

# Topical azelastine has a 12-hour duration of action as assessed by histamine challenge-induced exudation of $\alpha_2$ -macroglobulin into human nasal airways

L. GREIFF, M. ANDERSSON, C. SVENSSON and C. G. A. PERSSON\*

Departments of Otorhinolaryngology, Head and Neck Surgery and \*Clinical Pharmacology, Lund University Hospital, Lund, Sweden

## Summary

**Background** Oral anti-histamine drugs are widely used in the treatment of seasonal allergic rhinitis. Recently, anti-histamines have become available also for topical treatment. **Objective** The present study, involving healthy subjects, examined the effect of topical azelastine on luminal entry of  $\alpha_2$ -macroglobulin and symptoms evoked by repeat histamine challenges during 24 h. The effect was compared to a clinical dose of the oral anti-histamine cetirizine and to placebo treatments.

**Methods** Placebo and azelastine (0.254 mg per nasal cavity) were delivered as two consecutive actuations per nasal cavity using a nasal spray device. Oral placebo and cetirizine (10 mg) were given as single doses in a placebo-controlled (double-dummy), double-blind, and cross-over design. Histamine-challenges were given 1 h before treatment, and 1, 6, 9, 12, and 24 h after each treatment. The nasal mucosal surface was lavaged after each challenge. The lavage-fluid levels of  $\alpha_2$ -macroglobulin were determined to assess mucosal exudation of bulk plasma, and nasal symptoms were scored.

**Results** Histamine (40–400  $\mu\text{g/mL}$ ) produced dose-dependent exudation and symptoms. Compared between each treatment and placebo, azelastine and cetirizine reduced the 40 and/or 400  $\mu\text{g/mL}$  histamine-induced mucosal exudation of plasma from 1–12 h after treatment. In addition, cetirizine reduced the 40  $\mu\text{g/mL}$  histamine-induced mucosal exudation of plasma 24 h after treatment. Differences between the two treatments were not evident regarding nasal symptoms.

**Conclusion** Histamine challenge-induced mucosal exudation of plasma appears to be a useful method for studies of the duration of action of antihistamines. We conclude that topical azelastine is suited for b.i.d. therapy and that neither the exudative process nor watery secretion may impede the efficacy or the duration of action of this nasal drug.

**Keywords:** allergy, antihistamine, rhinitis

*Clinical and Experimental Allergy*, Vol. 27, pp. 438–444. Submitted 14 May 1996; revised 16 July 1996; accepted 22 September 1996.

## Introduction

Antihistamines have been used in the treatment of allergic airways disease for more than 40 yr. Recently, antihistamines such as azelastine have been introduced also for topical use in

allergic rhinitis. The duration of the pharmacological effect would be a major aspect of topical antihistamines in deciding dose intervals for efficacy around the clock. Weiler *et al.* [1] have shown that a clinical dose of topical azelastine may reduce major symptoms of seasonal allergic rhinitis for up to 10 or 12 h during natural pollen exposure. In a study involving patients with seasonal allergic rhinitis out of season, Thomas *et al.* [2] have demonstrated that topical azelastine reduces histamine challenge-induced sneezes for 10 h after

Correspondence: L. Greiff, Department of Otorhinolaryngology, Head and Neck Surgery, Lund University Hospital, S-221 85 Lund, Sweden.



treatment, whereas the histamine challenge-induced increase in nasal airway resistance (as measured by posterior rhinomanometry) was reduced for only 1–2 h after treatment. It appears that further information on the duration of action of topical azelastine is warranted, particularly concerning its ability to counteract different pharmacological effects of histamine.

We have shown previously that repeated histamine challenges may evoke reproducible exudative effects (luminal entry of bulk plasma) over several hours [3]. The exudative action of histamine applied on the human nasal mucosa is concentration-dependent in the range 40–2000  $\mu\text{g/mL}$  [4]. Hence, repeated histamine-induced mucosal exudation of plasma might be employed as a method for determination of the duration of action of antihistamine drugs. Furthermore, the plasma exudation response may be a major action of histamine because this effect brings a wide range of adhesive proteins and other biologically active peptides/proteins to the lamina propria, the basement membrane, the epithelium, and the mucosal surface of the allergic mucosa.

In the present study, we have examined the duration of the pharmacological effect of topically applied azelastine on luminal entry of plasma induced by repeated histamine-challenges. In addition, we have examined treatment effects on histamine-induced nasal symptoms. The effects of topically applied azelastine have been compared to the effect of the orally administered antihistamine drug cetirizine and to placebo.

## Methods

### Study design

The study was of a placebo-controlled (double-dummy), double-blind, and cross-over design. Subjects were treated on three occasions, i.e. with active nasal spray (azelastine) and placebo tablets, with placebo nasal spray and active tablets (cetirizine), and with placebo nasal spray and placebo tablets. The wash-out time was 2 weeks. Placebo and drug treatments were given as single doses and histamine-challenges were given 1 h before and 1, 6, 9, 12, and 24 h after each treatment. The nasal mucosal surface was lavaged after each challenge and the lavage-fluid concentrations of  $\alpha_2$ -macroglobulin were determined as an index of mucosal exudation of plasma. Furthermore, baseline and histamine-induced nasal symptoms were scored after each challenge.

### Subjects

Twelve healthy subjects, 23–28 yr of age (mean age 25 yr), received histamine-challenges and placebo and drug treatment. The subjects had no history of general, allergic or recent nasal disease, and no history of recent drug treatment.

The study was approved by the local ethics committee, and informed consent was obtained.

### Nasal pool challenge and lavage technique

A nasal pool device was used for concomitant histamine-challenge and lavage of the nasal mucosa [4]. The nasal pool device is a compressible plastic container equipped with a nasal adapter. The adapter is inserted into one of the nostrils and the container is compressed by the sitting subject leaning forward in a 60° flexed neck position. The nasal pool fluid is then instilled in one of the nasal cavities and maintained in contact with a large and reproducible area of the mucosal surface for a determined period of time. When the pressure on the device is released, the fluid returns into the container. In the present study the total volume of the nasal pool fluid was 14 mL.

### Drug treatment and histamine challenges

The topical placebo and azelastine (0.254 mg per nasal cavity) drug solutions were delivered as two consecutive actuations per nasal cavity using a nasal spray device (0.254 mg azelastine corresponds to 0.280 mg azelastine hydrochloride). Oral placebo and cetirizine (10 mg) were given as single oral doses. Using the nasal pool device, isotonic saline and histamine (40 and 400  $\mu\text{g/mL}$ ) were employed as challenge and lavage solutions 1 h before, and 1, 6, 9, 12 and 24 h after each treatment. The solutions were given consecutively at each time point, and each solution was maintained in the unilateral nasal cavity for 10 min. The lavage fluids were centrifuged (325 g, 10 min, 4°C) and samples were obtained from the supernatant and frozen (–20°C) to await analysis of  $\alpha_2$ -macroglobulin.

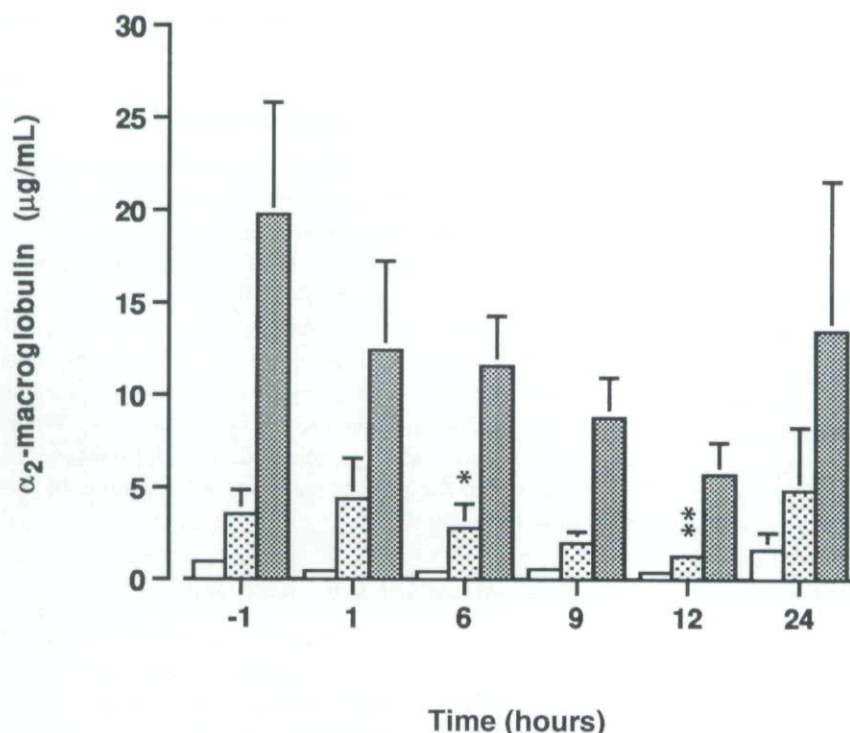
### Analysis of $\alpha_2$ -macroglobulin

The lavage fluid levels of  $\alpha_2$ -macroglobulin were measured using a radioimmunoassay sensitive to 7.8 ng/mL. Rabbit anti-human  $\alpha_2$ -macroglobulin (Dakopatts, Copenhagen, Denmark) was used as anti-serum and standard human serum (Behringwerke Diagnostica, Marburg, Germany) as standard. Human  $\alpha_2$ -macroglobulin (Cappel-Organon Teknika, Turnhout, Belgium) was iodinated using the lactoperoxidase method. Tracer and standard (or sample) was mixed with anti-serum before adding goat anti-rabbit anti-serum (Astra Draco, Lund, Sweden). The bound fraction was measured using a gamma counter (Pharmacia, Uppsala, Sweden). The intra- and inter-assay coefficients of variation are between 3.8–6.0% and 3.1–7.2%, respectively.

### Symptom score

Nasal symptoms, i.e. sneezes, secretion and blockage, were





**Fig 1.** Histamine produced dose-dependent mucosal exudation of bulk plasma ( $\alpha_2$ -macroglobulin) 1 h before treatment and 1–24 h after placebo treatment. The response to 40  $\mu\text{g/mL}$  histamine decreased with time (Friedman  $P < 0.05$ ). The reduction was significant at 6 and 12 h after treatment compared with before treatment. (Comparisons between levels obtained before treatment and 1–24 h after treatment, \* $P < 0.05$ , \*\* $P < 0.01$ .) Although mean values were reduced by repeat histamine challenge, there was no significant tachyphylaxis to 400  $\mu\text{g/mL}$  histamine (Friedman  $P > 0.05$ ). □ = control saline; ▤ = histamine (40  $\mu\text{g/mL}$ ); ▨ = histamine (400  $\mu\text{g/mL}$ ).

scored by the subjects immediately after each challenge using a symptom score: No = 0, mild = 1, moderate = 2, severe = 3 symptoms.

#### Statistics

Differences in histamine-induced nasal symptoms and  $\alpha_2$ -macroglobulin levels between the placebo and the two antihistamine treatments were analysed by the Wilcoxon signed rank (WSR) test. Differences in nasal symptoms and  $\alpha_2$ -macroglobulin levels within each treatment group were analysed by the Friedman test and the WSR test. A  $P$ -value less than 0.05 was considered significant. Data are presented as mean  $\pm$  SEM.

#### Results

##### Reproducibility of control saline and histamine challenges

The mean of the intra-individual coefficients of variation calculated on lavage fluid levels of  $\alpha_2$ -macroglobulin after challenges with control saline, histamine (40  $\mu\text{g/mL}$ ) and histamine (400  $\mu\text{g/mL}$ ), respectively, on three occasions before treatment were 0.71, 0.61 and 0.71. The mean of intra-individual coefficients of variation calculated on lavage fluid levels of  $\alpha_2$ -macroglobulin after challenges with control saline, histamine (40  $\mu\text{g/mL}$ ) and histamine (400  $\mu\text{g/mL}$ ), respectively, at the six challenge series

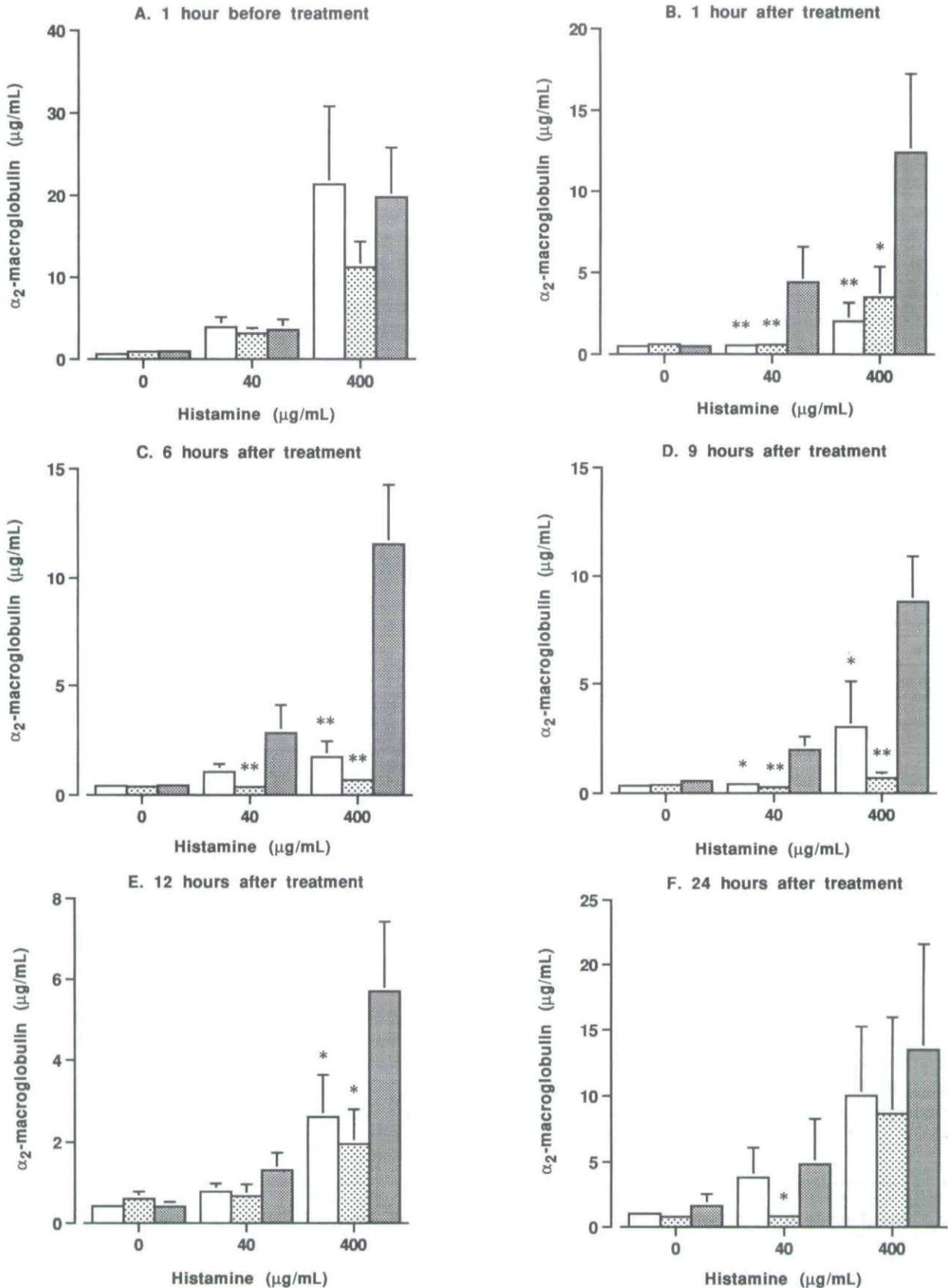
before and after placebo were 0.69, 0.86 and 0.84. The latter coefficients are influenced by any degree of tachyphylaxis to histamine and by any effects of topical and oral placebo.

##### Effect of treatment on mucosal exudation within the placebo group

The response to 40  $\mu\text{g/mL}$  histamine in the placebo group decreased with time (Friedman  $P < 0.05$ ). The reduction was significant at 6 and 12 h after treatment compared with before treatment (WSR  $P < 0.05$  and 0.01, respectively) (Fig. 1), confirming a certain degree of tachyphylaxis to histamine [5]. Because of this tachyphylaxis in the plasma exudation response to histamine after placebo treatment, the primary comparisons in the present study are performed between each treatment and placebo at each time point. Although mean values were reduced by repeat challenge, there was no statistically significant tachyphylaxis to 400  $\mu\text{g/mL}$  histamine (Friedman  $P > 0.05$ ).

##### Effect of treatment on mucosal exudation between the treatment groups

There were no differences in lavage fluid levels of  $\alpha_2$ -macroglobulin after control saline and histamine challenge, respectively, between the treatment groups and placebo 1 h before treatment. The azelastine-induced reduction in





histamine (40 µg/mL) mucosal exudation was significant when compared with placebo at 1 and 9 h after treatment (Fig. 2B and D) and the reduction in histamine (400 µg/mL) mucosal exudation was significant compared with placebo at 1, 6, 9, and 12 h after treatment (Fig. 2B, C, D and E). The cetirizine-induced reduction in histamine (40 µg/mL) mucosal exudation was significant compared with placebo at 1, 6, 9, and 24 h after treatment (Fig. 2B, C, D and F) and the reduction in histamine (400 µg/mL) mucosal exudation was significant compared with placebo at 1, 6, 9 and 12 h after treatment (Fig. 2B, C, D and E).

#### *Effect of treatment on nasal symptoms between the treatment groups*

The treatment with azelastine as well as cetirizine reduced the histamine-induced sneezes and secretion but not blockage when symptoms between the treatment groups and placebo were compared (Table 1 A–C). There were no differences for either symptom between the treatment groups before treatment. When comparing the differences between azelastine and ceterizine, respectively, and placebo, azelastine as well as cetirizine significantly reduced the sneezes after histamine (400 µg/mL) 1, 9 and 12 h after treatment (Table 1A). Azelastine reduced the secretion after histamine (40 µg/mL) 1 h after treatment as well as after histamine (400 µg/mL) 12–12 h after treatment (Table 1B). Cetirizine reduced the secretion after histamine (400 µg/mL) and 24 h after treatment as well as after histamine (40 µg/mL) 9 h after treatment.

#### **Discussion**

The present study, involving healthy subjects, has demonstrated that a single dose of topical azelastine significantly reduces nasal histamine challenge-induced mucosal exudation of  $\alpha_2$ -macroglobulin for 12 h. In addition, this drug with a similar duration of action reduced the sneezing and the secretory responses evoked by the histamine challenges. Topical azelastine was generally comparable to oral cetirizine concerning effect and duration of action.

In allergic rhinitis, the acute response to allergen challenge is dependent on histamine, and treatment with anti-histamines have marked anti-allergy effects in allergen challenge models [6–8]. Histamine challenge, similar to acute allergic airway conditions, produces several symp-

toms along with mucosal exudation of plasma. As expected [9], mucosal exudation of  $\alpha_2$ -macroglobulin, contrasting measurements of symptoms, was a sensitive and graded response suited for quantitative measurements (this study). Histamine at the lower concentration (40 µg/mL) thus produced significant mucosal exudation of plasma in the absence of symptoms, and at the larger concentration (400 µg/mL) it produced an approximately 20-fold increase in lavage fluid levels of  $\alpha_2$ -macroglobulin compared to baseline. The mean exudative response to histamine was reduced by repeated challenges (seen with both dose levels but statistically significant only with the lower dose). Such a reduction has previously been recorded in the nose [5] and may relate to a tachyphylaxis that may occur with histamine-type mediators at the level of microvascular permeability regulating cells [10]. The primary comparison was, therefore, made between each treatment and placebo.

The anti-exudative effect and its duration was 12 h for both drugs. Cetirizine appeared at least as potent as azelastine with somewhat superior inhibition at 6 and 9 h after treatment. Cetirizine also was the only drug that showed some efficacy after 24 h and then exclusively against the low concentration of histamine. These data may need confirmation, particularly since they differed from the 12-h findings. The present findings suggest that around the clock anti-exudative effects require administration twice daily of either topical azelastine or oral ceterizine.

The present observations on symptoms confirm and extend the work by Thomas *et al.* [2] who observed a 10-h duration of action of topical azelastine on histamine-induced sneezing. Thomas *et al.* [2] further reported that topical azelastine only had effect for 2 h on histamine challenge-induced increase in nasal airway resistance. In accordance, the present study demonstrated little effects in general on nasal blockage: Only a non-significant tendency ( $P = 0.06$ ) was recorded at 1 h after topical azelastine treatment. In addition, this study recorded a 12-h duration of effect of secretion by azelastine. This may reflect a true pharmacological inhibition although the recording of 'subjective' secretion could have been somewhat influenced by the repeated nasal lavage procedures.

A potentially more important aspect concerns the fact that azelastine had a long duration of action despite the lavages since these could have removed the topically applied drug. Indeed, the antihistaminic efficacy of azelastine at 1 h before the first lavage had been carried out was generally not

**Fig 2.** Effects of topical azelastine, oral ceterizine and placebo on histamine challenge-induced mucosal exudation of bulk plasma ( $\alpha_2$ -macroglobulin). Treatments were given at time point zero and challenges with control saline histamine (40 and 400 µg/mL) were given 1 h before treatment and 1–24 h after each treatment. (Comparisons between each treatment and placebo, \* $P < 0.05$ , \*\* $P < 0.01$ ). □ = azelastine; ■ = cetirizine; ▨ = placebo.



**Table 1.** Effects of topical azelastine, oral ceterizine and placebo on histamine challenge-induced sneezes. Histamine challenges were given 1 h before treatment and 1, 6, 9, 12, and 24 h after each treatment. (Comparisons between each treatment and placebo, \* $P < 0.05$ , \*\* $P < 0.01$ ).

Time	Azelastine			Cetirizine			Placebo		
	Control	Histamine		Control	Histamine		Control	Histamine	
		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$
-1	0	0.25 $\pm$ 0.18	1.92 $\pm$ 0.89	0	0.50 $\pm$ 0.29	1.33 $\pm$ 0.38	0	0.08 $\pm$ 0.08	2.17 $\pm$ 0.69
1	0	0	0*	0	0	0*	0	0.33 $\pm$ 0.19	1.42 $\pm$ 0.53
6	0	0	0	0	0	0	0	0.25 $\pm$ 0.25	0.33 $\pm$ 0.26
9	0	0	0*	0	0	0*	0	0	1.67 $\pm$ 0.51
12	0	0	0*	0	0	0*	0	0	1.00 $\pm$ 0.39
24	0	0	0.50 $\pm$ 0.36	0	0	0	0	0	0.42 $\pm$ 0.26

**Table 2.** Effects of topical azelastine, oral ceterizine and placebo on histamine challenge-induced secretion. Histamine challenges were given 1 h before treatment and 1, 6, 9, 12, and 24 h after each treatment. (Comparisons between each treatment and placebo, \* $P < 0.05$ , \*\* $P < 0.01$ ).

Time	Azelastine			Cetirizine			Placebo		
	Control	Histamine		Control	Histamine		Control	Histamine	
		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$
-1	0	0.42 $\pm$ 0.15	1.00 $\pm$ 0.17	0	0.58 $\pm$ 0.19	1.17 $\pm$ 0.21	0.08 $\pm$ 0.08	0.42 $\pm$ 0.19	1.17 $\pm$ 0.24
1	0	0.17 $\pm$ 0.11*	0.33 $\pm$ 0.14*	0.17 $\pm$ 0.11	0.25 $\pm$ 0.18	0.50 $\pm$ 0.19	0	0.50 $\pm$ 0.15	1.00 $\pm$ 0.21
6	0.17 $\pm$ 0.11	0.33 $\pm$ 0.19	0.33 $\pm$ 0.19*	0	0.17 $\pm$ 0.11	0.50 $\pm$ 0.19	0	0.42 $\pm$ 0.15	0.83 $\pm$ 0.24
9	0.08 $\pm$ 0.08	0.17 $\pm$ 0.11	0.42 $\pm$ 0.15*	0	0*	0.25 $\pm$ 0.13*	0.08 $\pm$ 0.08	0.50 $\pm$ 0.15	1.08 $\pm$ 0.26
12	0.08 $\pm$ 0.08	0.17 $\pm$ 0.11	0.25 $\pm$ 0.13*	0	0.08 $\pm$ 0.08	0.50 $\pm$ 0.15	0	0.25 $\pm$ 0.13	0.92 $\pm$ 0.15
24	0.08 $\pm$ 0.08	0.25 $\pm$ 0.13	0.75 $\pm$ 0.25	0	0.08 $\pm$ 0.08	0.33 $\pm$ 0.15**	0	0.33 $\pm$ 0.14	1.08 $\pm$ 0.23

**Table 3.** Effects of topical azelastine, oral ceterizine and placebo on histamine challenge-induced blockage. Histamine challenges were given 1 h before treatment and 1, 6, 9, 12, and 24 h after each treatment. (Comparisons between each treatment and placebo, \* $P < 0.05$ , \*\* $P < 0.01$ ).

Time	Azelastine			Cetirizine			Placebo		
	Control	Histamine		Control	Histamine		Control	Histamine	
		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$		40 $\mu\text{g/mL}$	400 $\mu\text{g/mL}$
-1	0.17 $\pm$ 0.11	1.08 $\pm$ 0.19	2.00 $\pm$ 0.17	0.17 $\pm$ 0.11	1.17 $\pm$ 0.27	2.00 $\pm$ 0.25	0.08 $\pm$ 0.08	0.58 $\pm$ 0.15	1.92 $\pm$ 0.19
1	0.17 $\pm$ 0.11	0.33 $\pm$ 0.22	0.92 $\pm$ 0.26	0.33 $\pm$ 0.19	0.75 $\pm$ 0.25	1.33 $\pm$ 0.31	0.50 $\pm$ 0.15	0.68 $\pm$ 0.19	1.58 $\pm$ 0.29
6	0.25 $\pm$ 0.13	0.42 $\pm$ 0.19	1.50 $\pm$ 0.23	0.08 $\pm$ 0.08	0.67 $\pm$ 0.19	1.42 $\pm$ 0.23	0.25 $\pm$ 0.13	0.75 $\pm$ 0.25	1.50 $\pm$ 0.29
9	0.17 $\pm$ 0.11	0.42 $\pm$ 0.15	1.50 $\pm$ 0.19	0.17 $\pm$ 0.11	0.50 $\pm$ 0.19	1.42 $\pm$ 0.29	0.25 $\pm$ 0.13	0.83 $\pm$ 0.30	1.58 $\pm$ 0.34
12	0.08 $\pm$ 0.08	0.33 $\pm$ 0.14	1.25 $\pm$ 0.33	0.25 $\pm$ 0.13	1.00 $\pm$ 0.25	1.83 $\pm$ 0.27	0.25 $\pm$ 0.07	0.58 $\pm$ 0.19	1.58 $\pm$ 0.31
24	0.08 $\pm$ 0.08	0.50 $\pm$ 0.15	1.50 $\pm$ 0.19	0	0.17 $\pm$ 0.11*	0.75 $\pm$ 0.22*	0.42 $\pm$ 0.19	0.92 $\pm$ 0.23	1.58 $\pm$ 0.34



greater than that recorded at later time points. This observation further indicates that the repeated histamine-evoked plasma exudation and secretory responses across the nasal mucosa did not impede the efficacy of the topical drug. On one hand it was reassuring to know that the topical antihistamine drug is not washed away from mucosal sites of histamine actions by proteinaceous and watery lavages of the mucosal tissue and surface. On the other hand these data may underscore the importance of careful studies of any contribution of systemically absorbed azelastine to the nasal actions of this drug.

The primary effect parameter in the present study was the induced plasma exudation response. Histamine may act directly on the endothelial cells of post-capillary venules to increase the macromolecular permeability of the sub-epithelial airway microcirculation [11]. Through the gaps in the venular wall non-sieved bulk plasma is extravasated along a hydrostatic pressure gradient: When this response is evoked in the superficial microcirculation of the airway mucosa, the extravasated plasma first distributes in the lamina propria and then moves up between epithelial cells and produces paracellular pathways for its clearance into the airway lumen [12]. Since the luminal entry is a prompt event and a major clearance route for exuded plasma, the extravasation process in the airways can be well monitored by analysing the concentrations of plasma proteins in airway mucosal surface liquids. The present study confirms the exudative effect of histamine and demonstrates, as expected, marked anti-exudative effects of oral cetirizine and nasal azelastine. It is likely that the anti-permeability effects of the antihistamines in the present study reflect actions on  $H_1$ -receptors on the permeability regulating endothelial cells of the subepithelial microcirculation [13]. Effects on the permeability of the epithelial lining are not likely as the movement of bulk plasma through paracellular epithelial pathways appears to be a self-sustained process regulated by an increased hydrostatic pressure created by the exudate itself [12].

We conclude that topical azelastine and systematic cetirizine reduce histamine-induced mucosal exudation of plasma and symptoms in human nasal airways. The duration of the pharmacological effects of azelastine support a b.i.d. dose regimen of this antihistamine. We suggest that histamine-induced mucosal exudation of bulk plasma is a useful clinical experimental model to determine the duration of the pharmacological effect of anti-histamines.

### Acknowledgements

The present study is supported by the Swedish Medical

Research Council (project 8308), the Medical Faculty of Lund University, and the Swedish Association against Asthma and Allergy. We thank Ms Berit Holmskov and Ms Christel Larsson for expert laboratory and bioanalytical assistance.

### References

- 1 Weiler JM, Meltzer EO, Benson PM et al. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. *J Allergy Clin Immunol* 1994; 94:972–80.
- 2 Thomas KE, Ollier S, Ferguson H, Davies RJ. The effect of intranasal azelastine, Rhinolast<sup>®</sup>, on nasal airways obstruction and sneezing following provocation testing with histamine and allergen. *Clin Exp Allergy* 1992; 22:642–7.
- 3 Svensson C, Baumgarten CR, Pipkorn U, Alkner U, Persson CGA. Reversibility and reproducibility of histamine induced plasma leakage in nasal airways. *Thorax* 1989; 44: 13–18.
- 4 Greiff L, Pipkorn U, Alkner U, Persson CGA. The 'nasal pool-device' applies controlled concentrations of solutes on human nasal airway mucosa and samples its surface exudations/secretions. *Clin Exp Allergy* 1990; 20:253–9.
- 5 Greiff L, Andersson M, Svensson C, Alkner U, Persson CGA. Glucocorticoids may not inhibit plasma exudation by direct vascular effects in human airways. *Eur Resp J* 1994; 7:1120–4.
- 6 Bousquet J, Lebel B, Chanal I, Morel A, Michel FB. Anti-allergic activity of  $H_1$ -receptor antagonists assessed by nasal challenge. *J Allergy Clin Immunol* 1988; 82:881–7.
- 7 Naclerio RM, Kagey-Sobotka A, Lichtenstein LM, Firethoff L, Proud D. Terfenadine, an  $H_1$  antihistamine, inhibits histamine release in vivo in the human. *Am Rev Respir Dis* 1990; 142:167–71.
- 8 Greiff L, Persson CGA, Svensson C, Enander I, Andersson M. Loratadine reduces allergen-induced mucosal output of  $\alpha_2$ -macroglobulin and tryptase in allergic rhinitis. *J Allergy Clin Immunol* 1995; 96:97–103.
- 9 Svensson C, Andersson M, Greiff L, Alkner U, Persson CGA. Exudative hyperresponsiveness of the airway microcirculation in seasonal allergic rhinitis. *Clin Exp Allergy* 1995; 25:942–50.
- 10 Svensjö E, Joyner WL. The effects of intermittent and continuous stimulation of microvessels in the cheek pouch of hamsters with histamine and bradykinin on the development of leaky sites. *Microvasc Endothel Lymph* 1984; 1:381–96.
- 11 Majno G, Palade GE, Schoeffl GI. Studies on inflammation II. The site of action of histamine and serotonin along the vascular tree: a topographic study. *J Biophys Biochem Cytol* 1961; 11:607–26.
- 12 Persson CGA, Andersson M, Greiff L et al. Airway permeability. *Clin Exp Allergy* 1995; 23:807–14.
- 13 Grega GJ, Persson CGA, Svensjö E. Endothelial cell reactions to inflammatory mediators assessed by fluid and solute flux analysis. In: Ryan US, ed. *Endothelial cells*. Boca Raton: CRC Press, 1988:103–19.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.