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Peanut Oral Immunotherapy Dose Variations Do Not Result in Allergic Reactions

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Running Title: POIT dose variations and tolerance

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To the Editor:

Peanut allergy is the leading cause of death related to food-anaphylaxis in the United States and a growing public health concern with the prevalence of peanut allergies tripling in the last 10 years, currently affecting 2% of the population (1,2). It occurs early in life and only 20% of children may outgrow their allergy causing a significant decline in quality of life (3,4).

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Peanut oral immunotherapy (POIT) has been demonstrated to be effective for peanut desensitization. POIT is administered daily with dose increments every 2 weeks. Doses are generally well tolerated with the incidence of home dose reactions at around 3.5% (5). Symptoms range from mild to severe allergic reactions, with mild upper respiratory and cutaneous findings being the most common complaints (5,6). Previously published POIT studies have demonstrated evidence of clinical desensitization and immunologic changes suggesting the development of potential long-term sustained unresponsiveness (7-8). However, POIT is still an investigational treatment and is still not recommended for clinical practice. Adverse reactions are the primary concern during POIT treatment and occur commonly during up-dosing. Differences in potency between expired and unexpired lots of peanut flour could potentially result in allergic responses in POIT patients. The goal of this study was to demonstrate that POIT subjects could tolerate adjustments ~~variations~~ when transitioning from an expired to unexpired lot of peanut flour

This single center phase 1 peanut oral immunotherapy protocol was prospectively reviewed and approved by the Institutional Review Board of Baylor College of Medicine. Eleven subjects with peanut allergy from Texas Children's Hospital were enrolled. This protocol was performed similarly to prior protocols (7). Inclusion criteria included: 1) 5-16 years of age with a history of an adverse reaction upon peanut ingestion; 2) peanut immediate hypersensitivity skin test (IHST) wheal size >3 mm greater than the negative control, and 3) peanut IgE >7kU/L. Exclusion criteria for the study included: 1) Grade 4 or 5 anaphylaxis, 2) persistent asthma, 3) poorly controlled or persistent atopic dermatitis, 4) ongoing allergen immunotherapy treatment or 5) active eosinophilic esophagitis. All subjects underwent a double-blind placebo controlled food challenge (DBPCFC) at screening. Clinical reactivity was defined as any signs of allergic reaction (i.e. ≥ 1 on the Bock criteria) (9).

Up-dosing occurred every 2 weeks until the maintenance dose (3900 mg protein) was achieved. Due to concerns about lot-to-lot variation and potency and to ensure tolerance of unexpired (new lot) peanut flour, a subject would experience a "dose variation", which was defined as a subject's dose being reduced by 50% when receiving a dose for the

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first time from the unexpired (new lot) flour. If the dose on the unexpired (new lot) was tolerated for 2 weeks, the subject would return to the same dose, as previously tolerated on the expired (old lot) flour. The transition back to the previously tolerated dose was a 100% increase. The delta dose of the unexpired peanut flour was the difference between the “return dose” and the “de-escalation dose” in milligrams. The “de-escalation dose” is the 50% dose reduction from the baseline expired (old lot) peanut flour dose. The “return dose” is *equal* to the expired (old lot) peanut flour dose before de-escalation. Peanut samples from the expired and unexpired lots were analyzed by SDS-PAGE to determine if *Ara h1* and *Ara h2*, protein content was similar between the two lots. Factors assessed for each patient included: dose variation; gender; starting age of POIT; peanut IHST; peanut and *Ara h2* specific IgE levels (Phadia ImmunoCap) prior to POIT; threshold symptom eliciting dose with entry DBPCFC; duration on POIT prior to dose variation. Allergic reactions and symptoms associated with increased peanut protein dosing were recorded. Spearman’s rank correlation (r) was used to analyze the influence various factors might have on dose change (delta dose).

A total of 11 subjects were evaluated on this study. The demographics and clinical data for the POIT subjects evaluated for the dose variations and delta dose between the expired and unexpired peanut flour are highlighted on Table 1. Overall, no patients experienced an allergic reaction with increased dosing as a result of lot-to-lot dose variations.

Correlations were not observed between the delta dose (mg) and the following: 1) starting age; 2) DBPCFC reaction dose; 3) the baseline peanut IHST; 4) baseline peanut IgE; or 5) *Ara h2* IgE. A correlation was observed between the delta dose (mg) and duration on POIT prior to the dose change (months) (Spearman $r=0.72$; 95% CI 0.184-0.923; $p=0.013$) (Figure 1). No differences were observed between the presence of peanut *Ara h1* and *Ara h2* proteins when comparing the protein content between expired and unexpired lots on SDS-Page (Figure 2).

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In this study, POIT participants who underwent dose variations on the unexpired lots of peanut flour were able to successfully tolerate the 100% dose increase, following a 2-week tolerance of a 50% dose reduction on the unexpired lot of peanut flour. No symptoms were observed in this cohort given POIT dose variations of up to 450 mg. The implications of these observations are important for the future application of POIT as a widespread clinical treatment. The risk of reactions when large dose changes occurred following a previously tolerated dose was assessed. This is the first study to report the findings of tolerance due to dose variations in a POIT trial. The risk of variations in daily peanut protein dose in POIT patients may not be as high as previously considered. The amount of tolerated dose variation correlated with the duration on POIT prior to dose change. The amount of tolerated dose variation did not correlate with the baseline peanut or *Ara h2* IgE, peanut IHST, DBPCFC reaction dose or starting age. Therefore, our observations suggest that short term disruptions of treatment may not result in loss of the acquired desensitization. The findings suggest that non-compliant patients could potentially be restarted on POIT with minimal loss of efficacy. Our findings will require further direct observations on a larger population with variable dose changes.

In summary, this study showed evidence of the durability of maintaining the desensitization state in subjects in the buildup phase during POIT, demonstrating that once an individual was desensitized to a dose, doses could be reduced by 50% for a period of 2 weeks and immediately increased back to the previously tolerated dose without adverse events. Future studies should determine if the findings are generalizable for a larger cohort and with higher doses and if the sustained desensitization could be maintained for more than 2 weeks.

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Figure 1: Correlation between Delta Dose (mg) and Duration on Peanut Oral Immunotherapy (POIT) prior to Dose Change (months). Correlation was assessed between delta-dose and duration on POIT in 11 pediatric patients.

Figure 2: No lot difference in the amount of peanut-components *Ara h1* and *Ara h2*. Crude peanut extract (CPE) was isolated from a mixture of flour and PBS then visualized via SDS Page Gel. Two different lots processed: unexpired (**A**) and expired (**B**).

Table 1: Demographic and clinical data for peanut oral immunotherapy (POIT) subjects evaluated for dose variations and delta dose between the expired and unexpired peanut flour

Variable	Peanut OIT Subjects (n=11)
Starting Age, years; median (range)	8 (5-12)
Male n (%)	6 (55%)
Baseline peanut specific IgE, kU/L; median (range)	201.2 (20.4-707)
Baseline Ara h2 IgE, kU/L; median (range)	165.5 (11.9-504)
Baseline peanut IHST, millimeters; median (range)	20 (7-40)
6-Month peanut IHST, millimeters; median (range)	12 (3-29)
Threshold eliciting dose with entry food challenge, milligrams; median (range)	75 (15-500)
Starting Peanut OIT (POIT) dose, milligrams; median (range)	3.6 (1.8-60)
Duration on POIT prior to dose change, months; median (range)	3 (2-7.5)
Number of home doses administered during the lot-to-dosing analysis period	3169
Number of home doses causing an allergy reaction as a result of lot-to-lot variation; n (%)	0 (0%)
Number of home doses causing mild-to-moderate reactions independent of lot-to-lot variation; n (%)	105 (3.31%)
Number of home doses causing severe reactions independent of lot-to-lot variation; n (%)	0 (0%)
"Delta Dose" tolerated without reaction, milligrams; median (range)	40 (14.4-450)

Abbreviations: peanut oral immunotherapy (POIT)

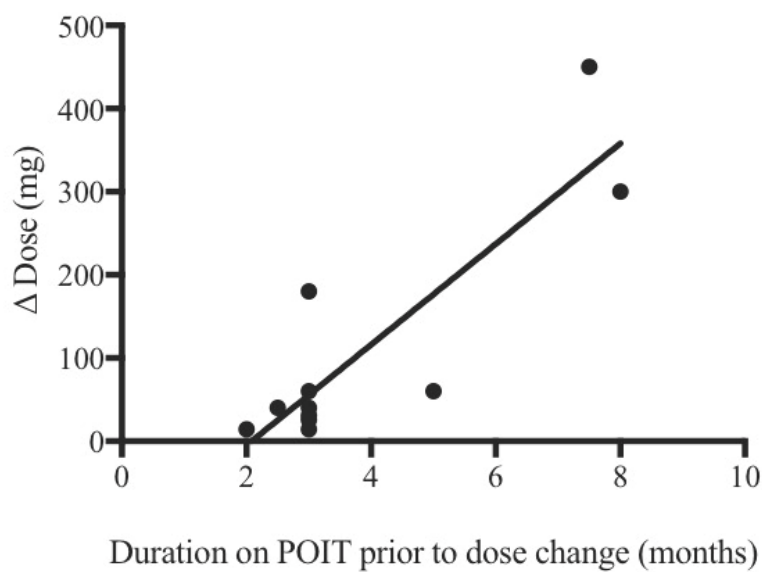


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Figure 1

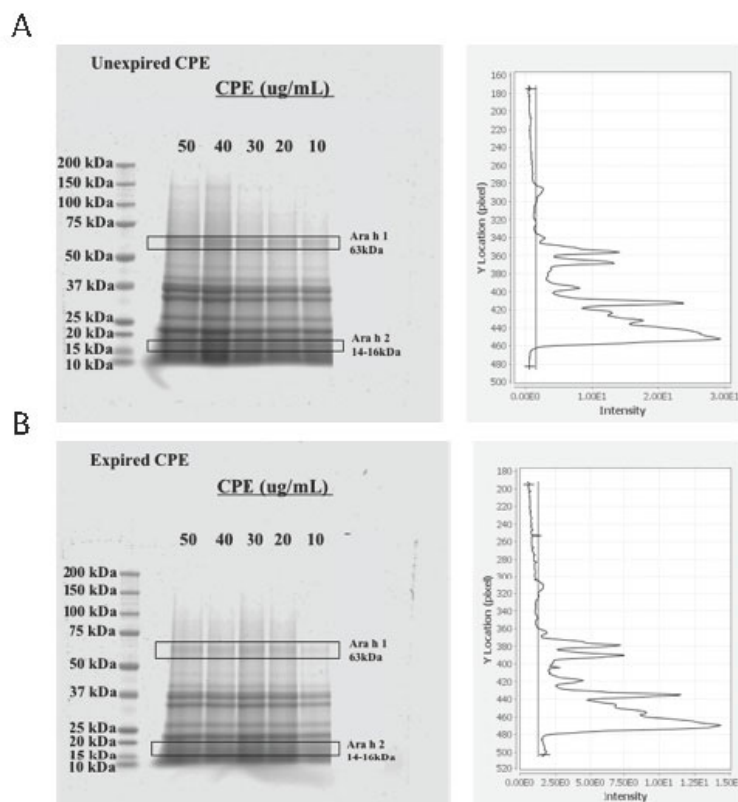


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Figure 2