

Double-Blind Crossover Trial Comparing Systemic Chromone-Carboxylic Acid with Placebo in Patients with Atopic Dermatitis

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35 adult patients with atopic dermatitis were included in a double-blind crossover trial comparing chromone-2-carboxylic acid, FPL 57787 18 mg $\times$ 4, with placebo. Each treatment period lasted for 6 weeks with clinical assessment every 3 weeks. 28 patients completed 3 weeks of each period. Significant differences at the 5% level in favour of FPL 57787 were seen in the group starting on placebo. 17 patients completed the study. After 6 weeks there were no significant differences. 10 patients experienced dyspeptic side-effects. Further studies are warranted on clearly allergic sub-groups of atopic dermatitis patients.

Key words: atopic dermatitis; chromone-carboxylic acid; double-blind crossover trial; systemic.

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CLINICAL ASPECTS

Since 1967 the effect of disodium cromoglycate preventing allergic reactions when applied directly to the target organ has been greatly appreciated. Efforts have been made to produce drugs also active in oral administration with similar properties. The present study concerns the effect of one such drug, chromone-2-carboxylic acid (FPL 57787), in adult patients with atopic dermatitis. Although shown to be effective in animal models and in *in vitro* studies on human basophils, we regret that the drug seems to help only a minority of patients with atopic dermatitis. Accordingly the search should be continued for drugs with anti-allergic properties for systemic administration.

A double-blind trial comparing systemic treatment of atopic dermatitis (14 patients) with chromone-carboxylic acid (FPL 57787, 6 mg $\times$ 4) to placebo (13 patients) did not show any significant difference (5). This might be due to an insufficient amount of drug used. This trial was designed to investigate the effect of the drug after trebling the dose.

MATERIAL AND METHODS

The new drug is a tricyclic chromone, FPL 57787, or chromone-2-carboxylic acid, with the empirical formula $C_{17}H_{18}O_5$ and structural formula as shown in Fig. 1. It is chemically related to the bis-chromone derivative disodium cromoglycate (Fig. 2). Whereas the

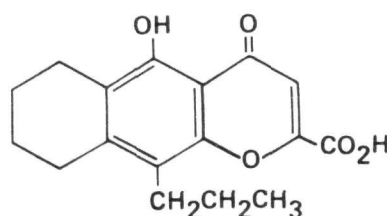


Fig. 1. Structural formula of FPL 57787, chromone-2-carboxylic acid.

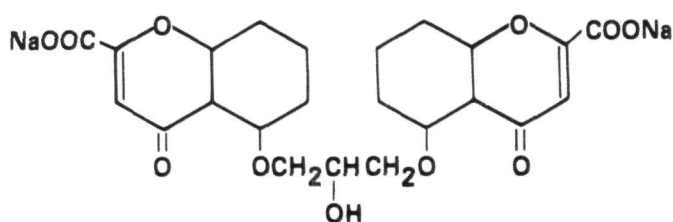


Fig. 2. Structural formula of disodium cromoglycate.

latter is only poorly absorbed when administered orally, FPL 57787 has been shown to be active given orally against experimental and clinical asthma. FPL 57787 has been shown to possess anti-allergic activity in a rat model using passive cutaneous anaphylaxis test as well as reflecting very good intestinal absorption when administered intravenously. FPL 57787 inhibits *in vitro* antihuman IgE-induced histamine release from human basophil leukocytes. Sodium cromoglycate is inactive in this *in vitro* system and also when given by the intestinal route (1).

Thirty-five patients were entered in the trial. A written, informed consent was obtained. All but one were 18 years of age. A 15-year-old girl was included with her parents' consent. The patients were selected in accordance with the criteria laid down by Hanifin & Lobitz (4). Females were instructed not to become pregnant during the trial. Patient characteristics are listed in Table 1.

The object of the trial was to compare the efficacy and safety of FPL 57787 with a matched placebo in the treatment of chronic atopic dermatitis. The study was designed as a

double-blind crossover trial with patients being allocated at random to one of the order groups. The study was carried out in the winter months. The patients were supplied with a 1% hydrocortisone cream to use when necessary. Initially a clinical assessment form was completed recording patient characteristics and details of disease extent and severity. The patients were then started on a 2-week baseline period, recording on diary cards their symptoms as itching, disturbance of sleep and severity of disease grading 0 to 2 and applications of local treatment. After this baseline period they were reassessed clinically and started on a 12-week treatment period with crossover after 6 weeks and clinical assessment every 3 weeks. The dose of the test drug was 18 g × 4 daily. Crossover could be made after 3 weeks of a treatment period if the eczema increased in severity or the patient complained of lack of efficacy. The following laboratory investigations were performed at the controls: ESR, full blood count, haematocrit, MCV, MCH, MCHC, differential white cell count, platelets, prothrombin time, sodium, potassium, calcium phosphate, albumin, urea, creatinine, acid phosphatase, basic phosphatase, SGOT, SGPT, LDH, bilirubin and cholesterol. Urine was analyzed for protein, dextrose and blood. Wilcoxon's method for statistical analysis was made at the two-tail 5% level.

Patient compliance

Seven patients did not complete the first 3-week treatment period, leaving 13 in the FPL 57787-placebo order group and 15 in the other. Dyspeptic side-effects caused four patients to break off the trial, one became pregnant, one failed to show up without giving any reason and one moved to the south of Norway.

Only 17 patients completed the trial, eight in the FPL 57787-placebo group and nine in the other. Four patients in the placebo-FPL 57787 group wished to switch after 3 weeks as their eczema increased in severity, and four in the FPL 57787-placebo group found the treatment inefficacious and wanted to change. Two patients changed surroundings, which greatly in-

Table 1
Patient characteristics

Order group	FPL 57787 – Placebo	Placebo – FPL 57787
Age	26.9 (15–37)	22.3 (18–42)
Male	6	8
Female	11	10
Duration of disease	23.7 (11–35)	20.6 (9–41)
Other allergic diseases		
Asthma	5	6
Hay fever	8	9
None	6	4
Family history of allergy	15	10

The patients had suffered from extensive atopic dermatitis most of their lives. Other allergic diseases were present in more than 70% of the cases, as was a positive history of familial allergy.

Table 2

Analysis of clinician's scores at week 3 of each treatment period. Symptom scale = 0–3

	Order group	Baseline mean	FPL 57787 mean	Placebo mean	Significance
Severity of area affected	FPL 57787 – Placebo	1.76	1.56	1.60	<i>P</i> < 0.05
	Placebo – FPL 57787	1.80	1.08	1.64	
	All patients	1.78	1.30	1.62	
Lichenification	FPL 57787 – Placebo	1.57	1.18	1.23	<i>P</i> < 0.05
	Placebo – FPL 57787	1.54	0.84	1.35	
	All patients	1.55	1.00	1.29	
Excoriation	FPL 57787 – Placebo	1.60	1.41	1.50	<i>P</i> < 0.05
	Placebo – FPL 57787	1.68	1.11	1.58	
	All patients	1.64	1.25	1.54	
Redness	FPL 57787 – Placebo	1.71	1.47	1.62	<i>P</i> < 0.05
	Placebo – FPL 57787	1.78	1.20	1.68	
	All patients	1.75	1.32	1.65	

28 patients completed the first 3 weeks of each treatment period. For each patient the mean score of four areas was taken to represent the symptom score (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The baseline value was taken as the mean of the two pre-treatment assessments.

Table 3

Analysis of diary card scores using last 4 weeks of each treatment period

Symptom	Order group	Baseline mean	FPL 57787 mean	Placebo mean	Significance
Itching	FPL 57787 – Placebo	9.98	8.86	7.65	<i>P</i> < 0.05
	Placebo – FPL 57787	9.56	7.95	9.67	
	All patients	9.74	8.34	8.82	

17 patients completed 6 weeks of each treatment period, the numbers are weekly symptom score totals, symptom scale 0–3.

fluenced their disease activity. One patient left because of dyspeptic side-effects. The fact that most patients had to travel all day to get to the clinic may have contributed to the high drop-out rate.

RESULTS

Twenty-eight patients completed the first 3 weeks of each treatment period. The clinician's scores for evaluation of symptoms as overall severity, lichenification, excoriation and redness in the affected areas are listed in Table 2.

Significant differences in favour of FPL 57787 were only seen in the placebo-FPL 57787 group. The FPL 57787-placebo group showed the lowest symptom score during the active period but the difference was not significant.

Seventeen patients completed the study. The analysis of the clinician's symptom scores showed the same trend as at week 3 but the differences were not significant. Both the clinician and the patients favoured FPL 57787, the clinician more so, but in neither case were the differences significant.

The only significant difference in the patient diary cards was reduced itching for FPL 57787 in the placebo-FPL 57787 group (Table 3). There were no significant differences in the application of local treatment. Ten patients experienced dyspeptic side-effects; seven from FPL 57787, two from placebo and one from both. This caused five withdrawals, three on FPL 57787 and two on placebo. There were no laboratory side-effects.

DISCUSSION

The suggestion has been made that FPL 57787 has a broader spectrum of activity than disodium cromoglycate (1). FPL 57787 has been shown effective as protection against exercise-induced asthma (7). Oral disodium cromoglycate has no such effect, disodium cromoglycate has to be inhaled to protect against asthma (2). It is necessary to apply directly to the target organ. In this way oral disodium cromoglycate can be useful against allergic reactions to food as it prevents the release of mediators after an antigen-antibody reaction in the gut (3). Patients with dermatitis herpetiformis have also benefited from oral disodium cromoglycate, it is suggested that the membranes of the neutrophilic granulocytes are stabilized, preventing the release of lysosomal enzymes from the contact with immune complexes (6). As FPL 57787 has been demonstrated to be effectively absorbed after oral administration in a rat model (1) it should be of value to relieve that part of disease activity in patients with atopic dermatitis that is provoked by type-I allergic reactions. These antigens may come from the surroundings, they may be ingested or even be part of the microbial flora of the patient's skin.

The present study suggests that systemic chromone derivatives relieve certain symptoms in patients with atopic dermatitis. However, statistically significant results in favour of FPL 57787 were obtained only in the group that started on placebo and only after the first 3 weeks of treatment. This may be due in part to the reduced sample at 6 weeks, and possibly also to an increasing awareness during the trial on the part of the patients of the importance of

antigen avoidance. There may even have been carry-over effects from the active period relieving the symptoms in the placebo period. Further studies should be made on a more selected group of atopic dermatitis patients with allergic reactions clearly relevant to disease activity. Attempts should be made to prevent the dyspeptic side-effects.

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