Rhinology, 20, 63-72, 1982

A survey of rhinitis in Japan and an evaluation of the treatment with sodium cromoglycate

M. Okuda, Tokyo, Japan

SUMMARY

4.907 cases reports of patients with rhinitis have been analysed in Japan; the majority were classified as allergic on the basis of positive skin and nasal provocation tests and a nasal eosinophilia. The patient characteristics have been evaluated and they are very similar to those seen in a European population. There was a high incidence of sensitivity to house dust, pollens and fungi.

Treatment with Nasal Intal powder produced an effective therapeutic response in most patients diagnosed as allergic rhinitis both seasonal and perennial. Patients in whom the major symptoms were sneezing and rhinorrhoea responded better than those with nasal obstruction. There was a clinically significant withdrawal or reduction of concomitant therapy particularly oral corticosteroids. In the majority of patients the therapeutic effect of Intal Nasal was observed after two weeks. The incidence of side effects was low and all were of a minor nature, the predominant one being nasal irritation.

INTRODUCTION

Allergic rhinitis is an acute or chronic, non infective inflammatory disease of the nasal airways due to an acquired reactivity to an exogenous antigen. It is common in all countries but data on the true incidence is lacking; in Japan the figures are about 10% in adults and 7-8% in children (Okuda, 1971). A survey in the USA of college freshman showed a very high incidence of seasonal rhinitis, 21%, although that for non seasonal allergic rhinitis was only 5.2% (Hagy and Settipane, 1969). Clinical experience in Japan dictates that allergic rhinitis is a common disease; two factors which may be contributory are that the majority of the population live along the coast and the climate is generally warm and humid; both are favourable for the growth of moulds and fungi and for the reproduction of the house dust mite; such conditions favour the term 'Climate rhinitis' (Viner and Jackman, 1976).

The objective of this paper is to review the data from 4,907 case reports collected from 480 clinics over a 4 year period throughout Japan in order to firstly define the character of allergic rhinitis in this country and, secondly, to confirm the effectiveness safety and practical usefulness of sodium cromoglycate on a large number of patients in the clinical situation.

Sodium cromoglycate (Intal Nasal®, Rynacrom®) is a well documented drug effective in the treatment of allergic rhinitis (Engstrom et al., 1971; Hopper and Dawson, 1972; Holopainen et al., 1972). A double blind study on the efficacy and safety of this drug was previously conducted by the author (Okuda et al., 1975). These studies, however, were limited in terms of the numbers of patients and doctors participating. By using a much larger number of patients and doctors the benefits of this drug can be confirmed in the practical clinical situation.
As the absolute effect of the sodium cromoglycate is already well established by double blind trials and the large number of patients and doctors included in this work minimise any potential deviations, no control group was included in the study. The results were subsequently found to be in agreement with the earlier double blind study by the author.

MATERIALS AND METHODS

Data were collected between April 1976 and October 1979 from 450 hospitals and clinics, a total of 4,907 case reports were analysed. The majority were submitted by ear, nose and throat specialists.
A definitive diagnosis was made in 4,787 (Table 1). The accepted criteria in Japan for a definitive diagnosis of allergic rhinitis is that at least two of the following three investigations are positive; skin test, nasal provocation test and a nasal secretion eosinophilia. Allergic rhinitis is suspected if the patient presents with the typical triad of symptoms and the nasal mucosa is pale and swollen but only of the previously mentioned tests is positive. A diagnosis of vasomotor rhinitis is made when the symptoms are atypical, all investigations are negative and there is no evidence of allergy.
The majority of patients were classified as perennial rhinitis (61.3%), many of these had seasonal exacerbations; the seasonal rhinitis only had symptoms in the spring due to Cedar pollen or in the summer and early autumn when grass pollen is prevalent.
The age and sex distribution is shown in Figure 1. There was a predominance of males in the age group 0–20 years and of females aged 21 to 50 years; only 7.2% of the patients were over the age of fifty. Nearly a quarter of patients stated that the disease started before the age of eleven and the majority of these were males;

Table 1. Confirmed diagnosis in children and adults

age	allergic rhinitis	suspected allergic rhinitis	vasomotor rhinitis	total
0–15	1,099 (87.3%)	144 (11.4%)	16 (1.3%)	1,259
16 +	2,886 (81.8%)	487 (13.8%)	155 (4.4%)	3,528
total	3,985 (83.2%)	631 (13.2%)	171 (3.6%)	4,787

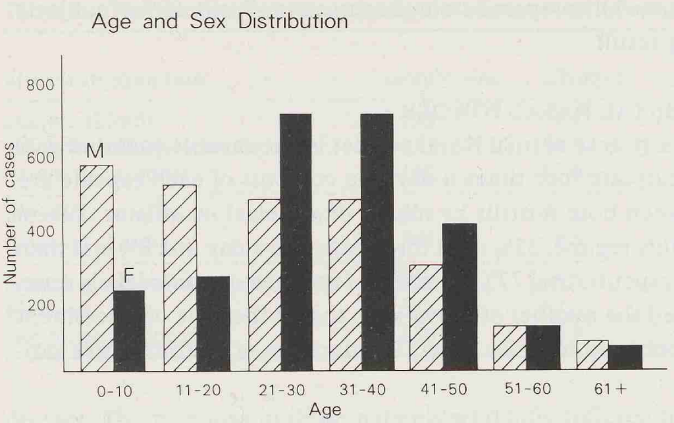

Fig. 1. Age and sex distribution

there was another peak of onset between the ages of 21 and 40 years predominantly in females. The average age of onset was 21.4 years in males and 26.7 years in females. Most of the patients had symptoms for between 2 and 5 years with some 25% having had symptoms for more than 5 years.

The severity of the disease was graded as either moderate or severe and almost all had received some form of therapy before being treated with Intal Nasal®; the common therapy was antihistamines followed by oral steroids and hyposensitization.

41% of patients had another disease or an observed abnormality. Asthma was associated with rhinitis in 494 (10.1%) patients, sinusitis in 834 (17.6%) and atopic dermatitis in 204 (4.2%); a deviated nasal septum was noted in 423 (8.6%) and nasal polyps in 67 (1.4%).

A quarter of patients gave a past history of atopic disease and 21% a positive family history of atopy in close relatives.

The presenting symptoms in those patients diagnosed allergic rhinitis is shown in Table 2.

The major allergen was house dust (72%) followed by pollens (30%) and fungi (26%); many patients had a positive test to more than one allergen. Nasal smears were examined for the presence of eosinophilia and were graded as + + +, + +,

Table 2. Symptoms of patients diagnosed allergic rhinitis

symptom	perennial	seasonal	total
sneezing and rhinorrhoea	1,383 (60)	1,034 (69)	2,417 (63)
blocking	457 (20)	220 (14)	677 (18)
combination of both	460 (20)	254 (17)	714 (19)
total	2,300	1,508	3,808

Figures in parenthesis indicate percentages.

+ or absent using a specially prepared stain (Eosinostain–Torii); 89% of subjects tested had a positive result.

TREATMENT WITH INTAL NASAL POWDER

The recommended daily dose of Intal Nasal powder is one capsule containing 20 mg of sodium cromoglycate four times a day, the contents of each capsule are equally divided between both nostrils by means of a special insufflator. 59% of patients adhered to this regime, 32% used three capsules a day and 8% less than three. During the therapeutic trial 77% of patients remained on a fixed daily dose, the remainder reduced the number of capsules so that at the time of assessment 25% were receiving only two capsules a day. The duration of treatment was variable (Figure 2).

Initially 66% of patients received additional therapy, this was generally an antihistamine (72%), oral steroids (25%) and vasoconstrictors (15%); some patients received more than one additional drug; also 46% were undergoing some form of hyposensitization therapy.

RESULTS

The therapeutic effect of Intal Nasal powder was assessed as effective (an excellent or good response) or mildly effective or no effect. The percentage response rates for various parameters are shown in Table 3.

There was no difference in response with respect to age, sex, and duration of

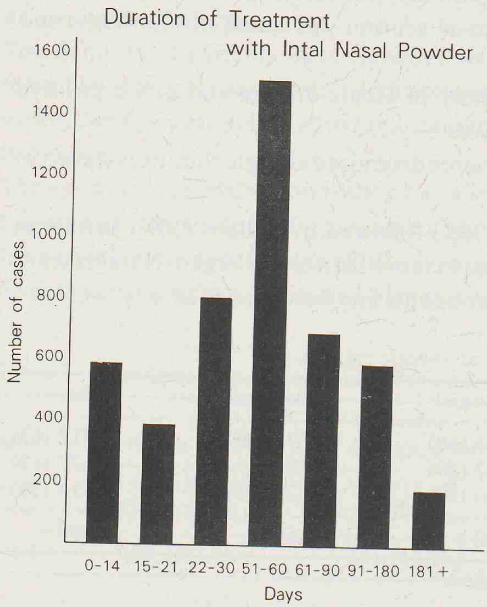

Figure 2.
Duration of treatment with Intal Nasal Powder

Table 3. Therapeutic response expressed as a percentage of sample size

disease or symptom	sample size	effective	mildly effective	no effect
allergic rhinitis	3,930	76.2	17.5	6.2
suspected allergic rhinitis	611	64.5	25.0	10.4
vasomotor rhinitis	162	63.6	24.1	12.3
perennial rhinitis	2,851	71.5	20.5	8.0
seasonal rhinitis	1,805	78.5	16.0	5.5
sneezing and rhinorrhoea	2,933	75.5	18.1	6.4
blocking	918	67.6	22.4	10.0
combined symptoms	830	76.8	17.2	6.0

disease. The response in those patients who only suffered from rhinitis was the same as in those with other diseases except for a small group of patients who had nasal polyps in association with perennial rhinitis, in these the response rate was 56%.

In an analysis of therapeutic benefit related to allergens it was the group of patients in whom pollen predominated that the best response was seen, 84.4%, in those in whom fungi was the major allergen the figure was 69.4%; the largest group of patients, sensitive to house dust, had a response rate of 70.2%.

The success rate was higher in those patients who had either strongly positive skin tests or nasal provocation tests than in those who had negative tests; a similar pattern was seen with respect to nasal eosinophilia.

In those patients who had negative skin tests but grade + + + or + + nasal eosinophilia the success rate was 76%; similarly in those who had weak or negative nasal provocation tests but grade + + + or + + nasal eosinophilia there was a response in 70%.

Impairment in sense of smell was noted in 1,185 patients and in these an improvement was noted in 900 (75.9%).

A small group of patients had a nasal challenge test both before and after treatment with a fixed dose of antigen, most were sensitive to house dust. There was a

Table 4. Comparison of pre- and post-treatment (4 weeks) Nasal Provocation Tests (NPT) in housedust allergic rhinitis patients.

		post-treatment NPT			
baseline NPT	nos. of patients	0	+	+ +	+ + +
+	29	22	7	-	-
+	12	5	4	3	-
+ + +	7	1	3	0	3

definite reduction in the nasal response following treatment with Intal Nasal powder and this was evident after four weeks therapy (Table 4).
The reduction in nasal reactivity correlated with the clinical response.
A measure of response to Intal Nasal is the reduction or withdrawal of concomitant therapy (Table 5). Further evidence of the response is provided by comparison with previous therapy (Table 6).

The patients were reviewed at frequent intervals and thus it was possible for the clinician to state at what time after commencing treatment a therapeutic benefit had been obtained; in many patients this was after only several days thus 75% had some response within 14 days (Figure 3).

SIDE EFFECTS

The total number of side effects reported was 282 in 237 patients (4.83%). The most frequent reports were nasal irritation (156), headache (35) and excessive sneezing (23), Side effects directly involving the nose were rare, there being one report of epistaxis and five of eczema of the vestibilum nasi. The majority of side effects were noted within the intitial seven days of treatment, such patients were carefully monitored by the clinician and in 82% their side effects had disappeared within 14 days.
A total of 105 patients (2.1%) stopped treatment; the reasons were nasal irritation (40), exacerbation of symptoms (25), throat symptoms (11), skin symptoms (10) and various others (19). In no case were side effects considered serious.

DISCUSSION

The pattern of allergic rhinitis in Japan is similar to that found in Europe. It is predominantly a disease of young people and is prevalent in children. Within the age range 0–19 years there was a very definite predominance of males, this is the same pattern as occurred in a survey of 1,271 perennial rhinitis in Europe (Viner and Jackman, 1976). The predominance of females in the age range 21 to 50 years is also similar. Although in this survey patients were classified as both seasonal and perennial rhinitis, the age and sex distribution are very similar to those surveyed in Europe. It is not known why males predominate in the first two decades and thereafter females; this sex difference has been seen in other atopic diseases. In a

Table 5. Reduction and withdrawal of concomitant therapy.

concomitant therapy	no. of patients	withdrawn	reduced	failed reduction
steroids	949	616 (64.9)	261 (27.5)	72 (7.6)
antihistamines	2,272	1,156 (50.9)	888 (39.1)	228 (10.0)
vasoconstrictors	739	397 (53.7)	275 (37.2)	67 (9.1)

Figures in parenthesis are percentages of sample size.

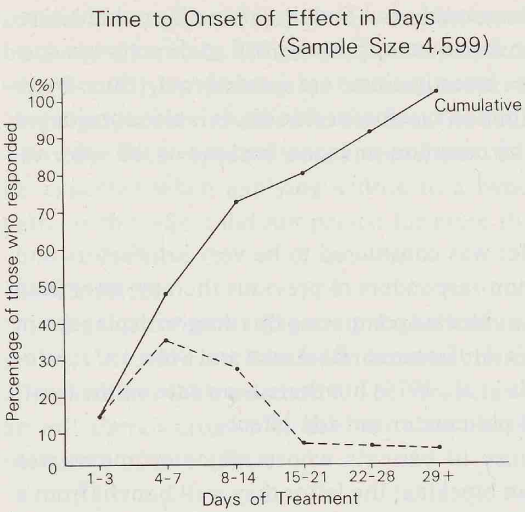

Figure 3.
Time to onset of effect in days (sample size 4,599)

survey carried out in Australia (Cullen, 1972) there were significantly more boys than girls with a diagnosis of asthma and seasonal rhinitis.

It is important to diagnose and treat allergic rhinitis in the young because effective and safe therapy is now available; there are other important reasons. Some children may develop a blockage and malfunction of the Eustachian tube which produces a serous otitis media with consequent loss of hearing (Rapp and Fahey, 1973); this in turn will create problems in education. A major concern is the possibility that patients with allergic rhinitis could develop ashma; in a report dealing only with children (Smith, 1971) it has been shown that 22.2% of untreated ragweed hay fever patients developed asthma, the figure for those was 4.7%. There is no doubt that many children with allergic rhinitis are undiagnosed and therefore mismanaged. A study of 100 children over a period of three to five years showed that "triggering colds" were in fact rhinitis in 70% (Holzel, 1968).

A very high proportion of patients was diagnosed as allergic rhinitis as compared with the small numbers labelled suspected or vasomotor rhinitis. This can be ex-

Table 6. Comparison with previous therapy.

previous therapy included	nil or poor response to previous therapy	previous therapy replaced by intal good/total	other therapy plus intal good/total
antihistamines*	1,347	333/423 (79%)	636/924 (69%)
vasoconstrictors*	333	68/79 (86%)	178/254 (70%)
steroids	554	109/134 (81%)	297/420 (71%)

* Patients additionally taking steroids are excluded from these two groups.

plained by the fact that 38.7% were seasonal cases and therefore all would be classified as allergic but also because in Japan many patients will go directly to a specialised clinic where full allergic investigations are carried out, thus fewer patients will be indiscriminately labelled vasomotor rhinitis. It is also considered likely that allergic rhinitis would be common in Japan because of the environmental and climatic conditions.

The response to Intal Nasal powder was considered to be very satisfactory and many patients who were poor or non-responders to previous therapy, benefited by its use. Clinical trials have been published comparing this drug with placebo in both seasonal and perennial rhinitis (Holopainen, Backman and Solo, 1971; Sunderman and Crawford, 1973; Okuda et al., 1975) but there is no date on the treatment involving a large number of patients or on side effects.
There was clearly a better response in patients whose major symptom was rhinorrhea and sneezing rather than blocking; the latter may well benefit from a solution of sodium cromoglycate (Holopainen et al., 1975) particularly if the delivery system ensures an even distribution over the whole of the nasal mucosa (Mygind, 1978)).

The efficacy of a drug can be assessed by the amount of concomitant therapy required. Antihistamines have been widely used in the past for rhinitis but have not been particularly effective in perennial rhinitis and sedation is often a problem. The prolonged use of vasoconstrictors induces a rhinitis medicamentosa. The problems associated with oral steroids are well documented and a possible cautious approach to their use in the steroid non-responder group of patients (Table 6) may account for the comparatively high response rate with Intal. Overall therefore it was encouraging to see that the majority of patients were able to eliminate or reduce other therapy.

The therapeutic response to Intal Nasal powder was rapid as an improvement was seen within two weeks. This was a subjective assessment but has been confirmed by objective measurements of nasal airways resistance and flow in a study in which these parameters were measured weekly in a group receiving sodium cromoglycate solution (Lomusol®) compared with a placebo group (Girard and Bertrand, 1975). These investigators found a significant improvement in resistance and flow on the active drug after only one week. In those patients in whom blocking is the major symptom an adequate response may take longer as they will have chronic inflammatory changes in the nasal mucosa and sodium cromoglycate does not have a specific anti-inflammatory effect (Brain et al., 1974).
The observation that in a few patients nasal hyperreactivity was reduced following a period of treatment of one month is of interest. It suggests that the use of

sodium cromoglycate may have a fundamental effect on the disease process as has been seen in the asthmatic following treatment with Intal (Altounyan, 1970) where sensitivity to histamine has been reduced in some patients. Clearly further investigations are required to confirm the finding.
The side effects reported were minimal and of a mild nature. Nasal irritation is to be expected when applying a drug to a hypersensitive mucosa but in many patients this effect did not persist for more than a few days.

CONCLUSION

Rhinitis is a common disease in Japan and resembles that found in Europe. If patients are fully investigated in hospital clinics the majority will be found to be allergic rather than vasomotor. Therefore it is logical to treat such patients with an anti-allergic drug which has been shown to be very effective and has a very low incidence of side effects.

ZUSAMMENFASSUNG

4907 Untersuchungs-Berichte über Patienten mit Rhinitis sind in Japan analysiert worden. Die meisten davon wurden als allergisch klassifiziert, auf der Basis von Haut- und Nasal-Provokationstests und einer Nasen-Eosinophilie. Die Patienten-Charackeristiek wurden ausgewertet und sind denen der europäischen Bevölkerung sehr ähnlich. Grosse Empfindlichkeit gegen Hausstaub, Pollen und Pilze wurde wahrgenommen.
Die Behandlung mit Intal Nasal Pulver erzeugte eine therapeutisch wirksame Reaktion in den meisten Patienten in welchen saisonbedingte oder ganzjährige allergische Rhinitis diagnostiziert wurde. Patienten bei denen die Hauptsymptome Niesen und Rhinorrhoe waren reagierten besser als die, welche unter Nasenblockade litten. Eine klinisch bedautsame Weglassung oder Reduzierung einer Begleittherapie, besonders im Gebrauch von Corticosteroiden per os, wurde demonstriert. Bei den meisten Patienten wurde die therapeutische Wirkung von Intal Nasal nach zwei Wochen sichtbar. Es gab nur wenige Neben-Erscheinungen und alle waren unbedeutend; vorwiegend war Nasenreizen.

ACKNOWLEDGEMENTS

The author acknowledges with thanks all those clinicians who provided case records and Messr. Fujisawa Pharmaceutical Co., Ltd. (Osaka, Japan) for their collaboration, also Dr. A. S. Viner of Fisons Pharmaceuticals Ltd. (UK) for his valuable assistence and useful suggestions in writing this paper.

REFERENCES

1. Altounyan, R. E. C., 1970: In Disodium Cromoglycate in Allergic Airways Disease. Editors J. Pepys and A. W. Frankland. Butterworths, London, page 47.

2. Brain, D. J., Singh, K. P., Trotter, C. M. and Viner, A. S., 1974: Sodium Cromoglycate 2 per cent solution in perennial rhinitis: a clinical and histological study, Journal of Laryngology and Otology 88, 1001–1017.
3. Cullen, K. J., 1972: Climate and chest disorders in school children, British Medical Journal 4, 65–67.
4. Engstrom, I., Oberger, E., Blyckert, A. and Kraepelin, S., 1971: Disodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivis, Annals of Allergy 29, 505–509.
5. Girard, J. P. and Bertrand, J., 1975: Study of 2% of sodium Cromoglycate in perennial rhinitis assessed by subjective and objective parameters, Clinical Allergy 5, 301–309.
6. Hagy, G. W. and Settipane, G. A., 1969: Bronchial asthma, allergic rhinitis and allergy skin tests among college students, Journal of Allergy 44, 323–332.
7. Holopainen, E., Backman, A. and Salo, O. P., 1971: Effect of disodium cromoglycate on seasonal allergic rhinitis. Lancet 1, 55–57.
8. Holopainen, E., Salo, O. P. and Backman, A., 1972: Experience with disodium cromoglycate in the treatment of seasonal and perennial allergic rhinitis, Rhinology 10, 119–126.
9. Holopainen, E., Viner, T., Backman, A., Salo, O. P., Hannuksela, M. and Malmberg, H., 1975: Clinical trial of a 2% solution of DSCG in perennial rhinitis, Acta Allergologica 30, 216–226.
10. Holzel, A., 1968: The allergic toddler, Practition 200, 369–375.
11. Hopper, I. and Dawson, J. P., 1972: The effect of disodium cromoglycate in perennial rhinitis, Journal of Laryngology and Otology 86, 725–730.
12. Mygind, N. and Vesterhauge, S., 1978: Aerosol distribution in the nose, Rhinology 16, 79–88.
13. Okuda, M., 1979: Practice of diagnosis and treatment of allergic rhinitis. Kanehara Publishing Ltd., Tokyo.
14. Okuda, M., 1975: Treatment of nasal allergy with disodium cromoglycate (Intal), Practica Otologica 68, 399–425.
15. Rapp, D. J. and Fahey, D., 1973: Review of chronic secretory otitis and allergy, Journal of Asthma Research 10, 4, 193–218.
16. Smith, J. M., 1971: A five year prospective survey of rural children with asthma and hay fever, Journal of Allergy 47, 23–30.
17. Sunderman, J. and Crawford, W. A., 1973: Sodium cromoglycate in the treatment of chronic allergic rhinitis, Medical Journal of Australia 1, 1189–1190.
18. Viner, A. S. and Jackman, N., 1976: Retrospective survey of 1271 patients diagnosed as perennial rhinitis, Clinical Allergy 6, 251–259.

Professor M. Okuda
Department of OtoRhinoLaryngology
Nippon Medical School
Sendagi, Bunkyo-ku, Tokyo
Japan