Comparison of the efficacy and safety of budesonide turbuhaler administered once daily with twice the dose of beclomethasone dipropionate using pressurised metered dose inhaler in patients with mild to moderate asthma

***J. O. Ohaju-Obodo[1], C. Chukwu[2], J. Okpapi[3], E. Egbagbe[4], M. O. Ige[5], C. Chukwuka[6] and D. A. Adedapo**

[1]Medical Department, AstraZeneca, P. O. Box 3560, Ikeja, Lagos
[2]Department of Medicine, Lagos University Teaching Hospital, Lagos,
[3]Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria,
[4]Department of Medicine, University of Benin Teaching Hospital, Benin-City,
[5]Department of Medicine, University College Hospital, Ibadan
[6]Department of Medicine, University of Nigeria Teaching Hospital, Enugu
Department of Clinical Pharmacology/Therapeutics, University of Ibadan, Ibadan.

Summary

Background: **Current treatment guidelines have clearly defined the central place and benefits of inhaled glucocorticoids in the management of bronchial asthma. However, compliance with therapy is often poor due to complexity of treatment regimens.**

Therefore, a single once daily regimen with a simple device, the turbuhaler might be expected to result in improved compliance and better efficiency.

Study design: **This was a prospective open randomized trial with parallel groups conducted in five tertiary medical institutions. Asthmatic patients who met the enrolment criteria were randomized to receive either budesonide 400μg daily or beclomethasone dipropionate 400μg twice daily for eight weeks.**

Result: **At the end of the study, both drugs were found to be effective in reducing the symptoms of asthma, reduction of β_2 agonist usage and improvement in lung function tests. However Budesonide Turbuhaler provided better effects in all parameters ($p < 0.05$). Both drugs were well tolerated.**

Conclusion: **It is therefore concluded that Budesonide Turbuhaler administered once daily at a dose of 400μg is more efficacious than Beclomethasone dipropionate 400μg twice daily administered via pressurized metered dose inhaler.**

Key-words: ***Bronchial asthma, Budesonide, Beclomethasone dipropionate, Efficacy, Safety.***

Résumé

Introduction: Les directives du traitment actuelles avaient clairement défini l'importance et les avantages dans le glucocorticoide inhalé dans la prise en charge du l'asthme bronchique. Toutfois, l'observation de la thérapie est le plus souvent mauvaise, attribuable à la complecité du régime du traitement. Donc, un seul régime tous les jours avec une méthode simple, on espère que le turbuhaler pourrait provoquer une amélioration dans l'observation et une meilleure efficacité.

Plan d'étude: Il s'agit d'une épreuve en prospective. Ouverte et randomisée avec des groupes parallèles effectuée dans cinq centres hospitalier tertiaires. Des patients asthmatiques qui ont satisfait à des critères de sélection ont été randomisés de recevoir soit 400 ug de budesonide ou 400 ug de beclomethasone dipropionate deux fois tous les jours pendant huit semaines.

Résultats: À la fin de cette étude, on a noté que les deux drogues sont efficace pour réduire les symptômes de l'asthme, une baisse dans l'utilisation d'agonist B2 et une amélioration dans l'épreuve du fonction du poumon. Toutefois, Turbuhaler Budesonide a fourni des meilleurs effects dans tous les paramètres ($P < 0,05$). Les deux drougues ont été bien tolerées.

Conclusion: En conclusion, Turbuhaler Budesonide administré une fois tous les jours d'une dose de 400 ug est plus efficace que dipropionate Beclométhosone de 400 ug deux fois tous les jours administré a travers la dose inhalatrice sous pression et compteur.

Introduction

Bronchial asthma is a chronic inflammatory disorder of the airways and has prevalence rate of 5 - 10% in Nigeria.[1-3] The disease is often associated with significant mobidity and in some instances, mortality.[4-7]

Current treatment guidelines help ameliorate these problems, though quite a good number of patients have poorly controlled asthma which may be partly related to suboptimal treatment strategies and poor patient compliance with drug therapy.[8-9]

Inhaled glucocorticoids such as budesonide and beclomethasone dipropionate have a central place in the management of asthma.[10] They have been shown to be effective as first-line therapy in both adults[11] and children[12] inhibiting the underlying airway inflammation and thereby improving symptoms and bronchial reactivity. As a result, current treatment guidelines recommend the use of inhaled glucocorticoids as first-line preventive treatment in the majority of patients.[13-18]

However, despite the proven benefits of inhaled glucocorticoid therapy, compliance is often poor[16] and such non-compliance is an important cause of asthma-related morbidity.[17] One possible cause of poor compliance is the use of complicated treatment regimens, requiring dosing several times daily. A simple, one-daily dose regimen might be expected to result in improved compliance, maintained efficacy and a reduced risk of treatment failure.

A number of studies have been performed trying to establish the relation in potency between Turbuhaler and the available pressurized metered dose inhalers (budesonide and beclomethasone dipropionate).[18-19] Some data indicate that there is a higher deposition of budesonide in the lung after inhalation with Turbuhaler as compared to the pMDI.[20]

* *Correspondence*

Another study showed that while providing the same level of asthma control, this was achieved by a lower dose of budesonide turbuhaler than of beclomethasone dipropionate.[12]

This study was therefore designed to compare the efficacy and safety of budesonide with beclomethasone dipropionate in patients with mild-to-moderate asthma.

Patients and methods

This was a multicentre, open randomized design trial with parallel groups conducted in five(5) tertiary medical institutions in Nigeria.

Male and female Nigerian patients aged 16 years or older were enrolled if they met the following criteria.

- Documented history of asthma.
- Have $FeV_1 \geq 65\%$ of predicted demonstrated at screening or at any time between screening and start of treatment.
- Showed a $\geq 15\%$ improvement in FeV_1 or PEF to a dose of terbutaline (four inhalations of Bricanyl pMDI 0.25mg/inhalation) demonstrated at screening or at any time between screening and the start of therapy.
- Have a total daytime asthma symptoms score of at least seven (≥ 7) in the last seven days of screening period.
- Demonstrate the ability to comply with the trial regimen and to use the peak flow meter and diary card correctly.
- All females enrolled in the trial who are of child bearing potential and were sexually active, used a reliable method of birth control.
- Informed consent.

Prospective patients were excluded from entry to the screening period if any of the following conditions apply.

- Usage of inhaled steroids or leukotriene receptor antagonists during the last 3 months prior to visit 1.
- Usage of oral and parenteral steroids during the last one month prior to visit 1.
- Hypersensitivity to budesonide or beclomethasone dipropionate.
- Past or present cardiovascular, renal, liver, endocrine diseases, chronic lung disease or any other significant disease which may interfere with the study or put the patient at risk because of participating in the study.
- Previous randomization in this study.
- Pregnancy, lactation or lack of adequate contraception.
- Upper respiratory tract infection that would interfere with the trial as judged by the investigator.
- Usage of any investigational drug within one month prior to visit 1, and
- Patients who are scheduled to undergo in-patient surgery during the course of the study.

Trial design, drug administration and treatment periods

The study started with a two-week run-in period. Thereafter, patients who fulfilled all the inclusion criteria and none of the exclusion criteria were randomized to an 8-week treatment period with either budesonide Turbuhaler or beclomethasone dipropionate pMDI. Approximately equal numbers of patients were meant to receive either budesonide Turbuhaler in the evening or beclomethasone dipropionate pMDI 400ug mornings and evenings. Four visit schedules and assessments were performed at the start of the study, after the run-in period and after 4 and 8 weeks of treatment.

During the screening period, patient recorded asthma symptoms, peak expiratory flow rate (PEFRs) and $beta_2$-agonist use on daily cards. Other assessments during this period were the medical history, physical examination and laboratory investigations including biochemistry and haematological parameters. Pregnancy test was obtained for all females of child bearing age who enrolled in the trial.

On each day, patients assessed and recorded their day-time and night-time asthma symptoms as earlier described by spector et al[20].

0 - Absence of asthmatic symptoms.
1 - Mild asthmatic symptoms which did not interfere with activities.
2 - Moderate asthmatic symptoms which interfered with some activities.
3 - Severe asthmatic symptoms which interfered with many activities.

Patients with cumulative symptoms score of 7 or more over seven consecutive days were then randomized to either group at visit 2.

The third visit (week 4) coincided with four weeks of use of the drug while the fourth visit (week 8) was at the sixth week of use of the medications. During the treatment periods, patients recorded on diary cards, daytime asthma symptoms score, mornings and evenings PEFRs, night-time awakenings, mornings with asthma and $beta_2$-agonist use.

During each visit to the clinic, pulmonary function tests were done using spirometry to determine the measure of efficacy. The safety (tolerability) of the drugs were assessed by records of adverse experience (spontaneously provided by patients or elicited through interviews), the result of laboratory investigations, physical examination and chest radiography (where indicated).

Statistical analysis

The statistical package EPI-INFO Version 6.02 was used to enter the data obtained. The baseline characteristics of the patients were compared using the Students' t-test for numerical variables and chi-square comparison test for categorical variables. Changes in the baseline characteristic and parameters during subsequent visits were compared in each treatment group using the Analysis of Variance (ANOVA) technique.

All statistical tests were two tailed and carried out at the 5% probability level of significance.

Result

A total of one hundred and nine (109) patients with mild-to-moderate asthma particpated in the trial. Fifty-four (49.5%) were randomized to use Beclomethasone dipropionate and fifty-five (50.5%) were in the budesonide treatment group. Table 1 shows the baseline characteristics of these patients

Follow up of patients' characteristics

The summary of pulmonary function tests and asthma

Table 1 Baseline characteristics of patients

Characteristics	Total	Mean	S. D	
	Budesonide	Beclom. dipropionate	Budesonide	Beclom. dipropionate
Age in years	35.4	31.2	(12.6)	(3.2)
Sex (n)	55(21M, 34F)	54(25M, 29F)		
Duration of asthma (weeks)	128.9	144.4	(9.61)	(11.1)
Visit PEFR	310.7	311.8	(85.6)	(97.4)
Visit FEV_1	2.1	2.0	(0.5)	(0.8)
Predicted FEV_1	2.6	2.4	(0.6)	(0.6)
% Predicted FEV_1	76.9	76.6	(11.7)	(13.9)
% Reversibility	25.8	24.64	(8.3)	(8.23)
Mornings with asthma (n/wk)	4.5	4.3	(2.2)	(2.4)
Morning PEFR	287.7	299.2	(82.6)	(111.6)
Evening PEFR	293.6	309.0	(86.6)	(107.8)
Night-time asthma (n/wk)	6.7	6.7	(4.1)	5.5
$Beta_2$-agonist use (n/wk)	21.4	21.8	(12.9)	(16.2)

PEFR = Peak Expiratory Flow Rate
FEV_1 = Forced Expiratory Volume in 1 Second
S.D = Standard Deviation
n = Number
M-Male
F-Female

Table 2[A] Summary statistics of patients' pulmonary function tests at various visits by treatment groups

Pulmonary Function Tests	Treatment Groups	Visits I		II		III		IV		P
		Mean	S. D	Mean	S. D.	Mean	S. D.	Mean	S. D.	value
FEV_1	Beclometh	2.07	(0.51)	2.15	(0.55)	2.42	0.63	2.47	(0.67)	0.0001
	Budesonide	2.00	(0.78)	1.99	(0.81)	2.33	0.85	2.62	(0.82)	0.0001
PEF	Beclometh.	310.7	(85.6)	334.9	(85.1)	378.4	87.0	393.0	(78.9)	0.0001
	Budesonide	311.8	(97.4)	331.0	(98.1)	391.2	119.6	431.7	(125.9)	0.0001

Table 2[B] Summary statistics of patients' asthma symptoms at various visits by treatment groups

Asthma Symptoms Parameters	Treatment Group	Visits II		III		IV		P
		Mean	S. D.	Mean	S. D.	Mean	S. D.	value
Night time awakening	Beclometh.	6.67	(4.05)	3.72	(4.67)	2.52	(3.54)	0.0001
	Budesonide	6.76	(5.49)	2.55	(2.74)	1.34	(2.93)	0.0001
Morning asthma	Beclometh.	4.47	(2.19)	2.12	(2.07)	1.71+	(1.85)	0.0001
	Budesonide	4.26	(2.39)	2.45	(2.15)	0.81+	(1.76)	0.0001
Morning peak flow (PEF)	Beclometh.	287.7	(82.6)	332.9	(86.8)	352.5	(89.7)	0.0001
	Budesonide	299.2	(111.6)	360.3	(125.2)	396.8	(137.8)	0.0001
Day time asthma	Beclometh.	10.28	(2.90)	4.04	(4.15)	2.73	(2.75)	0.0001
	Budesonide	11.00	(3.01)	4.85	(4.03)	2.54	(3.48)	0.0001
Evening peak flow (PEF)	Beclometh.	293.6	(86.6)	330.7	(83.8)	354.1+	(86.7)	0.0001
	Budesonide	309.0	(107.8)	352.4	(118.8)	403.6+	(139.6)	0.0001
$Beta_2$ agonist use	Beclometh.	21.37	(12.9)	12.57	(11.55)	8.0	(9.13)	0.0001
	Budesonide	21.83	(16.23)	11.65	(14.05)	4.59	(8.92)	0.0001

+ Statistically significant

symptoms at various visits by treatment groups is shown in Table 2[A] and 2[B]. The mean FEV_1, showed an increase from the baseline value of 2.07 ± 0.51 to a mean value of $2.47 + 0.67$ by the final visits in the beclomethasone dipropionate treatment group. Similarly, there was an increase in the FEV_1 from 2.00 ± 0.78 at baseline to 2.62 ± 0.82 by the end of the trial for patients using budesonide. Therefore the increase over the visits was statistically significant in the two treatment group ($P < 0.05$).

Also, the PEF measured at the clinics showed an increase from a baseline value of 310.7 ± 85.6 to 393.0 ± 78.9 by visit 4 for patients on beclomethasone dipropionate, the increase was also noticed for patients on budesonide from baseline value of 311.8 ± 97.4 to a final mean PEF of 431.7 ± 125.9 and the subsequent increase over the visits was statistically significant ($P < 0.05$).

The average number of times patients had night time awakenings due to asthma reduced by the final visit in the

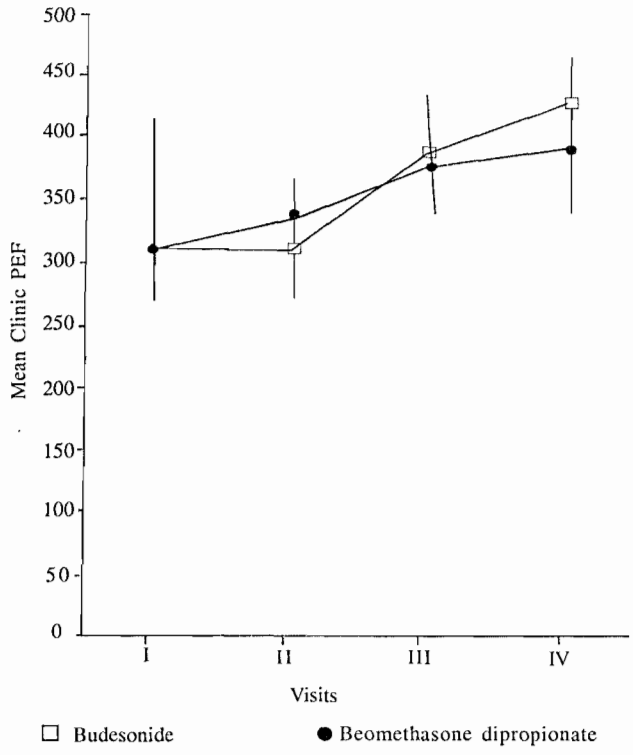

Fig. 1 ***Pattern of PEF at various visits in both budesonide and beclomethasone dipropionate treatment group***

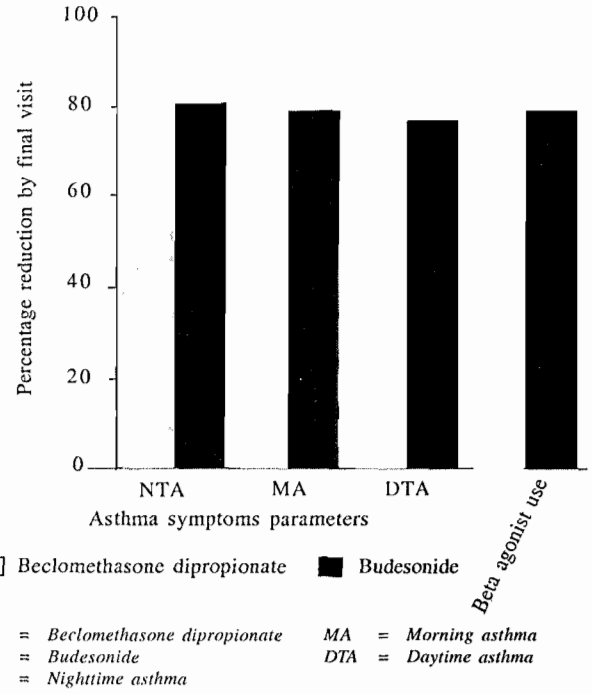

Fig. 2 ***Percentage reduction in asthma symptoms of patients in both budesonide and beclomethasone dipropionate treatment group***

two treatments groups. While the patients on budesonide had their morning asthma reduced from baseline value of 4.47 ± 2.19 to a mean value of 1.71 ± 1.85, their counterparts on beclomethasone dipropionate had their morning asthma reduced from 4.26 ± 2.39 to 0.89 ± 1.76, this reduction was statistically significant for the two treatments group ($P < 0.05$).

Meanwhile the morning and evening PEF rate also showed an increase over the visits in the two treatment groups. The patients on beclomethasone dipropionate treatment had their morning PEF rate increased from baseline value of 287.7 ± 82.6 to 352.5 ± 89.7 at the final visit, while their counterparts on budesonide had their PEF rate increased to 396.8 ± 137.8 by the final visit. Also the evening PEF rate for patients on beclomethasone dipropionate increased from 293.6 ± 86.5 to 354.1 ± 86.7 while those on budesonide had their evening PEF rate increased to 403.6 ± 139.6. The increase over the visits for the two parameters was also statistically significant ($P < 0.05$).

The mean Day Time Asthma reduced from 10.28 ± 2.90 to 2.73 ± 2.75 for patients using beclomethasone dipropionate while those on budesonide reduced from 11.00 ± 3.01 to 2.54 ± 3.48, similarly the use of $Beta_2$-agonist (bricanyl) also reduced significantly in the two treatment groups ($P < 0.05$).

The increase in FEV_1, clinic PEF, morning and evening PEF rate was statistically significant immediately after the commencement of the treatment in the two treatments, so also was the reduction observed for the asthma symptoms parameters. The mean changes in FEV_1 was higher for patients in budesonide group, this was statistically significantly different from the mean changes recorded in beclomethasone dipropionate treatment group ($P < 0.05$). Similarly, patients n budesonide treatment had a higher mean changes in clinic PEF compared to changes recorded for those in beclomethasone dipropionate treatment. This was also statistically significant ($P < 0.05$). Both the mean and median changes in the parameters, Night Time Asthma, Mornings with Asthma. Morning /evening PEF, and $beta_2$ agonist use were higher in budesonide treatment than the median changes observed in beclomethasone dipropionate but the differences do not reach the 5% level of statistical significant ($P > 0.05$).

Although, patients in budesonide treatment group appear better in terms of the final values for all the parameters examined, only the Morning Asthma and Evening Peak Flow rate were statistically significantly different between the two treatment groups ($P < 0.05$).

The summary of average and median changes between the second visit and final visit values in all the parameters for the two treatment groups is shown in Table II^A and II^B, figures I & II.

Side effects

Both drugs were well tolerated and the (eight) 8 cases of side effects reported were mild and resolved completely on follow-up. These were fever (4), headache (2), sore throat (1) and abdominal upset (1).

Discussion

When inhaled steroids were first introduced in the 1970s, they were given in fixed doses four times daily. As experience with inhaled therapy increased, and newer, more potent, agents in higher doses became available, dose regimens became more flexible and were tailored to the individual patient's needs. It is now clear that patients with mild to moderate disease can achieve satisfactory asthma control with once or twice daily administration.

In the management of asthma, using inhaled glucocorticoids, the lowest dose that satisfactorily controls asthma designates optimal treatment. The results obtained in this study show that budesonide Turbuhaler administered once daily at a dose of 400mg is more efficacious than beclomethasone dipropionate pMDI administered at a dose of 400mg twice daily. The safety of the two treatments was also assessed, there were no serious treatment related adverse events, nor was there any significant difference between the treatment groups in the frequency of adverse events.

Previous comparisons of the efficacy of budesonide and beclomethasone dipropionate have mostly used pMDIs with or without spacers as delivery devices. [24] These studies have generally not shown any significant differences. However other studies which used budesonide Turbuhaler have demonstrated a more efficacious effect with budesonide.[25 - 26] The dry powder Turbuhaler device can deliver approximately twice the dose of budesonide through a pMDI.[25] Available data demonstrating greater lung deposition of budesonide and a greater clinical efficacy considered budesonide delivered by Turbuhaler a different clinical entity other than burdesonide delivered by pMDI. It is therefore to be expected, that the administration of budesonide by Turbuhaler would not only provide greater efficacy than budesonide given by pMDI, but also greater efficacy than BDP administered by pMDI. The results obtained here confirm some earlier findings[27-28] which showed that Turbuhaler allows a dose reduction of budesonide in asthmatic children while maintaining, or even improving the control of the disease. In the same way, Brambilla et al[29] had demonstrated in adults that the budesonide Turbuhaler allowed a lower dose of budesonide than beclomethasone dipropionate to be used in the control of asthma.

Moreover, pharmacological data in animals as well as in humans have demonstrated that budesonide has higher anti-inflammatory properties than beclomethasone dipropionate. The results obtained in this study might have been due to the pharmacological difference between the two drugs and the devices used.

It could therefore be inferred that budesonide at a dose of 400ug administered via Turbuhaler is more efficacious than beclomethasone dipropionate at a dose of 400mg twice daily using pressurised metered dose inhaler.

Acknowledgements

We wish to thank our colleagues in the Department of Medicine of the five tertiary institutions where the clinical trials were conducted. The staff of the laboratories where investigations were carried out were most co-operative and this is highly appreciated.

The trial was supported by ASTRAZENECA which provided clinical trial materials paid for investigations and provided other logistic support.

Professor Afolabi Bamgboye, a Consultant Biostatistician of the University of Ibadan carried out the statistical analysis. Miss Blessing Nwoko of Reals Pharmaceutical Ltd. Lagos helped with the secretarial work.

We are really grateful to all.

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