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FURTHER STUDIES ON THE EFFECT OF ORAL DOXANTRAZOLE ON ALLERGEN-INDUCED BRONCHOSPASM

By

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In an initial study on the effect of oral doxantrazole on allergen-induced bronchoconstriction in man (3), we could not confirm the significant inhibition of the immediate bronchial reaction as described by Haydu et al. (2). We decided to extend our experiments to other treatment schedules.

PATIENTS AND METHODS

All patients (Tables 1 and 2) included in these studies had a positive history for allergy, positive intracutaneous and prick tests with one or more inhalant allergens, and a positive RAST for one or more allergens.

All patients suffered from bronchial asthma but were in a stable phase of their disease when they were investigated. They agreed to take part in the study after its nature and purpose had been fully explained to them. No patient was receiving DSCG prior to the test period, and all sympathomimetics were stopped 12 h before each test.

Bronchial challenge was performed as previously described (3). The allergen concentrations used (dry weight/vol.) are indicated in Tables 1 and 2.

In the first study we compared the effect of a single oral administration of 200 mg with 400 mg of doxantrazole in a double-blind cross-over study on 10 patients.

The doxantrazole was taken 1 h before challenge on an empty stomach. The second study was performed on seven patients. They received, in a double-blind cross-over study during two consecutive periods of 14 days, either 400 mg doxantrazole or placebo three times per day. Bronchial challenge was performed at the beginning of the study and at the end of each 14-day period. The last tablet of the preceding period was taken on an empty stomach 1 h before the challenge.

TABLE 1
Patients included in the first study.

Patient No.	Sex	Age	Allergen	Dry weight/vol. mg/ml
1	M	25	derm. pter.*	1.2
2	F	19	grass pollen	0.6
3	M	33	derm. pter.	0.12
4	F	21	grass pollen	0.6
5	M	27	derm. pter.	1.2
6	F	28	derm. pter.	0.12
7	M	42	derm. pter.	0.12
8	F	35	derm. pter.	1.2
9	M	38	house dust	5
10	F	38	derm. pter.	1.2

* *Dermatophagoides pteronyssinus*.

TABLE 2
Patients included in the second study.

Patient No.	Sex	Age	Allergen	Dry weight/vol. mg/ml
1	M	38	derm. pter.*	0.12
2	M	29	derm. pter.	1.2
3	M	16	derm. pter.	0.12
4	M	15	derm. pter.	0.12
5	F	37	derm. pter.	1.2
6	F	33	grass pollen	6
7	M	21	derm. pter.	1.2

* *Dermatophagoides pteronyssinus*.

In both studies, bronchial challenge was started at around 9 a.m. and lung function parameters (FEV₁ and Raw) were measured before and 15, 30, 60, 120, 240 and 480 min after the allergen inhalation.

Lung function tests were performed as described previously (3).

RESULTS

The results of the first study are illustrated in Figs. 1-3. Fig. 1 shows the mean changes in FEV₁ of the 10 patients after in-

Effect of chronic doxantrazole treatment on allergen challenge

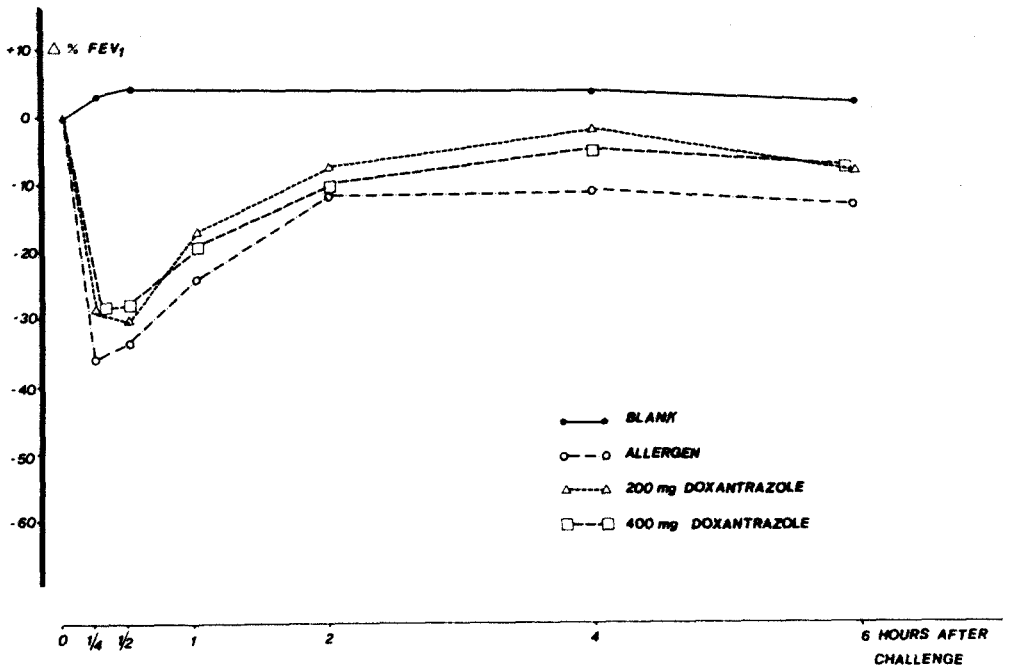


Fig. 1.

Mean change in FEV₁ (as per cent of the initial value) on the different tests days during the first study.

Effect of chronic doxantrazole treatment on allergen challenge

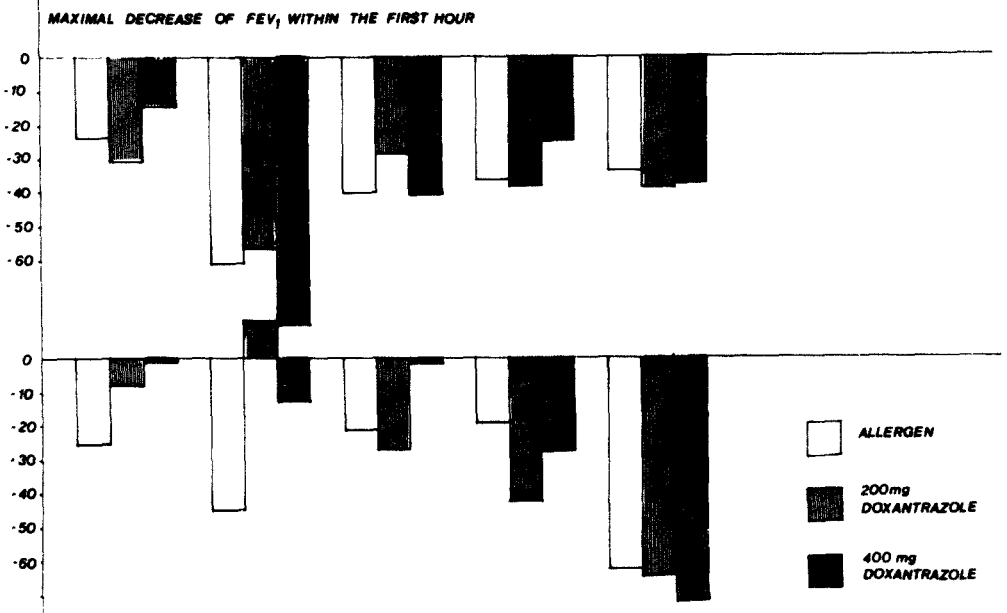


Fig. 2.

Individual result of the maximal decrease of FEV₁ (as per cent of the initial value) within the first hour after collagen challenge and the effect of 200 and 400 mg doxantrazole on these results.

Effect of chronic doxantrazole treatment on allergen challenge

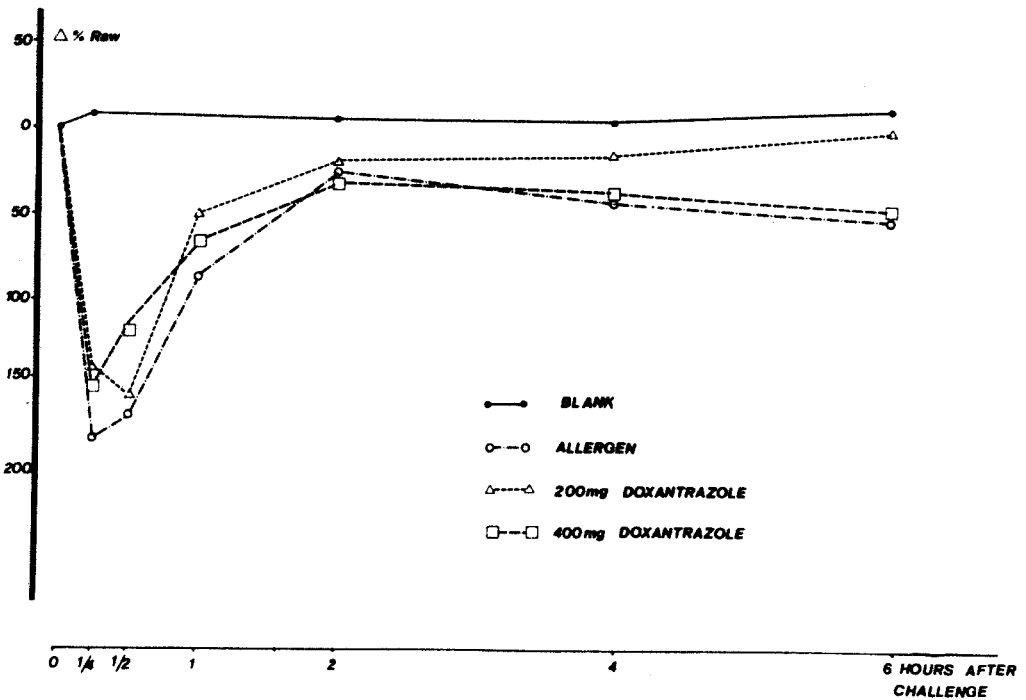


Fig. 3.

Mean change in airways resistance (as per cent of the initial value) on the different test days during the first study.

haling Coca's solution alone, or after inhaling allergen, and the effect of prior dosing with 200 mg or 400 mg doxantrazole on the allergen-induced FEV_1 decrease. The mean results for the 10 patients predosed with 200 mg or 400 mg doxantrazole were at no time associated with a significant inhibition of the mean fall in FEV_1 . However, the intake of 200 mg doxantrazole was associated with a significant inhibition of the FEV_1 decrease in two out of the 10 patients (Fig. 2). The same two patients plus one other were significantly protected by 400 mg doxantrazole (Fig. 2). Fig. 3 illustrates the mean results of the change in airways resistance of the 10 patients on the different test days. Doxantrazole had no significant effect on the mean increase in airways resistance following allergen challenge. Fig. 4 illustrates the mean change of FEV_1 following bronchial challenge with allergen on the different test occasions in the second study.

Effect of chronic doxantrazole treatment on allergen challenge

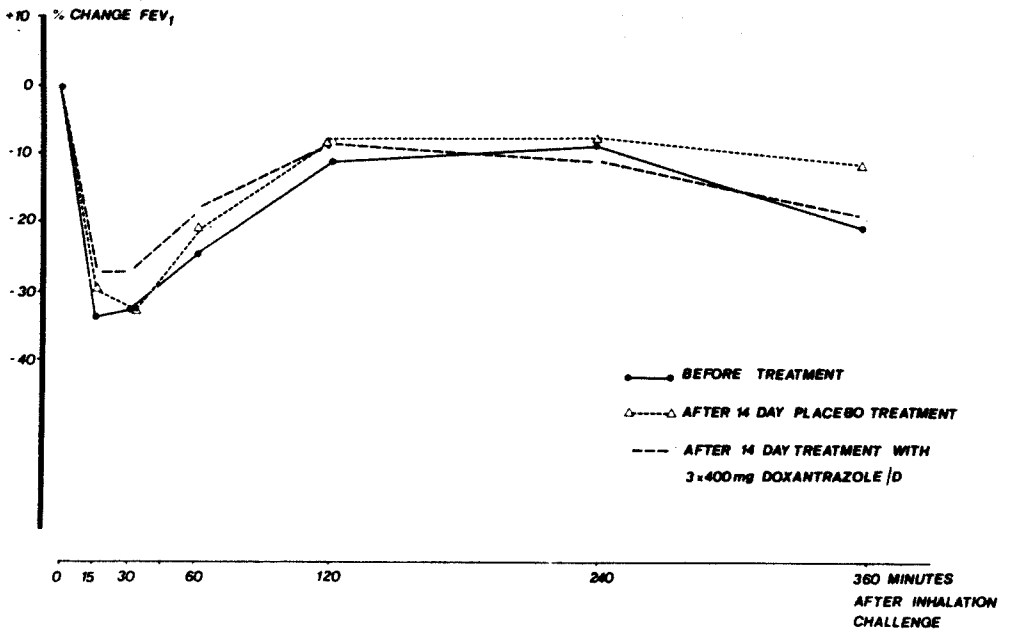


Fig. 4.

Mean change in FEV₁ (as per cent of the initial value) on the different test occasions during the second study.

Effect of chronic doxantrazole treatment on allergen challenge

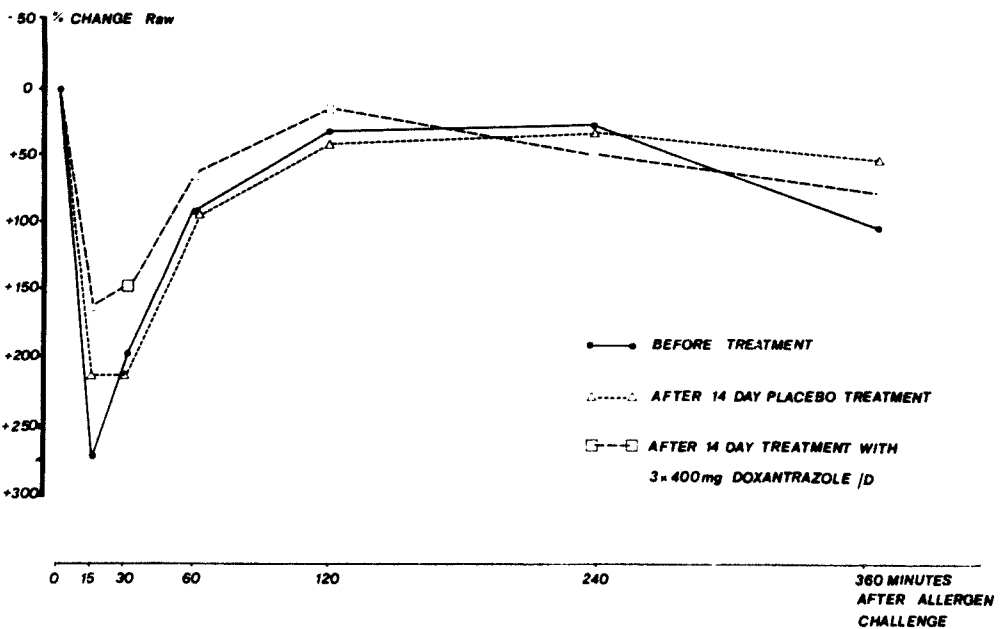


Fig. 5.

Mean change in airways resistance (as per cent of the initial value) on the different test occasions during the second study.

There was no significant effect on the mean of the seven patients after a 14-day treatment with either doxantrazole or placebo. However, two patients out of seven were significantly protected after 14 days of doxantrazole treatment.

One patient on placebo treatment showed a clear inhibition of the FEV₁ decrease after bronchial challenge. Fig. 4 shows the mean results of the Raw measurements for the seven patients during the second study. Here again, there was no significant difference between placebo and doxantrazole treatment.

DISCUSSION

Doxantrazole and DSCG have been shown to act similarly in immediate-type hypersensitivity in animals in that they inhibit the antigen-induced mediator release (1). Preliminary experiments in man (2) suggested that they had a potent inhibitory effect on allergen-induced immediate-type bronchoconstriction.

Our studies do not confirm these initial results. Doxantrazole appears to have only a slight protective effect on allergen-induced bronchoconstriction. The effect is limited to a restricted number of patients, and increasing the dose from 200 mg to 400 mg, either as a single dose or as a 14-day treatment, did not give a significantly better result. There was no significant difference in the effect produced by treatment with doxantrazole or placebo over a 14-day treatment period.

The reason for the difference between our results and those reported previously is not clear. Similar studies and clinical studies are needed for a further evaluation of this new drug.

SUMMARY

The protective effect of oral doxantrazole on allergen-induced bronchoconstriction in man has been tested in two different treatment schedules. A single administration of 200 mg or 400 mg doxantrazole did not result in significant protection for a group of 10 patients. Only two patients after 200 mg,

and three patients after 400 mg received meaningful protection.

A 14-day period of treatment with three times 400 mg doxantrazole per day had no significantly different effect compared with placebo treatment on allergen-induced bronchoconstriction.

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