FPL 58668KC for the Treatment of Allergic Rhinitis*

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SUMMARY **Fifty-three patients with allergic rhinitis, being treated at three medical centres in Bangkok Metropolis, were subjects of this double–blind comparative study, the aim of which was to evaluate the effectiveness of a new anti–allergic agent, FPL 58668KC, given in doses of 250 mg via nostrils four times a day for 28 days. Although there were no significant side-effects during the trial, the results revealed no significant benefits compared with the use of a placebo.**

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According to the manufacturer's document,[1] FPL 58668KC, the calcium salt of a novel oxygen-containing heterocyclic acid, is a new chromone which possesses significant anti - allergic activity against immediate hypersensitivity in animal models. It is 30 times more potent than disodium cromoglycate in passive cutaneous anaphylaxis in rats and, when given by inhalation to asthmatic volunteers, significantly inhibited antigen-induced experimental asthma. The same report indicates the use of FPL 58668KC, in the form of a pressurized aerosol, for treatment of allergic conditions of the lung and the upper respiratory tract.

The objective of this study was to evaluate the efficacy of and patients' tolerance to FPL 58668KC used in the management of allergic rhinitis.

MATERIALS AND METHODS

Patients in this study were those known to have a history of allergic rhinitis which required treatment for a minimum of two consecutive years. The study comprised a total of 53 cases (23 males and 30 females) from three general hospitals in metropolitan Bangkok (18 from Siriraj Hospital, 16 from Chulalongkorn Hospital and 19 from Pramongkutkloa Hospital). The patients' ages ranged from 14 to 53 years, with a mean of 28 years. They had received neither steroid therapy in any form nor hyposensitization during the preceding 12 months. The onset of allergic rhinitis occurred at ages varying from 5 to 40 years (mean, 21 years); details of the patients' characteristics are shown in Table 1. There appeared to be no significant difference in the characteristics between patients in the FPL group and those in the placebo group, which indicates no selection bias.

Upon beginning the trial, intracutaneous tests were performed on every patient. A standard panel of 12 common allergenic extracts such as house dust, house-dust mite, pollens, moulds and household insects were used and positive reactions recorded. When the admission form for trial had been completed, the patients were instructed to spray the aerosols provided into both nostrils four times a day for 28 days. Using an identifying code, the aerosols were allocated at random, the contents being unknown to the patients and the investigators. The FPL 58668KC dose was 20 micrograms four times daily; the same aerosol formulation, but without the active drug, was used as the placebo dose.

During the trial, one or the other of the antihistaminic agents chlorpheniramine and brompheniramine was provided for all patients with instructions to take the drug only when necessary. Patients were asked to record on the diary card provided the details concerning the severity of symptoms, the admistration of aerosol and the use of antihistamine or any other therapy that became necessary during the trial. The severity of the patients' symptoms was to be rated on a scale of 0 to 3 (0 none, 1 mild, 2 moderate, 3 severe) for running nose, blocking, itching and sneezing, as well as itching and running of the eyes. They were asked to return to the clinic after

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Table 1 Patients' characteristics

		Patients received FPL 58668 KC (N = 28)	Placebo (N = 25)
Age, yr	Mean	28.2	27.6
	Range	15-46	14-53
Sex	Male	13	10
	Female	15	15
Age at onset of rhinitis	Mean	21.8	20.5
	Range	5-40	11-31
Severity of condition	Mild	1	0
	Moderate	17	14
	Severe	10	11
Troublesome symptoms (nose)	Running	14	10
	Sneezing	12	15
	Blocking	13	10
	Itching	8	9
(eyes)	Running	8	8
	Itching	12	12
Previous medications	Antihistamine	21	19
	Expectorant	0	1
	Nasal spray	1	1
	Vasoconstrictor	1	0
	Bronchodilator	2	2
	Corticosteroids	0	1
	Cold tablets	5	5

seven days so that their diary cards could be checked. At the end of the trial, the patients were asked to return to the clinic with their diary cards and the remainder of aerosols and antihistamine. A clinician then completed final assessment of the forms.

At the beginning and end of the trial, blood and urine samples were collected for laboratory analysis. The relevant data included haemoglobin concentration, haematocrit, white-cell and platelet counts, serum protein, creatinine, bilirubin, alkaline phosphatase, aspartate transaminase, and urine sugar, protein and microscopic sediments.

Data on the two groups (FPL 58668KC and placebo) were compared using the Mann-Whitney U-test. For statistical comparison, a two-tailed test at the 95 per cent level was used to indicate significance or non-significance (NS; $p > 0.05$).

RESULTS

Among the 53 patients studied, 28 received aerosols containing FPL 58668KC; the remaining 25 received placeboes.

Table 2 shows the positive results of the skin tests with various allergens.

Although there were no defaulters, eight patients deviated somewhat from the assigned treatment. Data on five of them had to be excluded from the analysis, but the first two weeks of data on the other three were used.

The results of the symptom scores recorded on the diary cards are summarized in Table 3. The information was evaluated by assessing the weekly symptom scores calculated from both the first and the second weeks of the trial as well as the total period. Regarding their symptoms, there were no statistically significant differences between the two groups of patients. Analysis of symptom scores was also carried out separately using data from individual hospitals on patients whose first week scores were severe (i.e. score$\geqslant$7). The results again showed no statistically significant difference.

While there was no difference in the use of antihistamines (Table 4) between the two trial groups, it was noted that patients from Pramongkutkloa Hospital had a higher consumption rate which tended to be fixed according to individual patients throughout the study.

Few additional symptoms were recorded in seven patients receiving FPL 58668KC compared with six in the placebo group. Most of these symptoms could be related to rhinitis, although in the FPL 58668KC group, one patient developed headache and two patients complained of a burning sensation in their nostrils immediately after using the spray.

Table 2 Positive results of skin tests with various allergens

	Patients received FPL 58668 KC (N = 28)	Placebo (N = 25)
House dust	25	23
D. farinae	15	13
D. pteronyssinus	22	20
Kapok	11	8
A. niger	1	1
Grass	10	11
Animal dander	2	0
Aspergillus	10	14
Alternaria	2	0
Candida albicans	9	5
Penicillium	6	7

Results of haemo-analysis, performed separately in the three hospitals, revealed no significant difference between pre-treatment and post-treatment data at any of the

Table 3 Analysis of diary cards using weekly totals

Symptoms	Weeks	Mean (Sample Size) FPL 58668 KC	Placebo	Mann-Whitney U-Value
Nose :				
Blocking	1-2	6.6 (25)	6.9 (22)	265
	3-4	5.8 (24)	5.1 (20)	257
	1-4	6.2 (24)	5.8 (20)	260
Running	1-2	6.9 (25)	6.5 (22)	263
	3-4	6.6 (24)	5.5 (20)	277
	1-4	6.8 (24)	6.3 (20)	254
Sneezing	1-2	5.2 (25)	6.0 (22)	249
	3-4	5.0 (24)	6.0 (20)	211
	1-4	5.1 (24)	6.1 (20)	212
Itching	1-2	2.8 (25)	3.2 (22)	253
	3-4	2.1 (24)	3.0 (20)	173
	1-4	2.3 (24)	3.0 (20)	201
Eyes :				
Itching (day-time)	1-2	2.5 (21)	2.7 (18)	178
	3-4	1.8 (21)	1.7 (16)	183
	1-4	2.2 (20)	1.9 (16)	164
Running (day-time)	1-2	1.0 (21)	1.4 (18)	173
	3-4	1.2 (21)	1.7 (16)	162
	1-4	1.2 (20)	1.7 (16)	146
Itching (night-time)	1-2	1.6 (20)	2.1 (18)	160
	3-4	1.2 (19)	1.7 (16)	150
	1-4	1-4 (19)	1.7 (16)	139
Running (night-time)	1-2	0.9 (20)	1.1 (18)	173
	3-4	0.6 (19)	0.6 (16)	147
	1-4	0.8 (19)	0.9 (16)	152

Table 4 Antihistamine consumption

Number of tablets used in 28-day period	Patients received FPL 58668KC	Placebo
0	2	4
1-14	8	5
15-28	5	2
29-56	8	5
> 56	1	2

hospitals. Urinalysis was negative at the beginning of the trial, except for those patients in the FPL 58668 KC group who were examined at Chulalongkorn Hospital; at the beginning of the trial, three of the latter patients showed a trace of protein and at the end of the trial one of them showed a trace without previous finding.

DISCUSSION

Although there are a variety of medications for allergic rhinitis, nasally applied drugs providing significant protective effects without side effects are highly desirable. After Altounyan in 1967[2] reported on the effectiveness of disodium cromoglycate (DSCG) for the treatment of allergic bronchial asthma, it has been tried in the treatment of allergic rhinitis because of its anti-allergic action.[3-10] The mode of action of DSCG is its ability to protect mast cells from releasing chemical mediators during antigen-antibody reactions. Its toxicity and side effects were shown to be negligible. At present, the application of DSCG by nasal insufflation provides a favourable form of treatment for allergic rhinitis. However, the mode of application of DSCG into the nose is a rather cumbersome method of administration. Thus, any similarly effective new chemical entity formulated for delivery from a pressurized aerosal giving approximate metered doses, is a welcome alternative.

A new chromone, coded FPL 58668KC, that has been preliminarily reported by its manufacturer to be of particular value in the prophylactic treatment of allergic rhinitis both in the laboratory and in clinical trials, is delivered in the above mentioned manner. Unfortunately, however, its efficacy was not confirmed in the present study; the drug showed only trivial side-effects on the patients tested.

The unyielding unfavourable results of our trial which tested this new compound may be attributable to the low potency of the drug itself, associated with or without other factors, such as the insufficient solubility of the drug in aqueous media resulting in inadequate penetration of the nasal mucosa. Also, the trial period might have been too short to allow active prevention of allergic reactions, which usually requires a longer period of time.

The unexpectedly high success rate in the placebo group of patients remains unexplained. Were psychological effects responsible for the determination of the success or failure rate in each patient, then a crossover design would be preferable for comparing the active drug and the placebo in any future trial. Perhaps, forthcoming derivatives of FPL 58668KC will provide substantial benefits for the victims of allergic rhinitis.

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