A COMPARATIVE STUDY ON THE EFFICACY AND SAFETY OF CICLESONIDE AND FLUTICASONE IN ASTHMA

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ABSTRACT

BACKGROUND

Asthma is one of the most common chronic diseases worldwide, imposing a substantial social burden. Inhaled glucocorticosteroids (ICS) are currently the most effective anti-inflammatory medications for treatment of asthma and they have revolutionised asthma therapy. Ciclesonide is a new once daily ICS with similar efficacy to other ICS in asthma, and it possesses potential advantages in terms of reduced local and systemic adverse effects.

AIM

To study the comparative efficacy and side effect profile of inhaled ciclesonide once daily with that of fluticasone twice daily in patients with asthma.

METHOD OF STUDY

An open labelled randomised controlled trial conducted during the period from Aug 2007 to Aug 2009 in patients with moderate persistent asthma. The patients were randomised into two groups to receive either Ciclesonide 160 mcg once daily or Fluticasone 250 mcg twice daily. Followup assessment done at 4th week, 8th week, and 12th week during which pre and post-bronchodilator spirometry was done. The number of doses of rescue medications used, any exacerbations after the previous visit, any adverse effects experienced were all recorded during each visit. Post-trial analysis was done using ANCOVA (Analysis of Covariance). A p value of <0.05 was considered significant.

RESULTS

During the study period, both groups showed significant improvement in pulmonary function. The overall improvement in FEV_1 and PEFR from baseline to the end of 12 weeks was better with ciclesonide when compared to fluticasone and was statistically significant with a p value of <0.05. There was a significant reduction in the number of doses of rescue medications used in the ciclesonide group with p value <0.01. With respect to the incidence of local adverse effects, ciclesonide was safer than fluticasone.

CONCLUSIONS

Compared to fluticasone, ciclesonide showed significantly better improvement in pulmonary function of patients with asthma without any local adverse effects.

KEYWORDS

Asthma, Inhaled Corticosteroid, Ciclesonide, Fluticasone.

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INTRODUCTION: Asthma is one of the most common chronic diseases worldwide, imposing a substantial social burden. There is evidence that over the last 20 years its prevalence has considerably increased.[1] Inhaled glucocorticosteroids (ICS) are currently the most effective anti-inflammatory medications for treatment of asthma and they have revolutionised asthma therapy.[2]

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Studies have demonstrated their efficacy in improving lung functions, decreasing airway hyperresponsiveness, reducing symptoms, frequency and severity of exacerbations and thereby improving quality of life.[3] Ciclesonide is a new once daily ICS with similar efficacy to other ICS in asthma, and it possesses potential advantages in terms of reduced local and systemic adverse effects. Pharmacodynamic studies have shown that inhaled ciclesonide has potent anti-inflammatory activity in patients with asthma, and does not appear to have clinically relevant systemic effects, even at high doses. It is highly protein-bound and rapidly metabolised by the liver, and thus has a low oral bioavailability. Once daily dosing regimen of ciclesonide should enhance patient compliance, which could potentially improve outcomes for patients with asthma.[4]

AIM: To study the comparative efficacy and side effect profile of inhaled ciclesonide once daily with that of fluticasone twice daily in patients with stable asthma.

METHOD OF STUDY: This study was designed as an open labelled randomised controlled trial and was approved by the Institutional Ethics Committee. Patients were selected from the outpatient clinic in the Department of Pulmonary Medicine in a tertiary care teaching institution in North Kerala during the period from Aug 2007 to Aug 2009. After taking written informed consent from the patients, detailed history and physical examination was done. Smokers and those who had treatment for tuberculosis were excluded. The selected patients with clinical suspicion of asthma were taken to the pulmonary function testing laboratory. Physical parameters like height and weight were recorded. They were given a brief explanation about the test to be performed. Spirometry was performed using computerised spirometer (Pneumotachograph) and the pulmonary functions like forced vital capacity (FVC), forced expiratory volume in 1st second (FEV_1) and Peak Expiratory flow rate (PEFR) were recorded. Patients with diagnosis of moderate persistent asthma as per GINA guidelines were included.[5] Those who cannot perform acceptable spirometry manoeuvre were excluded. The spirometry was repeated 20 minutes after administration of inhaled short acting β2 agonist salbutamol 200 mcg MDI to assess the reversibility. Patients who met reversibility criteria (≥ 12% and or ≥200 mL increase in FEV_1 from prebronchodilation value) were included in the study.[6] They were given a washout period of two weeks.

During this period, patients were advised to stop any inhalational or systemic steroids as well as leukotriene receptor antagonists they were using, and given inhaled salbutamol 200 mcg MDI as rescue medication as and when needed for symptomatic relief. Those who were on theophylline or antihistamine continued these medications with no change in dose. During the baseline visit (0 week) after the wash out period, spirometry was performed and repeated 15 minutes after inhalation of 200 mcg salbutamol. Then, the patients who had a reversible bronchodilatation were randomised into two groups to receive either Ciclesonide 160 mcg once daily (Group A) or Fluticasone 250 mcg twice daily (Group B). Randomisation is done with block randomisation using random number table of 10 each. Group A received Ciclesonide MDI 160 µg OD at bedtime, Group B was given Fluticasone MDI 250 µg BD. All patients were asked to record the daytime and nocturnal symptoms and to note down the number of doses of rescue medication used every day in a card provided to them. They were instructed to bring the card with the recording during the subsequent followup visit for documentation. The followup visits were arranged at 4th week, 8th week, and 12th week during which pre and post-bronchodilator spirometry was done. All patients had to withhold salbutamol for ≥ 6 hrs., theophylline, ciclesonide or fluticasone for ≥ 12 hrs. prior to clinic visits. The number of doses of rescue medications used, any exacerbations after the previous visit, any adverse effects experienced were all recorded during each visit.

Analysis of Data: A total no. of 116 patients were enrolled in the study out of which 100 patients completed. Seven patients failed to turn up for review after the 4 weeks' visit. Two patients were lost to followup after the 8 weeks' visit. Seven patients were unable to perform the spirometry manoeuvre and were dropped out. Post-trial analysis was done using ANCOVA (Analysis of Covariance). A p value of <0.05 was considered significant.

OBSERVATIONS: A randomised controlled study comparing the efficacy and safety of once daily inhalational steroid ciclesonide with that of twice daily inhalational steroid fluticasone in patients with mild-to-moderate persistent asthma was conducted. A total number of 100 patients consisting 50 in each group completed the treatment period. The baseline parameters were as shown in Table. 1.

	Ciclesonide	**Fluticasone**
Total No. of patients included in the study	60	56
No. of patients completed the study	50	50
Sex - M/F	25/25	12/38
Mean age in years (X±SD)	29.26±10.8	34.02±15.7
Mean prebronchodilator FEV1(L/s)	2.2±0.60	1.98±0.59
Mean post bronchodilator FEV1(L/s)	2.48±0.63	2.21±0.60
Mean prebronchodilator PEF(L/s)	4.72±1.30	4.56±1.81
Mean post bronchodilator PEF(L/s)	5.25±1.81	4.68±1.63

Table 1: Comparison of Baseline Parameters

In the ciclesonide group, there were twenty five males and twenty five females, whereas in the fluticasone group, there were 12 males and 38 females. Out of the total patients who presented with the symptom of wheeze in the fluticasone group, 70% had wheeze both during day and night while in the ciclesonide group this was only 54%. Similarly, cough was present in 84% in the fluticasone group both day and night, while it was only 56% in the ciclesonide group. House dust was the precipitating factor in 62% of patients in the fluticasone group and 56% in the ciclesonide group. Out of the patients with positive family history, 14% in the ciclesonide group and 24% in the fluticasone gave a history of asthma in their father.

Symptoms		Ciclesonide n (%)	Fluticasone n (%)
Wheezing	Daytime	6(12)	4(8)
	Nocturnal	17(34)	11(22)
	Both	27(54)	35(70)
Cough	Daytime	7(14)	0(0)
	Nocturnal	15(30)	8(16)
	Both	28(56)	42(84)
Rhinitis	Yes	45(90)	11(22)
	No	5(10)	39(78)
Eczema/ Atopy	Yes	7(14)	11(22)
	No	43(86)	39(78)
Precipitating factors	Dust	28(56)	31(62)
	Cold Air	12(24)	8(16)
	Multiple	10(20)	11(22)
Duration of asthma	<1 yr.	2(4)	14(28)
	1-2 yrs.	24(48)	36(72)
	>2 yrs.	24(48)	0(0)
Asthma severity	Mild Persistent Asthma	18(36)	23(46)
	Moderate Persistent Asthma	32(64)	27(54)
Family h/o asthma	Sibling	5(10)	0(0)
	Father	7(14)	12(24)
	Mother	10(20)	6(12)
	No Family h/o	28(56)	32(64)
H/o childhood asthma	Yes	28(56)	28(56)
	No	22(44)	22(44)

Table 2: Comparison of Baseline Clinical Data

Patients in both groups showed improvement of FEV_1 from 0 weeks towards the end of 12 weeks (Table. 3).

The overall improvement in FEV_1 was better in the ciclesonide group compared to fluticasone group of patients at the end of 12 weeks which was statistically significant (p value < 0.05).

		Mean FEV_1 (l/s)			
Visit week		0 wk	4 wk	8 wk	12 wk
Ciclesonide	Pre	2.2±0.6	2.34±0.59	2.37±0.66	2.45±0.64
	Post	2.48±0.63	2.5±0.58	2.51±0.67	2.56±0.63
Fluticasone	Pre	1.98±0.59	2.11±0.64	2.14±0.71	2.19±0.69
	Post	2.21±0.6	2.28±0.66	2.31±0.73	2.31±0.72

Table 3: Comparison of Improvement in FEV_1

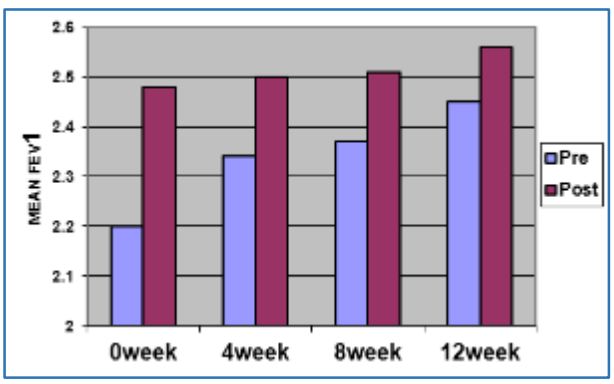

Fig. 1: Mean FEV_1 Ciclesonide Group

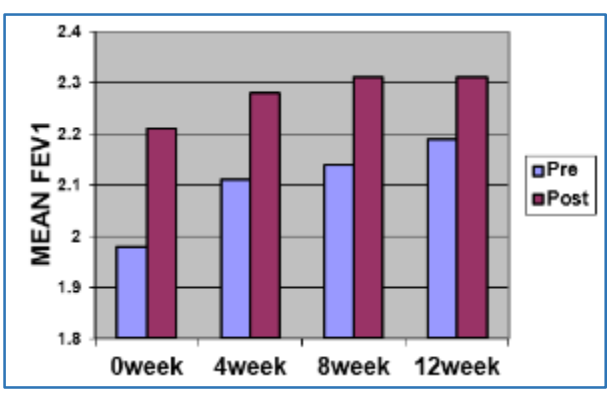

Fig. 2: Mean FEV_1 Fluticasone Group

		Mean PEF(L/s)			
Visit week		0 wk.	4 wk.	8 wk.	12 wk.
Ciclesonide	Pre	4.72±1.30	5.43±1.21	5.49±1.35	5.29±1.22
	Post	5.25±1.81	5.78±1.34	5.84±1.26	5.84±1.49
Fluticasone	Pre	4.56±1.45	4.80±1.08	5.06±1.40	5.16±1.40
	Post	4.68±1.63	4.75±1.78	5.40±1.70	5.68±1.60

Table 4: Comparison of improvement in PEF

Patients in both groups showed improvement of peak expiratory flow rate from 0 weeks towards the end of 12 weeks. In comparison to fluticasone, ciclesonide showed a better improvement which was statistically significant with P value <0.05.

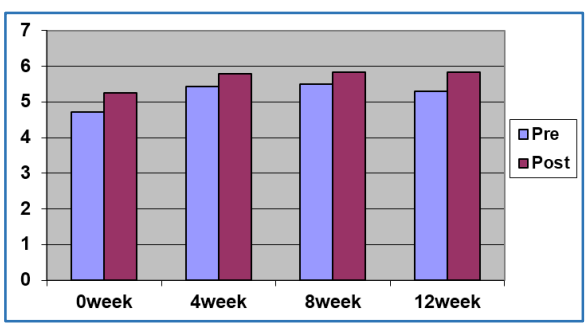

Fig. 3: Mean PEF-Ciclesonide Group

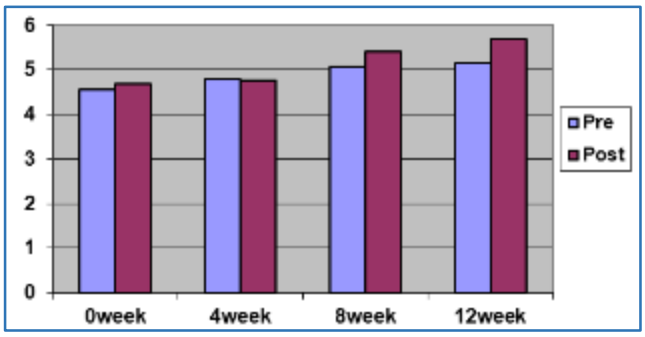

Fig. 4: Mean PEF-Fluticasone Group

Group	Week				Total No. of Doses of Rescue
	0	4	8	12	
Ciclesonide	37	26	13	9	85
Fluticasone	45	29	23	14	111

Table 5: Rescue Medication Usage

There was a consistent reduction in the number of doses used from 0-12 weeks in both groups. The number of doses of rescue medication used by the patients were significantly less in the ciclesonide group compared to fluticasone group. Overall, there was a reduction in the need for rescue medication usage in the ciclesonide group which was statistically significant with p value <0.01. The only adverse effect seen during the study period was oral thrush of varying severity which was noted in 4 patients (8%). All of them were in the fluticasone group and were given clotrimazole mouth paint and relieved.

DISCUSSION: Bronchial asthma is a chronic inflammatory disorder with a very variable prevalence rate which has become a burden on health economics. The drugs used in the treatment of asthma can be broadly divided into two categories, the β_2 agonist bronchodilators called as "relievers" and the anti-inflammatory agents called as "preventers".[7] Long term maintenance therapy in most patients has to be with an inhaled steroid since this is considered as the most effective treatment available for the control of the asthmatic bronchial wall inflammation.

Inhaled corticosteroids have become the mainstay of therapy for control of bronchial asthma. However, as with other inhaled or oral asthma drugs, compliance to inhaled steroids is often poor. Among the manifold reasons underlying noncompliance, complicated regimens and increased number of dosing are considered to be significant factors.[8] Initially inhaled steroids were recommended to be used four times a day, but later numerous studies have shown that in the majority of patients, a twice daily schedule can effectively control asthma and this is presently considered as the standard scheme. Weiner P et al[9] suggested that decreasing the dosing frequency to once daily might further enhance adherence to the prescribed regimen for achieving a better asthma control.

But there are relatively few studies comparing the dosing frequency of various inhalational steroids. Ciclesonide is a new once daily inhalational steroid and the present study is a randomised controlled study to compare the efficacy and safety of once daily ciclesonide with twice daily fluticasone in patients with mild to moderate asthma. During the study period the subjects in both groups showed significant improvement in pulmonary function. The overall improvement in FEV_1 from baseline to the end of 12 weeks was better with ciclesonide when compared to fluticasone and was statistically significant with a p value of <0.05 (Table 3). The overall improvement in PEF was also significantly better with ciclesonide with a p value of <0.05 (Table 4).

Studies by Buhl et al[10] showed that ciclesonide produced significant improvement in FEV_1 and PEF ($P < 0.01$) which was equivalent to fluticasone. Similar results were also observed in a study of 697 patients in persistent asthma.[11] Busse et al[12] compared ciclesonide with fluticasone and following 12 weeks treatment, similar results were obtained. In both treatment groups in the present study, the use of reliever medications was reduced from baseline and the reduction in the number of doses used was significantly better in those patients in the ciclesonide group with p value < 0.01(Table 5). This data was similar to other clinical studies.[10-12] In both groups, no exacerbations were noted during the study period.

The only adverse event noted during the present study period was oral candidiasis which was seen in 8% of patients, all of them in the fluticasone group. This data is comparable with the study done by Bateman ED et al.[13] A study by Richter et al[14] showed that the combined deposition of CIC and des-CIC in the oropharynx was only 53% of that of FP. Furthermore, only 17% of the CIC deposited was converted into the active metabolite des-CIC. The concentration of des-CIC in the oropharynx 60 minutes after inhalation was only 8% of the FP concentration (i.e. 12.5 times more FP than des-CIC).

The observed efficacy and safety of ciclesonide in this and other studies may be due to its unique pharmacodynamic and pharmacokinetic properties. Ciclesonide has a low affinity for the glucocorticoid receptor and is converted to its active metabolite desisobutyryl-ciclesonide (des-CIC) in the lungs. Des-CIC has a high affinity for the glucocorticoid receptor which, combined with its small particle size, high pulmonary deposition and formation of lipid conjugates in the lungs, may also contribute to the observed efficacy. Additionally, minimal conversion of ciclesonide to des-CIC in the oropharynx and low oral deposition may explain the minimal incidence of oropharyngeal adverse events observed with ciclesonide treatment.[15] Results of the present study suggest that 160 μg of inhaled ciclesonide once daily in the morning is superior in efficacy and safety compared to 250 μg of fluticasone twice daily in the treatment of asthma as assessed by improvement in lung function, reduction in the use of rescue medications and local adverse effects.

CONCLUSIONS: Compared to fluticasone, ciclesonide showed significantly better improvement in pulmonary function of patients with asthma during the study period.

The use of rescue medication was significantly reduced with ciclesonide when compared to fluticasone. The only adverse effect noted during the study was oral candidiasis which was seen in 8% of patients, all in the fluticasone group. Thus, ciclesonide is safer than fluticasone with respect to reduction in local adverse effects. Ciclesonide as a once daily inhalational steroid is likely to improve adherence with treatment among asthmatics, when compared to fluticasone which requires twice daily dosing, thus can help in achieving better control in patients with mild-to-moderate persistent asthma. As the present study included a small number of patients within a limited period, further studies with large number of patients has to be carried out to establish the above data.

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