

Original article

Inhibition of nasal polyp mast cell and eosinophil activation by desloratadine

Nasal polyp tissue which contains mast cells and eosinophils is similar to the inflamed airway mucosa in cellular composition and mediator content. This investigation assessed the effect of desloratadine (DL), on activation of cells in nasal polyp tissue. Polyps were obtained from 22 patients with chronic rhinosinusitis [nine aspirin acetylosalitic acid (ASA)-sensitive and 13 ASA-tolerant]. Polyp tissue was dispersed by digestion, and preincubated with DL and incubated with anti-immunoglobulin E (IgE) or calcium ionophore. LTC₄, eosinophil cationic protein (ECP) and tryptase concentrations in supernatants were measured by immunoassays. Desloratadine (1, 10 and 50 µM) inhibited calcium ionophore-induced LTC₄ release by a mean of 29%, 50% and 63% respectively, and anti-IgE-induced LTC₄ release by a mean of 27%, 35% and 39% respectively. Calcium ionophore-induced tryptase release was inhibited 60% and 69% by 10 and 50 µM of DL, respectively, and anti-IgE-induced tryptase release was inhibited 33%, 47% and 66% for 1, 10 and 50 µM of DL. Desloratadine 10 µM and 50 µM inhibited ECP release by and 45% and 48% respectively. Polyp tissue from ASA-sensitive patients when compared with ASA-tolerant patients released at baseline significantly more ECP (medians 120.0 µg/ml, range: 69.0–182.0 vs 63.4 µg/ml, range: 3.7–172.0; $P < 0.05$), but similar amounts of tryptase and LTC₄. This study demonstrated that DL inhibits activation of both eosinophils and mast cells derived from a site of airway mucosal inflammation.

**M. L. Kowalski¹, A. Lewandowska¹,
J. Wozniak¹, J. Makowska¹,
A. Jankowski², L. DuBuske³**

¹Department of Clinical Immunology and Allergy, Faculty of Medicine, Medical University, Lodz, Poland; ²ENT Department, Medical University, Lodz, Poland; ³Immunology Research Institute of New England, Fitchburg, MA, USA

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Professor Marek L. Kowalski
Department of Clinical Immunology and Allergy
Medical University of Lodz
251 Pomorska Str.
92-213 Lodz
Poland

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Antihistamines are widely regarded as effective treatment of various allergic conditions including allergic rhinitis and chronic urticaria (1). Their clinical efficacy seems to be directly related to H1 receptor inhibition with subsequent abrogation of effects of histamine released during allergic reactions from mast cells and basophils (2). Studies published over last two decades demonstrated that most second generation antihistamines in addition to the H1 receptor-mediated effects also can produce a significant influence on inflammatory cell activity *in vitro* (2). Desloratadine (DL) the primary active metabolite of loratadine is a potent H1 receptor antagonist (3). Desloratadine can inhibit release of mediators from isolated mast cells and basophils (4–6) down-regulate cytokine expression in human nasal epithelial cells (7), inhibit adhesion molecule expression on epithelial cells (8) and activation of endothelial cells (9). The relevance of the *in vitro* antiallergic activity of antihistamines to their clinical effectiveness *in vivo* is not clear since antihistamines are active *in vitro* typically at micromolar concentrations, especially with respect to histamine and leukotriene release inhibition, thus requiring concentrations which are greater than serum concentrations which are nanomolar. However, it is possible that antihistamines

may accumulate at the site of inflammation achieving locally a greater concentration than seen in serum.

The cellular composition and mediator content of nasal polyp tissue is similar to the inflamed airway mucosa (10). It contains not only mast cells and eosinophils, but also other cells such as mononuclear cells, neutrophils, epithelial cells and fibroblasts that are able to modulate activation of effector cells. Accessibility of nasal polyp tissue allows for easy assessment of cells derived from a site of inflammatory reactions, which also accounts for interacting between different cell types similar to the situation occurring *in vivo*. Utilization of dispersed nasal polyp cell preparations allows unique opportunities to assess individual features of the inflamed tissue such as the degree of eosinophilia and assess the impact of characteristics of patient disease such as clinical severity, which may affect responses to the compound tested. Some patients with nasal polyps suffer from aspirin acetylosalitic acid (ASA)-sensitivity, which is associated with particularly severe rhinosinusitis/asthma recurrent nasal polyposis and prominent tissue eosinophilia (11, 12). Chronic inflammation in ASA-sensitive patients is difficult to manage and often resistant to standard treatment with topical glucocorticosteroids (13).

The aim of the study was to assess the capacity of DL to inhibit release of mediators from nasal polyp tissue obtained from a well-characterized group of patients. This is the first study, which relates the *in vitro* response to an antihistamine to cellular characteristics of the inflammatory tissue and clinical characteristics of patients.

Materials and methods

Patients

Nasal polyps were obtained from 22 patients (12 men or 10 woman, age 23–70) with chronic rhinosinusitis undergoing elective nasal surgery for reasons unrelated to the goals of this study. Ten patients had positive skin prick test to at least one inhalant allergen from a panel of 12 inhalant allergens tested, and in patients with seasonal symptoms nasal surgery was performed out of the pollen season. Nine patients had a positive history of bronchial and nasal reaction to ASA or other nonsteroidal anti-inflammatory drugs, confirmed by positive nasal or bronchial inhalation challenge with lysine ASA. None of the patients had received oral or intranasal steroids for at least 4 weeks before surgery.

The study was approved by a local medical ethics committee and all subjects gave their informed consent.

Nasal polypectomy and tissue handling

Nasal polypectomies were performed under local anesthesia. Prior to surgery, 2% tetracaine HCl and 0.25% phenylephrine HCl were applied topically to the turbinates, nasal septum and middle meatus and subsequently the polyp was injected with 2–4 ml of 1% lidocaine with 1 : 100 000 epinephrine. Then, the polyp was removed using gentle traction and snare technique. Polyps were placed in 0°C Medium 199 (Sigma, St Louis, MO, USA) and immediately transported to the laboratory in a thermoinsulation container (temperature 4–6°C).

Nasal polyps dispersed cells preparation

Polyps were dissected with scissors into pieces of approximately 2 mm³. Dissected polyp tissue was placed in RPMI 1640 (Sigma) culture medium containing 0.75 mg/ml of hyaluronidase (Sigma), 1.5 mg/ml collagenase (Sigma) and 2 mg/ml protease type XIV (Sigma) for 120 min, according to a method previously described (14). Cell dispersion was performed at 37°C. At the end of the dispersion period, the cells were filtered to separate them from any undigested tissue. The cells were resuspended in 15 ml of M199 (Sigma) and washed three times to remove the enzymes. The cells were resuspended at a concentration of 1×10^6 cells/ml in M199. Dispersed nasal polyp cells were preincubated with DL (10^{-5} – 10^{-9} M) or medium for 30 min and stimulated with 10^{-5} M calcium ionophore (Serva, Heidelberg, Germany) or ϵ -chain-specific anti-immunoglobulin E (IgE) (1, 10, and 100 µg/ml) for 45 min at 37°C.

Measurement of mediators

Eosinophil cationic protein (ECP) and tryptase release was assayed by using the Pharmacia UniCap system (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden) and LTC₄ generation was measured by specific enzyme-linked immunosorbent assay (ELISA) immunoassay (Cayman, Ann Arbor, MI, USA)

Statistical analysis

Statistical analyses were performed with Wilcoxon's W test. For comparisons of mediator release between ASA-hypersensitive and ASA-tolerant patients the nonparametric Mann–Whitney U-test was used.

Results

Effect of desloratadine on LTC₄ release

Preliminary experiments with DL demonstrated that a significant inhibitory effect of DL on calcium ionophore-induced LTC₄ release was observed only for micromolar concentrations (data not shown). Based on this observation 10^{-6} – 5×10^{-5} M concentrations of DL were used in inhibitory experiments.

Stimulation of dispersed nasal polyp tissue with calcium ionophore resulted in a significant increase in LTC₄ generation (median 37.1 pg/ml; range 10.8–174.0 to 273.3 pg/ml, range: 66.2–1048.6, $P < 0.001$; $n = 22$) and the mean increase in LTC₄ generation was 755.0% DL 10 µM (10^{-5} M) did not affect baseline generation of LTC₄, but significantly inhibited calcium ionophore-induced increase in LTC₄ generation by a mean of 49.0% ($P < 0.005$) (Table 1).

The inhibitory effect of DL was dose-dependent, 1 µM, 5 µM, 10 µM, 50 µM, and 100 µM DL inhibiting LTC₄ generation by 29%, 26%, 50%, 63% and 95% respectively (Fig. 1A).

Stimulation of cells with anti-IgE increased generation of LTC₄ from 37.1 pg/ml, range: 10.8–174.0 to 325.9 pg/ml, range: 72.8–849.2, 1155.3 pg/ml, range: 421.7–1314.7, and 1228.4 pg/ml, range: 520.0–1538.0 for 1 µg/ml, 10 µg/ml, and 100 µg/ml anti-IgE respectively. Desloratadine 10 µM significantly decreased LTC₄ generation induced by 10 µg/ml of anti-IgE by a mean of 18.0% ($n = 19$, $P < 0.05$) (Table 1) but did not affect LTC₄-induced by 1 and 100 µg/ml of anti-IgE. Although in individual patients 1, 10, and 50 µM of DL inhibited anti-IgE-induced LTC₄ generation, the mean inhibition induced for this small number of patients ($n = 8$) did not achieve statistical significance (Fig. 1B).

Effect of desloratadine on tryptase release

Calcium ionophore 10^{-5} M increased tryptase release into nasal polyp cell supernatants from 5.4 µg/l, range: 1.0–14.3 to 10.1 µg/l, range: 2.4–26.2 ($n = 19$) representing a mean 221% increase from baseline. Desloratadine 10 µM significantly decreased calcium ionophore-induced tryptase release (mean inhibition 64.0% ($n = 19$)) (Table 1). Study of a smaller group of patients ($n = 8$) demonstrated a mean decrease of 45%, 60% and 69% for 1 µM, 10 µM, and 50 µM of DL respectively, although only for two later doses was the mean inhibition of tryptase release statistically significant (Fig. 2A).

Table 1. The effect of 10 μ M of desloratadine (DL) on mediator release from nasal polyp dispersed cells ($n = 19$)

	Baseline	Stimulus	$P_{<}$	Stimulus + DL	$P_{<^*}$	Inhibition (%)
LTC ₄ (pg/ml, $n = 22$)						
Calcium ionophore	37.1 (10.8–174.0)	273.3 (66.2–1048.6)	0.00004	234.6 (31.0–901.0)	0.0002	49
Anti-IgE 1	37.1 (10.8–174.0)	325.9 (72.8–849.2)	0.00004	314.9 (69.0–800.0)	0.24	24
Anti-IgE 10	37.1 (10.8–174.0)	1155.3 (421.7–1314.7)	0.00004	1006.0 (131.0–1447.0)	0.01	18
Anti-IgE 100	37.1 (10.8–174.0)	1228.4 (520.0–1538.0)	0.00004	1228.4 (300.0–1507.0)	0.46	8
Tryptase (μ g/l, $n = 19$)						
Calcium ionophore	5.4 (1.0–14.3)	10.1 (2.4–26.2)	0.0001	4.7 (1.8–16.2)	0.0002	64
Anti-IgE 100	5.4 (1.0–14.3)	7.3 (1.9–27.9)	0.0001	5.1 (1.3–21.9)	0.0002	51
ECP (μ g/l, $n = 19$)						
Calcium ionophore	99.3 (3.7–182.0)	152.0 (4.3–202.0)	0.0002	125.0 (2.0–200)	0.0002	58
Anti-IgE 100 ($n = 10$)	91.6 (3.7–182.0)	106.5 (3.6–200.0)	0.34	117.0 (2.0–219.0)	NS	0

Data represented median (range).

* Significance of difference when compared with stimulus alone.

IgE, immunoglobulin E.

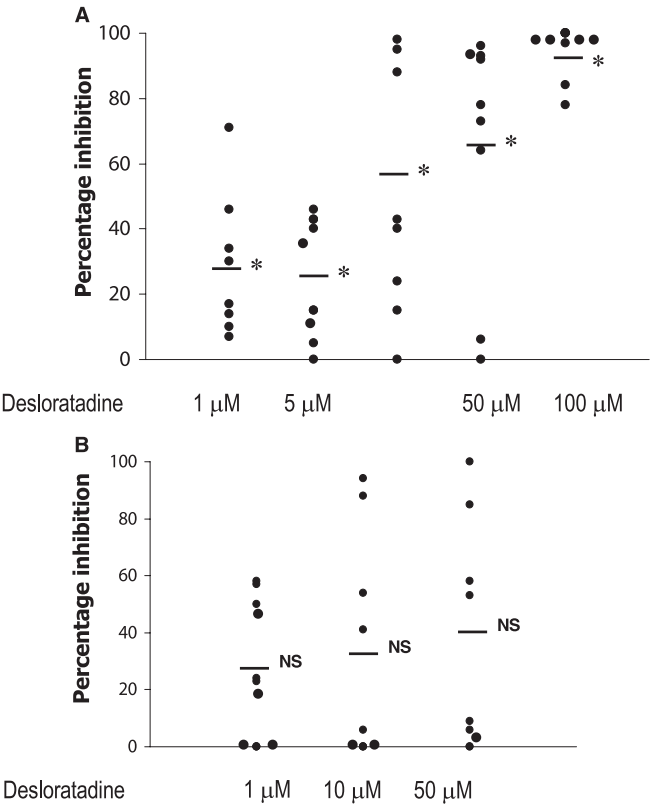


Figure 1. The effects of desloratadine on LTC₄ generation from nasal polyp cells ($n = 8$) induced by (A) calcium ionophore (10^{-5} M) and (B) anti-immunoglobulin E (IgE) (100 μ g/ml).

Stimulation with anti-IgE (100 μ g/ml) increased basal generation of tryptase from 5.4 μ g/l, range: 1.0–14.3 to 7.3 μ g/l, range: 1.9–27.9 μ g/l representing a mean 80% increase from baseline. For the whole group ($n = 19$) 10 μ M DL significantly decreased anti-IgE-induced

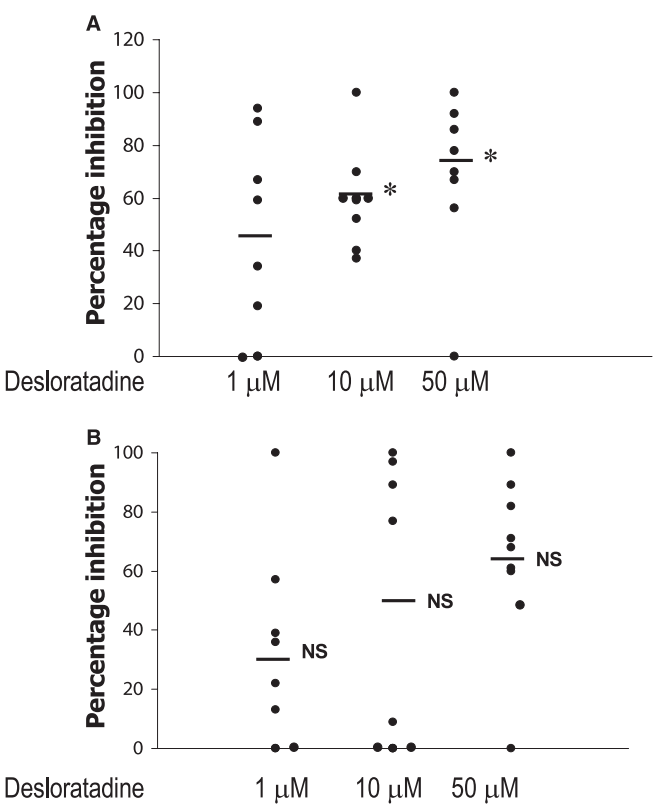


Figure 2. The effects of desloratadine on tryptase release from nasal polyp cells ($n = 8$) induced by (A) calcium ionophore (10^{-5} M) and (B) anti-immunoglobulin E (IgE) (100 μ g/ml).

tryptase release ($P < 0.05$; mean inhibition 51%). Desloratadine 1 μ M, 10 μ M, and 50 μ M decreased tryptase release by a mean of 33%, 47% and 66% respectively, although for this group ($n = 8$) the decrease was not statistically significant (for 50 μ M, $P < 0.06$) (Fig. 2B).

Effect of desloratadine on ECP release

Baseline release of ECP was significantly increased after stimulation with 10^{-5} M calcium ionophore by a mean of 63% ($n = 19$; $P < 0.01$). Stimulation with anti-IgE (10 μ g/ml or 100 μ g/ml) did not increase basal generation of ECP.

Desloratadine 10^{-5} M significantly decreased calcium ionophore-induced ECP release (mean inhibition 58%). Desloratadine 1 μ M, 10 μ M, and 50 μ M decreased ECP release by 23% (NS), 45% ($P < 0.05$) and 48% ($P < 0.05$) respectively (Fig. 3).

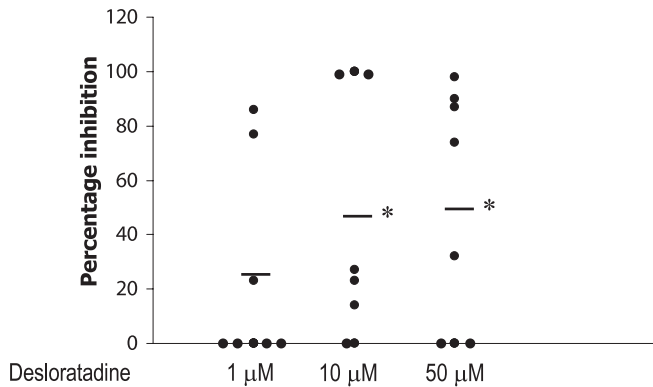


Figure 3. The effects of desloratadine on calcium ionophore (10^{-5} M)-induced eosinophil cationic protein (ECP) release from nasal polyp cells ($n = 8$).

Inhibition of mediator release from nasal polyp cells by desloratadine from ASA-sensitive and ASA-tolerant patients

Nasal polyp cells from ASA-sensitive patients contained more eosinophils (15% vs 8% of cells, $P < 0.05$) and released significantly more ECP at baseline and after stimulation with calcium ionophore which compared with cells from ASA-tolerant patients (Table 2). Basal levels and calcium ionophore or anti-IgE-stimulated levels of LTC₄ and tryptase were similar in ASA-sensitive and ASA-tolerant patients.

Anti-IgE-induced release of LTC₄ and tryptase were both inhibited by 10 μ M DL only in ASA-sensitive (by 28% and 56% respectively; $P < 0.05$), but not in ASA-tolerant patient nasal polyp cells (11% and 47% respectively; $P > 0.05$). Calcium ionophore-induced tryptase and ECP releases were significantly inhibited by DL in both ASA-sensitive and ASA-tolerant patients (Table 2).

The inhibitory effect of DL for different stimuli and mediators was not correlated to the presence of asthma or atopic status, degree of tissue eosinophilia, or the magnitude of stimulated LTC₄, tryptase and ECP release.

Discussion

In order to investigate cellular effects of the new antihistamine DL, a preparation of mixed cells derived from the site of nasal inflammation, namely human

Table 2. Inhibitory effect of desloratadine on release of mediators from nasal polyp dispersed cells in ASA-sensitive (AS) and ASA-tolerant (AT) patients

	AS	AT	<i>P</i> <
LTC ₄ (pg/ml)	<i>n</i> = 9	<i>n</i> = 13	
Basal	49.0 (18.0–116.8)	35.5 (10.8–174.0)	0.62
Calcium ionophore-induced	201.0 (131.0–988.0)	357.2 (66.2–1048.6)	0.37
Calcium ionophore-induced + DL	85.7 (31.0–901.0)**	193.2 (75.2–814.9)*	0.12
Inhibition (%)	60	41	
Anti-IgE-induced (10 μ g)	1080.0 (421.7–1242.0)	1205.1 (779.7–1314.7)	0.07
Anti-IgE-induced + DL	850.5 (131.0–1173.0)*	1082.1 (905.2–1447.0)	0.06
Inhibition (%)	28	11	
Tryptase (μ g/l)	<i>n</i> = 9	<i>n</i> = 10	
Basal	5.4 (1.0–14.3)	4.5 (1.0–8.8)	0.68
Calcium ionophore-induced	10.1 (2.4–26.2)	10.5 (4.9–23.1)	0.93
Calcium ionophore-induced + DL	4.7 (1.8–16.2)*	7.1 (2.0–16.0)*	0.46
Inhibition (%)	71	58	
Anti-IgE-induced (100 μ g)	8.8 (1.9–27.9)	5.08 (2.4–18.2)	0.68
Anti-IgE-induced + DL	5.1 (1.3–17.0)*	5.5 (1.4–21.9)	0.81
Inhibition (%)	56	47	
ECP (μ g/l)	<i>n</i> = 9	<i>n</i> = 10	
Basal	120.0 (69.0–182.0)	63.4 (3.7–172.0)	0.007
Calcium ionophore-induced	200.0 (131.0–202.0)	97.3 (4.3–200.0)	0.0089
Calcium ionophore-induced + DL	142.0 (70.0–200.0)*	91.7 (2.0–187.0)*	0.086
Inhibition (%)	74	44	

Data represented median (range).

* Significantly inhibited when compared with stimulus; * $P < 0.05$, ** $P < 0.005$.

nasal polyps was employed. Nasal polyp tissue is characterized by the presence of both recruited, effector cells such as mast cells and eosinophils typical of allergic inflammation and also structural cells such as epithelial cells and fibroblasts which contribute to the local inflammatory response (10). By measuring mediators specific for particular cells such as mast cell-derived tryptase or eosinophil-derived ECP it was possible to analyze the response of each cell population to the inhibitory effect of DL. This investigation demonstrated that DL was capable of inhibiting in a dose-dependent fashion cell activation evoked by various stimuli. This inhibitory effect was not limited to a particular mediator or cell type: inhibition of tryptase as well as ECP release allowed for identification of at least two cell types, mast cells and eosinophils, which are susceptible to the inhibitory effect of DL. This study extended the previous studies, which demonstrated a similar inhibitory activity of DL on isolated basophils (4, 6, 15) or epithelial cells (7, 16).

The inhibitory effect of DL was not dependent on the type of stimulus as both calcium ionophore and anti-IgE-induced release of tryptase were inhibited to the same degree, indicating that DL affects intracellular mechanisms common for different activation pathways. Although several mechanisms including interference with calcium influx (17) and inhibition of the lipoxygenase pathway have been postulated (18, 19) the mechanisms of the various inhibitory effects of DL are not well-established. When analyzing the effect of DL on nasal polyp cells from individual patients there was intersubject variation 1 and 10 μM of DL inhibited release of tryptase, LTC_4 and ECP by more than 60% sometimes reaching nearly 100% inhibition. On the contrary, in a few patients 50 μM of DL did not inhibit mediator release, whereas 100 μM concentration of DL-induced 100% inhibition of LTC_4 release in six of eight polyp cell preparation and 80% inhibition in remaining two polyp cell preparation.

This study demonstrates that DL is capable of inhibiting activation of tissue eosinophils, playing a potentially critical role in the development of allergic inflammation. Desloratadine at 10 and 50 μM concentrations significantly inhibited calcium ionophore-induced release of ECP by a mean of 58%, and in a few individual patients almost complete inhibition of ECP release was observed. Stimulation with anti-IgE did not induce ECP release from nasal tissue preparations, confirming the lack of functional $\text{Fc}\epsilon$ receptors on nasal polyp eosinophils.

Aspirin-sensitivity is associated with a particular subpopulation of nasal polyposis characterized by persistent and relatively treatment resistant form of rhinosinusitis/asthma (13). At the tissue level an extensive eosinophilia is a typical feature of mucosal inflammation both in the upper and lower airways (11, 12). This study confirmed previous reports that ASA sensitivity is associated with a

greater degree of tissue eosinophilia and accordingly significantly more ECP was released from nonstimulated or stimulated nasal polyp dispersed cells (NPDC) from ASA-sensitive patients (12). Basal and stimulated release of LTC_4 was similar in nasal polyp cells from both subpopulations of patients, arguing against the hypothesis that mucosal inflammation in ASA-sensitive patients is leukotriene driven. Conversely, these findings suggest that overproduction of cysteinyl-leukotrienes which are detected in the urine of ASA-sensitive patients may reflect an increase in the total number or mass of leukotriene producing cells such as eosinophils and mast cells rather than leukotriene overproduction at the cellular level. This observation may explain results of studies which demonstrated similar effectiveness of montelukast, a LT_1 receptor antagonist, in reducing nasal or bronchial symptoms in ASA-sensitive and ASA-tolerant patients with nasal polyposis (20, 21).

The inhibitory effect of DL on tryptase and LTC_4 release was observed in both ASA-sensitive and ASA-tolerant patients, and could not be associated with any cellular or clinical characteristics of the patient subpopulations. Anti-IgE-induced release of both LTC_4 and tryptase were inhibited by DL only in ASA-sensitive patients. Since the difference in response to the inhibitory effects of DL could not be attributed to any other clinical or laboratory feature of this patient subpopulation, the inflammatory responses in ASA-sensitive patients may be particularly susceptible to inhibition by DL. This hypothesis requires confirmation in future *in vitro* and clinical studies.

An *in vitro* inflammatory cell stabilizing effect seems to be typical for many new H_1 receptor antagonists, including loratadine, cetirizine, fexofenadine, terfenadine, azelastine and mizalastine (4, 7, 15, 19, 22–26). However, the clinical relevance of *in vitro* 'anti-inflammatory' effects of the antihistamines is not clear, as the inhibitory concentrations are usually within the micromolar range which are greater than concentrations achieved in serum. It is possible that chronic administration of antihistamines results in accumulation in tissues achieving concentrations, which allow for effective anti-inflammatory activity at the site of inflammation (27).

In summary, this study demonstrates that DL can produce a potent inhibitory effect on activation of cells derived from a site of inflammation, namely nasal polyp cells, suggesting that the antiallergic, anti-inflammatory effect of DL may be relevant to its clinical efficacy in chronic allergic rhinitis.

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