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# The effect of montelukast on wheal reactions in skin prick tests: A double-blind-placebo-controlled randomized trial

Keziban Bulan [a], Metin Aydogan [b,*], Rengin Siraneci [c], Cigdem Yilmaz Aydogmus [d]

[a] Bakirkoy Maternity and Children's Education and Research Hospital, Istanbul, Turkey
[b] Kocaeli University, Faculty of Medicine, Department of Pediatric Allergy/Immunology, Kocaeli, Turkey
[c] Department of Infectious Disease, Bakirkoy Maternity and Children's Education and Research Hospital, Istanbul, Turkey
[d] Departments of Allergy & Immunology, Bakirkoy Maternity and Children's Education and Research Hospital, Istanbul, Turkey

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ABSTRACT

*Objective:* It is well-known that number of drugs may interfere with wheal reactions in skin prick test. However, the effect of long-term use of montelukast, a cystenil leukotriene receptor antagonist, on skin prick test hasn't been full elucidated. The aim of present study was to demonstrate the effect of montelukast on skin prick tests (SPT).

*Methods:* This is a single-center, randomized, double-blinded, placebo-controlled study including two treatment periods with a wash-out interval. The subjects received montelukast (5 mg per day), fexofenadine HCl (60 mg per day) and placebo (lactose) with a double-blinded manner during 7- and 21-days treatment periods with a 14 days wash-out period. *Dermatophagoides farinae* (*D. farinae*) was used as the skin test material, while histamine as positive control and normal saline as negative control. Overall, 7 skin prick tests were performed at following time points: before treatment periods, on the last days of both treatment periods, 24 h after completion of treatment periods, and on the last day of 14-days interval.

*Results:* Sixty house dust mite (HDM) allergic children (23 girls and 37 boys) with allergic rhinitis and/or asthma completed the study. Mean age was $8.3 \pm 2.0$ years. In the fexofenadine group, a significant suppression was observed in post-treatment values when compared to baseline values in SPT with *D. farinae* ($p = 0.019$). In the montelukast group, no significant suppression was observed in SPT with *D. farinae* at all time points when compared to baseline.

*Conclusions:* Our results showed that montelukast had no effect on measurements of SPT. Thus, we concluded that there is no need to discontinue the treatment in order to perform SPT in patients receiving montelukast, even in those on montelukast treatment for at least 21 days.



## 1. Introduction

Skin tests have been used to confirm diseases mediated by IgE such as allergic rhinitis, asthma and anaphylaxis to some allergens such as aeroallergens, foods, insect venoms and certain therapeutic agents [1]. It is known that several drugs may interfere with the reactions in SPTs and make interpretation of these tests more challenging by modulating either flare or wheal. It is known that H1 receptor antagonists suppress the reactions in the SPTs [2,3]. Montelukast is an orally active cystenil leukotriene type-1 receptor antagonist of leukotriene D4 with high selectivity [4]. The Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 revision proposed the use of oral leukotirene receptor antagonist in seasonal allergic rhinitis (AR) in both adult and pediatric patients [5]. It is also found to be effective in patients with mild persistent asthma and near-normal pulmonary function [6].

There are limited numbers of randomized, double-blinded, placebo-controlled studies evaluating the potential effects of leukotriene receptor antagonists on cutaneous responses to an allergen in diagnostic procedures with conflicting results [7–11]. All previous studies focusing on the effect of leukotriene receptor antagonists on SPT provided results on the effects of treatments ≤7days. However, it is imprecise whether it is need to discontinue the treatment with leukotriene receptor antagonists before diagnostic SPT.

* Corresponding author at: Kocaeli Universitesi Tıp Fakülesi, Kocaeli Üniversitesi Umuttepe Yerleşkesi, 41380 Kocaeli, Turkey. Tel.: +90 262 3037405; mobile: +90 506 598 5039.
*E-mail addresses:* keziban1_bulan@mynet.com (K. Bulan), mmetinaydogan@hotmail.com (M. Aydogan), renginsiraneci@gmail.com (R. Siraneci), cigdem1572@hotmail.com (C.Y. Aydogmus).

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In the present study, it was aimed to determine the effect of montelukast treatment (5 mg per day) for 7 and 21 days on wheal reaction in SPT.

## 2. Methods

### 2.1. Study group

The study protocol was approved by Institutional Ethics Committee. All subjects gave written informed consent prior to participation.

Children aged 6–15 years with allergic rhinitis and/or mild asthma, who had house dust mite (HDM) sensitivity, were included to the study. Only the patients with skin test positivity to HDM alone were included. Persistent allergic rhinitis was defined according to ARIA guidelines [12]. Asthma was defined as presence or recurrence of at least 2 of 3 symptoms including cough wheezing and shortness of breath within prior 12 months. This clinical definition was solely based on the appearance of recurrent symptoms; thus, it was independent of the hyperresponsiveness level defined in GINA (Global Initiative for Asthma) guidelines [13].

The patients with acute illness or comorbid chronic diseases, those received antihistamines or oral corticosteroid within previous month, those with history of immunotherapy, those with any systemic symptom after skin tests and those with history of adverse reaction to any antihistamines or leukotriene receptor antagonists were excluded.

### 2.2. Study design

This is a single-center, randomized, double-blinded, placebo-controlled study including two treatment periods with a wash-out interval. The subjects received montelukast (5 mg per day), fexofenadine HCl (60 mg per day) and placebo (lactose) with a double-blinded manner during 7- and 21-days treatment periods with a 14 days wash-out period. Montelukast, fexofenadine and placebo were dispensed as identical tablets. Compliance to treatment regimens were prompted by reminder phone calls and by checking drug containers. Fexofenadine was used as the positive control to assess suppression of wheal and placebo was used as a negative control.

All study medications were prepared by a registered pharmacist at Sanovel Pharmacy and dispensed in double-blinded fashion to all participants.

### 2.3. Skin test materials

Skin tests were performed between 09:00 and 12:00 AM on the next day after the last dose of study drug or placebo. The disposable, metal prick test lancets (1 mm in length) which were specially designed for SPT were used. *D. farinae* (Allergopharma, Germany) was used as standard allergen extract, while histamine (1 mg/mL; Allergopharma, Germany) as positive and normal saline (Allergopharma, Germany) as negative control.

**Table 1**
Characteristics of the study groups.

| | Montelukast | Fexofenadine | Placebo | *P* |
|---|---|---|---|---|
| Number | 21 | 18 | 21 | |
| Age (years) (mean ± SD) | 8.7 ± 2.1 | 8.4 ± 2.3 | 7.8 ± 1.6 | 0.37 |
| Sex (girl/boy) | 8/13 | 7/11 | 8/13 | 0.98 |

### 2.4. Skin test procedure

The skin tests were applied to volar surface of both forearms at a point 5 cm from elbow crease and 3 cm from wrist. There was 3 cm distance between tests. All tests were applied by the same trained researcher, which were then recorded by another researcher blinded to application. Tests were assessed after 20 min. Wheal responses were encircled by using a pen and transferred to a transparent tape. Wheal size was measured as the mean of the longest diameter and midpoint perpendicular diameter. Overall, 7 skin prick tests were performed at following time points: before treatment periods, on the last days of both treatment periods, 24 h after completion of treatment periods, and on the last day of 14-days interval (Fig. 1).

### 2.5. Statistical analysis

Chi-square test was used for qualitative data. In the analysis, mean of duplicate wheal responses was used. Non-parametric tests were used to analyze mean wheal responses to *D. farinae* in SPT after montelukast, fexofenadine and placebo treatment periods and wash-out period. Wilcoxon rank sum and Mann–Whitney U tests were used for intra-group and inter group analyses, respectively. All tests were two-tailed and $p < 0.05$ was considered as statistically significant. All statistical analyses were performed by using SPPS for Windows 13.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

Overall, 65 HDM allergic children with allergic rhinitis and/or asthma were enrolled to the study. Five children were withdrawn from the study before randomization due to incompliance. The remaining 60 children (23 girls and 37 boys) completed the study and included to primary efficacy analysis. Mean age was 8.3 ± 2.0 years. Patient characteristics according to study groups are summarized in Table 1.

Tables 2 and 3 present the mean wheal sizes before and after treatment period and at wash-out period and standard deviations for *D. farinae* intradermal challenges in 3 treatment groups. No significant reduction was observed in skin wheal response with montelukast, fexofenadine of placebo use after first treatment period of 7 days ($p > 0.05$; Table 2).

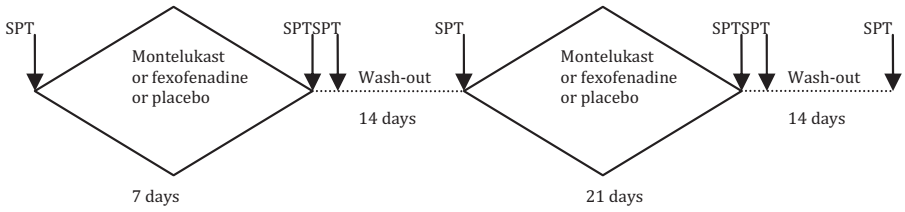


**Fig. 1.** The study scheme: Montelukast (5 mg daily) or fexofenadine HCl (60 mg daily) or placebo as a reference drug were given to the volunteers for 7 days and 21 days in a double blind with at least 14 days of wash-out period. Skin prick tests (SPT) were performed pre/posttreatment and first day within wash-out periods, and on the last day of 14-days interval.