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EFFECT OF INDOMETHACIN IN ASTHMA: EVIDENCE AGAINST A ROLE FOR PROSTAGLANDINS IN ITS PATHOGENESIS

A.P. SMITH
Chest Unit, King's College Hospital, London SE5 9RS

1 A clinical trial of the effects of indomethacin (200 mg daily) failed to show any objective evidence of improvement in six patients.

2 The same dose failed to inhibit exercise and antigen challenge induced bronchoconstriction, and this was considered to be evidence against the hypothesis that prostaglandins act as chemical mediators in the pathogenesis of asthma.

Introduction

Prostaglandins are released by lung tissue during anaphylaxis, (Piper & Walker, 1973) and are known to have potent effects on human bronchial muscle. It has been suggested that bronchoconstrictor prostaglandins could act as chemical mediators in the allergic response, and thereby contribute to the bronchospasm that occurs in asthma. Indomethacin inhibits prostaglandin synthesis, a property which could account for its anti-inflammatory and analgesic activity (Vane, 1971). The effects of indomethacin were therefore studied in patients with bronchial asthma.

Methods

Three clinical trials of indomethacin were conducted in twenty-one asthmatic patients aged 15-34 years. All had a family history of atopic disorders, positive skin prick tests to common allergens, and had well documented variability in symptoms. A careful history was taken to exclude idiosyncracy to analgesics, and each patient's consent obtained prior to each experiment.

Double-blind controlled trial of indomethacin

Six asthmatic patients were treated for 2 weeks. Clinical details are shown in Table 1. Indomethacin, (25 mg orally, four times daily and 100 mg per rectum at night) was taken for a week, and identical capsules and suppositories containing inert material only was taken for a second week. The order of drug and placebo administration was randomized and the trial conducted under double-blind conditions. Each patient noted the best of

Table 1 Clinical details of patients taking part in the controlled trial of indomethacin (200 mg daily)

Patient	*Age (years)*	*Sex*	*Pre-trial peak flow rate (litres/min)*	*% Predicted*	*Other treatment*
1	15	M	126	22.7	Disodium cromoglycate, salbutamol
2	36	F	117	28.5	Prednisone (5 mg daily), salbutamol
3	32	F	285	47.5	Predisone (5 mg daily), salbutamol
4	22	M	280	43.8	Beclomethazone diproprionate
5	23	F	172	41	Hyposensitization, beclomethazone diproprionate
6	24	M	316	48.6	Salbutamol

Pre-Trial peak flow rate (litres/min) refers to a mean of three readings taken on three occasions within the week preceeding the trial.

three consecutive peak flow rate (Wright's peak flow meter) recordings at 09.00 h, 12.00 h and 21.00 h each day and completed a daily diary card recording the degree of breathlessness, the number of times each day he used a bronchodilator aerosol and the number of nocturnal attacks of asthma. The results for all patients were measured and compared with corresponding values obtained during the placebo week by Student's *t*-test.

Effect of indomethacin on exercise-induced asthma

Six of the asthmatic patients exercised on a bicycle ergometer for six minutes at a maximum tolerable level. Measurements of forced expired volume in 1 s (FEV_1) were obtained before, immediately after exercise and at 5 min intervals thereafter. Each patient then received for one week indomethacin (200 mg daily by mouth and as suppositories) and the exercise was repeated.

Effect of indomethacin on the response to antigen challenge

Nine patients were studied. Bronchial challenge tests were performed as a means of selection and assessment before a trial of hyposensitization treatment with *D. pteronyssinnus* antigen. Freeze dried *D. pteronyssinnus* antigen (Bencard) was diluted on a weight/volume basis in normal saline. Ten breaths of each increasing successive tenfold dilution were administered via the nebulizer of a Bennett respirator, and the dose resulting in a clearly-defined immediate fall in FEV_1 of at least 15% was determined. Patients were admitted to hospital for the procedure and discharged the following day, taking indomethacin (200 mg daily by mouth and as suppositories). The following week the challenge test was repeated.

Table 2 Mean change in thrice daily peak flow rate readings (litres/min) in six allergic asthmatic patients during a week of treatment with indomethacin (200 mg/24 h) or placebo respectively. ($P > 0.8$ Student's *t*-test)

	Mean peak flow rate (litres/min) at		
Treatment	*09.00 h*	*12.00 h*	*21.00 h*
Indomethacin	230	242	247
Placebo	221	232	236

Results

Double-blind trial

The results are shown in Table 2. All patients completed the study but three suffered from diarrhoea during the week of active treatment. There was no improvement in any of the symptoms recorded on the diary card, or in peak flow rate, but one experienced an increase in symptoms during the week of indomethacin treatment.

Table 4 Effect of indomethacin on response to antigen challenge. Antigen dose w/v dilution. $P > 0.1$, Wilcoxon's test

Patient	*Antigen dose*	*% fall in FEV_1* *Before*	*After*
1	10^{-5}	28.6	30
2	10^{-4}	22.2	13.7
3	10^{-6}	17.1	9.5
4	10^{-4}	29.4	16.6
5	10^{-3}	26	51.5
6	10^{-5}	66.7	33.3
7	10^{-6}	25	33.3
8	10^{-4}	34.6	26.9
9	10^{-5}	25	23.1
Mean	—	30.5	26.5
s.e. mean		4.8	4.3

Table 3 Mean (± s.e. mean) FEV_1 (litres) in six asthmatic patients following 5 min maximal exercise. Indomethacin had no significant effect on FEV_1 changes at 5 or 10 min from cessation of exercise. ($P > 0.1$ Student's *t*-test).

	FEV_1 before exercise (litres)	*FEV_1 at intervals after 5 min maximal exercise (litres)*		
		1 min	*5 min*	*10 min*
Before indomethacin treatment	3.0(0.3)	3.2(0.3)	2.1(0.4)	2.2(0.3)
After indomethacin treatment	2.7(0.4)	2.8(0.4)	2.2(0.4)	2.1(0.5)

Exercise asthma

There was a slight increase in FEV_1 during exercise (Table 3). Indomethacin treatment had no effect on the post-exercise bronchoconstriction.

Antigen challenge

The dilutions of antigen that caused a definite fall in FEV_1 and the percentage changes in FEV_1 before and after indomethacin are shown in Table 4. Mean FEV_1 ± s.e. mean fell from 2.51 ± 0.16 litres to 1.7 ± 0.19 litres (mean 30.5%), after 1 week's treatment mean FEV_1 fell from 2.8 ± 0.25 litres to 2.1 ± 0.26 litres (26.5%). These results were not significantly different. The responses of patients 2, 3 and 4 were reduced after indomethacin. The reason for this may have been due to challenge with antigen that had been dissolved the previous week which may have lost some of its potency. Subsequent tests were performed with fresh antigen on each occasion.

Discussion

The suggestions that have been made concerning the possible importance of prostaglandins in the pathogenesis of asthma have been based upon the observations that prostaglandins E_2 and $F_{2\alpha}$ occur in the lungs and bronchi (Karim, Sandler & Williams, 1967), have opposite and antagonistic effects on bronchial muscle (Sweatman & Collier, 1968, Smith & Cuthbert, 1972) and are released along with other chemical mediators of anaphylaxis (Piper & Vane, 1969, Piper & Walker, 1973). Recently it has been shown that the prostaglandin metabolite 15-keto, 13, 14, dihydro $PGF2\alpha$ appears in the blood following antigen challenge of asthmatic patients (Gréen, Hedquist & Svanborg, 1974) suggesting the release of $PGF_{2\alpha}$ during allergen provoked bronchospasm. Measurement of $PGF_{2\alpha}$ synthesis *in vitro* (Dunlop & Smith, unpublished data) confirms that this bronchoconstrictor substance is released from passively sensitised human bronchus during bronchospasm provoked by allogen exposure.

Indomethacin (200 mg daily) reduces urinary excretion of prostaglandin metabolites by 98% (Samuelsson, 1973) suggesting that this dose of the drug almost completely inhibits prostaglandin synthesis. The asthmatic patients however showed no improvement in asthmatic symptoms nor became resistant to antigen or exercise challenge after receiving indomethacin for one week, and these results must cast doubt on the hypothesis that prostaglandins are important mediators of bronchospasm in asthma. Similar results were obtained by Strandberg & Hamberg (1974) in the guinea-pig. Complete supression of a urinary prostaglandin metabolite by indomethacin had no effect on the antigen challenge response of the airways although increased levels of metabolite had been recorded during challenge of untreated animals. This suggests that prostaglandin release during antigen challenge is a secondary phenomenon, perhaps as a result of bronchial muscle contraction (Orehek, Douglas, Lewis & Bouhuys, 1973) or cell distortion during exocytosis of histamine granules. Further experiments which are in progress will clarify these matters.

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