

Time efficacy of a single dose of montelukast on exercise-induced asthma in children

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The aim of this study was to evaluate the timing of onset and the duration of action of a single oral-dose treatment with montelukast in comparison to placebo on exercise-induced asthma (EIA) in asthmatic children. Nineteen children (7–13 years) with stable asthma were evaluated. Patients undertook three consecutive treadmill exercise tests, respectively, 2, 12 and 24 h after a single-dose administration. A double-blind randomized, single-dose, placebo-controlled, crossover design was used. To assess bronchoconstriction after the exercise challenge, the maximal percentage fall in FEV₁ (Δ FEV₁) from the baseline value was considered. Two hours after dosing, Δ FEV₁ was -15.33 ± 2.93 for placebo and -13.33 ± 2.03 for montelukast. At 12 h, Δ FEV₁ was -18.69 ± 2.83 for placebo, -9.78 ± 1.85 for montelukast ($p < 0.005$). No difference was observed between placebo (Δ FEV₁ -10.21 ± 2.07) and montelukast (Δ FEV₁ -9.10 ± 2.02) at 24 h. Analysis of the degree of protection showed a significant efficacy of montelukast ($p = 0.02$) in comparison with placebo only at 12 h. Montelukast showed a significant protective effect 12 h after dosing, but no effect after 2 and 24 h. In mild asthmatics, the timing of administration of single dosage before exercise should be strictly considered in order to obtain the drug protective effects.

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Exercise-induced asthma (EIA) occurs in 70–80% of children with symptomatic asthma, often leading to exercise avoidance, which in turn may affect the children's psychosocial development (1). In mild to moderate asthmatic children, regular treatment with inhaled steroids is usually effective in controlling symptoms and reducing by 50% or more the extent of EIA (2). However, because cysteinyl-leukotrienes are considered to play a pivotal role in causing EIA (3), the leukotriene-receptor antagonists (LTRA) provide further protection and attenuation of the fall in pulmonary function following exercise (4–7). This class of drugs is usually prescribed on a regular scheduled basis. However, patients who manifest EIA symptoms only after strenuous activity could be potentially treated with LTRA as needed in addition to, or instead of, other treatments (8). At present few data are available

on the time of onset, the duration of action and the potency of LTRA in protecting asthmatics from EIA (8). In the present study, we aimed to investigate the effectiveness during the daytime of a single dose of a LTRA, montelukast, in comparison with placebo in asthmatic children requiring daily controller medications.

Methods

Patients

Nineteen children (7–13 yr) (13 boys and 6 girls) with a positive clinical history of EIA were evaluated. Subjects' characteristics are shown in Table 1. All the children had stable, mild to moderate asthma and they required regular steroid treatment; they all were sensitive to house dust mites, *Dermatophagoides pteronyssinus* and *fari-*

Table 1. Characteristics of subjects randomized in the study

Patient	Age (years)	Gender	Height (cm)	Weight (kg)	FEV ₁ (% of predicted)	FEV ₁ (L/s)	Actual therapy Total daily dose
1	12	M	151	44	99	2.36	Bud 400
2	11	M	140	39	93	1.79	Bud 400
3	13	M	160	59	85	3.14	FP 200
4	13	M	159	59	90	2.91	FP 200
5	11	M	137	35	89	1.75	FP 500
6	11	M	151	36	82	2.11	BUD 400
7	08	M	131	35	99	1.35	BUD 200
8	11	M	145	42	80	1.66	FP 200
9	13	F	150	45	85	2.21	FP 200
10	11	F	132	31	80	1.44	FP 200
11	13	F	158	53	84	2.53	FP 500
12	10	M	142	45	80	1.78	FP 200
13	09	F	136	30	87	1.71	FP 200
14	13	F	152	70	89	2.40	BUD 200
15	07	M	134	32	104	1.98	BUD 200
16	10	M	151	59	88	1.43	FP 200
17	13	M	173	70	91	3.53	FP 300
18	10	F	137	36	103	2.10	FP 200
19	12	M	155	40	87	2.52	FP 200

FEV₁ is expressed as the percentage of predicted normal value.
M: male; F: female; FD: fluticasone propionate; Bud: budesonide.

nae, as demonstrated by positive SPTs and positive RAST (score ≥ 3) for the allergens. Children performed baseline exercise challenges at 10.00 and 20.00 hours and a fall in FEV₁ after exercise $\geq 15\%$ confirmed the diagnosis of EIA (9).

Study design

A double-blind randomized, single-dose, placebo-controlled, crossover design was used. Each patient undertook three treadmill exercise tests in the consecutive 24 h after drug administration, respectively, 2 (10.00 hours), 12 (20.00 hours) and 24 h (8.00 hours) after dosing. Each drug administration (active vs. placebo) and the following three exercise tests were performed 3–5 days apart in order to eliminate any carry-over effect. To assess bronchoconstriction after the exercise challenge, the maximal percentage fall in FEV₁ (Δ FEV₁) from the baseline value was considered. The percentage of protection was calculated as $P_s - P_t / P_s$, where P_s is the percent fall in FEV₁ at the screening test, and P_t is the percent fall in FEV₁ after each treatment.

Treadmill exercise tests

A standardized exercise test protocol was used (9,10). Briefly, children performed baseline spirometry and then ran for 6 min on a treadmill at a speed to obtain an increase at 80% of their maximum heart rate in a dedicated room with constant temperature (21°C) and humidity

(40–50%). Nose clips were applied to ensure mouth breathing. After the exercise challenge, FEV₁ was measured at 1, 5, 10, 15, 20 and 30 min after the tests.

Safety

During the study period, children performed daily peak flow and weekly spirometry evaluations.

Statistical analysis

Results are expressed as mean $\pm$ SEM. Wilcoxon's rank sum test on paired data was used to compare the effects of the two treatments (placebo and montelukast). Protection was evaluated by analysis of variance for a factorial block design. The percentages of clinically protected children were compared using the Cochran *Q*-test. Statistical analyses were performed using the GLIM package (GLIM 3.77, Royal Statistical Society, London, UK). The Local Hospital Ethical Committee approved the study, and the children and their parents gave their informed consent.

Results

Efficacy

Single patient results are shown in Table 2. The Δ FEV₁ of the baseline challenge, expressed as

Table 2. Maximum percentage fall in FEV₁ (Δ FEV₁) at baseline tests (10.00 and 20.00 hours) and at different times (2 and 12 h) after drug administration

Patient	Basal test 10.00 hours	Basal test 20.00 hours	Placebo after 2 h	Placebo after 12 h	Montelukast after 2 h	Montelukast after 12 h
1	15.25	16.06	1.90	7.69	12.94	13.41
2	16.20	26.74	17.54	27.98	16.67	12.08
3	15.29	16.33	13.51	12.33	12.56	15.00
4	15.46	16.26	54.02	40.00	32.74	30.99
5	15.43	16.49	0.00	6.57	9.81	6.82
6	33.18	20.55	18.47	34.39	23.98	13.69
7	57.35	49.39	3.79	13.79	19.85	17.60
8	21.08	20.48	24.62	41.04	17.87	6.12
9	15.66	24.89	23.84	27.10	16.56	2.47
10	44.44	16.54	24.47	33.15	19.79	19.90
11	16.60	30.92	20.74	25.10	26.64	13.55
12	18.28	20.22	13.93	20.00	10.87	3.15
13	22.81	15.28	3.70	5.64	9.18	5.13
14	28.75	18.01	9.59	21.25	5.14	3.41
15	41.41	28.26	25.96	16.13	6.12	15.51
16	16.78	23.55	9.47	0.00	8.94	3.53
17	19.55	16.72	6.81	5.63	1.56	0.00
18	23.33	16.92	16.11	7.77	1.97	1.74
19	20.24	15.28	2.81	9.64	0.00	1.70

mean $\pm$ SEM, was -22.84 ± 3.01 at 10.00 hours and -21.31 ± 2.60 at 20.00 hours. When the exercise test was performed 2 h after dosing at 10.00 hours the percent fall in FEV₁ was -15.33 ± 2.93 for placebo and -13.33 ± 2.03 for montelukast. At 12 h, Δ FEV₁ was -18.69 ± 2.83 for placebo and -9.78 ± 1.85 for montelukast, respectively ($p < 0.005$). No difference was observed between placebo (Δ FEV₁ -10.21 ± 2.07) and montelukast (Δ FEV₁ -9.10 ± 2.02) at 24 h.

Protection

No significant difference in the percentage of protection was observed between placebo (35%) and montelukast (41%) when the challenges were performed 2 h after dosing. At 12 h there was a significant difference in the percentage of protection between placebo (31%) and montelukast (56%) ($p = 0.02$). The evaluation at 24 h confirmed no statistical difference in protective effect between placebo (42%) and montelukast (48%).

Montelukast conferred clinical protection (percentage fall after receiving the active drug half or less of the percentage fall after receiving placebo) in 3 (15%) at 2 h, in 12 (63%) at 12 h and in 5 (26%) at 24 h of the 19 evaluated patients.

Safety

No adverse event or significant modification of lung function was observed during the study period.

Discussion

LTRAs are effective in reducing the extent of EIA by 40–70% (4–7), and have the advantage that this protection lasts throughout the day and does not appear to diminish with regular use (11). At present it is still unclear whether a single dose of LTRA could produce protection in EIA: in our study drug efficacy was demonstrated at 12 h, while the effects were not evident at the beginning (2 h) and at the end (24 h) after a single dose. We administered montelukast in the morning, even if the manufacturer does not recommend this, because it has been demonstrated that morning administration may increase the apparent terminal life and the maximum plasma concentration of LTRA, leading to a possible increased bioavailability (12). Few previous studies have dealt with the onset and duration of action of LTRA. In a recent study in adults, single doses of different LTRAs, montelukast and zafirlukast were able to produce significant effects within 1 h of ingestion, with the maximal effect at 4 h, and offered a long-lasting efficacy, equal to that seen with a long-acting β_2 -agonist (8). In that study only 60% of the patients regularly used inhaled steroids leading to a better response to LTRA, while in our study all patients were treated with inhaled corticosteroids. In another study in children it has been demonstrated that zafirlukast, in a single dose, significantly attenuated EIA when the exercise test was performed 4 h after drug administration, reaching a complete protection against EIA in 55% of patients (5). Once again none of the patients

regularly used steroids leading to more room for improvement. In our study, the placebo effect was rather evident, particularly when the tests were performed at 24 h. The placebo effect in EIA has been previously described, particularly in children, and it seems to be characterized by a dose and time duration of action (13,14). A recent study showed that during the double-blind period 64% of the challenges after placebo did not result in an effective fall in FEV₁ (5). In our study, even if a fall in FEV₁ of at least 15% was considered as an entry criterion, during the study period 40% of the challenges after placebo did not reach a 15% fall in FEV₁. However, the percentage of challenges, which did not reach a 15% fall in FEV₁, was increased with montelukast (66%). In order to limit the placebo effect it would be necessary to consider that EIA depends on exercise load. High exercise load tests are better correlated to inflammatory activity than the low exercise load tests (15), but this could be difficult to obtain in children.

The results of our study are in accordance with previous findings that have found montelukast assuring protection from EIA in 6- to 14-year-old asthmatic children (4); however, even in that study when the challenges were performed 24 h after the last of two consecutive doses, montelukast did not provide complete protection against EIA (4). In contrast to prevalent practice a single dose may be all that is required to produce a beneficial effect and there is no need to establish a stable blood level; hence long-term use is not a prerequisite (8). This observation should simplify treatment regimens as either first-line or add-on therapy in children in whom EIA is a manifestation of their asthma. The finding that a single dose was effective in protecting at 12 h but not at 2 and at 24 h suggests that the timing of administration of a single dose before exercise should be strictly considered in order to obtain the maximal drug efficacy.

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