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Spa therapy and bronchial hyperresponsiveness associated with cigarette smoking in asthmatics in the elderly

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Abstract : Clinical effects of spa therapy were examined in 60 elderly asthmatics in comparison between ex-smokers with a long history of cigarette smoking more than 20 years and never-smokers. Spa therapy was effective in 47 of the 60 subjects (78.4%) with asthma. Ragarding the influence of cigarette smoking, the therapy was effective in 16 of the 24 asthmatics (66.7%) with a long history of cigarette smoking. In contrast, the therapy was effective in 31 of the 36 asthmatics (86.1%) without smoking history. The spa efficacy was significantly larger in asthmatics without smoking history than those with ($p<0.05$). There was no significant correlation between spa efficacy and IgE-mediated reactions. Bronchial hyperresponsiveness was significantly higher in subjects with slight or no efficacy of spa therapy than in those with marked and moderate efficacy both in ex-smokers and never-smokers as well as in total subjects. The generation of leukotriene B4 (LTB4) by leucocytes was significantly increased in subjects with slight or no efficacy of spa therapy than in those with marked and moderate efficacy in total subjects and in those with smoking history, but not in those without smoking history. The generation of leukotriene C4 (LTC4) by leucocytes was not significantly correlated with spa efficacy in total subjects, and also either in ex-smokers or never-smokers. The results demonstrate that clinical effects of spa therapy are influenced by long-term cigarette smoking, which increases bronchial hyperresponsiveness and the generation of LTB4 by leucocytes.

Key words : cigarette smoking, spa therapy, elderly asthmatics, bronchial hyperresponsiveness

Introduction

Cigarette smoking as well as aging influences the pathophysiology of asthma in the elderly[1-3]: cigarette smoking increases immunoglobulin (Ig) E-mediated allergy, bronchial hyperresponsiveness, and generation of leukotriene B4 (LTB4), but not leukotriene C4 (LTC4). Cigarette smoking increases the inflammatory burden of the lower respiratory tract through a number of related, but separate mechanisms. These include the recruitment of increased numbers of inflammatory cells, alteration in cell sub-types, enhancement of some cellular functions, and pro-inflammatory mediator release[5]. Exposure to cigarette smoke increases sensitization to food allergens in the few years of life[6], but not associated with sensitization to inhaled allergens[7]. However, cigarette smoke exposure enhances existing symptoms of allergic airway reactions such as bronchial hyperresponsiveness[8].

Cigarette smoking is also known to be closely related to the onset mechanisms of chronic obstructive pulmonary disease[9,10]. An association between smoke exposure and the induction[11] or exacerbation of asthma has been reported[12].

Regarding adult asthma, a recent case-control study showed that adult onset of asthma was not associated with a history of smoking[8]. In contrast, current smoking has been shown to increase asthma severity[13], and higher incidences of asthma are found in current and former smokers, compared with never-smokers[14-16].

It has been shown that spa therapy is effective in patients with asthma[17-25], even in asthmatics with an increased low attenuation area (LAA) of the lungs on high resolution computed tomography (HRCT) and an increase in residual volume[26-28], as well as in those with pulmonary emphysema[29-31]. However, the influence of cigarette smoking on effects of spa therapy for elderly asthmatics still remains unclear.

In the present study, the influence of cigarette smoking on effects of spa therapy for asthmatics in the elderly was examined in relation to IgE-mediated allergy, bronchial hyperresponsiveness and generation of LTB4 and LTC4 by leucocytes.

Subjects and Methods

The subjects of this study was 60 patients with asthma (26 females and 34 males). Their age was all over 65 years (mean age 71.4 years). Twenty four of them had a long history of cigarette smoking more than 20 years (mean 41.4 pack-year). All of them were ex-smokers, and residual 36 were never-smokers. All subjects had spa therapy including swimming training in a hot spring pool[18,32], fango therapy and inhalation with iodine salt solution[33] at Misasa Medical Center for 1-3 months. The efficacy of spa therapy was evaluated by comparing their symptoms and pulmonary function before and after the therapy. The efficacy was assessed in four degrees, marked, moderate, slight and no efficacy. The efficacy was evaluated to be effective for subjects with marked and moderate efficacy.

Serum IgE level was measured by immunosorbent test (RIST), and IgE antibodies against inhalant allergens including house dust mite, pollens, moulds, and animal danders were measured using the Pharmacia CAP system (Pharmacia Diagnostic AB, Upsalla, Sweden).

Bronchial hyperresponsiveness to methacholine was measured by an Astograph (TSK6100, Chest Co.) before spa therapy. Different concentration of methacholine (49, 98, 195, 390, 781, 1563, 3125, 6250, 12,500 and 25,000 μg/ml) were prepared for bronchial challenge according to the method used by Chai et al.[34].

The increase of total respiratory resistance (Rrs) after methacholine inhalation was measured by the oscillation method. A methacholine concentration causing significant increase in Rrs was assessed as Cmin (minimum concentration). All medications were stopped 12 hours prior to examination.

The generation of LTB4 and LTC4 by the peripheral leucocytes was assessed as previously described[35-37]. Five milliliters of 6 % dextran (molecular weight −200,000 kDa) (Nacalai Teque., Inc, Kyoto) were added to 20 ml of heparinized peripheral blood, and the mixture was left for 1 hour at room temperature. The leucocytes-rich plasma supernatant was then removed and used. The number of cells was adjusted to $5x10^6$ cells/ml in Tris CM, and 1 μg of calcium ionophore A 23187 (Sigma, St Louis, Mo, USA) was then added to the cell suspension. The solution was mixed and incubated for 15 minutes at 37℃. After a 4x volume of pre-chilled ethanol (final, 80% ethanol) was added. This was centrifuged at 3,000 rpm for 30 minutes. The filtrate through a syringe filter (Toyo Roshi Co., Tokyo) was decompressed and dried to solid. LTB4 and LTC4 were quantified by means of high-performance liquid chromatography, as described by Lam et al.[38]. Quantities of LTB4 and LTC4 were expressed as nanogram per $5x10^6$ cells.

Statistically significant differences of the mean were estimated using the unpaired Student's t test and χ^2 test. A p value of <0.05 was regarded as significant.

Results

The clinical effects of spa therapy were observed in 47 of the 60 elderly asthmatics (10 patients with marked efficacy and 37 with moderate). The efficacy rate was 78.4%. The efficacy of spa therapy was found in 16 of the 24 patients with smoking history (4 with marked efficacy and 12 with moderate, efficacy rate 66.7%). In contrast, the efficacy was observed in 31 of the 36 patients without smoking history (6 with marked efficacy and 25 with moderate, efficacy rate 86.1%). The efficacy rate of spa therapy was significsantly higher in patients without a history of smoking than in those with a long history of smoking ($p<0.05$) (Fig. 1).

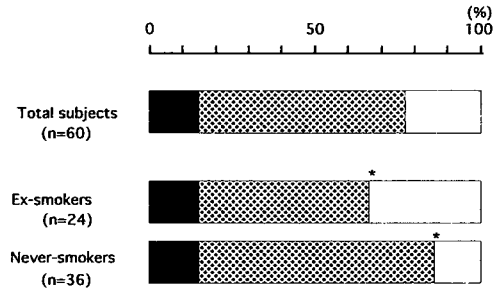

Fig.1. Clinical effects of spa therapy for asthmatics in the elderly. (■): marker efficacy, (▨): moderate efficacy, and (□): slight or no efficacy. *p<0.05.

Serum IgE level was not significantly correlated with the efficacy of spa therapy in total subjects and either in ex-smokers or never-smokers (Table 1).

Table 1. Clinical effects of spa therapy and serum IgE level in asthmatics in the elderly

	Clinical efficacy		
	Marked	Moderate	slight or no
Total subjects	571* (47-2929)	227 (2-2918)	399 (2-2350)
Ex-smokers	921 (20-2929)	334 (9-1480)	500 (19-2350)
Never-smokers	337 (160-880)	323 (9-2918)	222 (54-461)

*IU/ml

The number of patients with a positive RAST score against inhalant allergens was not significantly different among subjects with marked, moderate, and slight or no efficacy. However, the frequency of patients showing a positive RAST score was significantly higher in ex-

smokers than in never-smokers of patients with moderate efficacy (Table 2).

Table 2. Clinical effects of spa therapy and specific IgE antibodies against inhalant allergens in asthmatics in the elderly

	Clinical efficacy		
	Marked	Moderate	slight or no
Total subjects	6/10 * (60.0%)	23/37 (62.2%)	8/13 (61.5%)
Ex-smokers	3/4 (75.0%)	11/12 [a] (91.7%)	6/8 (75.0%)
Never-smokers	3/6 (50.0%)	12/25 [a] (48.0%)	2/5 (40.0%)

*No of patients with a positive RAST score against inhalant allergens. a:p<0.05.

Bronchial hyperresponsiveness to methacholine was significantly larger in patients with slight or no efficacy compared with that in those with marked ($p<0.001$) and moderate efficacy ($p<0.001$) in all subjects. The hyperresponsiveness was also significantly higher in subjects with slight or no efficacy than in subjects with marked and moderate efficacy in each group of ex-smokers and never-smokers. Furthermore, bronchial hyperresponsiveness was significantly higher in patients with a history of smoking than in those without in subjects with moderate efficacy ($p<0.02$) (Table 3). The responsiveness tended to decrease as clinical effects of spa therapy became predominant (Fig. 2).

Table 3. Bronchial hyperresponsiveness to methacholine and clinical effects of spa therapy in asthmatics in the elderly

	Clinical efficacy		
	Marked	Moderate	slight or no
Total subjects	1269 [*a] (±810)	1612 [b] (±1659)	276 [ab] (±191)
Ex-smokers	828 [c] (±563)	659 [dg] (±469)	168 [cd] (±101)
Never-smokers	1562 [e] (±856)	2070 [fg] (±1834)	308 [ef] (±290)

*Methacholine concentration (μg/ml). a and b: p<0.001, c and d: p<0.01, e: p<0.02, f: p<0.05, g: p<0.02.

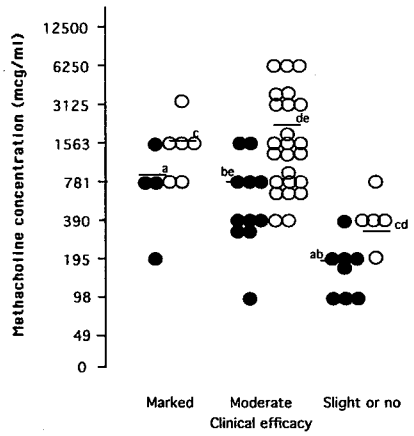

Fig.2. Bronchial hyperresponsiveness and clinical effects of spa therapy in asthmatics in the elderly. (●): ex-smokers, (○): never-smokers. a and b:p<0.01, c and d:p<0.05, e:p<0.02.

The generation of LTB4 was significantly larger in patients with slight or no efficacy than in those with marked ($p<0.001$) and moderate efficacy ($p<0.001$) in all subjects. Regarding cigarette smoking, the LTB4 generation was significantly more increased in patients with slight or no efficacy than in those with marked ($p<0.01$) and moderate efficacy ($p<0.01$) in ex-smokers, but no significant correlation was found between LTB4 generation and spa efficacy in never-smokers. The LTB4 generation was also significantly larger in ex-smokers than in never-smokers of patients with moderate efficacy (Table 4).

Table 4. Leukotriene B4 generation by leucocytes and clinical effects of spa therapy in asthmatics in the elderly

	Clinical efficacy		
	Marked	Moderate	slight or no
Total subjects	76.9 [*a] (±27.1)	82.2 [b] (±30.8)	111.6 [ab] (±29.0)
Ex-smokers	75.0 [c] (±44.3)	103.4 [de] (±17.4)	128.9 [cd] (±19.4)
Never-smokers	61.8 (±23.9)	72.0 [e] (±30.9)	84.0 (±18.1)

*ng/5x10^{6}cells. a and b:p<0.001, c,d, and e:p<0.01.

The generation of LTB4 showed a tendency to increase as the spa effects became less in ex-

smokers, but not in never-smokers (Fig. 3).

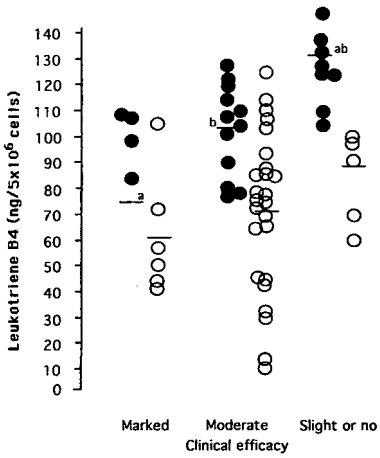

Fig.3. Leukotriene B4 generation by leucocytes and clinical effects of spa therapy in asthmatics in the elderly. (●): ex-smokers, (○): never-smokers. a and b: p< 0.01.

The LTC4 generation was not significantly correlated with spa efficacy in all subjects, and either in ex-smokers or never-smokers. The LTC4 generation was significantly larger in never-smokers than in ex-smokers of patients with moderate efficacy (Table 5).

Table 5. Leukotriene C4 generation by leucocytes and clinical effects of spa therapy in asthmatics in the elderly

	Clinical efficacy		
	Marked	Moderate	slight or no
Total subjects	42.5* (±31.6)	40.6 (±28.0)	54.2 (±31.4)
Ex-smokers	63.2 (±31.6)	48.6 [a] (±23.3)	49.4 (±38.7)
Never-smokers	28.6 (±25.0)	71.5 [a] (±30.9)	62.0 (±14.8)

*ng/5x10 ^{6}cells. a:p<0.05.

Discussion

Spa therapy is effective for patients with asthma[17-25,39]. Spa effects have been observed in asthmatics in the elderly[40] and in those with hypersecretion[41] and with bronchiolar obstruction[42]. Spa therapy is also effective in asthmatics with emphysematous changes such as an increase in residual volume[26-28] and in patients with pulmonary emphysema[29-31]. However, clinical effects of spa therapy for patients with asthma and/or pulmonary emphysema are influenced by various conditions found in the pathophysiological changes of these diseases. Of various conditions affecting spa effects, aging, IgE-mediated allergy, and cigarette smoking have been noticed in recent years[1-3]. Aging influences the pathophysiology of asthma : an increase in LAA of the lungs on HRCT and an increase in residual volume (RV) are observed with aging[43,44]. IgE-mediated allergy also influences the pathophysiology of asthma by enhancing the generation of LTC4[36].

In the present study, the influence of cigarette smoking on the effects of spa therapy was examined in asthmatics in the elderly. The clinical efficacy of spa therapy was significantly higher in never-smokers of asthmatics than in those with a long history of smoking. There was no significant difference in serum IgE levels between patients with spa efficacy and those without. The frequency of patients with a positive RAST score against inhalant allergens was not correlated with the efficacy of spa therapy, although the frequency of these patients was significantly larger in ex-smokers compared with never-smokers. Bronchial hyperresponsiveness to methacholine was significantly higher in patients with slight or no efficacy than in those with moderate and marked efficacy both in ex-smokers and never-smokers. The bronchial hyperresponsiveness was significantly higher in ex-smokers than in never-smokers of asthmatics with moderate efficacy. The results demonstrate that the long-term cigarette smoking enhances bronchial hyperresponsiveness, and that bronchial hyperresponsiveness is closely related to spa efficacy in asthmatics in the elderly.

Regarding the generation of LTB4 and LTC4 by leucocytes, the LTB4 generation was significantly larger in patients with slight or no efficacy compared with those with marked and moderate efficacy in ex-smokers, but not in never-smokers. The LTB4 generation was significantly larger in ex-smokers than in never-smokers in asthmatics with moderate efficacy of spa therapy. The LTC4 generation was not significantly related to spa efficacy. The results suggest that cigarette smoking enhances IgE-mediated allergy, bronchial hyperresponsiveness, and LTB4 generation by leucocytes in asthmatics in the elderly (Table 6), and that these changes is closely correlated with spa efficacy.

Table 6. Influence of cigarette smoking on IgE-mediated allergy, bronchial hyperresponsiveness and LTB4, LTC4 generation an asthmatics in the elderly

	Ex-smokers	Never-smokers
IgE-mediated allergy	↑	→
Bronchial hyper-responsiveness	↑	→
LTB4 generation	↑	→
LTC4 generation	→	→

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高齢者気管支喘息における喫煙による気道過敏性の亢進と温泉療法の臨床効果

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高齢者喘息60例を対象に，長期的喫煙の温泉療法の効果に及ぼす影響について検討した。温泉療法は60例中47例(78.4%)に有効であった。喫煙の影響については，喫煙歴の有る24例中16例(66.7%)で温泉療法は有効であったが，一方，非喫煙例36例では31例（86.1%）で有効であり，温泉療法の有効性は非喫煙例で有意に高いことが示された。温泉療法の有効性とIgE系反応との間には有意の関連はみられなかった。気道過敏性は喫煙例，非喫煙例いずれにおいても，有効例（著効ないし有効）に比べ無効例（ややで有効ないし無効）において有意に高い傾向を示した。LTB4産生は喫煙例では，無効例で有効例と比べ有意の亢進が見られたが，非喫煙例では関連は見られなかった。これらの結果は，長期間の喫煙が，気道過敏性や白血球のLTB4産生を亢進させ，その結果として温泉療法の臨床効果に影響を与える可能性が高いことを示しているものと考えられる。