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ICI 74,917: A NEW ANTI-ALLERGIC DRUG ADMINISTERED BY PRESSURISED AEROSOL

By

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The discovery of disodium cromoglycate (DSCG, Intal®) by Altounyan (1) not only contributed to an understanding of immediate hypersensitivity reactions, but is also a valuable addition to the treatment of certain types of asthma and allergic rhinitis (2, 12). DSCG, however, has some shortcomings. It does not act in all patients suffering from allergic asthma and rhinitis (3). As the effective dose is large, DSCG cannot be given in a pressurised aerosol and is therefore given as a powder. The duration of the protective effect is short, and continuous protection, particularly during the night, is difficult to maintain (3, 7).

ICI 74,917 is a phenanthroline with anti-allergic properties. It inhibits passive cutaneous anaphylaxis in the rat and mouse and is approximately 300 times as potent as DSCG (5, 6). In the guinea pig, bronchospasm induced by allergen is reduced when the animal is treated with ICI 74,917 before allergen challenge. These actions are not due to antagonism of mediators released during Type I allergic reactions, but are due to inhibition of release of mediators (6). ICI 74,917 may, therefore, be of value in the treatment of asthma and allergic rhinitis. Because of its potency, the small quantities of ICI 74,917 can be administered by a pressurised aerosol.

The present trial was designed to answer two questions:

1. Is ICI 74,917 active during provocation with allergen in patients with allergic rhinitis?

2. What is its degree of efficacy and duration of action compared with DSCG?

PATIENTS AND METHODS

Ten young persons suffering from allergic rhinitis with hypersensitivity to grass pollen were studied between February and April, a period which is outside the grass pollen season. Each informed subject gave consent and was exposed to serial challenges with intranasal allergen on three occasions with intervals of at least 1 week. The challenges were carried out with the same dose of allergen before, and 30 min, 2 hours and 4 hours after administration of treatment. The three treatments given in random sequence to each test person were:

1. ICI 74,917 0.5 mg (1 puff) into each nostril delivered from a pressurised aerosol canister equipped with a special nasal adaptor.
2. Matching placebo for ICI 74,917, 1 puff into each nostril.
3. DSCG powder 10 mg into each nostril delivered from the commercially available Rynacrom® applicator.

None of the subjects had previously received treatment with DSCG. Before each challenge series they were informed that the aerosol/powder might be active or might be placebo.

Several studies on allergic rhinitis have included measurements of nasal airway resistance by rhinomanometry. This method, however, is less suitable for serial challenges because the single challenge may provoke some degree of delayed nasal obstruction (10). We therefore decided to quantify two other clinical features, namely sneezing and rhinorrhoea. The following procedure was evaluated and was found to be simple and sufficiently reliable for the purpose. Immediately after the challenge, the subject assumed a "praying" position with the head bent forward and the hands folded. For a period of 15 min the subject counted and registered the number of sneezes and drips from the nose. These were added together to give the "sneeze-drip score".

In a preliminary session the allergen dosage for each subject was determined such that a sneeze-drip score of between 15 and 30 was obtained. In three patients 2,000–6,000 pollen grains from timothy grass (manufacturer: Allergologisk Laboratorium, Copenhagen) were applied by means of a rubber balloon and a capillary tube. In seven patients 0.25 ml of a dialysed allergen extract of timothy grass was sprayed intranasally (manufacturer: Allergologisk Laboratorium, Copenhagen). The concentration varied from 1/20 to 1/50 w/v. These doses of allergen represent a severe challenge as they correspond to the amount of allergen inhaled during 1 day–1 week in the grass pollen season.

The first challenge was carried out between 8 and 9 a.m. When the nose was again completely clear, as checked by rhinoscopy, the trial medication was given; this usually required an interval of 1 hour. The patient was challenged half an

TABLE I
Nasal Symptom Scores Induced by Local Application of Allergen Before, and Half an Hour, 2 Hours and 4 Hours After Intranasal Administration of ICI 74,917, DSCG or Placebo.

Patient no.	ICI 74,917				Disodium cromoglycate				Placebo			
	Before	30 min	2 hours	4 hours	Before	30 min	2 hours	4 hours	Before	30 min	2 hours	4 hours
1	18	4	9	16	20	12	16	25	25	20	20	30
2	30	9	19	25	24	22	17	25	15	12	16	15
3	35	16	10	22	41	26	33	38	31	28	46	38
4	26	8	22	24	27	6	18	30	23	30	21	22
5	34	0	25	25	51	47	52	62	42	37	33	32
6	35	9	15	21	45	46	64	44	40	38	44	36
7	20	24	17	22	18	21	31	22	25	18	21	22
8	10	0	4	10	15	11	14	14	10	16	15	14
9	34	14	14	22	41	16	24	44	30	33	27	46
10	22	29	27	30	33	15	36	34	32	40	36	65

TABLE 2
Mean Number of Sneezes and Drips.

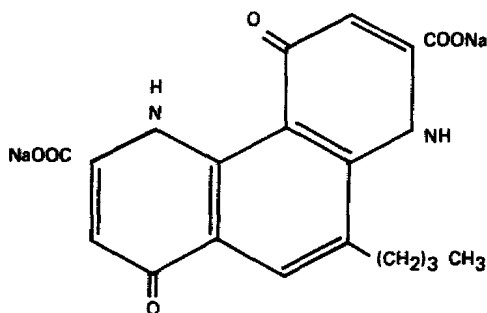
	Pre-treatment	Time after treatment		
		30 min	2 hours	4 hours
ICI 74,917	26.4	11.2	16.2	23.7
DSCG	31.5	22.2	30.5	33.9
Placebo	27.3	27.2	27.9	32.0

hour, 2 hours and 4 hours after the treatment was applied to the nasal mucosa. Each time, the nostril with the greater air flow was chosen for challenge.

The number of challenges with allergen never exceeded four in a single day. After this, most patients had minor nasal symptoms for some days. Symptoms were alleviated by giving the patient xylometazolin (Otrivin®) and beclomethasone dipropionate aerosol (Beconase®) for 2 days after each challenge series. In all cases at least 1 week passed between finishing one treatment and starting the next challenge series.

RESULTS

Patients pretreated with placebo showed no evidence of a decreasing sneeze-drip score after repeated challenge over the period of 4 hours (Table 1). In addition, there was no evi-



ICI 74,917 disodium salt

Fig. 1.

ICI 74,917 disodium salt.

TABLE 3

Treatment Means Adjusted for Pre-Treatment Values and also for the Bias Caused by the Imbalance in the Random Scheme According to which Treatments were Assigned. The Standard Error of the Difference between any Two Means is Given.

	Time after treatment		
	30 min	2 hours	4 hours
ICI 74,917	11.7	16.1	24.0
DSCG	22.4	29.8	34.2
Placebo	27.4	27.9	32.4
S.E. of the difference in means	4.59	3.88	4.32

dence of local hyposensitization from session to session in spite of the administration of 12 challenges over a period of 1-2 months.

The individual responses are shown in Table 1 and the

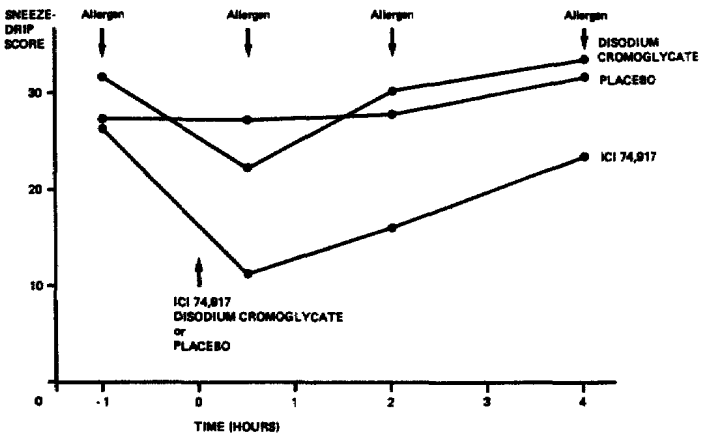


Fig. 2.

Mean nasal symptom score, measured during a 15-min period after nasal challenge. Challenges were carried out before, and half an hour, 2 hours and 4 hours after intranasal use of medicine or placebo.

mean values in Table 2 and Fig. 1. Analysis of covariance has been used on the data, the pretreatment score being taken as covariate, and the main effects being treatment, period of trial, and volunteer. The adjusted means so derived are shown in Table 3.

Thirty minutes after treatment with ICI 74,917 the mean number of sneezes and drips was 11.7 which is significantly lower than the mean of 22.4 when volunteers received DSCG ($P < 0.05$) and 27.4 when the volunteers received placebo ($P < 0.01$).

After 2 hours there was a significant reduction in means when comparing ICI 74,917 with DSCG and also with placebo ($P < 0.01$ in both cases).

After 4 hours there was no statistically significant differences in treatment means.

No adverse effects occurred after ICI 74,917.

DISCUSSION

This trial showed ICI 74,917 to have a protective effect on the human respiratory mucosa during challenge with allergen. The effect was significantly greater than that of DSCG. This may be due to the distribution of ICI 74,917 by the pressurised aerosol which is more similar to that of the sprayed allergen. In contrast, we found the distribution of the DSCG powder as judged by rhinoscopy to be very poor. Immediately after a technically satisfactory delivery procedure, the major part of the DSCG powder was visible in the nostril and the anterior third of the nasal cavity. In addition to a more effective administration, ICI 74,917 may have greater activity in human challenge situations which parallels the increased potency in animal experiments (5, 6). The fact that the degree of DSCG protection in the trial was less than that found in other intranasal challenges (4, 8, 9) was probably due to the very large doses of allergen used in the trial. This may also account for the lack of local hyposensitization in contrast to the findings of Taylor & Shivalkar (11).

One of the major shortcomings in the treatment of allergic diseases of the airways by DSCG is the relatively short duration of maximum protective effect, making it difficult to obtain continuous protection, especially during the night (7). The present study indicates that ICI 74,917 may be superior in this respect, even though the duration of action of the drug cannot be exactly defined from the present study.

Administration by aerosol may be more acceptable to patients, and a more frequent use may be tolerated. However, these practical matters will have to be evaluated in clinical trials in which allergens are presented to the mucous membrane in a more "physiological way".

In conclusion, measures of nasal secretion and irritation after challenge with allergen showed a protective effect when subjects were pretreated with ICI 74,917. The results justify trials to evaluate ICI 74,917 in the treatment of allergic rhinitis.

SUMMARY

Ten patients with allergic rhinitis were challenged intranasally with allergen before, and half an hour, 2 hours and 4 hours after intranasal administration of placebo, disodium cromoglycate powder and an aerosol containing ICI 74,917, a new compound with anti-allergic action. ICI 74,917 had a maximum protective effect after half an hour, but was significantly better than placebo 2 hours after nasal use. The effect was significantly better than that of disodium cromoglycate powder. The results will encourage studies of ICI 74,917 in the treatment of allergic rhinitis.

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