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# Adverse Reactions During Peanut Oral Immunotherapy Home Dosing

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To The Editor:

Oral immunotherapy (OIT) is increasingly being investigated as a potential treatment for peanut and other food allergies, with a recent study demonstrating evidence of clinical desensitization and immunologic changes suggesting the development of long-term tolerance[1]. Unlike traditional subcutaneous immunotherapy for inhalant allergens, peanut OIT is administered daily, with the vast majority of doses given at home. In our peanut OIT protocols, subjects are seen in the research unit for observed dose escalations every two weeks, and subsequent doses are given at home. In the open-label study of peanut OIT, home doses were generally well-tolerated[2]. The incidence of allergic reactions with any home dose was 3.5%, with mild upper respiratory and skin symptoms being the most common complaints.

Despite the infrequent incidence of symptoms with peanut OIT home dosing, certain patterns of reactions have surfaced during this phase. Characterizing these reactions and identifying potential triggers or factors which predispose to reactions may improve the safety of home dosing. Reactions occurring during investigational OIT or any immunotherapy protocol are challenging to study prospectively, due to ongoing modifications in the protocol and recommendations that are instituted to prevent further reactions. In subcutaneous aeroallergen immunotherapy, asthma has been identified as a risk factor for systemic reactions, prompting



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**Capsule Summary:** Although peanut oral immunotherapy (OIT) has a good safety profile, certain patterns have been associated with a propensity to react to a previously tolerated OIT dose. Addressing these factors can improve the safety of experimental immunotherapy protocols.

recommendations to evaluate respiratory symptoms and consider objective measures of airway function during administration[3].

Researchers studying milk and egg OIT noted certain "augmentation factors" that lowered threshold doses – namely, infection, exercise, pollen allergy, and irregular intake[4] – and identifying these factors and reducing the immunotherapy dose prevented further allergic reactions.

We have noted five patterns associated with a propensity to react to a previously tolerated dose of peanut OIT, including several not previously described. It is interesting that these factors would provoke symptoms after a given OIT dose when, in many of the examples noted, the dose had been tolerated for weeks to months without symptoms. Table I lists selected examples illustrating the observed patterns – (1) concurrent illness, (2) suboptimally-controlled asthma, (3) timing of dose administration after food ingestion, (4) physical exertion after dosing, and (5) dosing during menses. Addressing these factors (see Table II) has improved the safety profile of our peanut OIT protocol. While some of our recommendations mirror those instituted in subcutaneous immunotherapy protocols, most are unique to OIT administration. We expand on reports from other research centers[4, 5], which have described triggers such as infection, exercise, pollen allergy, and irregular intake, and this is the first report involving protocols for peanut allergy.

We have observed that dosing during febrile illnesses has been associated with systemic reactions to previously tolerated peanut OIT doses. We recommend withholding OIT during acute illnesses and advise subjects to resume dosing at home if fewer than three doses are missed. If three to five doses are missed, subjects return to the research unit for observed dosing. Those who miss more than five days of dosing may require significant dose reduction or repeat desensitization.

In our open-label study[2], asthma was associated with a higher rate of chest symptoms during OIT. Of the subjects reporting chest symptoms during home dosing, 82% had co-existing asthma. Several subjects receiving peanut OIT noted cough and wheezing after doses. Some also had chronic cough or exercise-induced respiratory symptoms. Although we did not observe changes in pulmonary function in these subjects, their symptoms improved with the initiation of asthma controller medications (see Table I), highlighting the importance of diagnosing and treating co-morbid atopic conditions. Regular peak flow measurements and pulmonary function testing has been implemented to optimize asthma control.

It has not been uncommon for a subject taking a daily OIT dose without eating a meal or snack in the two hours before dosing to have symptoms with a dose that has been previously tolerated; taking the same dose with food the next day and thereafter prevents further reactions. Additionally, several subjects have experienced allergic symptoms with exercise after OIT dosing, and we advise these individuals to avoid exertion for two hours after dosing. Finally, one subject had several systemic reactions when menses was coupled with exercise despite no symptoms with daily dosing in the interval between episodes and was eventually withdrawn from the study. She was not taking other medications (e.g. non-steroidal anti-inflammatory drugs). Of note, she did not have systemic reactions each time she exercised during menses. At this time, the role of menses is unclear, and further study is needed.

In the studies to date, peanut and food OIT have a good safety profile, and home dosing is infrequently associated with adverse reactions[2, 6]. However, allergic symptoms should be expected, and subjects and their families should be counseled about circumstances associated with an increased possibility of reacting to previously tolerated OIT doses. As OIT for food allergy becomes increasingly studied in research settings, implementing these recommendations and modifications can improve the safety of these experimental protocols.

## Abbreviations

| | |
|---|---|
| OIT | oral immunotherapy |
| IgE | immunoglobulin E |

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**Table I**

Examples of Reactions during Peanut OIT Home Dosing

| Subject | Age at reaction (months) | Pattern | Reaction | Dose | Length of time on OIT (months) | Length of time on dose | Baseline IgE (kU/L) | IgE at time of reaction | Treatment | Recommendations to this subject |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 70 | Fever | AE, LR | 300 mg | 12 | 5 months | 23.6 | 13.9 | H1, E, A | Hold dose if ill |
| **2** | 131 | Fever | AE, U, LR | 1200 mg | 19 | 3 months | >100 | 136.5 | H1, E, CS, A | Hold dose if ill |
| **3** | 38 | Asthma | LR | 300 mg | 10 | 4 months | 22.7 | 9.3 | H1, A | Start inhaled CS |
| **4** | 83 | Empty stomach | U, LR, G | 1800 mg | 27 | 7 months | >100 | 115 | H1, A | Take all doses with meal |
| **5** | 102 | Exertion | LR | 2400 mg | 49 | 2 months | 58.3 | 4.7 | H1, A | Avoid exercise for 2 hours after dose |
| **6** | 99 | Exertion | U, LR | 3000 mg | 47 | 2 days | 73.1 | 7.3 | H1,CS | Avoid exercise for 2 hours after dose; decrease dose to 2400 mg |
| **7** | 145 | Menses and exertion | AE,U, UR, LR, G | 4000 mg | 20 | 9 months | 85.1 | 59.5 | H1, E, CS | Discontinued participation in study after 2nd occurrence |

AE = angioedema
U = urticaria
UR = upper respiratory
LR = lower respiratory
G = gastrointestinal
IgE = immunoglobulin E
H1 = H1 antagonist
E = epinephrine
CS = corticosteroids
A = albuterol

**Table II**

Recommendations for Future OIT Investigations

- Hold daily dose if febrile or ill with symptoms of viral illness (e.g., upper respiratory infection, gastroenteritis)
  - Resume dosing at home if < 3 missed daily doses
  - Return to research unit for observed dose if 3–5 missed daily doses
  - Consider repeat desensitization or significant dose reduction if more than 5 missed daily doses
- Closely monitor lower and upper respiratory symptoms
  - Initiate asthma controller medication if needed
  - Perform peak flow and spirometry monitoring
  - Ensure optimal control of allergic rhinitis
- Take daily OIT dose with meal or snack
- In subjects with exercise-induced symptoms, limit exertion for 2 hours post-dosing
- Closely monitor during menstrual cycle – especially when coupled with infection or exercise