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# Influence of Azelastine and Some Selected Drugs on Mucociliary Clearance

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**Abstract.** The effect of azelastine and some selected compounds on ciliary beating frequency (CBF) was investigated in vitro using human mucosal samples and in vivo using anesthetized guinea pigs. Further influence of azelastine on mucus secretion was evaluated in mice and on mucociliary clearance in anesthetized rabbits. Azelastine influenced the ciliary beating frequency neither in vitro nor in vivo. Azelastine, similarly to salbutamol, ambroxol, and bromhexine, increased mucus secretion measured by the tracheal output of phenol red. Azelastine dose-dependently enhanced mucociliary clearance measured by elimination of $^{99m}$Tc-labeled erythrocytes in rabbits. The activity of azelastine proved to be about 10 times stronger than that of bromhexine. Since the ciliary activity remained unchanged under the influence of azelastine, it is likely that azelastine increases the mucociliary clearance by enhancing bronchial secretion. It is possible that the observed increase in mucociliary clearance may contribute to the beneficial effect of azelastine in the treatment of respiratory diseases.

**Key words:** Azelastine—Tracheobronchial secretion—Mucociliary clearance—Animal—Human mucosal explants.

## Introduction

The lung is the largest surface of our organism in direct contact with the environment. Inspired air contains dust particles and viable organisms, which are trapped on this surface. During evolution, various mechanisms developed to remove particles and to protect the lung and the organism from damage. The most important mechanisms, cough and ciliary transport, are effective only in the presence of airway mucus. Bronchial mucus is a complex secretion con-

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sisting of water, electrolytes, proteins, carbohydrates, and phospholipids. Its macromolecular component, the mucus glycoproteins, confers upon airway mucus its characteristic physical properties: elasticity, viscosity, and adhesiveness.

Mucus and ciliated cells set up a functional unit called mucociliary clearance. This pulmonary cleansing mechanism depends upon the interaction of 2 main factors: the ciliary beating activity of the epithelial cells and the physical properties of the bronchial secretions. Several bronchial diseases, such as chronic bronchitis and asthma, result in destruction of the ciliated epithelium or in abnormal mucus production that precludes normal ciliary function, or both [8, 10, 18, 19, 22, 26]. Drugs used in the treatment of respiratory diseases often influence this functional unit of the bronchopulmonary tract in different ways [12]. Even if the therapeutic significance of drugs that promote the secretion of more liquid mucus is not well-established, it is likely that drugs negatively influencing the mucociliary clearance cannot be advantageous in the therapy of bronchial asthma.

Azelastine, a novel antiasthmatic/antiallergic drug, has been shown to possess several pharmacologic activities related to its therapeutic effect [3, 5, 23, 24, 28].

It has recently been demonstrated [2] that microviscosity in bronchoalveolar lavage fluid (BAL) obtained from actively sensitized guinea pigs 20 hr after aerosol antigen challenge is greatly increased, indicating an enhanced secretion of more viscous mucus during the late phase of the allergic asthmatic response. Microviscosity of BAL has been considerably, almost totally, normalized by pretreatment of animals with azelastine. These results suggest that azelastine can restore the normal mucus quality either by inhibiting release and/or synthesis of inflammatory mediators or by increasing the production of more liquid mucus. The aim of the present investigation was to evaluate changes induced by azelastine both in mucus secretion and mucociliary clearance using healthy animals. The influence of azelastine on the ciliary beating frequency (CBF) was also investigated in guinea pigs and in vitro using human mucosal samples.

## Materials and Methods

### *Animals*

Male NMRI mice (20–25 g) (Fa. Savo, Kisslegg, FRG), female Dunkin-Hartley guinea pigs (average weight 715 g; Mollegaard Ltd., Lilleskensved, Denmark), and New Zealand rabbits (2.8–3.0 kg; LATI, Budapest, Hungary) of both sexes were used. The animals were maintained under constant environmental conditions: temperature, 22 ± 1° C; air humidity, 55 ± 5%; dark/light rhythm, 14/10 hr. They received standardized pellet food. Water was available ad libitum.

### *Human Mucosal Samples*

From 29 patients of both sexes, pieces (approx. 5 × 5 mm) were excised from maxillary sinuses (n = 24), sphenoidal sinus (n = 4), mastoid antrum (n = 1), and from the middle turbinate of the

nose (n = 1) during the exploration of maxillary sinusitis, transsphenoidal hypophysectomy, or mastoidectomy in saccus decompression, respectively. Explants were transported to the laboratory in containers filled with aerated Locke-Ringer's solution at room temperature within 30 min following excision.

## *Measurement of CBF in Vitro*

Ciliary beating frequency (CBF) was measured in the human mucosal explants using a modification [14, 19] of the method published by Mercke et al. [16]. The equipment for the measurement of ciliary activity consisted of a microscope (Carl Zeiss 47 50 57) with Schott 1500 cold light source, connected with fiberoptics to its objective and with a photodetector tube (Carl Zeiss 47 74 15; electric current source Carl Zeiss PMT 47 42 82) in 1 of the ocular tubes. The measurement area was 380 $\mu m^2$. The electrical signal from the photodetector was electronically processed so that waveform could be recorded both slowly (4 min recording time) and with high resolution (8 sec recording time).

Each mucosal explant was attached, inner surface outwards, to a slightly convex piece of silicone rubber with 4 needles. The explant was then placed in the measurement chamber, which was kept warm (37 ± 0.1°C) from beneath by circulating water, and moist from above with a flow (2 L/min) of heated (37 ± 1°C), humid (>95%) air. Measurements were commenced 10 min after the tissue samples were prepared.

In previous investigations [20] with samples from healthy and infected mucosa, the authors could demonstrate that ciliary beating frequency from infected samples normalized as soon as the excrete was removed by simple washing. At first mucosal explants were immersed in drug-free Locke-Ringer's solution for 10 min (basal value). The drug-containing solution was carefully pipetted on the bottom of the chamber (not directly onto the explant), until the surface of the liquid covered the explant totally. Just before the CBF was measured, the solution was removed by suction. After the CBF was measured, which took approximately 1 min, the chamber was filled with the drug-containing solution again. The procedure was repeated at 10, 20, 40, 60, and 90 min. Each explant was used only for measuring the effect of 1 drug concentration.

## *Measurement of CBF in Vivo*

Guinea pigs were anesthetized intraperitoneally with a combination of midazolam (7.5 mg/kg), fentanyl (0.473 mg/kg), and fluanisone (15 mg/kg). The ventral neck area was dissected, vena jugularis cannulated, and the trachea carefully liberated from surrounding tissues. Then the trachea was incised from the 2nd to the 6th cartilage caudally from the larynx, and gently elevated from below by a slightly convex steel support to prevent respiratory movements from shaking the measurement area. The animal was placed on a heated blanket, and the dissected area was covered with a plastic shroud, into which warm (37° C) and humid (>95%) air was blown continuously (2 L/min).

Measurement of the CBF was performed technically as described above for human explants. CBF was recorded initially (basal value) and 30, 38, 46, 54, 62, 70, 78, 86, and 94 min after intravenous drug administration.

CBF (Hz; beat/sec) was calculated from undistorted sections of the recording. The significance of the differences (azelastine vs. controls) was analyzed using analysis of variance (SPSS/PC$^+$, version 3.1, SPSS INC., IL, USA). Differences in CBF values within each group (before vs. after immersion or azelastine administration) were analyzed using 2-way analysis of variance (ANOVA) and Scheffe's test. Differences producing values of $p < 0.05$ were considered statistically significant.

## *Measurement of Tracheal Mucus Output*

The method has been described elsewhere [9]. Phenol red (500 mg/kg) was injected intraperitoneally to mice fasted overnight. Thirty minutes later, the animals were sacrificed by $CO_2$ and their tracheas

were dissected. The whole trachea free of the surrounding tissue was washed for 30 min in 1 ml physiological saline. To stabilize the pH of the lavage fluid, 0.1 ml of 1 mol/L NaOH was added. The concentration of phenol red was then measured photometrically at 546 nm. Test compounds were given intragastrically 30 min before phenol red was injected.

### *Measurement of Mucociliary Clearance*

Rabbits were anesthetized by intravenous pentobarbitone (25 mg/kg). The trachea and a jugular vein were cannulated. The $^{99m}$Tc-labeled homologous blood cell suspension was prepared freshly just before being applied by inhalation, according to the method of Hamilton and Anderson [11] and had an activity of 250–270 MBq/ml. With the use of a respirator (MEDICOR B 200, Budapest, Hungary), 0.3 ml of labeled blood cell suspension was nebulized by consuming 12 L air at the same time. The size of the aerosol particles was in the range of erythrocytes (7–10 $\mu$m). The tracheal cannula was connected to the reservoir filled up by the labeled red-cell-containing aerosol. Animals inhaled this aerosol 3 times for 3 min with 2 min breaks in between. Thereafter, the radioactivity was measured over the closed chest using a gamma-camera (GAMMA MB9190, Medicor, Budapest, Hungary) and stored and evaluated online by means of a computer (MB 9101, Medicor, Budapest, Hungary). The radioactivity was registered over 60 min after inhalation of the marker. In this period 60 pick ups were made on either side of the lungs. By means of a computer program, a time–activity curve was generated. Since the decrease of radioactivity over time is of first-order kinetics, a curve of monoexponential function was fitted on the basis of data measured. The elimination half-life of radioactivity ($t_{1/2\,eff}$) was determined and then corrected by using the physical half-life of $^{99m}$Tc (360 min), resulting in the biological half-life of the inhaled red blood cells ($t_{1/2\,biol}$). Mucociliary clearance was expressed as the percentage of inhaled red blood cells eliminated during 1 hr. Test compounds were applied intravenously 15 min before aerosol administration. There was no evidence that deposition of activity was influenced by azelastine.

### *Drugs*

The following drugs were used: salbutamol hemisulfate (Glaxo, Bad Oldesloe, FRG), ambroxol, and bromhexine (both from Thomae, Biberach, FRG). Azelastine was synthesized by ASTA Pharma, Department of Chemistry. Tasuldine HCl was a generous gift of Heumann Pharma (Nuremberg, FRG). Drugs were suspended in 1% carboxymethylcellulose (Hoechst AG, Frankfurt, FRG) and given orally. When drugs were injected intravenously, they were dissolved in distilled water. For in vitro studies, azelastine was dissolved in saline and then diluted with Locke-Ringer's solution. For intravenous administration it was dissolved in saline. For labeling the red blood cells, sodium $^{99m}TcO_4$ with a specific activity of 3.0–3.2 GBq/ml was used.

### *Statistical Analysis*

The effect of the test compounds was evaluated by using t-test or ANOVA if multiple sets of data were given [4]. The $ED_{50}$ was evaluated using linear regression [28]. In the in vivo experiments, the differences between basal values (before drug application) and values after drug administration were analyzed by paired t-test. When p values were less than 0.05, differences were considered to be significant.

## Results

### *Influence on Ciliary Beating Activity in Vitro*

In human explants, azelastine did not influence the CBF in vitro up to the high concentration of $10^{-4}$ M (Table 1).

**Table 1.** Influence of azelastine on ciliary beating activity (beats/sec) of human airway mucosal samples

| | Concentration of azelastine (M) | | |
|---|---|---|---|
| | $10^{-4}$ | $10^{-6}$ | $10^{-7}$ |
| Basal value after drug administration | 17.1 ± 1.5 | 16.2 ± 2.0 | 18.4 ± 1.3 |
| 10 min | 18.3 ± 1.2 | 16.4 ± 1.3 | 18.2 ± 1.7 |
| 40 min | 17.0 ± 1.6 | 17.4 ± 1.5 | 18.1 ± 1.5 |
| 90 min | 17.5 ± 1.3 | 18.5 ± 0.3 | 18.5 ± 1.6 |

Each value represents the mean +/− SEM of at least 6 mucosal samples

**Table 2.** Effect of intravenous azelastine on ciliary beating frequency (beats/sec) measured in the trachea of anesthetized guinea pigs

| | Control | Azelastine (mg/kg) | |
|---|---|---|---|
| | | 0.5 | 2.0 |
| Basal value | 16.0 ± 0.5 | 15.7 ± 0.4 | 16.6 ± 0.5 |
| CBF after drug administration at | | | |
| 30 min | 16.5 ± 0.4 | 18.3 ± 0.5* | 16.9 ± 1.2 |
| 62 min | 15.9 ± 0.5 | 15.4 ± 1.2 | 16.9 ± 1.4 |
| 94 min | 16.0 ± 1.1 | 15.4 ± 1.3 | 15.5 ± 1.3 |

Values are mean ± SEM of 6 animals per group
* Signif. difference to basal value ($p < 0.05$)

### *Influence on Ciliary Beating Activity in Vivo*

The ciliary beating activity measured in the trachea of anesthetized guinea pigs did not change after intravenous administration of azelastine up to 2.0 mg/kg (Table 2). There was but 1 value significantly different from controls (30 min after 2 mg/kg intravenously) that might indicate a slight but short-lasting increase in ciliary beating activity due to azelastine. However, there were no such changes after administration of the higher dosage.

### *Influence on Tracheal Phenol Red Secretion*

Within 30 min, the basal secretion of phenol red into the trachea was 0.53 $\mu$g. As shown in Table 3, azelastine enhanced the tracheal phenol red output with an oral $ED_{50}$ value of 0.52 mg/kg that was not statistically different from $ED_{50}$ values obtained after administration of ambroxol or salbutamol. Known expectorants such as bromhexine and tasuldine also increased intratracheal phenol

**Table 3.** Effect of oral azelastine and some selected drugs on tracheal secretion of phenol red in mice

| Compound | $ED_{50}$ (mg/kg, with 95% confidence limits) | Slope |
|---|---|---|
| Azelastine | 0.52 (0.17–1.57) | 35.2 |
| Ambroxol | 0.61 (0.55–0.68) | 30.8 |
| Salbutamol | 1.56 (0.40–6.04) | 86.4 |
| Bromhexine | 25.20 (6.70–94.50) | 38.9 |
| Tasuldine | 37.90 (29.00–49.40) | 83.7 |

**Table 4.** Influence of azelastine and bromhexine on the mucociliary clearance rate of $^{99m}$Tc-labeled erythrocytes in the lungs of anesthetized rabbits

| Compound | Dosages (mg/kg, intravenously) | Mucociliary clearance rate (%) |
|---|---|---|
| Control | — | 8.71 ± 2.43 |
| Azelastine | 1 | 13.83 ± 2.65 |
| | 2 | 18.02 ± 6.01 |
| | 5 | 22.25 ± 4.70 |
| Bromhexine | 25 | 18.56 ± 7.43 |

All results were significantly ($p < 0.001$) different from control value

red secretion (Table 3). According to the slope of the dose–response curves one may assume that at least 2 different types of effects are present: salbutamol and tasuldine being different from the other compounds investigated. However, azelastine had a slope comparable to ambroxol and bromhexine.

### *Effect on Mucociliary Clearance*

To control the stability of the isotope-loaded erythrocytes, 1 of the animals was sacrificed immediately after inhalation on each experimental day. Radioactivity deposited in the lungs was determined with concomitant measurement of the blood activity. The average radioactivity in the lungs amounted to 467 kBq at the end of the marker inhalation. The radioactivity detected in the blood was, however, only 0.0471 kBq/ml, indicating that loss of marker from labeled erythrocytes and absorption by the lungs was practically zero.

In control animals, the radioactivity measured over the lungs was cleared by 8.71 ± 2.43% during the first 60 min following the inhalation of labeled red corpuscules. Azelastine shortened the biological half life ($t_{1/2\,biol}$) of $^{99m}$Tc-labeled red blood cells in the lungs in a dose-dependent manner (Table 4).

Consequently, mucociliary clearance was increased by azelastine. Bromhexine, at a dosage of 25 mg/kg intravenously also increased the mucociliary activity in anesthetized rabbits (Table 4). Comparing the effect of the 2 compounds, the intravenous dosage of 2 mg/kg azelastine proves to be as effective as 25 mg/kg bromhexine intravenously.

## Discussion

The physicochemical properties of mucus and the ciliary activity of epithelial cells set up a functional unit that is well characterized by the term "mucociliary clearance." In the present study, azelastine increased the mucociliary clearance in rabbits. In the mouse, it enhanced the mucus output. The ciliary beating frequency remained unchanged by azelastine both in vitro and in vivo.

Mucociliary clearance as a complex interaction between quality and quantity of respiratory mucus and ciliary activity is often disturbed in asthmatic persons. Therefore, the possible effects of drug treatment of asthma are of major interest and importance. $\beta$-Adrenoceptor agonists have been shown to stimulate the ciliary function [21]. Some investigators [15, 17, 26] have also observed an enhancement in mucociliary transport, but the clinical efficacy of $\beta_2$-mimetics to improve mucociliary clearance in patients with lung disease is still uncertain [13].

In most obstructive lung diseases such as bronchial asthma, mucus secretion is disturbed and the abnormal secretion may aggravate the illness. It is known that changes in the water/mucin balance of the respiratory mucus may alter its physical properties, such as viscosity, elasticity, and adhesiveness. In the treatment of obstructive lung diseases, drugs that enhance the water secretion, normalize the pathologically altered glycoprotein output, or increase the mucociliary clearance may be advantageous.

Azelastine, similar to ambroxol and bromhexine, increased the tracheal secretion of phenol red in mice. An earlier study demonstrated a correlation between phenol red output and mucus secretion [9]. Although the reason for this positive correlation is still unknown, it appears likely that enhanced phenol red output may represent increased water secretion. Similar results have recently been published by Chand et al. [5] and Diamantis et al. [7]. It has also recently been demonstrated [2] that azelastine administered orally is able to normalize the microviscosity in the bronchoalveolar lavage fluid obtained from actively sensitized guinea pigs during the late-phase reaction provoked by antigen challenge. Besides a possible increase in water secretion, other effects of azelastine such as inhibition of leukotriene synthesis and/or release [1] may also be involved in this phenomenon.

Azelastine increases mucociliary clearance in healthy anesthetized rabbits. This beneficial effect of the compound can be explained by several factors. Azelastine may enhance the output of more liquid bronchial secretions, as shown in the present study. It can apparently normalize the viscosity in bronchial secretions [2] either by increasing water secretion or by normalizing glyco-

protein pattern or by both. All these effects of azelastine can result in an increased mucociliary clearance. It is likely that these factors are responsible for the enhanced mucociliary clearance, since azelastine does not increase the ciliary beating activity.

The present results allow us to conclude that azelastine, a novel antiasthmatic/antiallergic agent is capable of increasing mucociliary clearance in normal animals. Clinically, it may be important that in human respiratory mucosa azelastine did not reduce mucociliary beating in vitro. Although the relevance of these results for therapeutic applications remains unclear, they suggest that azelastine will probably not impair mucociliary function.

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