

Antiallergic actions of high topical doses of terbutaline in human nasal airways

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It is debatable whether β_2 -receptor agonists produce antiallergic effects in human airways. This question has been addressed in the present study by examination of both mast-cell indices and the physiologic response to allergen challenge in human nasal airways. Twelve asymptomatic patients with seasonal allergic rhinitis were investigated outside the pollen season. Intranasal allergen provocation was carried out with diluent and three increasing doses of allergen. Topical terbutaline sulfate (1.0 mg) was given 5 min prior to each allergen challenge and nasal lavage was carried out 10 min after each challenge. The study design was double-blind, placebo-controlled, crossover, and randomized. The allergen challenge-induced mast-cell activation and the ensuing physiologic response of the airway tissue were investigated by measuring a mast-cell-derived mediator (tryptase) and plasma proteins (albumin and α_2 -macroglobulin), respectively, in the lavage fluids. Allergen provocation produced dose-dependent increments of nasal symptoms and lavage fluid levels of tryptase, albumin and α_2 -macroglobulin. Both nasal symptoms ($P < 0.05$) and lavage fluid levels of tryptase ($P < 0.05$), albumin ($P < 0.05$), and α_2 -macroglobulin ($P < 0.01$) were reduced by pretreatment with topical terbutaline sulfate. We conclude that high doses of topical terbutaline may produce significant antiallergic effects in human airways by equally reducing both tryptase release and plasma exudation in the acute allergic reaction in human airways. Further studies are now warranted to determine whether microvascular antipermeability effects of β_2 -receptor stimulation contribute to the present observations.

C. Svensson¹, L. Greiff¹, M. Andersson¹,
U. Alkner², R. Grönneberg³,
C. G. A. Persson⁴

¹ Department of Oto-Rhino-Laryngology, Head and Neck Surgery, University Hospital, Lund;

² Department of Bioanalysis, Astra Draco, Lund;

³ Department of Medicine Division for Respiratory and Allergic Diseases, Huddinge University Hospital, Karolinska Institute;

⁴ Department of Clinical Pharmacology, University Hospital, Lund, Sweden

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Christer Svensson
Department of Oto-Rhino-Laryngology
University Hospital
S-221 85 Lund
Sweden

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It was the vasoconstrictor property of epinephrine that prompted the first successful trial of this drug in asthma in 1903 (1). The drug's bronchodilator action was established by work carried out in Prague in 1907 (2). This action was soon considered important in asthma whereas the vasoconstrictor property remained important mainly for nasal therapies. In the 1960s and 1970s, Assem & Schildt and others added "antiallergic" mast-cell inhibitory effects to the list of potentially important antiasthma actions and laid down that this property, as the bronchodilation, resided in the β_2 -receptor agonist activity of these drugs (3). The potential antiallergic efficacy of β_2 -agonists has received attention in clinical trials carried out in subjects with allergic rhinitis or allergic asthma. However, the results have not been unequivocal, and the effects of β_2 -agonists on specific mast-cell indices such as tryptase appear not to have been assessed in human airways.

In the present study, we have employed challenge with a series of dosages of allergen in individuals with seasonal allergic rhinitis (outside the pollen season), and terbutaline was applied topically to ensure that large local concentrations of the β_2 -agonist were present. Nasal lavage fluid levels of tryptase were determined to investigate effects on mast-cell activation (4). Furthermore, the concentrations of albumin and α_2 -macroglobulin were determined to quantitate plasma exudation (5, 6), which is a physiologic response to inflammatory provocations of the airway mucosa. Finally, allergen challenge-induced nasal symptoms were determined.

Material and methods

Study design

Twelve patients with seasonal allergic rhinitis were investigated outside the pollen season when they

were asymptomatic. The effects of topical terbutaline on the nasal response to allergen challenge were studied in a double-blind, randomized, placebo-controlled, and crossover manner. Nasal symptoms were monitored and the levels of plasma proteins (albumin and α_2 -macroglobulin) and a mast-cell mediator (tryptase) were determined in pre- and post-challenge nasal lavage fluids.

Subjects

Five male and seven female subjects between the ages of 21 and 49 years (mean age 29 years) participated. All patients had a history of pollen-induced allergic rhinitis and a positive skin prick test to either birch ($n = 11$) or timothy ($n = 1$) pollen extracts. The patients had no other organic manifestations of their allergic disease. No drugs were permitted during the study of during a 3-week period before entering the study. All participants gave their informed consent before entering the study, which was approved by the ethics committee at the University of Lund, Sweden.

Study drug

The manufacturer's solution of terbutaline sulfate (Bricanyl[®], Astra Draco, Lund, Sweden), 10 mg/ml, was used for topical treatment. The diluent for the active compound was used as placebo. Terbutaline and placebo were administered with a nasal spray-

pump delivering 50 μ l per actuation. A dose of 1.0 mg of terbutaline was given 5 min prior to administration of the diluent and each of the three allergen provocations.

Nasal lavage and challenge procedure

The nasal lavage and challenge procedure is outlined in Fig. 1. The right nasal cavity was used for topical pretreatment, allergen challenges, and nasal lavages. Nasal lavages were made using the "nasal pool" device method, as previously described (7). Isotonic saline solution (0.9%) at room temperature was used for lavages. While the patient was positioned with head flexed forward (60°), the unilateral nasal cavity was gently filled by compressing the nasal pool containers (volume 14 ml). After two quick lavages (duration 30 s each) to clean the nasal mucosa from accumulated secretions, 15 min elapsed before the first nasal lavage was performed (duration 2.5 min). Immediately afterward, terbutaline (1.0 mg) or placebo was given topically. Five minutes later, a diluent challenge was performed, followed by another nasal lavage (duration 2.5 min) after 10 min. With identical time intervals between terbutaline/placebo administration, allergen challenge, and postchallenge lavages, three increasing doses of allergen (100, 1000, 10000 SQ-U of Aquagen[®], ALK, Denmark) were given. The lavage fluid was immediately centrifuged (325 g for 10 min) and the supernatants were frozen (-20°C) until analyzed. At least

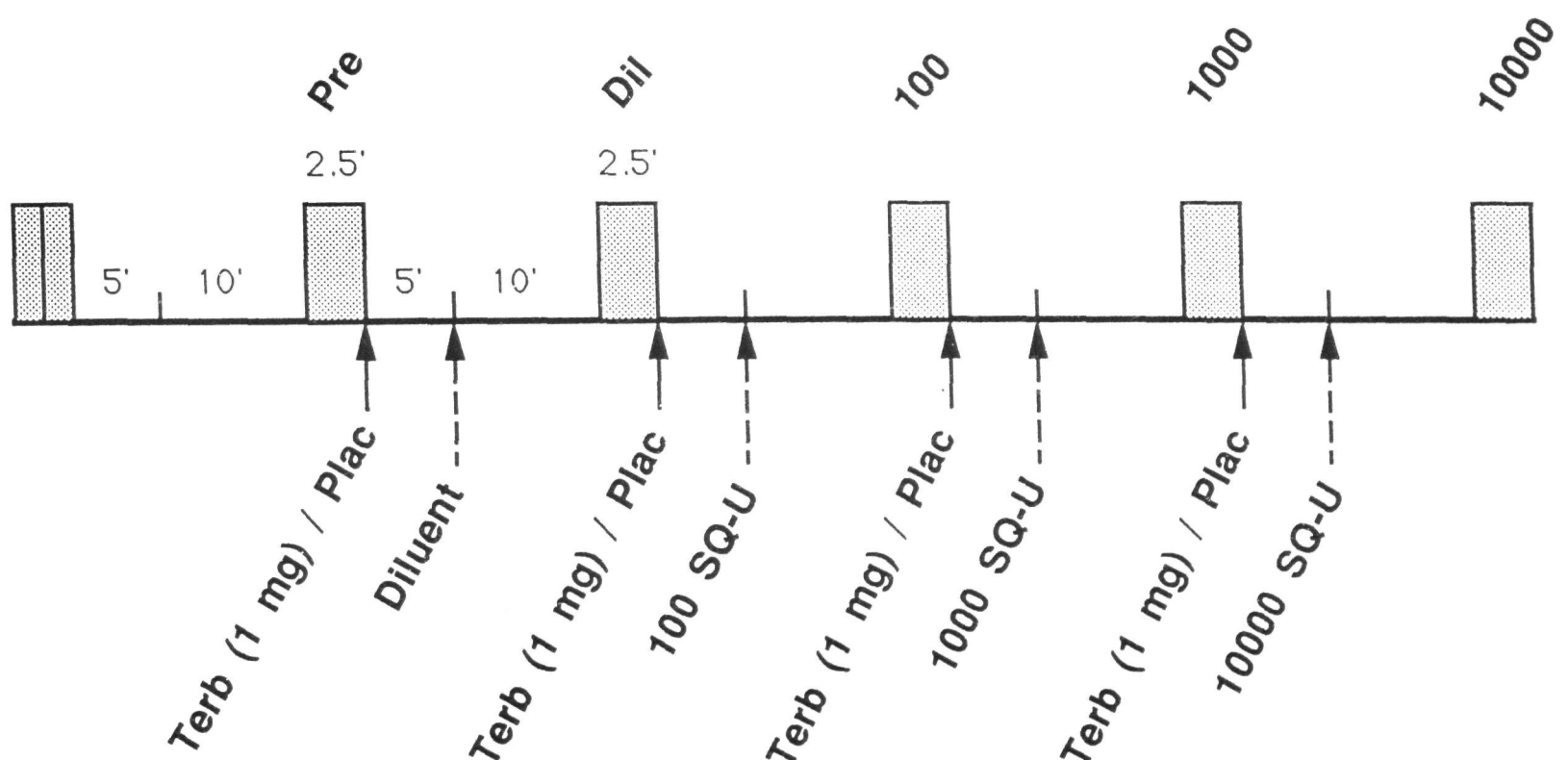


Fig. 1. Schematic presentation of experimental set-up. Bars above line indicate nasal lavages. Nasal treatment and provocations are indicated below line. Placebo (Plac), terbutaline solution (Terb), and allergen extracts were given with nasal spray device in right nasal cavity. Nasal lavages were carried out in right nasal cavity with "Nasal pool" device (duration: 2.5 min). The two prewashes (duration: 30 s) were discarded and not analyzed. Terbutaline or placebo was given 5 min to each provocation with diluent and increasing allergen doses. Registration of nasal symptoms and pulse rate was made immediately before each lavage.

4 weeks elapsed between the two challenge procedures.

Analytic assays

Albumin. Albumin was measured using a radioimmunoassay sensitive to 6.25 ng/ml with antiserum (rabbit antihuman albumin) (Dakopatts, Copenhagen, Denmark) and commercial standard (Calbiochem, San Diego, CA, USA). Iodination was performed by a lactoperoxidase method (8) to a specific activity of 2 mCi/nmol. Tracer and standards (or samples) were mixed with antiserum before adding goat antirabbit antiserum (Astra Draco, Lund, Sweden). The bound fraction was measured in a gamma counter (Clinigamma; Pharmacia Diagnostics, Uppsala, Sweden), and the data were evaluated using RIA CALC (Pharmacia Diagnostics, Uppsala, Sweden). The intra- and interassay coefficients of variation were 5% of 10%, respectively.

α_2 -Macroglobulin. α_2 -Macroglobulin was measured with a radioimmunoassay sensitive to 7.81 ng/ml. Rabbit antihuman α_2 -macroglobulin (Dakopatts, Copenhagen, Denmark) was used as antiserum, and standard human serum (Behringwerke Diagnostica, Marburg, Germany) as standard. Human α_2 -macroglobulin (Cappel/Organon Teknika, Turnhout, Belgium) was iodinated by the lactoperoxidase method (8). Tracer and standards (or samples) were mixed with antiserum before adding goat antirabbit antiserum (Astra Draco, Lund, Sweden). The bound fraction was measured in a gamma counter (Clinigamma; Pharmacia Diagnostics, Uppsala, Sweden), and the data were evaluated using MultiCALC (Wallac Oy, Åbo, Finland). The intra- and interassay coefficients of variation were 4–6% and 3–7%, respectively.

Tryptase. Tryptase was measured with a radioimmunoassay (Pharmacia Tryptase RIAC; Pharmacia Diagnostics, Uppsala, Sweden) sensitive to 2 ng/ml (9). Both the intra- and interassay coefficients of variation were approximately 2% (9).

Assessment of symptoms

Nasal symptoms (blockage, itching and secretion) were estimated by the patients and scored from 0 to 3 (0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms) together with registration of the number of sneezes during each of the 10-min periods that elapsed after the diluent/allergen challenges and the following nasal lavage. The number of sneezes was transformed to scores as follows: 0 = no sneezes, 1 = 1–4 sneezes, 2 = 5–9 sneezes, and 3 = 10 or more sneezes. A total (composite)

symptom score was calculated by the sum of the different nasal symptoms. Pulse rate registration (manual palpation of arteria radialis for 60 s) was done immediately before each nasal lavage.

Statistical analysis

Nonparametric statistics were used for comparison of nasal symptoms, lavage fluid levels of plasma proteins, and mast-cell-derived mediators (Wilcoxon signed rank sum test) and for calculations of correlation (Spearman rank correlation test). A *P*-value less than 0.05 was considered significant. All data are presented as mean $\pm$ SEM.

Results

Lavage fluid analysis

The nasal lavage fluid levels of tryptase, albumin, and α_2 -macroglobulin all increased dose-dependently on allergen challenge (Table 1 and Fig. 2). Pretreatment with terbutaline reduced the allergen challenge-induced increments of tryptase, albumin, and α_2 -macroglobulin. Statistical calculations showed reduced levels of α_2 -macroglobulin after the second allergen challenge (1000 SQ-U) (placebo vs terbutaline: *P* < 0.05) and reduced levels of all three mediators after the last allergen dose (10 000 SQ-U) (placebo vs terbutaline: *P* < 0.05 for albumin, *P* < 0.01 for α_2 -macroglobulin, and *P* < 0.05 for tryptase) (Fig. 2).

Nasal symptoms

Nasal symptoms increased dose-dependently on allergen challenge (Table 1 and Fig. 3). Terbutaline seemed to reduce all of the allergen challenge-induced nasal symptoms, but statistical calculations showed significant reductions only for nasal blockage and composite nasal symptom score after

Table 1. Dose-response comparison (*P*-values for Wilcoxon signed-rank test) of allergen-induced increments of nasal lavage fluid levels of mediators (tryptase, albumin, and α_2 -macroglobulin) and nasal symptoms elicited by repetitive challenges in right nasal cavity of increasing allergen doses (diluent, 100, 1000, and 10 000 SQ-U of timothy or birch pollen extract) with placebo pretreatment

	Tryptase (<i>P</i>)	Albumin (<i>P</i>)	α_2 -Macroglobulin (<i>P</i>)	Total nasal symptoms (<i>P</i>)
Pre vs Dil	NS	NS	NS	NS
Dil vs 10 ² SQ-U	<0.05	<0.01	<0.01	<0.05
Dil vs 10 ³ SQ-U	<0.05	<0.01	<0.01	<0.01
Dil vs 10 ⁴ SQ-U	<0.01	<0.01	<0.01	<0.01
10 ² vs 10 ³ SQ-U	NS	<0.05	NS	<0.01
10 ² vs 10 ⁴ SQ-U	<0.01	<0.01	<0.01	<0.01
10 ³ vs 10 ⁴ SQ-U	NS	<0.01	<0.01	<0.01

Pre = prechallenge; Dil = diluted challenge.

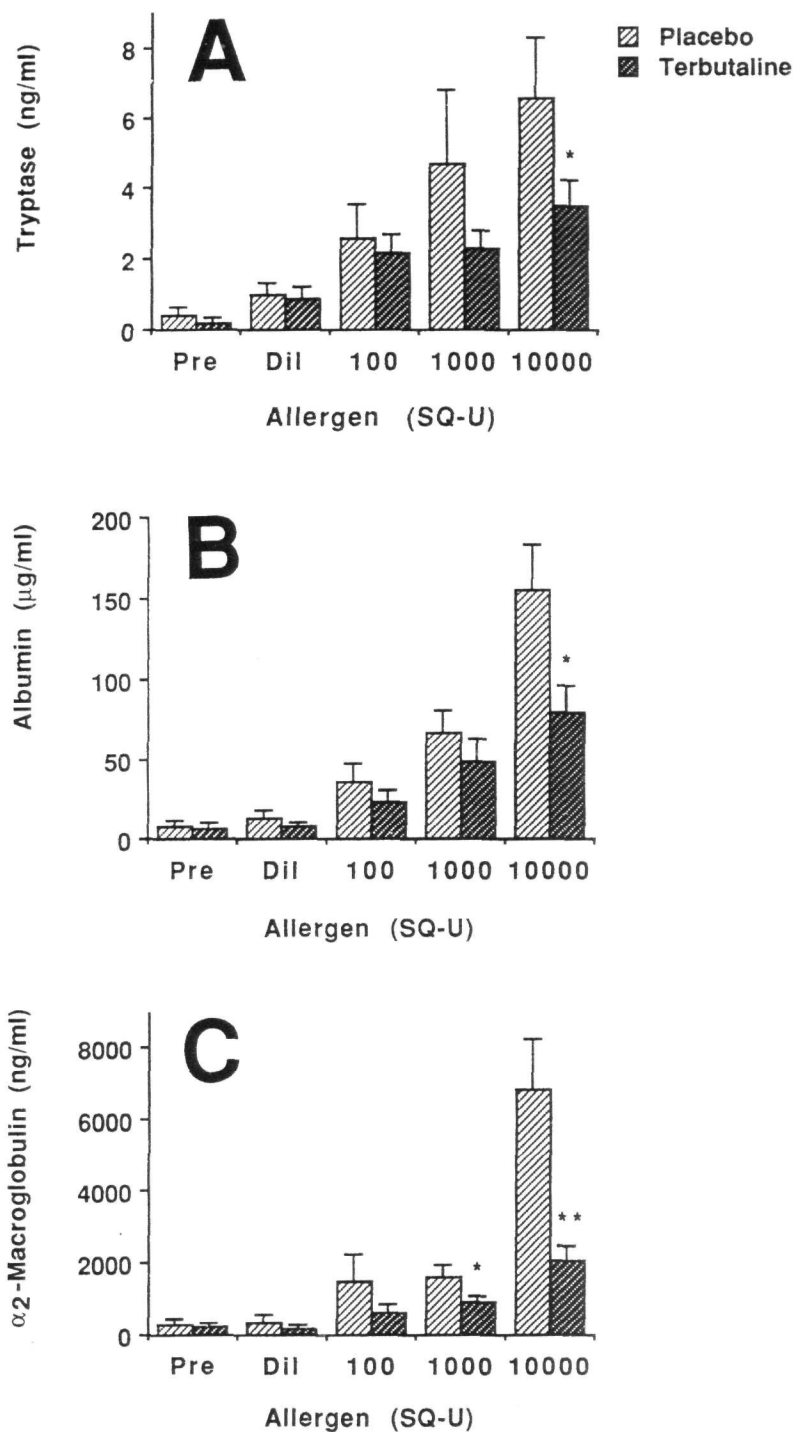


Fig. 2. Levels (mean $\pm$ SEM) of (A) tryptase, (B) albumin, and (C) α_2 -macroglobulin in pre- and post-allergen-challenge lavage fluids at the two challenge occasions (light bars: placebo pretreatment; dark bars: terbutaline pretreatment). There were low baseline levels of these mediators and dose-dependent increments after allergen challenge. Terbutaline pretreatment significantly reduced allergen challenge-induced increased levels of tryptase, albumin, and α_2 -macroglobulin at last allergen provocation (terbutaline vs placebo, Wilcoxon Signed rank test; * $P < 0.05$; ** $P < 0.01$). Pre = prechallenge; Dil = diluent challenge.

10000 SQ-U (placebo vs terbutaline: $P < 0.05$ for nasal blockage and $P < 0.01$ for composite nasal symptom score) (Fig. 3).

Side-effects

The pulse rate did not increase after placebo treatment while significant increments were recorded after the last two doses of terbutaline (comparison with terbutaline 0 mg: $P < 0.05$ for terbutaline 3 mg and $P < 0.01$ for terbutaline 4 mg). In comparison

with placebo, a significant pulse rate increment was demonstrated only after the last terbutaline dose, i.e., at the accumulated terbutaline dose of 4 mg (placebo vs terbutaline: $P < 0.05$) (Fig. 4). Nine of the participants experienced slight tremor on terbutaline treatment, while no side-effects were reported with placebo.

Correlations

Correlations between composite nasal symptom score and the lavage fluid levels of the mast-cell mediator and plasma proteins are presented in Table 2. Mediators showed fairly strong correlations with each other and to nasal symptom scores. An especially strong correlation was found between albumin and α_2 -macroglobulin.

Discussion

In this study involving subjects with allergic rhinitis, we have demonstrated that topical airway application of terbutaline prior to allergen challenge reduces both cellular (tryptase) and exudative (albumin and α_2 -macroglobulin) indices of inflammation. The present data suggest that β_2 -receptor agonists at high doses inhibit human mast-cell activation *in vivo* and that this action is of functional importance because allergic inflammation-induced physiologic effects and symptoms are also inhibited.

The purpose of this study was to investigate the nonbronchodilator actions of terbutaline in acute airway inflammation. The human nasal mucosa, lacking the smooth-muscle constriction response of the lower airways, is a suitable and accessible part of the airways where well-controlled experimental conditions can be achieved for studies of mucosal inflammatory reactions. In this study, allergen challenges and topical terbutaline were sprayed onto the nasal mucosa, ensuring a wide and even distribution of the β_2 -agonist and allergen within the nasal cavity. A nasal pool device was used for the nasal lavages. With this technique, a large area of the nasal mucosa is efficiently lavaged with a high lavage fluid recovery (6, 7).

Table 2. Correlations (r = Spearman rank correlation coefficient) for nasal symptoms and lavage fluid levels of tryptase, albumin, and α_2 -macroglobulin. Calculations made on both pre- and postchallenge values (Pre + Dil + 100 + 1000 + 10000 SQ-U) with placebo pretreatment

	Albumin (r)	α_2 -Macroglobulin (r)	Total nasal symptoms (r)
Tryptase	0.70	0.68	0.65
Albumin		0.96	0.78
α_2 -Macroglobulin			0.75

$P < 0.001$ for all r -values. Pre = prechallenge; Dil = diluent challenge.

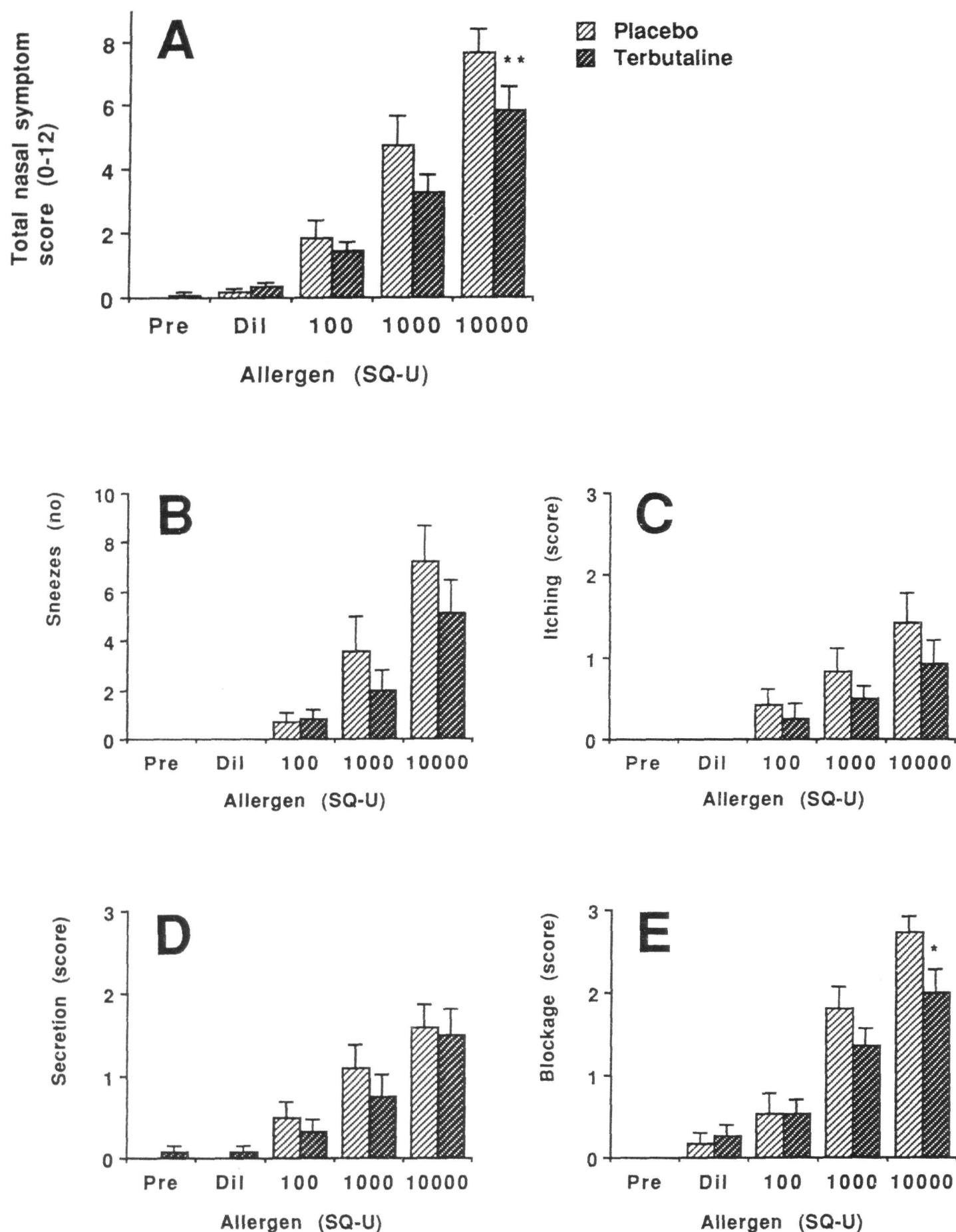


Fig. 3. A) Composite nasal symptom score, B) number of sneezes, C) itching score, D) secretion score, and E) blockage score (mean $\pm$ SEM) recorded during two challenge occasions (light bars: placebo pretreatment; dark bars: terbutaline pretreatment). Composite nasal symptom score was calculated from individual nasal symptoms. Nasal symptoms increased dose-dependently after allergen challenge. Terbutaline pretreatment significantly reduced allergen challenge-induced nasal blockage and total nasal symptom score at last allergen dose (terbutaline vs placebo, Wilcoxon signed rank test; * $P < 0.05$; ** $P < 0.01$). Pre = prechallenge; Dil = diluent challenge.

Previous studies of the effects of β_2 -agonists in allergic rhinitis have generated equivocal results; some studies showed that β_2 -agonists have an in-

hibitory effect on allergen-induced nasal symptoms (including nasal blockage measured with posterior rhinomanometry), while other studies could not de-

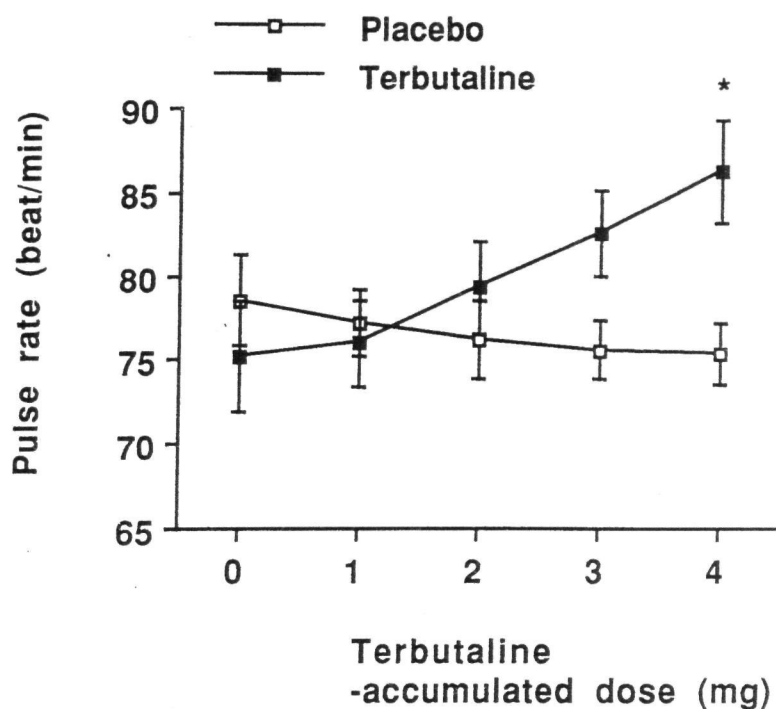


Fig. 4. Pulse rates (mean $\pm$ SEM) recorded during two challenge occasions (open squares: placebo pretreatment; filled squares: terbutaline pretreatment). Pulse rate increased significantly on terbutaline pretreatment at accumulated doses of 3 mg ($P < 0.05$) and 4 mg ($P < 0.01$) (comparison with 0 mg; Wilcoxon signed rank test).

tect any effect (10–12). Hence, the clinical significance of any antiallergic effect of β_2 -agonists remains obscure. The present study demonstrated that even a very high dose of the β_2 -agonists producing systemic effects only marginally reduced allergen challenge-induced symptoms. This observation suggests that current β_2 -agonists are not a therapeutic option in allergic rhinitis.

In this study, we determined the luminal entry, or mucosal exudation, of two different-sized plasma proteins. Mucosal exudation of plasma in the airways is a specific inflammatory response that may be used as a quantitative measurement of the tissue involvement in airway inflammatory reactions (5). Important structures for this response are the sub-epithelial network of microvessels and the epithelial lining. Endothelial cells of postcapillary venules are separated upon stimulation with inflammatory mediators leading to extravasation of plasma macromolecules by hydrostatic intravascular forces. The further passage of extravasated plasma macromolecules into the airway lumen takes place between epithelial cells without disrupting the epithelial cell lining or changing its absorption barrier functions. Also the outward-directed epithelial passage of plasma macromolecules probably reflects a hydrostatic pressure-induced transient opening of epithelial cell junctions that exhibit a valve-like function (for review, see Persson et al. 5). In guinea pig tracheobronchial and human nasal airways, the mucosal exudation response is a sensitive, reversible, and dose-dependent process induced by allergen and

inflammatory mediators. The exudation appears to be a little size-restricted exudation of bulk plasma. This notion is further strengthened by the present finding of excellent correlations between albumin (MW 70 000) and α_2 -macroglobulin (MW 720 000).

In the present study, terbutaline pretreatment reduced allergen challenge-induced nasal symptoms and lavage fluid levels of tryptase, albumin, and α_2 -macroglobulin. Our interpretation of the present results is that high-dose topical terbutaline may primarily inhibit allergen challenge-induced release of mast-cell-derived mediators. The sum action of this β_2 -agonist-induced inhibition of mast-cell activation was beneficial in the sense that terbutaline treatment also resulted in reduced nasal symptoms and reduced mucosal exudation of plasma. Hence, this study cannot support the notion that high-dose topical β_2 -agonists that inhibit mast-cell activation are associated with proinflammatory actions. Studies involving nasal allergen challenge and treatment with oral antihistamines have demonstrated that histamine is probably the most important exudation-inducing mediator in acute airway allergy (13). Reduced release of mast-cell-derived histamine could thus explain the reduction of mucosal exudation of plasma demonstrated in the present study. Whether reduced luminal entry of tryptase to some extent may be coupled to the reduced movement of plasma proteins through airway tissue compartments into the lumen remains an intriguing speculation.

It has been demonstrated that β_2 -agonists may exert significant microvascular antipermeability effects in different animal tissues (14). However, terbutaline-induced microvascular antipermeability effects have been recorded in the skin of both guinea pigs (15) and man (16, 17). The microvascular effect could also be recorded in the airways of guinea pigs (18, 19), where the antiexudative action of β_2 -agonists was sensitive to the magnitude of the exudative challenge. For example, just by doubling the dose of bradykinin, a marked inhibitory effect of terbutaline could be completely blunted (19). There was no such dependence of challenge dose in this study. On the contrary, at the highest allergen challenge level, the terbutaline-induced reduction of plasma output was very pronounced (Fig. 2). If the guinea pig data (19) translates to human airways, these findings suggest that direct vascular antipermeability actions may not have been the most important β_2 -agonist-induced action in the present study. We have previously demonstrated that systemic doses of terbutaline, producing plasma levels of 5 ng/ml, do not inhibit histamine challenge-induced plasma exudative responses in the human nose (20). However, these latter findings do not exclude the possibility that a direct vascular antipermeability effect of high concentrations of terbuta-

line in part has contributed to the reduced exudation in this study.

In conclusion, this study demonstrates that high-dose topical terbutaline inhibits nasal symptoms together with lavage fluid levels of mast-cell tryptase and mucosal exudation of α_2 -macroglobulin in acute airway allergy. These findings suggest a mast-cell inhibitory effect of terbutaline in acute airway allergy and that the effect of this action results in inhibition of an inflammatory tissue response.

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