Beclomethasone dipropionate and Flunisolide: an Open-crossover Comparative Trial in Perennial Allergic Rhinitis*

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SUMMARY **Flunisolide nasal solution which is a newly synthesised topical corticosteroid was compared with a well-documented beclomethasone dipropionate aerosol by an open-crossover trial in a group of 45 perennial rhinitis patients.**

Both flunisolide and BDA have been shown to effect significant control of itching, sneezing, stuffy nose and running nose. In both groups, there were no significant changes of the absolute eosinophil count, the number of eosinophils in the nasal smear, and the nasal swabs for bacteria and fungi. But the symptom scores rated after the nasal provocative test decreased significantly after each treatment. The total serum IgE level increased in both groups, but it was statistically significant only in the flunisolide group. The side-effects were reported more frequently in the group of flunisolide users but most of them were mild. The physicians' and patients' opinions about the effectiveness of each treatment were similar although the overall changes in mean symptom scores of all symptoms and the patients' preference favoured the use of BDA. We concluded that flunisolide is probably a valuable alternative to BDA when perennial rhinitis requires treatment with a topical corticosteroid.

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Beclomethasone dipropionate aerosol (BDA) has since 1973 been used intranasally in treating patients with hay fever.[1] Its efficacy has also been proved in our perennial allergic rhinitis patients.[2] At present, another new potent topical corticosteroid, "flunisolide", which is closely related to fluocinolone acetonide, has been introduced for the treatment of patients with allergic rhinitis. Many clinical trials on the use of flunisolide nasal spray have demonstrated its superiority to a placebo for the treatment of perennial rhinitis[3-8] and seasonal allergic rhinitis.[8-10] A similar result was also observed in children with a lack of any serious side-effects.[11,12] Therefore, it may be concluded that BDA and flunisolide are safe and effective steroid analogues for use intranasally in treating cases of nasal allergy. A parallel comparison between the effectiveness of BDA and flunisolide has been performed; it showed that both of them are equally effective.[13] However, our clinical study to compare the effectiveness of BDA and flunisolide in perennial rhinitis patients was carried out in an open-crossover design to evaluate the superiority of these two preparations in order to use them properly.

MATERIALS AND METHODS

Forty-eight patients were involved in this study. They were all attending the ENT Allergy Clinic of Siriraj Hospital for treatment of their perennial rhinitis symptoms. Only 45 patients (30 females and 15 males) completed the study. Their ages ranged from 16 to 57 years; the average age was 28.5 years. The duration of symptoms ranged from one to 22 years, the average duration being 7.3 years. Four patients also had bronchial asthma which was not severe enough for them to use bronchodilators regularly. None had received any form of steroid therapy during the preceding six months. It should be stressed that no BDA had been prescribed previously for this

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group of patients. No patient had any signs nor symptoms of infection in the nose, throat and sinuses at the beginning of and throughout the trial period. A family history of allergic diseases was positive in 34.1 per cent of the patients.

The duration of this trial was eight weeks. Patients were given one kind of treatment for four weeks then another kind for another four weeks. In order to minimise any bias among the physicians who were familiar with BDA from our previous trial, the treatment given to each patient was accomplished on weekly basis by one of our technicians. The physicians who evaluated the results did not know the kind of treatment the patients were being given.

The wash-out period was not designed in this trial because it was stated that the effect of BDA lasted only 1-2 days after it was discontinued.[14] In our own observation, the carry-over effect of flunisolide lasted fewer than 72 hours.

Prior to the commencement of treatment, every patient was tested intracutaneously with a standard panel of 12 common allergenic extracts such as house-dust, house-dust mite, pollens, moulds and household insects. Roentgenography of the chest and paranasal sinuses was also performed; if any abnormality was detected, the patient was excluded from the study. On admission and at the end of each treatment period, every patient had received or undergone the following:

a. a complete routine ENT examination,

b. nasal swabs for bacteriological as well as fungal studies,

c. nasal provocation test with house-dust mite extract.

d. eosinophil estimations of nasal secretions.

e. complete blood count.

f. total serum IgE determination (by Phadebas IgE PRIST test kits).

With regard to BDA, each patient was instructed to inhale one puff in each nostril four times a day for four weeks. This represented a daily dose of 400 micrograms per day.

As for flunisolide, the dosage used was two sprays in each nostril twice daily giving a total daily dose of 200 micrograms of flunisolide per day. This was also done for four weeks.

All patients were also given a kind of antihistamine tablet (chlorpheniramine maleate 4 mg or a combination of tripolidine HCl 2.5 mg and pseudoephedrine HCl 60 mg) to be used supplementarily as necessary.

Patients were assessed on admission to the trial and at the end of each test medication on the following symptoms using a graded scoring system: itching, sneezing, stuffiness and running nose, each rated on a 4-point scale (0= none, 1= slight, 2= moderate, and 3= severe).

Tests for significance of the findings were performed using the Chi-square test, the paired-t test and the student's t test where appropriate.

Earlier studies in experimental animals showed that inhaled flunisolide in doses of less than 4.0 mg per day did not suppress the plasma cortisol levels.[15] Also, investigations on the use of flunisolide in man showed no sign of adrenal suppression at the therapeutic dose.[3-13] There is also sufficient evidence to indicate that long-term use of BDA produces no systemic effect.[1,16-22] Therefore, no test for adrenal function was included in this study.

RESULTS

The 33 patients who received BDA first were allocated to group I and the 12 patients who received flunisolide first were allocated to group II. In the intracutaneous test, every patient showed at least a 2+ reaction to more than two common allergens. By the end of the trial, all patients had used both BDA and flunisolide each for one month and the overall changes of the symptom scores for each symptom after each therapy are shown in Table 1.

Both drug groups showed significant reductions of symptom scores from the control group with regard to itching, sneezing, stuffy nose and running nose. However, when the effects of the two drugs were compared by using the overall symptom scores for all symptoms, BDA was shown to be significantly superior to flunisolide ($p<0.0005$).

The mean changes of the symptom scores of group I and group II were also recorded separately (Table 2).

This again shows significant symptomatic relief in both the BDA and the flunisolide groups.

The mean admission score for sneezing, stuffy nose and running

Table 1 Overall changes in mean symptom score in all patients using BDA and flunisolide (for one month each).

Symptom	Mean change from admission (mean ± S.D.)	
	Beclomethasone dipropionate group	Flunisolide group
Itching	− 1.18 ± 0.58***	− 0.44 ± 1.12*
Sneezing	− 1.56 ± 0.65***	− 0.8 ± 1.03***
Stuffy nose	− 0.93 ± 0.93***	− 0.87 ± 0.99***
Running nose	− 1.27 ± 0.69***	− 0.8 ± 1.03***
Total score	− 4.96 ± 1.99***	− 2.91 ± 3.34**

* = $P<0.05$; ** = $P<0.005$; *** = $P<0.0005$.
Calculated by using the paired-t test.

Table 2 Mean symptom scores on therapy. (mean ± S.D.)

Symptom	Group I Mean admission score	Group I Mean change from admission Period I (BDA)	Group I Mean change from admission Period II (flunisolide)	Group II Mean admission score	Group II Mean change from admission period I (flunisolide)	Group II Mean change from admission Period II (BDA)
Itching	1.76 ± 0.90*	− 1.39 ± 0.55***	− 0.42 ± 1.11*	1.08 ± 1.08	− 0.50 ± 0.996*	− 0.58 ± 0.67*
Sneezing	2.30 ± 0.68	− 1.64 ± 0.67***	− 0.76 ± 1.03***	1.92 ± 0.9	− 0.92 ± 0.95**	− 1.33 ± 0.79***
Stuffy nose	1.76 ± 0.83	− 1.00 ± 0.87***	− 0.79 ± 1.02***	2.08 ± 0.9	− 1.08 ± 0.95***	− 0.75 ± 0.98*
Running nose	2.00 ± 0.87	− 1.33 ± 0.60***	− 0.79 ± 1.02**	1.92 ± 1.08	− 0.83 ± 1.08*	− 1.08 ± 0.94***
Total scores	7.82 ± 1.70	− 5.40 ± 1.71***	− 2.76 ± 3.41***	7.00 ± 2.17	− 3.33 ± 3.05***	− 3.75 ± 2.60***

* = $P < 0.05$; ** = $P < 0.005$; *** = $P < 0.0005$
(using the paired-t test to compare the admission score with that of period I and period II)

nose between the two groups was not significantly different. Only the mean admission score for itching in group I was slightly more than that of group II; nevertheless, when the mean of the overall symptom scores was analysed, it showed no significant difference between the two groups.

Among the various investigations carried out during the trial, viz. absolute eosinophil count, eosinophils in the nasal smear, nasal provocation test and total serum IgE, the results were collected and recorded for three groups

1. The control group (= before commencing the treatment)
2. After using BDA for four weeks
3. After using flunisolide for four weeks

The result of the nasal provocative test was expressed by rating the nasal manifestations which occurred after the provocation on the 4-point scale as described earlier. The overall results of these investigations are summarised and shown in Table 3.

There were no significant changes in the absolute eosinophil count and the number of eosinophils in the nasal smear from the control after using both BDA and flunisolide. But the symptom scores rated after the nasal provocative test decreased significantly after each treatment. Total serum IgE increased in both treatment groups, but it reached the statistically significant level only in the flunisolide group.

Table 3 Various investigations accomplished at the beginning and at each follow-up visit.

	Control	BDA	Flunisolide
Abs. Eos. (mean ± S.E.)	528.46 ± 131.47	377.18 ± 49.74	290.40 ± 69.39
Eos. in nasal smear (mean ± S.D.)	5.11 ± 6.38	8.95 ± 16.78	3.71 ± 9.07
Nasal provocative test (mean ± S.D.)	3.53 ± 3.00	1.6 ± 1.50***	2.29 ± 2.25*
IgE (mean ± S.E.)	595.58 ± 62.43	663.55 ± 91.41	845.44 ± 214.07***

* = $P < 0.05$; ** = $P < 0.005$; *** = $P < 0.0005$
Calculated by paired-t test comparing the control and patients after using BDA and Flunisolide.

Three nasal swabs taken from every patient at the beginning and after each treatment period revealed some growth of bacteria and fungi but they did not differ significantly between each interval. No growth of Monilia was reported.

Most of the patients also used antihistamine tablets during the trial, but only in small amounts; they were comparable in both the BDA and flunisolide groups.

Three patients on BDA treatment and nine patients on flunisolide experienced some side-effects which were considered to be probably drug-related (see Table 4). Some patients reported more than one side-effect; however, only one patient with rash discontinued therapy after using flunisolide for three weeks, but we did not exclude this case from the study.

The assessments of the effectiveness of each kind of treatment by patients and physicians at the end of the trial are shown in Table 5.

The patients' and physicians' opinions were similar and both drugs showed a significant control of symptoms. There was no statistically significant difference between the two treatments ($p = 0.3305$ for patients and $p = 0.3394$ for physicians).

At the end of the study, the pa-

Table 4 Number of side-effects reported.

Side-effect	BDA	Flunisolide
Burning sensation	1	9
Nasal irritation	–	1
Nasal obstruction	1	–
Throat dryness	1	–
Headache	1	1
Dizziness	1	–
Insomnia + night mare	1	–
Rash	–	1
Total	6	12

Table 5 Comparison of effectiveness of drugs. (using the Chi-squared test)

Evaluated by	Very effective	Effective	Moderately effective	Not effective
Patients				
BDA	11	18	13	3
Flunisolide	9	6	13	17
(p = 0.3305)				
Physicians				
BDA	6	18	17	4
Flunisolide	4	11	12	18
(p = 0.3394)				

Very effective = 100% control of symptoms
Effective = 75% control of symptoms
Moderately effective = 50% control of symptoms
Not Effective = < 50% control of symptoms

Table 6 Preferences at end of study.

	BDA	Flunisolide	Same	None
Patients	35 (77.78%)	7 (15.56%)	1 (2.22%)	2 (4.44%)

tients expressed a preference for BDA (see Table 6).

DISCUSSION

In general, the overall symptom scores and the patient preference in our study have shown that BDA is superior to flunisolide. This is quite a different outcome than that of another comparative study where flunisolide was proved to be equally effective as BDA.[13] Some of our patients noted that both BDA and flunisolide were equally effective in controlling their nasal symptoms; however, they preferred the use of BDA. One possible reason for this high preference may be due to the different presentation of the two drugs. Flunisolide nasal spray is a mildly viscous aqueous solution of 0.025% flunisolide in a mixture of 20% propylene glycol and 15% polyethylene glycol delivered by a metered dose pump while beclomethasone dipropionate is a suspension propelled by fluorochlorohydrocarbon (Freon) delivered by a metered dose aerosol. The presentation of BDA and its vehicle may have been more acceptable for our patients. Among many side-effects reported by flunisolide users, a burning sensation in the nose was the most frequent. This is probably due to its vehicle; in the earlier studies which compared flunisolide with its vehicle control, this side-effect was also encountered. This vehicle provides an advantage over the mild discomfort encountered as it makes possible the administration of flunisolide via the intranasal spray without having to use halogenated hydrocarbon propellants.

Another complaint of a few patients who using flunisolide nasal spray was that the solution ran down the back of their throat and sometimes returned through their nostrils. However, this complaint is not considered a side-effect. It is interesting to note that epistaxis, which is one of the side-effects reported in a study of intranasal corticosteroids, in the Western Hemisphere, did not happen in our patients. This may be attributable to the climate of our country which is warm and humid rather than to the drug itself.

Our results confirmed the findings that both BDA and flunisolide are safe and effective treatments for patients with perennial rhinitis. In the group of patients who preferred the use of flunisolide nasal spray, there were some who really appreciated its effective control of their nasal symptoms. Furthermore, the twice-a-day dosage regimen of fluni-

solide is also more suitable for the patient than the four-times-a-day dosage of BDA.

Therefore, flunisolide was certainly valuable as an intranasal treatment in the group of perennial rhinitis patients who responded satisfactorily to its use. It was also valuable as an alternative in another group of perennial rhinitis patients who did not respond to BDA or who used to respond well but after long-term use, developed tolerance to BDA.

In a comparative study, flunisolide was shown to be significantly superior to sodium cromoglycate in the overall assessment of symptom control in hay fever patients.[23] Flunisolide aerosol was also found to be an effective and well-tolerated alternative to oral corticosteroids in the treatment of steroid-dependent asthma in both adults[24] and children.[25] In a study of a group of patients using BDA for asthma, their accompanying perennial rhinitis was substantially controlled by flunisolide nasal solution without significant effect on plasma cortisol levels and on the incidence of overgrowth of Candida.[26] Flunisolide used at the therapeutic dose for the treatment of perennial rhinitis for a period of three months was proven to exert no significant effect on the collagen content or the surface epithelium of the nasal mucosa. There was also no sign of atrophic rhinitis or any infective process induced by the drug.[27] Hence, flunisolide is another form of topical steroid which can be used alternatively or concurrently with BDA for controlling allergic symptoms of the airways with considerable effect and safety.

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