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Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges

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Summary

Background The prevalence of food anaphylaxis due to masked allergens has increased within the last 10 years. Contamination of manufactured products by food allergens is a key concern for food industries.

Objective To determine quantities eliciting reactions in patients who have an IgE-dependent food allergy, thanks to standardized oral provocation tests. To evaluate the subsequent levels of sensitivity required for the detection tests of allergens for egg, peanut, milk and sesame.

Methods Prick-in-prick tests, Cap system RAST, and single or double-blind placebo-controlled food challenges (SBPCFC or DBPCFC) were performed. The doses of natural food were gradually increased from 5 to 5000 mg for solid food and from 1 to 30 mL for peanut oil, sunflower oil, soy oil and sesame oil.

Results Data from 125 positive oral challenges to egg, 103 to peanut, 59 to milk and 12 to sesame seeds were analysed. Haemodynamic modifications were observed in 2%, 3%, 1.7%, and 8% of the oral challenges (OCs) to egg, peanut, milk and sesame, respectively. Respiratory symptoms were observed in 12%, 20%, 10% and 42% of egg, peanut milk and sesame allergies, respectively. A cumulative reactive dose inferior or equal to 65 mg of solid food or 0.8 mL of milk characterized 16%, 18%, 5% and 8% of egg, peanut, milk and sesame allergies, respectively. 0.8% of egg allergies, 3.9% of peanut allergies, and 1.7% of milk allergies reacted to 10 mg or less of solid food or to 0.1 mL for milk. The lowest reactive threshold has been observed at less than 2 mg of egg; 5 mg of peanut, 0.1 mL of milk and 30 mg of sesame seed. Ten out of 29 OC with peanut oil, two out of two OC with soy oil and three out of six OC with sunflower oil were positive. Five out six OC with sesame oil were positive: 1 and 5 mL induced an anaphylactic shock.

Conclusion The risk of asthma and anaphylactic shock to sesame and peanut is confirmed. Minimal reactive quantities show that, in order to guarantee a 95% safety for patients who are allergic to egg, peanut and milk, and on the basis of consumption of 100 g of food, the detection tests should ensure a sensitivity of 10 p.p.m. for egg, 24 p.p.m. for peanut and 30 p.p.m. for milk proteins. Oil allergies being considered, the limit of sensitivity should fall to 5 p.p.m.

Keywords cow's milk allergy, DBPCFC, egg, food allergy, peanut, risk assessment, sesame, oil, threshold
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Introduction

The prevalence of food allergies has steadily increased within the last 10 years. It affects 3.24% of the whole French population [1]. Five to eight per cent of the paediatric population could be affected [2], 1.1% of the US population, 0.61% of children and 0.48% of adults in GB are allergic to peanut or other nuts [3, 4]. Present concerns focus upon serious accidents of food anaphylaxis [5–8]. The risk of recurrent reactions cannot be totally prevented by strict management plans [9]. It is essential to identify those patients mostly at risk in order to prevent recurrent and potentially lethal accidents.

What determines the amount of food needed to induce a clinical reaction is important. Indeed, the lower the amount, the more predictable the risk of accident to a masked allergen. Fatal accidents from tiny amounts of food have been reported [10]. The risk of accidents caused by contamination of manufactured products is a major concern for food industries. The tests aimed at detecting food contaminating proteins are put forward, but the level of sensitivity has to be evaluated according to the thresholds of clinical reactivity.

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Indeed, knowing the minimal reactive doses as well as the amount that is currently consumed would make it possible to determine the tolerance level of contamination.

Standardized oral challenges (OCs) can be used to determine the reactive dose of food in IgE-dependent allergies. In this type of allergy, symptoms induced by OC are generally observed within 30 min. The administration of increasing amounts along a scale of doses then allows the determination of reactive doses [11, 12].

This study is aimed at determining thresholds of clinical reactivity in a large series of patients with IgE-dependent allergies to milk, egg, peanut and sesame seeds. It provides data on the lowest doses triggering allergic reactions.

Methods

Patients

Patients presenting classical manifestations leading to the suspicion of food allergies: anaphylactic shock, angioedema, urticaria, asthma, vomiting, diarrhoea, atopic dermatitis, oral syndrome, rhinitis and conjunctivitis [13].

IgE-dependent sensitization is established by prick-in-prick tests with native foods [14] and/or RAST Cap System Phadebas®.

The diagnosis of food allergy relies on positive single- or double-blind placebo-controlled food challenges (SBPCFC or DBPCFC): one hundred and twenty-five to egg (123 children and two adults), 103 to peanut (91 children and 12 adults), 59 positive OC to milk (52 children and seven adults) and 12 to sesame seeds (three children and nine adults).

Oral challenge methodology

Oral challenges were carried out according to the procedure including placebo, food and single-or double-blind tests [12, 15, 16], with the informed consent of the patients or of their parents. Stewed apples or mashed potatoes are commonly chosen as placebo since they are not allergenic (rare cases excepted, but not encountered in this series). Dried biscuit powder may be included to simulate crushed peanut or sesame seeds. The food is hidden in the vehicle, i.e. the placebo. The tested food are a milk without lactose (O-lac®, Mead Johnson, NY, USA), raw egg white, roasted crushed peanuts, crushed sesame seeds and different vegetal oils bought in a supermarket. Peanut oil, sunflower and soy oil are heat-treated, refined oils. The amount of protein in refined peanut oil is estimated to be between 0.1 and 0.2 μg/g [17]. For refined sunflower oil and refined soy oil, the amounts are, respectively, 0.22 μg/mL [18] oil and 0.32 μg/mL [19]. Sesame oil is a crude commercial oil. The quantities of proteins in non-refined oils are estimated to be between 3 and 13 μg/g [20]. The quantities in crude sesame oil are probably similar or equivalent.

A scale of increasing amounts of milk or solid foods was used: each dose is given every 20 min during a period of 3 h. For solid foods, a first progression comprises the following doses: 5, 10, 50, 200 and 700 mg. The cumulative dose (CD) is 965 mg. The second progression is 10, 100, 500, 1500 and 5000 mg (CD: 7110 mg). A negative result of the challenge led to testing of higher amounts: 10 and 20 g. For milk, the first series corresponded to 0.1, 0.2, 0.5, 1.5 and 4.5 mL (CD: 6.8 mL), the second series corresponded to: 1, 2, 5, 15 and 40 mL (CD: 63 mL) and the third series corresponded to: 10, 20, 50 and 150 mL (CD: 230 mL). OC with oils were carried out on 2 days (vegetal oil and paraffin oil as placebo, at 24-h intervals) and 1, 5, 10 and 15 mL were successively tested. The time interval between the three progressions was 24 h.

Monitoring of oral challenges

Pulse, blood pressure (BP), breath sounds, peak flow rate (PFR) and any skin and/or mucosae colour modifications were observed every 20 min, during 12 h. The clinical score for atopic dermatitis (SCORAD) was calculated 8 and at 24 h later [21].

Criteria of positivity

Objective clinical signs were taken into account: tachycardia, drop in BP (= 3 points) urticaria, angio-oedema, audible wheeze, cough, drop in PFR or forced expiratory volume (FEV) > 20%, rhinorrhoea, conjunctival redness, diarrhoea, vomiting, immediate rash on eczema and delayed exacerbation of eczema (SCORAD increase of 10 points at least).

Abdominal pain is the single subjective criterion considered in children (see the discussion).

Clinical reactions monitoring

Objective manifestations were treated by epinephrin, IV crystalloid solutions infusion, β-adrenergic agents and ipratropium aerosols, corticosteroids and anti-H1 drugs, according to the nature of symptoms.

Determination of the thresholds of the reactive foods

The threshold of reactivity is defined as the addition of the doses ingested previously referred to as the cumulative reactive dose (CRD). Special attention was paid to the lowest observed immuno-allergic effect levels (LOAEL) according to Taylor et al. [22]. The patients were classified consecutively according to these CRD = 15 mg; from 15 to 65 mg; from 65 to 965 mg and from 965 to 7110 mg. For milk, the CRD levels were: 2.3; 2.3 to 6.8; 6.8 to 23; 23 to 63; 63 to 200 mL.

The equivalent quantities of proteins were calculated for each food according to the information provided by biochemical data.

Results

Serious clinical reactions were observed for the four allergens, with a significant occurrence of asthma during DBPCFC to sesame ($P<0.02$) (Table 1). Isolated abdominal pain characterized 3.3% of the positive PCFCs.

A threshold inferior or equal to 65 mg of solid food or 0.8 mL of milk, characterized 16% of egg allergies, 18% of peanut allergies, 8% and 5% of milk and sesame allergies, respectively.

A low threshold inferior or equal to 15 mg of solid food or 0.3 mL of milk was observed in 5.6% of egg allergies, 3.9% of

Table 1. Percentage of PCFCs with serious clinical reactions

Food	Positive PCFC	Drop in BP and/or tachycardia *n*	(%)	Asthma and/or ↓ FEV *n*	(%)
Egg	124	3	2	15	12
Peanut	103	3	3	21	20
Milk	59	1	1.7	6	10
Sesame	12	1	8	5*	42*

*χ^2: $P<0.02$, compared to OC to milk or egg.
PCFCs, placebo-controlled food challenges; BP, blood pressure; FEV, forced expiratory volume.

peanut allergies and 1.7% of milk allergies (Tables 2–4). The lowest reactive threshold was observed at less than 2 mg of crude egg white, 5 mg of peanut (four cases), 0.1 mL of milk and 30 mg of sesame seed.

Up to 30 mL peanut oil, sesame oil, soy and sunflower oils were tested. Ten out of 29 OC with peanut oil were positive; five of them were positive to a CRD of 5 mL. Five out of six OC with sesame oil were positive. One mL and 5 mL induced an anaphylactic shock (AS) in two patients. 2/2 OC with soy oil and 3/6 OC with sunflower oil were also positive (Table 5).

Discussion

Objective signs were taken into account, according to the general consensus [23–25]. Some authors propose subjective signs if the double-blind method is carried out [16]. However subjective signs such as pruritus, metallic taste, tingling and dizziness are often linked to stress conditions, either with placebo or with food. This is the main reason for selecting only objective signs, with the exception of abdominal pain in young children (3.3% of cases). In the latter case, the child stops playing, his face tenses, loses colour and then cries because of abdominal pain. Carrying on with incremental dose constantly induces gastrointestinal signs and wheezing or asthma. The risk of severe reactions can be postulated when PCFCs induce serious symptoms [5]. The risk of AS is foreseeable when a drop in BP and a tachycardia are observed, pointing to the major risk of sesame allergy. On the other hand, a fall of PFR and audible wheeze occurring during OC are worth considering since most lethal reactions are due to acute asthma [5, 7, 8]. The data confirm risk being twice as high for peanut as for milk and egg. Asthma induced by sesame could be even more severe. Sesame allergy is not frequent, but its potential severity must be emphasized.

A severe food allergy may occur when OC are positive with CRD inferior to 65 mg of solid food and 1 mL of milk. These quantities are equivalent to 6.5 mg egg proteins, 16 mg peanut proteins, 32 mg milk proteins and 12.3 mg sesame proteins [26]. This represents 16% of egg allergies, 18% of peanut allergies and 5% of milk allergies (Table 6). Sicherer et al. [3] reported that 11% of egg allergies and 25% of milk allergies reacted to the doses of 100 mg of solid foods. Rance et al. [27] observed positive challenges to peanut to a cumulative dose below 100 mg in 36.2% of cases.

Table 2. Distribution of the CRD in 125 positive oral challenges to egg

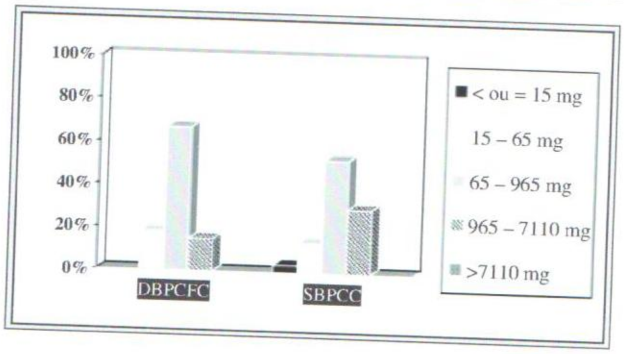


Table 3. Distribution of the CRD in 103 positive oral challenges to peanut

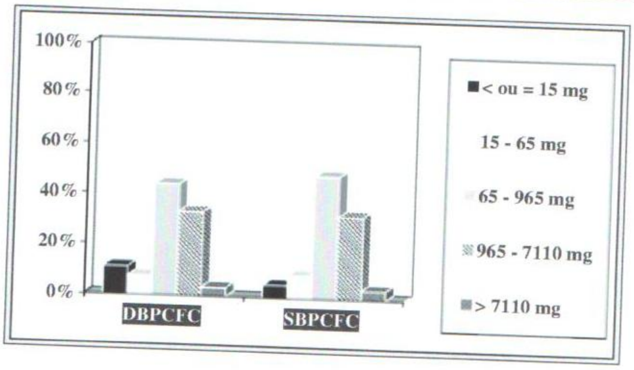
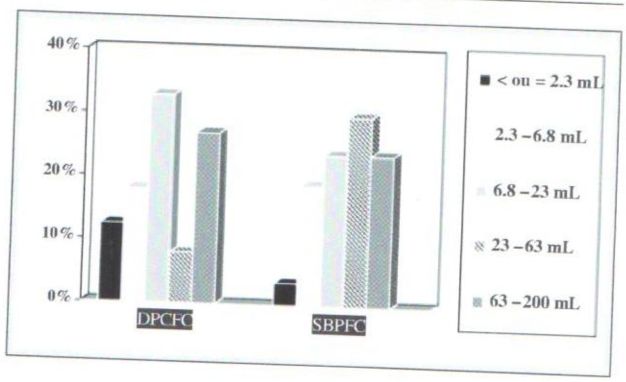


Table 4. Distribution of the CRD in 59 positive oral challenges to milk



The lowest observed immunoallergic effect levels could be compared to the LOAEL of toxicological studies [22, 28]. However, LOAEL are established by toxicological studies on animals and recur in every study. As far as allergy is concerned, the lowest doses may characterize particular subjects, being not thoroughly representative of the general population allergic to the considered food, owing to the wide range of IgE-dependent hypersensitivity. The fact that 125

Table 5. Results of PCFCs with vegetal oils

Oil	PCFC (*n*)	Positive PCFC	CRD (mL)	Symptoms AS	Asthma and/or ↓ FEV	Vomiting and/or abdominal pain	Rhinitis, conjunct.	Exacerb. eczema	U and/or AO
Peanut oil	29	10	5		+	+			
			5		+				
			5					+	
			5						+
			5					+	
			5			+			
			6			+			
			10				+		
			15		+	+			
			6		+				
Sesame seed oil	6	5	1	+					
			5	+					
			3						+
			30						+
			6			+	+		+
Sunflower oil	6	3	5			+			+
			5		+				
			15			+			
Soy oil	2	2	30		+				
			16						+

AO: angio-oedema; AS: anaphylactic shock; CRD: cumulative reactive dose; FEV: forced expiratory volume; U: urticaria.

Table 6. Distribution of positive PCFCs according to the thresholds

	Positive PCFC (*n*)	CRD (%) Solid food = 65 mg Milk = 0.8 mL	CRD (%) Solid food = 15 mg Milk = 0.3 mL	CRD (%) Solid food = 5 mg Milk = 0.1 mL	LOAEL (*n*)
Egg	124	16	5.6	3.2	2 mg (1)
Peanut	103	18	3.9	3.9	5 mg (4)
Milk	59	5	1.7	1.7	0.1 mL (1)
Sesame seed	12	8	ND	ND	30 mg (1)

PCFCs, placebo-controlled food challenges; LOAEL, lowest observed immuno-allergic effect levels; CRD, cumulative reactive dose.

OC to egg, 123 OC to peanut and 59 OC to milk were carried out, gives a sound basis to consider that the observed percentage of patients who react to minimal doses is truly representative of reality (Table 6). Three milligrams of milk proteins (0.1 mL of milk) is not far from values shown to be reactive among known data [29]. An exceptional case of allergy to 100 μg/day of α-lactalbumin has been published. Since α-lactalbumin represents 4% of the total amount of milk proteins, this quantity is provided by 2.5 mg of milk proteins [30]. Likewise, quantities from 200 to 1200 μg of egg and peanut proteins are in the range of previous observations [11, 27, 31]. In one study, 100 μg of peanut was considered as a reactive dose [11].

One particular area concerns positive reactions to oils [17–20, 32–34]. These reactions emphasize extremely tiny amounts of residual allergens inferior to 220 μg of proteins per L [20]. Previous studies reveal conflicting results regarding allergenicity of oils. Challenges with refined peanut and soy oils are regularly negative in adults [35, 36]. Some positive oral challenges with peanut crude oil have been observed [37]. However, the situation is different among infants and young children: DBPCFC to peanut refined oil are undoubtedly positive [12]. The recent demonstration of trace allergenic proteins in refined sunflower oil substantiates a case of anaphylaxis documented by DBPCFC [18, 33].

AS can be induced in adults by sesame oil. It should be noted that subjects reacting to few milligrams of proteins in sesame oil, reacted only to 100 mg up to 7 g of sesame seeds. This striking difference in reactive protein quantities may indicate an interaction between sesame allergens and the lipidic matrix, which could considerably increase allergenicity. Such an interaction has been demonstrated with the mustard major allergen [38].

The prevention of food anaphylaxis needs informative labelling of allergens intentionally added to foods. Nevertheless, the problem of contaminants in foods has to be faced. Assays detecting proteins have already been developed with different levels of sensitivity. The validation of such detection tests needs to assess the necessary level of sensitivity. This point depends on the estimation of the thresholds of clinical reactivity.

For a threshold of solid food < 65 mg and a threshold of milk < 1 mL, it is necessary to detect 6.5 mg egg proteins (corresponding to 65 mg of egg white), 16 mg peanut proteins (corresponding to 65 mg of peanut) and 32 mg milk proteins (corresponding to 1 mL of milk).

Preliminary estimation can be put forward on the basis of the ingestion of 100 g of a composed food. The detection of 1 p.p.m. in 100 g of food means that 100 μg of allergenic proteins are identified. The required sensitivity of the test can then be calculated at 65 p.p.m. for egg proteins, 165 p.p.m. for peanut proteins and 300 p.p.m. for milk proteins.

However, 0.8% of egg allergies, 3.9% of peanut allergies and 1.7% of milk allergies react to 10 mg or less of solid food or to 0.1 mL for milk. The same calculation shows that a sensitivity of 10 p.p.m. for egg, 24 p.p.m. for peanut and 30 p.p.m. for milk proteins is needed. Such sensitivity of detection tests could ensure a safety of 99% for egg allergic patients, 96% for peanut allergic patients and 98% for milk allergic patients.

avant procédé

Taking LOAEL into account, the assays should comply with limits equal to 2 p.p.m. for egg, 12 p.p.m. for peanut and 30 p.p.m. for milk.

13,75 → protéines d'œuf

Ultimately, oil allergies being considered, the reactive threshold is inferior to 1 mg of proteins [20]. The limit of sensitivity should fall to 5 p.p.m. for vegetal allergenic proteins.

3 protéines lait

In toxicological studies, the estimation of safe doses is based on the non-observed adverse effect level (NOAEL). As it was previously underlined [22, 39, 40], there are no previous known data nor did this study succeed in determining safe doses, since one patient at least in each series reacted to the first dose.

Conclusion

The seriousness and the lethal risk of food allergies led the European Community to carry a resolution on 6th September 2001 concerning the labelling of principal food allergens, when they are intentionally added.

However, only a part of the problem will be solved. Food industries will increasingly have to face the important issue of unintentional contaminating allergens at different stages: crops, manufacturing, handling and packaging. It is true that separate production lines should reduce contamination risks. But other safety processes to improve food security should be devised. Among them, the control of manufactured products through detection tests must be considered. The development of such tests must absolutely meet two requirements: on the one hand, the need of specificity; on the other, sufficient sensitivity to identify the level of contamination at risk of inducing reactions. Knowing the thresholds of allergic reactions could become a benchmark for sensitivity limits. Precise evaluation of the percentage of people reacting to minimal quantities of natural foods is essential. The authorities in charge of food security have to decide the accurate proportion of the allergic population that would have to be protected: 95% or 98%, or even more. According to this choice, they could rely upon the minimal reactive doses observed through DBPCFC in that section of the population. The data of this study indicate the need for a sensitivity limit of 10 p.p.m. for egg, 24 p.p.m. for peanut and 30 p.p.m. for milk, in order to guarantee a safety of 99%, 96% and 98%, respectively, for patients allergic to those foods. The possibility of determining non-reactive quantities in large series would moreover be a notable improvement. Further studies should pay particular attention to NOAEL, using a more precise approach by way of tiny doses less than 5 mg of natural foods.

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