Montelukast as add-on therapy to beta-agonists and late airway response

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Short title for running head: montelukast and late phase airway response

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Total word count: 2765
Abstract (197 words)

Introduction: We investigated whether single-dose oral LTRA as add-on therapy to short acting beta agonists immediately after allergen challenge blocks the late phase airway response.

Methods: 35 mild asthmatics (19 male, mean age 24 years) sensitized for house dust mites underwent two courses of bronchial allergen challenge. After the early allergic response (EAR), subjects received salbutamol once and were randomly assigned to either 10 mg of montelukast or placebo (double-blind, crossover). To identify a late allergic response (LAR), FEV$_1$ was monitored over the following eight hours. Baseline exhaled NO was determined ahead of each allergen challenge.

Results: Baseline NO-levels differed significantly depending on the reaction to allergen challenge. Twelve subjects showed no significant response, 11 an EAR only, and 12 had a dual response and underwent further analysis. The area under the FEV$_1$ time-response curve 3-8 hours after bronchial allergen challenge was -0.77 (+1.68) from the pre-challenge values on montelukast compared to -2.47 (+1.32) on placebo (p<0.05). Baseline FeNO of subjects without an EAR was significantly (p<0.05) lower than of those presenting a dual response.

Conclusion: Our results demonstrate that single-dose LTRA given orally right after the EAR can significantly inhibit the LAR after bronchial allergen challenge.

Keywords: asthma, bronchial allergen challenge, early asthmatic response, FeNO, late asthmatic response, montelukast
Introduction:

Allergic asthma is characterized by bronchial hyperresponsiveness and airway inflammation. In asthmatic patients NO in exhaled air (FeNO) is increased and correlates with asthma severity, sputum eosinophils, and methacholine reactivity \(^{[1-3]}\). As inhaled allergens contribute to asthmatic inflammation, allergen challenge is a useful clinical tool to study the mechanisms underlying asthma. Bronchial allergen challenge in susceptible individuals leads to an early asthmatic response (EAR) due to cross-linking of surface-bound IgE on mast cells causing the release of inflammatory mediators like histamine, prostaglandins, and cysteinyl-leukotrienes. This mediator release results in smooth muscle contraction and mucosal oedema triggering bronchoconstriction \(^{[4,5]}\). The EAR, although caused by inflammatory mediators, can be completely inhibited or resolved by bronchodilators such as \(\beta_2\)-agonists \(^{[6]}\).

Approximately 30 – 50% of asthmatic subjects with a positive bronchial allergen challenge will experience a bi-phasic response to inhaled allergens \(^{[7]}\). The late asthmatic response (LAR), which may follow the EAR within 3-8 hours after allergen challenge, involves acute inflammation and swelling of the airway wall. The inflammatory process is driven by activated neutrophils, eosinophils, mast cells, and T-lymphocytes and leads to epithelial desquamation, altered mucociliary function, and reduced clearance of respiratory tract secretions, thus resulting in airway obstruction \(^{[8-10]}\). This inflammation can be attenuated by corticosteroids, anti-IgE, and anti-leukotrienes, whereas beta-agonists only have bronchodilatory capacities and lack anti-inflammatory effects.

The cysteinyl-leukotrienes LTC4, LTD4, and LTE4 are not only potent bronchoconstrictors, but have several biological actions in the pathogenesis of asthma, including increased vascular permeability, formation of oedema, and enhanced mucus production, too \(^{[11]}\). These biological properties can be attenuated by anti-leukotriene drugs. Reduction of inflammation and a decrease in FeNO following montelukast treatment is thought to occur via two distinct mechanisms involving leukotrienes: direct inhibition at the receptor level, or inhibition of eosinophil recruitment into the lung, which indirectly reduces the capacity for further release of leukotrienes \(^{[12,13]}\). However, the mechanisms by which montelukast modulates NO production are not yet completely understood.

Previous studies have shown that montelukast attenuates both early and late-phase responses to aspirin \(^{[14]}\), exercise-induced bronchoconstriction \(^{[15]}\) and allergen challenge \(^{[16]}\), in both children \(^{[17]}\) and adults \(^{[18]}\). Furthermore Dockhorn et al. were able to show a quick onset of action for single doses of intravenous and oral montelukast \(^{[19]}\). Orally administered montelukast led to a significant increase in the FEV\(_1\) within two hours suggesting leukotriene receptor antagonists (LTRA) as a treatment option in acute asthma.

However, there have been no studies evaluating the acute effects of a single dose of oral montelukast in a bronchial allergen challenge model. In this study we sought to evaluate the acute effects of montelukast on the
LAR after allergen exposure in adults with house dust mite-induced asthma by using a well-characterized allergen challenge model.

Methods:

Subjects

35 atopic adults (19 male, 16 female, mean age of 24 years; range 18-31) with mild and on time of the study stable physician-diagnosed asthma (FEV₁ ≥ 80%, VC ≥ 80%) were recruited from the campus population by means of public posting. All subjects were sensitized to house dust mite (IgE specific for Dermatophagoides farinae at least RAST class 2) and had a history of episodic asthma (Tabl.1). Subjects were free of controller therapy (including long lasting beta-agonists, anti-cholinergics, theophylline, oral and inhalative corticosteroids, cromoglycate, anti-histamines, and leukotriene-antagonists) eight weeks before and during the study. Seven of the subjects smoked occasionally or regularly (1-15 cigarettes/day, see Tabl.1) but didn’t change their smoking habits during the study. None of the subjects used medication that could influence the results of this study. All subjects were in good clinical condition; none of them had experienced a respiratory tract infection within two weeks before and during the study, or suffered from any respiratory complaints on the day of the study. All patients supplied written informed consent prior to the study. Human experimentation guidelines of Good Clinical Practice, the German Drug Act and the declaration of Helsinki were followed in the conduct of clinical research. Local ethical committee approval was obtained.

Study design

The study was a randomized, double-blind, single-dose, placebo controlled, crossover trial with a washout period of at least two weeks. Subjects attended the department for three visits (Fig.1). On the first visit, entry criteria were assessed by interviewing the subjects, performing a physical examination, and drawing a venous blood sample for further analysis (total IgE, specific IgE (RAST), blood count). On the second visit, house dust mite sensitized subjects were checked for signs of airway infection, underwent a spirometry, and FeNO was determined. Only healthy subjects with a FEV₁ and FVC ≥80% were challenged as explained later.

Ten minutes after completion of the final allergen dosing, subjects underwent spirometry. When an EAR (drop of the FEV₁ >20%) or a clinical reaction occurred, subjects received one puff of salbutamol (0.1 mg) and either montelukast (2 x 5 mg tablets) or matching placebo immediately. During the following eight hours, FEV₁ was monitored hourly. If subjects showed a LAR (FEV₁ drop >15% 6-8 hours after bronchial allergen challenge), they
received a long lasting β₂-agonist (formoterol 12 µg, 1 puff) after finishing the test. On the third visit at least 14 days later (14-42 days), the same procedure was repeated, crossing-over montelukast and placebo.

**Lung function tests:**

Baseline spirometry (before inhalation of sterile saline 0.9% and before allergen challenge), was performed with the MasterScreen® bodyplethysmograph by VIASYS Healthcare GmbH (Hoechberg, Germany). Before and 0-8 hours after bronchial allergen challenge, subjects measured FEV₁ hourly using the SpiroPro® by VIASYS Healthcare GmbH (Hoechberg, Germany).

**Measurement of exhaled NO (FeNO):**

Measurements of exhalative NO were done using the NIOX® (by Aerocrine, Solna, Sweden). The NIOX® measures NO in exhaled air according to ATS guidelines [20]. This chemiluminescence gas analyzer is sensitive to measure NO at concentrations from 1.5 ppb to 200 ppb with a deviation from mean value of ±2.5 ppb <50 ppb or ±5% of the measured value >50 ppb.

**Allergen Inhalation Challenge Protocol:**

Solutions of Dermatophagoides farinae allergen extract (Allergopharma, Reinbek, Germany). were prepared according to the instruction manual. The lyophilized D. farinae allergen extract was resuspended in the solution provided by the manufacturer (containing sodium, phenol and water) resulting in aliquots of 5000 mg/ml; aliquots were stored immediately after preparation at 4°C until applied. All subjects were exposed in a single-blinded fashion by inhalation of sterile saline 0.9% followed five minutes later by increasing concentrations of D. farinae. The solutions were delivered via a medic aid nebulizer and the aerosol provocation system APS® powered by compressed air (by VIASYS Healthcare GmbH, Hoechberg, Germany). This system calculates the administered dose by breath from a constant flow and the inspiration time of any breath cycle, thus calculating the exact dose to be administered automatically. Mouthpieces and nebulizers were changed after each subject to avoid cross contamination. The doses of inhaled D. farinae were increased every eight minutes according to the following pattern from step 1 to 8: 0, 10, 20, 40, 80, 160, 320, 640 mg. Thus, the entire protocol delivered cumulative doses of 0, 10, 30, 70, 150, 310, 630, 1270 mg. This procedure had been developed in earlier studies, was found to be extremely safe, avoiding overdosing and detecting potential side effects as early as possible [21]. The challenge test was stopped when any of the following criteria was met: 1. the FEV₁ decreased at least 20% from individual baseline (EAR); 2. significant clinical complaints were reported by the subjects (e.g., chest pain), 3. a cumulative dose of 1270 mg had been achieved. Clinical monitoring accompanied each
provocation for at least eight hours, and then the subjects could leave the hospital remaining in touch via telephone with a physician involved in the study.

**End Points and Statistical analysis**

Our primary end point was the area under the FEV$_1$ time response curve 3-8 hours after bronchial allergen challenge (FEV$_1$-AUC$_{3-8}$ hours) in those subjects with an EAR and LAR (dual response) to bronchial allergen challenge. As established in the literature, it is given dimensionless. To identify a dual response, a significant EAR was defined as a drop in the FEV$_1$ >20% and a significant LAR was defined as a drop in the FEV$_1$ >15%. The Wilcoxon matched pairs test was used to analyze differences in FEV$_1$ values, FeNO–levels were compared with the Mann-Whitney-U test. The level of statistical significance was set at a probability (p) value of less than .05.

**Results:**

**FEV$_1$**

Thirty five subjects underwent two allergen challenge tests and completed the study. Twelve subjects showed no significant EAR on one or both study days and were excluded from further analysis.

Of the remaining 23 subjects, 12 (52%) had a dual response (EAR and LAR) and were therefore analyzed. There were no significant differences in baseline lung function between these three groups (Tabl.1).

In eight of 12 subjects the dose applied varied only within one dosage step, thus making the provocation schedule comparable. Six of 12 subjects tolerated higher house dust mite doses on the montelukast day.

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The difference in FEV₁ 3-8 hours after allergen challenge from baseline values was expressed as the area under the dimensionless FEV₁-time-response curve (FEV₁-AUC₃-₈ hours, Fig. 2). We compared the FEV₁ values of each patient during the LAR (3-8 hours post bronchial allergen challenge) on placebo with the results on montelukast. One of the subjects with a dual response had a smaller decrease of FEV₁-AUC₃-₈ hours on placebo than on montelukast, while 11 showed better results with montelukast. The FEV₁-AUC₃-₈ hours of the 12 subjects on placebo was -2.47 ±1.32 of the pre-challenge values compared to -0.768 ±1.68 on montelukast (p<0.005). In order to control for an influence of the allergen dose applied, we additionally made a subgroup analysis of those who received the same allergen dose on both visits. Subjects treated with montelukast experienced significantly less

### Subjects with no LAR

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| mean   | 22.90 | 110.8 | 112.20 | 23.4 | 460.36 | 427.45 |

### Subjects with a dual response

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<th>FEV₁ (%)</th>
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<th>montelukast</th>
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| mean   | 30.05 | 109.0 | 111.80 | 37.3 | 619.42 | 500.36 |
FEV\textsubscript{1} decrease than those after placebo (FEV\textsubscript{1}-AUC\textsubscript{3-8hrs}; \(p=0.0391\)). When pooling data from all study subjects, we also found a trend of higher FEV\textsubscript{1} values after montelukast (means 98.2 SD +/-8.6 versus 94.9% SD +/-7.7), which did not reach statistical significance. Additionally, we matched the baseline FEV\textsubscript{1} values of each patient with the greatest decrease in FEV\textsubscript{1} 6-8 hours after bronchial allergen challenge following placebo or montelukast, respectively (Fig.3).

**FeNO**

Thirty five subjects performed baseline FeNO measurements. The 12 subjects showing no EAR on one or both study days had baseline NO-levels of 21.0 ppb (95%CI 13.9–28.1) compared to 39.0 ppb (95%CI 2.62–75.4) in those subjects with an EAR on both study days and 56.4 ppb (95%CI 27.6–85.2) of the subjects with a dual response. The comparison of the subjects without an EAR and those with a dual response reached statistical significance (\(p<0.05\)).

There was no correlation between baseline FeNO and response to montelukast in our subjects, although there was a slight trend towards higher baseline FeNO values in the subjects with a poor response to montelukast. In a subgroup of subjects (\(n=8\)), we followed-up FeNO until 24 hours after bronchial allergen challenge. There was no significant difference between pre-challenge FeNO [median, range] (verum: 24.3, 15-120; placebo: 34.0, 12-82), and FeNO after eight hours (verum: 36.5, 12-150; placebo: 27.1, 9-60), respectively. After 24 hours there was a significant increase in both groups (verum: 73.6, 30 -219; placebo: 90.8, 29-248), but we were not able to show a significant difference between verum and placebo at any timepoint.

**Discussion:**

Cysteinyl leukotrienes play a pivotal role in different types of inflammatory lung diseases including allergic asthma [22]. They are particularly involved in the mechanisms leading to bronchoconstriction during the early and late asthmatic response. There are also sufficient data demonstrating that activation of leukotriene receptors results in induction of NO release [23-25]. Studies on an effect of fluticasone or budesonid compared with montelukast revealed a positive impact of all three substances on an early asthmatic response, with steroids being superior in improving bronchial hyperresponsiveness [26, 27]. Additionally, also a positive impact of inhalative corticosteroids on the late asthmatic response could be demonstrated [28]. Keeping the side effects of steroids in mind, our goal was to further investigate montelukast as add-on option to beta-mimetics in mild bronchial asthma.

Our subjects with a history of mild allergic asthma and no need for a controller therapy (GINA I) were challenged twice with house dust mite allergen. Twenty-three subjects (65.7%) had an EAR on both study days (drop in the
FEV₁ of ≥20%) and only 12 (34.3%) had a dual response. Furthermore, as baseline FeNO levels differed significantly among our patients, our results suggest that baseline FeNO might be useful to distinguish between subjects who develop a LAR from the subjects who don’t. This is in keeping with the findings of Kharitonov et al. [29].

This study is the first to evaluate the acute effects of a single-dose of montelukast on airway function when being given orally after an early asthmatic response. We were able to show that montelukast significantly blocked the late asthmatic response in subjects responding dually upon an allergen challenge. Interestingly, six of 12 subjects tolerated higher house dust mite doses on the montelukast day, supporting our concept of a beneficial effect. These results suggest an acute inhibiting effect on a leukotriene driven inflammatory process as the LAR generally leads to bronchoconstriction due to inflammation. Furthermore these results suggest a rapid onset of action of montelukast even when only given once orally. This is of clinical value, as many patients use a short-acting β₂-agonist (SABA) for symptom relief after allergen exposure. In the absence of a preventive effect, they have to be administered repeatedly once LAR occurs. Thus, LTRA offer a new therapeutical option in this setting. However, it is known from the literature that there are some subjects who have little response to leukotrienes. Our present findings concur nicely with these results. It is essential to determine predictors for a positive response to montelukast as the rapid onset of action entitles LTRA as asthma medications for patients responding to the substance.

Szefler et al. [30] recently identified the female gender, a greater decrease in FEV₁ from baseline, young age, or a short duration of the disease, and the FEV₁/ FVC ratio as predictors for a better LTRA response. In contrast, allergies and high levels of FeNO indicated a response to corticosteroids. We could not confirm the positive and negative predictive values of those parameters with the restriction of a small sample size not only in the Szefler, but also in our study.

We and other investigators showed that single doses of montelukast initiated sustained effects. Dockhorn et al compared the kinetics of i.v. montelukast with oral montelukast and placebo in patients with severe asthma [19]. They were able to demonstrate an effect of montelukast on FEV₁ when given intravenously within one hour. This was confirmed by other authors [31-34]. Additionally, they showed that a single dose of oral montelukast led to a significant increase in FEV₁ within 2-3 hours. Other studies have shown the protective effect of an orally administered single-dose LTRA in exercise-induced asthma in children and adults [13,18]. In these studies, montelukast demonstrated to improve pulmonary function within 3-12 hours after ingestion. This effect of a single-dose lasted up to 24 hours. In other trials, the onset of action of montelukast applied orally was in the range of 1-3 days [12,15,16]. Furthermore it was suggested, that LTRA are able to reduce both the early and late asthmatic response in allergic subjects when given before allergen challenge [32].
The aim of our study was to investigate a therapeutical option to better control late asthmatic symptoms in mild allergic asthmatics. The property of SABA to potentially attenuate the LAR has been studied extensively and was found to have no sustained effect on bronchial obstruction after 4-8 hours. Maybe a very mild and early LAR could be missed in our setting. On the other hand, our placebo control would have had the potential to distinguish when a more pronounced LAR occurred. Moreover we found it not ethical justified withholding SABA in our setting. Thus we routinely provided SABA after the challenge, which is a routine procedure according to GINA guidelines and serves the patients’ safety. Despite this manoeuvre was performed in all subjects, we clearly could demonstrate better lung function values in the montelukast group.

Our present study was not designed as a therapeutical trial but to provide a pharmacological proof of concept. Given the heterogeneity of some of the individual responses, we estimate that our relatively small study population raises the possibility of unrecognized type 1 and type 2 statistical errors, and that larger comparative investigations will be needed to confirm the effect of a single dose of oral montelukast. Future trials will have to evaluate, which patients profit and if this effect shown is only due to the anti-obstructive effect of montelukast, or whether additional anti-inflammatory mechanisms attenuating the LAR will be detectable.

To conclude, we proved a bronchodilative effect of montelukast added to salbutamol with an onset of action of 3-8 hours in an allergen challenge model. In our setting we couldn’t show an anti-inflammatory effect. Further studies are necessary to evaluate the clinical efficacy of montelukast given on demand.


**Fig.1: Study Design**
Fig. 2

Area under the FEV1 time-response-curve 3-8 hours after bronchial allergen challenge
Box and whiskers for montelukast and placebo respectively
(Shown are Max and Min values, the 95% CI and the Median)
Fig. 3 Comparison of individual FEV1 values on placebo and montelukast respectively

Baseline (100%) vs late asthmatic response (maximum percent fall 6-8 hours after bronchial challenge)

p < 0.05

mean: 90%

mean: 78%