

# The clinical efficacy of Fluticasone Propionate (Fluvent) compared with Beclomethasone Dipropionates (Becotide) in patients with mild to moderate bronchial asthma at the University College Hospital, Ibadan, Nigeria.

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## Summary

This open, randomized trial was conducted at the Medical Out patient Department of University College Hospital, Nigeria to compare the clinical efficacy of Beclomethasone dipropionate (Becotide) with Fluticasone propionate (Fluvent) in patients with mild to moderate bronchial asthma.

The study was performed as a week screening, 8 - weeks open comparative clinical trial involving Fluticasone propionate (Fluvent) at a daily dose of 220µg and Beclomethasone Dipropionate (Becotide) at a dose of 400µg daily delivered through pressurized metered-dose inhaler (pMDI). The main objective of this study is to assess the efficacy of Fluvent in patients with mild to moderate asthma compared to Becotide.

At the second visit (end of 1 week), 10 patients were given either Becotide or Fluvent but all were maintained on as needed beta<sub>2</sub>-agonist (Salbutamol inhaler) therapy throughout the study.

Efficacy was assessed by changes in symptoms, number of times beta<sub>2</sub>-agonist was used and results of pulmonary function tests (PEFR and FEV1) while safety was assessed by adverse event experiences.

The baseline characteristics of the patients randomized into the two drug groups were comparable and of no statistical significance.

The changes in the pulmonary function tests as well as the reduction in the asthma symptoms suggest a statistically significant improvement in the asthma status of the patients. However, these changes were more rapid among the patients using Fluvent. Also, there was higher percentage decline in the episodes of asthma symptoms either in the morning, day or night in the Fluvent group than Becotide group.

The drugs were well tolerated and no adverse event was noticed on any of the patients. We therefore concluded that Fluvent would be more efficacious than Becotide in the treatment of Asthma.

**Keywords:** Asthma, Fluticasone Propionate (Fluvent), Beclomethasone dipropionate (Becotide), Inhaled steroids.

## Résumé

Cette épreuve randomisée et ouverte a été effectuée au service médical des consultations externes du Collège Hospitalier Universitaire au Nigeria afin de comparer l'efficacité clinique de la dipropionate Beclomethasone (Becotide) avec la propionate Fluticasone (fluvent) chez les patients avec l'asthme bronchique bénin à la moyenne.

Cette étude a été effectuée durant le dépistage d'une semaine, 8 semaines d'épreuve clinique comparée ouverte impliquant la propionate Fluticasone (Fluvent) à l'administration du 220 g tous les jours et la Dipropionate Beclomethasone (Becotide) à l'administration du 400 g tous les jours rendu à travers le metered -dose inhaler (PMD) sous pression. Le but principal de cette étude est d'évaluer l'efficacité du Fluvent chez les patients atteints d'asthme bénin à la, moyenne par rapport à la Becotide. Durant la deuxième visite (à la fin de la première semaine) 10 patients ont été donnés soit Becotide soit Fluvent mais on les avait entretenus sur la thérapie bêta<sub>2</sub> agoniste exigée (salbutamol inhalateur) pendant toute la durée

de cette étude.

L'efficacité avait été évaluée à travers les changements dans les symptômes; la fois dont on avait utilisé le bêta<sub>2</sub> agoniste et les résultats d'épreuve pulmonaire fonctionnelle (PEFR et FEV) tandis qu'on avait évalué la sécurité à travers les expériences des événements hostiles.

Les traits caractéristiques de base des patients randomisés dans les deux groupes de drogues ont été comparés, et il n'y avait pas de statistique sensible.

Les changements dans les épreuves pulmonaires fonctionnelles aussi bien que la réduction dans les symptômes d'asthme ont suggérés une aliénation quant à la statistique sensible dans le niveau de l'asthme des patients.

Toutefois, ces changements étaient plus rapides chez les patients qui utilisent Fluvent. De plus, il y avait une baisse élevée du pourcentage quand aux incidents des symptômes de l'asthme soit au matin, dans la journée, soit dans la nuit chez le groupe Fluvent plus que chez le groupe Becotide.

Les drogues ont été bien tolérées et on n'avait pas remarqué aucun événement hostile chez n'importe qui des patients. Donc, nous tenons à conclure que le Fluvent pourrait bien être efficace plus que Becotide dans le traitement de l'asthme:

## Introduction

Inhaled corticosteroids (ICS) have been used for more than 20 years to treat bronchial asthma. At first, they were used for patients who otherwise would have been treated with oral steroids, and were also used in low and fixed doses. The standard dose of beclomethasone dipropionate (BDP) being 200µg twice daily or Fluticasone 110µg twice daily.<sup>1-3</sup>

The information gained over time on the efficacy and safety of ICS has resulted in their increased use. Today, ICS are given as first-line therapy to patients with newly detected asthma of all types of severity, including mild cases<sup>1-5</sup>.

Since early 1996, the management of bronchial asthma follows a stepwise pattern depending on the degree of severity<sup>3-4</sup>. The use of regular inhaled anti-inflammatory agents like beclomethasone 100-1400mcg twice daily or Fluticasone 50-200µg twice daily starts from step 2. Patients not well controlled received increasing doses of up to 800-2000µg daily of beclomethasone or 400-1000µg of Fluticasone through a large volume spacer plus regular prednisolone tablets in a single daily dose at step 5<sup>3,4</sup>. There is the need to use β<sub>2</sub>-agonist like Salbutamol or Salmeterol as needed medication. Salmeterol is used on regular basis from step 4 to step 5<sup>4</sup>.

Fluticasone propionate is a synthetic trifluorinated corticosteroids. Unlike currently available corticosteroids (beclomethasone), the drug is synthesized from a 19-carbon andosterone nucleus rather than a 21-carbon pregnane nucleus. Halogenation at positions 6 and 9 and addition of a double bond at the 1, 2 position of the andosterone molecule increases the anti-inflammatory activity of Fluticasone propionate<sup>6</sup>. Esterification of the oxygen at position 17 of andosterone nucleus and the addition of a second group of fluoromethyl carbothioate group at position 17 increase the anti-inflammatory activity of fluticasone propionate compared with beclomethasone dipropionate<sup>6,7</sup>.

In clinical efficacy, Fluticasone 220µg per puff, is

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approximately four times more potent than beclomethasone<sup>7</sup>. In patients requiring high-dose inhaled corticosteroids or regular use of oral corticosteroid, fluticasone is very effective in reducing symptoms and in minimizing the effects of oral corticosteroids<sup>7</sup>.

Fluticasone propionate (Fluvent) and Beclomethasone Dipropionate Becotide) are steroids use for the management of Asthma. Series of clinical trials elsewhere had proven the efficacy of the two drugs separately in the management of asthmatic patients. While Becotide has been subjected to series of clinical trials in our own setting. Fluvent is still new in the country. Therefore it will be highly necessary to examine its efficacy in the treatment of asthma in our own settings in Nigeria.

In this study the clinical efficacy of Fluticasone propionate 110µg twice daily was compared with beclomethasone dipropionate (BDP) 200µg twice daily delivered by pressurized metered-dose inhaler (pMDI)

### Patients and Methods

This trial was conducted at the Medical Out patient Department of University College Hospital (U.C.H.) Ibadan, Nigeria between 1st of February to April 2001.

A total of 30 patients aged 16-65 years were screened for the trial but 20 patients who met the following criteria were enrolled to participate.

- Confirmed diagnosis of bronchial asthma, using the short acting inhaled beta<sub>2</sub>agonist only.
- FEV<sub>1</sub> ≥ 60% of predicted and reversibility of airway disease demonstrated by a least a 15% increase in FEV<sub>1</sub> and/or PEF<sub>R</sub> after inhalation of 400µmcg salbutamol pMDI during the week of screening.
- Had a total day time asthma symptom score of at least 10 (≥10) in the last seven days of the screening period.
- Demonstrated the ability to comply with the trial regimen, ability to use the peak flow meter appropriately and complete the diary card correctly.

The following exclusion criteria were applied:

Exacerbation of asthma requiring additional therapy (e.g oral steroid) or a respiratory infection requiring treatment during the month preceding entry or during the screening period; long term (more than 14 days) or short-term (1-14 days) treatment with oral, or parenteral steroids during the month preceding entry.

During the screening period, patients recorded asthma symptoms, beta<sub>2</sub>agonist use, Peak expiratory flow rates (PEFRs) on diary cards.

Patients used a Mini-Wright Peak Flow Meter (Clement Clarke International Ltd. London U.K) to measure PEF<sub>R</sub> and recorded the highest of three forced exhalations each morning on waking up and evening before going to bed.

Patients assessed and recorded their daytime and night-time asthma symptoms (night time awakening). The day time asthma symptoms were assessed as described by Djukandic et al<sup>8</sup>.

On each day, they recorded as follows:

- 0 for no asthmatic symptoms
- 1 for mild asthmatic symptoms (which did not interfere with activities)
- 2 for moderate asthmatic symptoms which interfered with some activities
- 3 for severe asthmatic symptoms which interfered with most activities.

Patients that had a cumulative symptoms score of 10 or more over 7 consecutive days during the screening period and fulfilled the other inclusion criteria were randomized on either Beclomethasone dipropionate or Fluticasone propionate.

FEV<sub>1</sub> was measured by spirometry. The percentage of predicted FEV<sub>1</sub> was calculated at screening (at least 4 hours after beta agonist use) and at the end of the screening period. Salbutamol

(Ventolin) inhaler was given to patients for use as a rescue medication throughout the trial.

### Study design

This was an open, randomized study with 20 patients enrolled for the drug trial. The trial visit schedule consisted of the screening week (1 week) and a treatment period of 8 weeks. All the patients were maintained on inhaled salbutamol pMDI as needed therapy throughout the study. After 1 week run in period (screening) 10 patients are randomized either to Becotide pMDI 200µg twice daily (b.d) or Fluvent pMDI 110µg b.d respectively.

The third visit (week 5) coincided with four weeks while the fourth visit (week 9) was at the eight week of treatment.

During the treatment period, patients recorded on diary cards daytime asthma symptoms scores, morning and evening PEF<sub>R</sub>, night time awakenings, morning with asthma symptoms (asthma symptoms on awakening) and beta<sub>2</sub>agonist use.

Pulmonary function test (FEV<sub>1</sub> and PEF<sub>R</sub>) were carried out at least 4 hours after beta<sub>2</sub>agonist use at each visit as a measure of efficacy. This other parameters for outcome measures were changes in asthma symptoms and beta<sub>2</sub>agonist use.

Adverse events were recorded, and inhalation technique was checked at each visit. Compliance with treatment was monitored by questioning and by measurement of unused study medication.

### Data set and statistical analysis

The statistical package EP1 INFO Version 6.0 was used for data entry. Logical and consistent checks were introduced to ascertain quality and reliability of the data entered. Another statistical package, the Stat Pac Gold was used for further statistical analysis.

The weekly average of night time asthma, morning asthma, daytime asthma and use of Beta<sub>2</sub>agonist (Ventolin) were used in the analysis. Descriptive statistics such as arithmetic mean, standard deviation, proportion and percentages were used to summarize the baseline characteristics of the subjects, their follow-up data and changes from baseline to end point for each outcome measure. The one-way analysis of variance technique was used to examine the statistical significance of the pulmonary function tests and the asthma symptoms recorded during the clinic visits. A two-way analysis of variance (ANOVA) was used to examine the simultaneous effects of the drug and period of the changes on the outcome measure variables during the trial. The paired t-test was used to investigate the statistical significance of the changes in the pulmonary function tests and asthma symptoms at the end of week 1 (visit 2) and 9th week (visit 4). All statistical tests were two sided carried out at 50% probability level.

All patients enrolled gave written informed consent and the trial was approved by the Joint Ethical Committee of the University College Hospital/University of Ibadan.

### Results

The age-sex distribution of the patients is shown in Table 1. A total of twenty patients participated in the trial with 10 patients in each of the two treatment groups. However, there was no statistical significant difference in the age and sex distribution of the patients between the two drug groups (P>0.05)

The summary statistics of patient's anthropometrics parameters was shown in Table 2 none of which was statistically significantly different between the two treatment groups (P>0.05).

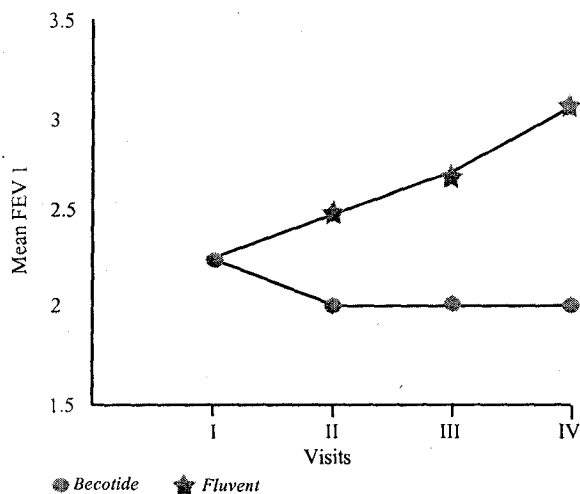
Table 3 shows the summary statistics of patients baseline pulmonary function test and the asthma symptoms by treatment groups none of the pulmonary function test was statistically significantly different between patients in the two groups, so also the baseline asthma symptoms (P>0.05).

**Table 1** Distribution of Patient's age and sex by treatment groups

Characteristic	Drug Groups				X <sup>2</sup>	P-Value
	Becotide		Fluvent			
	Freq.	%	Freq.	%		
<b>Age</b>						
16 - 19	4	40.0	3	30.0	2.94	0.040
20 - 49	4	40.0	5	50.0		
50+	2	20.0	2	20.0		
<b>Sex</b>					0.81	0.37
Male	6	60.0	3	30.0		
Female	4	40.0	7	70.0		

**Table 2** Summary statistics of Patient's age, weight and height by treatment groups

Charac- teristics	Summary Statistics	Drug groups		t	P-Value
		Becotide	Fluvent		
Age	Mean	29.30	36.00	0.98	0.66
	S. D.	15.20	15.46		
	Range	16.0 - 56.0	16.0 - 61.0		
Weight	Mean	56.7	60.00	0.97	0.65
	S.D.	7.79	7.48		
	Range	47 - 72	51 - 75		
Height	Mean	164.80	163	0.71	0.51
	S. D.	5.59	5.04		
	Range	153.0 - 172.0	153.0 - 170.0		



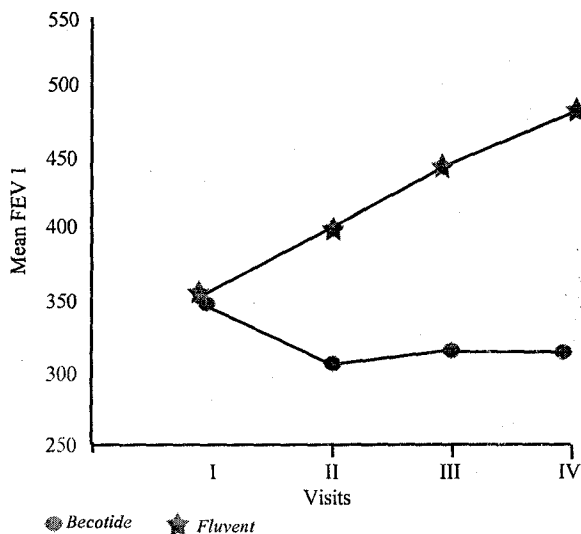
**Fig. 1** Pattern of patients FEV1 at each visit by treatment groups

The summary statistics of patients pulmonary function test, asthma symptoms and usage of Ventolin (Beta<sub>2</sub>agonist) are as presented in Table 4 and Figure 3. There was an increase in the mean FEV<sub>1</sub> of all patients from the baseline value of 2.22 ± 0.43 to 2.58 ± 0.62 at the last clinic visit. However, the increase in FEV<sub>1</sub> value recorded among patients on Fluvent was statistically significant (P<0.05) unlike that of Becotide. The Clinic PEFR of all patients also increased from the baseline value of 349.5 ± 68.32 to 390.5 ± 95.72 at the last clinic visit (visit 4). But the increase in the PEFR over the visits was only statistically significant among patients in the Fluvent treatment group (P<0.01).

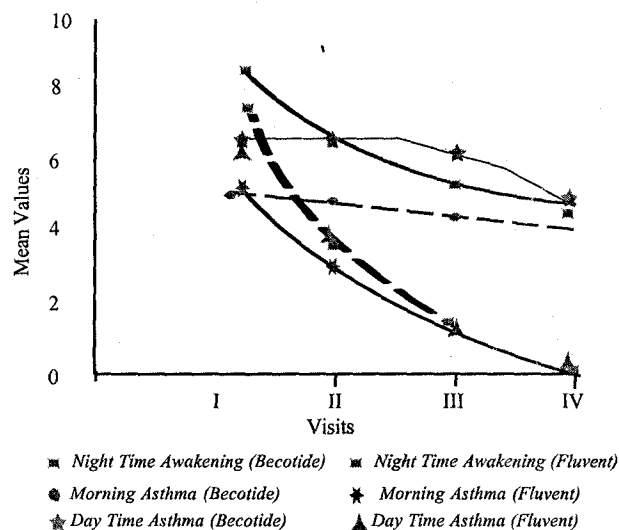
There was a reduction in the number of night time awakening and this was statistically significant in the two treatment groups although the percentage

**Table 3** Summary statistics of patients baseline pulmonary function test asthma symptoms and Ventolin use by treatment groups

Characteristic	Summary Statistics	Treatment groups		t	P-Value
		Becotide	Fluvent		
Duration of Asthma	Mean	10.9	5.22	3.71	0.05
	S. D.	6.62	4.55		
Clinic PEFR	Mean	343.0	356	0.42	0.69
	S. D.	57.13	88.58		
Clinic FEV <sub>1</sub> Predicted	Mean	2.23	2.21	0.10	0.92
	S.D.	0.36	0.52		
FEV <sub>1</sub> % Predicted	Mean	2.92	2.57	1.79	0.09
	S.D.	0.55	0.28		
Ventolin Usage	Mean	76.80	83.50	1.34	0.20
	S. D.	8.55	13.37		
Reversibility	Mean	20.91	2.71	0.56	0.59
	S.D.	5.54	8.57		
Night Time Awakening per week	Mean	8.70	7.50	1.16	0.26
	S. D.	2.50	2.12		
Morning Asthma	Mean	5.70	5.90	0.40	0.70
	S. D.	1.16	1.10		
Daytime Asthma	Mean	7.0	7.00	0.00	1.00
	S. D.	0.0	0.0		
Ventolin Usage	Mean	38.0	37.5	0.16	0.87
	S.D.	7.72	6.13		



**Fig. 2** The pattern of Peak Flow Rate (PEFR) at each visits by treatment groups



**Fig. 3** Pattern of patient's Asthma symptoms at each visit by treatment groups

reduction recorded in Fluvent group was statistically significantly higher than that of Becotide group. Similarly the number of times with morning asthma per week reduced from a baseline value of  $5.7 \pm 1.16$  to  $3 \pm 1.27$  at the last visit. The reduction was statistically significant in each of the two treatment groups.

The number of days per week with daytime asthma also

suggests that Fluvent was more efficacious and effective over Becotide in the treatment of asthma. This does not contradict findings in earlier studies<sup>10,11</sup>.

Engel et al<sup>12</sup> documented a greater decline in night time asthma, morning asthma, day time asthma score and frequency of beta<sub>2</sub>agonist use in the Fluvent group than Becotide. The

**Table 4 Summary statistics of patient's pulmonary functions, Asthma symptoms and Ventolin use at various visits by treatment group**

Pulmonary function	Drug group	Visits								F	P value
		I		II		III		IV			
		Mean	S. D.	Mean	S. D.	Mean	S. D.	Mean	S. D.		
Clinic FEV1	Becotide	2.23	0.36	2.0	0.42	2.07	0.47	2.10	0.41	0.51	0.68
	Fluvent	2.21	0.52	2.43	0.43	2.70	0.35	3.06	0.35	7.70	0.0004
Clinic PEFR	Becotide	343	57.1	305	37.19	313.5	33.83	311	27.16	1.76	0.17
	Fluvent	356	80.58	388	67.30	441	76.22	470	67.54	4.92	0.006
Night Awakening	Becotide	8.7	2.50	6.30	1.34	4.7	1.25	3.5	1.27	18.05	0.00001
	Fluvent	7.50	2.12	3.7	1.06	1.0	0.67	0.1	0.32	71.63	0.0001
Morning Asthma	Becotide	5.7	1.16	5.1	0.99	4.2	1.23	3.3	1.27	7.49	0.001
	Fluvent	5.8	1.10	3.2	0.79	4.3	1.2	0.0	0.0	132.38	0.00001
Day Asthma	Becotide	7.0	0.0	6.5	0.85	5.4	1.27	3.7	1.40	18.79	0.00001
	Fluvent	7.0	0.0	3.6	0.84	1.3	0.68	0.1	0.32	291.58	0.00001
Usage of Ventolin	Becotide	38.0	7.72	33.3	7.07	3.8	1.40	22.8	9.69	6.80	0.001
	Fluvent	37.5	6.13	17.7	6.36	0.1	0.32	0.9	1.52	118.65	0.00001

decreased in patients for the two treatment groups. The day time asthma decreased from 7.00 to 1.95. Also, the reduction was more pronounced in the Fluvent group than the Becotide group but the decrease over the visits was statistically significant in each of the two drug groups.

The usage of beta2agonist (Ventolin) was also reduced from a baseline of  $37.75 \pm$  per week to only  $11.85 \pm 13.11$  at the end of the trial. The patients using Fluvent were almost not using Ventolin by the end of the trial period. The reduction in Ventolin usage was also statistically significant in the two treatment groups ( $P < 0.05$ ).

Figures 1 and 2 show the pattern of increase of pulmonary functions by treatment groups in general, the increase was steady in patients on Fluvent with a steeper slope in FEV<sub>1</sub> and PEFR. Patient on Becotide did not show any significant change with time.

#### Adverse events and withdrawal

All the twenty patients that started the trial also completed it at the end of the 9th week of trial. No adverse event was noticed on any of the patients.

#### Discussion

It is now widely accepted that asthma is an inflammatory airway disease and that anti-inflammatory treatments are important for its control.

The lowest dose that satisfactorily controls asthma is the designated optimal treatment for all patients using inhaled corticosteroids (ICS). Therefore, it is wise to start treatment with ICS to determine the best possible level of airway function and symptom control<sup>9</sup>.

In recent years, the need for individually adjusted doses of ICS to obtain the wanted efficacy, but also to avoid unnecessary systemic side-effects with high doses, has been repeatedly addressed.

In this study, the airway function, measured by FEV<sub>1</sub> and PEF, did not deteriorate in either treatment group indicating that the given treatment at the end of the follow up was as effective as the beginning of the study. However, these changes in the pulmonary function test were more rapid among the patient using Fluvent. The data are consistent with those of Brambilla et al, who demonstrated that Fluvent was twice more efficacious given by pMDI to control asthma than Becotide<sup>10</sup>.

This drug trial shows a higher percentage decline in the symptoms of asthma either in the morning, during the day or night was recorded in the Fluvent group than Becotide group. This

improvement in the pulmonary function (PEFR and FEV1) was also noticed to be more rapid in the Fluvent group. He therefore concluded that Fluvent is approximately twice as effective as Becotide administered through the pMDI. Similar observation was made by Farschou et al<sup>13</sup> to support the efficacy of either drug and the superiority of Fluvent over Becotide.

In this study, we observed that the patients on Fluvent had better control of their asthma symptoms and pulmonary functions than those with Becotide with about half of the dose of the former. This may be due to greater pharmacologic potency of Fluvent which when readily available in Nigeria will help with asthma treatment.

We therefore conclude that Fluvent is more efficacious as ICS than Becotide in asthma management and may be effective in reducing symptoms, improving the lung function, minimizing the adverse effects of corticosteroids in patients requiring regular use of oral or high-dose inhaled corticosteroids.

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