

The effect of a new anti-allergic drug ICI 74, 917, given by aerosol, on nasal stenosis induced by allergen

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Summary

Nasal airways resistance was measured in ten patients with allergic rhinitis during intranasal application of an extract of grass pollen. Pretreatment with placebo did not inhibit the increase in nasal airways resistance, whereas ICI 74,917 administered from a pressurized aerosol gave almost complete protection. ICI 74,917 was well tolerated and no evidence was obtained of local hyposensitization during the period of the study.

Introduction

Of the various treatments for allergic rhinitis, agents which are believed to act by stabilization of mast cells have stimulated considerable interest. The first generally available such compound, disodium cromoglycate, has contributed to a better understanding of type I allergic reactions and has been extensively tested in allergic reaction of the nose. Administration of disodium cromoglycate to the nose by an insufflator (Ryncomar, Rynacrom) is cumbersome and efficacy cannot be demonstrated in all cases.

ICI 74,917 is a phenanthroline which inhibits passive cutaneous anaphylaxis in rats, not by antagonism of mediators, but in a similar way to disodium cromoglycate (Evans *et al.*, 1974; Evans & Thomson, 1975). ICI 74,917 is, however, approximately 300 times as potent as disodium cromoglycate and can, therefore, be administered from a pressurized aerosol. Recently, Mygind & Thomsen (1975) have demonstrated protection against sneezing and rhinorrhoea when ICI 74,917 was administered to the nose before challenge with allergen in patients with nasal allergy. The protection was significantly greater than occurred with placebo or with disodium cromoglycate.

No reports have been published on the effects of ICI 74,917 on the nasal obstruction induced by allergen. Previous studies from this laboratory have evaluated beclomethasone dipropionate and sodium cromoglycate using a new method for the measurement of nasal airways resistance (Vilsvik, Jenssen & Walstad, 1975; Jenssen, 1973). Similar methods have now been applied to assess ICI 74,917.

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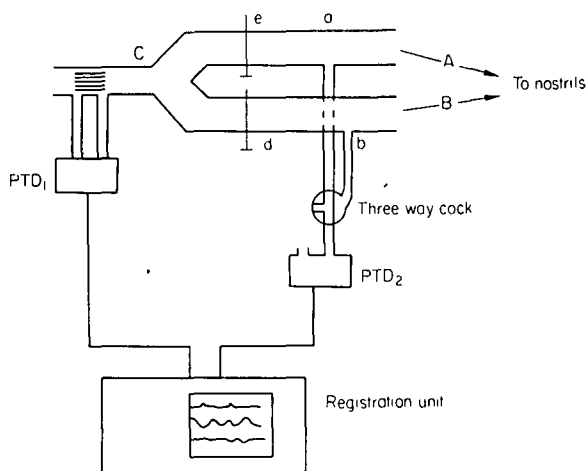


Fig. 1. Apparatus for measuring nasal resistance to airflow (see text).

Materials and methods

Nasal airways resistance

The method for measuring nasal airways resistance has been described in detail previously (Jenssen, 1973; Vilsvik *et al.*, 1975). Figure 1 shows the design of the system. It consists of an Elema Schonander Mingograf used as registration unit and a Fleisch tube (C) for measuring air flow. The Fleisch tube is connected through a Y-shaped tube (AB) to two disposable plastic tubes which are inserted into the patient's nostrils. The branches of the Y-shaped tube can be independently clamped at (e) and (d). The pressure between the clamp and the patient's nostrils is measured on either side by a pressure transducer (PTD₂). By clamping tube (A) at (e) and asking the patients to inspire through the nose, the air flow through the Fleisch tube (C) and the appropriate nasal cavity can be measured. The negative pressure in tube (A) at (a) is equal to the pressure gradient between the atmosphere and the naso-pharynx providing that the nasal cavity connected to the tube (A) is not completely obstructed.

The flow was determined at a standard pressure gradient of 20 cmH₂O. From flow and pressure, the nasal airways resistance was determined. The standard deviation due to apparatus error was less than 3%.

Patients

Ten outpatients (five females and five males), aged 14–36 years, were admitted to the study after giving informed consent. All of them had allergic rhinitis due to grass pollen. None were using drugs other than those being assessed during the study and none had been hyposensitized.

Drugs

ICI 74,917 was administered from a pressurized aerosol through a nasal adaptor to the nasal passages. One actuation containing 0.5 mg was delivered to each nostril. The placebo aerosol was identical in external appearance and contained sodium sulphate to impart a bitter taste similar to that of ICI 74,917.

Procedure

Each patient attended for four tests. On the first occasion the dose of allergen was determined and the response was measured. On the fourth visit this procedure was repeated to check whether hyposensitization had occurred.

At the second and third visits placebo or ICI 74,917 was administered according to a random scheme and in double blind fashion. At least 1 week passed between repeated challenge in the same nostril.

For each test, patients attended the clinic at 08.00 hours. Nasal airways resistance (NAR) was measured before administration of the treatment under test. After 15 min, allergen was administered to the nostril and after a further interval of 15 min, NAR was measured again.

Allergen

Mixed grass-pollen 1:100 manufactured by Allergen Laboratoriet, Kobenhavn.

Statistical analysis

Student's *t*-test was used for statistical evaluation.

Results

Nasal airways resistance

(1) *Effect of allergen.* Administration of allergen after pretreatment with placebo caused a nine-fold increase in NAR (Table 1 and Fig. 2). Pretreatment with ICI 74,917 caused a large reduction in the response to allergen and the increase in NAR was significantly smaller than after placebo ($P < 0.05$). These results are shown in Fig. 2.

(2) *Effect of repeated challenge.* During the first and last challenges (Table 1) when no pretreatment had been given, NAR showed a large increase. The increase in NAR was greatest at the final test which shows that for the group as a whole, hyposensitisation did not occur.

Table 1. Values for nasal airways resistance (mean $\pm$ s.e. for ten patients) before and after challenge

		None (First visit)	Placebo	ICI 74,917	None (Final visit)
Nasal airways resistance (cmH ₂ O/L/sec)	Before challenge	19.3 $\pm$ 3.1	20.0 $\pm$ 2.1	17.9 $\pm$ 1.7	22.7 $\pm$ 3.3
	After challenge	143 $\pm$ 89.4	178 $\pm$ 98.8	28.2 $\pm$ 8	287 $\pm$ 109

Subjective response

Seven of the ten patients had a definite subjective preference for ICI 74,917; the values in NAR confirmed the benefit in these patients.

One patient had no preference. The increases in NAR after placebo and after ICI 74,917 were similar. Two patients preferred placebo.

All patients tolerated ICI 74,917 well and no adverse effects occurred.

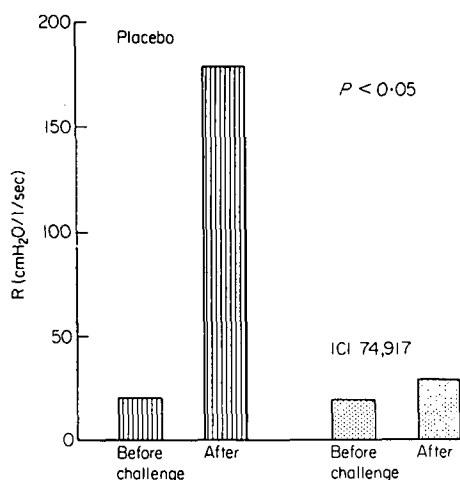


Fig. 2. Nasal resistance before and after allergen challenge in the ten patients included in the study.

Discussion

The patients admitted to the present study were allergic to grass pollen only. None was using drugs or had undergone hyposensitization therapy. The trial was performed in February to avoid the influence of airborne pollen during the course of the trial. As can be seen in Table 1, the patients were in a stable state during the whole study and no 'carry-over' effect was demonstrable.

During the course of the trial, no hyposensitization has been detected. On the contrary, a slightly increased reactivity occurred. This is in contrast to the findings of Taylor & Shivalkar (1972).

The nasal provocation performed in this trial was a massive challenge. The modest increase in NAR of 64% after ICI 74,917 contrasts with the large increase in NAR of 790% after placebo. This large difference suggests impressive protection with ICI 74,917. The preferences of the patients paralleled the objective measurements.

Our previous results have shown consistency with those from other centres (Jenssen, 1973; Vilsvik *et al.*, 1975; Pelikan *et al.*, 1970; Taylor & Shivalkar, 1971; Mygind, 1973). Similarly, our results with ICI 74,917 in nasal provocation conform with those of Mygind & Thomsen (1975).

ICI 74,917 appears to have a similar mode of action to disodium cromoglycate. Administration of disodium cromoglycate to the nasal passages and to the lungs is complicated. The administration of ICI 74,917 as an aerosol is simpler and, therefore, preferable.

The result of the present trial justifies further clinical studies, not only in allergic rhinitis, but also in patients with allergic asthma.

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