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The combination of single-dose montelukast and loratadine on exercise-induced bronchospasm in children

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ABSTRACT: The aim of the study was to evaluate the protective effect of single-dose, combination treatment comprising montelukast (5 mg) and loratadine (10 mg), on exercise-induced bronchoconstriction in asthmatic children. The combination was compared to placebo, loratadine and montelukast alone.

Nineteen children were enrolled in a double-blind randomised, single-dose, crossover study. For each treatment patients undertook two treadmill exercise tests, 2 and 12 h respectively after single-dose administration.

No significant differences were seen in the maximum fall in forced expiratory volume in one second (FEV_1) 2 h after treatment and placebo. Whereas significant differences in maximum fall in FEV_1 were observed between treatment groups 12 h after administration. Loratadine alone did not show any significant protection or any additional effect in comparison with montelukast alone. Single doses of montelukast and montelukast plus loratadine were significantly more effective than loratadine at 12 h.

The present study, performed using single-dose treatments, demonstrated that maximal protective effect by montelukast was obtained 12 h after dosing and that montelukast plus loratadine did not result in significant additive bronchoprotective effects on exercise-induced bronchoconstriction.

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The role of leukotrienes in asthma is demonstrated by several studies showing positive prechallenge effects by leukotriene-receptor antagonists (LTRAs) in exercise- [1, 2] and allergen-induced bronchoconstriction [3]. The LTRAs, such as montelukast, provide protection against exercise-induced bronchoconstriction (EIB) attenuating the fall in pulmonary function following exercise with no induced tachiphylaxis. β_2-agonists are highly effective in reducing the symptoms. However, recent studies highlighted that the extent of protection diminishes with their exclusive regular use after 6–8 weeks both for short-acting and long-acting agonists (reviewed in [4]). Histamine has been implicated in EIB but antihistamines have been shown to offer modest protection against EIB [5]. However, there is some evidence that combined mediator blockade with both leukotriene and histamine-receptor antagonists results in greater symptom control than LTRAs alone in patients with persistent asthma [6]. In fact, it has been demonstrated that cysteinyl-leukotrienes and histamine synergise *in vitro* as immunoglobulin (Ig) E-dependent bronchoconstriction mediators [7]. Furthermore, the combination of zafirlukast, a leukotriene antagonist, and loratadine was significantly more effective than either drug alone during allergen-induced early and late obstruction [3]. The aim of this study was to investigate if single doses of the combination of a LTRA, montelukast, and a histamine-receptor antagonist, loratadine, may determine an addictive protective effect on EIB in children in comparison to either drug alone.

Methods

Patients

Allergic-asthmatic children (n=19) with a positive clinical history of EIB were evaluated whilst living at high altitude in the Italian Alps, in a house dust mite-free environment. The patient characteristics are summarised in table 1. Because of the effects of prolonged stay at high altitude none of the patients were receiving inhaled or oral steroids, antihistamines or antileukotrienes. The patients had not presented with infectious diseases of the upper airways in the previous month. β_2-agonists were allowed for as-needed medication until at least 12 h before the challenges. On the day of admission to the study the subjects performed baseline exercise challenges at 10:00 and 20.00 h. A fall in the forced expiratory volume in one second (FEV_1) after exercise of $\geqslant 15\%$ of the pre-exercise value was considered diagnostic of EIB.

Table 1. – Patient characteristics

Patient no.	Age yrs	Sex	Height cm	Weight kg	Asthma duration yrs	FEV_1 at recruitment %	Methacholine PC_{20} $mg \cdot mL^{-1}$
1	11	M	140	39	7	84	2.2
2	13	M	160	59	10	101	12.0
3	13	M	159	59	8	95	12.0
4	11	M	137	35	9	87	2.5
5	8	M	131	35	5	76	1.06
6	12	M	151	44	6	95	6.5
7	11	M	151	36	5	80	5.3
8	11	M	145	42	7	77	0.27
9	13	F	150	45	10	76	3.5
10	11	F	132	31	6	80	12.0
11	13	F	158	53	10	84	12.0
12	10	M	142	45	7	83	0.8
13	9	F	136	30	5	87	2.5
14	13	F	152	70	8	89	1.4
15	7	M	134	32	4	104	9.0
16	10	M	151	59	5	88	7.5
17	13	M	173	70	8	91	6.5
18	10	F	137	36	6	103	12.0
19	12	M	155	40	6	87	6.4

FEV_1: forced expiratory volume in one second; PC_{20}: provocative concentration causing a 20% fall in FEV_1; M: male; F: female.

Study design

The study was performed during the winter in order to eliminate the influence of pollens. A double-blind randomised, single-dose, crossover design was used. For each patient four double-blind randomised single-dose treatments of placebo, loratadine, montelukast and the combination montelukast plus loratadine, were administered on four different days at 08:00 h. Each patient undertook two treadmill exercise tests following each drug administration 2 (10:00 h) and 12 h (20:00 h) after dosing. Each drug administration and the following exercise tests were performed 3–5 days apart.

Treadmill exercise tests

Children performed a baseline spirometry and then ran for 6 min on a treadmill, at speed, to obtain an increase of 80% in their maximum cardiac frequency in a specially designated room with constant temperature (21°C) and humidity (40–50%). Following the exercise challenge, FEV_1 was obtained at 1, 5, 10, 15, 20 and 30 min. To assess bronchoconstriction after the exercise challenge, the maximal percentage fall in FEV_1 (ΔFEV_1) from the baseline value and the area under the curve ($AUC_{0-30min}$) with percentage change in FEV_1 data over time were considered. Percentage of protection was calculated as:

$$P_s - P_t / P_s \quad (1)$$

where P_s is the percentage fall in FEV_1 at the screening visit, and P_t is the fall after each treatment. Clinical protection was considered to be obtained if the percentage fall after receiving active drug was one-half or less of the percentage fall after receiving placebo.

Statistical analysis

The effects of treatment on the response to exercise challenge were compared using ΔFEV_1 expressed as the percentage of the prechallenge baseline. An analysis of variance model for repeated measures (ANOVA) in a crossover design was used to compare treatment groups. The hospitals' ethical committee approved the study and the parents gave informed consent.

Results

Safety

No adverse effects on safety were observed during the study period.

Efficacy

There was no significant difference between patients' baseline FEV_1 after each drug administration (table 2). The ΔFEV_1 during the screening test, expressed as mean±SEM, were: -22.84±3.01 at 10:00 h and -21.31±2.60 at 20.00 h.

When the exercise test was performed 2 h after the drug administration the ΔFEV_1 was -15.33±2.93 for placebo, -13.9±2.67 for loratadine, -13.33±2.03 for montelukast and -10.07±1.96 for the combination, with no significant differences. At 12 h the ΔFEV_1 was -18.69±2.83 for placebo, -14.64±2.55 for loratadine, -9.78±1.85 for montelukast and -9.51±2.55 for montelukast plus loratadine. Significant differences were observed between placebo and montelukast ($p<0.02$), placebo and the combined treatment ($p<0.02$) and between respectively montelukast and

Table 2. – Baseline forced expiratory volume in one second (FEV_1) with the different exercise-challenge tests

Patient no.	Screening		Placebo		Loratadine		Montelukast		Montelukast+Loratadine	
	2 h	12 h	2 h	12 h	2 h	12 h	2 h	12 h	2 h	12 h
1	1.79	1.72	1.69	1.58	1.66	1.67	1.79	1.70	1.68	1.79
2	3.14	3.00	3.23	3.20	3.10	3.07	3.21	3.04	3.27	3.16
3	2.91	2.89	2.98	2.96	2.91	2.95	3.04	2.87	3.08	2.87
4	1.75	1.94	1.78	1.66	1.62	1.74	1.75	1.76	1.77	1.83
5	1.36	1.64	1.58	1.56	1.62	1.53	1.70	1.79	1.86	1.81
6	2.36	2.18	2.28	2.18	2.30	2.11	2.46	2.40	2.31	2.23
7	2.11	2.19	2.22	2.19	2.18	2.16	2.07	2.20	2.00	2.09
8	1.66	1.77	1.74	1.72	1.77	1.80	1.68	1.71	1.94	1.93
9	1.98	2.21	1.90	2.13	2.19	1.99	2.14	2.20	2.15	1.96
10	1.44	1.33	1.57	1.57	1.61	1.50	1.71	1.68	1.63	1.54
11	2.53	2.49	2.64	2.61	2.52	2.60	2.62	2.67	2.76	2.79
12	1.86	1.78	1.95	1.73	1.71	1.90	2.07	1.96	2.19	2.09
13	1.71	1.62	1.51	1.55	1.68	1.64	1.63	1.62	1.69	1.70
14	2.40	2.60	2.35	2.48	2.33	2.25	2.45	2.45	2.54	2.42
15	1.98	1.84	1.88	1.81	1.94	2.00	1.92	1.91	1.94	1.83
16	2.43	2.42	2.17	2.39	2.76	2.31	2.29	2.14	2.32	2.41
17	3.53	3.29	3.66	3.75	3.84	3.46	3.68	3.49	3.40	3.56
18	2.10	1.95	1.89	1.95	2.06	2.00	2.07	1.95	1.86	1.88
19	2.52	2.16	2.71	2.73	2.83	2.75	2.92	2.93	2.85	2.89

the combination in comparison to loratadine ($p< 0.05$). No significant difference was observed between placebo and loratadine.

At 2 h $AUC_{0–30min}$, (% x min) expressed as mean± SEM, was -34.32±11.5% for placebo, -50.66±20.46% for loratadine, -23.74±10.06% for montelukast and -18.87±7.14% for the combination, with no significant differences. When the challenges were performed 12 h after the drug administration, $AUC_{0–30min}$ was -43.60±9.34% after placebo, -39.6±10.89% after loratadine, -15.03±5.38% after montelukast and -7.76±6.14% after the combination, with significant differences between montelukast and montelukast plus loratadine in comparison to placebo ($p<0.01$) and to loratadine alone (=0.02).

Protection

At 2 h after dose administration, no significant difference in the percentage of protection was observed between placebo (33%), loratadine (43%), montelukast (47%) and montelukast plus loratadine (59%). At 12 h there was a significant difference in the percentage of protection between placebo (20%) and montelukast (63%) ($p<0.01$), and between placebo and the combination (59%) ($p<0.01$), but not between placebo (20%) and loratadine (45%). Montelukast provided clinical protection in three subjects (15%) at 2 h and in 12 subjects (63%) at 12 h. The combination of the two drugs gave a similar trend with clinical protection in six subjects (31%) at 2 h, and in 12 subjects (63%) at 12 h.

Discussion

The aim of the study was to verify if the association of a LTRA, montelukast, plus an antihistaminic drug, loratadine, may exert an additive effect in the prevention of EIB. It has been previously shown that LTRAs are able to protect against early and late allergen-induced responses, even without any changes in inflammatory indices such as sputum eosinophil percentage or activity [8]. Furthermore, it has been demonstrated that the combination loratadine and zafirlukast, inhibited both early and late reactions following allergen challenge by ~75% [3]. As the efficacy has appeared to begin acutely, different anti-inflammatory mechanisms might be involved including effects on the vascular system, the airway oedema, mucous production and neurogenic inflammation [9]. These events may also contribute to the development of the hypertonicity of airway lining fluid which seems to be the major determinant of EIB, determining mediator release by inflammatory cells. In the present study, the authors analysed drug efficacy at 2 and 12 h, and the effects of the combination at the beginning and the end of a once-daily single dosage were investigated. In several studies two or more doses of montelukast were used in order to achieve steady-state blood levels [1, 2]. In the present study the use of a single administration of drugs was adopted in an attempt to clarify, as much as possible, the contribution of both antileukotriene and antihistaminic drugs in the protection from EIB. To the best of the authors' knowledge this is the first study examining the effect of a single dose of montelukast and loratadine alone and in combination. No statistically significant additive effect using the combination of the two drugs in comparison to montelukast alone was obtained. However, results showed that even after 2 h there was a trend towards protection when the children were treated with the combination. Mean values of the ΔFEV_1 and the percentage of protection obtained after both drug administration (2 and 12 h respectively) did not change significantly, but at 2 h there was a strong placebo effect. This effect in EIB has been described

previously in children, and it has been characterised by dose and duration time effect [10]. At 12 h montelukast and the combination were significantly more effective than placebo and loratadine alone.

To conclude, the combination of montelukast and loratadine single-dose administration, demonstrated no additive effect in exercise-induced bronchoconstriction protection. However, since antileukotrienes in association with antihistamines have been demonstrated to provide a significant improvement in chronic asthma [6] and allergic rhinitis [11, 12] in adults, combined and prolonged oral therapy should also be evaluated in children. Further studies are necessary to evaluate long-term clinical effects of this and other therapeutic combinations on asthma and exercise-induced bronchoconstriction in childhood.

References

1. Kemp JP, Dockhorn RJ, Shapiro G, *et al.* Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998; 133: 424–428.
2. Pearlman D, Ostrom N, Bronsky E, Bonuccelli C, Hanby L. The leukotriene D4-receptor antagonist zafirlukast attenuates exercise-induced bronchoconstriction in children. *J Pediatr* 1999; 134: 273–279.
3. Roquet A, Dahlen B, Kumlin M, *et al.* Combined antagonism of leukotrienes and histamine produces predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. *Am J Respir Crit Care Med* 1997; 155: 1856–1863.
4. Bisgaard H. Long-acting β_2 agonists in management of childhood asthma: a critical review of the literature. *Ped Pulmonol* 2000; 29: 221–224.
5. Gong H, Tashkin DP, Dauphinee B, Djahed B, Wu T. Effects of oral cetirizine, a selective H_1 antagonist, on allergen- and exercise-induced bronchoconstriction in subjects with asthma. *J Allergy Clin Immunol* 1990; 85: 632–641.
6. Reicin AS, White R, Weinstein SF, *et al.* Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 2000; 160: 2481–2488.
7. Bjorck T, Dahlen S. Leukotrienes and histamine mediate IgE-dependent contractions of human bronchi: pharmacological evidence obtained with tissues from asthmatic and non-asthmatic subjects. *Pulm Pharmacol* 1993; 6: 87–96.
8. Diamant Z, Grootendorst D, Veselic-Charvat M, *et al.* The effect of montelukast (MK-0476), a cysteinyl leukotriene receptor antagonist, on allergen-induced airway responses and sputum cell counts in asthma. *Clin Exp Allergy* 1999; 29: 42–51.
9. Wenzel SE. Inflammation, leukotrienes and the pathogenesis of the late asthmatic response. *Clin Exp Allergy* 1999; 29: 1–3.
10. Boner AL, Vallone G, Peroni D, Piacentini G, Gaburro D. Efficacy and duration of action of placebo responses in the prevention of exercise-induced asthma in children. *J Asthma* 1988; 25: 1–5.
11. Meltzer EO, Malmstrom K, Lu S, *et al.* Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2000; 105: 917–922.
12. Wilson AM, LC Orr, EJ Sims, Lipworth BJ. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. *Clin Exp Allergy* 2001; 31: 61–68.