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Topical cromolyn can modify human allergic skin reactions

CROMOLYN sodium has been used orally and topically in the treatment of asthma, allergic rhinitis, and keratoconjunctivitis with varying success (1). Theoretically, topical application of cromolyn could modify the allergic IgE-mediated response seen after skin prick testing. The present study tested the effect of a new 4% cromolyn cream formulation (Ascent Pharmaceuticals) upon the cutaneous allergic response after skin prick testing. The study was performed in two parts; (I) to determine whether immediate pretreatment of the skin with cromolyn could modify the allergic response; (II) to determine the effect of pretreatment of the skin with 4% cromolyn cream or solution on this response.

■ **Part I.** Twenty volunteers known to be allergic to at least two standard antigens (including ragweed, grass, tree pollen, dog or cat fur, and house-dust mite) were enrolled. A placebo cream (vehicle alone) or active cream (vehicle containing 4% cromolyn sodium) was applied to

the left and right forearms in a randomized, blinded manner. Prick testing was done by the puncture method with Dome-Hollister lancets, 15 min, 30 min, and 1 h after cream application. Different forearm sites, as well as a control area of untreated skin on the upper inner arm, were used. Wheal and flare size was measured after 15 min by tracing onto transparent sheets, and calculating the surface area.

■ **Part II.** Ten volunteers who were known to be allergic to at least two standard antigens used in prick testing were enrolled. The antigens were diluted to give a mild to moderate wheal response of 3–5-mm diameter. Subjects were then randomly allocated to cromolyn 4% cream to be applied four times a day for 3 days to one forearm and cromolyn 4% solution (Nasacrom®) to be applied four times a day for 3 days to the other forearm. On day 4, subjects were rechallenged on treated and untreated areas. The level of itching at each prick test site was graded on a scale of 0–10 (0 = none, 10 = maximum). The differences in areas of wheal and flare, as well as level of itch in skin treated with cream, solution, and untreated sites, were calculated.

Data were entered into a verified dBASE IV database and analyzed with SAS statistical package software. In both sets of analyses, the outcome measures were the size of the wheal and the flare. All subjects received both treatments and control so that the specific outcome measure was the difference between the areas. In both phases, the outcome measure was modeled in terms of the factors treatment, antigen, and concentration by the analysis of variance (PROC GLM in the SAS statistical package). Hypotheses were tested at the 5% level without correction for multiple comparisons.

■ **Part I.** There were no significant effects on the wheal and flare response distinguishing treatment from control when cromolyn application immediately preceded skin prick testing.

■ **Part II.** For wheal and flare, either the cream or the solution provided a significant reduction in area compared to control regardless of the antigen used (Table 1). Pretreatment with cromolyn resulted in significantly smaller areas of flare than control ($P < 0.01$). Wheals in areas pretreated with cream were significantly smaller than control areas ($P < 0.05$). The itch score was significantly lower after pretreatment of the skin with cromolyn solution compared to control. In every analysis,

Table 1. Flare, wheal and itch, by treatment for 18 subjects* (mean $\pm$ standard deviation)

	Treatment		
	Solution	Cream	Control
Flare area (cm ²)	3.60 $\pm$ 3.50	4.80 $\pm$ 4.10	7.10 $\pm$ 5.10
Wheal area (cm ²)	0.18 $\pm$ 0.14	0.13 $\pm$ 0.07	0.18 $\pm$ 0.01
Itch score	3.10 $\pm$ 2.90	4.20 $\pm$ 2.70	4.60 $\pm$ 2.60

* Two subjects, scores for antigen concentration ratio 1:1 were excluded.

potential confounders, such as the antigen used, were not significant.

■ Our data suggest that prolonged pretreatment with topical cromolyn in cream or solution formulation can modify the wheal and flare responses seen in skin prick testing. Immediate pretreatment of the skin has no such effect.

There have been several studies with topical cromolyn in various vehicles. Simultaneous administration of topical cromolyn with antigen did not modulate human allergic skin reactions (2), while pretreatment of the skin with a cromolyn nebulizer solution inhibited human allergic skin reactions (3).

In a randomized, double-blind group trial of topical 10% cromolyn ointment, patients with atopic dermatitis showed significant improvement in cutaneous inflammation, lichenification, cracking, and pruritus (4). More recent, controlled randomized studies reported that cromolyn nebulizer solution was effective in treating atopic dermatitis (5). The success of topical cromolyn in some trials and its failure in others may be related to the concentration of cromolyn, its vehicle, and the duration of the treatment.

Topical cromolyn is remarkably free of adverse side-effects. Because of the risks of prolonged use of topical steroid preparations, particularly in children, it would seem worth pursuing the potential benefits of topical cromolyn. The present results suggest that pretreatment with topical cromolyn can modulate itch, and wheal and flare responses in the skin.

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Angiolymphoid hyperplasia with eosinophilia associated with immunotherapy

Key words: angiolymphoid hyperplasia with eosinophilia; immunotherapy.

PATIENTS receiving immunotherapy can develop atypical localized delayed reactions such as: localized fibrosis (1), subcutaneous nodules in reaction to $Al(OH)_3$ (2, 3), and localized urticaria a frigore (4). We report one case of angiolymphoid hyperplasia with eosinophilia caused by immunotherapy vaccination.

■ A 42-year-old white woman received 4 years'

A case of lymphoid nodules at the site of grass pollen immunotherapy injections.

immunotherapy with gramineous pollen extracts for the treatment of allergic rhinoconjunctivitis. Extracts absorbed onto aluminum hydroxide were used for the first 3 years, and extract absorbed

onto tyrosine was used during the fourth year.

One year after the last dose, she developed three 1-cm superficial and inflammatory nodules in her right arm and one nodule in her left arm. There was no lymphadenopathy and no abnormality anywhere else. Both her chest radiograph and her hematologic profile were normal.

Patch testing with the European standard series and Cl_3Al_2 (H_2O 2%) and the two extracts used (as is) showed no reactions.

Histologic examination showed several large vascular spaces surrounded by a lymphocytic and eosinophilic infiltrate. Plump endothelial cells protruded into the lumina. Lymphoid follicles replete with germinal centers were identified in the dermis and subcutaneous tissues. Angiolymphoid hyperplasia with eosinophilia was diagnosed.

■ Angiolymphoid hyperplasia with eosinophilia is an unusual benign condition. Its cause is uncertain. Originally, angiolymphoid hyperplasia with eosinophilia was thought to be equivalent to Kimura's disease. However, recent clinicopathologic studies have suggested that these are two separate entities with different clinical and histologic features (5). Other theories, such as an origin in benign vascular neoplasm or a secondary result of infectious agents, have been discarded.

An atopic reaction to various agents appears to be an alternative hypothesis. This is supported by

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