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Oral Provocation Tests with Aspirin and Food Additives in Asthmatic Patients

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Aspirin and food additives are known to induce bronchoconstriction, angioedema or urticaria in susceptible patients. To evaluate the incidence of hypersensitivity to aspirin and food additives, 36 subjects with bronchial asthma, 33 of whom were non-allergic asthmatics and 3 were allergic asthmatics who had a history of aspirin sensitivity, were challenged orally with six compounds: acetylsalicylic acid (ASA), sodium bisulfite, tartrazine, sodium benzoate, 4-hydroxy benzoic acid, and monosodium L-glutamate. Significant bronchoconstrictions were found in 15 (41.7%) of the 36 subjects tested. Eight of the 15 subjects showed positive asthmatic responses to the aspirin, two showed asthmatic responses to the food additives, and five responded to both aspirin and the food additives. It is suggested that ASA and food additives could be causes of clinically significant bronchoconstriction in moderately severe non-allergic asthmatic patients.

Key Words: Bronchial Asthma, oral provocation test, aspirin, food additives

Aspirin, probably the most common medication in the world today, is well tolerated by the majority of people, but already recognized as early as 1902 (Hirschberg), intolerant reactions to aspirin such as asthma, rhinitis, urticaria, angioneurotic edema and anaphylaxis have often been described (Samter and Beers 1968; Schlumberger 1980; Spector *et al.* 1979; Speer *et al.* 1981).

The concern about the dangerous responses to aspirin increased when it was realized that similar responses might occur following ingestion of other nonsteroidal anti-inflammatory drugs (NSAIDs). Speer (1958) stated, that agents used in artificial coloring were the cause of asthma in sick children. Because of modifications in nutritional habits and developments in food technology, the consumption of additives and the frequency of food allergy is likely to increase. The extensive use of chemical substances in foods, drugs, cosmetics, and other contact substances may facilitate a hypersenstivitiy or intolerance. Indeed, a few of the allergologists carry on the oral challenges with additives that can prove intolerance. The labeling of food additives is not practiced in most countries, and most physicians are not aware of their potential involvement in the observed symptoms. The present study focuses upon the incidences and the manifestations of hypersensitivity to aspirin and food additives in asthmatic patients in Korea.

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MATERIALS AND METHODS

Patients

The study included 36 asthmatic subjects, 17 men and 19 women and their ages ranged from 16 to 65, as listed in Table 1. Among the asthmatics referred to this Department from June 1, 1987 to June 30, 1988, the subjects were selected according to the following criteria: (1) Negative responders on the skin prick test to 50 common inhalant allergens (pollens, house dust mites, animal danders and molds). (2) Patients who were defined as non-allergic asthmatics because they were RAST class 0 to the reactive allergens on the skin prick test and/or negative responses to allergen bronchoprovocation tests. (3) Patients who had a history of drug hypersensitivity to aspirin or to NSAIDs. Among these 36 subjects, 33 subjects were non-allergic and 3 subjects were allergic patients. One of these 3 patients had worked at a dye factory and was considered to be an occupational asthma patient (case No. 15 at Table 6). Ten of the 36 subjects had

Table 1. Age and sex distribution of patients studied

Age	positive responders (n=15)		negative responders (n=21)		Total (n=36)
	male (n=9)	female (n=6)	male (n=8)	female (n=13)	
⩽ 20	0	0	2	0	2
20 - 29	2	2	2	3	9
30 - 39	2	0	1	3	6
40 - 49	4	1	1	5	11
⩾50	1	3	2	2	8
mean (range)	42.3 (21 - 65)		37.1 (16 - 64)		

Table 2. Challenge agents and doses for oral challenge battery

Agents	doses
Aspirin	lactose, 1, 3, 5, 10, 30, 50, 100, 200, 300, 500, 650 mg
$NaHSO_3$	1, 5, 10, 20, 30, 50, 100 mg
Tartrazine	10 mg
Sodium benzoate	400 mg
4-Hydroxy benzoic acid	200 mg
Monosodium L-glutamate	2.5, 5.0 mg

Table 3. Incidence of asthmatic reactions in oral challenge battery

Agents	positive reactors	negative reactors
Aspirin only	8 (22.2%)	(1*)
Aspirin + others#	5 (13.9%)	(1**)
Others	2 (5.6%)	(1***)
Total	15 (41.7%)	21 (58.3%)

* Urticaria was induced by aspirin
** Urticaria was induced by aspirin and tartrazine
*** Rhinitis symptoms were induced by tartrazine
\# Others include bisulfite, tartrazine, sodium benzoate, 4-hydroxy benzoic acid and monosodium L-glutamate

Table 4. Results of oral challenge battery according to the past history of an adverse reaction to NSAIDS

History of adverse reaction	Positive reactor	Negative reactor	Total
Presence	7	3	10
Absence	8	18	26
Total	15	21	36

a history of drug hypersensitivity to aspirin or to NSAIDs.

Methods

Patients were requested to have a low allergenic diet free from food additives on admission for 3 days. Bronchodilators and steroids, administered before the study to keep the disease stable, were continued during the challenges. The patients underwent a single blind placebo-controlled challenge over several days. Substances used in the oral provocation tests are listed in Table 2. The Broncho-obstructive response was assessed by measuring the forced expiratory volume in 1 second (FEVI) and maximum mix-expiratory flow (MMEF) by the use of an autospirometer (HI 298, Japan). A decline in the FEVI value of 20% or greater, or a decline in the MMEF value of 25% or greater, as compared with the baseline, was considered to be a positive reaction. Progressively increasing doses, not higher than amounts ingested daily in a normal diet as listed in Table 2, were chosen, until a positive reaction occurred.As a placebo, lactose 1.0gm was administered at the beginning of the daily test session. Pulmonary function testing was repeated at 30-minute intervals following the ingestion of the test dose. This was done for 2 hours with each dose of substances, except sodium bisulfite and monosodium L-glutamate. The former was for 1 hour with 30-minute intervals and the latter for 12 hours with 60-minute intervals. If no significant change in the FEVI or MMEF occurred in 2 hours, the next larger dose was given. If the patient showed significant bronchoconstriction, the test was terminated for that day. In the aspirin oral provocation tests, the test was re-tried on the next day from the dosage that produced a positive reaction from the last challenge. Aspirin was increased sequentially until a 650mg dose was used as a single

challenge dose when it was considered to produce a desensitized state, and aspirin was administered continuously with maintenance dosage of 650mg or 1300mg a day.

RESULTS

The results of open challenges are summerized in Table 3. Significant bronchoconstrictions were found in 15 of 36 subjects tested. Eight of the 15 subjects showed a positive asthmatic response to aspirin only, and 5 additional subjects responded to both aspirin and food additives. The other 2 subjects developed asthmatic symtpoms from food additives, not from aspirin. Among the 21 negative responders, one subject developed acute urticaria following the ingestion

Table 5. Provoked manifestations according to clinical symptoms on admission

Provoked manifestation	Symptoms on admission			
	Asthma (n=17)	Asthma + Rhinitis (n=16)	Asthma + Urticaria (n=2)	Asthma + Rhinitis + Urticaria (n=1)
Asthma only	6 (*1)	0	0	0
Asthma + Rhinitis	3	2 (*1)	0	1
Asthma + Urticaria	0	2	0	0
Asthma + Rhinitis + Urticaria	0	0	1 (*1)	0
	9	4	1	1

*: Severe abdominal pain and diarrhea were provoked.

Table 6. Clinical summary of 15 positive reactors on oral challenge battery

Case No.	Age	Duration (yr)	Adverse reaction history (aspirin or NSAIDs)	Atopy by skin prick test	RAST	Allergen BPT	Total eosinophil count (/mm³)	Total IgE (IU/ml)	Challenge Agents					
									Aspirin	Sodium bisulfite	Tartrazine	Sodium benzoate	4-Hydroxy benzoic acid	Monosodium L-glutamate
1	64	1	+	–	ND	ND	310	165.5	+	–	–	–	–	ND
2	65	5	–	–	ND	ND	520	748.16	+	–	–	–	–	ND
3	53	1	–	–	ND	ND	380	29.31	+	–	–	–	–	–
4	25	1	+	+	–	ND	500	130.84	+	–	–	–	–	–
5	45	12	–	–	ND	ND	1,100	122.11	+	–	–	–	–	ND
6	47	4	+	+	–	ND	900	591.2	+	–	–	–	–	ND
7	24	0.5	+	+	+	+	610	>1,000	+	–	–	–	–	ND
8	21	1	–	–	ND	ND	430	83.65	+	–	–	–	–	–
9	49	1	–	–	ND	ND	120	58.85	+	–	–	–	–	+
10	26	6	+	+	–	ND	880	66.9	+	–	+	+	–	ND
11	47	0.5	–	+	+	–	600	65.27	+	+	–	–	–	–
12	61	21	+	+	–	ND	670	7.85	+	+	+	–	+	ND
13	36	0.3	+	+	–	ND	740	356.92	+	+	+	+	–	–
14	41	2	–	–	ND	ND	830	>1,000	–	+	–	–	–	–
15	31	2	–	+	–	+	1,720	421.47	–	+	+	–	+	ND
	42.3##	3.9##	7/15	8/15	2/8	2/3	688.0±382#		13/15	5/15	4/15	2/15	2/15	1/7
Negative group (n=21)														
	37.1	8.6	3/21	13/21	*2/12	**1/6	431.1±304.5#	267.4±287.1#						0/7

ND: not done, BPT: bronchoprovocation test, RAST: radioallergosorbent test

Case No. 7 and 15: Positive bronchoprovocation test to house dust mite (Dermatophagoides pteronyssinus)

* : One: positive to crab and shrimp, but no history of allergic symptoms provoked by foods

** : Past history of drug sensitivity, and positive RAST and BPT to house dust mite, ragweed.

: Mean ± S.D. ##: Mean

Table 7. Aspirin desensitization in 13 aspirin intolerant asthmatics

Case (No.)	Dose to provoke first reaction (mg)	Cumulative dose to provoke first reaction (mg)	Total number of reactions prior to desensitization	Desensitization (Success/Fail)	Maintenance dose (mg)
Intolerance to aspirin only					
1	50	99	(2)*	Fail	–
2	3	4	3	Success	650
3	100	199	1	Success	1,300
4	30	43	(4)*	Fail	–
5	50	99	1	Success	650
6	10	12	(2)*	Fail	–
7	300	600	2	Success	1,300
8	30	49	7	Success	1,300
Intolerance to aspirin and others					
9	30	49	(4)*	Fail	–
10	10	13	(1)*	Fail	–
11	3	4	(6)*	Fail	–
12	200	398	3	Success	650
13	30	49	(3)*	Fail	–

( )*: Numbers in parentheses mean the total trial number of aspirin desensitization before giving up.
Case 6, 7: Combined treatment with immunotherapy due to positive bronchoprovocation test

of 99mg of aspirin, but his pulmonary function test did not change from the baseline. Another subject developed urticaria from both aspirin and tartrazine, and an additional subject developed sneezing and marked rhinorrhea from tartrazine. High proportion (70%) of patients with a history of hypersensitivity to aspirin or NSAIDs was positive to the oral provocation test. Eight subjects (30.8%) without a history of hypersensitivity were positive responders on the oral challenge battery (Table 4).

Provoked manifestations during the oral challenge test are illustrated in Table 5. Most of them experienced asthmatic symptoms alone (40%) or asthma and rhinitis symptoms (40%). Three subjects experienced severe abdominal cramps and diarrhea during the challenge. Details of the 15 positive responders are summarized in Table 6. The mean duration of asthma among the positive responders was 3.9 years; and it is noticeable that many subjects had short duration of about 1 to 2 years. There was no significant difference of duration between the positive and negative responders. An intolerance to aspirin was observed in 13 patients. Among them, five patients experienced an asthmatic attack from aspirin and food additives. The other two patients developed an asthmatic attack from the food additives alone, not from aspirin. In summary, intolerance to aspirin was observed in 13 patients (86.7%) among the positive responders, and sodium bisulfite in 5 patients (33.3%), tartrazine in 4 patients (26.7%), sodium benzoate in 2 patients (13.3%), 4-hydroxy benzoic acid in 2 patients (13.3%), and monosodium L-glutamate in one patient (14.3%).

For 13 aspirin intolerant patients, desensitization was tried, and the results are illustrated in Table 7. Six patients could be desensitized by 650mg of aspirin, and were able to tolerate 650mg of aspirin once or twice a day.

DISCUSSION

Until now, there have been many reports about the hypersensitivity from aspirin, NSAIDs or food additives. The adverse reactions to synthetic colorants was first reported by Lockey (1959). Chafee and Settipane (1967) reported asthmatic symptoms precipitated by tartrazine, FD&C red dye No. 4 (both azo dyes), and sodium benzoate in an aspirin sensitive asthmatic woman. Richard *et al.* (1979) reported that the incidence of bronchoconstriction following aspirin ingestion was 44% in 45 non-allergic asthmatic patients. Castillo and Picado (1986) reported that ASA sensitivity was detected by the provocation test in 19% of hospitalized asthmatic patients. In this study, 13 (36.1%) of 36 patients developed an asthmatic attacks from aspirin. This difference in the incidence might be caused by the different criteria that was employed

for a positive test and the fact that the study was performed under single blind conditions.

Samter and Beers (1967) reported an incidence of bronchoconstriction with tartrazine in 6% of 222 aspirin-sensitive patients, but none in 40 non-aspirin-sensitive asthmatics. Also Stenius and Lemola (1976) reported on adverse reactions to tartrazine in 114 asthmatic patients. Among them, fifty percent of aspirin sensitive, and 20% of non-aspirin-sensitive asthmatics, met their criteria for a positive reaction. Donald *et al.* (1986) reported 6 (4%) of the 150 patients met their criteria for a positive reaction, which was a 25% fall in the FEVI on single blind testing. But at a later date, a repeated double blind challenge in 5 among them proved that none experienced a positive reaction. In this study, 3 (23.1%) of 13 aspirin-sensitive patients and 1 (4.3%) of 23 non-aspirin-sensitive patients developed bronchoconstriction by tartrazine.

The incidence of ingested metabisulfite sensitivity in an asthmatic population was reported by Simon (1982). He reported that 5 (8.2%) of 61 patients reacted to metabisulfite in double-blind placebo-controlled challenges. But Bush *et al.* (1986) reported that 10.3% of asthmatic patients were sensitive to sulfite agents in a single-blind study, but in a double-blind study, only 3.9% of asthmatic patients were sensitive. However their population contained a larger number of steroid-dependent asthmatic patients than would be found in the general asthmatic population. Therefore, the prevalence of sulfite sensitivity in the asthmatic population would be less than 3.9%. In this study, 5 (13.9%) of 36 asthmatic patients had a positive response and this incidence is slightly higher than the above reports, but this difference in incidence would be caused by the fact that a single blind study was employed in this study.

The provocation of asthmatic symptoms by monosodium L-glutamate (MSG) in two patients was reported by Allen and Baker (1968). Allen *et al.* (1987) performed oral MSG challenges in 32 asthmatic patients. Thirteen of them showed significant bronchoconstriction. Eight of these 13 patients gave a history of asthmatic attack after chinese restaurant meals or other similarly spiced meals. Although 13 of 32 patients reacted to the challenge with MSG, this should not be regarded as the prevalence of MSG induced asthma in the community at large because patients were highly selected. In this study, 1 (7.1%) of 14 patients showed bronchoconstriction by MSG. But the subjects of this study are a small number to represent the general incidence of MSG hypersensitivity.

Weber *et al.* (1979) reported the challenge test with and without withholding morning bronchodilators. They discovered 7 of 44 patients showed significant bronchoconstriction after the tartrazine challenge without withholding bronchodilators. When they repeated the challenge in the same patients with bronchodilators, the FEVI values declined by less than 20%. They suggested that withholding bronchodilators allows tartrazine to provoke asthma and administering bronchodilators blocks or covers the target organ response to tartrazine. On the other hand, "tartrazine provocation" is in reality a false positive asthmatic event generated by withholding bronchodilators in certain asthmatics with unstable airways. Pleskow *et al.* (1982) suggested that corticosteroids and theophylline do not block aspirin provoked asthmatic reactions. Administering beta-agonists can produce a falsely elevated baseline lung function value. During the next 3 to 4 hours, the FEVI values may drift down to the true baseline, giving the erroneous impression that an asthmatic reaction has occurred. Cromolyn and antihistamines delay the onset of response to aspirin without blocking the intensity of the asthmatic response. In this study, the patients keep bronchodilators and steroids during the challenges as administered before the study.

It is also noteworthy that many patients had a short duration of asthma for less than two years (Table 6). That is, new asthmatic patients were also sensitive to aspirin and food additives. In this study, three patients complained of cramping abdominal pain and diarrhea with a decline of more than 20% in FEVI values during the ASA challenge. Such abdominal pain persisted more than 30 minutes and subsided spontaneously without control by epinephrine injection.

Concerning the mechanism of aspirin hypersensitivity, there are several hypotheses to explain the findings. In some patients, the clinical symptoms are of an anaphylactic type and suggest an allergic pathogenesis. Acetylated proteins (Farr 1970) or aspirin anhydride impurities (de Weck 1971) have been proposed as possible antigens. Aspirin and other NSAIDs inhibit cyclo-oxygenase, an enzyme which converts arachidonic acid to endoperoxides that are further metabolized to prostaglandins and thromboxane (Szczeklik *et al.* 1977; Szczeklik and Gryglewski 1983). In the presence of inhibited cyclo-oxygenase, more arachidonic acid is available for the alternative lipoxygenase pathway leading to the production of leukotrienes and/or lipoxins. The leukotriene products would provide potent mediation of neutrophil influx into the tissue via the action of leukotriene (LT) B4 and potent stimulation for bronchoconstriction, mucosal permeability with edema formation, and

mucus secretion by the actions of LTC4, LTD4 and LTE4 (Lewis and Austen 1984; Samuelsson 1983). Recently Ameisen *et al.* (1985) demonstrated that aspirin and NSAIDs could activate platelet functions in vitro in sensitive patients but not in normal controls suggesting a direct participation of platelets in immediate hypersensitivity reactions. But the nature of the factors released by activated platelets remains to be elucidated. Slapke *et al.* (1986) reported that a defect in the plasma protease-inhibitor system might exist in aspirin-sensitive asthmatic patients and para-aminomethylbenzoic acid, a plasmin specific protease inhibitor, was effective in antagonizing their aspirin-induced adverse reactions.

Tartrazine itself does not inhibit cyclo-oxygenase (Gerber *et al.* 1979), a pharmacologic characteristic shared by all cross reacting, nonsteroidal, anti-inflammatory drugs including aspirin. (Mathison and Stevenson, 1979). There have been many reports on the cross sensitivity between aspirin and tartrazine (Samter and Beers 1968; Spector *et al.* 1979); but cross sensitivity between aspirin and tartrazine in asthmatic subjects is not supported by the reports by some research groups (Donald *et al.* 1986; Tarlo and Broder 1982; Vedantham *et al.* 1977; Weber *et al.* 1979).

In cases of asthma by sulfites, defects in sulfite oxidase activity may potentially be of importance in the pathogenesis of adverse reactions to sulfite (Jacobsen *et al.* 1984). On the other hand, the mechanism of bronchoconstriction during inhalation of SO_2 is a cholinergic reflex response (Boushey 1982). Premedication of six sulfite sensitive asthmatics with nebulized atropine (1 to 4mg) inhibited bronchoconstriction from capsules of metabisulfite in three subjects, and partially abrogated the response in an additional two; thus lending support to the cholinergic reflex as the mechanism for the bronchoconstrictive response (Simon *et al.* 1984).

In cases of monosodium L-glutamate induced asthma, monosodium L-glutamate is a naturally occurring substance, ingested by all of us in free and bound form everyday. It is a neurotransmitter in the central nervous system. It has recently been demonstrated to be a central nervous system transmitter of baroreceptor afferents (Reis *et al.* 1981), and is neuroexcitory in the peripheral nervous system which accounts for its flavor enhancing properties (Olney 1980). The development of asthma in close association with the onset of symptoms of the chinese restaurant syndrome suggests a peripheral neuroexcitatory effect, such as the stimulation of irritant receptors in the lung leading to reflex bronchoconstriction. In view of the central effects of MSG, a possible explanation for delayed asthmatic reactions would be a central augmentation of reflex activity to the lung.

In conclusion, aspirin intolerance was relatively common, and food additives could be causes of clinically significant bronchoconstriction in asthmatic patients. Oral provocation tests with aspirin and food additives proved to be necessary and feasible to prevent accidental asthmatic attacks or aggravation.

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