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Elevation of serum soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin levels in bronchial asthma

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SUMMARY

Adhesion molecules such as ICAM-1 and E-selectin have been shown to play important roles in the production of allergic inflammation. In the present study, we measured serum soluble ICAM-1 (sICAM-1) and soluble E-selectin (sE-selectin) levels by ELISA in 42 patients with bronchial asthma (22 atopic and 20 non-atopic) during asthma attacks and in stable conditions in order to assess the state of ICAM-1 and E-selectin in allergic inflammation. Both serum sICAM-1 levels and serum sE-selectin levels in sera obtained during bronchial asthma attacks were higher than those in sera obtained in stable conditions. These findings were observed regardless of atopic status. To examine the regulatory mechanism in the elevation of serum sICAM-1 and sE-selectin levels, serum tumour necrosis factor-alpha (TNF-α) levels were measured by ELISA. TNF-α levels in sera obtained during bronchial asthma attacks were higher than those in sera obtained in stable conditions. There was a correlation between the nature of change in serum TNF-α levels and the nature of change in serum sICAM-1 levels or serum sE-selectin levels, though serum TNF-α levels did not correlate with serum sICAM-1 levels or serum sE-selectin levels. These results suggest that higher levels of sICAM-1 and sE-selectin during asthma attacks may reflect the up-regulation of ICAM-1 and E-selectin expression in allergic inflammation, and that the soluble form of these adhesion molecules may be useful markers for the presence of allergic inflammation. TNF-α is shown to enhance the expression and release of ICAM-1 and E-selectin *in vitro*, however; the regulatory mechanism in the elevation of serum sICAM-1 and sE-selectin levels remains to be clarified.

Keywords bronchial asthma soluble ICAM-1 soluble E-selectin tumour necrosis factor-alpha

INTRODUCTION

Bronchial asthma is a disease that is characterized by an episode of reversible airway obstruction, airway hyperresponsiveness to exogenous and endogenous stimuli, and allergic inflammation in the airway [1]. Recent evidence indicates that a variety of cells such as eosinophils, neutrophils, mast cells, basophils, monocytes/macrophages, platelets and lymphocytes and their products have a potential for contributing to the feature of allergic inflammation [2,3]. In the allergic inflammatory response in the lung, circulating inflammatory cells accumulate in the pulmonary capillaries and migrate through the vascular endothelium to the submucosa of the asthmatic airway. A primary step of the infiltration of inflammatory cells into the submucosa of the asthmatic airway is the adherence of these cells to vascular endothelium, which is mediated by the interaction of adhesion molecules on these cells and their counter receptors on vascular endothelium [4].

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At the sites of allergic inflammation, increased expression of ICAM-1 and E-selectin on vascular endothelium and increased expression of ICAM-1 on bronchial epithelium have been demonstrated [5–9]. In addition, our preliminary study showed that serum sICAM-1 levels in 10 patients with bronchial asthma (five atopic and five non-atopic) were elevated during asthma attacks [10]. Direct evidence concerning the role for adhesion molecules in allergic inflammation has been shown by employing primate models [7–9]. Attenuation of the infiltration of eosinophils and neutrophils into the airway by antibodies to adhesion molecules resulted in the reduced infiltration of these cells and airway hyperresponsiveness. These results indicate that these adhesion molecules are up-regulated in allergic inflammation, and play a critical role in the pathogenesis of allergic inflammation.

In the present study, we made the levels of serum sICAM-1 more precise by increasing the numbers of the study population of bronchial asthma, and we also measured the levels of serum sE-selectin. This study attempted to analyse the change in serum sE-selectin levels as well as serum sICAM-1 levels during asthma attacks and in stable conditions to assess further the state of

allergic inflammation in bronchial asthma. If the levels of the soluble form of these adhesion molecules vary between patients with bronchial asthma during asthma attacks and those in stable conditions, it would be very useful to assess the state of allergic inflammation of this disease.

PATIENTS AND METHODS

Study population

The study group was comprised of 20 patients with atopic bronchial asthma (13 women and seven men) with a mean age of 38·4 years (range 20–65 years), 22 patients with non-atopic bronchial asthma (12 women and 10 men) with a mean age of 53·2 years (range 27–70 years), 25 normal subjects (14 women and 11 men) with a mean age of 34·8 years (range 24–46 years), and 18 patients with pneumonia (11 women and seven men) with mean age of 40·2 years. All patients with bronchial asthma met the American Thoracic Society's definition of asthma [1]. We emphasize that all asthmatic patients had a history of episodes of wheezes and dyspnoea, reversible bronchoconstriction, and airway hyperresponsiveness. All atopic asthmatic patients had a history of bronchoconstrictive response after allergen exposure, elevated total serum IgE levels (>250 U/ml), and elevated specific IgE levels against house dust mite (*Dermatophagoides farinea*) ($>0{\cdot}34$ PRU/ml) and/or positive skin prick tests to *D. farinea*. Non-atopic asthmatic patients generally had a history of post-infectious onset of bronchial asthma, no history of allergen-induced bronchospasms, and normal total IgE levels together with normal specific IgE levels against a standard set of allergens, and negative skin prick tests. At the time of this study, 26 patients (12 atopic and 14 non-atopic) were taking inhaled beclomethasone dipropionate (BDP) (200–400 μg/day), but none of the patients was taking oral corticosteroids. Asthma attacks and stable conditions (asymptomatic period) were defined on the basis of the presence of clinical symptoms such as wheeze and chest tightness, and/or values of peak expiratory flow rate (PEFR). The patients had wheeze and chest tightness, and/or decreased values of PEFR during asthma attacks, whereas they were asymptomatic and/or their PEFR values were greater than 70% of the predicted in stable conditions. Serial serum specimens were obtained during asthma attacks and in stable conditions. The healthy normal control subjects had no history of allergy and bronchial asthma, had normal total and specific IgE levels, and were not taking any medication. The patients with pneumonia (eight bacterial and 10 mycoplasmal) had symptoms such as fever, cough and pneumonic shadow on their chest radiogram. Eight patients were diagnosed bacterial pneumonia by sputum bacteriology and laboratory findings, including neutrophilia and elevated levels of C-reactive proteins. Ten patients were diagnosed mycoplasmal pneumonia by elevated antibody titres against *Mycoplasma pneumoniae*. Informed consent was obtained from all patients and normal control subjects.

Measurement of serum sICAM-1 levels

Double-determinant immunoassay (DDIA) using the FAST system (Becton Dickinson, Mountain View, CA) was employed in order to measure the levels of sICAM-1 in serum. This DDIA for measurement of sICAM-1 was developed by Imai *et al.*, as described elsewhere [11]. Two MoAbs (CL207 and HA58) which recognized different epitopes of ICAM-1 were used in DDIA. Briefly, the beads, attached to the lip of a 96-well microtitre plate, were first incubated with CL207 and then non-specific binding was blocked with PBS (pH 7·4) containing 3% bovine serum albumin (BSA) at 37°C for 2 h. Aliquots of serum samples diluted 1:200 in PBS were then incubated with the beads for 2 h. After being washed with PBS containing 0·05% Tween 20, the beads were incubated with biotinylated HA58 for 2 h. Avidin-conjugated peroxidase (Vector, Burlingame, CA) was diluted 1:1000 in 0·05 M PBS with 0·5 M NaCl pH 8·0, and incubated with the beads for 1 h. The degree of substrate reaction was determined with OPD at 492 nm in a Micro-ELISA Autoreader MR 580 (Dynatech, Cambridge, MA). Results were expressed as units (1 U correspondence to 2 ng/ml of purified antigen which was obtained from the supernatant of cultured pancreatic carcinoma Panc-1 cells) calculated from the titration curve of ICAM-1 antigen.

Measurement of serum sE-selectin and tumour necrosis factor-alpha levels

Serum levels of sE-selectin and tumour necrosis factor-alpha (TNF-α) were measured by commercially available ELISA kits (British Bio-Technology Products Ltd., Oxford, UK, and T Cell Sciences Inc., Cambridge, MA). ELISA was performed according to the manufacturers' instructions.

Percentage of decrease in serum sICAM-1, sE-selectin and TNF-α levels

The percentage of decrease in serum sICAM-1 levels between during asthma atacks and in stable conditions was calculated by the following equation:

$$\text{The percentage of decrease in serum sICAM-1 levels} = \frac{\text{serum sICAM-1 levels during asthma attacks} - \text{serum sICAM-1 levels in stable conditions}}{\text{serum sICAM-1 levels during asthma attacks}} \times 100$$

The percentage of decrease in serum sE-selectin and TNF-α levels was calculated by the same equation as described above.

Statistical analysis

Statistical significance was analysed using Mann–Whiteny *U*-test. Spearman's test was used for correlation analysis. $P<0{\cdot}05$ was considered significant.

RESULTS

Serum levels of sICAM-1

Sera from patients with atopic bronchial asthma during asthma attacks contained more sICAM-1 ($n=20$; $50{\cdot}7\pm20{\cdot}6$ U/ml (mean $\pm$ s.d.); median 46·0 U/ml (range 27·0–122·0 U/ml)) than those in stable conditions ($38{\cdot}3\pm9{\cdot}3$; 37·0 (25·0–58·0); $P<0{\cdot}05$) (Fig. 1a). Similar observations were obtained in patients with non-atopic bronchial asthma, i.e. sera from patients with non-atopic bronchial asthma during asthma attacks contained more sICAM-1 ($n=22$; $44{\cdot}3\pm9{\cdot}4$; median 43·5 (range 28·0–66·0)) than those in stable conditions ($36{\cdot}7\pm9{\cdot}0$; 38·0 (19·0–51·0); $P<0{\cdot}01$) (Fig. 1b). The mean percentage of decrease in serum sICAM-1 levels in atopic bronchial asthmatics and in non-atopic bronchial asthmatics was $21{\cdot}5\pm20{\cdot}2\%$ (range $-24{\cdot}2$–$72{\cdot}1\%$) and $15{\cdot}3\pm21{\cdot}5\%$ (range $-43{\cdot}2$–$55{\cdot}8\%$), respectively. The distribution of patients in the percentage of decrease in

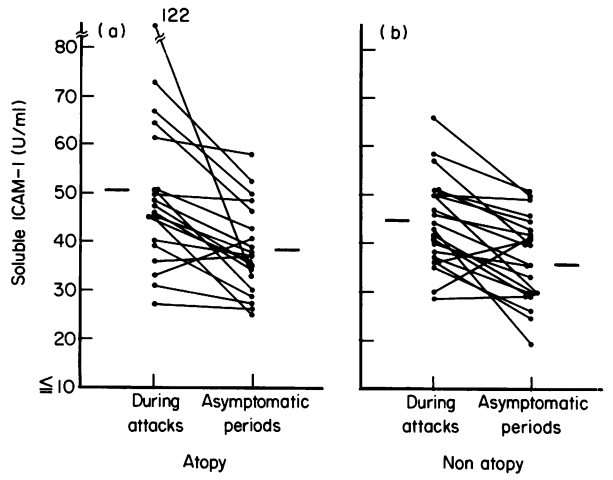

Fig. 1. Serum sICAM-1 levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum sICAM-1 levels in (a) patients with atopic bronchial asthma and (b) patients with non-atopic bronchial asthma during asthma attacks and in stable conditions were measured. Horizontal short lines represent mean of each group. Serum sICAM-1 levels in normal control subjects and non-asthmatic control subjects (patients with pneumonia) were 31·0±7·0 U/ml and 34·2±9·7 U/ml (mean±s.d.), respectively.

serum sICAM-1 levels is summarized in Table 1. A decrease of more than 10% in serum sICAM-1 levels was observed in 15/20 patients with atopic bronchial asthma and 13/22 patients with non-atopic bronchial asthma.

Serum levels of sE-selectin

Sera from patients with atopic bronchial asthma during asthma attacks contained more sE-selectin ($n=18$; 80·7±33·8 ng/ml; median 78·3 ng/ml (range 37·6–138·0 ng/ml)) than those in stable conditions (60·0±28·0; 51·8 (22·4–116); $P<0·05$) (Fig. 2a). Similar observations were made in non-atopic bronchial asthma: i.e. sera from patients with non-atopic bronchial asthma during asthma attacks contained more sE-selectin ($n=15$; 75·2±26·9 ng/ml; median 77·0 ng/ml (range 16·0–112·8 ng/ml)) than those in stable conditions (53·4±22·9; 48·0 (5·0–96·8); $P<0·05$) (Fig. 2b). The mean percentage of decrease in serum sE-selectin levels in atopic bronchial asthmatics and in non-atopic bronchial asthmatics was 25·0±18·2% (range −4·4–70·5%) and 30·0±17·2% (range 11·0–68·8%), respectively. The distribution of patients in the percentage of decrease in serum sE-selectin levels is summarized in Table 1. A decrease of more than 10% in serum sE-selectin levels was observed in 14/18 patients with atopic bronchial asthma and in all 15 patients with non-atopic bronchial asthma.

Serum levels of TNF-α

The expression and release of ICAM-1 and E-selectin from cell membrane are regulated by various cytokines such as TNF-α [12]. Therefore, it was of interest to measure the levels of TNF-α in sera obtained during asthma attacks and in stable conditions. Sera from patients with atopic bronchial asthma during asthma attacks contained more TNF-α ($n=14$; 71·0±52·1 pg/ml; median 59·3 pg/ml (range 20·9–227·3 pg/ml)) than those in stable conditions (27·9±16·3; 22·1 (10·3–63·3); $P<0·05$) (Fig. 3a). Similar observations were obtained in patients with non-atopic bronchial asthma: i.e. sera from patients with non-atopic bronchial asthma during asthma attacks contained more TNF-α ($n=15$; 74·5±40·8; median 69·4 pg/ml (range 26·7–159·0 pg/ml)) than those in stable conditions (33·5±19·0; 37·1 (<10·0–80·6); $P<0·01$) (Fig. 3b). The mean percentage of decrease in serum TNF-α levels in atopic bronchial asthmatics and in non-atopic bronchial asthmatics was 50·7±26·8% (range 3·2–89·2%) and 40·3±34·2% (range −14·9–100%), respectively. The distribution of patients in the percentage of decrease in serum TNF-α levels is summarized in Table 1. A decrease of more than 10% in serum TNF-α levels was observed in 13/14 patients with atopic bronchial asthma and 12/15 patients with non-atopic bronchial asthma.

Relationship between serum TNF-α levels and serum sICAM-1 levels or sE-selectin levels

No significant correlation between serum TNF-α levels and serum sICAM-1 levels was found in patients with atopic bronchial asthma ($r=-0·12$) or in patients with non-atopic bronchial asthma ($r=-0·27$) (Fig. 4a). Similarly, no significant correlation between serum TNF-α levels and serum sE-selectin levels was found in patients with atopic bronchial asthma ($r=-0·04$) or in patients with non-atopic bronchial asthma ($r=-0·04$) (Fig. 4b).

Serum levels of sICAM-1, sE-selectin and TNF-α in patients with bronchial asthma, normal control subjects and non-asthmatic control subjects (patients with pneumonia)

Serum levels of sICAM-1, sE-selectin and TNF-α in patients with bronchial asthma, normal control subjects and non-asthmatic control subjects (patients with pneumonia), and statistical difference in these factors between study groups are summarized in Table 2.

Serum levels of sICAM-1, sE-selectin and TNF-α in patients with bronchial asthma receiving inhaled BDP and those in patients with bronchial asthma not receiving inhaled BDP

Inhaled corticosteroids have been shown to be effective in controlling allergic inflammation in the asthmatic airway [13]. It was therefore of interest to compare serum levels of sICAM-1, sE-selectin and TNF-α in patients with bronchial asthma during asthma attacks who were receiving inhaled BDP with those in patients with bronchial asthma who were not receiving inhaled BDP. The results are summarized in Table 3. There was no significant difference between them in the levels of the soluble form of these adhesion molecules and TNF-α.

DISCUSSION

Our results show that the levels of sICAM-1, sE-selectin and TNF-α in sera from patients with bronchial asthma obtained during asthma attacks were higher than those in sera in stable conditions. These findings were obtained regardless of atopic status. Our results with the elevation of serum sICAM-1 and sE-selectin levels during asthma attacks may reflect the up-regulation of these adhesion molecules in allergic inflammation, since increased expression of ICAM-1 on vascular endothelium and bronchial epithelium, and increased expression of E-selectin on vascular endothelium at the sites of allergic inflammation have been demonstrated in allergic diseases and animal models of allergy [5–9]. It would be very useful to determine the

Table 1. Distribution of patients in the percentage decrease in serum sICAM-1, sE-selectin and tumour necrosis factor-alpha (TNF-α) levels

	Number of patients					
	sICAM-1		sE-selectin		TNF-α	
Per cent decrease	Atopy	Non-atopy	Atopy	Non-atopy	Atopy	Non-atopy
≦10	5	9	4	0	1	3
11–20	4	5	3	4	1	2
21–30	7	4	5	7	1	1
31–40	1	2	4	1	2	1
41≦	3	2	2	3	9	8

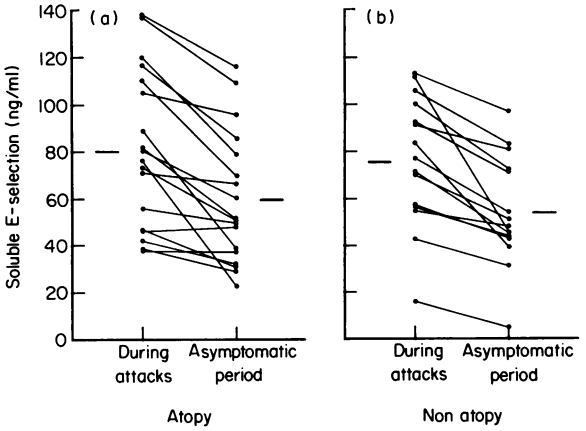

Fig. 2. Serum sE-selectin levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum sE-selectin levels in (a) patients with atopic bronchial asthma and (b) patients with non-atopic bronchial asthma during asthma attacks and in stable conditions were measured. Horizontal short lines represent mean of each group. Serum sE-selectin levels in normal control subjects and non-asthmatic control subjects (patients with pneumonia) were 34·1±18·0 ng/ml and 28·9±12·3 ng/ml (mean+s.d.), respectively.

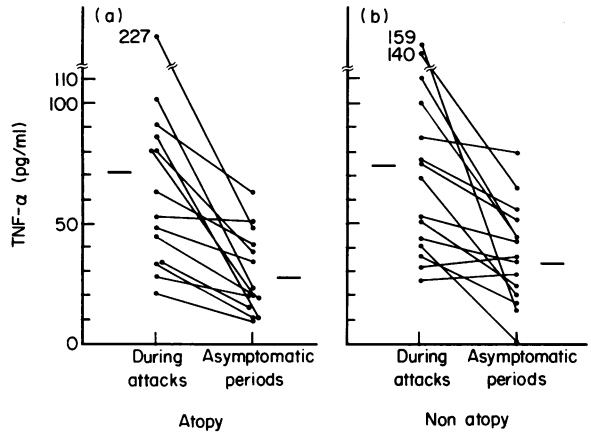

Fig. 3. Serum tumour necrosis factor-alpha (TNF-α) levels in patients with bronchial asthma during asthma attacks and in stable conditions. Serum TNF-α levels in (a) patients with atopic bronchial asthma and (b) patients with non-atopic bronchial asthma during asthma attacks and in stable conditions were measured. Horizontal short lines represent mean of each group. Serum TNF-α levels in normal control subjects and non-asthmatic control subjects (patients with pneumonia) were 24·2±9·8 pg/ml and 33·9±11·5 pg/ml (mean±s.d.), respectively.

magnitude of change that would appear to be significant in clinical practice. Increasing the number of subjects would answer this important question. The elevation of serum sICAM-1 levels has been shown in several diseases [14–17]. More recently, Newman *et al.* [18] have shown that serum sE-selectin levels were elevated in patients with septic shock. In the present study we extended our earlier study by measuring the levels of sE-selectin as well as sICAM-1. To our knowledge, this is the first report on the detection of sE-selectin in sera of patients with bronchial asthma.

Vascular endothelial cells are thought to be important sources of serum sICAM-1 and sE-selectin, and TNF-α and IL-1 are known to enhance the expression and release of ICAM-1 and E-selectin from human umbilical endothelial cells (HUVEC) [12]. We therefore examined whether these cytokines could contribute to the elevation of serum sICAM-1 and sE-selectin levels during asthma attacks. The levels of serum TNF-α in patients with bronchial asthma were elevated during asthma attacks, and were decreased in stable conditions to levels comparable to normal control subjects. The nature of change in serum TNF-α levels was similar to the results where serum

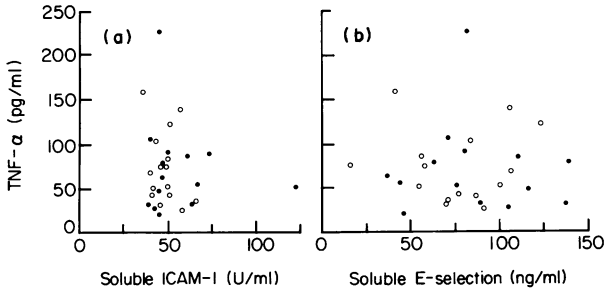

Fig. 4. Relationship between serum tumour necrosis factor-alpha (TNF-α) levels and serum sICAM-1 levels or serum sE-selectin levels. (a) Relationship between serum TNF-α levels and serum sICAM-1 levels was analysed in 14 patients with atopic bronchial asthma (●) and in 15 patients with non-atopic bronchial asthma (○). (b) Relationship between serum TNF-α levels and serum sE-selectin levels was analysed in 14 patients with atopic bronchial asthma (●) and in 15 patients with non-atopic bronchial asthma (○).

Table 2. Serum levels of sICAM-1, sE-selectin and tumour necrosis factor-alpha (TNF-α) in patients with bronchial asthma, normal control subjects and non-asthmatic subjects (pneumonia)

	Atopic asthmatics		Non-atopic asthmatics			
Factors	Attack (+)	Attack (−)	Attack (+)	Attack (−)	Normal controls	Pneumonia
sICAM-1	46·0***†† (27·0–122·0)	37·0** (25·0–58·0)	43·5***†† (28·0–66·0)	38·0* (19·0–51·0)	31·0 (18·0–49·0)	33·0 (18·0–48·0)
sE-selectin	78·3***†† (37·6–138·0)	51·8**†† (22·4–116·0)	77·0**†† (16·0–112·8)	48·0**†† (5·0–96·8)	28·4 (10·0–73·6)	26·2 (12·2–52·2)
TNF-α	59·3**† (20·9–227·3)	22·1 (10·3–63·3)	69·4***†† (26·7–159·0)	37·1 (< 10·0–80·6)	24·4 (< 10·0–42·4)	33·1 (< 10·0–52·4)

Results are expressed as median values (range).
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ compared with normal controls.
†$P < 0.05$; ††$P < 0.01$ compared with patients with pneumonia.

Table 3. Serum levels of sICAM-1, sE-selectin and tumour necrosis factor-alpha (TNF-α) in patients with bronchial asthma receiving inhaled beclomethasone dipropionate (BDP) and those in patients with bronchial asthma not receiving inhaled BDP

	Atopic asthmatics		Non-atopic asthmatics	
Factors	BDP (+)	BDP (−)	BDP (+)	BDP (−)
sICAM-1	45·0 ($n = 12$; 33·0–73·0)	48·5 ($n = 8$; 27·0–122·0)	44·0 ($n = 14$; 28·0–66·0)	43·5 ($n = 8$; 35·0–57·0)
sE-selectin	80·1 ($n = 12$; 37·6–138·0)	78·3 ($n = 6$; 42·0–110·0)	70·5 ($n = 10$; 16·0–106·0)	100·4 ($n = 5$; 42·2–112·8)
TNF-α	48·6 ($n = 9$; 20·9–107·0)	86·0 ($n = 5$; 53·4–227·3)	46·2 ($n = 10$; 26·7–85·4)	123·0 ($n = 5$; 53·3–159·0)

Results are expressed as median values (number; range).

sICAM-1 and sE-selectin levels were elevated during asthma attacks and were decreased in stable conditions. Furukawa *et al.* [15] have found a significant correlation between serum sICAM-1 levels and serum TNF-α levels during the acute stage of Kawasaki disease. Taking their observations and ours into account, it was of interest to determine whether there was any association of serum TNF-α levels either with serum sICAM-1 levels or serum sE-selectin levels. There was a correlation between the nature of change in serum TNF-α levels and the nature of change in serum sICAM-1 levels or the serum E-selectin levels, but serum TNF-α levels correlated neither with serum sICAM-1 levels nor with serum sE-selectin levels. In addition to determination of serum TNF-α levels, we also measured the levels of serum IL-1β, since IL-1 has been shown to regulate expression and release of ICAM-1 and E-selectin from HUVEC [12]. However, the levels of serum IL-1β were below the limits of reliable assay sensitivity. Other factors such as bacterial infection might be considered to contribute to the elevation of serum sICAM-1 and sE-selectin levels, since bacterial products such as endotoxin induce the expression and release of ICAM-1 and E-selectin from HUVEC [12]. However, this possibility can be excluded, since serum sICAM-1 levels in patients with bacterial pneumonia [14] and serum sE-selectin levels in patients with bacteraemia [18] were not elevated, and our patients with bronchial asthma in the present study had no evidence of bacterial infection assessed by clinical symptoms, neutrophil counts and examination of C-reactive proteins. Inflammatory stimuli and cytokines such as TNF-α and IL-1 are known to enhance the expression and release of ICAM-1 and E-selectin from HUVEC [12]. However, the regulatory mechanisms involved in the elevation of serum sICAM-1 and sE-selectin during asthma attacks and a potential source of these adhesion molecules remain to be clarified.

Functional activities of sICAM-1 have been investigated [19,20]. Soluble ICAM-1 has been shown to inhibit the natural killer cell and lymphokine-activated lymphocyte activities [19]. This is presumably mediated by inhibition of adherence by competition. Soluble ICAM-1 released into serum of bronchial asthma patients during asthma attacks may compete with membrane ICAM-1 on vascular endothelium for its ligand CD11a/CD18 on eosinophils and neutrophils, and thus prevent adherence of these cells to vascular endothelium and subsequent infiltration into the asthmatic airway. Similarly, sE-selectin released into serum may compete with membrane E-selectin for its ligand Sialy Lewis X on neutrophils, and thus prevent the adherence of neutrophils to vascular endothelium and sub-

sequent infiltration into the asthmatic airway. Together with an inhibitory effect of sE-selectin on neutrophil adherence to vascular endothelium, this molecule has been shown to activate a neutrophil function [21]. It is postulated that sICAM-1 and sE-selectin may have these functional activities, but further studies are needed to clarify the precise function of the soluble form of these adhesion molecules in allergic inflammation.

Finally, we compared serum levels of sICAM-1, sE-selectin and TNF-α in patients during asthma attacks who were receiving inhaled BDP with those in patients who were not receiving inhaled BDP. There was no significant difference in the levels of the soluble form of these adhesion molecules and TNF-α. We are currently examining a dosage effect of inhaled BDP on serum sICAM-1 and sE-selectin levels.

In conclusion, our study demonstrated the elevation of serum sICAM-1 and sE-selectin levels in patients with bronchial asthma during asthma attacks. These results suggest that higher levels of serum sICAM-1 and sE-selectin may reflect the up-regulation of ICAM-1 and E-selectin expression in allergic inflammation, and that the soluble forms of these adhesion molecules may be useful markers for the presence of allergic inflammation.

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