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Topical vasoconstrictor (oxymetazoline) does not affect histamine-induced mucosal exudation of plasma in human nasal airways

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Summary

Mucosal exudation of almost unfiltered plasma proteins, plasma-derived mediators and fluid has recently been advanced as a major respiratory defence mechanism. Oxymetazoline chloride is a commonly used decongestant agent. By reducing blood flow it may reduce mucosal exudation and thus compromise the mucosal defence capacity. This study examines the effect of topically applied oxymetazoline on histamine-induced plasma exudation into human nasal airways. Twelve normal volunteers participated in a double-blind, randomized, cross-over and placebo-controlled study with pretreatment with a single dose oxymetazoline chloride (5 μg or 50 μg; a dose previously known to reduce nasal mucosal blood flow by almost 50%) prior to the histamine challenge sequence. Nasal lavages were performed every 10 min for 140 min, and three histamine challenges were performed at 30-min intervals during this period. The concentrations of two exudative indices, *N*-alpha-tosyl-L-arginine methyl ester (TAME)-esterase activity and albumin, were measured in the nasal lavage fluids. Nasal symptoms (sneezing, nasal secretion and blockage) were assessed by a scoring technique.

Histamine induced all three symptoms with correlatively raised levels of the biochemical markers for plasma exudation. Oxymetazoline chloride caused a significant decrease in nasal stuffiness, but did not influence the other nasal symptoms or the histamine-induced plasma exudation. It is concluded that histamine-induced plasma exudation is not influenced by topical oxymetazoline. Thus, an important airway defence reaction such as plasma exudation may be little affected by topical α-adrenoreceptor-mediated vasoconstriction. It is further suggested that the antiblockage effect of oxymetazoline can be utilized in nasal research without interfering with the exudative indices which appear on the mucosal surface as a quantitative reflection of the airway tisue involvement in inflammatory processes.

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Introduction

Mucosal exudation of almost unfiltered plasma and plasma-derived mediators has recently been advanced as a major respiratory defence mechanism [1]. Inflammatory mucosal provocations produce exudative responses without disrupting the epithelial lining and without increasing the airway tissue penetration of luminal material [2–4]. The prompt and quantitative luminal entry of plasma tracer-macromolecules has also made it possible to assess the extravasation of plasma from the subepithelial microcirculation just by determining exudative indices in mucosal surface liquids [5]. Thus, histamine produces concentration-dependent and well repeatable exudative effects in the human nose [6,7].

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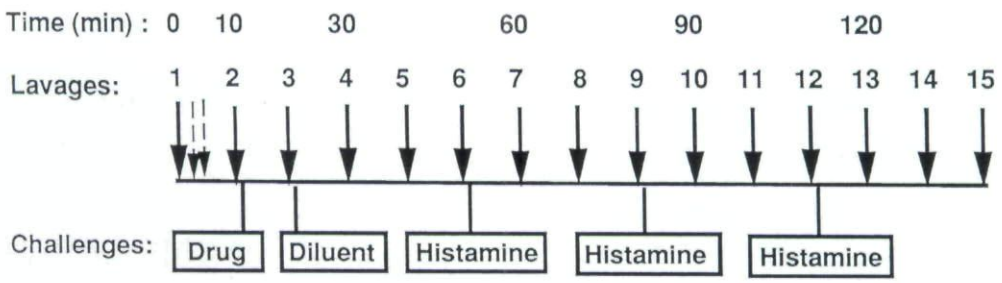

Fig. 1. This scheme illustrates the challenge model. The arrows indicate the lavages. After three quick lavages (the last two discarded and not further counted, as indicated with dashed arrows), nasal lavages were performed at 10 min intervals. Nasal symptoms were assessed immediately prior to each lavage. Immediately after lavage number 2, oxymetazoline chloride (5 μg or 50 μg) or placebo was administered topically. Lavage number 3 was immediately followed by a challenge with diluent and lavages numbers 6, 9 and 12 by a challenge with histamine (1 mg), as indicated below.

The specific inflammatory extravasation occurs between transiently separated endothelial cells in the wall of post-capillary venules [8,9]. During a brief period of time there are open holes in the venular endothelial barrier and through these unfiltered plasma is moved into the tissue by the intravascular hydrostatic pressure. The active separation of endothelial cells and the pressure gradient are the major determinants, but additionally, changes in blood flow may determine the degree of extravasation. This latter possibility has received great attention. Thus, a two-mediator hypothesis proposes that both endothelial cell separation (increased permeability) and vasodilatation are required to produce significant exudation [10]. Conversely, it is thought that vasoconstriction is a very effective way of inhibiting exudation.

In this study involving healthy human subjects we have examined the effect of oxymetazoline on histamine-induced exudation of plasma across the nasal mucosa. Histamine is used because it produces a well repeatable exudative response in the human nasal mucosa [7]. Oxymetazoline has been selected since this decongestant drug, being an agonist at both α_1- and α_2-adrenoceptors, has been demonstrated to markedly reduce nasal mucosal blood flow [11–14].

Materials and methods

Study design

This study was designed as a double-blind, randomized, cross-over and placebo-controlled study. Nasal challenges with histamine were performed in 12 normal subjects on three separate days. Repeated nasal lavages were used to harvest nasal mucosal surface liquids, which were analysed for the content of plasma proteins. Topical oxymetazoline chloride, in two different concentrations, or placebo was given prior to the challenges.

Subjects

Twelve normal individuals (nine male and three female subjects) between the ages of 24 and 42 years (mean age, 31 years) were recruited. The participants had no history of allergic or chronic nasal disease and no symptoms from the airways at the time of the study. Neither of the participants were on regular medication and, except for contraceptives, even occasional medication was prohibited during the trial. The study was approved by the Ethics Committee of the University of Lund.

Nasal challenge procedures

A previously described method of repeated nasal lavages has been used [7]. Ten millilitres of isotonic saline solution (0·9%) was divided and instilled into both nasal cavities while the subject flexed his/her head gently backward (approximately 30° from the horizontal) during closure of the soft palate. The subject maintained this position for a few seconds and then the subject leaned forward and expelled the nasal fluid into a collection vessel. Nasal fluid and secretion delivered with sneezes were added to the appropriate lavage-fluid sample. Three prechallenge lavages were made in order to reduce cell-free mediators to a baseline level (the fluid from the last two of these three lavages were discarded and not counted) and thereafter nasal lavages were performed at 10 min intervals for 140 min (Fig. 1). Immediately after lavage number 2, oxymetazoline chloride (0·05 mg/ml or 0·5 mg/ml) (Nezeril®, Draco AB, Lund, Sweden) or placebo (identical with the vehicle for the active substance) was given. With a nasal spray-pump a volume of 0·10 millilitres was delivered into each nasal cavity, i.e. 5 μg and 50 μg of oxymetazoline into each nasal cavity respectively. Immediately after lavage number 3, each nasal cavity was challenged with 0·10 millilitres of the diluent used for histamine (a solution of

0·9% saline and 0·25% human serum albumin), and immediately after lavages numbers 6, 9 and 12 each nasal cavity was challenged with 0·10 millilitres of a histamine-solution (10 mg/ml of histamine hydrochloride in the above described solution), i.e. 1 mg histamine into each nasal cavity. The returned fluid was measured and processed for the chemical analyses described below. At least 3 days elapsed between the different treatment alternatives.

Assessment of symptoms

During the challenge procedure, the subject continuously scored their symptoms in a symptom-chart using a 4-point scale (0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe symptoms). Nasal stuffiness, nasal secretion and sneezing were estimated.

Analytical assays

After delivery, the lavage fluids were kept cold and centrifuged at 250 ***g*** for 10 min. The supernatants were then divided into aliquots and stored at −30°C until analysis.

The TAME-esterase activity was measured with a radiochemical assay essentially as described by Imanari [15] and adapted for the nasal lavage procedure [16]. Albumin was measured with a radioimmunoassay sensitive to 6·25 ng/ml with antiserum (rabbit anti-human albumin) (Dakopatts, Copenhagen, Denmark) and commercial standard (Calbiochem, San Diego, California, U.S.A.). Iodination was made with the lactoperoxidase method [17] to a specific activity of 2 mCi/nmol. Tracer and standards (or samples) were mixed with antiserum before adding goat anti-rabbit antiserum (Draco AB, Lund, Sweden). The bound fraction was measured in a gamma counter (Clinigamma, Pharmacia Diagnostica Norden AB, Uppsala, Sweden) and the data evaluated using RIA CALC (Pharmacia Diagnostica Norden AB, Uppsala, Sweden). The intra- and inter-coefficient of variation were 5% and 10% respectively.

Statistical analyses

The statistical evaluation was performed on a micro-computer (Macintosh™, Apple Computer, Cupertino, U.S.A.) with the help of a statistical software package (Statview 512+ by Brainpower Inc™, Calabasas, California, U.S.A.). Non-parametric statistics was used to compare the symptom scores (Wilcoxon signed-rank test). The levels of albumin and TAME-esterase activity were compared using an analysis of variance for repeated measurements (ANOVA) and Student's *t*-test. A *P*-value of $<0{\cdot}05$ (two-sided alternative) was considered significant.

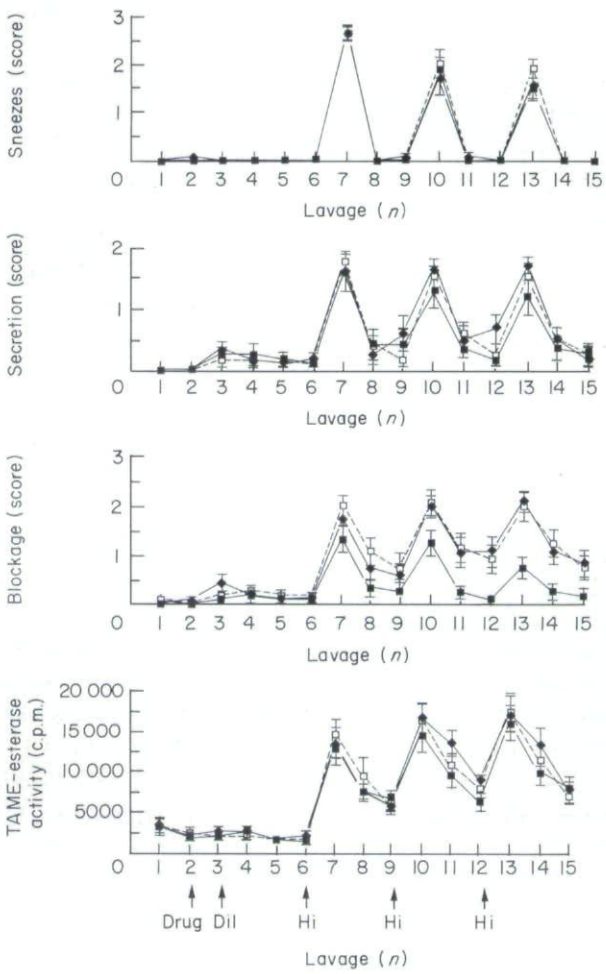

Fig. 2. Nasal symptoms (mean ± s.e.m.) are shown on the three top graphs and the TAME-esterase activity (mean ± s.e.m.) in the nasal lavage fluids is seen below (c.p.m. = counts per min; $n = 12$ in all graphs). The arrows below indicate the challenges with drug, diluent (dil) and histamine (hi). Histamine increased both nasal symptoms and the TAME-esterase activity in the nasal lavage fluids. The 50 μg dose of oxymetazoline reduced the nasal blockage but not the other symptoms. The histamine-induced increases in TAME-esterase activity were not affected by oxymetazoline. ---□---, placebo. —◆—, 5 μg. —■—, 5 μg.

Results

Data from all 12 subjects were available for analysis. The nasal lavages, the histamine provocations and the pre-treatment with oxymetazoline were well tolerated. The mean symptoms scores are shown in Fig. 2. Neither the challenge with diluent, nor the drug-treatment (including placebo) induced any nasal symptoms. Sneezing- and secretion-scores rose markedly after every histamine challenge. Sneezing was most pronounced after the first histamine challenge, while the second and third challenge

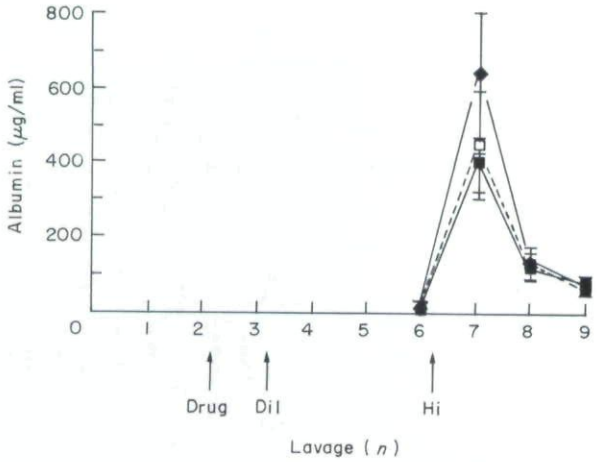

Fig. 3. The concentrations of albumin (mean ± s.e.m.) in the nasal lavage fluids were determined after the first histamine challenge ($n = 12$). The increased levels of albumin were not affected by pretreatment with oxymetazoline. ---□---, placebo. —◆—, 5 μg. —■—, 50 μg.

gave slightly lower but similar scores. Secretion-scores showed almost identical peak-levels after every histamine provocation. Between the provocations, sneezing and nasal secretion almost ceased. There were no differences between the three treatment alternatives concerning sneezes and secretion. Also the blockage-scores were markedly increased after every histamine challenge and showed almost identical peak-levels and a partial decrease between the provocations, though not to baseline-level. Oxymetazoline at the 50 μg dose, but not at the 5 μg dose, reduced nasal blockage (being statistically significant, $P < 0{\cdot}05$, at lavage number 10 to number 15, i.e. 80 to 130 min after oxymetazoline was given).

The TAME-esterase-activity and the concentrations of albumin in the nasal lavage fluid are presented in Fig. 2 and Fig. 3 respectively. The recovery of the instilled lavage fluid was always more than 75% and with a few exceptions more than 80%. There was a low baseline TAME-esterase activity before the histamine challenges. Every histamine provocation increased the TAME-esterase activity to about the same mean peak-level. Between the provocations, TAME-esterase activity decreased to a level about three times the baseline activity seen before any challenge. No differences were demonsrated in lavage fluid TAME-esterase activity between the three treatment alternatives. The levels of albumin were analysed in four lavages (number 6 to number 9), demonstrating the albumin-levels after the first histamine challenge. The lavage fluid levels of albumin increased markedly from baseline-level and no significant differences were demonstrated between placebo and the active drug alternatives. The albumin-levels decreased almost to baseline values before the second histamine challenge.

Mean-values ± s.e.m. for baseline (lavage number 6) and post challenge (lavage number 7) were for albumin (μg/ml): $7{\cdot}8 \pm 1{\cdot}8$ *vs* 446 ± 144 (placebo), $10{\cdot}7 \pm 2{\cdot}9$ *vs* 632 ± 166 (oxymetazoline 5 μg), and $6{\cdot}7 \pm 1{\cdot}5$ *vs* 397 ± 72 (oxymetazoline 50 μg); and for TAME-esterase activity (c.p.m.): 1751 ± 402 *vs* 14378 ± 2057 (placebo), 2092 ± 578 *vs* 13522 ± 1916 (oxymetazoline 5 μg), and 1354 ± 289 *vs* 13167 ± 2336 (oxymetazoline 50 μg).

Discussion

This study has demonstrated that oxymetazoline, at a dose level previously shown to produce a large decrease in mucosal blood flow, almost 50% [11–14], is without effect on histamine-induced mucosal exudation of plasma in the human nose. As shown by Bende and Andersson [11,12] and confirmed by Olsson [14], the blood flow reduction is fully developed in about 15 min and may last for about 6 hr [18]. Hence, if an anti-exudative effect would have been produced by the oxymetazoline-induced vasoconstriction this should have been fully expressed during the first histamine challenge in this study. However, neither albumin nor TAME-esterase activity was reduced by oxymetazoline at this time point. The TAME-esterase activity in the nasal surface liquid represents a proteas activity corresponding to several enzymes from different sources. Baumgarten *et al.* [19] reported that while the TAME-esterase activity after *ailergen*-challenge was due both to plasma, cellular and glandular products (70% due to plasmakallikrein, 25% due to mast cell tryptase, and 5% due to tissue kallikrein), after *histamine*-challenge it was solely due to plasma products (a complex of plasmakallikrein and α_2-macroglobulin). Hence, in this study the TAME-esterase activity is probably a marker of the mucosal exudation process. Histamine itself may have slightly increased the blood flow [20] or, at the present dose level, histamine may not have altered the nasal mucosal blood flow at all [21,22]. Judging from studies of the ocular vasoconstrictive activity of oxymetazoline, this drug would also inhibit any hyperaemia induced by histamine [23].

Based on animal *in vitro* experiments, it was recently claimed that albumin can be secreted in the airways [24]. Results supporting this notion from the human nasal mucosa has been difficult to achieve. Thus, Raphael *et al.* [25] could only demonstrate a small (three-fold) increase in the level of albumin even after a very large topical dose of *methacholine* (25 mg), that produced systemic side-effects. It is well-known that *histamine*-challenge induces a cholinergic reflex-mediated nasal glandular secretion in the contralateral nasal cavity, but it has not been possible to demonstrate a raised level of albumin in this secretion even when quite a large dose of histamine (10 mg) was on

the nasal mucosa [26]. On the other hand, the same authors reported that in the ipsilateral nasal cavity a much smaller dose of histamine increased the albumin-levels dramatically as a result of a direct effect on vascular permeability. This latter finding was a confirmation of earlier observations from our laboratory where an almost fiftyfold increase of the albumin-levels could be demonstrated after a nasal topical dose of 0·5 mg histamine [7]. Thus, it seems clear that the increased levels of albumin in our study is a result of mucosal exudation of plasma and that any glandular contribution in this situation remains speculative. A further, strong evidence for the vascular origin of the histamine-induced increased levels of albumin in airway surface liquids is the co-exudation of non-secreted large plasma macromolecules, like fibrinogen (MW 340 000 Da) and FITC-dextran (MW 70 000 Da and 156 000 Da), together with albumin that has been reported both in guinea-pig tracheobronchial airways [5, 27, 28] and human nasal airways [29].

In confirmation of our previous study [7], repeated histamine provocations at half hour intervals produced the same degree of nasal blockage and secretion, whereas sneezing was most pronounced after the first provocation. This challenge-model shows a good reproducibility both in nasal symptoms and exudative indices as previously reported [7]. Oxymetazoline's decongestant effect was evident after the second histamine provocation and nasal blockage was thereafter further reduced. This is in agreement with previous investigations on the onset of decongestant effect of oxymetazoline [30,31]. These investigators found the decongestant effect of oxymetazoline to be fully developed between 60 [30] and 120 min [31] after administration. Different kinetics for development of contraction of the capacitance (mainly large venous sinusoids) and resistance vessels may explain the longer time-course for the development of decongestion as compared to the immediate reduction of mucosal blood flow [11,13,14]. The latter effect is prompt probably because oxymetazoline reduces flow by acting on microvessels positioned just beneath the epithelium. As shown by the repeated TAME-esterase activity measurements in this study there was no tendency at any time point that oxymetazoline should have exerted an anti-exudative effect.

The poor ability of a vasoconstrictor to reduce exudation in this study agrees with findings in guinea-pig tracheobronchial airways where moderate changes in blood flow appeared to be of little consequence for the exudative response [27]. At the extreme level vasoconstriction logically is a powerful inhibitory mechanism. Thus, stopping blood flow and blanching the airway mucosa by topical application of large doses of adrenalin will result in complete inhibition of airway exudation of plasma [32]. It has to be emphasized that the idea of a major importance of blood flow in the regulation of plasma exudation emanates from the interpretation of skin data [10]. In the skin there is a low baseline blood flow [33] compared with the well developed and well perfused subepithelial microvasculature of the airways [11]. Hence, in contrast to what may be maintained for the skin, the airway mucosal blood flow may not normally be crucial to the plasma exudation process. Oxymetazoline's lack of effect on exudation in this study suggests that also other (blood flow dependent) respiratory defence mechanisms may not be severely compromised by this vasoconstrictor. The present study was performed in healthy volunteers challenged with histamine. In chronic disease conditions the airways microcirculation may be abnormally vulnerable to vasoconstrictor influences. However, in these conditions topical decongestants should be used with caution. A further inference of the present findings is that oxymetazoline can be employed to reduce the problem of blockage in experimental nasal research where exudative indices on the mucosal surface are important markers of airway inflammatory processes [34].

In conclusion this study demonstrates that topically applied oxymetazoline is without effect on histamine-induced plasma exudation in the human nasal mucosa. Hence, the role of mucosal exudation in airway defence may not be compromised by this decongestant drug. The suggestion that α-adrenoceptor-mediated vasoconstriction is an effective means of reducing plasma exudation in inflammatory airway disease is not supported by the present results which, however, were obtained in the nasal mucosa of healthy subjects.

Acknowledgments

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