

Ketotifen treatment of atopic dermatitis and other food allergy diseases*

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Patients with atopic dermatitis (AD) and other food allergy manifestations differ from those with asthma and hayfever in having a much higher frequency of immediate positive skin tests (SPT) to foods (1) and much greater levels of circulating food-specific IgE as measured by Phadebas RAST® (2, 3, 4). They are also particularly liable to food-induced hypersensitivity reactions of rapid onset, most commonly contact urticaria (5), generalised urticaria and vomiting. It is thought likely that the mechanism is classical type I hypersensitivity in its "immediate phase", as recently demonstrated by Sampson (6). In this study, a double-blind placebo controlled food challenge demonstrated the frequency of this kind of reaction in patients with atopic dermatitis, the association with a concurrent rise in plasma histamine, and the close correlation with positive prick tests and IgE antibody measurement. Sampson also studied the "late-phase" of IgE-mediated type I reactions in the skin (6). Eosinophils were demonstrated in patients with AD (7) with presence of major basic protein (MBP), a cytotoxic protein secreted almost exclusively by eosinophils. MBP is known to damage skin epithelial cells and promote further mast cell histamine release.

In recent years, the appearance of oral sodium cromoglycate has led to a new approach of this very complex disease. Various authors have

obtained good results from the use of this drug orally for treatment of food allergies (8-14).

More recently, several authors in open- and double-blind studies have confirmed the efficacy of ketotifen in patients sensitized to different foods suffering after ingestion from various cutaneous, nasal, conjunctival, respiratory and GI disorders (15-22).

Ketotifen is an oral tricyclic benzochloephathiophene agent (Sandoz, Switzerland, Zaditen®), and has the chemical structure and action mechanisms shown in Figs. 1 and 2 (23). Its principal pharmacological effect is to block the release of chemical mediator from human leucocytes, and has an antihistamine effect, anti-SRSA effect, and CA^{++} antagonism. It has also been reported to have an inhibitory effect on the tachyphylaxis of β -receptors (24). It is possible that ketotifen will show inhibitory effects on allergic reactions mediated by basophils and neutrophils, as it has been shown that this drug exerts an anti-SRSA effect in basophils and neutrophils (24, 25).

One of the novel modes of ketotifen action is the inhibition of eosinophil degranulation as observed in a patient with cow's milk allergy manifested as bronchial asthma (26).

More recently, ketotifen given to patients with AD, seemed not only to improve clinical symptoms, but to reduce significantly the number of peripheral blood hypodense eosinophils (activated eosinophils in the allergic responses (27)).

We report here the preliminary results obtained with this drug in patients with AD and food allergy problems.

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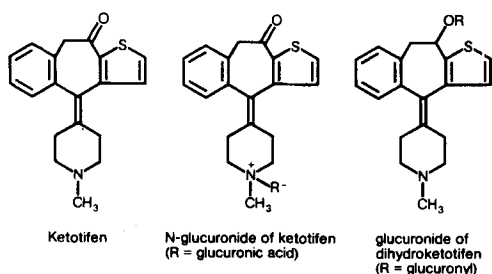


FIG. 1. Ketotifen and its two major metabolites in man.

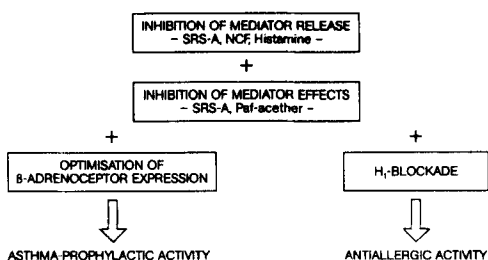


FIG. 2. Biologic systems involved in the mechanism of action of ketotifen. NCF, neutrophil chemotactic factor.

(from CRAPS L. - J. Allergy Clin. Immunol. 1985)

Figs. 1 and 2.

MATERIAL, METHODS, AND PROCEDURE

Clinical material

A total of 20 patients with food allergy entered this open study. All were selected according to clinical history after challenge with food. The ages of the patients varied from 6 months to 40 years. The group contained 16 children and 4 adults: 10 atopic dermatitis, 6 urticaria or/and angiooedema (2 of which with oropharynx pruritus, oedema of the lips, and anaphylactic shock episode), 2 asthma and 2 gastrointestinal disorders.

Skin tests

All were characterized by positive skin tests (SPT). Wheal sizes ≥ 6 mm to common foods

were obtained with glycerinated extracts (Stallergènes Lab, France). Controls were performed with codein phosphate. Thirteen common inhalant allergens were tested including allergens (mite, cat and dog, grass pollens) and nine ingested allergens including cow's milk, beta-lactoglobulin, alpha-lactoalbumin and casein, egg white and yolk, fish, orange, and wheat. Other suspicious foods were tested, such as tomato, potato, shrimp, etc.

Laboratory tests

Total IgE (Phadebas IgE PRIST®, Pharmacia, Sweden) was performed in 18 patients. High levels of IgE were recorded mainly when patients were suffering from severe AD or when inhalant allergy was involved (4).

Specific IgE tests (Phadebas RAST®, Pharmacia, Sweden) were performed in 18 patients against milk, egg, wheat, orange, and other food allergens when SPT were positive, and four other common inhalant allergens were also tested. RAST values higher than 0.35 Phadebas RAST Unit (PRU/ml) were considered positive.

Oral provocation tests

The basal oral tests were carried out after an overnight fast. Doses were geared to elicit the exact same clinical symptoms described in the history. All patients were instructed to discontinue antihistamine or steroids for at least 10 days before administration.

Foods selected for food challenge were on the basis of skin test results and/or a history strongly suggestive of food allergy. Symptoms resulting from the food challenge were recorded as to type, time of onset, severity and duration on a standardized sheet.

Clinical evaluations for AD patients were made by the same trialist at the beginning of the study, after a 15-day exclusion diet, and after food challenge tests. These evaluations were made by considering 20 discrete areas of skin surface. A score on a 0-to-3 scale was

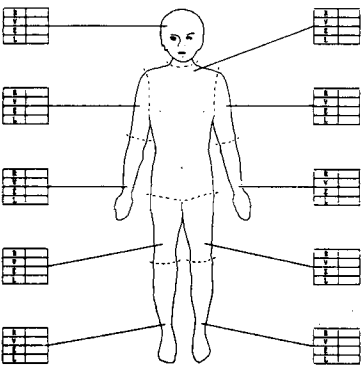
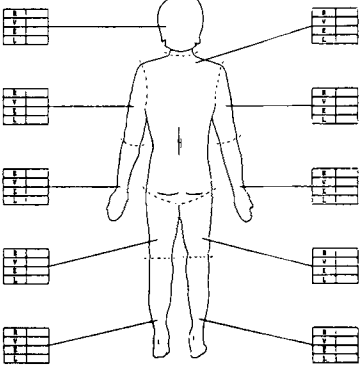
AREA SCORE CHART - FRONT Name: _____ Trial No: _____ Visit No: _____  Please draw the outline of affected areas on the diagram and assess the severity of the eczema using the headings: <table border="0" style="width: 100%;"> <tr> <td style="width: 50%;"> R = Redness V = Vesiculation, weeping and crusting on a scale E = Excoriations L = Lichenifications </td> <td style="width: 50%;"> 0 = None 1 = Mild 2 = Moderate 3 = Severe </td> </tr> </table>	R = Redness V = Vesiculation, weeping and crusting on a scale E = Excoriations L = Lichenifications	0 = None 1 = Mild 2 = Moderate 3 = Severe	AREA SCORE CHART - BACK Name: _____ Trial No: _____ Visit No: _____  Please draw the outline of affected areas on the diagram and assess the severity of the eczema using the headings: <table border="0" style="width: 100%;"> <tr> <td style="width: 50%;"> R = Redness V = Vesiculation, weeping and crusting on a scale E = Excoriations L = Lichenifications </td> <td style="width: 50%;"> 0 = None 1 = Mild 2 = Moderate 3 = Severe </td> </tr> </table>	R = Redness V = Vesiculation, weeping and crusting on a scale E = Excoriations L = Lichenifications	0 = None 1 = Mild 2 = Moderate 3 = Severe
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Fig. 3.

recorded for each area rating: R = redness, V = vesiculation, E = excoriation, L = lichenification (total score = 240) which gives a total symptomatic score (Fig. 3).

Measurement of intestinal permeability

Gastrointestinal permeability was evaluated on 3 occasions in 5 patients according to the technique described by André (28-30) by oral administration of mannitol 10% 10 mL/10 Kg, a marker of small molecule absorption and lactulose 50% 1.5 mL/10 Kg, a marker of large molecule absorption with subsequent measurement of mannitol and lactulose urinary excretion.

RESULTS

Compared with a control group of healthy children and adult subjects, the food-allergic patients showed a normal urinary recovery of mannitol and a slightly greater urinary recovery of lactulose.

Intestinal permeability was also studied immediately after ingestion of an offending food allergen. This challenge test resulted in a decrease of mannitol recovery and an increase in lactulose recovery.

Ketotifen administered 6 h before the provocation test protected 5 patients against symptoms and abnormal intestinal permeability (Fig. 4).

Medication

Patients were put on an hypoallergenic diet during the first 2 months. Ketotifen was administered in the dose of 1 mg twice a day every 12 h in syrup in all children, and as capsules in adults. The treatment period lasted from 2 to 20 months. During the first 2 months, patients were assessed at the start of the study and subsequently every 2 weeks. Patients or children's parents recorded eventual symptoms on a diary card. Patients continuing after the initial 2-month treatment, returned for a monthly visit during 6 months, then every 2 months.

RATIOS OF LACTULOSE AND MANNITOL URINARY OUTPUT IN 5 PATIENTS ASSAYED IN 3 OCCASIONS

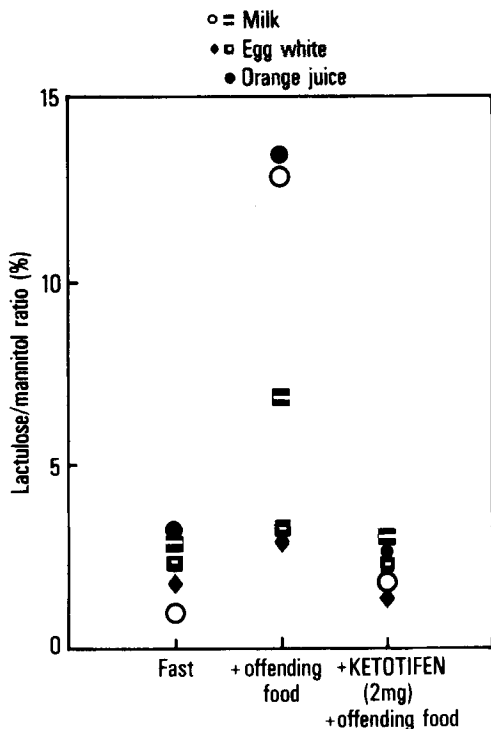


Fig. 4.

In patients with AD, the usual treatment consisted of a combination of a topical emollient, a non-corticosteroid ointment. In two adult patients (Pr D. Herman, Hôpital Lariboisière, Paris), ketotifen was given when oral cromoglycate did not protect the patients after new challenge tests.

Of the 10 patients with atopic dermatitis, 4 patients were greatly improved, 3 improved somewhat and 3 remained the same. After 4 weeks of hypoallergic diet with ketotifen, the scores of redness and lichenification were more significant than the changes in excoriation, which improved when the drug was continued during the following month (75%). These results were in good agreement with those reported by the patients or the children's parents in the diary cards. During the ketotifen treatment, there was a great decrease in pruritus both day and night after 6 weeks of treatment. The opin-

ions of physician and parents were in agreement during the subsequent months.

Ten other patients - 6 children and 4 adults suffering from gastrointestinal symptoms, asthma, urticaria or angioedema, oropharynx pruritus with oedema of the lips with anaphylactic shock - all recovered completely and none relapsed after a new challenge test.

DISCUSSION

The present study suggests that ketotifen administered in a dose of 1 mg twice daily over a long period of time may produce significant protection in patients with AD and food allergy symptoms. Administration of 2 mg of the drug 6 h before a challenge test with the offending food may protect some patients against symptoms and abnormal intestinal permeability. The first finding is in agreement with that of Neffen et al. (15) who described the protective effect in patients with food and multiorgan manifestations after their ingestion. Two published studies provide encouraging clinical results with ketotifen in children and adults suffering from skin, respiratory, and gastrointestinal disorders related to food allergens, additives, and dyes (31, 32). Recently Romanski et al. (33) found a new method for food allergy diagnosis based on the direct observation of pathological changes in

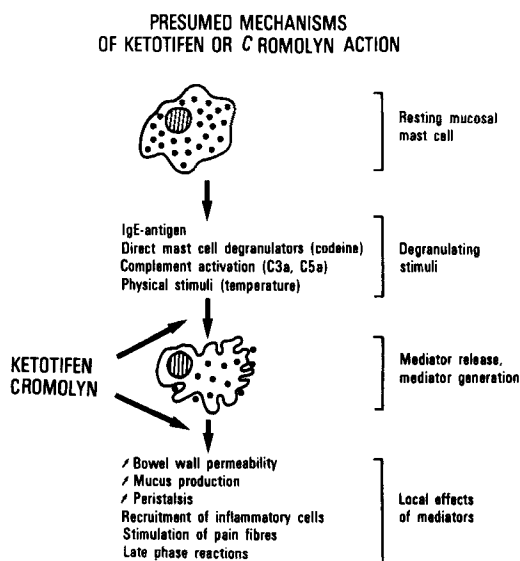


Fig. 5. Presumed mechanism of ketotifen action.

the gastric mucosa provoked by sensitizing foods. Using a gastrofibroscope, they described macro- and microscopic changes of the gastric mucosa well-documented by colour pictures and microscopic preparations. They studied 12 patients with food allergy symptoms in which the direct provocative test with food extracts introduced into the stomach by gastrofibroscope provoked modifications in a few minutes such as mucosa pale and/or hyperemic, with punctate haemorrhages on its surface. After 14 days of treatment with ketotifen all allergic disorders disappeared in 11 patients and repeated provocative tests were negative in the 11 patients (33). The same authors repeated the same study with oral cromoclycate and obtained the same results (34).

These findings are supported by André (28) that oral cromoglycate may protect patients with food allergy against clinical symptoms and abnormal intestinal permeability, and by our own findings that ketotifen may protect against food-induced intestinal permeability.

Recent clinical and immunological investigations tend to suggest that ketotifen is an anti-allergic and anti-anaphylactic drug able to play a role in IgE-dependent and in non-IgE-mediated mechanisms (35).

It has been proposed that specific and/or non-specific stimuli can activate mast cells, basophils, and other cells such as macrophages, eosinophils, and platelets, reevaluation of the role mediators play in the acute allergic reaction and the cellular origin of allergic mediators in the gut. The possible pathophysiological consequences of mast cell degranulation within gastrointestinal tissue are summarized in Fig. 5 (36, 37).

Recent *in vitro* studies have suggested the inhibitory action of ketotifen on eosinophil granule discharge attributable to the release of cytotoxic MBP in patients with cow's milk allergy (38). Ketotifen inhibited direct and antibody-dependent allergic autotoxicity induced by challenge with food antigens among patients sensitive to corn, cow's milk, and wheat. Observed dose-dependent linear inhibition in ACT suggests the existence of a ketotifen cellular binding protein.

More recently, ketotifen has been studied as a possible inhibitor of the potent action of PAF acether in the inflammatory process (39). Although the effect of ketotifen is quickly apparent in experimental studies, about 6 to 12 weeks of treatment are required to show its clinical efficacy (40).

Eosinophilia is a prominent feature of allergic diseases, and some parasitic infestations (41). The data convincingly demonstrate that the eosinophil is an active participant in inflammation (42) and can contribute to tissue injury through release of cellular constituents such as MBP, granular enzymes and products of oxidative metabolism.

Also important to our further understanding of the role of eosinophils in diseases is the observation that blood and tissue eosinophils represent a heterogeneous population for function, membrane receptors and cell density (43). Blood low density:hypodense eosinophils (HEs) have been identified in parasitic syndromes, asthma, allergic rhinitis, and more recently in patients with AD (27, 44). It has been demonstrated by Leiferman that eosinophils are increasing with the progress of dermatitis, and that deposition of MBP at the site of AD contributes to the pathology (7). Miyasato et al. (27) showed that ketotifen decreases peripheral eosinophils, and that this effect is directly related to improvement of the symptoms of allergic diseases. These investigators attempted to elucidate the clinical significance of the increased blood eosinophils in allergic diseases by determining quantitative dynamic changes in this blood cell population. They measured the density distribution in the peripheral blood and evaluated the morphology. Ten patients with AD received 2 mg of ketotifen for 2 weeks. Following the improvement of clinical symptoms, the number of peripheral eosinophils was significantly decreased as compared to controls. After the measurement of density distribution by a Nicodenz density gradient, it was found that the decreased rate of hypodense eosinophils was remarkable. The authors suggested that if ketotifen is able to decrease hypodense eosinophils, which are activated eosinophils, and can also inhibit the activation of eosinophils *in*

vivo, it could also be thought that this inhibitory effect of the drug may be a reason for the ketotifen-induced improvement of clinical symptoms.

These pharmacological properties of ketotifen make it suitable for the treatment of asthma, allergic rhinitis, conjunctivitis, acute and chronic urticaria, food allergy and food intolerance. In our study, ketotifen was well tolerated. We did not register any side effects, even drowsiness which affects 10% to 15% of adult patients in the first week of treatment but subsequently passes. Sedation is observed less frequently in children.

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