Preoperative Steroid Therapy Inhibits Cytokine Production in the Lung Parenchyma in Asthmatic Patients*

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**Objectives:** During or after surgery, asthma attacks due to airway hyperresponsiveness (AHR) are likely to occur in patients with bronchial asthma. Preoperative administration of corticosteroid for prevention of perioperative asthma attacks is useful. We examined the mechanism of prevention of perioperative asthma attacks by the preoperative administration of corticosteroid in vitro.

**Design:** Five patients with asthma were treated with 20 mg of prednisolone orally for 2 preoperative days and 80 mg of methylprednisolone IV immediately before and after surgery. In another five patients without asthma, no steroids were administered. A noncarcinomatous part of the resected tissue from each patient with lung cancer was passively sensitized with the serum of an atopic patient. In the patients without asthma, the tissue was treated with or without dexamethasone, and then mite antigen was added.

**Measurements:** The culture supernatant and lung tissue were recovered, and the supernatant was assayed for histamine, leukotriene E$_4$ (LTE$_4$), interleukin (IL)-5, and tumor necrosis factor (TNF)-α. Degranulation of mast cells was measured by tryptase staining of the lung tissue, and the expression of messenger RNA (mRNA) of IL-5 and TNF-α was determined by the reverse transcriptase-polymerase chain reaction method.

**Results:** While preoperative administration of corticosteroid did not suppress the release of histamine and LTE$_4$ from the lungs of asthmatic patients, it completely suppressed IL-5 and TNF-α production at the mRNA level. The same results were obtained in lung tissues of nonasthmatic patients treated in vitro with dexamethasone.

**Conclusions:** Our results suggest that corticosteroid treatment reduces AHR and prevents perioperative attacks of asthma primarily by suppressing the production of inflammatory cytokines.

Key words: airway hyperresponsiveness; corticosteroid; cytokines; interleukin-5; perioperative asthma; tumor necrosis factor-α

Abbreviations: AHR = airway hyperresponsiveness; cDNA = complementary DNA; IL = interleukin; LAR = late asthmatic response; LTE$_4$ = leukotriene E$_4$; mRNA = messenger RNA; PCR = polymerase chain reaction; RT-PCR = reverse transcriptase-polymerase chain reaction; TNF = tumor necrosis factor

Patients with asthma are at increased risk of specific complications during and after surgical operations, *ie*, acute bronchoconstriction triggered by intubation, hypoxemia and possible hypercapnia, impaired effectiveness of cough, atelectasis, and respiratory infection due to airway hyperresponsiveness (AHR), airflow obstruction, and mucus hypersecretion. Therefore, preoperative evaluation of the state of asthma and systemic administration of corticosteroid to maintain pulmonary function at its best are important precautions to reduce the risk during the perioperative period. However, corticosteroid administration increases the likelihood of respiratory infections, wound infections, difficulties in wound healing, complications of adrenal insufficiency; therefore, its dosage preoperatively must be carefully evaluated. In our hospital, we have administered corticosteroid preoperatively to > 100 asthmatic patients and noted the effectiveness of such therapy in

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preventing asthmatic attacks during the perioperative period (unpublished observation; August 2000). The National Institutes of Health also established the following guideline: "For patients who have received systemic corticosteroids during the past 6 months, give 100 mg hydrocortisone every 8 hours intravenously during the surgical period and reduce the dose rapidly within 24 hours following surgery."

The mechanism of action of corticosteroid as an antiasthma agent is not entirely clear, but it is considered to suppress eosinophilic inflammation of the airway and AHR by controlling the production of inflammatory cytokines such as interleukin (IL)-5 and tumor necrosis factor (TNF)-α. On the other hand, corticosteroid has no inhibitory effect on the release of chemical mediators such as histamine and leukotriene from mast cells, and it is considered to be ineffective for immediate-type airway obstruction, in which chemical mediators are involved.5–7

We hypothesized that corticosteroid administered preoperatively prevents perioperative attacks of asthma by suppressing AHR through a reduction of production of inflammatory cytokines. The present in vitro study was conducted to verify this hypothesis by preparing a passively sensitized lung model of lung tissues obtained from asthmatic patients preoperatively treated with corticosteroid.

**Materials and Methods**

The subjects were five asthmatic and five nonasthmatic patients. All 10 patients had lung cancer. Table 1 shows the characteristics of each patient. The diagnosis of bronchial asthma and the grading of its severity were based on the guideline set by Global Initiative for Asthma.8 Patients 2, 4, and 9 had pulmonary emphysema. None of the patients had received preoperative anticancer chemotherapy or radiotherapy. Corticosteroid was administered preoperatively to the asthmatic patients using the following regimen: 20 mg of oral prednisolone for 2 days before the operation and 80 mg of IV methylprednisolone immediately before and after the operation. No steroid was administered to the control nonasthmatic patients. Induction (fentanyl) and maintenance (nitrous oxide sevoflurane) of anesthesia were achieved using the same drugs in both groups of subjects, and no significant difference was observed between the two groups with regard to age, male/female ratio, preoperative pulmonary function, and mean operation time. Only mild wheezing appeared in one asthmatic patient after extubation, but no asthma attacks occurred in the remaining four patients. The absence of side effects of corticosteroid therapy either during or after surgery was confirmed by a review of the surgical records and interviews of the patients by the attending physicians. The mean operation time of both groups of patients was 3 h and 47 min, and the mean period from the beginning of surgery to resection of the specimens was 2 h. The study was carried out after the approval by the Ethical Committee of Nagasaki University School of Medicine, and informed consent was obtained from each patient prior to participation in the study.

**Table I—Characteristics of Patients*”

<table>
<thead>
<tr>
<th>Patient No./Age, Sex</th>
<th>Smoking Index</th>
<th>Asthma</th>
<th>Therapy Before Operation</th>
<th>VC, % Predicted</th>
<th>FEV1/FVC, %</th>
<th>Dlco/VA, ml/min/mmHg/L</th>
<th>Surgery</th>
<th>Duration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1/43/male</td>
<td>1,120</td>
<td>Nonatopic</td>
<td>Mild intermittent</td>
<td>11 min</td>
<td>Theophylline</td>
<td>91</td>
<td>69</td>
<td>4.38</td>
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<tr>
<td>2/77/male</td>
<td>2,290</td>
<td>Nonatopic</td>
<td>Mild persistent</td>
<td>2 min</td>
<td>Pranlukast, DSCG plus salbutanol</td>
<td>96</td>
<td>60</td>
<td>3.30</td>
</tr>
<tr>
<td>3/66/male</td>
<td>0</td>
<td>Atopic</td>
<td>Mild intermittent</td>
<td>2 yr</td>
<td>Salbutamol</td>
<td>91</td>
<td>77</td>
<td>4.61</td>
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<tr>
<td>4/70/male</td>
<td>900</td>
<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>4 yr</td>
<td>FP, 400 μg DSCG plus salbutanol, theophylline</td>
<td>98</td>
<td>55</td>
<td>3.88</td>
</tr>
<tr>
<td>5/55/female</td>
<td>0</td>
<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>10 yr</td>
<td>FP, 400 μg DSCG plus salbutanol</td>
<td>111</td>
<td>88</td>
<td>4.31</td>
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<tr>
<td>Nonasthma patients</td>
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<td></td>
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<td>0</td>
<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>10 yr</td>
<td>FP, 400 μg DSCG plus salbutanol</td>
<td>97</td>
<td>86</td>
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<tr>
<td>7/43/male</td>
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<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>10 yr</td>
<td>FP, 400 μg DSCG plus salbutanol</td>
<td>91</td>
<td>77</td>
<td>4.01</td>
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<td>8/48/male</td>
<td>840</td>
<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>10 yr</td>
<td>FP, 400 μg DSCG plus salbutanol</td>
<td>93</td>
<td>76</td>
<td>4.88</td>
</tr>
<tr>
<td>9/71/male</td>
<td>1,120</td>
<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>10 yr</td>
<td>FP, 400 μg DSCG plus salbutanol</td>
<td>93</td>
<td>63</td>
<td>3.72</td>
</tr>
<tr>
<td>10/56/male</td>
<td>420</td>
<td>Nonatopic</td>
<td>Moderate persistent</td>
<td>10 yr</td>
<td>FP, 400 μg DSCG plus salbutanol</td>
<td>112</td>
<td>80</td>
<td>4.12</td>
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</table>

* DSCG = sodium cromoglycate; FP = fluticasone propionate; VC = vital capacity; Dlco = diffusing capacity of the lung for carbon monoxide; VA = alveolar volume.
Culture of Lung Tissues

The noncarcinomatous parts of surgically resected lung tissues were cut and passively sensitized. For this purpose, the resected lung tissue was minced into fragments of 300 mg and washed twice with RPMI1640 (Gibco; Grand Island, NY) to prevent contamination by blood cells. For stimulation via IgE receptors, the lung tissue was passively sensitized with serum of an atopic patient who showed a mite radioallergosorbent test score of ≥ 5 over 2 h, and cultured in RPMI1640 alone or RPMI1640 containing 1.5 μg/mL of mite antigen for 48 h. Dexamethasone (Sigma Chemical; St. Louis, MO) was added at 10^-8 mol/L for in vitro treatment of lung tissues of nonasthmatic patients. The lung tissues of asthmatic patients, who had already been treated with corticosteroid before surgery, were not treated in vitro with dexamethasone. To examine whether the reaction was induced via IgE, the lung tissues of nonasthmatic patients without passive sensitization and treatment in vitro with dexamethasone were directly stimulated with mite antigen. The culture supernatant and lung tissues were recovered after a predetermined period following stimulation; histamine, leukotriene E4 (LTE4), IL-5, and TNF-α concentrations in the supernatant were determined. The lung tissues were stained for tryptase, mast cells were counted, total RNA was extracted from part of the tissues, and the expression of messenger RNA (mRNA) of IL-5 and TNF-α was measured by the reverse transcriptase-polymerase chain reaction (RT-PCR) method. Cultures were prepared invariably at 37°C in 5% CO2 with the addition of 100 U/mL of penicillin (Meiji Seika; Tokyo, Japan) and 100 μg/mL of streptomycin sulfate to RPMI1640. The endotoxin level in the culture medium measured using Toxicolor test (SRL; Tokyo, Japan) was ≤ 50 pg/mL.

Measurement of Chemical Mediators and Cytokines in Supernatant of Lung Fragments

Based on the method described previously,9 radioimmunoassay was used to measure histamine concentration 30 min after stimulation with mite antigen and LTE4 concentration after 60 min, when their productions reach peak levels in this model. IL-5 concentration 24 h after stimulation with mite antigen and TNF-α concentration 4 h after stimulation were determined using a commercial enzyme-linked immunosorbent assay kit (Quantikine; R&D Systems; Minneapolis, MN) when their productions reach peak levels in this model. All results were expressed as production per 300 mg of lung tissue.

RT-PCR

To analyze the expression of cytokine mRNA, we first extracted the total cellular RNA by the guanidinium thiocyanate method, and then amplified complementary DNA (cDNA) by reverse transcription of total cellular RNA, as previously described.9 After stimulation with RPMI or mite antigen for 30 min, 1 h, or 24 h, the lung tissues were cut with scissors into small pieces on a Petri dish placed on ice, then placed in a glass homogenizer with TRIzol reagent (1 mL/100 mg lung tissue; Gibco, BRL) and homogenized. The homogenate was mixed with 0.2 mL of TRIzol/mL of chloroform, and then centrifuged at 12,000 g for 15 min. In the next step, the liquid phase was collected and mixed with isopropanol to extract total RNA. RNA pellets were washed in 75% ethanol and dried, and then dissolved in diethyl pyrocarbonate-treated water and stored at -80°C.

Total cellular RNA was reverse transcribed with oligo deoxythymidinie, 10× reverse transcriptase motion buffer, deoxynucleotide triphosphates (deoxyadenosine triphosphate, deoxytymidine triphosphate, deoxycytidine triphosphate, deoxynanosine triphosphate, deoxyguanosine triphosphate), SuperScript II RNAase H-reverse transcriptasease (Gibco), 0.1 mol/L dithiothreitol, and 25 mM MgCl2 to prepare cDNA. RNA was reacted at 42°C for 50 min, and then at 70°C for 15 min. Polymerase chain reaction (PCR) buffer containing MgCl2, 25 mM deoxynucleotide triphosphate mix, Taq polymerase, and diethyl pyrocarbonate-treated water comprised a volume of 42 μL. To this solution, we added 3 μL of cDNA, 2.5 μL of cytokine 3-primer, and 2.5 μL of cytokine 5-primer (total volume, 50 μL).

Figure 1. Sections of the resected lung. Top, a: without asthma; this patient was not administered corticosteroid before surgery. Middle, b: mild persistent asthma; this patient was treated with oral administration of pranlukast and inhalation of sodium cromoglycate plus salbutamol via nebulizer. Bottom, c: moderate persistent asthma; this patient was treated with inhalation of fluticasone propionate, 400 μg/d, and inhalation of sodium cromoglycate plus salbutamol via nebulizer. The patients in b and c were administered corticosteroid preoperatively. No eosinophil infiltration or detachment of the airway epithelium was observed in the asthmatic lungs, indicating satisfactory control of asthma (hematoxylin-eosin, original × 800).
Specific cytokine oligonucleotide PCR primers were designed based on published cDNA sequences (Genbank; Los Alamos National Laboratory; Los Alamos, NM). For all primers, an amplifier set (Clontech Laboratories; Palo Alto, CA) was used. Thirty cycles of reactions were induced using a thermocycler under the following conditions: IL-5, denaturation at 94°C for 30 s, annealing at 49°C for 30 s, and extension at 72°C for 60 s; TNF-α, denaturation at 94°C for 30 s, annealing at 47°C for 30 s, and extension at 72°C for 60 s. The last extension was performed at 72.5°C, and the final products were stored at 4°C until electrophoresis. For electrophoresis, 10 μL of PCR-amplified product was placed on a 2% agarose gel, and then visualized by ultraviolet illumination.

**Immunohistochemistry**

Lung tissues were stained for tryptase within 30 min after stimulation with RPMI or mite antigen. The recovered lung fragments were fixed with 20% formalin and embedded in paraffin. Tissue sections were placed on glass slides, deparaf-finized, and treated with trypsin. Endogenous peroxidase activity was blocked by incubating slides in methanol containing 3% hydrogen peroxide for 30 min, followed by washing in phosphate-buffered saline solution. After blocking with 10% normal rabbit serum for 20 min, sections were incubated overnight at 4°C with a mouse monoclonal anti-human mast cell tryptase antibody (AA1; Dako; Tokyo, Japan) at a dilution of 1 × 500 of a 105 μg/mL solution. Following application of the primary antibody, we applied a biotinylated rabbit antimouse antibody (Nichirei; Tokyo, Japan), followed by the addition of peroxidase-conjugated avidin for 20 min at room temperature. Chromogen-fast diaminobenzidine (DAB; Sigma Chemical) was used for 5 min, and the slides were counterstained in hematoxylin and mounted.

**Statistical Analysis**

Data are presented as mean ± SEM. Differences between the asthmatic lungs and nonasthmatic lungs were compared by two-group unpaired t test, and differences in the same patient between measurements performed before and after stimulation or treatment were compared by two-group paired t test. A p value < 0.05 was considered significant.

**Results**

**Lung Histology**

Figure 1 shows hematoxylin-eosin–stained lung sections. No inflammatory cell infiltration including eosinophils or detachment of the airway epithelium was noted in the asthmatic lungs probably because of adequate preoperative control of asthma and preoperative administration of corticosteroid.

**Release of Chemical Mediators Induced by Dermatophagoides farinae Allergen Stimulation**

The release of chemical mediators from the passively sensitized lung induced by stimulation with
D farinae allergen via IgE was examined. Significant release of histamine was observed in the lungs of passively sensitized asthmatic subjects preoperatively treated with corticosteroid and the lungs of the passively sensitized nonasthmatic patients not treated with corticosteroid, and the amount of histamine release was comparable between the two groups. Furthermore, in vitro stimulation of the lungs of passively sensitized nonasthmatic patients with mite antigen after treatment with dexamethasone failed to suppress the release of histamine (Fig 2, left, A). The release of LTE₄ was similar to that of histamine (Fig 2, right, B). To examine whether the reaction was induced via IgE, the lung tissues of nonasthmatic patients without passive sensitization and treatment in vitro with dexamethasone were directly stimulated with mite antigen. Both histamine and LTE₄ levels were below the detectable ranges, and the release of chemical mediators by stimulation with the mite antigen in the passive sensitization model was considered a reaction via IgE.

Immunostaining for Tryptase

Mast cells in the lung tissues were counted by immunostaining using antihuman tryptase antibody. The number of mast cells per 200 epithelial cells of the bronchial epithelium and mucosa was not significantly different between asthmatic and nonasthmatic lungs (Fig 3). No significant difference was noted in the degree of degranulation of mast cells after antigen stimulation between asthmatic and nonasthmatic lungs. Tryptase-positive cells decreased due to degranulation after antigen stimulation in the passively sensitized asthmatic lungs preoperatively treated with corticosteroid and the passively sensitized nonasthmatic lungs treated in vitro with dexamethasone (Fig 4). These results indicate that preoperative or in vitro corticosteroid administration did not suppress degranulation of mast cells in the lungs of passively sensitized asthmatic or nonasthmatic patients.

Cytokine Production by D farinae Allergen Stimulation

No IL-5 production was noted when the lungs of the passively sensitized asthmatic patients preoperatively treated with corticosteroid were stimulated with D farinae allergen. In contrast, significant IL-5 production was induced by D farinae allergen stimulation in the lungs of passively sensitized nonasthmatic patients who did not receive preoperative corticosteroid administration, and this IL-5 production was suppressed by in vitro pretreatment with dexamethasone (Fig 5, left, A). Similar changes were observed with regard to TNF-α production (Fig 5, right, B). To examine whether the reaction was induced via IgE, the lung tissues of nonasthmatic patients without passive sensitization and treatment in vitro with dexamethasone were directly stimulated with mite antigen. Both IL-5 and TNF-α levels were below the detectable ranges, and the production of cytokines by stimulation with the mite antigen in the passive sensitization model was considered a reaction via IgE. Mite extracts often contain a large amount of endotoxin, but the endotoxin level in the culture medium containing D farinae allergen measured using Toxicolor test (SRL; Tokyo, Japan) was ≤ 50 pg/mL. The result suggested that the production of cytokines was not affected by endotoxins in mite extracts.

Expression of Cytokine mRNAs

We examined the expression of IL-5 and TNF-α mRNAs in the lungs of passively sensitized asthmatic and nonasthmatic patients after stimulation with mite antigen by using the RT-PCR method. Figure 6 shows typical gels. No expression of mRNA of either IL-5 or TNF-α was noted 30 min after antigen stimulation. One hour after antigen stimulation, no expression of mRNA of either IL-5 or TNF-α was noted in the lungs of the passively sensitized asth-
matic patients preoperatively treated with corticosteroid while mRNA of both IL-5 and TNF-α was clearly expressed in the lungs of passively sensitized nonasthmatic patients who did not receive preoperative corticosteroid administration and was still expressed even after 24 h. The latter expression was suppressed by in vitro dexamethasone treatment. These results suggest that preoperative and in vitro corticosteroid treatments suppress the production of cytokine proteins and expression of mRNA induced by *D. farinae* allergen stimulation in the lungs of passively sensitized asthmatic and nonasthmatic patients.

**Discussion**

The major findings of our study were as follows: (1) production of histamine and LTE₄ from human mast cells was not reduced by corticosteroid treatment after stimulation with specific allergen; (2) production of IL-5 and TNF-α was, however, significantly suppressed in lung tissues of passively sensitized asthmatic patients preoperatively treated with corticosteroid, compared with those in lung tissues of nonasthmatic patients without corticosteroid treatment; and (3) production of IL-5 and TNF-α was suppressed in the lung tissues of passively sensitized nonasthmatic patients treated in vitro with corticosteroid similar to the lung tissues of the passively sensitized asthmatic patients preoperatively treated with corticosteroid.

Bronchial asthma is a chronic eosinophilic inflammatory disorder of the airway, and inhalation of specific allergens causes biphasic airway obstruction. Chemical mediators such as histamine and leukotriene produced by mast cells via IgE antibody are involved in immediate allergic response that occurs shortly after inhalation of allergen. On the other hand, the degree of late allergic response (LAR) observed about 6 h after inhalation of allergen is related to the degree of eosinophil infiltration, and the involvement of inflammatory cytokines in this process has been suggested. In LAR, granular proteins are thought to be continuously released from eosinophils accumulating in the airway, and the consequent impairment of the airway epithelium is speculated to induce AHR. Although corticosteroid is the most effective antiasthmatic treatment available today, its precise mechanism of the action has not yet been clarified. Treatment of asthmatics with corticosteroid results in suppression of LAR but not immediate asthmatic response.¹⁰ It has also been reported that in vitro corticosteroid treatment does not suppress the IgE-dependent release of histamine and cysteinyi-leukotrienes from mast cells.⁵,⁶ Our results showed that the release of chemical mediators induced by stimulation with specific allergen...
was not suppressed either by preoperative treatment of asthmatics with corticosteroid or in vitro corticosteroid treatment of lungs of nonasthmatic patients. The results of tryptase staining also suggested that degranulation of mast cells after stimulation with specific allergen could not be prevented by corticosteroid. Thus, our results indicate that corticosteroid does not act as antiasthmatic agent by inhibiting the release of chemical mediators.

In contrast to its effect on chemical mediators, preoperative corticosteroid therapy resulted in almost complete suppression of production of IL-5 and TNF-α proteins and inhibition of their mRNA expressions in response to stimulation with specific allergen. Similar results were obtained also in the lungs of nonasthmatic patients after in vitro corticosteroid treatment. IL-5 and TNF-α are inflammatory cytokines that increase locally on allergen administration through the airway of asthmatic patients and play important roles in eosinophilic airway inflammation through activation of various eosinophils and expression of adhesion molecules, respectively.9,11,12 As mentioned above, corticosteroid has a suppressive effect on LAR and alleviates AHR by a short-term high-dose therapy.3 These findings support our hypothesis that preoperative corticosteroid therapy prevents perioperative asthmatic attacks primarily by reducing the production of inflammatory cytokines such as IL-5 and TNF-α and, thus, suppressing AHR.

There are three problems with this study. Firstly, the dosage of steroid used in the present study might be significantly greater than that given in the National Institutes of Health guideline. Based on our clinical experiences, we had determined the dosage of steroid. Any steroid-related severe adverse effect had never occurred. Secondly, our population samples did not include asthmatic patients who did not receive preoperative corticosteroid administration. To evaluate preoperative corticosteroid administration to asthmatic patients, it is necessary to examine a control group of asthmatic patients who had not received corticosteroid preoperatively. However, we encountered one patient with mild intermittent asthma and two patients with mild persistent asthma
who underwent surgery under general anesthesia without preoperative administration of corticosteroid. Surgery was discontinued in the first patient because of bronchospasm triggered by intubation, the second patient had an asthma attack with confusion after surgery, and the third patient had bronchospasm triggered by removal of the tube. These findings suggest that surgery under general anesthesia is a risk for asthmatic patients with airway hyperreactivity even when symptoms are stable. Therefore, we could not ethically study the tissues of asthmatic patients who had not been administered corticosteroids preoperatively. Previous studies have shown that asthmatic patients exhibit a high number of mast cells in their airway, enhanced sensitivity to immunologic stimulation, and increased spontaneous release of inflammatory mediators, compared with healthy individuals. In this study, however, there were no differences in the number of mast cells present in the airway epithelial and mucosal layer, the degree of mast cell degranulation induced by stimulation with specific antigen, and concentrations of chemical mediators in the supernatant between asthmatics and nonasthmatic patients. Long-term administration of corticosteroid has been reported to reduce the number of mast cells in the airway and, consequently, to reduce the response to allergen challenge. In this study, some patients were receiving long-term corticosteroid inhalation therapy before surgery, and corticosteroid was also administered immediately before operation. Such a treatment could possibly explain the lack of significant difference between the two groups. The third problem is that cytokine-producing cells were not identified. All cells with IgE receptors in lung tissues are potential cytokine-producing cells, but it has been reported that mast cells are most important among them. Previously, we confirmed that cytokines were not produced by stimulation with CD3 (1 μg/mL) in the same experimental model. Therefore, T cells were considered noncytokine-productive cells. Eosinophils also have low-affinity IgE receptor, but no eosinophils were detected in the hematoxylin-eosin–stained lung tissues. Alveolar macrophages also have low-affinity IgE receptors, but the number of IgE receptors is

Figure 6. mRNA expression of IL-5, TNF-α, and β-actin in the lungs of passively sensitized asthmatic and nonasthmatic patients determined at 0.5 h, 1 h, and 24 h after Dermatophagoides antigen stimulation. Representative gels are shown. Lane 1: sensitization plus RPMI (asthma). Lane 2: sensitization plus D farinae (asthma). Lane 3: sensitization plus RPMI (nonasthma). Lane 4: sensitization plus D farinae (nonasthma). Lane 5: sensitization plus D farinae plus dexamethasone, 10⁻⁶ mol/L (nonasthma). Clear expression of mRNA of IL-5 and TNF-α was observed in the lungs of passively sensitized nonasthmatic patients who did not receive preoperative steroid therapy from 1 h after stimulation with mite antigen. In vitro dexamethasone treatment completely inhibited such expression. The expression of IL-5 or TNF-α mRNAs was not observed in the lungs of passively sensitized asthmatic patients who received preoperative steroid therapy ≥ 1 h after stimulation. P = positive control (cDNAs for IL-5, TNF-α, and β-actin from Clontech Laboratories, Palo Alto, CA); M = φ × 174/Hae; bp = base pair.
very low or undetectable in healthy subjects without atopy.22 These findings suggest that mast cells are the main source of the cytokines measured in this study. Identification of cytokine-producing cells by either in situ hybridization or in situ PCR is necessary in future studies.

In conclusion, we have demonstrated in the present study that preoperative corticosteroid therapy did not suppress histamine or LTE₄ production induced by specific allergen in lung tissues of asthmatic patients, but it significantly suppressed both IL-5 and TNF-α production. Our results suggest that corticosteroid prevents perioperative asthmatic attacks by suppressing the inflammatory cytokine production and, thus, alleviating AHR.

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