Allergy 2009 DOI: 10.1111/j.1398-9995.2009.01982.x

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DOI: 10.1111/j.1398-9995.2009.01982.x

Short communication

Successful oral tolerance induction in severe peanut allergy

Background: Peanut allergy is common, potentially severe and rarely resolves causing impaired quality of life. No disease-modifying treatment exists and there is therefore a need to develop a therapeutic intervention.
Aims of the study: The aim of this study was to investigate whether peanut oral immunotherapy (OIT) can induce clinical tolerance to peanut protein.
Methods: Four peanut-allergic children underwent OIT. Preintervention oral challenges were performed to confirm clinical allergy and define the amount of protein required to cause a reaction (dose thresholds). OIT was then administered as daily doses of peanut flour increasing from 5 to 800 mg of protein with 2-weekly dose increases. After 6 further weeks of treatment, the oral challenge was repeated to define change in dose threshold and subjects continued daily treatment.
Results: Preintervention challenges confirmed peanut allergy and revealed dose thresholds of 5–50 mg (1/40–1/4 of a whole peanut); one subject had anaphylaxis during challenge and required adrenaline injection. All subjects tolerated immunotherapy updosing to 800 mg protein and i.m. adrenaline was not required. Each subject tolerated at least 10 whole peanuts (approximately 2.38 g protein) in postintervention challenges, an increase in dose threshold of at least 48-, 49-, 55- and 478-fold for the four subjects.
Conclusions: We demonstrated a substantial increase in dose threshold after OIT in all subjects, including the subject with proven anaphylaxis. OIT was well tolerated and conferred protection against at least 10 peanuts, more than is likely to be encountered during accidental ingestion.

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Key words: anaphylaxis; desensitization; food allergy; immunotherapy; peanut.

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Accepted for publication 12 December 2008

Peanut allergy is common, affecting up to 2% of young children in the UK (1), and unlike other common childhood food allergies (e.g. to cow's milk), it rarely resolves. The quality of life of the affected families is reduced because of constant fear over food choices and the likelihood of anaphylaxis. Despite the current best management to provide advice on avoidance of peanut and emergency medication including treatment plans, a significant proportion of children continue to have accidental reactions each year, of which some of them are severe (2).

There is a recognized need to develop a disease-modifying therapy for peanut allergy (3). Oral immunotherapy (OIT) is being investigated for the treatment of persistent hen's egg and cow's milk allergy, with some success (4). We investigated OIT as a treatment for peanut allergy.

Method

This study was approved by the Local Research Ethics Committee and each family gave informed consent. We enrolled four male children aged 9–13 years with suspected peanut allergy. Two subjects reported accidental reactions to peanut prior to the study. Skin prick tests were performed (peanut extract; ALK-Abello, Madrid, Spain), and serum was analysed for peanut-specific IgE (CAP-system FEIA; Phadia, Uppsala, Sweden).

Double-blinded placebo-controlled food challenges (DBPCFC) were performed according to an international consensus statement (5). Placebo and active (peanut flour) doses were administered on separate days and dose intervals were at least 30 min. Challenge doses included 1, 5, 25, 50, 75 and 100 mg of peanut protein. If DBPCFCs were negative, open challenges up to a higher cumulative dose were performed (12 weighed peanut kernels). Preintervention challenges were used to both confirm the presence of clinical allergy to peanut and identify the amount of protein required to cause a reaction (dose threshold).

All subjects were provided with oral antihistamines, adrenaline injection and a treatment plan, with training. Oral immunotherapy was administered as daily oral doses of peanut flour (50% protein, light roast; Golden Peanut Company, Alpharetta, GA, USA) mixed with yoghurt – see Table 1 for dosing schedule. Starting doses were chosen based on the pre-OIT threshold and perceived clinical severity. All challenges and dose increases took place in the Wellcome Trust Clinical Research Facility, Cambridge and subjects were observed for at least 2 h. Doses were then taken at home once daily for 2 weeks, followed by further updosing on the research ward. Doses were approximately doubled at each step to a maximum of 800 mg of peanut protein/day (1600 mg flour – see Table 1). At the final updose, subjects were given the choice of continuing to take peanut flour or 2.5 ml of smooth peanut butter daily (800 mg protein).

Table 1. Pre- and postoral immunotherapy (OIT) challenge results and updosing schedule

Subject #	1	2	3	4
Age (years)	12	13	9	13
SPT (mm)	8	5	6	5
Peanut IgE (kU/l)	>100	>100	16.1	6.4
Pre-OIT challenge				
Pre-OIT challenge threshold*	5 mg	50 mg	50 mg	50 mg
Symptoms/signs	AP/OI/E/N	Anaphylaxis	U/NV/E	AP/RC
Protein (mg)	Oral immunotherapy			
5	✔OI			
6		✔E/AP		
12	✔OI/N/AP	✔E/U/RC		
25	✔RC/V	✔E/RC		✔
50	✔	✔RC	✔RC	✔
75		✔		
100	✔	✔	✔RC	✔
200	✔	✔RC/OI	✔	✔
300		✔		
400	✔		✔	✔
500		✔		
800	✔	✔AP	✔	✔
Postintervention challenge				
Highest tolerated dose†	12 peanuts = 2.39 g	10 peanuts = 2.38 g	12 peanuts = 2.76 g	12 peanuts = 2.47 g
Increase in threshold	478×	48×	55×	49×

AP, abdominal pain; OI, oral itching; E, erythema; N, nausea; V, vomiting; U, urticaria; RC, rhino conjunctivitis; A, angio-oedema; SPT, skin prick test wheal diameter (mm).
✔indicates that dose has been eventually tolerated.
*Challenge thresholds are the smallest amount of peanut protein required to cause a reaction during each challenge.
†Highest dose of peanut protein tolerated during the final challenge; expressed as the number of ingested peanuts and the actual weight of peanut protein (g).

Six weeks after the final updose to 800 mg protein, subjects underwent an open postintervention challenge to 2.38–2.76 g peanut protein (approximately 12 whole peanuts). The highest tolerated dose was compared with the initial dose threshold defined by preintervention challenge. Dosing intervals were at least 30 min. After the final challenge, subjects continued to take 800 mg peanut protein per day, either as 1.6 g peanut flour, 2.5 ml smooth peanut butter, or five whole roasted peanuts as maintenance.

Results

All subjects had a history of eczema (still active in subjects 2 and 3), positive peanut skin prick test (range 5–8 mm wheal diameter) and positive peanut serum-specific IgE (range 6.4 to >100 kU/l). Preintervention challenges revealed a spectrum of clinical severity between subjects (Table 1). Subjects 1, 3 and 4 experienced generalized reactions and were treated with oral antihistamines alone. Subject 2 developed anaphylaxis during initial challenge, with sudden onset of severe abdominal pain, wheezing, breathlessness and a fall in peak expiratory flow rate (370 l/min, reduced to 300 l/min). Intramuscular adrenaline (500 μg), nebulized salbutamol (5 mg), i.v. chlorphenamine (10 mg) and i.v. hydrocortisone (100 mg) were administered. The preintervention challenges also defined dose thresholds for each subject (5–50 mg protein; for comparison, one peanut contains approximately 150–200 mg protein), to compare with thresholds elicited during the postintervention challenge. One subject (#3) had a negative DBPCFC and positive open peanut challenge, which elicited rapid onset objective signs (vomiting and generalized urticaria). The time interval between initial challenge and commencement of OIT was 17, 74, 6 and 5 days for subjects 1–4 respectively.

The intervention (OIT) was well tolerated (see Table 1) with no reported severe reactions and i.m. adrenaline was not required. In general, if symptoms occurred, they would be present for <1 h after a dose increase and would be observed again after the next 2–3 doses. Subsequent doses were tolerated. When mild reactions occurred, subjects were advised to continue taking the current dose. On two occasions, subjects experienced mild abdominal pain whilst taking a previously tolerated dose. This was associated with the subject being tired (e.g. woken up from sleep to take the dose) or performing vigorous exercise within 1 h of taking the dose. All subjects completed updosing to a maximum 800 mg protein/day and continued to tolerate this daily dose for 6 weeks (an increase in dose threshold of 16- to 160-fold).

During the final open challenge, subjects 1, 3 and 4 tolerated 2.39, 2.76 and 2.47 g peanut protein, respectively (equivalent to 12 peanuts each), without reaction giving an increase over their pre-OIT challenge threshold of at least 49–478 fold. Subject 2 tolerated 2.38 g protein (equivalent to 10 peanuts) without any reaction but developed mild abdominal pain after ingesting a further 0.52 g of peanut protein (two peanuts), showing an increase in dose threshold of at least 48-fold.

Conclusions

Thus, a substantial improvement in the tolerated dose occurred in all subjects (48- to 478-fold), including the subject with anaphylaxis on initial challenge. In all four subjects, OIT conferred protection against at least 2.38 g peanut protein (10 peanuts), more than is likely to be encountered during accidental ingestion. In three subjects, it was not possible to provoke a reaction post-OIT despite challenge to 2.39–2.76 g protein (12 peanuts). The dose tolerated in the final challenge was two to three times greater than the maximum maintenance OIT dose. However encouraging, these results are preliminary and peanut OIT should not yet be attempted outside clinical trials.

This intervention would be most valuable to children with severe peanut allergy and/or low dose thresholds. In this study, OIT with home dosing was well tolerated by a

child with anaphylaxis and a child with a very low dose threshold (5 mg protein). Our data should provide reassurance for researchers considering whether to include such children in future studies. In our view, it is important that the treatment effect and safety be defined for children with high severity and/or low thresholds by larger studies.

Each subject is currently tolerating approximately 800 mg protein (five peanuts) per day, and can tolerate at least double that amount on oral challenge. Tolerance may be lost if subjects were to stop OIT at this stage, and it is likely that long-term maintenance is required, as for other forms of immunotherapy. Follow-up studies are therefore required to examine the duration and frequency of maintenance therapy required to induce long-term tolerance.

Acknowledgments

We are grateful to the Evelyn Trust, Cambridge for funding this study. We would like to acknowledge the staff of the Cambridge Wellcome Trust Clinical Research Facility where the research was carried out. We thank the Golden Peanut Company for providing materials and finally, we are indebted to Professor Wesley Burks from Duke University, NC, USA for his invaluable help and advice in developing the immunotherapy protocol.

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