peanut solutions (see text). Continuous dotted line indicates increasing daily doses of peanut (in mg of peanut). Single triangles indicate the grade of the reactions encountered according to Ref. 8: grade 0, no reaction; grade 1, nonspecific or mild; grade 2, moderate.

of abdominal symptoms after eating peanuts and mild-to-moderate sensitization (baseline specific IgE, 2.13 kU_A/L; positive oral challenge test with 5 g of peanut). The authors induced tolerance to 40 g of peanut with a 7-day hospital-based regimen and concomitant use of loratadine (10 mg/d) and ranitidine (300 mg/d), with no adverse reactions. The result of SPT with peanut became negative, IgE values decreased, and no changes were observed in post-IOT specific IgG4 values.

More recently, Clark et al [6] described 4 children (aged 9-13 years) with varying degrees of peanut allergy (specific IgE, 6.4->100 kU_A/L; threshold challenge dose, 5-50 mg of peanut protein). The novelty of their regimen was that it started from the dose inducing a reaction at the food challenge test. The dose was doubled weekly on the hospital ward and maintained daily thereafter at the patient's home. The least sensitized patient tolerated the regimen without adverse events, whereas the other 3 had varying degrees of adverse reactions (none of them severe). The dose increased 48-478-fold from baseline to the end of therapy. In our case, the dose increased 88-fold. The authors did not comment on immunological parameters.

Finally, in the largest series published to date, which used a different protocol design, Jones et al [7] induced tolerance to 300 mg of peanut as a maintenance dose in 29 out of 39 children enrolled. Thereafter, 27/29 (93%) children tolerated 3.9 g of peanut at the open food challenge performed after 4-22 months on the maintenance dose. Thorough immunological workups showed this induction of clinical tolerance to be accompanied by significant changes such as a decline in wheal size after SPT for peanut and in basophil counts at 6 months, a decline in specific IgE values by 12 to 18 months, and significant increases in specific IgG4 values and in secretion of interleukin (IL) 10, IL-5, interferon γ , and tumor necrosis factor α from peripheral blood mononuclear cells, together with downregulation of genes in apoptotic pathways. Most of the patients (93%) experienced some kind of symptoms during the escalation phase; however, fewer patients experienced symptoms during the build-up phase (46%) and home-dosing phase (3.5%) [9].

As for the changes in immunological parameters seen in our patient (Table 2), although most studies on food IOT report no significant changes in specific IgE values and notable increases in specific IgG4 values [10,11], based on our experience with IOT to cow's milk (data not published), one can observe an initial increase in specific IgE, followed by a subsequent decline and an initial mild increase in specific IgG4 followed by more notable increases. In general, individuals who achieve higher IgG4 levels acquire better tolerance; however, a light variation in specific IgG4 values does not preclude acquiring good tolerance, as shown in the present case. We expect to see similar results to those published by Jones et al [7] at the one-year follow-up visit of this patient.

Conclusions

We present the case of a severely peanut-allergic child who achieved successful food tolerance to a dose that was high enough to prevent adverse reactions upon inadvertent ingestion of peanut or peanut-containing foods, with the

subsequent improvement in the quality of life of the patient and his relatives. Although the regimen took longer than initially expected, it proved to be safe, with no severe adverse reactions or need for systemic corticosteroids or epinephrine. IOT with whole food is an emergent treatment that is proving to be an effective alternative to the traditional practice of food avoidance. While IOT protocols may vary, they all generally show good efficacy and acceptable safety results. Selecting one or another regimen should be based on the safety and efficacy profile, although the organizational capabilities of the patient and the center carrying out the treatment should also be taken into account. These approaches should always be applied by specifically trained physicians.

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