Histamine-induced airway mucosal exudation of bulk plasma and plasma-derived mediators is not inhibited by intravenous bronchodilators

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Abstract. Experimental data suggest the possibility that common bronchodilators, such as the xanthines and β2-adrenoceptor agonists, may produce microvascular anti-permeability effects in the subepithelial microcirculation of the airways.

In this study, we have examined the effect of bronchodilators given intravenously on exudation of different-sized plasma proteins (albumin and fibrinogen) and the generation of plasma-derived peptides (bradykinins) in human nasal airways challenged with histamine. In a double-blind, crossover, placebo-controlled and randomised trial, 12 normal volunteers were given IV infusions of terbutaline sulphate, theophylline and enprofylline to produce therapeutic drug levels. The effect of topical nasal provocation with histamine was closely followed by frequently nasal lavage with saline.

The lavage fluid levels of albumin, fibrinogen and bradykinins increased significantly after each histamine provocation. The ratio of albumin-to-fibrinogen in plasma and the lavage fluid was 24 and 56, respectively, indicating that topical histamine provocation induced a largely nonsieved flux of macromolecules across the endothelial-epithelial barriers. The systemically administered drugs did not affect the nasal symptoms (sneezing, secretion and blockage), nor did they significantly reduce the levels of plasma proteins and plasma-derived mediators in the nasal lavage fluids.

The present data suggest that systemic xanthines and β2-adrenoceptor agonists, at clinically employed plasma levels, may not affect the microvascular (and epithelial) exudative permeability and the bradykinin forming capacity of human airways.

Key words: Nasal airways, Plasma exudation, Xanthine derivatives; fibrinogen, bradykinins, terbutaline, theophylline, nasal mucosa, nasal lavage, histamine provocation test

Xanthines and β2-adrenoceptor agonists are used orally and intravenously in the treatment of asthma. They are bronchodilators and they may also exert other effects. Animal studies have demonstrated an inhibitory effect of these drugs both on capsaicin- and bradykinin-induced exudation of plasma in tracheobronchial airway of the guinea pig [1, 2]. It is not known whether the drugs also have an anti-exudative effect in human airways. Sneezing and the enhanced levels of TAME-esterase activity and kinins in nasal lavage fluid obtained after allergen challenge were diminished by oral treatment with theophylline [3, 4]. This effect might be explained by a vascular anti-permeability action of theophylline on the endothelial-epithelial barriers [5], or it might reflect the ability of theophylline to attenuate the activity of inflammatory cells [6]. Increased microvascular permeability and plasma exudation are characteristic of an inflammatory reaction [7, 8]. Plasma exudation may be a substantial factor both in normal airway defence and in the pathogenesis of airway diseases, such as rhinitis and asthma [9, 10]. In the airway mucosa, increased vascular permeability leads to the extravasation of plasma and further passage of the exuded plasma across the epithelium into the airway lumen, where it can be harvested by lavage [11, 12]. Human airway studies addressing the possibility of an anti-exudative effect of β2-adrenoceptor agonists and xanthines seem not to have been carried out.

Repeated nasal lavage (NAL) is a convenient method to monitor pathophysiological events in human airway mucosa. In previous studies, we demonstrated that histamine applied to the human nasal mucosa produced a significant exudative response. The peak rate of exudation occurred within 10 min and its duration was less than 30 min. The histamine-induced exudation was well repeated when challenges were applied at only 0.5 h intervals [13, 14]. We have now examined whether systemic treatment with a β2-adrenoceptor agonist and two xanthine drugs influenced the exudative response to histamine, including its repeatability and the generation of plasma-derived mediators. We analysed different-sized plasma proteins in the nasal lavage fluid to learn more...
Nasal challenges with histamine were performed in order to induce placebo-controlled and randomised study. They were given a concentration of histamine (10 mg/ml histamine hydrochloride in the above described solution), i.e. 1 mg histamine into each nasal cavity. A mechanical nasal spray pump was used for the challenges. The recovered lavage fluids were measured and processed for chemical analysis as described below. All subjects were challenged on four occasions, with a least six days between each session. 

**Subjects**

Twelve normal individuals (6 m, 6 f) between the ages of 18 and 30 y (mean age, 25.6 y) were recruited. The participants had no history of allergic or other nasal disease and no symptoms of airway disease at the time of the study. Medication was not allowed during the study, nor was the intake of xanthine-containing beverages (coffee, tea or cola-drinks) allowed for 6 h prior to the challenge session. All participants gave informed consent before taking part in the study, which was approved by the Ethics Committee at the University of Lund.

**Study drugs**

The drugs studied were terbutaline sulphate, theophylline and enprofylline. They were all given as a continuous IV infusion. A loading infusion was started 120 min before the lavage procedure in order to produce a steady-state concentration of the drug before the challenge procedure started. It was followed by a maintenance infusion for 140 min covering the entire challenge procedure (Fig. 1). The drugs were injected into a peripheral vein using an electrical pump for continuous infusion (Injectomat®-S, Fresenius AG, Bad Homburg, Germany). Plasma concentration curves were simulated for each drug, taking into account their pharmacokinetic properties and the infusion times used in the study. From these curves, and knowledge of the weight of the subject, the volume and speed of each infusion was individually calculated to ensure a therapeutic plasma level of the drug during the lavage procedure. Thirty min after the start of the nasal lavage procedure, two 5 ml blood samples were obtained for analysis of the plasma concentration of the appropriate drug, albumin and fibrinogen. The doses of the different drugs are presented in Table 1. The drug-preparations were supplied by Astra Draco AB, Lund, Sweden: terbutaline sulphate 0.035 mg/ml (Bri-canyl®), theophylline 20 mg/ml (Theofyllin®) and enprofylline 10 mg·mg⁻¹.

**Nasal lavages procedure**

A previously described method for repeated nasal lavages was used [13]. Isotonic saline solution 10 ml (0.9%) was divided and instilled into each nostril, 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 leaned forward and expelled the nasal fluid into a collection vessel. Nasal fluid and secretion delivered with sneezes was added to the appropriate lavage sample. Three prechallenge lavages were made to reduce cell-free mediators to a baseline level. The fluid from the first two of the three lavages was discarded and not counted. Thereafter nasal lavage was performed at 10-min intervals (Fig. 1). After lavage no.3 (20 min), each nasal cavity was challenged with 0.10 ml of the diluent used for histamine (a solution of 0.9% saline and 0.25% human serum albumin). After lavages no. 6 (50 min), 9 (80 min) and 12 (110 min), each nasal cavity was challenged with 0.10 ml of a solution of histamine (10 mg·ml⁻¹ histamine hydrochloride in the above described solution), i.e. 1 mg histamine into each nasal cavity. A mechanical nasal spray pump was used for the challenges. The recovered lavage fluids were measured and processed for chemical analysis as described below. All subjects were challenged on four occasions, with a least six days between each session.

**Assessment of symptoms**

During the challenge procedure, the subjects continuously registered their symptoms on 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.

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**Table 1. Loading and maintenance doses of the drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading dose (µg·kg⁻¹·min⁻¹)</th>
<th>Maintenance dose (µg·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbutaline sulphate</td>
<td>0.05</td>
<td>0.0375</td>
</tr>
<tr>
<td>Theophylline</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>Enprofylline</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

**Fig. 1.** Schematic flow-chart of the challenge model. Drug-infusion (loading dose) started 120 min prior to the challenge procedure. Then followed a maintenance infusion for 140 min (i.e. during the entire challenge session). The arrows above the line indicate the lavages. After three quick lavages (the first two discarded and not further counted, as indicated with thin arrows), nasal lavages were performed at 10-min intervals. Nasal symptoms were assessed immediately prior to each lavage. Lavage no. 3 (20 min) was immediately followed by a challenge with diluent, and lavage no. 6 (30 min), 9 (80 min) and 12 (110 min) were followed by topical histamine provocations, as indicated below the line. Blood samples were taken after 30 min.

**Fig. 2.** Plasma-concentrations of the drugs 30 min after the start of the lavage procedure. Terbutaline (n = 12), theophylline (n = 12) and enprofylline (n = 11). The therapeutic intervals for clinical effective plasma concentrations are for theophylline 5–20 mg·l⁻¹ and for terbutaline 1–6 ng·ml⁻¹. Enprofylline is about four times as potent as theophylline in asthma.

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about the nature of the mucosal crossing by the plasma exudate, in particular whether the microvascular wall and the epithelium had a significant sieving function that also might be affected by the drugs.

**Subjects and methods**

**Study design**

Twelve normal subjects participated in a double-blind, crossover, placebo-controlled and randomised study. They were given a continuous IV infusions of terbutaline, theophylline and enprofylline. Nasal challenges with histamine were performed in order to induce plasma exudation and repeated nasal lavage was done to harvest nasal surface liquids.

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