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Sesame allergy threshold dose distribution

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ABSTRACT

Background: Sesame is a relevant food allergen in France. Compared to other allergens there is a lack of food challenge data and more data could help sesame allergy risk management. The aim of this study is to collect more sesame challenge data and investigate the most efficient food challenge method for future studies.
Method: Records of patients at University Hospital in Nancy (France) with objective symptoms to sesame challenges were collected and combined with previously published data. An estimation of the sesame allergy population threshold was calculated based on individual NOAELs and LOAELs. Clinical dosing schemes at Nancy were investigated to see if the optimal protocol for sesame is currently used.
Results: Fourteen patients (10 M/4 F, 22 ± 14.85 years old) with objective symptoms were added to previously published data making a total of 35 sesame allergic patients. The most sensitive patient reacted to the first dose at challenge of 1.02 mg sesame protein. The ED_{05} ranges between 1.2 and 4.0 mg of sesame protein (Log-Normal, Log-Logistic, and Weibull models) and the ED_{10} between 4.2 and 6.2 mg. The optimal food challenge dosing scheme for sesame follows semi-log dose increases from 0.3 to 3000 mg protein.
Conclusion: This article provides a valuable update to the existing clinical literature regarding sesame NOAELs and LOAELs. Establishment of a population threshold for sesame could help in increasing the credibility of precautionary labelling and decrease the costs associated with unexpected allergic reactions. Also, the use of an optimal dosing scheme would decrease time spent on diagnostic and thereafter on the economic burden of sesame allergy diagnosis.

1. Introduction

Sesame seed is a relevant food allergen in France and was responsible of 3% of reported life threatening allergic reactions to foods in France in 2002 (Moneret-Vautrin et al., 2005). This allergy appears early in life, does not resolve naturally with time, and tends to persist in 80% of cases (Cohen et al., 2007). Sesame is listed in the European Union (EU), Canada and Australia/New Zealand directives regarding mandatory allergen labelling (Gendel, 2012). Avoidance diet and treatment of acute emergencies represent the current management of sesame allergy. However, sesame seeds are difficult to control in food production equipment due to their particulate nature and electrostatic properties (Derby et al., 2005). Total avoidance diets by allergic individuals are difficult (Taylor et al., 1986). Unintentional cross contact of food allergens with other products on the production is a main concern for food industries, food legislators and patients. In order to warn allergic consumers of possible unintended presence of allergens in their products, food producers use precautionary labelling in addition to mandatory contains labelling. Due to inconsistencies in the application of precautionary labelling by the food industry, many products contain unnecessary precautionary labelling (Hefle et al., 2007). These unnecessary warnings make avoidance diets more restrictive and some allergic patients are beginning to ignore all these precautionary labelling labels (Hefle et al., 2007), a practice which poses a risk for allergic reactions. Removing unnecessary precautionary labelling would increase confidence in labels and potentially reduce the number of unexpected food allergic reactions. The amount of food required to cause a reaction is important for allergy

List of abbreviations: DBPCFC, Double Blind Placebo Controlled Food Challenge test; ED, Eliciting Dose; EU, European Union; LOAEL, Lowest Observed Adverse Effect Level; NOAEL, No Observed Adverse Effect Level.

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and allergen management. Knowing the individual minimum reactive doses as well as the amount of each product consumed would make it possible to manage the risk for the allergic population (Crevel et al., 2007).

Preventing accidental exposure to food allergens could decrease the economic burden of food allergy anaphylaxis. In 2007, the Allergy Vigilance Network in France defined anaphylaxis as a systemic reaction in two or more organ systems, a drop in blood pressure, or serious respiratory symptoms. They assessed the economic cost of anaphylaxis between January 2004 and June 2006 (Flabbee et al., 2008). The direct cost of each emergency visit due to anaphylaxis ranged from 75 Euros to 4445 Euros depending on the severity of the reaction and the treatment received by the patient. The most severe cases of anaphylaxis required additional hospitalisation which had added costs of 2115 Euros per day. These are the estimated costs for hospitalization and emergency visits which do not take into account the indirect costs of absenteeism, loss of productivity and annual consultation or further tests because of adverse reactions to foods. Currently for sesame and other allergens, University Hospital in Nancy (France), uses up to three progression challenges plus a placebo on four separate days to diagnose food allergies. Using the optimal dosing scheme for sesame in the food challenge test could decrease the cost of hospital stays during diagnosis. An optimal dosing scheme would cover the most sensitive patients with lowest doses and could provoke reaction in patients that react to higher doses also if the dose escalation is appropriately designed, as proposed by Klein Entink et al. (Klein Entink et al., 2014). The No Observed Adverse Effect Level (NOAEL) is defined as the largest amount of food that an individual can ingest without causing an adverse reaction. The Lowest Observed Adverse Effect Level (LOAEL) is the lowest dose of an allergen ingested that produces an adverse effect. The individual threshold dose lies between NOAEL and LOAEL. Using individual NOAELs and LOAELs, it is possible to statistically calculate threshold dose distributions for an overall population. International stakeholders, including the UK FSA and the US FDA, agreed that probabilistic modelling is the most favourable approach to use for allergen risk assessment (Madsen et al., 2009) (Gendel et al., 2008). Previous studies used this method for the determination of threshold levels for a number of food allergen (Taylor et al., 2014) (Bindslev-Jensen et al., 2002) (Taylor et al., 2009). Data for sesame in these papers were limited to 21 patients from four different studies (Kanny et al., 1996) (Kolopp-Sarda et al., 1997) (Morisset et al., 2003) (Leduc et al., 2006) and more data could strengthen current modelling distributions for the sesame allergic population.

This study aimed to determine NOAELs and LOAELs for additional sesame allergic individuals and update the population threshold estimate for sesame. The current study combines new patients and data retrieved from previously published clinical data. Knowing the population threshold distribution for sesame could help in establishing reference doses for sesame which gives more guidance for all food allergy stakeholders when applying precautionary labelling. Furthermore, the clinical dosing schemes used were evaluated to investigate if the optimal protocol for sesame is currently implemented in clinical practice.

2. Material and methods

The study population consisted of 14 patients who had positive food challenge tests for sesame at University Hospital Nancy (France) between 2006 and 2013. Patients were included even if they had a history of severe reactions. Medical records were retrospectively consulted for information on age, sex, personal and family history and for other allergies, skin prick tests, specific IgE values and double blind placebo control food challenge (DBPCFC) tests for sesame. An informed written consent form was signed before the beginning of the protocol.

DBPCFC tests were performed according to the consensus protocol for the determination of the threshold doses for allergenic foods (Taylor et al., 2004). Patients underwent DBPCFC with crushed sesame seeds using stewed apple as a vehicle and stewed apple without sesame as a placebo. Sesame seeds were crushed and mixed with stewed apple. Doses were given cold and patients wore a nose clip to decrease organoleptic perception. Placebo consisted of stewed apple with crushed popcorn to mimic the texture of sesame mix with the vehicle. Progressive dosing schemes were spread over 3 days (plus a 4th placebo day) and ranged from 1 to 7010 mg of crushed sesame seeds (equivalent to 0.17–1200 mg of sesame proteins). Dosing schemes were adjusted depending on the patient's clinical history and severity of prior reactions. An interval of 15 min was observed between two doses. The challenge ended only when the patient experienced objective symptoms or when the highest dose of the challenge was achieved (in our case 7010 mg of sesame or 1200 mg of sesame protein). Objective symptoms included diarrhea, vomiting, conjunctivitis, urticaria, lip and throat swelling, bronchoconstriction, wheezing, angioedema, etc. Abdominal pain was considered as an objective symptom in children who didn't have symptoms with placebo food challenge (Taylor et al., 2010). Symptoms were graded according to the score of Astier et al. (Astier et al., 2006). This score was adapted by adding laryngeal pruritis to grade 1. Patients were asked to stop antihistamines one week before the challenge; beta antagonists and corticosteroids were stopped 24 h before the DBPCFC. Both discrete and cumulative NOAELs and LOAELs were recorded for each patient. These values were expressed in mg of total protein from sesame seed, which accounts for 17% of sesame seeds content (USDA, 2014).

Sesame NOAELs and LOAELs were combined with previously published data (Taylor et al., 2014). Data from twenty-one patients were used for the determination of the VITAL reference dose for sesame and came from 4 different studies previously published by Nancy research teams (Kanny et al., 1996) (Kolopp-Sarda et al., 1997) (Morisset et al., 2003) (Leduc et al., 2006).

Population threshold distributions were determined using the method proposed by Taylor et al. (Taylor et al., 2009). NOAELs and LOAELs were analyzed using an Interval-Censoring Survival Analysis (ICSA) approach. Statistics were performed in SAS v9.3 (SAS Research Institute) using the LIFEREG procedure. The (ED_{05}) or the eliciting dose that is predicted to provoke reaction in 5% of the population and the (ED_{10}) that could trigger reaction in 10% of the population (ED_{10})were estimated using the Log-Normal, Log-Logistic and Weibull parametric models.

We compared the three dosing schemes used for the diagnosis of sesame allergy by University Hospital in Nancy (Taylor et al., 2010), with the dosing schemes recommended by EuroPrevall (Sampson et al., 2012). The first Nancy dosage progression had a cumulative dose of 44.4 mg of sesame (7.5 mg sesame protein); the second Nancy dosage progression had a cumulative dose of 965 mg of sesame (164 mg sesame protein) and the third Nancy dosage progression with a cumulative of 7010 mg of sesame (1200 mg sesame protein). The discrete dosing scheme used by EuroPrevall was the same across all foods challenged: 0.003 mg, 0.03 mg, 0.3 mg, 3 mg, 30 mg, 100 mg, 300 mg, 1000 mg and 3000 mg food protein (cumulative dose of 4333.333 mg of protein).

3. Results

Fourteen new patients (10 M/4 F, 22 ± 14.85 years old) with objective symptoms during DBPCFC to sesame were considered for this study (Table 1). Patients 1 and 7 had a history related directly to sesame ingestion and/or manipulation. The 12 other patients had