

From Department of Chest Diseases, Academic Hospital, Ghent, Belgium.
(Dir.: Prof. Dr. M. Van Der Straeten)

THE EFFECT OF ORAL DOXANTRAZOLE ON ALLERGEN-INDUCED BRONCHOSPASM

By

R. PAUWELS, H. LAMONT & M. VAN DER STRAETEN

Doxantrazole, 3-(5-tetrazolyl)-thioanthone 10, 10-dioxide, and disodium cromoglycate (DSCG) act similarly on the inhibition of mediator release in immediate type hypersensitivity (1). The anti-allergic effect of oral doxantrazole has been demonstrated in rats and in a small number of human volunteers (2). The compound appears to be free of significant side effects in animals and in man (1). We studied the effect of an oral administration of a single dose of 200 mg doxantrazole on allergen-induced bronchospasm in 15 patients and compared it with the effect of a single 20 mg inhaled dose of disodium cromoglycate.

PATIENTS AND METHODS

Fifteen patients with a positive history of allergy, positive intracutaneous tests with one or more inhalant allergens, and a positive RAST for one or more allergens were studied. All patients suffered from bronchial asthma and attended the out-patient department of our clinic for diagnostic investigations. They agreed to take part in the study after its nature and purpose had been fully explained to them. No patient had received DSCG prior to the test period and all sympathicomimetics and methylxanthines were stopped 12 h before each test.

Bronchial challenge was performed using an aerosol containing allergen (Bencard) dissolved in Coca's solution. The aerosol was used in a Wiesbadener Doppelinhalator with an airflow of 6 l per min. Inhalation began on each occasion about 9.00 a.m. and lasted 3 min. Lung function tests were performed before, and 15, 30, 60, 120, 240 and 360 min after this.

All patients were first tested (Occasion 1) with an inhalation of Coca's solution alone to exclude any non-specific reaction. On the second test day (Occasion 2) an appropriate allergen concentration was chosen to test the drug effect;

TABLE 1

Pat. No.	Age	Sex	Allergen	Concentration
1	13	M	Dermatophagoides Pteronyssinus	1.2 mg/ml
2	25	M	Derm. Pter.	1.2 mg/ml
3	13	F	Derm. Pter.	0.12 mg/ml
4	28	M	Derm. Pter.	1.2 mg/ml
5	18	M	Derm. Pter.	0.12 mg/ml
6	29	M	Derm. Pter.	1.2 mg/ml
7	21	M	Derm. Pter.	0.12 mg/ml
8	18	M	Grass pollen	6 mg/ml
9	17	M	Derm. Pter.	0.12 mg/ml
10	30	F	Derm. Pter.	1.2 mg/ml
11	39	M	Derm. Pter.	0.12 mg/ml
12	27	F	House dust	50 mg/ml
13	15	M	Grass pollen	0.6 mg/ml
14	19	M	Grass pollen	0.6 mg/ml
15	26	M	Derm. Pter.	0.12 mg/ml

the allergen concentration was increased stepwise to 10-fold at 30 min intervals until a decrease in FEV_1 of more than 20 per cent of the initial value occurred. Lung function parameters were followed for 6 h afterwards.

On the 3rd and 4th test days inhalation using the optimum antigen dose chosen on occasion 2 was preceded by the inhalation of 20 mg DSCG or by taking a tablet containing 200 mg doxantrazole. DSCG was inhaled, using a Spinhaler, 5–10 min before allergen challenge. Doxantrazole was taken by mouth 1 h before inhalation challenge. The order of administration of the two compounds was randomized and there was an interval of at least 1 day between tests.

Lung function tests were performed using a closed circuit spirometer (Godart Expirograph) and the FEV_1 value reported was the highest value obtained in three consecutive manoeuvres.

Airway resistance (R_{aw}) was measured using a constant volume plethysmograph (Jaeger Body Plethysmograph) and the reported value was the mean of six consecutive manoeuvres.

Statistical evaluation was made by *t* test for paired measurements.

RESULTS

Table 1 lists the age and sex of the patients and the nature and concentration of allergen used. The inhalation of Coca's

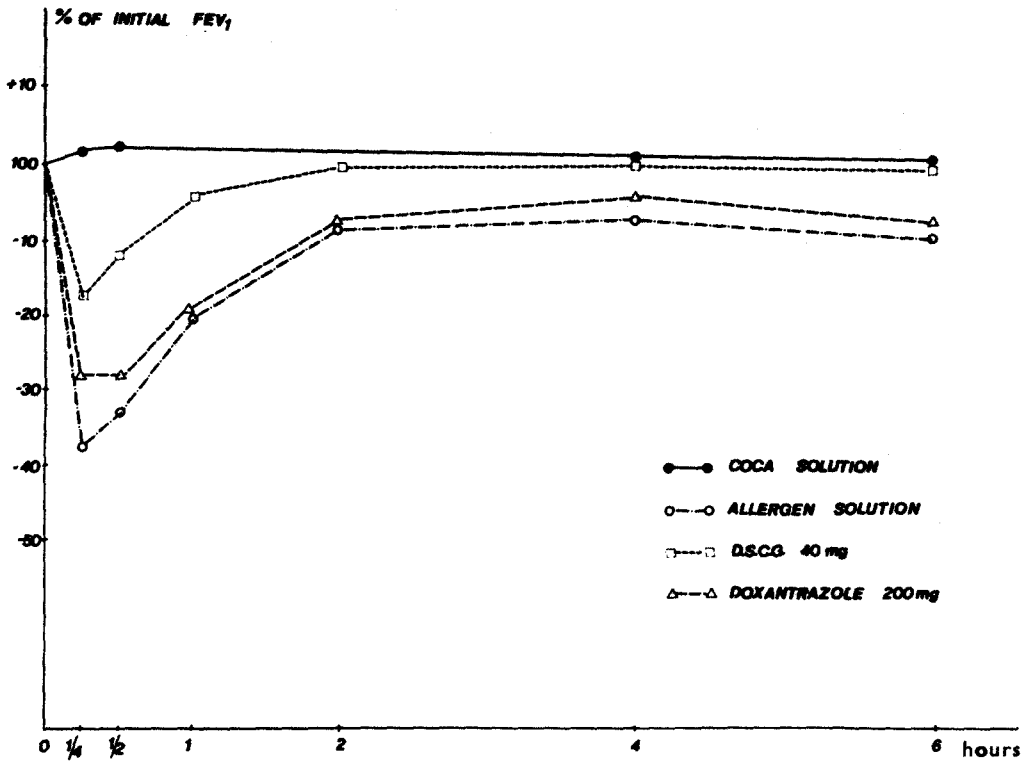


Fig. 1.

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

solution did not cause a significant alteration in FEV₁ or Raw in any of the patients.

Fig. 1 illustrates the mean results of the FEV₁ on the different test days. The inhalation of 20 mg DSCG prior to allergen challenge caused a significant inhibition of the mean fall in FEV₁ at 15, 30 and 60 min after allergen inhalation. No significant effect was seen at later measurements. A 200-mg tablet of doxantrazole taken 1 h before the allergen challenge did not, however, appear to significantly inhibit the mean fall in FEV₁ at any time.

If we assume that in any individual an inhibition of more than 20 per cent of the initial FEV₁ value can be regarded as a clinically useful protection then this was found in nine out of 15 patients after DSCG (Fig. 2) and in four out of 15 patients after doxantrazole. All of these four patients responded well to DSCG.

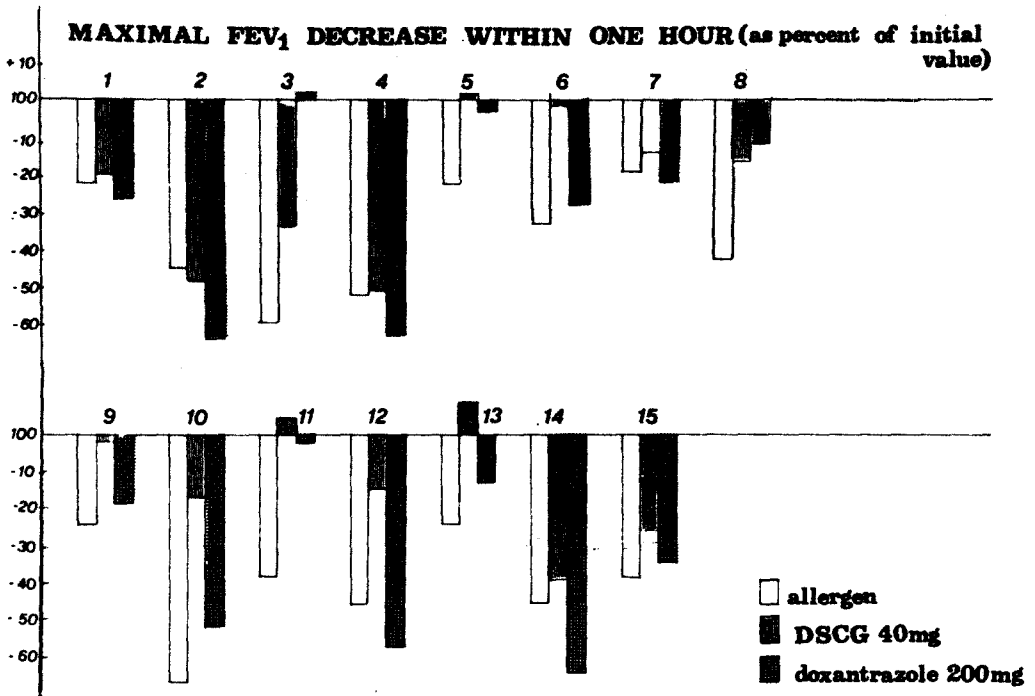


Fig. 2.

Individual results of the maximal decrease of FEV₁ (as per cent of the initial value) within the first hour after allergen challenge.

Fig. 3 illustrates the mean results of the Raw on the different test days. DSCG administration significantly inhibited the increase in Raw at 15, 30 and 60 min. There was no such effect with doxantrazole. Neither drug had a consistent effect on the decrease in FEV₁ and increase in Raw after 6 h.

DISCUSSION

Disodium cromoglycate (3, 4) has been shown to be a useful drug in the treatment of many cases of bronchial asthma. Although its mode of action has not been fully clarified, DSCG has been shown to inhibit, both *in vivo* and *in vitro*, the release of mediators during an immediate-type hypersensitivity reaction (5). Since DSCG is not active when given orally, several drugs have been developed with *in vitro* properties similar to DSCG and with good oral absorption (6, 7, 8). Doxantrazole, when given orally, inhibited rat PCA and anaphylactic

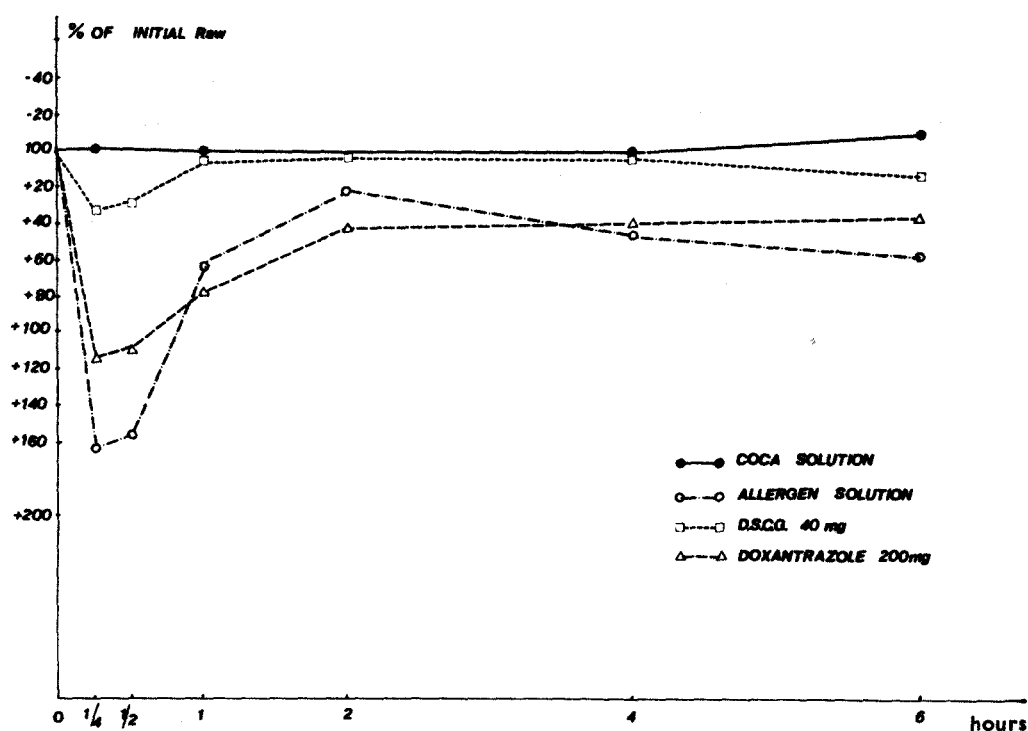


Fig. 3.

Mean change in airway resistance (as per cent of the initial value) on the different test occasions.

bronchoconstriction (1). Two hundred milligrams of the sodium salt of doxantrazole given in a solution 1 h before allergen challenge has also been reported as significantly inhibiting allergen-induced bronchoconstriction in a group of eight asthmatic subjects (2). Our results do not confirm this. The same dose of doxantrazole given in tablet form, did not significantly inhibit allergen-induced bronchospasm in a group of 15 similar patients although this group responded well to the inhalation of DSCG. Only four out of the 15 patients showed a significant inhibition of their bronchoconstriction after the oral intake of doxantrazole, and all were from the group of nine patients who responded to DSCG. The reason why doxantrazole was less effective in our study compared with the initial reports is not clear. Difference in formulation, i.e. drug solution versus tablet, cannot be responsible since absorption in both situations is equal (9). We are now continuing our study of doxantrazole with a higher dose.

SUMMARY

The protective effect of 200 mg doxantrazole given orally on allergen-induced bronchoconstriction has been compared with 20 mg inhaled disodium cromoglycate (DSCG) in 15 patients with bronchial asthma and immediate-type hypersensitivity. Only four out of the 15 patients showed a significant inhibition of their bronchoconstriction after the oral intake of doxantrazole. Nine patients were significantly protected by 20 mg DSCG. All patients responding to doxantrazole also responded well to DSCG.

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Authors' address:

Dr. Romain Pauwels
Department of Chest Diseases
Academic Hospital
De Pintelaan 135
9000 Ghent
Belgium

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