

Original article

Montelukast 10 mg improves nasal function and nasal response to aspirin in ASA-sensitive asthmatics: a controlled study vs placebo

Aspirin-induced asthma (AIA) is a clinical syndrome characterized by acute airway reaction to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). The most recent etiological hypothesis is that an overexpression of the enzyme LTC₄ synthase occurs in AIA, with the consequent production of sulfidopeptide leukotrienes (LTs).

Aim: Aim of the present study was to assess the effect of Montelukast, a selective cys-LT receptor antagonist, on nasal function, nasal reactivity to ASA and blood markers of eosinophilic inflammation in mild-to-moderate AIA.

Material and methods: Thirty-six nonsmoker subjects with AIA (17 males, 22–52 years) performed a nasal provocation test (NPT) with lysine-aspirin (L-ASA) in baseline and after a 4-week Montelukast 10 mg or placebo treatment. Nasal function was assessed by the acoustic rhinomanometry, and they also performed a lung function test (forced expiratory volume in 1 s), and a blood sample for the eosinophil count and the eosinophil cationic protein (ECP) plasma measurements. After both treatments, all subjects repeated the NPT, the lung function, and the ECP and the eosinophil blood count.

Statistical analysis: *t*-Test was used to compare mean values $\pm$ SD between groups, and $P < 0.05$ was assumed as the level for statistical significance.

Results: Airway patency was never affected by the NPT with L-ASA. In baseline, NPT with L-ASA precipitated a nasal reaction in all subjects, with a substantial increase in nasal resistance (calculated resistance [REQ]; from 0.89 ± 0.18 to 2.2 ± 0.17 cmH₂O/l/min in group M, $P < 0.001$; and from 0.91 ± 0.48 to 2.3 ± 0.21 cmH₂O/l/min in group P, $P < 0.001$); and a significant reduction in total nasal volume in at least one nostril (volume [VOL]; from 11.1 ± 3.2 to 8.1 ± 4.1 cm³ in the group M, $P < 0.001$, and from 12.3 ± 4.1 to 7.9 ± 4.5 cm³ in the group P, $P < 0.001$). The nasal reaction to L-ASA remained unchanged following placebo, but it was completely minimized following a 4-week treatment with Montelukast. Also nasal function, the nasal symptom score, and the markers of eosinophilic inflammation proved significantly affected and improved by the active drug only.

Conclusions: Montelukast 10 mg daily for 4 weeks, but not placebo, improves nasal function and nasal response to Aspirin substantially in ASA-sensitive asthmatics.

**C. Micheletto, S. Tognella,
M. Visconti, C. Pomari, F. Trevisan,
R. W. Dal Negro**

Lung Department, Orlandi Hospital, Bussolengo,
Verona, Italy

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C. Micheletto
Lung Department
Orlandi Hospital
Bussolengo
Verona
Italy

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Aspirin-induced asthma (AIA) is a clinical syndrome characterized by acute airway reactions to aspirin (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) (1) which affects 5–20% of adult asthmatics (more frequently women) (2), and is rarely present in asthmatic children. Ingestion of aspirin in these individuals is followed within 1–2 h by the onset of bronchospasm, which may be accompanied by rhinitis and/or skin reactions (such as, urticaria).

In sporadic patients only nasal symptoms are elicited by aspirin (3). Watery rhinorrhea and nasal obstruction,

leading to frequent development of nasal polyps, precede the appearance of asthma and aspirin intolerance for months or years (4). Aggressive nasal polyps and asthma run a protracted course, despite the avoidance of ASA and cross-reacting drugs. Blood eosinophil counts are raised, and eosinophils are present in nasal mucosa and bronchial airways (5). The AIA is difficult to treat and frequently these patients require therapy with systemic corticosteroids to control symptoms.

The precise mechanism behind this nonimmunological hypersensitivity still remains unknown; however, it has

been postulated that the power of these agents to provoke asthma is related to their capability as inhibitors of cyclooxygenase (COX) (6–8). The most recent hypothesis is that an overexpression of the enzyme LTC₄ synthase occurs in AIA, with the consequent production of leukotrienes (LTs): it might predispose to AIA and rhinitis exacerbations (9).

There are several observations which can support the hypothesis that LTs also may mediate AIA (10–12); in particular it has been assessed a mean fourfold increase in urinary LTE₄ levels 3–6 h following aspirin ingestion (13).

Nasal provocation test (NPT) with Lysine-aspirin (L-ASA) has been introduced a few years ago for assessing AIA also in patients with instable asthma (14): the test has been described as an highly specific and sensitive one, but negative results do not exclude possible intolerance to aspirin (predictive value of a negative result 78.6%) (14). More recently, the acoustic rhinomanometry has been suggested as the most helpful diagnostic procedure as its use is less limited than anterior rhinomanometry by the presence of nasal polyps and nasal obstructions (15).

Aim of the present study was to assess *vs* placebo the effect of Montelukast, a selective cysteinyl-LT receptor antagonist, on nasal function, nasal reactivity to L-ASA (assessed by NPT coupled with the acoustic rhinomanometry), and on blood markers of eosinophilic inflammation in mild to moderate AIA with nasal symptoms.

Materials and methods

Study design and Subjects

The study was carried out according to a randomized, double-blind, parallel group, placebo-controlled design.

After their written informed consent, 39 nonsmoker patients with AIA who had experienced chronic nasal symptoms for about 3 years preceding the study were initially screened to undergo a diagnostic NPT with L-ASA (Table 1), being patients with nasal polyps excluded. As the test could not be performed because of their total obstruction of at least one nostril, the results of the acoustic rhinomanometry led to exclude three patients. Thirty-six subjects entered the study and performed the NPT with L-ASA after having stopped their medications (oral antihistamines for 7 days; nasal cromolyn sodium and nasal corticosteroids for 1 week, and nasal inhaled ant-H1 agents for at least 48 h before NPT): they also performed a blood sample for measuring blood eosinophils (%) and eosinophil cationic protein (ECP) plasma levels (mcg/ml; Immulite One, DPC, Los Angeles, CA). Subjects were then randomized in two matched groups: group Montelukast (*n* = 18), to be treated with Montelukast 10 mg once-a-day for 4 weeks, and group

Placebo (*n* = 18), with placebo for the same duration. Following both treatments, all subjects performed a second NPT with L-ASA, together with the lung function, the eosinophil count and the measurement of the ECP plasma levels. The nasal symptom score was also assessed before and after both treatments.

Acoustic rhinomanometry for NPT with L-ASA

Each patient performed the NPT according to the method described by Casadevall et al. by means of the acoustic rhinomanometry (15). This method consists in the measurement of acoustic reflections from the nasal cavity of a sound pulse created by a spark in a sound tube connected to the nasal cavity via a nosepiece. Unlike conventional rhinomanometry, acoustic rhinomanometry does not require generation of nasal flow, and therefore its use is less limited by the presence of nasal polyps and nasal obstruction. The response was evaluated by the Eccovision Acoustic Rhinomanometry System (TM Hood Laboratories, Pembroke, MA) with the measurement of (16):

- 1. calculated resistance, based on a tube with the same area and laminar flow (calculated resistance [REQ], mmH₂O/l/min). It is less than the actual resistance but is useful for comparative analysis;
- 2. the total volume of the nostrils (VOL, cm³) represents the nasal cavity volume in the analysis segment;
- 3. the minimal cross sectional area (cm²) and
- 4. its distance from the nosepiece (cm).

Rhinomanometric measurements were performed while the subject was in apnoea after a nonforced expiration. The rhinomanometer was calibrated daily with a calibration tube provided by the manufacturer. The analysis of data was performed using the Kwikstat program (TM Texassoft, Cedar Hill, TX).

The clinical symptoms score included rhinorrhea; nasal congestion; itching or burning of the nose, ear, palate or throat; sneezing and lacrimation. The intensity of these symptoms were expressed with the following scale: 0, none; 1, mild; 2, moderate; 3, severe. The total nasal score at each time interval was calculated as the sum of the above individual scores (maximal score, 15 points).

Baseline nasal function was measured with Acoustic Rhinomanometry, while the subjects were in a sitting position, before and after a nasal challenge with saline (0.9% NaCl). Then 80 µl of L-ASA solution (180 mg/ml L-ASA, equivalent to 100 mg/ml acetylsalicylic acid) was applied locally through nose droplets on the inferior nasal concha in both nostrils. The total deposited dose of L-ASA was equivalent to 25 mg of acetylsalicylic acid. Acoustic Rhinomanometry was then performed bilaterally every 10 min for the next 2 h.

Lysine-aspirin was prepared freshly each day by dissolving crystalline L-ASA in 0.9% sodium chloride to produce a solution containing 180 mg/ml.

The NPT was considered positive when: nasal resistance increased more than 40% in at least one nostril as compared with the corresponding baseline value; when the volume of one nostril decreased more than 10% from baseline; both parameters sustained for at least two consecutive measurements, and were accompanied by clinical symptoms persisting at least 30 min (the minimal score amounting to 3 or more). The dose of aspirin, the duration of the observation period, and criteria for positivity of the test were established on the basis of previous experiments (14, 15).

Simultaneously, pulmonary function (forced expiratory volume in 1 s, FEV₁) was measured by using a computerized pneumotachograph (Masterlab, Jaeger, Wuerzburg, Germany).

We only considered the maximal fall for REQ, volume (VOL) and FEV₁ observed in the 2 h following the NPT.

Table 1. Demographics of the total sample (*n* = 36) and of the two subgroups of subjects

	Total sample	Sub-group Montelukast	Sub-group placebo
Mean age (years)	41.0 ± 10.2	42.3 ± 9.7	39.6 ± 10.8
Range of age (years)	22–52	22–52	22–51
Sex	17 males	9 males	8 males

Table 2. Sub-group Montelukast $n = 18$

	Test 1 PreMontelukast			Test 2 PostMontelukast		
	Basal	Post-ASA	P-value	Basal	Post-ASA	P-value
FEV ₁	87.1 ± 5.4	84.5 ± 4.2	ns	88.2 ± 4.8	85.7 ± 5.1	ns
REQ	0.89 ± 0.18	2.2 ± 0.17	0.001	0.42 ± 0.20	0.48 ± 0.22	ns
VOL	12.9 ± 3.2	8.1 ± 4.1	0.001	14.6 ± 3.8	13.8 ± 3.9	ns
EOS	6.8 ± 1.86			4.27 ± 0.7		0.001
ECP	21.6 ± 5.3			12.1 ± 1.8		0.001

FEV₁, forced expiratory volume in 1 s; REQ, calculated resistance; VOL, volume; EOS, eosinophils; ECP, eosinophil cationic protein; ns, not significant.

Table 3. Sub-group placebo $n = 18$

	Test 1 Preplacebo			Test 2 Postplacebo		
	Basal	Post-ASA	P-value	basal	Post-ASA	P-value
FEV ₁	84.3 ± 3.2	81.9 ± 4.6	ns	83.9 ± 4.5	82.3 ± 5.7	ns
REQ	0.91 ± 0.48	2.3 ± 0.21	0.001	0.93 ± 0.46	2.4 ± 0.76	0.001
VOL	12.3 ± 4.1	7.9 ± 4.5	0.004	11.9 ± 4.2	7.6 ± 3.6	0.002
EOS	6.6 ± 2.1			6.81 ± 0.9		ns
ECP	20.3 ± 4.9			21.7 ± 2.1		ns

FEV₁, forced expiratory volume in 1 s; REQ, calculated resistance; VOL, volume; EOS, eosinophils; ECP, eosinophil cationic protein; ns, not significant.

Statistical analysis

Mean value ± SD obtained before and after both NPTs for each variable were compared by *t*-test, and $P < 0.05$ was assumed as the limit for statistical significance.

Results

The two groups were comparable in terms of their nasal and bronchial function in baseline, and also of eosinophil count (%) and ECP plasma levels (mcg/l) (*t*-test = ns; Tables 2 and 3).

Airway patency was not affected by both NPTs with L-ASA in both subgroups of subjects (Tables 2 and 3). In all subjects, the first nasal instillation of L-ASA precipitated a local reaction with increased resistance and significant reduction of the total volume in at least one nostril (Tables 2 and 3).

After a 4-week treatment, subjects who assumed placebo showed an unchanged nasal reaction after the second NPT. The nasal reaction proved minimized only in patients treated with Montelukast (Tables 2 and 3).

When changes obtained were expressed as the % variation vs baseline, patients treated with Montelukast had a REQ mean change of $+147.1 \pm 68.9\%$ following the first (pretreatment) NPT, and only of $+14.2 \pm 19.3\%$ after the second NPT ($P < 0.001$). The corresponding mean REQ change in subjects treated with placebo was of $+152.4 \pm 77.7\%$ after the first NPT, and of $+158.2 \pm 64.9\%$ after the second (post-treatment) NPT ($P = ns$) (Fig. 1).

As concerns total volume, the mean % change from baseline was of $-37.2 \pm 6.3\%$ after the first NPT, and of

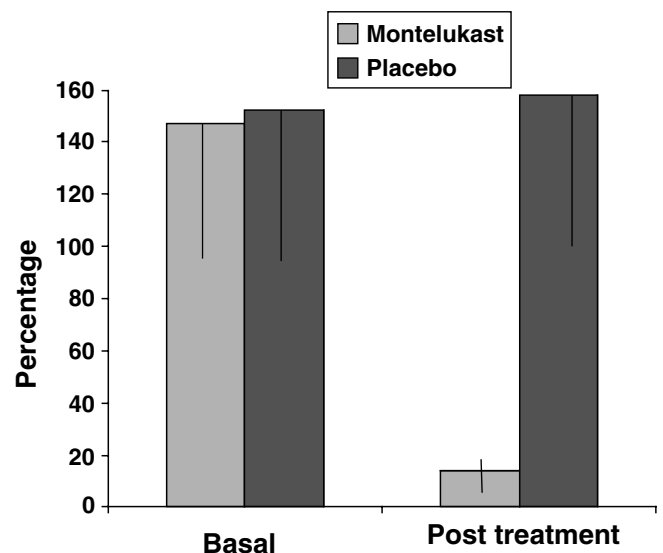


Figure 1. Change in nasal resistances because of nasal provocation test (NPT), expressed in both groups as % variation vs the corresponding pre-NPT values; $*P < 0.001$. The second (post-treatment) NPT did not cause any significant resistive effect only following the active treatment.

$-5.4 \pm 3.9\%$ after the second NPT in patients treated with Montelukast ($P < 0.001$), while the corresponding mean change in subjects treated with placebo was of $-35.7 \pm 9.7\%$ after the first NPT, and of $-36.1 \pm 11.4\%$ after the second NPT ($P = ns$) (Fig. 2).

Furthermore, also the basal pattern of nasal function (such as REQ and VOL measured before the two challenges with L-ASA) was significantly improved only

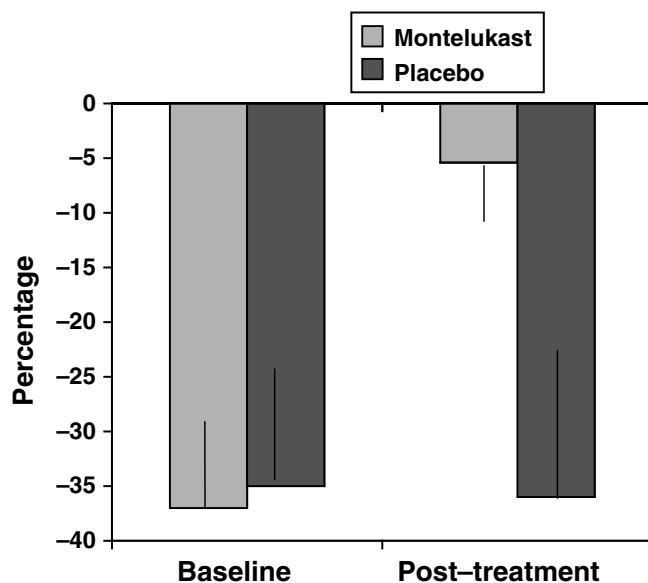


Figure 2. Change in nasal volume because of nasal provocation test (NPT), expressed in both groups as % variation vs the corresponding pre-NPT values; * $P < 0.001$. The second (post-treatment) NPT did not cause any significant volumetric effect only following the active treatment.

in patients treated with Montelukast, but not in those treated with placebo: REQ changed from 0.89 ± 0.18 to 0.42 ± 0.20 cmH₂O/l/min, and VOL from 12.9 ± 3.2 to 14.6 ± 3.8 cm³ in the M group (both $P < 0.001$), while REQ changed from 0.91 ± 0.48 to 0.93 ± 0.46 cmH₂O/l/min, and VOL from 12.3 ± 4.1 to 11.9 ± 4.2 cm³ in the P group (both $P = \text{ns}$) (Fig. 3).

The markers of eosinophilic inflammation were reduced significantly following Montelukast treatment: blood eosinophils changed from 6.8 ± 1.86 to $4.27 \pm 0.7\%$ ($P < 0.001$) and ECP plasma level from 21.6 ± 5.3 to 12.1 ± 1.8 mcg/l ($P < 0.001$). On the contrary, Placebo did not affect these biological indicators: eosinophils changed from 6.6 ± 2.1 to $6.81 \pm 0.9\%$ ($P = \text{ns}$) and the ECP plasma level from 20.3 ± 4.9 to 21.7 ± 2.1 mcg/l ($P = \text{ns}$) Tables 1 and 2).

The nasal symptom score changed from 10.1 ± 2.6 to 6.0 ± 1.3 in the Montelukast group ($P < 0.001$), and from 9.2 ± 2.2 to 10.1 ± 2.2 in the placebo group ($P = \text{ns}$).

Discussion

The AIA develops according to a pattern characterized by a sequence of symptoms (4): first, persistent rhinitis, then asthma, aspirin intolerance and finally nasal polyposis appear. After the appearance of rhinitis it is important to precise AIA, because such a particular asthma has to be considered a 'difficult' asthma which frequently requires systemic steroids to control symptoms.

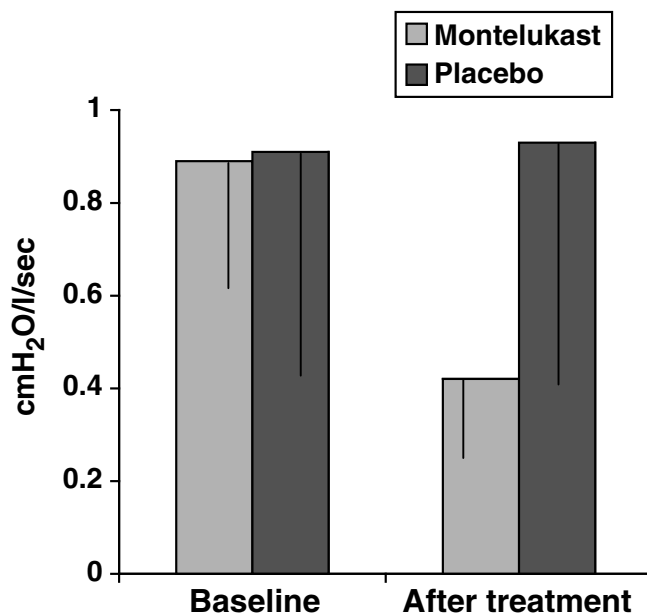


Figure 3. Prenasal provocation test (NPT) nasal resistance before and after both treatments; $P < 0.001$. Only the active treatment lowered the pre-NPT nasal resistance, so emphasizing that nasal patency of all subjects was abnormal already in baseline and that Montelukast proves active in normalizing also the basal condition of aspirin intolerant subjects.

There is no *in vitro* test for identification of aspirin intolerance, and the diagnosis can be only confirmed by oral (17) or by inhalation (18, 19) aspirin provocation test. Both these procedures have several limits: while oral test can sometimes precipitate a severe asthmatic reaction and it should then be performed only in specialized centers provided of or close to an intensive care unit, inhalation of increasing concentrations of L-ASA solution is considered as unsuitable for patients whose asthma is not in clinical remission and whose FEV₁ is lower than 70% of predicted value.

At present, NPT is suggested as the method of choice for assessing AIA in aspirin intolerant subjects, although only a few contributions are still available on this particular topic (14, 15).

In the present study, the NPT with L-ASA has been performed in order to evaluate the nasal response of subjects with AIA and assess its respiratory tolerability in terms of changes in lung function. The NPT confirmed as a quick, simple and highly safe test for diagnosing AIA, and then it should represent the method of choice in the next future to check the hypersensitivity to aspirin which manifested by symptoms of upper respiratory tract only. In particular, differently from the older and usual diagnostic approach, NPT when based on the assessment of ASA-induced acoustic rhinomanometrical changes consented the absolute protection of lung function,

which proved in fact completely unaffected by the nasal instillation of ASA. For these reasons, this novel procedure should be used more widely as the first-line diagnostic approach to the diagnosis of hypersensitivity to aspirin, also in patients with instability of the bronchial tree and when bronchial or oral provocation test with aspirin cannot be carried out for safety reasons.

The precise mechanism behind the nonimmunological hypersensitivity to ASA or NSAIDS still remains unknown; however, it has been postulated that the capacity of these pharmacological agents to provoke asthma could be related to their capability to inhibit COX (6–8). Furthermore, the most recent hypothesis is suggesting that an overexpression of the enzyme LTC₄ synthase occurs in AIA (9), with the consequent over-production of LTs, which represent a pool of potent asthmogenic mediators also in humans (20–24). From this point of view, there are several observations which are supporting the hypothesis that LTs may also mediate AIA (10–12); in particular it has been assessed a mean fourfold increase in urinary LTE₄ levels 3–6 h following aspirin ingestion (13), and the genetic predisposition to the up-regulation of the cys-LTs pathway (9). Moreover, the severity of respiratory reactions during oral ASA challenge was associated with the degree of elevation of baseline LTE₄ expression (25), thus suggesting that asthmatics with aspirin-sensitive respiratory disorders have a spectrum of reactions in which LTs seem to play a crucial role. Finally, a further proof of the critical role of cys-LTs in AIA has been provided by the advent of anti-LTs drugs. The airway response to inhalation of Lysine-ASA proved substantially inhibited by LTs-antagonists, thus providing the direct evidence that LTs act as mediators of ASA-induced bronchoconstriction (26).

Montelukast is a potent and specific oral Cys-LT₁ receptor antagonist which has recently shown to be an highly potent and long-lasting antagonist of LT D₄-induced bronchoconstriction in asthma (27). Montelukast also improves the sign and symptoms of asthma (28) and decreases airway eosinophilic inflammation (29). It has

also been shown that the addition of Montelukast can improve asthma in AIA over and above what can be achieved by inhaled glucocorticoids (30).

In the present study only subjects treated with Montelukast 10 mg daily achieved a significant improvement in the basal (such as, pre-NPT) pattern of both nasal resistance and volume, together with a substantial drop in the nasal symptom score after a 4-week treatment, thus suggesting and emphasizing the pre-existence of a basal condition already characterized by an abnormal nasal involvement and flow limitation in these patients. This condition was likely because of the up-regulated basal production of LTs, which in fact proved mainly sensitive to a therapeutic course with a specific LT₁ receptor antagonist, such as Montelukast: to recall in fact that all subjects had been regularly treated with inhaled steroids for several weeks before entering the study: this suggestion is further emphasized by the significant improvement of the nasal symptom score following Montelukast assumption only. These data contribute to better specify the only previous experience carried out in this field on subjects with only a positive history for AIA and nasal polyps (31).

The present study was originally mainly oriented to the assessment (vs placebo) of the effects of the LT₁-receptor antagonism on the nasal response to L-ASA in AIA patients. Also from this point of view data we had evidence that Montelukast, but not placebo, was able to minimize the nasal response to L-ASA challenge, both in terms of nasal resistance and nasal volume: this therapeutic intervention also produced the substantial drop of the eosinophilic inflammation which on the contrary may add a further contribute to the beneficial effects of Montelukast in AIA.

In conclusion, being the diagnostic approach to AIA highly simplified and much more safe with the use of NPT monitored by means of the acoustic rhinomanometry, Montelukast 10 mg daily should be regarded as a very effective choice for affecting nasal function and controlling the nasal response to aspirin in ASA-sensitive asthma. When further confirmed, data of the present study could lead to implications of high clinical impact in the daily management of such a kind of difficult asthma.

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