The effect of montelukast on respiratory symptoms and lung function in wheezy infants

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Methods

Patients

Full-term infants and very young children (>37 weeks gestation), age 6 to 24 months, who had experienced at least one physician-diagnosed wheezing episode and history of troublesome dyspnoea and wheeze and a successfully performed methacholine challenge test were included. Exclusion criteria were: use of ICS within 8 weeks prior to the first visit, a cumulative life-time systemic prednisolone use more than 3 days at a dose of 2 mg/kg, an equipotent dose of another systemic corticosteroid or life-time ICS use more than 4 weeks, respiratory infection in the 14 days preceding the lung function measurement or any obvious tracheobronchomalacia or other structural defect. The study was approved by the Ethics Committee of the Helsinki University Central Hospital. Written informed consent was obtained from the childrens´ parents.

Study protocol

This was a single-center, parallel-group, randomized, placebo-controlled study. Between September 2004 and April 2008, 367 consecutive infants and very young children less than 24 months of age referred to Helsinki University Central Hospital Department of Allergy, a tertiary paediatric centre, for the measurement of lung function because of troublesome respiratory symptoms were screened for study enrolment. A total of 113 children fulfilling the inclusion criteria were randomized to the study (visit 1). On the first visit, demographic details and a full clinical history were recorded, and a physical examination was performed. Children entered a 1-2 week run-in period and received as needed inhaled terbutaline 0.25 mg/dose via the steel spacer, Nebuchamber®, (manufactured by AstraZeneca, Lund, Sweden) to relieve respiratory symptoms.

The children were randomly assigned to receive either montelukast 4 mg as oral granules formation or placebo once in the evening in pureé for 8 weeks. The drug and the nebuchambers were supplied by the pharmacy of Helsinki University Hospital. Patients were randomized to treatment in balanced blocks of four.

Lung function was measured again at the end of the 8 week treatment period (visit 3). At visit 1, thorax X-ray and skin-prick tests (SPT) were performed and at visits 1 and 3 blood samples were taken for analysis of total eosinophil count and immunoglobulin E levels. Atopy was defined by a positive SPT to food or aeroallergens. Sensitization was tested to egg white, cow's milk, wheat, soy bean, cod, shrimp, peanut, birch pollen, timothy grass pollen, dog epithelial dander, cat epithelial dander, house dust mite *Dermatophagoides pteronyssinus*.

Safety and tolerability were assessed by clinical evaluation and adverse experience monitoring. An adverse experience included any unfavourable change or worsening in the patients during the treatment period.

Outcome measures

The primary efficacy outcome was the number of symptom-free days. During the run-in and treatment periods, parents kept daily record cards of their child´s respiratory symptoms, recording separately the daytime and night-time scores together for wheeze, dyspnea, or shortness of breath using a Visual Analog Scale, ranging from 0 for no symptoms to 10 for the most severe symptoms. Symptom free days was defined as a VAS score ≤ 0.5 for day and night time and no use of rescue medicine. The number of occasions on which rescue terbutaline was used to relieve respiratory symptoms during each day and night was also recorded. The parents were trained to record the symptoms by an experienced asthma nurse at a guidance session during visit 1. The secondary efficacy endpoints evaluated the effect of montelukast on lung function, AR, $FE_{NO,}$ use of rescue medication and the number of asthma exacerbations.

Between 1-2 doses of inhaled terbutaline 0.25 mg/dose could be used as a rescue medication throughout the study, up to a maximum of six times per day. In the case of wheezing attack, the administration of bronchodilating agents was allowed. An exacerbation was defined as any three consecutive days and/or nights with symptoms and at least two treatments of inhaled terbutaline per day or healthcare resource use or hospitalization because of wheeze. Patients were withdrawn from the study if they required inhaled or systemic steroid treatment. Inhaled terbutaline was stopped 12 hours prior to the lung function measurement.

Lung function testing

The basic lung function was measured using commercial equipment (Babybody Masterscreen; Jaeger GmbH, Wurtzburg, Germany) according to the protocol used in Helsinki University Central Hospital as described earlier [1]. The functional residual capacity (FRC) and specific airway conductance (sGaw) were measured using an infant whole-body plethysmograph [1-3]. Thereafter, the maximal flow at functional residual capacity ($V'max_{FRC}$) was recorded using the squeeze technique [1, 4]. Flow was measured with a pneumotachometer from a mask covering the infant´s nose and mouth. Application of silicone putty was made around the mouth and nose and to the facemask to ensure an airtight seal. Optimal jacket pressure was determined by repeated manoeuvres with 1-2 kPa increments. The mean $V'max_{FRC}$ of three technically acceptable expiratory flow volume curves obtained at that compression pressure was recorded. The baseline lung function results were expressed as z-scores, which equal the number of standard deviations by which the observed value deviates from the length- and sex-corrected reference value [1-4].

Methacholine challenge

The dosimetric methacholine challenge test was performed as described in detail previously [1]. A calibrated nebulizer (Salter Labs 8900, Arvin, CA) was connected to an auto-

matic, inhalation-synchronized dosimeter (Spira Electro II, Spira Respiratory Care Center Ltd, Finland) [5]. By calculating the number of breaths with nebulized methacholine, a dosage scheme with four non-cumulative dose steps was delivered (0.1, 0.3, 0.9 and 1.8 mg), with $V'_{max,FRC}$ being recorded after each dose. There were two endpoints in the challenge test; a fall of 40% or more in $V'_{max,FRC}$ or reaching the maximal dose of methacholine. The provocative dose of methacholine causing a 40% fall in $V'_{max,FRC}$ (PD_{40} $V'_{max,FRC}$) was determined from the dose-response curves. In cases where the maximal dose was reached and $PD_{40}V'_{max,FRC}$ could not be determined from the dose-response curves, for statistical purposes, $PD_{40}V'_{max,FRC}$ was defined as twice the highest dose of methacholine, 3.60 mg.

During lung function measurements and the challenge test, oxygen saturation and heart rate were continuously monitored with a pulse oximeter (Biox 3700e, Ohmeda, Louisville, KY). Following the challenge test, the children received inhaled salbutamol (0.6 mg) (Ventoline Evohaler 0.1 mg/dos) via Nebuchamber.

Nitric oxide in exhaled air

Before the methacholine challenge test, the fraction of FE_{NO} was assessed with a modification of the online single-breath measurement [6]. Under sedation, the babies breathed spontaneously room air through a mask which had a pneumotachometer attached to it. A rapid thoracoabdominal compression technique was applied to generate a forced expiration starting from end-inspiration. By using the shutter mechanism of the pneumotach and a 3-way valve, the expired air was led to a chemiluminescence analyzer (Niox, Aerocrine, Sweden) via a dynamic resistor that restricted the expiratory flow to 50 ml/s. Sampling of exhaled air occurred in the proximity of the 3-way valve, with a dead space including the mask and valve/shutter system of about 25 ml. FE_{NO} was measured from the end-expiratory sample by using the plateau phase of the NO profile. Repeated exhalations were performed in order to obtain three reproducible FE_{NO} measurements (variation less

than 10 % or 5 ppb). The mean value of these measurements was recorded as well as the ambient NO during the test. Only measurements with ambient NO < 10 ppb were considered acceptable.

Statistical analysis

All analyses were performed on the intention-to-treat population, which consisted of all randomized patients who took at least one dose of study medication. The study was designed to detect a difference between the treatment groups, based on the primary endpoint i.e. the proportion (%) of symptom-free days at the end of treatment. A 5% significance level, one-way hypothesis and a power of 90% was used in calculating the sample size. A previous randomized, double-blind, parallel study design [7] in hospitalized infants with respiratory syncytial virus (RSV) bronchiolitis revealed that montelukast treatment resulted in symptom free days of 22%, compared to 4% in the control group, during the follow-up of 28 days. Anticipating a similar effect in the infants with asthmatic wheeze, the present study was estimated to require 56 infants in both treatment arms, if one wished to detect a statistical difference. All daily diary card variables were analyzed as changes from baseline. Symptoms and rescue medication use in the last week of the run-in period and in the treatment weeks were analysed for each parameter. We chose the seventh treatment week as the endpoint.

For categorical variables Chi-squared test or Fisher´s exact test were used. The Mann-Whitney´s U-test or t-test was used for between treatment comparisons in lung function and inflammatory markers. The interaction between time and group in symptom-free days and the use of rescue medication was analyzed using ANOVA with repeated measures. In the post hoc analysis, the relationships between changes in symptom-free days and use of rescue medications and atopic eczema, family history of asthma, SPT positivity, total eosinophil count or FE_{NO} values were examined by ANOVA with repeated measures. Two-

sided p-values < 0.05 were considered statistically significant. The data were analyzed using SPSS for Windows software version 17.0 (Inc, Chicago, IL).

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TABLE 4: Incidence of drug-related adverse events*

	Montelukast N = 52	Placebo N = 54
Abdominal pain	0 (0)	1 (1.9)
Diarrhea	0 (0)	1 (1.9)
Itchiness	2 (3.8)	0 (0)
Tiredness	1 (1.9)	0 (0)
Anxiety	2 (3.8)	0 (0)
Total	5 (9.6)	2 (3.7)

* Data expressed as number of patients (%).

TABLE 5: Clinical adverse experiences in treatment groups regardless of causality*

	Montelukast N = 52	Placebo N = 54
Diarrhea	6 (11.5)	8 (14.8)
Pyrexia	12 (23.1)	9 (16.7)
Nasopharyngitis	19 (36.5)	20 (37.0)
Conjuctivitis	4 (7.7)	2 (3.7)
Otitis	16 (30.8)	8 (14.8)
Bronchitis	1 (1.9)	4 (7.4)
Pneumonia	0 (0)	2 (3.7)
Varicella	1 (1.9)	1 (1.9)
Antibiotic treatment	15 (28.8)	14 (25.9)

*Data expressed as number of patients (%)