

Effect of oral sodium cromoglycate and ketotifen in fish-induced bronchial asthma

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ABSTRACT The effects of sodium cromoglycate and ketotifen were studied in a group of 20 patients in whom fish repeatedly provoked an attack of wheezing and dyspnoea within one hour of its being eaten. Fish ingestion resulted in a fall in forced expiratory volume in one second (FEV₁) of at least 15%. All patients had a weal greater than 4 mm in response to fish antigen in the skinprick test and most had blood eosinophilia and raised serum IgE levels. Administration of drugs and placebos was carried out under double-blind conditions, in a randomised fashion, on different days. Cromoglycate blocked the fall in FEV₁, either completely or significantly in 16 patients. Ketotifen did not appear to have any significant effect in the group as a whole.

Food allergy has been a contentious subject for almost as long as it has been recognised as a clinical entity. It has sometimes been diagnosed without objective criteria and at times ignored despite strong clinical suggestion.¹⁻³ Most of the confusion seems to have arisen from a poor definition of the condition and a readiness by some to implicate it in a wide variety of clinical states. Various adverse reactions to foods have been loosely labelled "allergic" even though no immunological mechanism could be clearly identified. Recent reports^{4,5} have clarified the matter by defining food allergy as an immediate hypersensitivity reaction to a specified food or foods, with evidence of specific IgE in the form of positive responses to skinprick tests or radioallergen sorbent tests.

This paper reports the effects of the prophylactic agents sodium cromoglycate (Nalcrom) and ketotifen given orally to a group of 20 asthmatic patients in whom fish repeatedly caused an attack of wheezing and breathlessness within an hour of its ingestion.

Methods

Twenty asthmatic patients (14 men, six women with an age range of 19-55 years) agreed to participate in the study. Each claimed to have attacks of asthma precipitated by various varieties of fish, whether

fresh, canned, or frozen. Fish forms an important part of the local diet and patients were often unwilling to eliminate it, preferring to eat it and then treat the resulting attack with bronchodilator drugs. In none of the patients did ingestion of fish ever cause a severe attack of asthma. In this study cod was chosen in preference to any of the local fish because its allergen, allergen M, is perhaps the best known and characterised food allergen.^{6,7} Allergen M is a parvalbumin which is remarkably resistant to denaturants and mild tryptic digestion and is also heat stable.⁸

Skinprick tests were carried out on the volar aspect of the forearm with commercially available (Bencard Ltd) cod allergen extracts, as well as extracts of the pollen allergens of *Prosopis juliflora*, *Chenopodium album*, and *Cynodon dactylon*, which are the commonest allergens in Kuwait.⁹ Serum immunoglobulins and the number of blood eosinophils were also measured in all patients. Investigations were carried out in the outpatient department and at no time did any patient have severe asthma.

The patients were selected on the basis of a history of repeated attacks of asthma precipitated by fish ingestion. A preliminary oral challenge with 100 g of boiled cod showed a fall in forced expiratory volume in one second (FEV₁) of at least 15% in all patients. For the definitive study the patients stopped their usual treatment three days before each challenge day. None had ever taken either corticosteroids or the drugs under study. Oral sodium cromoglycate, ketotifen, and their placebos were

given on a randomised, double-blind basis to each subject on four different occasions. The patients were told that the drugs might or might not help them. Each drug and placebo was given for three days before the challenge day, with a final dose 30 minutes before the fish challenge. Cromoglycate or its placebo was given in a dose of 400 mg dissolved in hot water four times a day, with a final dose of 400 mg. The dose of ketotifen or its placebo was 1 mg twice a day with a further 1 mg 30 minutes before challenge. The FEV₁ was measured by means of a dry wedge spirometer (Vitalograph) immediately before the ingestion of fish and 15, 30, 45, 60, and 120 minutes later. The best of three successive technically acceptable attempts was chosen. Statistical significance was assessed by Student's *t* test.¹⁰

Results

The results of skinprick testing with cod extract and determination of blood eosinophil and serum immunoglobulin levels are shown in the table. Skin testing produced a weal of at least 5 mm in all patients and most also had blood eosinophilia and high serum total IgE levels. Four patients (Nos 9, 12, 15, and 20) had low levels of serum IgA.

The preliminary challenge with 100 g of cod resulted in a fall in FEV₁ ranging from 15% to 26.5% with a mean of 18.5% (fig 1). The time at which the lowest FEV₁ was measured varied from 15 to 60 minutes (mean of 37.5 min).

In the definitive study there were no significant differences between the initial FEV₁ values on the different treatment days. Oral sodium cromoglycate inhibited the fish-induced fall in FEV₁ completely in

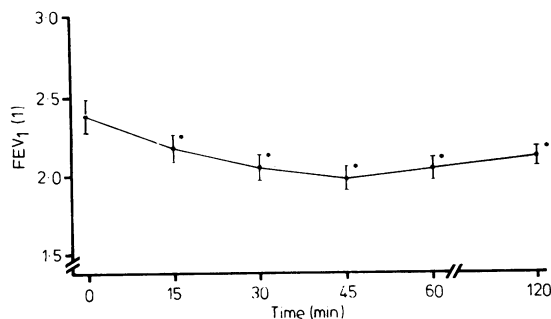


Fig 1 Effect of eating 100 g fish on forced expiratory volume in one second (FEV₁): group mean values \pm SEM for 20 patients. *Points significantly different from initial FEV₁ ($p < 0.001$).

eight patients (Nos 1, 2, 6, 7, 12, 13, 15, and 17) and offered almost complete protection in a further eight (Nos 4, 5, 8, 9, 11, 16, 18, and 20). It had no effect in the remaining four patients. The equivalent placebo was marginally effective in three patients (Nos 8, 16, and 18). The mean effects of cromoglycate and its placebo (fig 2) show a significant difference with no overall change in FEV₁ on challenge after pretreatment with cromoglycate. The fall in FEV₁ was significantly less after placebo administration ($p < 0.05$) than after cromoglycate at each time interval except after 15 minutes.

Ketotifen appeared to provide a small degree of protection in three patients (Nos 4, 10, and 19); but its placebo caused a similar reduction in the fall in FEV₁ in five asthmatic patients (Nos 4, 10, 18, and 19), and the mean results after ketotifen and

Immunological data on the 20 patients

Patient No	Age (y)	Sex	Skinprick test response (weal diam, mm)	Blood eosino- phils/mm ³	IgE (IU/ml)	IgG (mg %)	IgM (mg %)	IgA (mg %)
1	26	M	10	855	950	844	68	139
2	33	M	7	1270	650	1375	139	240
3	45	M	6	750	1339	780	153	92
4	25	F	8	1115	755	1250	56	113
5	37	M	5	880	1106	1530	175	166
6	41	F	10	440	800	1140	163	84
7	19	F	12	580	196	570	106	101
8	30	M	8	720	656	995	98	119
9	35	M	7	1155	850	1200	215	57
10	50	M	5	480	1235	1320	76	128
11	34	M	7	750	105	855	129	88
12	29	F	10	950	95	450	196	46
13	22	M	15	365	229	1100	156	125
14	55	M	8	930	500	1260	89	155
15	31	F	10	400	480	1070	105	62
16	27	M	5	305	167	880	255	266
17	36	F	8	960	633	1310	125	105
18	40	M	6	1220	857	1290	144	89
19	29	M	9	320	1447	610	296	340
20	32	M	12	590	915	1110	131	39

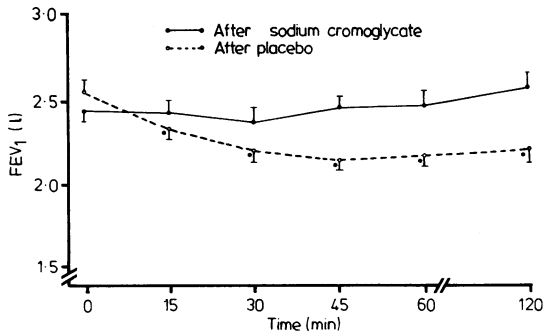


Fig 2 Effect of oral sodium cromoglycate and placebo on FEV_1 in 20 patients after ingestion of 100 g fish: group mean values \pm SEM. *Points significantly different from initial FEV_1 ($p < 0.0001$).

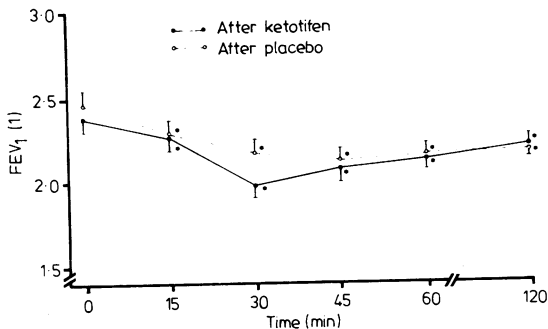


Fig 3 Effect of ketotifen and placebo on FEV_1 in 20 patients after ingestion of 100 g fish: group mean values \pm SEM. *Points significantly different from initial FEV_1 ($p < 0.001$).

placebo were similar (fig 3). Comparison of the fall in FEV_1 at each time interval after challenge showed no significant difference between the values obtained after administration of ketotifen and of its placebo.

Discussion

Van Helmont appears to have been the first to describe fish-induced bronchial asthma.¹¹ In 1662 he recorded a vivid description of a monk who had asthmatic attacks when "he eateth fishes fried with Oil."

It would have been ideal to have also administered the fish under double-blind conditions but this was not feasible. The use of double-blind food challenge eliminates many false associations between foods and symptoms.¹² Recognition of an association is perhaps more difficult when the reaction is delayed. All the patients studied in this group had

"immediate" asthmatic reactions to challenge with fish and often had other symptoms, including rhinorrhoea, itching sensations in the roof of the mouth and back of throat, perioral and periorbital swellings, and urticaria. Ingestion of fish consistently and repeatedly provoked airflow obstruction detected by significant falls in the FEV_1 . The double-blind administration of placebos did not prevent the onset of an asthmatic attack but cromoglycate often did.

Only four patients (Nos 7, 11, 12, and 16) had normal total serum IgE levels and in four others (Nos 3, 5, 10, and 19) the levels were over 1000 IU/ml. All patients had positive skin reactions to the pollen allergens tested. The four patients with greatly increased levels of serum IgE had strongly positive skin reactions to a wider variety of allergens. In three of the four patients in whom sodium cromoglycate failed to protect against fish challenge the total serum IgE level was very high (>1200 IU/ml). It has previously been shown in mite-sensitive asthmatic patients after challenge with aeroallergens that cromoglycate tends to be less effective in patients with high total IgE or allergen-specific IgE levels.¹³ In the present group of patients serum IgA levels were low in four (Nos 9, 12, 15, and 20), all of whom were protected by cromoglycate. Persistently low levels of IgA have been associated with an increased incidence of allergy.¹⁴ This may be due to a failure of IgA to prevent interactions between antigens and cell-bound IgE, IgG, or IgM at the mucosal level. The possibility that impaired antigen exclusion by the intestinal mucosa may have a role in the development of food allergy by increasing the risk of immunisation with antigens is further supported by the fact that there is a considerably increased incidence of antibodies to dietary proteins in IgA deficiency.¹⁵

The mode of action of sodium cromoglycate remains uncertain.^{16,17} In food allergy sodium cromoglycate probably prevents mediator release from superficial mast cells in the gastrointestinal tract, thereby reducing gut permeability. In several well-documented studies sodium cromoglycate has been shown to cause decreased entry of antigen through the gut and diminished immune-complex formation and to prevent atopic symptoms.¹⁸⁻²⁰

Ketotifen, a benzocycloheptathiophene, is said to be an orally active compound with mast-cell stabilising and antihistaminic properties,²¹ and it may also interfere with the lipoxygenase pathway of arachidonic acid metabolism.²² Several studies have shown it to be as effective as sodium cromoglycate in preventing asthma,^{23,24} and to have a steroid-sparing effect,²⁵ but other workers have reported ketotifen to be ineffective.^{26,27} In this study ketotifen did not appear to provide any significant protection

against fish challenge. This may be due to the fact that the drug was given for only three days before challenge. It has, however, been reported that similar treatment periods²⁸ and even single 2-mg doses of ketotifen²⁹ protect asthmatic patients against challenge with specific allergen. Maximum serum drug concentrations are reached only three hours after oral administration of 2 mg ketotifen and in this study the final dose was given half an hour before challenge; but adequate drug concentrations (1–2 ng/ml) are known to be achieved when the drug is given in doses of 1 mg twice daily.³⁰ The real role of ketotifen in the management of asthma requires further study.

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