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Abstract

Immunoallergological studies were carried out to clarify the differences between 24 patients with drug-induced asthma (DIA) and 240 with non-drug-induced asthma (non-DIA). The mean values of age, skin reaction to *Candida albicans* (*C. albicans*), serum IgE levels, specific IgE antibodies to house dust (HD) and *C. albicans*, bronchial sensitivity and leukotriene B₄ (LTB₄) synthesis from peripheral venous blood in patients with DIA were not significantly different from those in patients with non-DIA. In contrast, the frequency of positive skin reaction to HD and histamine release from peripheral basophils by anti-IgE were significantly lower in DIA than in non-DIA. These results agree with the reports that DIA was often observed in non-atopic asthma. But, the mean value of serum IgE was very high in DIA as well as in non-DIA. This result suggests that IgE mediated reaction in DIA is important. Furthermore, the proportion of neutrophils in bronchoalveolar lavage fluid (BALF) was significantly lower in DIA than in non-DIA. Our findings suggest that a decrease of intrapulmonary neutrophils might play an important role in the pathophysiology of DIA.

KEYWORDS: drug allergy, aspirin-induced asthma. IgE-mediated reaction, chemical mediator, bronchoalveolar lavage

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IgE-Mediated Allergic Reaction in Drug-Induced Asthma

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Immunoallergological studies were carried out to clarify the differences between 24 patients with drug-induced asthma (DIA) and 240 with non-drug-induced asthma (non-DIA). The mean values of age, skin reaction to *Candida albicans* (*C. albicans*), serum IgE levels, specific IgE antibodies to house dust (HD) and *C. albicans*, bronchial sensitivity and leukotriene B₄ (LTB₄) synthesis from peripheral venous blood in patients with DIA were not significantly different from those in patients with non-DIA. In contrast, the frequency of positive skin reaction to HD and histamine release from peripheral basophils by anti-IgE were significantly lower in DIA than in non-DIA. These results agree with the reports that DIA was often observed in non-atopic asthma. But, the mean value of serum IgE was very high in DIA as well as in non-DIA. This result suggests that IgE mediated reaction in DIA is important. Furthermore, the proportion of neutrophils in bronchoalveolar lavage fluid (BALF) was significantly lower in DIA than in non-DIA. Our findings suggest that a decrease of intrapulmonary neutrophils might play an important role in the pathophysiology of DIA.

Key words : drug allergy, aspirin-induced asthma, IgE-mediated reaction, chemical mediator, bronchoalveolar lavage

While aspirin is useful as a non-steroidal anti-inflammatory drug, it has some adverse reactions. In patients with bronchial asthma, it has been reported that symptoms of an asthmatic attack were provoked by the administration of aspirin (1, 2), and asthmatic patients sensitive to aspirin have been diagnosed as having aspirin-induced asthma (AIA). It has been reported that tartrazine, reactive yellow 4, hydrocortisone succinate and other drugs can elicit asthmatic symptoms (3-5). Therefore, we defined the patients with bronchial asthma who were sensitive to analgesics, artificial dyes, corticosteroids and other drugs, as having drug-induced asthma (DIA).

Immunoallergological analysis of IgE mediated reaction and bronchoalveolar lavage (BAL) were carried out in patients with bronchial asthma to examine some

differences between DIA and non-DIA.

Subjects and Methods

Subjects. This is a retrospective study carried out in January 1990. There were 264 subjects (126 females and 138 males) with a mean age of 42.4 years (range, 4-85 years) treated in Misasa Branch Hospital in this study. Asthmatic patients who had a typical history of asthma attacks induced by non-steroidal anti-inflammatory drugs, artificial dyes, steroid hormones or other drugs that usually did not elicit asthmatic attack were defined as DIA in this study. Asthmatics who had never experienced such an asthmatic attack were defined as non-DIA in this study. The cases whose history of asthma attacks induced by some drugs was unclear were excluded in this study.

Skin test. Skin tests were performed on the volar surface of the forearm by intradermal injection of 0.02 ml 1:10³ HD and 1:10⁴ *C. albicans* dilution (w/v) of allergen extracts. Evaluations of

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skin tests were made after 20 min. Wheals greater than 9 mm and flares greater than 20 mm were recorded as positive reactions.

IgE and specific IgE. Serum levels of total IgE were measured by a Pharmacia RIA kit and specific IgE antibodies to HD and *C. albicans* were measured by a Pharmacia RAST RIA kit.

Bronchial sensitivity. Bronchial sensitivity to methacholine was measured by the astograph method. The result was expressed as a respiratory threshold to methacholine, C_{min} (6).

Histamine release. Histamine release from basophilic leucocytes induced by anti-IgE was examined by the method described by Tanizaki *et al.* previously (7, 8). The results were expressed as a percentage of the total histamine content.

Leukotriene B_4 synthesis. Neutrophils-rich fraction was separated from peripheral leukocytes by counterflow centrifugation elutriation with a JE-6B rotor (Beckman). Then, the neutrophils-rich fraction was adjusted to 5×10^6 cells/ml in Tris-ACM. One μ g of Ca-ionophore A23187 was added into 1 ml of the cell suspended solution. The sample was incubated at 37°C for 15 min, and added to 4 ml of 100% ethanol. After being centrifuged, the supernatant was analyzed by high performance liquid chromatography (HPLC). The sample was vacuum dried and resuspended in 250 μ l of HPLC solvent ($CH_3CN/H_2O = 1:1$). The resuspended solution was applied to HPLC (C-18 reversed phase column, detection 280 nm) and LTB_4 was assayed (9).

Bronchoalveolar lavage. Bronchoalveolar lavage was performed when patients were free of symptoms. Informed consent for BAL examination was obtained from all the subjects. The bronchoalveolar lavage fluid (BALF) taken by a bronchofiberscope and filtered through sterile steel mesh was centrifuged at 1200 rpm for 10 min at 4°C, and the cell pellet was resuspended in Tris-ACM. Smear preparations were made using cell suspension. The slide were air-dried and stained with May Giemsa for a differential cell count. Analysis of cellular composition in the BALF was performed by differentiating 500 cells. In the BAL cytological analysis, basophilic leucocytes and mast cells were assessed as basophilic cells (10).

Statistical analysis. The Student's *t* test was used for comparing DIA with non-DIA, and results of skin test and

radioallergosorbent test (IgE RAST) were analyzed by χ^2 test.

Results

Twenty-four cases (14 females and 10 males) with a mean age of 48.3 ± 17.4 years (range, 13-67) were diagnosed as having DIA of asthma attacks, including 18 cases (10 females and 8 males) of AIA. In this study, as was seen in previous reports, middle-aged female cases predominated, but there was no significant difference in the mean values of patient age between DIA and non-DIA (41.8 ± 23.6 years) (11).

It is regrettable that the majority of the patients studied here did not consult otorhinolaryngologists, so we were unable to conduct precise comparisons of their nasal symptoms.

Table 1 Immediate skin reaction to house dust and *Candida albicans* in drug-induced asthma (DIA) and non-DIA

Antigen	Number of patients showing positive skin test/Total (%)	
	DIA	Non-DIA
House dust	7/24 (29.2)	118/204 (57.8)*
<i>Candida albicans</i>	10/23 (43.5)	81/167 (48.5)

*Significantly different between DIA and non-DIA ($p < 0.02$).

Table 2 Serum IgE in drug-induced asthma (DIA) and non-DIA

Types of asthma	No. of Cases	Serum IgE (IU/ml)
DIA	24	697 ± 1511
Non-DIA	233	700 ± 1053

Table 3 Specific IgE antibodies to house dust and *Candida albicans* in drug-induced asthma (DIA) and non-DIA

Antigen	Types of asthma	Number of patients					Positive/Total (%)
		RAST score					
		0+	1+	2+	3+	4+	
House dust	DIA	13	0	4	2	0	6/19 (31.6)
	Non-DIA	96	8	19	67	16	102/206 (49.5)
<i>Candida albicans</i>	DIA	20	0	4	0	0	4/24 (16.7)
	Non-DIA	165	13	16	4	0	20/198 (10.1)

0+~1+: Negative; 2+~4+, Positive.

RAST: Radioallergosorbent test.

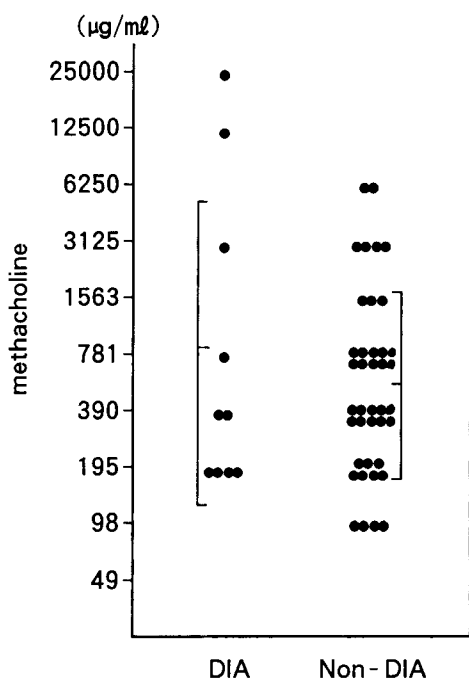


Fig. 1 Bronchial sensitivity (respiratory threshold to methacholine) by astograph in drug-induced asthma (DIA) and non-DIA.

Skin test. Immediate skin reaction to HD was examined in 228 patients with asthma. The DIA group had half the frequency of positive reaction to HD extract as the non-DIA group, a significant difference. However, there was no significant difference in skin reaction to *C. albicans* in the 190 tested out of 264 (Table 1).

IgE and specific IgE. The results of the study of serum IgE in 257 patients with asthma showed no significant difference between 24 cases of DIA and 233 cases of non-DIA (Table 2).

Specific IgE antibodies to HD were examined in 225 subjects. The percentage of RAST-positive cases to HD was 31.6 in the DIA group, and 49.5 in the non-DIA group. The RAST score for *C. albicans* was examined in 222 cases. RAST-positive cases to *C. albicans* were 16.7 % in the DIA group, and 10.1 % in the non-DIA group. There was no significant difference between the groups (Table 3).

Bronchial sensitivity. Bronchial sensitivity was studied in only 50 asthmatics. The mean value of the respiratory threshold to methacholine, using logarithmic

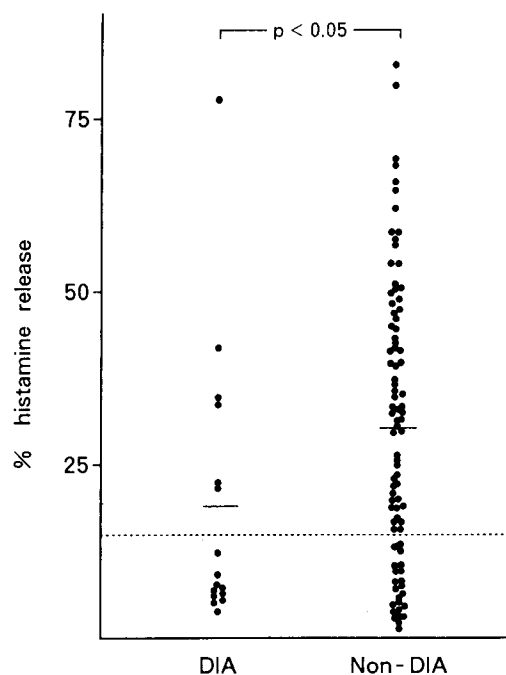


Fig. 2 Histamine release from basophils in drug-induced asthma (DIA) and non-DIA. Broken line represents 15 %. Histamine release more than 15 % was judged as significant.

analysis, was $1016 \mu\text{g}/\text{ml}$ in 10 cases of DIA and $452 \mu\text{g}/\text{ml}$ in 40 cases of non-DIA (Fig.1).

Histamine release. Histamine release from basophils by anti-IgE was carried out in 108 subjects. The mean value of histamine release was $19.3 \pm 20.2 \%$ in 16 cases of DIA and $31 \pm 20.3 \%$ in 92 cases of non-DIA. A significant amount of histamine (more than 15 %) was released in 6 cases (37.5 %) of DIA, and 68 cases (73.8 %) of non-DIA. Patients with large amounts of histamine release were more numerous in non-DIA than in DIA (Fig. 2).

Leukotriene B_4 synthesis. LTB_4 synthesis from peripheral leukocytes was measured in 59 asthmatics. The mean value of LTB_4 was $32.4 \pm 14.8 \text{ ng}/10^6$ cells in patients with DIA, and $37.6 \pm 25.7 \text{ ng}/10^6$ cells in those with non-DIA. There was no significant difference between the two groups (Fig. 3).

Bronchoalveolar lavage. BAL was carried out in 74 cases. The proportion of neutrophils in the BAL was $2.3 \pm 2.3 \%$ in DIA and $7.1 \pm 15.9 \%$ in non-DIA, a significant difference. The results of the tests of the other

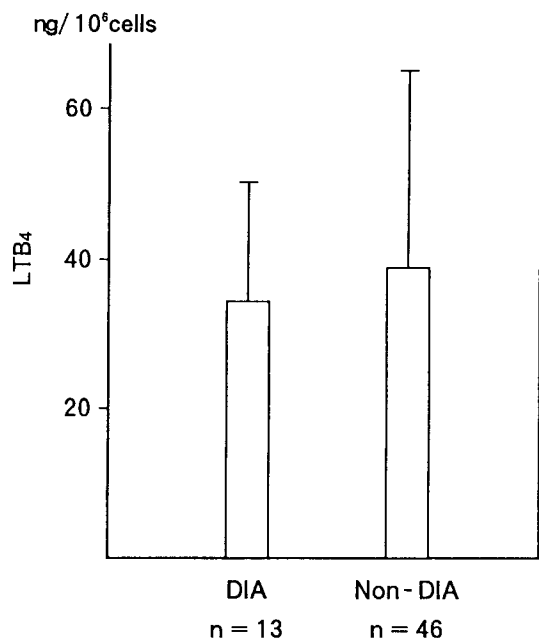


Fig. 3 Leukotriene B₄ synthesis from peripheral leucocytes in drug-induced asthma (DIA) and non-DIA.

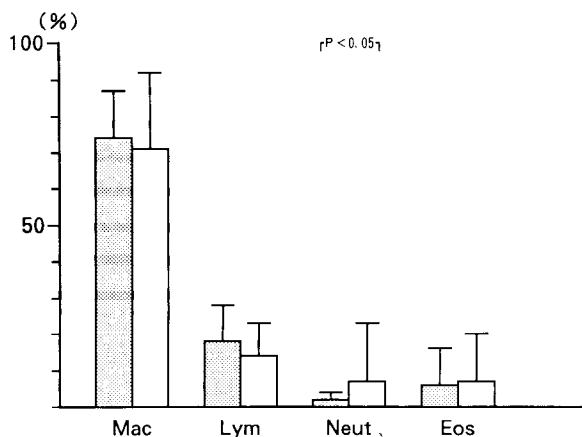


Fig. 4 Cellular components of the bronchoalveolar lavage fluid (BALF) of drug-induced asthma (DIA) (hatched bars; n = 14) and non-DIA (white bars; n = 60). Mac, Macrophages; Lym, lymphocytes; Neut, neutrophils; Eos, eosinophils.

cell components in BALF showed no difference between them (Fig. 4).

Discussion

It has been reported that AIA often appears in middle-aged, non-atopic and female subjects, and has often been associated with nasal polyps (2, 11).

Exposure to several chemicals, artificial dyes and some drugs, that are structurally unrelated to aspirin can induce "aspirin-like" reactive symptoms. The structural dissimilarity of those compounds is so obvious that immunological cross-reactivity appears unlikely (11, 12-14). We defined both AIA and the bronchial asthma induced by some chemicals or drugs as "drug-induced asthma", and studied it immunoallergologically.

The DIA group had a lower frequency of positive skin reaction to HD, and a smaller amount of histamine release than did the non-DIA group. There were no differences between the groups in production of serum IgE and specific IgE antibodies to HD and *C. albicans*. However, the mean value of serum IgE was very high in DIA and non-DIA specimens. This result suggests that IgE mediated reaction in DIA is important, and some non-atopic asthmatic responses were observed in DIA.

There was no difference between the two groups in terms of bronchial sensitivity, which confirms other reports on AIA (15).

Although there was no difference of LTB₄ synthesis from peripheral neutrophils between DIA and non-DIA in this study, it might be necessary to extend this evaluation to other leukotrienes.

The proportion of neutrophils in the BAL was 2.3% in DIA, and 7.1% in non-DIA. There was a significant difference between the two groups, although no difference was found in the analyses of macrophages, lymphocytes, eosinophils or basophilic cells.

The mechanism of adverse reaction to aspirin and some other anti-inflammatory drugs remains unknown. In 1971, Vane found that indomethacin and aspirin inhibit prostaglandin biosynthesis, and postulated that aspirin-like drugs exert their anti-inflammatory effects through this mechanism of action (16). Subsequently, Szczeklik *et al.* attributed the acute asthmatic attack in aspirin-sensitive patients to the inhibition of prostaglandin biosynthesis (17). The most common theory to explain the mechanism of AIA is that the asthma attack is elicited

as a result of the increase of SRS-A by the activation of the lipoxygenase pathway following the inhibition of cyclooxygenase (18). In 1990, Ameisen *et al.* reported that in the presence of aspirin, platelets from aspirin-sensitive asthmatics released free oxygen radicals, and assumed that this phenomenon was related to cyclooxygenase inhibition (19). Recently, Guez *et al.* reported aspirin diminished the lymphocyte proliferative factors from aspirin-sensitive asthmatics (20).

Although we cannot find any direct correlation between the above-mentioned data and the decrease of the BAL neutrophils in the DIA specimens, it is almost certain that neutrophils of the airway play an important role in the pathophysiological mechanisms of DIA. There might be a possibility that a decrease in quality and quantity of specific cytokines released from BAL neutrophils elicited asthmatic attack. Therefore, we need to pay more attention to chemical mediators and cytokines released or synthesized from intrapulmonary neutrophils.

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