Effects of Azelastine on Allergen- and Exercise-induced Asthma*

Shinji Motojima, M.D.
Yuji Ohashi, M.D.
Tomohiro Otsuka, M.D.
Takeshi Fukuda, M.D.
Sohei Makino, M.D.

SUMMARY The effects of the new anti-allergic drug, azelastine, on allergen-and exercise-induced asthma were studied.

In six allergen inhalation tests for five asymptomatic asthmatic patients, the maximum percentage fall in $FEV_{1.0}$ immediately after inhalation of allergen extract was 37.2 ± 6.4 per cent (mean ± SEM). As compared with a placebo, the maximum percentage fall in $FEV_{1.0}$ with azelastine after inhalation of allergen extract in the same manner as with the placebo was 17.3 ± 6.9 per cent. The difference was statistically significant ($p<0.05$). The percentage fall in $FEV_{1.0}$ with placebo and azelastine in late asthmatic response (n = 4) was 36.0 ± 5.3 per cent and 10.0 ± 5.2 per cent, respectively. The difference was also statistically significant ($p<0.01$)

An exercise test was carried out on seven asymptomatic asthmatic patients using an inclined treadmill. The maximum percentage fall in $FEV_{1.0}$ without drugs, with diphenhydramine and azelastine was 38.9 ± 5.0 per cent, 20.1 ± 3.8 per cent and 11.3 ± 3.1 per cent, respectively. Significant differences were found among each group ($p<0.05$). Azelastine was regarded as having sufficient potency to inhibit exercise-induced asthma; however, placebo effects cannot be ruled out with regard to the effects of diphenhydramine.

These results suggests that chemical mediator release is involved not only in allergen-induced asthma but also in exercise-induced asthma, suggesting the clinical utility of azelastine.

ASIAN PACIFIC J ALLERG IMMUN 1985; 3 : 174-178.

It has been shown that chemical mediator release is involved in the onset of allergen- and exercise-induced asthma.[1-4] Azelastine [4-(p - chlorbenzyl) - 2 - (hexahydro - 1-methyl-1H-azepine-4-yl) 1 (2H)-phthalazinone hydrochloride] is an inhibitor of IgE-mediated chemical mediator release with a potent histamine H_1-receptor-blocking property.[5,6] It provides dose-dependent protection in aeroallergen-induced bronchospasm in conscious, sensitised guinea pigs.[5] It also inhibits leukotriene-mediated allergic bronchospasm in guinea pigs.[7] Azelastine has also been reported to inhibit antigen and calcium ionophore (A-23187)-induced histamine release from guinea pig mesenteric mast cells and rat peritoneal mast cells.[7,8]

In this study, we investigated the effects of azelastine on asthma induced by allergen inhalation and exercise.

SUBJECTS AND METHODS

1. Allergen-induced asthma

Five asthmatic patients, four females and one male with a mean age of 33 years (range 14-61 years), were studied. Table 1 shows the background factors of the subjects. None of the subjects showed recent acute bronchoconstriction, the basal $FEV_{1.0}$ being more than 70 per cent of the predicted value.

All drugs were withheld for at least 12 hours before the tests. Placebo was administered to the subjects at 6 a.m., then the allergen inhalation test was started at 10 a.m. Serial ten-fold dilution of allergen extracts were made by diluting the commercially delivered allergen (Torii, Japan) with physiological saline. Initially all subjects inhaled the aerosol of physiological saline by using a nebulizer with an airflow of five 1/min for three minutes, and $FEV_{1.0}$ was measured immediately after inhalation by using Autospirometer AS-2000 (Minato, Japan). When saline inhalation induced more than a 10 per cent decrease in $FEV_{1.0}$ as compared to $FEV_{1.0}$ before the test, the allergen inhalation tests were deferred.

*From the Department of Medicine and Clinical Immunology, Dokkyo University School of Medicine, Tochigi, Japan.

Table 1 Background factors of asthmatic patients who received allergen inhalation test

No.	Name	Age	Sex	Duration (years)	Severity	Positive allergen by prick test
1	T.O.	14	Female	10	Mild	House-dust, cotton, mugwort, orchard grass
2	R.N.	44	Female	11	Mild	House-dust, buckwheat
3	H.K.	15	Female	13	Modrate	House-dust
4	T.K.	33	Male	0.1	Moderate	House-dust
5	S.M.	61	Female	6	Mild	House-dust, buckwheat

(mean 33)

Then, allergen extract, with the concentration of the endpoint of the intradermal test, was administered in the same way as saline. Measurements of $FEV_{1.0}$ were carried out before and 5, 12 and 20 minutes after inhalation of allergen extract. If percentage fall in $FEV_{1.0}$ as compared to $FEV_{1.0}$ before the test was less than 15 per cent, allergen extract of ten-fold concentration was administered. When 15 per cent or more fall in $FEV_{1.0}$ was observed, then further measurements of $FEV_{1.0}$ were carried out ½, 1, 2, 3, 4, 5, 6, 7 and 8 hours after inhalation of the allergen extract.

More than seven days later, the effects of azelastine were tested. Four mg of azelastine (courtesy of Eisai, Japan) was administered at 6 a.m., then the allergen inhalation test was started at 10 a.m. Allergen extracts were administered in the same manner as the previous placebo test. The concentration of allergen extract was increased until the concentration was reached which provoked a 15 per cent or more fall in $FEV_{1.0}$ with the placebo.

Responses to inhaled allergens were defined as "immediate" if bronchoconstriction developed within one hour, and as "late" if bronchoconstriction developed three to eight hours after inhalation of the allergens.

Maximum percentage fall in $FEV_{1.0}$ was defined as follows:

$$\text{Maximum percentage fall (immediate) in } FEV_{1.0} = \left(1 - \frac{\text{minimum } FEV_{1.0} \text{ within 1 hour of inhalation}}{FEV_{1.0} \text{ before test}}\right) \times 100$$

$$\text{Maximum percentage fall (late) in } FEV_{1.0} = \left(1 - \frac{\text{minimum } FEV_{1.0} \text{ 3-8 hours after inhalation}}{FEV_{1.0} \text{ before test}}\right) \times 100$$

Table 2 Background factors of asthmatic patients who received exercise provocation test

No.	Name	Age	Sex	Duration (years)	Type	Severity
1	H.S.	42	Male	4	Mixed	Moderate
2	R.M.	32	Male	12	Mixed	Moderate
3	S.W.	23	Male	16	Atopic	Mild
4	K.M.	41	Male	4	Infectious	Severe
5	T.T.	45	Male	4	Mixed	Moderate
6	K.W.	32	Male	8	Mixed	Moderate
7	T.Y.	48	Female	3	Infectious	Moderate

(mean 38)

All subjects were challenged by house-dust except case No. 1 to whom house-dust and cotton inhalation tests were administered.

It was defined as effective if the maximum percentage fall in $FEV_{1.0}$ with azelastine was less than 50 per cent of that with no drugs.

2. Exercise-induced asthma

Seven asthmatic patients, six male and one female with a mean age of 38 years (range 23-48 years), were studied. Table 2 shows the background factors of the subjects. The basal $FEV_{1.0}$ was more than 70 per cent of the predicted value. All drugs were withheld for as least 12 hours before the test.

The subjects were tested with the following:

(1) drug free (in the first exercise test)

(2) azelastine 3 mg, per oral, at 6 a.m.

(3) diphenhydramine 30 mg, I.M., at 9:30 a.m.

Half the subjects received treatment No. 1 as described above in the second exercise test; treatment No. 3 in the third test; for the other half the treatment was vice-versa.

The exercise provocation test was started at 10 a.m. Exercise testing consisted of steady-state running on an inclined (10°) treadmill for 10 minutes at a speed of 80 m/min. Measurements of $FEV_{1.0}$ were carried out before and 2, 5, 10, 15, 20, 30 and 45 minutes after exercise using an Autospirometer AS-2000. Room temperature during the study was almost 20°C, relative humidity, 70 per cent. Maximum percentage fall (exercise) in $FEV_{1.0}$ was defined as follows:

$$\text{Maximum percentage fall (exercise) in } FEV_{1.0} = \left(1 - \frac{\text{minimum } FEV_{1.0}}{FEV_{1.0} \text{ before test}}\right) \times 100$$

It was defined as effective if the maximum percentage fall in $FEV_{1.0}$ with drug was less than 50 per cent of that with no drug.

3. Statistics.

A difference of $p < 0.05$ was considered significant by paired t-test.

RESULTS

1. Allergen-induced asthma

The four provocation tests on three subjects, dual asthmatic response was observed; however, two subjects showed immediate asthmatic response (IAR) only. Table 3 shows the results of allergen inhalation tests.

The maximum percentage fall (immediate) in $FEV_{1.0}$ with placebo and azelastine was 37.2 ± 6.4 (mean ± SEM) per cent and 17.3 ± 6.9 per cent, respectively. The difference was statistically significant ($p < 0.05$). Azelastine was effective in four of six immediate asthmatic response cases.

The maximum percentage fall (late) in $FEV_{1.0}$ with placebo and azelastine was 36.0 ± 5.3 per cent and 10.0 ± 5.2 per cent, respectively. The difference was also statistically significant ($p < 0.01$). Azelastine was effective in four of four late asthmatic response (LAR)

2. Exercise-induced asthma

Table 4 shows the results of exercise provocation tests. The maximum percentage fall (exercise) in $FEV_{1.0}$ was generally observed between five and 15 minutes after exercise. There were no significant differences in heart rate among three exercise tests not only before but also after exercise. The maximum percentage fall in $FEV_{1.0}$ without drugs, with diphenhydramine and azelastine, was 38.9 ± 5.0 (mean ± SEM) per cent, 20.1 ± 3.8 per cent and 11.3 ± 3.1 per cent, respectively. Significant differences were found among each group ($p < 0.05$). Azelastine was effective in five of seven exercise-induced cases of asthma.

DISCUSSION

Azelastine inhibited significant-

Table 3 Results of allergen inhalation test

1. Immediate asthmatic response

		Placebo			Azelastine		
No.	Allergen	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)
1	H.D.	2.07	1.62	21.7	2.10	2.07	1.4
1	cotton	2.07	1.12	45.9	2.27	2.10	7.5
2	H.D.	2.72	2.00	26.5	3.10	2.97	4.2
3	H.D.	2.07	0.77	62.8	2.02	1.52	24.8
4	H.D.	2.71	2.17	20.2	2.30	1.95	15.2
5	H.D.	1.80	0.97	46.1	1.87	0.92	50.8
	Mean ± SEM			37.2 ± 6.4			17.3 ± 6.9
							$p < 0.05$

2. Late asthmatic response

		Placebo			Azelastine		
No.	Allergen	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)
1	H.D.	2.07	1.42	31.4	2.10	2.07	0
1	cotton	2.07	1.50	27.5	2.27	1.97	13.2
2	H.D.	2.72	1.87	31.3	3.10	3.07	1.0
3	H.D.	2.07	0.95	54.1	2.02	1.50	25.7
4	H.D.	not observed					
5	H.D.	not observed					
	Mean ± SEM			36.0 ± 5.3			10.0 ± 5.2
							$p < 0.01$

Note: H.D. = house-dust

Table 4 Results of exercise provocation test

	Drug free			Diphenhydramine			Azelastine		
No.	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)	$FEV_{1.0}$ before (1)	Minimum $FEV_{1.0}$ (1)	Maximum % fall in $FEV_{1.0}$ (%)
1	3.15	2.27	28.0	3.55	3.22	9.3	3.67	3.32	9.5
2	2.95	2.30	22.0	3.35	2.82	15.8	3.10	2.80	9.7
3	3.52	1.95	44.6	3.65	2.92	20.0	3.55	3.32	6.5
4	2.42	1.40	42.1	2.25	1.92	14.7	2.62	2.62	0
5	1.72	1.15	33.3	2.17	1.55	28.6	1.70	1.45	26.5
6	1.90	1.40	24.3	2.20	1.32	40.0	2.32	2.00	15.7
7	1.87	0.95	58.9	1.50	1.32	12.0	1.67	1.45	13.2
Mean ± SEM			38.9 ± 5.0			20.0 ± 3.8			11.3 ± 3.1
			$p < 0.5$						$p < 0.05$

ly not only allergen-induced IAR but also LAR. When IAR was inhibited, LAR was also inhibited. This is similar to the inhibition by disodium cromoglycate (DSCG).[9]

It has been reported that the incidence of LAR in allergen provocation test is considerably high: 47 per cent by Booij-Noord *et al,*[10] and 47 per cent by Boulet *et al,*[11] which are consistent with our results. Thus, although LAR is important in clinical practice, the pathogenesis is still unclear. Pepys *et al* suggested that LAR is correlated with the type-III allergic reaction.[9] On the other hand, Hargreave *et al* thought it to involve the successive events to the type-I allergic reaction.[12] Recently, Durham *et al* showed that chemical mediator release occurs during LAR using neutrophil chemotactic activity (NCA) and plasma histamine as indicators of chemical mediator release from mast cells, and thought that this is one of the mechanisms involved in the onset of LAR.[13]

Many investigators have reported the results on the effects of drugs on allergen provocation tests in cases of asthma. In general, it has been reported that beta-agonist and H_1-blocker are effective on IAR with little effects on LAR; corticosteroids are effective on LAR only; and DSCG protects not only IAR, but also LAR.[9,10,14] So the protective mechanism of azelastine on IAR is thought to be both an H_1-blocking property and inhibiting property of chemical mediator release, that of azelastine on LAR being the latter mechanism. As to the effects of another oral anti-allergic drug, ketotifen, on allergen-induced asthma, the results are still controversial and not so reliable as that of DSCG.[15,27-29] The reason why azelastine was ineffective for two subjects is unknown. To make the reason clear a histamine release experiment from leukocytes by allergen in the presence of azelastine, in addition to the detection of plasma histamine, leukotriene and azelastine, will be needed.

Azelastine also significantly inhibited exercise-induced asthma. Although many mechanisms, such as vagal nerve reflex,[17,18] histamine release from mast cells,[19] activation of alpha-adrenergic receptor[20] and respiratory heat exchange,[3,21] are thought to be involved in the onset of exercise-induced asthma, the role of chemical mediator release is receiving much attention with reference to NCF-A.[22,23] This hypothesis of chemical mediator release is consistent with that of many reports, i.e., elevated plasma histamine level after exercise,[19] presence of refractory period after exercise,[24] effectiveness of DSCB[25-27] and effectiveness of H_1-antagonist.[27] In our study, although H_1-antagonist, diphenhydramine, inhibited exercise-induced asthma significantly, the placebo effect cannot be ruled out. The difference in the effects between azelastine and diphenhydramine may be due to the fact that azelastine has not only an H_1-blocking property but also an inhibiting property of chemical mediator release. The effectiveness of azelastine will support the hypothesis that chemical mediator release is involved in the onset of exercise-induced asthma. Several authors have reported on the effects of another oral anti-allergic drug, ketotifen; however the results are conflicting and not so reliable as DSCG.[15,27-29] As to the effects of oral anti-allergic drugs on allergen- and exercise-induced asthma, further investigations will be required.

Although asthmatic attacks are not induced by allergen and exercise only, the effectiveness of azelastine on allergen- and exercise-induced asthma suggests the clinical utility of this drug.

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