No apparent impact of incremental dosing on eliciting dose at double-blind, placebo-controlled peanut challenge

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TITLE PAGE

LETTER TO THE EDITOR

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To the Editor:

Oral food challenges (OFC) are the gold standard diagnostic for food allergy, but not without limitation. Administering incremental doses every 15-30min differs from a real-world exposure where ingestion occurs at a single episode. Blumchen et al. reported a median time to objective symptoms of 55min (range 5-210min);[1] if doses are given every 15min, this could significantly overestimate the reaction threshold.[1,2] This could also occur due to incremental dosing causing transient desensitisation.[3] With OFC increasingly used to determine starting doses for oral immunotherapy and guide dietary avoidance,[4] we assessed how clinical thresholds and symptoms at OFC compare to an ingestion more representative of real-world consumption.

Seventeen peanut-allergic adults (median age 24 years, range 18-40) underwent initial double-blind, placebo-controlled food challenge (DBPCFC) to peanut, as part of a clinical trial (TRACE Peanut study; ClinicalTrials.gov Identifier: NCT02665793). Detailed methods are described elsewhere.[5] Doses were given every 30 minutes (using a water-continuous dessert matrix) according to the following schedule: 3µg, 30µg, 300µg, 3mg, 30mg, 100mg, 300mg and 1000mg of peanut protein (or placebo), until stopping criteria were met.[5] Participants returned for two further DBPCFC. The first was an "abbreviated" DBPCFC using the same matrix, with the first active dose equivalent to the maximum tolerated dose at baseline DBPCFC (see Fig 1 and Table S1); this was done as a safety measure. Subjects allocated (by computer randomization) to placebo had two placebo doses first (Fig 1). The third DBPCFC used the same abbreviated protocol, but with the appropriate dose given as peanut butter (Kraft Foods) mixed into a soya-based spread (Wowbutter) and eaten as a small 3cm sandwich (Kingsmill 50/50 bread). Triangle testing demonstrated the suitability of Wowbutter for blinding, and prior tolerance to this was demonstrated in all participants. The study was approved by the NHS Human Research Authority (reference 15/LO/0286), and written informed consent from all participants.

At baseline DBPCFC, the median cumulative eliciting dose (cumED) was 133mg (IQR 83.3-433.3mg) peanut protein; 2/17 patients had anaphylaxis (WAO 2020 criteria). Median cumED at abbreviated challenge was 133mg (IQR 33.3-433.3mg) (Fig 2A). The shift in cumED was not significant ($p=0.10$, Wilcoxon sign-rank test), and there was no major differences in clinical symptoms observed (Fig S1). Fourteen subjects underwent the third DBPCFC using peanut butter sandwiches (one had too low a cumED for the appropriate dose to be accurately measured, and two declined). Median cumED at this challenge was 433mg (IQR 33.3-1433.3mg), representing a non-significant half-log increase in cumED ($p>0.05$; Fig 2B).

In a systematic review and meta-analysis of peanut-DBPCFC, 69% of peanut allergic-individuals show a shift in cumED over time; in 56%, this is limited to a half-log difference, equivalent to 1 dosing interval with a PRACTALL-based semi-log dosing regimen.[6] Indeed, Dua et al reported a fall of around 0.5-log (equivalent to 1 dosing increment) at subsequent OFC in these same participants.[5] Therefore, the non-significant shift in cumED with an abbreviated challenge protocol is entirely consistent with the inherent "noise" in determining cumED at OFC. We undertook a post hoc power calculation; our sample size would have been sufficient to detect a 1-log difference in cumED with at least 90% power i.e. greater than that due to the inherent intraindividual variability.

In summary, we did not find a significant difference in either cumED or symptoms following DBPCFC with a 30-minutely incremental dosing protocol, compared to an abbreviated challenge which is more representative of a normal consumption episode. In addition, there was no significant difference in cumED between baseline DBPCFC and a more "real-world" exposure to peanut butter in a sandwich. Therefore, using threshold data from OFC (with 30 minute dosing intervals) is a valid approach to individual allergen risk management.

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Competing interests

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FIGURE LEGENDS

Figure 1 Challenge protocol used for "abbreviated" food challenges

Figure 2. Change in cumulative eliciting dose (cumED) at DBPCFC. Panel **A** : cumED at baseline DBPCFC (using standard incremental protocol) compared to abbreviated protocol. Red bar represents median, whiskers the interquartile range. Panel **B** : log-change in cumED when the abbreviated DBPCFC was undertaken with peanut butter in contrast to DBPCFC (either abbreviated protocol or standard protocol) with the water-continuous dessert matrix. ns, not significant.