gin shortly, which it is hoped will confirm the trends established by the present study.

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Inhibition of Experimental Asthma in Man by a New Drug (AH 7725) Active When Given by Mouth

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Summary

A new drug, AH 7725, with properties similar to those of disodium cromoglycate (Intal) has the additional feature of being effective when taken by mouth. Six patients with allergic asthma were studied by bronchial challenge tests with antigen. In every one the drug was found to inhibit (either partially or completely) the immediate-type asthmatic response. Late responses were not influenced. The results were significant at the 0.5% level.

These findings suggest that AH 7725 given by mouth may be able to inhibit naturally occurring asthmatic attacks in allergic patients. In this case its particular advantage as a prophylactic drug would lie in the treatment of very young asthmatic children and other patients who cannot take drugs by inhalation.

Introduction

In clinical practice disodium cromoglycate (Intal) has proved to be a useful prophylactic drug in asthma. Experimental studies show that it inhibits immediate-type hypersensitivity

reactions to antigen both in vitro and in vivo (Cox, 1967; Altounyan, 1967). Disodium cromoglycate can also inhibit the immediate-type bronchial reaction after challenge with antigen, but as a single dose it does not consistently alter the late component in dual bronchial reactions (Pepys *et al.*, 1968). One of its limitations is that since it is poorly absorbed by the gut it is inactive when taken by mouth.

A new compound, AH 7725, has been shown to have similar properties to those of disodium cromoglycate both in laboratory models (Assem, 1973; Fullarton *et al.*, 1973) and when given by inhalation in experimental asthma (Gayard, 1974). This new drug has the additional property of being relatively well absorbed from the gut and can therefore be taken by mouth.

We here report experiments testing the protective effect of AH 7725 given by mouth to asthmatic patients subjected to bronchial challenge with antigen.

Materials and Methods

The structural formula of AH 7725 is shown in the fig. Blood levels after the administration of single doses by mouth to normal volunteers have been measured by Woodings (1974). After doses of 200 to 500 mg in solution peak levels ranging from 2.7 µg/ml of plasma were reached in one and a half to two and a half hours.

BRONCHIAL TESTING PROCEDURE

Tests were carried out by the closed-circuit method (Herxheimer, 1951; McAllen, 1961), in which antigenic material is nebulized into the circuit and measured amounts of antigen can be inhaled by the patient. Asthmatic attacks

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Structure of AH 7725 and of its predecessors AH 7079 and AH 6556.

of predictable degree can be induced by this method, and the amount of reduction in ventilatory function from a given dose of antigen is reproducible (McAllen *et al.*, 1970). Testing is started with a low dose of antigen, and only one test is done on any one day in order to record any reaction coming on after several hours. Tests are repeated at not less than weekly intervals in order to prevent unwanted local desensitization by the testing procedure (Assem and McAllen, 1973 a). The dosage of antigen is increased by 100 to 200% at each session until the required asthmatic response is obtained. For the purpose of this investigation a reduction in forced expiratory volume in one second (FEV₁) of 20 to 30% was thought necessary, so that the drug could be tested in as severe an asthmatic attack as we considered ethical to induce and which would be of no great discomfort to the patient.

The antigens used were grass pollen and house-dust mite extracts. The tests were carried out on patients who already had asthma due to these antigens and were done in winter months when grass pollen is absent from the air.

INTERPRETATION OF RESULTS

Immediate asthmatic reactions were measured by a fall in FEV₁ and forced vital capacity (FVC) coming on between 5 and 15 minutes after the inhalation was finished and lasting 15 to 30 minutes.

Late asthmatic reactions may be of two types. The first is a late component of a dual reaction, in which the immediate component is a typical immediate-type reaction and is followed in 4 to 12 hours by another drop in ventilatory function which usually lasts for several hours and may persist on and off for many days. The second type is similar in effect to the first but occurs in the absence of an immediate reaction. In this investigation late bronchial reactions were measured on Wright peak flow meters taken home by the patients.

PATIENTS

Volunteers were drawn from the asthma clinic at University College Hospital. All were adult men aged 25-45 years with typical allergic asthma easily reversible by bronchodilator drugs. All gave fully informed consent to the procedures. Six of them in whom immediate positive bronchial reactions had been established were chosen for study. Three had only immediate reactions and three had dual reactions. Five of them

were allergic to grass pollen and one was allergic to *Dermatophagoides pteronyssinus* (house-dust mite).

TRIAL DESIGN

After the preliminary challenge tests, in which it had been established that a reduction in ventilatory function of 20 to 30% could be provoked within 15 minutes of the test, the patients were given three further tests at seven-day intervals in the following order. (a) The dosage of antigen which provoked the required fall in ventilatory function was confirmed. (b) Pretreatment with a dose of 500 mg AH 7725 in 30 ml of water was given by mouth to the patient on an empty stomach two hours before the challenge test. The challenge was repeated with the same dose of antigen as in test a. (c) Pretreatment with a placebo of identical taste and appearance was given two hours before the test. Challenge was again repeated with the same dose of antigen. The trial was carried out as a single-blind procedure but the patients were under the impression that two drugs were being compared.

Results

The results set out below refer only to the immediate response to bronchial challenge, since the late responses were unchanged by the drug (table).

Prophylactic Effect of AH 7725 in Bronchial Challenge with Antigen

Subject No.	Antigen and Dose needed to induce Asthmatic Reaction	Test	Immediate Reaction to Allergen Challenge			Late Reaction (% Reduction in PEFR)
			% Maximum Reduction in:		Isoprenaline Required*	
			FVC	FEV ₁		
1	Grass pollen 2.5 µg	a	7	31	+	43
		b	0	0	—	39
		c	0	31	+	44
2	Grass pollen 5 µg	a	33	34	+	
		b	0	15	—	
		c	9	30	+	
3	Grass pollen 5 µg	a	16	32	+	24
		b	9	7	—	24
		c	10	26	+	26
4	House-dust mite 1.25 µg	a	27	26	+	
		b	8	15	—	
		c	20	26	—	
5	Grass pollen 1.5 µg	a	9	21	+	12
		b	0	8	—	14
		c	8	23	+	13
6	Grass pollen 7.5 µg	a	5	23	+	
		b	2	2	—	
		c	4	13	—	

*Isoprenaline was given by inhalation to cut short asthmatic attack if subject became uncomfortable.
PEFR = Peak expiratory flow rate.

In test a the mean fall in FEV₁ was 27.9% of the control level (range 21 to 34%) and in FVC 16.2% (range 5 to 33%). In test b the mean fall in FEV₁ was 7.9% (range 0 to 15%) and in FVC 3.2% (range 0 to 9%). No side effects were observed. In test c the mean fall in FEV₁ was 24.8% (range 13 to 31%) and in FVC 8.5% (range 0 to 20%).

FEV₁ showed the most sensitive response to bronchial challenge. When using the paired *t* test for statistical analysis the fall in FEV₁ was significantly less after pretreatment with the active drug than after placebo (0.001 < *P* < 0.005).

Conclusions

AH 7725 had an inhibitory effect on the immediate-type asthmatic response induced by inhaled antigen in bronchial challenge tests, but as a single dose it did not influence the delayed component of the dual response in the patients we examined.

The drug is active when taken by mouth.

Discussion

These results show that AH 7725 when given by mouth can inhibit the immediate bronchial response to inhaled antigen in asthmatic patients. It has no bronchodilator effect (Gayrard, 1974) and its activity is most likely to be explained by the inhibition of release of mediators of immediate-type allergic responses, which has already been shown in laboratory work.

AH 7725 has similar inhibitory properties to those of disodium cromoglycate and also to those of its own predecessors AH 6556 and AH 7079 (Assem, 1973; Assem and McAllen, 1973 b). It is, however, exceptional in being active when given by mouth. So far as we know this is the first report on a drug for the prophylaxis of asthma which is active when given by mouth.

Our results encourage the hope that AH 7725 has a potential in future clinical practice. Many asthmatic patients would prefer to take a prophylactic drug by mouth rather than by inhalation, and this new compound may be of particular value in very young children with asthma and in those adults who cannot master the necessary inhalation technique for using disodium cromoglycate. The possible use of AH 7725 in allergic conditions which require systemic treatment awaits investigation.

We wish to thank Dr. E. P. Woodings and Allen & Hanburys Limited for supplies of AH 7725 and for allowing us to report the results on the plasma levels of this drug.

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MEDICAL MEMORANDA

Mitral Regurgitation due to Rupture of Chordae Tendineae by Calcified Atrial Myxoma

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Patients with left atrial myxoma characteristically present with a history of progressive shortness of breath, often punctuated by syncopal attacks, and physical signs of mitral valve obstruction (Goodwin, 1963; Greenwood, 1968; Harvey, 1968). Predominant or "pure" mitral regurgitation due to left atrial myxoma has been reported but is uncommon (Cohen et al., 1963; Penny et al., 1967; Wittenstein et al., 1959). This report describes a patient with a calcified left atrial myxoma who presented with sudden severe mitral regurgitation due to ruptured chordae tendineae.

Case Report

A 44-year-old machinist, previously well and active, abruptly developed dyspnoea and orthopnoea during the first week of December 1972. He was admitted to his local hospital where he was found to have cardiac enlargement, pulmonary oedema, and bilateral pleural effusion. The electrocardiogram showed sinus rhythm with evidence of left atrial enlargement. A heart murmur had been heard one year earlier, but he was told "not to worry" about his heart. There was no history of rheumatic fever, chest pain, calf tenderness or swelling, or fever or chills. Digitalis (digoxin 0.25 mg/day) and a diuretic (Lasix

40 mg/day) were given but dyspnoea, orthopnoea, and fatigue persisted, atrial fibrillation developed, and he was referred for consultation.

On examination he was very thin and dyspnoeic at rest. Atrial fibrillation was present, the blood pressure was 110/60 mm Hg, there were no signs of peripheral embolism, and the optic fundi were normal. The carotid pulse was small and rapid, the venous pressure was raised, and there was prominent systolic pulsation of the neck veins. The apex beat was in the mid-clavicular line and there was a prominent, diffuse systolic pulsation in the third to fifth interspaces midway between the sternum and the apex. The pulmonary valve closure sound was increased and the aortic component normal. A loud first heart sound was followed by a grade III/VI regurgitant murmur heard best at the apex. There was a prominent early third heart sound and a faint mid-diastolic apical murmur. The lungs were clear. The liver was palpable 2 cm below the right costal margin in the mid-clavicular line. Chest x-ray examination showed enlargement of the left ventricle and left atrium, pulmonary venous congestion, and costophrenic septal (Kerley's B) lines.

After some initial improvement progressive dyspnoea and orthopnoea had recurred after three months. Cinefluoroscopy showed a mobile, calcified mass in the left atrium which appeared to enter and partially obstruct the mitral valve orifice during diastole. Pulmonary capillary wedge pressure and right heart pressure were raised (see table) and there was evidence of mitral and tricuspid regurgitation. At operation the left atrium was found to contain a large, calcified myxoma (see fig.) attached by a 1-cm pedicle to the atrial septum just below the limbus of the fossa ovalis. The mitral valve leaflets were thickened and damaged and many chordae tendineae were ruptured.

Cardiac Catheterization Data

Site of Sample	Oxygen Saturation (%)	Pressure (mm Hg)
Pulmonary capillary (wedge)	—	V — 45 (mean* 30)
Pulmonary artery	40, 41	85/45 (mean 44)
Right ventricle (body)	36, 37	85/10, Right ventricle end diastolic pressure — 20
Right ventricle (infundibulum)	37, 38	—
Right atrium	34	C — 25 } (mean 18)
Radial artery	—	V — 23 } (mean 80)
		110/70 (mean 80)

*Mean pressures are derived from the phasic pressures by electronic integration.

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