

The effect of partial beta adrenergic blockade on the bronchial response of hay fever subjects to ragweed aerosol

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One hypothesis of the cause of asthma proposes that it is the result of impaired autonomic homeostasis manifested by a partial blockade of the adrenergic beta receptors of cells. This study was undertaken to determine whether a pharmacologically induced beta blockade would increase the bronchial obstruction produced by ragweed aerosol challenge in subjects with hay fever. Ten volunteers with ragweed hay fever were studied before the ragweed season. Each subject was his own control. On each of two separate days the subject was challenged with progressively increased doses of an aerosol of ragweed extract. Before the second challenge, 5 mg. of propranolol, a potent beta adrenergic blocking agent, was given intravenously. A year later, these 5 subjects were again studied with the order of the propranolol and control tests reversed. The response to the aerosol was determined by comparing the volumes of the first second of a forced expiration (FEV_1) before and 15 minutes after the aerosol. The mean change in FEV_1 was -13 per cent with the control and -22 per cent with the propranolol. When the order of challenge with propranolol and the control was reversed, these values were much the same, -6 and -19. Partial beta blockade increased the bronchial response to inhaled allergen, a result consistent with the stated hypothesis.

The cause of asthma remains unknown despite a great deal of investigation into the allergic and emotional facets of the disease. Stemming from the Nineteenth Century concept of asthma as an affection of the nerves, a neurosis, there has also been continuing interest in the role of the altered autonomic nervous

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system reactivity in the atopic diseases. Recently, Szentivanyi¹⁻⁵ and others have suggested that a phenomenon common to all patients with asthma is a partial blockade of the beta adrenergic receptors regardless of what the precipitating factors may be clinically. The observation that people with asthma have a diminished response to some of the effects of beta adrenergic stimulation lends support to this suggestion.⁶

Propranolol, a specific beta adrenergic blocking agent, has been studied in the treatment of angina, arterial hypertension, arrhythmias, excess catecholamine activity in pheochromocytomas, and hyperthyroid states.⁷⁻¹² When this agent was administered to people with asthma who were not having symptoms at the time, acute airway obstruction began within 20 to 30 minutes.¹³ The possibility that patients with hay fever treated with this drug might also respond to the antigen exposure with asthma has not yet been examined.

The use of spirometry to evaluate the bronchial response to antigen aerosols was introduced by Lowell and Schiller.¹⁴ More recently, Townley, Dennis, and Itkin¹⁵ have demonstrated that some people with hay fever respond to an aerosol of specific allergen with a decreased first second vital capacity. With this background in mind, the present study was undertaken to determine whether a pharmacologically induced partial beta adrenergic blockade would increase the airway obstruction induced by the inhalation of ragweed aerosol by hay fever subjects.

PATIENT SELECTION AND METHOD

Ten ragweed hay fever subjects were selected from the University Hospital Allergy Clinic and were studied during the spring and early summer of 1965. Five of these subjects were studied again 1 year later. All subjects, except 2, had been receiving ragweed injection therapy for periods of 3 weeks to 5 years. They were screened carefully to exclude anyone with a history at all suggestive of asthma. As an additional precaution to exclude asthma, a standard methacholine aerosol provocative test¹⁶ was performed in all subjects. None had a change in the FEV₁ of more than -10 per cent. The 95 per cent confidence limits for patients with asthma are -10 to -65 per cent.

Prior to the testing, they became familiar with the use of an apparatus which consisted of a McKesson Vitalor spirometer and a DeVilbis No. 40 nebulizer connected by a T tube to a DeVilbis No. 501 air compressor. Special emphasis was placed on the inhalation technique so that the rate and depth of inhalation of aerosol would be as constant as possible.

The study was designed so that each subject was his own control. Each was tested twice, once with and once without propranolol.* The experimental protocols are shown in Tables I and II. This protocol was followed for each subject on two separate days at the same hour each day. The interval between the two tests varied from 24 hours to 3 weeks for the 1965 series and was 7 days for the 1966 series. The dose of aerosol ragweed extract was increased progressively for each subject during the 1965 series of tests to determine the amount of aerosol that

*Propranolol (Ayerst 64043), supplied by Dr. Alex Sahagian-Edwards of Ayerst Laboratories, New York, N. Y.

Table I. *Experimental protocol for the 1965 series*

<i>Time in minutes</i>	<i>Procedure</i>
0	Spirogram*
1	Propranolol 5 mg. intravenously, slowly*
20	Spirogram
21	20 Inhalations of aerosol of diluting solution
35	Spirogram
36	5 Inhalations of aerosol of 1,000 PNU†/ml. ragweed extract
50	Spirogram
51	5 Inhalations of aerosol of 10,000 PNU/ml. ragweed extract
65	Spirogram
66	20 Inhalations of aerosol of 10,000 PNU/ml. ragweed extract
80	Spirogram
81-90	Symptomatic treatment with phenylephrine and isoproterenol aerosol followed by spiograms to record reversal of airway obstruction.

*Omitted on the first occasion that each subject was tested.

†Protein nitrogen units.

Table II. *Experimental protocol for the 1966 series*

<i>Time in minutes</i>	<i>Procedure</i>
0	Spirogram
1	Propranolol 5 mg. intravenously on first occasion or saline 5 mg. on second occasion
20	Spirogram
21	Inhalation of aerosol of ragweed extract*
40	Spirogram
41	Symptomatic treatment with phenylephrine and isoproterenol aerosol followed by spiogram to record reversal of airway obstruction

*Each subject received the same total dose of ragweed as had been received in divided doses in 1965.

could be safely tolerated. Depending on the sensitivity, the same or a lesser amount of aerosol was given in progressive doses on the day that the subject received 5 mg. propranolol intravenously. For the 1966 series, the propranolol was given on the first occasion and the full aerosol dose was given all at one time. This could now be accomplished safely because the dose of aerosol each individual could tolerate without unreasonably severe reaction had been determined the preceding year.

The relative amount of aerosolized antigen that each subject did receive was expressed as a dose index, calculated as follows:

$$\text{Dose index} = \frac{(\text{No. of inhalations}) \times (\text{extract concentration in PNU}^*/\text{ml.})}{10,000 \text{ PNU/ml.}}$$

Thus, a dose index of 25.5 meant that the subject had had a total of 25 inhalations of 10,000 PNU per milliliter extract and 5 inhalations of 1,000 PNU per milliliter extract.

*Protein nitrogen units.

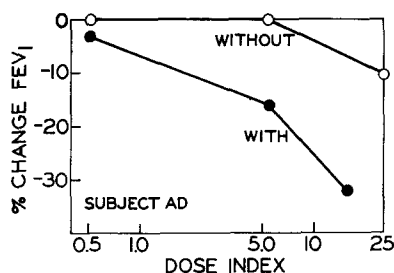


Fig. 1

The bronchial response to ragweed aerosol of subject No. 2 with and without propranolol.

Table III. *The effect of partial beta adrenergic blockade on the bronchial response of hay fever subjects to progressive ragweed aerosol challenge for the 1965 series; control first, propranolol second*

Subject No.	Skin test (100 PNU)	Months of treatment	With propranolol		Control	
			% change (FEV ₁)	Dose index	% change (FEV ₁)	Dose index
1	3+	63	-22	15.5	-21	25.5
2	3+	17	-32	15.5	-10	25.5
3	4+	14	-13	15.5	-10	15.5
4	4+	3	-21	5.5	-13	5.5
5	2+	4	-24	15.5	-16	25.5
6	3+	1	-12	2.5	-15	5.5
7	2+	10	-7	25.5	0	25.5
8	3+	0	-14	15.5	-10	25.5
9	2+	3	-52	3.5	-21	5.5
10	3+	4	-18	2.5	-14	5.5
Mean			-21.5	11.7	-10.9	16.5

The response to the aerosol is expressed as the percentage change in the first second volume of a forced expiration (FEV₁) and is expressed as follows:

$$\text{Per cent change FEV}_1 = \frac{(\text{initial FEV}_1) - (\text{FEV}_1 \text{ after maximum aerosol dose}) \times 100}{(\text{initial FEV}_1)}$$

RESULTS

Neither the propranolol, itself, nor the control aerosol of diluting fluid changed the FEV₁ of any of the subjects. Fig. 1 illustrates a typical response showing an increased change in the FEV₁ to a smaller dose of ragweed aerosol after the propranolol. In 1965, 9 out of the 10 subjects had a greater response to ragweed with propranolol than with the control (Table III). In 1966 all 5 subjects had a greater response with propranolol (Table IV). Subject No. 6, the one subject who did not respond in 1965, had a change in FEV₁ of -12 per cent with a dose index of 2.5 after propranolol. As it turned out, the dose index of 2.5 was too low because when the test was repeated in 1966, there was a 30 per cent drop in FEV₁ with a dose index of 6. For the group of subjects tested in

Table IV. *The effect of partial beta adrenergic blockade on the bronchial response of hay fever subjects to progressive ragweed aerosol challenge for the 1966 series; propranolol first, control second*

Subject No.	With propranolol		Control	
	% change (FEV ₁)	Dose Index	% change (FEV ₁)	Dose index
2	-27	15	- 3	15
4	-19	5	-10	5
5	-10	7	0	7
6	-30	6	-15	6
9	-10	3	- 4	3
Mean	-19	7.2	- 6	7.2

Table V. *Response of subject No. 2 to the same dose of ragweed aerosol on different days when propranolol or saline was given intravenously 20 minutes before*

Day	Intravenous injection	% change (FEV ₁)
1	Saline	- 4
7	Propranolol, 1 mg.	- 6
14	Saline	- 3
21	Propranolol, 5 mg.	-27

1965 there was a mean change in FEV₁ of -15 after a dose index of 16.5 for the control challenges. With propranolol the mean change in FEV₁ was -21.5 after a mean dose index of 11.7. In 1966, the order of the propranolol and control challenges was reversed and the dose was kept constant for each subject. The mean change in FEV₁ without propranolol was -6.4 and with propranolol was -19.2. Thus, the effect of propranolol was not altered by the sequence of the administration of the control or propranolol test. The response of the individual subjects is the same in 1965 and 1966, except for subject No. 9. Preseasonal injection treatment with ragweed extract was started for the first time in January, 1966. At the time of the challenge in 1966 the subject had received an injection of 5,000 PNU of ragweed 1 week previously.

Subject No. 2 was studied on four occasions in 1966 with two control challenges and two doses of propranolol. This subject had a greater response to a larger dose of propranolol (Table V).

The symptoms after the aerosol challenge were strikingly similar in all cases. None had symptoms of the eyes or the nose. The cardinal symptom was a feeling of tightness in the upper chest and at the root of the neck with an itching sensation over the skin of the neck. Most had a marked flushing and feeling of warmth and an increase in the effort of breathing. Some subjects had pain with forced inspiration or expiration. We attributed the local symptoms to acute inflammatory changes in the trachea and larger bronchi and the flushing to histamine release into the systemic circulation.

After the partial beta adrenergic blockade, the symptoms were less distressing

in all cases despite the increased airway obstruction. No wheezing was heard during the test without the beta adrenergic blockade, but wheezing was audible in 4 of the subjects after the blockade.

It was of interest that the airway obstruction and the painful sensation with forced breathing were only partially relieved by five inhalations of 1 per cent phenylephrine aerosol but disappeared almost immediately after five inhalations of 0.5 per cent isoproterenol.

DISCUSSION

Other than the well-known similarity in the antibody response and the frequent occurrence of allergic asthma and hay fever together, the relationship between these two is poorly understood. The skin test reactions and reagin titer of patients with asthma and hay fever are similar. The severity of the disease process does not correlate with the degree of the antibody response. One way to view the relationship between hay fever and asthma is as a continuum of degree of bronchial sensitivity to the mediators released by the antibody-antigen reaction. In other words, the difference is conceived to be quantitative rather than qualitative. Evidence suggesting this concept is the observation of Townley, Dennis, and Itkin,¹⁵ confirmed in the present study, that many but not all hay fever subjects experience some airway obstruction after the inhalation of antigen aerosol in the laboratory. These subjects state that they have never experienced similar symptoms with spontaneous exposure. An overlap in the degree of bronchial response to histamine and methacholine in people with hay fever and asthma has also been found.^{15, 16} In our study propranolol alone did not produce measurable airway obstruction in the patients who were carefully selected to exclude asthma, so the increased response to ragweed was not simply an additive effect of two bronchoconstrictive stimuli.

Our subjects were selected from the extreme low end of this continuum of bronchial sensitivity. The results indicated that a pharmacologically induced beta adrenergic blockade can shift the response from pure hay fever toward asthma, and that partial blockade can produce an asthmatic response to allergens. But, these results did not provide evidence that a beta adrenergic blockade was present in asthma. The same results would be expected with any defect in the complex process of maintenance of homeostasis of bronchial caliber. No light was shed on the locus of this defect. Regardless of whether the asthmatic patient was subjected to cholinergic stimulation with acetylcholine or to adrenergic blockade with propranolol, the response, airway obstruction, appeared to be the same.

Propranolol is contraindicated in patients with asthma,¹³ and the results of the present study seemed to indicate that propranolol should be used with caution in patients with hay fever when the antigen exposure is heavy.

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