

Original article

No effect of montelukast on asthma-like symptoms in elite ice hockey players

Background: Controlled clinical trials on the effects of leukotriene antagonists on asthma-like symptoms, bronchial hyperresponsiveness and airway inflammation have not been performed in elite athletes.

Methods: In 2001, we examined 88 of 102 (86%) players from three junior, national league ice hockey teams in Helsinki. Athletes were included in the intervention if they reported at least two exercise-induced bronchial symptoms (wheeze, cough, shortness of breath) weekly during the previous month on a previously validated respiratory-symptom questionnaire. Sixteen male ice hockey players fulfilled the study criteria. A double-blind, randomized, cross-over, placebo-controlled study included 4-week active treatment (10 mg oral montelukast, bedtime), 1-week washout period, and 4-week placebo treatment. Before entering the study, all patients were clinically examined, skin prick tested, filled in a respiratory symptom questionnaire, performed a spirometry and a histamine challenge test, and gave induced sputum samples. Exhaled NO was measured. These measures were repeated after both treatment periods. During the treatment the athletes kept daily diary on lower respiratory tract symptoms on a scale from 0 (no symptoms) to 10 (most severe symptoms), morning peak expiratory flow (PEF), training amount, and use of study medication. Primary end-point was daily lower respiratory tract symptom score.

Results: Montelukast had no effect on daily lower respiratory symptom scores, spirometry parameters [forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), FEV₁/FVC ratio, PEF], bronchial hyperresponsiveness, sputum eosinophil or neutrophil cell counts, exhaled NO measurements, or morning PEF. Nine subjects were atopic in skin prick test, but their results did not differ from the nonatopic subjects.

Conclusion: A leukotriene antagonist, montelukast, was of no benefit in the treatment of asthma-like symptoms, increased bronchial hyperresponsiveness or a mixed type of eosinophilic and neutrophilic airway inflammation in highly-trained ice hockey players.

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Exercise may increase ventilation up to 200 l/min for short periods of time in speed and power athletes such as ice hockey players (1), and for longer periods in endurance athletes, such as long-distance runners, cross-country skiers and swimmers (2–5). During heavy training sessions ice hockey players are strongly exposed to cold air and to carbon and nitrogen oxides from ice resurfacing machines in indoor ice arenas (6, 7).

The occurrence of bronchial hyperresponsiveness and asthma is higher in ice hockey players than in general population (1, 8), but airway inflammation has not been studied in them. A high proportion of athletes report exercise-induced bronchial symptoms (1, 3, 8, 9), but if they do not fulfil the functional criteria for asthma, they are usually left without effective anti-asthmatic treatment.

Controlled clinical trials on the effects of anti-asthmatic treatment on respiratory symptoms, bronchial hyperresponsiveness and asthma in ice hockey players have not been performed.

Cysteinyl leukotrienes mediate abnormalities of airway function, such as increased mucus production, increased vascular permeability, smooth muscle contraction, and recruitment of inflammatory cells (10, 11). The leukotriene antagonist, montelukast, has been effective against exercise-induced bronchospasm (12, 13). Montelukast has also reduced eosinophilic airway inflammation in asthmatics (14). There are no previous studies on the effects of leukotriene antagonists on airway inflammation, bronchial hyperresponsiveness, and symptoms of asthma in elite athletes. Thus, the role of cysteinyl leukotrienes have

remained unclear in the pathophysiology of athletes' asthma.

Our aim was to evaluate the effect of a leukotriene antagonist, montelukast, on asthma-like symptoms, increased bronchial responsiveness, and on indices of airway inflammation in elite ice hockey players in a double-blind randomized, placebo-controlled trial. By comparing the effects of a leukotriene antagonist with placebo, we also tested the role of cysteinyl leukotrienes in the pathophysiology of athletes' asthma.

Methods

Study design

Between November 2001 and February 2002, we screened ice hockey players from three junior, national league teams in Helsinki. The athletes were given a brief description of the purpose of the study after a usual training session. Eighty-eight of the 102 (86%) ice hockey players who attended the information sessions volunteered to take part in the screening phase. Of the nonparticipating athletes, three reported having physician-diagnosed asthma, which they considered to be well controlled.

Athletes were included in the intervention if they reported at least two exercise-induced bronchial symptoms (wheeze, cough, shortness of breath) weekly during the previous month on a previously validated respiratory-symptom questionnaire (9). Exclusion criteria were use of inhaled corticosteroid or other anti-asthmatic treatment within 4 weeks, other chronic disorder, smoking, or respiratory tract infection within 4 weeks.

Sixteen male ice hockey players (10 from the Finnish junior national team) fulfilled the study criteria (Table 1). Three of them had asthma previously diagnosed by a physician. The study period was during the active competitive season (November 2001–April 2002). A double-blind, randomized, cross-over, placebo-controlled study included 4-week active treatment (10 mg oral montelukast, bedtime), 1-week washout period, and 4-week placebo treatment (identical tablet). Before entering study, all patients were clinically examined, skin prick tested, filled in a respiratory symptom questionnaire (9), and performed a resting flow-volume spirometry, and

a histamine challenge test. Exhaled NO was also measured. On a separate day, athletes gave induced sputum samples. These measures, except skin prick testing, were repeated after both treatment periods. During the treatment periods, the athletes kept daily diary on asthma-like symptoms, morning peak expiratory flow (PEF), training amount, and use of study medication. Primary end-point was daily asthma-like symptom score.

The study was approved by local ethics committee, and all patients gave their written informed consent.

Questionnaire and diary

Before entering the study, the athletes completed a respiratory-symptom questionnaire, which contained questions on the diagnosis of asthma and allergy made previously by a physician, use of antiasthmatic medication, family history of asthma and allergic rhinitis, exercise-induced bronchial symptoms, competitive status and smoking habits (9). During the treatment periods, the athletes kept daily diary (15) on exercise-induced asthma-like symptoms on a scale from 0 (no symptoms) to 10 (most severe symptoms), morning PEF, training amount, respiratory tract infections, and use of study medication. Answers to the questionnaires were confirmed during clinical examinations.

Resting spirometry, histamine challenge test, exhaled NO, skin prick test

Resting spirometry was carried out according to the recommendations of the American Thoracic Society (16) with a flow-volume spirometer (Medikro, Medikro Oy, Kuopio, Finland). Values are expressed as percentages of reference (predicted) values for adult Finns (17).

Histamine challenges were performed by the dosimetric method with controlled tidal breathing (18). Non-cumulative histamine doses of 0.025, 0.1, 0.4 and 1.6 mg were inhaled and forced expiratory volume in 1 s (FEV₁) values measured 90 s after each inhalation. The dose of histamine that caused a 15% fall in FEV₁ (PD₁₅ FEV₁) was determined by logistic interpolation. Increased bronchial responsiveness was defined as PD₁₅ FEV₁ ≤ 1.6 mg (18). Dose/response rates (DRR) were calculated as a fall in FEV₁ divided by the maximal dose of histamine (19).

Exhaled NO was measured prior to histamine challenge test according to the recommendations of the American Thoracic Society (20) by the chemiluminescence method with a computerized system (Exhaled breath analyser, Aerocrine AB Stockholm, Sweden).

Skin prick tests were made with 10 allergen extracts (Soluprick SQ, 10 HEP; ALK-Abello, Hørsholm, Denmark) and positive (histamine dihydrochloride, 10 mg/ml) and negative (solvent) control solutions. The inhalant allergens used were: birch, timothy, meadow fescue and mugwort pollen, horse, cat, dog and cow dander, the mite *Dermatophagoides pteronyssinus*, and mould spores of *Cladosporium herbarum*. A subject was classified as atopic if any allergen caused a wheal of 3 mm or more in diameter while control solutions gave expected results.

Sputum examination

Sputum was induced without pretreatment by inhalation of hypertonic saline generated by an ultrasound nebulizer (Spira Ultra, Hengityshoitokeskus, Hämeenlinna, Finland) for 15 min (21). Sputum was examined as described previously (22). Differential cell counts of intact bronchial epithelial cells and leukocytes were made

Table 1. Clinical characteristics

Characteristic	Ice hockey players (n = 16)
Sex (M/F)	16/0
Mean (SD) age (years)	18.0 (1.0)
Mean (SD) duration of active sports career (years)	10.4 (2.3)
Mean (SD) training amount in previous year (h)	685 (200)
History of physician diagnosed asthma (n)	3
Atopic in skin prick test (n)	9
Mean (SD) forced expiratory volume in 1 s	
In liters	4.72 (0.41)
As percent of predicted*	100.9 (12.4)
Mean (SD) FVC	
In liters	5.66 (0.67)
As percent of predicted*	107.0 (10.0)
Mean (SD) peak expiratory flow	
In liters per minute	591.6 (67.2)
As percent of predicted*	101.6 (18.8)

* Reference values for adult Finns (17).

by counting at least 400 nonsquamous cells. The cell counts, made by two investigators (A.L., P.R.) blinded to the clinical characteristics of the study subjects, were averaged to yield the final percentages reported here. Sputum eosinophilia was defined as a sputum differential eosinophil count of $>2\%$ (23).

Statistical analysis

The sample-size requirement of 16 athletes was calculated using a study power of 80%, a type-I error α of 0.05, and an estimated effect size of 1.0. Effect size evaluation was based on an assumption that mean (SD) baseline asthma symptom score (primary endpoint) would be 3.0 (1.5) which then could be lowered down to a mean (SD) value of 1.5 (1.5).

Treatment periods were compared using McNemar's test, and Wilcoxon signed rank test. Carry over effect of the treatments was analyzed using two-way ANOVA. Two-tailed P -values of 0.05 or below were considered significant.

Results

None of the ice hockey players had a history of upper or lower respiratory tract infection within 4 weeks before baseline during the treatment periods. Two athletes had abnormally low FEV₁/FVC ratio [69 and 70% of predicted (17)] and one abnormally low FEV₁ [72% of

predicted (17)] in resting flow volume spirometry at baseline. Increased bronchial responsiveness was found in six (38%), atopy in nine (56%), and sputum eosinophilia ($>2\%$) in three (19%) of the 16 athletes at baseline (Tables 1 and 2).

Daily, weekly or monthly scores for exercise-induced symptoms did not differ in paired statistical analysis between montelukast and placebo treatments (Fig. 1; Table 2). Montelukast had no effect on spirometry parameters (FEV₁, FVC, FEV₁/FVC ratio, PEF), bronchial hyperresponsiveness (including DRR), sputum eosinophil or neutrophil cell counts, exhaled NO measurements, or morning PEF (Table 2).

The results of the endpoint parameters did not differ between atopic and nonatopic athletes.

No carry over effect of the treatments was observed (two-way ANOVA).

Discussion

The effects of leukotriene antagonists have not been studied earlier in elite athletes with symptoms suggesting asthma. This carefully controlled clinical study did not show montelukast to be any better than placebo in

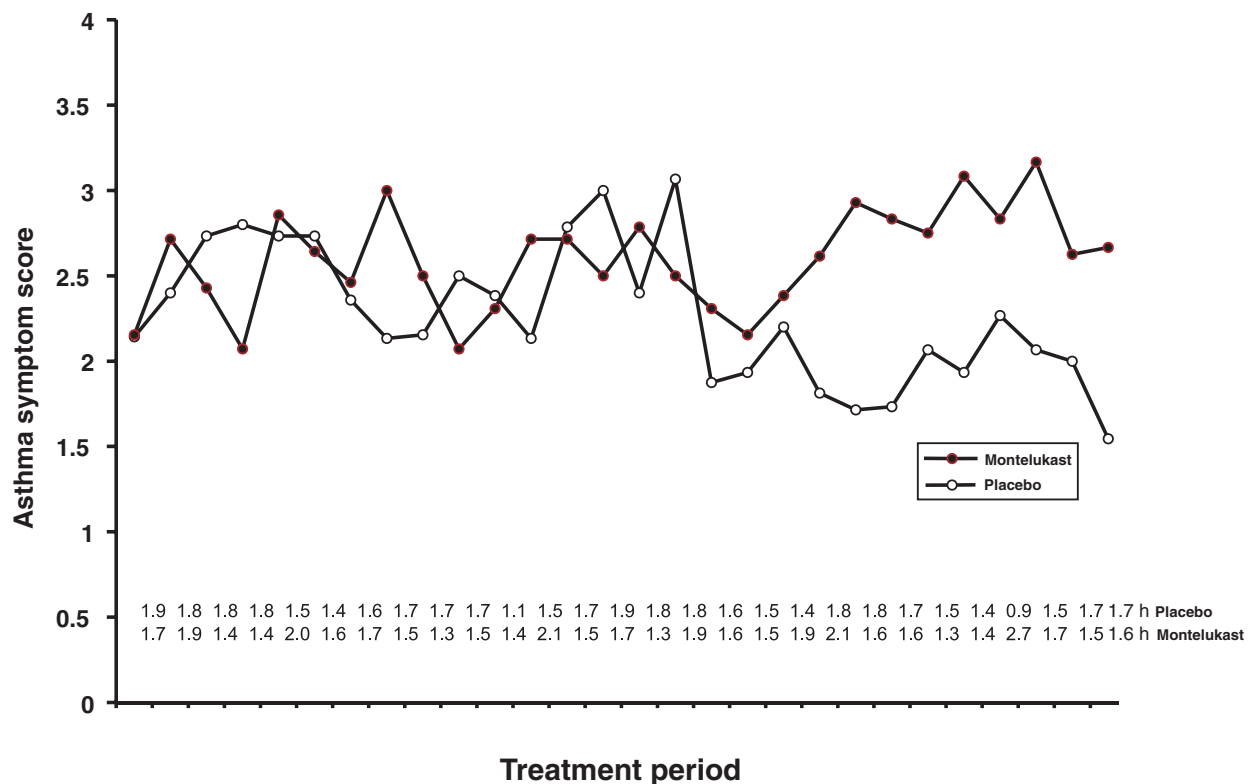


Figure 1. Mean daily lower respiratory tract symptom score (from 0, no symptoms to 10, most severe symptoms) in the active treatment (closed circle) and in the placebo treatment groups (open circle). A scale. No difference was observed between the study groups. Numbers down show mean daily training hours in both treatment groups.

Table 2. Effect of montelukast or placebo on study outcomes

Characteristic	Pretreatment	Placebo	Active treatment	P-value†
Mean (range) first week lower respiratory tract symptom score	—	2.61 (0–7)	2.56 (0–6.2)	NS
Mean (range) fourth week lower respiratory symptom score	—	2.01 (0–4.1)	2.58 (0–6.4)	0.59
Mean (range) treatment period lower respiratory symptom score	—	2.35 (0–4.0)	2.64 (0–4.0)	NS
Mean (range) first week morning peak expiratory flow (l/min)	—	570 (450–660)	560 (450–680)	NS
Mean (range) fourth week morning peak expiratory flow (l/min)	—	570 (450–675)	570 (450–690)	NS
Forced expiratory volume in 1 s				
In litres	4.72 (3.93–5.36)	4.74 (3.46–5.48)	4.71 (3.74–5.43)	NS
In percentage of reference values*	100.9 (72.0–125.0)	99.6 (65.0–124.0)	99.4 (71.0–127.0)	NS
Increased bronchial responsiveness (n)	6	4	6	NS
Dose response rate (%/mg)	23.0 (2.3–160.3)	12.9 (2.5–62.9)	11.0 (1.1–51.5)	NS
Mean (range) sputum differential eosinophil cell count (%)	1.3 (0–6.1)	0.9 (0–3.1)	1.1 (0–7.1)	NS
Mean (range) sputum differential neutrophil cell count (%)	88.7 (77.1–97.6)	76.3 (15.4–98.8)	77.1 (33.3–95.9)	NS
Mean (range) exhaled NO	18.2 (6.4–67.6)	24.0 (6.9–143)	16.3 (7.6–39.4)	0.10

* Reference values for adolescent and adult Finns (17).

† Between treatment groups.

NS, not significant.

treating exercise-induced asthma-like symptoms in young athletes. The clinical impact of this result is considerable taking into account the large number of young people suffering from these kinds of symptoms for prolonged periods. The result is, however, preliminary because of the small number of participating athletes. It should also be noted, that the bronchoconstriction observed in the young athletes was slight or nonexistent, which probably explains the lack of bronchoprotective effect of montelukast. Nevertheless, it is interesting that exercise-induced symptoms (especially cough) was not affected by montelukast.

The primary outcome was daily symptom score. It can be argued that the symptom scores were relatively low, mean values around 2.5 in a scale from 0 to 10, which would not give much room for improvement during active treatment. However, the scale was adapted from a previous study, where significant treatment effects were shown in patients who had about the same symptom score level at baseline (15). In the present study, altogether seven outcome parameters were evaluated, and none showed preference for montelukast. The result suggests that although cysteinyl leukotrienes are significant mediators of airway inflammation in asthmatics, their role is less important in the pathophysiology of athletes' asthma.

Validity of the data

Recruitment of the study subjects was carefully recorded. We wanted to perform the intervention during the very active competitive season, which restricted the length of the study period. Accordingly, no baseline period for symptom follow-up was included, but the subjects had to report at least two of three exercise-induced bronchial symptoms weekly during the previous month on a validated questionnaire (9). The present study was planned to evaluate a real-life situation in which not all athletes show clinically evident asthma, but long-lasting

exercise-induced bronchial symptoms. This may result in a more heterogeneous study population. However, it shows that in symptomatic athletes monotherapy with leukotriene antagonist fails to provide clinical benefit.

There has been no previous studies on leukotriene antagonists in elite athletes, and moreover no therapeutic interventions on asthma symptoms in ice hockey players. Thus, we were compelled to make assumptions when calculating sample-size requirement using accepted standard for study power (80%) and type-I error ($\alpha = 0.05$). This calculation may underestimate the sample-size requirement, as mean daily symptom scores were somewhat lower than estimated 3.0. However, the treatment effects of placebo as well as montelukast were quite similar without any trends. This may indicate that the conclusion would not be different with considerably larger sample size.

Treatment period was 4 weeks, which has been long enough in reducing eosinophilic airway inflammation (14), and against exercise-induced bronchospasm (12, 13). Compliance for the use of study medication was good according to the diaries (98% of all tablets were used). Wash-out period was 1 week, and no carry over effect was observed. The repeatability of the histamine challenge test (18), exhaled NO measurement (20), and the sputum inflammatory differential cell counting have been reported earlier (24).

Use of exercise challenge tests would have increased possible outcome measures. However, for compliance reasons, we tried to keep the study design as easy as possible for the athletes, because the study was performed during their active competitive season. It would have increased the number of visits from six to nine to the laboratory, if we had performed exercise challenges, as one cannot perform exercise challenge, histamine challenge, and induced sputum sampling on a same day.

Exercise-induced bronchial symptoms were recorded on a daily basis. As shown in Fig. 1, highly-trained ice

hockey players perform training daily. Thus, the athletes were able to report their symptoms on a daily diary.

Comparison with previous data

Airway inflammation has not been previously studied in ice hockey players. Karjalainen et al. (25) observed increased share of T-lymphocytes, neutrophils, and eosinophils in the lamina propria of bronchial biopsy samples from highly-trained cross-country skiers. We have observed earlier that mild eosinophilic and lymphocytic airway inflammation was aggravated in swimmers who remained active during a 5-year prospective follow-up study (5). In contrast, swimmers who stopped active training, eosinophilic airway inflammation, bronchial hyperresponsiveness, and asthma attenuated or even disappeared. Swimmers have also shown signs of neutrophilic airway inflammation in induced sputum samples (22). In the present study, ice hockey players showed signs of a mixed type of neutrophilic and eosinophilic airway inflammation. Much increased ventilation during exercise combined with exposure to cold air and nitrogen and carbon oxides (6, 7) may be responsible for asthma-like symptoms and airway inflammation in our athlete group. The irritant-induced airway inflammation observed in elite athletes, may significantly differ from that observed in nonathlete asthmatics in showing predominance of neutrophils over other cell types.

Sue-Chu et al. (26) observed that inhaled budesonide did not have any effect on airway inflammatory markers,

bronchial responsiveness or asthma symptoms as compared with placebo in cross-country skiers. A seasonal bias affected that study, since it began before active competitive season, and ended on it.

Why a leukotriene antagonist, montelukast, was of no benefit in treatment of symptomatic ice hockey players? The mechanism of irritant-induced airway inflammation seems not to be cysteinyl leukotriene-mediated. Exposure to irritating agents also continued throughout the treatment. In addition, not all asthma-like symptoms in elite athletes are because of irritant-induced airway inflammation or bronchial hyperresponsiveness or both.

In conclusion, a leukotriene antagonist, montelukast, had no effect on asthma-like symptoms, lung function, or indices of airway inflammation in symptomatic ice hockey players as compared with placebo treatment. Leukotrienes do not seem to be important mediators of airway inflammation, bronchial responsiveness or asthma-like symptoms in elite athletes.

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