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The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions

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Summary

Background Leukotrienes (LTs) appear to be crucial mediators of aspirin (ASA)-induced lower respiratory tract reactions. Therefore, it is logical to assume that leukotriene-modifier drugs (LTMDs) might block these reactions.

Objective The aim of this study was to determine whether concomitant treatment with LTMDs was associated with a reduction of ASA-provoked lower respiratory tract reactions in patients with aspirin-exacerbated respiratory disease (AERD), when compared to AERD patients who were not treated with LTMDs. Secondly, if ASA-induced lower respiratory tract reactions were prevented in LTMD-treated patients, was there then a higher prevalence of upper respiratory reactors or, alternatively, a higher prevalence of blocked reactions ('non-reactors') in this group.

Methods Of 271 patients suspected by history of having AERD, 96 were taking cys-LT receptor antagonists (cys-LTRAs) and 12 were taking zileuton at the time of oral ASA challenges. A matched control group of 163 patients was not receiving LTMDs. All subjects underwent standard oral ASA challenges. Reactions were classified as follows: classic [naso-ocular combined with a 20% or $>$ decline in forced expiratory volume of 1 s (FEV_1)]; pure lower (20% or $>$ decline in FEV_1 without naso-ocular); partial asthma (naso-ocular + 15–20% decline in FEV_1); upper only (naso-ocular with $<$ 15% decline in FEV_1); negative (no reactions).

Results In patients treated with cys-LTRAs, there were significant reductions in numbers of patients with ASA-induced bronchospastic reactions and a concomitant increase in upper respiratory reactors. There were no significant differences in mean provoking doses of ASA or the percent changes in FEV_1 values in both groups. In the 12 patients receiving zileuton, no reactions to ASA (16%) were similar to the cys-LTRA-treated group (11%) and the control group (15%).

Conclusion During oral ASA challenges, LTMD treatment appeared to shift target organ responses from both upper and lower respiratory tracts to upper tract alone. LTMD blocking of the entire respiratory tract did not appear to occur.

Keywords aspirin, asthma, leukotrienes, non-steroidal anti-inflammatory drugs
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Introduction

Aspirin-exacerbated respiratory disease (AERD) is characterized by aggressive inflammation of the respiratory tract with progressive nasal polyposis, sinusitis, and asthma [1]. In patients with AERD, the ingestion of full therapeutic doses of aspirin (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) induces asthmatic attacks, which are sometimes severe and may even be life-threatening. Unfortunately, there are no *in vitro* tests to identify AERD patients [1]. Therefore, ASA challenges have been developed to differentiate patients with AERD from patients with similar clinical presentations. There are three types of provocation test with ASA: oral [2], bronchial inhalation [3], and nasal inhalation [4]. In the USA, only oral ASA challenge is currently available. During oral ASA challenges, using considerable lower starting doses of ASA, respiratory reactions range from pure upper airway responses to lower airway bronchospasm or any combination in between [5].

The pathogenesis of ASA and NSAID-induced respiratory reactions is in part due to altered archidonate metabolism [6]. In fact, inhibition of cyclo-oxygenase-1 (COX-1) reduces synthesis of prostaglandin E_2 (PGE_2), which releases its braking effect on 5-lipoxygenase enzymes (5-LO) and mast cells. Because of this alteration, leukotrienes (LTs) are rapidly synthesized and histamine and tryptase are released from mast cells [7]. Pre-formed, as well as synthesized mediators, perhaps joined by others, are responsible for respiratory reactions. Blockade of the effects of histamine prevents upper airway reactions to ASA but has almost no blocking effect on the bronchospastic component of the respiratory reactions [8]. Leukotrienes stimulate cysteinyl

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leukotriene receptor-1 (cys-LT_1 receptors) in bronchial smooth muscles and induce powerful and prolonged bronchospasm, as well as vasodilation, secretion of mucus, and recruitment of additional eosinophils [9].

In the late 1990s, leukotriene-modifier drugs (LTMDs) were introduced in the USA for treatment of asthma. These drugs inhibit LT synthesis by blocking 5-LO or function as LT_1 receptor antagonists (LTRAs). Therefore, it was logical to assume that LTMDs might prevent ASA-induced lower respiratory reactions (smooth muscle constriction) and, possibly, upper airway reactions (vasodilation and mucus secretion).

The aim of this study was to determine whether treatment with LTMDs, while potential AERD patients were undergoing standard oral ASA challenges, was associated with a reduction of ASA-provoked lower respiratory tract reactions. And, if lower respiratory tract reactions were selectively blocked by LTMDs, was there a concomitant higher prevalence of pure upper respiratory reactors or alternatively a higher prevalence of non-reactors, when compared to control AERD patients who did not receive LTMDs.

Methods

Patients

Between 1996 and 2001, 271 patients who were suspected of having AERD were referred by their physicians and admitted to the General Clinical Research Center (GCRC) at Scripps Clinic. They signed institutional consent forms to undergo ASA oral challenges, followed by ASA desensitization. The 271 subjects enrolled in this study were 17–79 years of age; 58% were females and 42% were males. All patients had asthma, nasal polyposis, recurrent or chronic sinusitis, and anosmia. Most patients had undergone multiple surgical interventions to remove polypoid tissues from their nose and sinuses. Almost all were receiving topical nasal and bronchial corticosteroids and some received systemic corticosteroids to control respiratory tract inflammation. With a few exceptions, patients had experienced severe asthma attacks in the past, after ingesting full therapeutic doses of ASA or one of the other NSAIDs.

Seventy-five patients, who were admitted between 1996 and 1998, could not have been offered LTMD treatment by their referring physicians because these drugs were not available in the USA. In some patients, who were admitted after 1998, decisions to start LTMDs were made by their referring physicians as add-on therapy, presumably to control their asthma better. Because discontinuing LTMDs at time of admission to GCRC might significantly risk control of airway stability, LTMDs were continued during oral challenge studies. From the total group of 271 patients, 108 patients were taking LTMDs, 96 patients were taking LTRAs (75 montelukast 10 mg/day and 21 zafirlukast 20 mg twice a day) and 12 were taking the 5-LO inhibitor zilueton (600 mg four times a day). A control group of 163 patients were not receiving LTMDs on admission but were receiving topical and sometimes systemic corticosteroids. Because of the potential for bias for assignment into a less severe disease category, the 163 control patients were divided into those who could not have been offered LTMDs no matter how severe their disease (75 before 1998) and 88 patients admitted after 1998 to whom physicians could have offered LTMDs but elected not to add these controllers.

Study design

All 271 patients who were admitted to our study were evaluated and challenged with ASA in the same manner. The only difference was the consumption of LTMDs by 108 patients. All patients were admitted to the GCRC of Scripps Green Hospital 3 days before beginning ASA challenges. Patients were evaluated and consent forms were signed. Forced expiratory volume in 1 s (FEV_1) values (best of three expiratory efforts) were measured every hour during challenges. Placebo challenges were performed during the first part of their hospitalization. If FEV_1 values were less than 70% of a predicted value, subjects were not eligible for oral aspirin challenges. Some patients were excluded from challenges because of their fixed airway disease and a few received a burst of corticosteroids, rechallenged with placebo, and then challenged with ASA if they met appropriate criteria. The 271 patients participating in this study met all criteria for airway stability, FEV_1 values $> 70\%$ and full-day placebo challenges with FEV_1 values changing by $< 10\%$.

Oral ASA challenges were carried out using our standard protocol [2, 10], beginning with 30 mg of ASA and advancing doses (45 or 60 mg, 60 or 100 mg, 100 or 150 mg, 150 or 325 mg and 650 mg) every 3 h during 9 h/day over several days. Evidence for an ASA-induced respiratory reaction was assessed at least hourly and nurses checked patients frequently, responding to any symptoms between the hourly evaluations. Different types of ASA respiratory reactions were observed and included the following: classic reactions: decline of 20% or more in FEV_1 values combined with a naso-ocular reaction (nasal congestion, rhinorrhea, sneezing, conjunctival itching and or injection, periorbital oedema, and paranasal headache); pure lower respiratory reactions: wheezing and chest tightness combined with a 20% or $>$ decline in FEV_1 values; partial asthma reactions: asthma attacks with decline in FEV_1 values between 15 and 20%, combined with naso-ocular reactions; laryngospasm reactions: crowing sound over the neck, combined with a flat and notched inspiratory loop in the flow/volume curve; pure upper respiratory reactions: nasal and ocular reactions only; negative responses: even though the provoking doses of ASA were increased all the way to 650 mg, none of the above reactions occurred. If an ASA-induced respiratory reaction occurred, the challenge was suspended and the reaction was treated. Typically, reactions resolved between 2 and 4 h, but occasionally reactions lasted as long as 12 h.

Statistical analysis

Wilcoxon signed rank statistic was used to compare severity of disease components (Tables 1 and 2). Fisher's two-sided exact statistic was used to analyse the numbers of patients experiencing different ASA respiratory reactions in the patients treated with LTMD and in the control group, which was not treated with LTMD (Tables 1 and 2). The statistical software program used was Stat View 4.01 (Abacus Concept Inc., Berkeley, CA, USA) for IBM-compatible computers.

Results

In Table 1, AERD patient groups are compared, in order to determine whether or not treatment with LTMDs was linked to patients with more or less severe disease. On admission to

Table 1. Clinical comparison of patients taking leukotriene-modifier drugs and inhaled and/or systemic corticosteroids and those taking only inhaled corticosteroids and/or systemic corticosteroids

	LTMD Rx ($n = 108$)	No LTMD Rx ($n = 163$)	*P*-values
Age at entry into the study	45.6 years	48.4 years	NS†
Age at onset of AERD	32.5 years	35.2 years	NS†
Females	62 (57%)	94 (58%)	NS†
Males	46 (43%)	69 (42%)	NS†
Atopic diseases	72 (66%)	102 (62%)	NS†
Sinus infections/year	6.5	5.4	NS*
Prior sinus operations	3.4	3.1	NS*
Hospitalized for asthma	3.4	1.9	NS*
Emergency room visits for asthma	3.4	5.0	NS*
Anosmia score	0.85	0.80	NS*
Prior ASA- or NSAID-induced asthma attacks	105 (97%)	157 (96%)	NS†
No systemic corticosteroids	25 (23%)	43 (26%)	NS†
Bursts steroids	47 (44%)	74 (45%)	NS†
Prednisone once a day	19 (17%)	26 (16%)	NS†
Prednisone every other day	17 (16%)	20 (13%)	NS†
Mean daily prednisone dose	11.9 mg	10.2 mg	NS*

*Wilcoxon signed rank statistic. †Fisher's two-sided exact test. NS, no significant change (*P*-value > 0.05); LTMD, leukotriene-modifier drugs (montelukast, zafirlukast and zileuton); AERD, ASA exacerbated respiratory disease. Atopic disease defined as: One or more positive wheal and flare skin tests to inhalant allergens. Anosmia scores: 0 = No smell, 1 = Intermittent partial smell, 2 = Intermittent normal smell, 3 = Partial smell, majority of the time, 4 = normal smell at all times. Prior asthma attacks to full therapeutic doses of ASA or other NSAIDs. Mean daily prednisone included four times a day values, combined with half of each every other day value.

Table 2. Types of respiratory reactions induced by ASA in patients treated with leukotriene receptor antagonists (LTRA) and not treated with LTRAs

Types of reactions	Treated with LTRA ($n = 96$)	Not treated with LTRA ($n = 163$)	*P*-values
Classic (upper and lower)	19 (20%)	64 (39%)	0.001*
Pure lower respiratory	3 (2%)	4 (2%)	NS*
Partial asthma	15 (13%)	16 (9%)	NS*
All bronchospastic reactions	37 (39%)	84 (51%)	0.05*
% decline in FEV_1 values:	24.8	24.6	NS†
all bronchospastic reactions	(15–50)	(15–52)	
Mean ASA provoking	60.4	70.3	NS†
dose, mg (bronchial)	(30–150)	(30–325)	
Upper respiratory reactions only	49 (51%)	53 (32%)	0.004*
Mean ASA provoking	61.6	66.3	NS†
Dose, mg (nasal)	(30–150)	(30–325)	
Laryngospasm	0 (0%)	1 (0.06%)	NS*
Negative response	11 (11%)	25 (15%)	NS*

**P*-values were determined with Fisher's two-sided exact test. †*P*-values obtained, using non-parametric Wilcoxon signed rank test. NS, not significant (*P*-value > 0.05); LTMDs, leukotriene-modifier drugs.

GCRC, the average age of the patients was 45.6 years in the LTMD-treated group and 48.4 years in the control group. There were slightly more females in both groups. Average age of onset of the respiratory disease was 32.5 years versus 35.2 years, indicating that both groups had been afflicted with their disease for about 13 years. There were no significant differences in the two groups with respect to the clinical characteristics of AERD as listed in Table 1. We can reasonably conclude that the two study groups were comparable with respect to available clinical markers of AERD and disease severity.

As shown in Table 1, all but three of the patients treated with LTMDs, and all but six in the control group, had previously experienced severe asthmatic attacks after ingesting full therapeutic doses of ASA or other NSAIDs. In fact, the majority had experienced more than one reaction, usually because of lack of information about the universal cross-reactivity of the NSAIDs. During these asthma attacks, bronchodilator rescue medications were used and most patients were rushed to Emergency Departments for treatment. Some were admitted to hospitals and intubation was required for a few. The nine out of 271 patients without prior reactions had been avoiding ASA and NSAIDs on the advice of their physicians. All nine had asthma, sinusitis and recalcitrant nasal polyposis, which had stimulated their physicians to consider a diagnosis of AERD. They were included because their ASA oral challenges were all positive.

The use of topical corticosteroids was nearly universal in both groups but the use of systemic corticosteroids was not used in about a quarter of both groups (Table 1). It is again reassuring

to note that the use of bursts of corticosteroids, daily and alternate-day prednisone, was the same in both groups. Furthermore, the mean daily dose of prednisone was not significantly different (11.9 vs. 10.2 mg). Because systemic corticosteroids are withheld in patients with less severe disease, use of these drugs is a marker for disease severity.

Because the mechanism of action is different, when comparing zileuton to the LT receptor antagonists (montelukast and zafirlukast), these groups were analysed separately. In Table 2, the number of patients who responded to ASA challenges in each of the reaction categories is presented. Comparisons were made between those patients treated with LTRAs ($n = 96$) and control patients who were not receiving any LTMDs ($n = 163$). In the group of patients treated with LTRAs, respiratory reactions were recorded for all categories, including 20% with classic reactions, 2% with pure lower airway reactions, and 13% with partial asthma reactions. A substantial number of patients who were treated with LTRAs experienced selective naso-ocular reactions (51%). In the control group, the opposite pattern emerged, with 39% experiencing classic reactions and only 32% experiencing pure naso-ocular reactions. The differences in these two categories were significant (*P*-values 0.001 and 0.004, respectively). There were no significant differences between the two groups in numbers of patients who did not react to any dose of ASA (11% vs. 15%).

The mean percentage decline in FEV_1 values for all bronchospastic reactions was 24.8 (SEM $\pm$ 1.21, range 15–50) for the LTRA-treated group and 24.6 (SEM $\pm$ 1.00, range 15–52) for the control group. The mean provoking dose of ASA for bronchial reactions was 60.4 mg (SEM $\pm$ 2.9, range 30–150 mg) in the LTRA-treated group and 70.3 mg (SEM $\pm$ 5.0, range 30–325 mg) in the control group. None of these differences were statistically significant. For the nasal reactions, the mean provoking doses of ASA were 61.6 mg (SEM $\pm$ 10.1, range 30–150 mg) for the cys-LTRA treated group and 66.3 mg (SEM $\pm$ 3.4, range 30–325 mg) for the control group. Again, these differences were not statistically significant. In other words, treatment with LTRAs did not result in a decrease in the severity of the bronchospastic responses, as measured by FEV_1 values, nor did it force the use of larger provoking doses of ASA to elicit either the upper or lower respiratory reactions.

Even though there were no differences in any of the clinical parameters of the LTMD-treated versus the control groups in Table 1, the possibility of selection bias in the 196 patients admitted after 1998 could be raised. In order to pursue this possibility, we compared the 75 patients recruited prior to 1998, who could not have been treated with LTMDs, with the 88 patients, recruited after 1998, in whom LTMDs could have been prescribed but were not offered. If there was a bias toward less severe disease in this second group of 88 control patients, an additional theory might postulate that patients with less severe disease might have less severe respiratory responses to aspirin. However, the results do not support the above theories. For numbers of patients experiencing classic reactions to ASA, the untreated control group consisted of 64/163 (39%), with the breakdown groups of 29/75 (39%) and 35/88 (40%). For all bronchospastic reactions, the numbers of patients in the untreated control group was 84/163 (51%), with the subgroups experiencing 39/75 (52%) and 45/88 (51%). For pure nasal reactors, the control group contained 53/163 (32%), with subgroups of 23/75 (31%) and 30/88 (34%). Similar results for non-reactors and the mean changes in FEV_1 values or provoking doses of ASA were also noted. Therefore, there was no support for the theory that stratification by severity of reaction was innocently made by the addition of LTMDs to the controller regimens of only some patients after 1998.

Because of a perception that zileuton is a superior inhibitor of ASA-induced reactions, responses to ASA in the 12 patients treated with zileuton were separated and presented in Table 3. Only two of 12 patients (16%) failed to react to ASA, essentially the same as the control group, 25/163 (15%), and those treated with LTRA, 11/96 (11%). Four of 12 (33%) experienced classic reactions, with three patients reacting to 60 mg of ASA with 29–38% declines in FEV_1 values and one patient reacting to 45 mg of ASA with a 20% decline in FEV_1 values. This reaction rate is closer to the control group (39%) than the LTRA-treated group (21%) and does not suggest a superior blockade of the lower respiratory tract reactions by zileuton. Five of the 12 patients (41%) experienced naso-ocular reactions between the 51% reaction rate for LTRA-treated patients and the 32% reaction rate in the untreated control group. The idea that zileuton was a more effective blocker than the LTRAs of either the upper or lower respiratory responses to ASA is not supported by these data.

Discussion

Leukotrienes play an important role in ASA-induced respiratory reactions in patients afflicted with AERD. Early studies demonstrated that, during ASA challenges, urinary LTE_4 levels increased substantially, coinciding with the lower respiratory reactions, and disappeared as the respiratory reactions subsided. By contrast, these biochemical changes were not found in ASA-tolerant asthmatic patients [11–13]. Increased LTE_4 levels in the urine have been associated with the extent and severity of the respiratory reactions. Daffern et al. [14] measured urinary LTE_4 levels in 74 patients with suspected AERD at baseline and during ASA-induced respiratory reactions. At the time of respiratory reactions to ASA, urinary LTE_4 levels rose significantly in all patients; however, the LTE_4 levels were most strikingly increased in patients with the greatest ASA-induced bronchospastic reactions (decline in FEV_1 of $> 30\%$).

None of the above studies of LTs eliminate a role for other mast cell mediators in the induction of respiratory reactions. Fischer et al. [7] demonstrated that histamine, tryptase, and LTC_4 are released into nasal secretions during ASA-induced respiratory reactions. In fact, pre-treatment of AERD patients with antihistamine, prevented or substantially reduced ASA-induced upper respiratory reactions but did not prevent bronchospasm [8].

Prior studies showed that pre-treatment with leukotriene-modifiers, under certain conditions, prevented ASA-induced reactions. In a study by Christie et al. [15], the selective LT receptor antagonists SK&F 104353 prevented oral ASA-induced respiratory reactions in four out of five patients when the previous provoking dose of ASA was used (range of 30–120 mg). Dahlen et al. [16] found that pre-treatment with MK-0679, a leukotriene receptor antagonist, shifted the dose–response curve to the right, during inhalation challenges with ASA-lysine. Three of eight patients were protected, even after receiving the highest dose of ASA-lysine. The other five subjects

experienced bronchospastic reactions, as ASA-lysine was advanced to higher doses. In a study by Israel et al. [17], eight ASA-sensitive asthmatics, previously shown to react to threshold provoking doses of ASA (20–300 mg, mean of 90 mg), were protected from the same threshold doses of ASA after pre-treatment with zileuton. Doses of ASA were not advanced beyond the previously established threshold doses. In a more recent study of oral ASA challenges in AERD patients, when doses of ASA were advanced beyond the previous threshold doses, six out of six patients experienced respiratory reactions, despite pre-treatment with zileuton [18]. In that study, one patient had a severe ASA-induced asthma attack, with a 53% decline in FEV_1 values after only 45 mg of ASA, while being 'protected' by zileuton. Urine samples, taken during their reactions, contained high levels of LTE_4 in four of five subjects. During baseline challenges in these six patients, the mean provoking dose of ASA was 57 mg and, after pre-treatment with zileuton, the mean provoking dose increased to 122 mg. Stevenson et al. [19] reported data from 10 AERD patients who underwent oral ASA challenges and were then treated with montelukast 10 mg once a day over the next 8–12 days. Oral ASA challenges were repeated, while taking montelukast, and escalating doses of ASA were used until the patients experienced respiratory reactions or took 650 mg of ASA without a reaction. Only one of the 10 patients did not experience a reaction during the second oral ASA challenge while protected by montelukast. Nine of the 10 experienced at least naso-ocular reactions and four also experienced asthmatic reactions.

There are several conclusions from these prior studies that we might consider. First, ASA challenges exert a powerful broncho-constrictive effect on the airways that is only partially inhibited by montelukast or zileuton, particularly as the provoking doses of ASA are increased. Zafirlukast has not been studied in this experimental design but there is no reason to suspect that it will block ASA-induced reactions any more or less effectively than montelukast. Second, LT modifiers seem to have only minor blocking effects on ASA-induced upper airway reactions. This should not be surprising as histamine is released into the nasal secretions during ASA-induced nasal reactions [7, 20, 21] and available LTRAs only block cys-LT_1 receptors. Furthermore, extra bronchial effects of histamine, such as flushing, hives and abdominal pain, can be successfully treated with H1 and H2 receptor antagonists.

With this background information available, is it appropriate to continue asthma controller treatment with LTMDs during diagnostic oral ASA challenges? In other words, are the advantages of enhanced asthma control with LTMDs cancelled out by their blocking effects on ASA challenges? Our current study showed a significant reduction in ASA-induced bronchospastic reactions and a concomitant increase in pure upper respiratory reactions in those AERD patients treated with cys-LTRAs. These observations suggest that LTRAs were effective in modifying lower airway reactions in some patients but were not effective in eliminating or attenuating upper airway reactions. Furthermore, despite earlier suggestions that larger doses of ASA might be needed to overcome bronchial blockade by LTMDs in several small studies [18, 19], this was not the case in this large study of 96 asthmatic subjects treated with LTRAs. The severity of the asthmatic reactions and the provoking doses of ASA, which induced either upper or lower airway reactions, were uninfluenced by treatment with LTRAs.

Equally important, the incidence of no reactions to ASA was not significantly different in the LTRA-treated (11%) and untreated (15%) groups. Similarly, in the patients treated with zileuton, two out of 12 patients (16%) did not react to ASA (Table 3). These percentages of patients, who believed they were ASA-sensitive and yet underwent negative oral ASA challenges, were very similar to our prior 1983 study of 50 patients [5]. In that study, the incidence of negative challenges to ASA in patients who believed they were ASA-sensitive was eight out of 50 (16%). Based upon the comparative data from our current study and the historical data from a study that pre-dated the availability of current inhaled steroids and LTMDs, we can conclude that LTRAs or zileuton did not preferentially block both upper and lower respiratory reactions. As with systemic corticosteroids [22], LT modifier treatment can block respiratory reactions to ASA in an occasional patient [19]. However, this appears to be quite unusual and the benefit of insuring

Table 3. Potential AERD asthmatic patients: oral aspirin challenges while taking zileuton 600 mg four times a day ($n = 12$)

Patient no.	Nasal reactions	ASA dose (mg*)	Extra respiratory	FEV_1 % change	ASA dose (mg†)	Prednisone doses during challenges‡
1	NO	45	Pruritus	14	NA	4 mg once a day
2	NO	100	0	6	NA	0
3	NO	60	0	6	NA	10 mg once a day
4	NO	100	0	8	NA	0
5	NO	45	Urticaria	4	NA	0
6	NO	60	0	38	60	0
7	NO	60	0	31	60	10 mg every other day
8	NO	60	0	29	60	0
9	NO	45	Gastrointestinal reaction	20	45	0
10	0	100	Laryngeal	8	NA	0
11	0	NA	0	0	NA	0
12	0	NA	0	0	NA	60 mg once a day
Mean	63.5	29.5	52.5			

*Provoking dose of ASA that induced nasal reactions. †Provoking dose of ASA if asthmatic reaction was induced. ‡All12 patients were also taking inhaled and nasal corticosteroids. NO, naso-ocular reactions; NA, given 30 mg of ASA and increasing to 650 mg of ASA without a reaction.

airway stability probably outweighs the problem of a rare false negative challenge in a patient with AERD undergoing treatment with an LTMD. In fact, hyperirritable airways are a contraindication to oral ASA challenges and therefore withholding LTMDs could reduce the number of candidates who would be eligible to participate in oral ASA challenge procedures.

In conclusion, during oral ASA challenges, treatment with LTRAs blocked lower respiratory tract reactions in some patients, producing a higher prevalence of upper airway reactors, when compared to AERD patients who were not taking cysLTRAs. However, there is no evidence that a higher percentage of false negative challenges are associated with concomitant treatment with LTMDs. In clinical practice, it is our recommendation that in patients already taking LTMDs as controller agents to provide stability of the airways, these drugs should be continued at the time of oral ASA challenges.

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