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TO STUDY THE TREATMENT COMPARISON OF SALMETEROL WITH FLUTICASONE COMBINATION AND FORMOTEROL WITH FLUTICASONE COMBINATION IN THE MANAGEMENT OF PERSISTENT ASTHMA

General Medicine

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ABSTRACT

Background:-The object of this study was treatment comparison of salmeterol with fluticasone combination versus formoterol with fluticasone combination in the management of persistent asthma.

Material and methods:- This was a randomized, prospective, open-label study conducted in 50 patients of moderate persistent bronchial asthma after taking informed consent. After simple randomization patients were enrolled in group-1 and group-2 and compared the effects of 2 weeks of treatment of salmeterol, 50 µg with fluticasone propionate 100µg twice daily and formoterol, 6µg with fluticasone propionate 100 µg twice daily .

Result:- Based on findings of this study it was observed that evening mean PEF in group 1 & 2 (38.04± 22.34,32.92±39.16 respectively) was statistically significant (P<0.05) as well as morning mean PEF in group 1&2 (31.92±15.12, 25.64 ± 14.6) was also statistically significant (P<0.05) . The mean difference of FEV1 % predicted in group-1 and group-2 was 1.41 ± 5.67 which was
not statistically significant (p >0.05) as well as the mean difference of Evening and morning PEF in group-1 and group-2 was also not statistically significant (p >0.05).

Conclusion:- We conclude that the long-acting ß2-agonist and inhaled cortico-steroid combinations, formoterol with fluticasone propionate and salmeterol with fluticasone propionate improve morning and evening PEF, but without any significant difference in efficacy between the two combinations.

KEYWORDS

PEF(peak expiratory flow), FEV1(forced expiratory volume first second),COPD(chronic obstructive pulmonary disease)

Introduction:

Asthma is defined as a recurrent 'reversible' obstruction of the airways in response to stimuli which are not in themselves noxious and which do not affect non-asthmatic subjects. The asthmatic subject has intermittent attacks of dyspnea, wheezing, and cough. The characteristic features of asthma are bronchial hyper-responsiveness and inflammatory changes in the airways.It is increasing in prevalence and severity and has a rising mortality despite a substantial increase in prescribed asthma treatment.

In normal clinical practice, a maintenance dose appropriate to the severity of the patient's asthma of either combination is prescribed twice daily, and a separate short acting bronchodilator is used as needed to relieve breakthrough symptoms.

Material and methods:

This was a randomized, prospective, open-label study conducted in 50 patients of moderate persistent bronchial asthma after taking informed consent , comparing the effects of 2 weeks treatment with combination of salmeterol, 50 µg with fluticasone propionate 100µg twice daily, and formoterol, 6µg with fluticasone propionate 100 µg twice daily.

The selection of the patients was done according to American Thoracic Society criteria for asthma.

The diagnosis of bronchial asthma was based on:-

1. Clinical history
2. Physical examination
3. Radiological picture
4. Pulmonary function testing by Spirometry

Inclusion Criteria

1. Patients of the age > 15 years of either sex.
2. Patient with day time total asthma symptom score of at least 4/week and one nocturnal awakening or early morning awakening caused by asthma symptoms.
3. Asthma history of >3 months.
4. Absence of acute febrile illness.
5. Informed consent of the patient.

Exclusion Criteria

1. Patients who are pregnant or breast feeding mothers.
2. Patients who had an emergency treatment for asthma within one month or hospitalization for asthma within three months prior to enrollment.
3. Patient who has taken any bronchodilator or inhaled steroid in last 48 hrs.
4. COPD – defined as increase in FEV1 of < 12 %above the baseline value after the administration of a bronchodilator.
5. Patients with other active pulmonary diseases like tuberculosis and pneumonias.
6. Patients with acute exacerbation and respiratory failure.
7. Co-existing cardiac or renal diseases.
8. Hypertensive or diabetic patient.
9. Symptomatic prostatic hypertrophy.
10. Uncooperative patient.

All patients included in this study were investigated as under:-

1. A detailed clinical history including family history.
2. Thorough physical examination.
3. Sputum smears examination by Ziehl-Nelson method.
4. Blood examination for hemoglobin, total leukocyte count, differential leukocyte count, and total eosinophil count by Discombe´s direct dilution method (1946).
5. Fasting blood sugar, liver function test (serum bilirubin, SGOT, SGPT).
6. HIV serology.
7. Complete urine examination.
8. Electrocardiography

Study Procedure

At the initial screening visit, a full medical history was taken and a physical examination was performed. Baseline spirometry and peak expiratory flow (PEF) were measured, and airways reversibility was established by repeating these tests 15 min after inhaling 200µg salbutamol. All patients had normal ECG findings.

After simple randomization (alternate patient for either of the groups) patients were enrolled in

GROUP – 1

In this group each patient after base line PFT were given combination rotacaps containing formeterol 6 mcg with fluticasone 100 mcg as b.i.d. doses with the help of rotahalers for two weeks. Subjective and objective assessment of various parameters of efficacy was done at the end of first and second week.

GROUP – 2

In this group each patient after the base line PFT was given

combination rotacaps as salmeterol (50 mcg) with fluticasone (100 mcg) with the help of rotahalers as b.i.d. doses for two weeks. Subjective and objective assessment of various parameters of efficacy was done at the end of first and second week.

They were provided with a peak flow meter and a daily diary card, the diary card was used to record

1. Morning PEF measurements (prior to inhaler use)
2. Evening PEF measurements (prior to inhaler use)

Patients were trained in the proper use of the peak flow meter during their initial visit. They were seen after this 2-week period for identical measurements. Patients were asked not to use their short-acting ß2-agonist medication for 6 hr prior to each visit if possible. Capsule counts were made at final visit as a check on compliance.

Spirometry and PEF

FEV1 was measured using a dry wedge spirometer (Vitalograph; Buckingham, UK). Baseline values were measured after 15 min of rest and were recorded as the highest of three readings made at 1-min intervals.

PEF was measured using a standard peak flow meter (Mini-Wright; Clement Clarke International Ltd; Harlow, Essex, UK). These peak flow meters were given to patients for the daily measurement of PEF at home.

Bronchial Reversibility

Bronchial reversibility was assessed by the measurement of spirometry before and 15 min after the inhalation of 200 µg salbutamol from a metered-dose inhaler (MDI) via a spacer. Percentage reversibility was calculated as:

FEV1 (post-salbutamol) -- FEV1 (pre-salbutamol)/ FEV1 (pre-salbutamol) ×100

Statistical Analysis

Statistical analysis consisted of comparisons between treatments using a generalized linear model. This model consisted of fitting patient, period, and treatment effects. Since formoterol, salmeterol and fluticasone have proven efficacy in a twice-daily regimen, the sensitivity of the trial was established by analyzing the contrast of the mean effect of the active treatments at the 5% significance level. Both the possible pair wise contrasts were calculated, together with 95% confidence intervals (CIs) and associated p values for both primary and secondary efficacy variables.

Mean values were calculated from the 2 weeks of diary card values for each treatment group.

All patients with data recorded for treatment periods were included in the analysis. Values are expressed as the means with 95% Cis.

Results:

The table 1 shows baseline parameters(mean age, height weight, duration of disease, pulse rate, systolic BP, diastolic BP, respiratory rate, Hb, TLC and TEC) of patients in group-1 and in group-2 were not statistically significant (p>0.05).

TABLE-1 MEAN ± SD OF VARIOUS PARAMETERS

Parameter	Group-1	Group-2
Age	33.52 ± 8.29	36.4 ± 9.27
Height (cms.)	162.88 ± 7.33	164.5 ± 6.33
Wt(kg)	54.04 ± 11.60	55.1 ± 11.69
RR (per min.)	22.2 ± 1.84	22.0 ± 1.76
Hb	12.3 ± 1.48	12.5± 1.38
TLC	6900 ± 1897	7100 ± 1681
TEC	382 ± 69	399 ± 59

Table2 MEAN ± SD OF FEV1 (% PREDICTED) IN GROUPS

Group	FEV1 Observed (D-0)	FEV1 Observed (D-7)	FEV1 Observed (D-14)	Mean change ±SD	p-value
1	69.79±6.12	83.48±4.6	83.88 ± 3.9	13.68±6.61	p>0.05
2	70.10±6.48	84.2± 4.5	84.04±5.12	15.26±6.69	p>0.05

Table 2 shows mean increase in FEV1 % predicted from base line in group-1 and group-2 was not statistically significant (p>0.05).

Table3 Mean ± SD of evening PEF in groups

Group	Pre-treatment (D-0)	On treatment (D-7)	On treatment (D-14)	Mean change ±SD	p-value
1	404.08 ±15.12	437.48 ±34.57	436.72 ±32.16	38.04 ±22.34	<0.05
2	403.56 ±26.11	443.28 ±41.23	437.60 ±31.27	32.92 ±35.16	<0.05

The table -3 shows mean increase in evening PEF from base line in group-1 and group-2 was statistically significant (p<0.05).

TABLE-4
MEAN ± SD OF MORNING PEF IN GROUPS

Group	Pre-treatment (D-0)	On treatment (D-7)	On treatment (D-14)	Mean change ±SD	p-value
1	404.80 ±15.12	437.92 ±31.67	436.44 ±22.36	31.96 ±15.12	<0.05
2	406.76 ±30.23	430.80 ±30.02	431.60 ±31.18	25.64 ±14.64	<0.05

The table-4 shows mean increase in morning PEF from base line in group-1 and group-2 was statistically significant (p<0.05).

TABLE-5
MEAN CHANGE OF VARIOUS VARIABLES IN GROUPS

Variables	Group-1	Group-2	Difference ±SD	p-value
FEV1 % predicted	13.68 ±6.61	15.26 ±6.69	1.41 ±5.67	>0.05
Evening PEF	38.04 ±22.34	32.92 ±35.16	4.88 ±27.78	0.05
Morning PEF	31.96 ±15.12	25.64 ±14.64	5.20 ±18.73	>0.05

Table-5 shows mean difference of FEV1 % predicted in group-1 and group-2 was 1.41 ± 5.67 which was not statistically significant (p >0.05) as well as the mean difference of Evening and morning PEF in group-1 and group-2 was not statistically significant (p >0.05).

We found that the mean morning and evening PEF was greater for patients receiving both formoterol-fluticasone and salmeterol-fluticasone from the base-line, but with no significant difference between the active treatments.

Discussion

The present study compared the clinical effects of 2 weeks of treatment with inhaled formoterol-fluticasone and salmeterol-fluticasone in patients with persistent asthma whose symptoms were not completely controlled by treatment with high-dose inhaled or regular oral corticosteroids.

We found that the mean morning PEF was greater for patients receiving both formoterol-fluticasone and salmeterol-fluticasone from the base-line, but with no significant difference between the active treatments.

Formoterol and salmeterol are both highly selective and potent ß2 adrenoceptor agonists that relax bronchial smooth muscle *in vitro*.[1] However; formoterol is more potent than salmeterol *in vitro*, with a faster onset but a shorter duration of action[2]In addition, formoterol is a nearly full agonist, and salmeterol is only a partial agonist at the ß2-adrenoceptor.[3]

Single-dose studies with salmeterol and formoterol found that formoterol has a more rapid onset of bronchodilator action than salmeterol in asthmatic patients[4]but has a similar bronchodilator effect at 12 h. Relative potency estimates show that 50 µg salmeterol corresponds to 9 µg formoterol.[4] In addition, formoterol has a faster action in reversing methacholine-induced bronchoconstriction than salmeterol. [5]

However, formoterol has a greater maximal protective effect than salmeterol against methacholine induced bronchoconstriction in asthmatic patients, confirming that salmeterol is a partial agonist compared with formoterol in human airways *in vivo*.[6]

Previous studies[7,8,9] have demonstrated the effectiveness of regular treatment with salmeterol or formoterol compared with albuterol or placebo.In common with the present study, these studies showed improvements in morning PEF with long acting ß2-agonist treatment. Like the present study, these studies demonstrated improvements in evening PEF.

Three trials[10-12] of salmeterol in severe asthmatics demonstrated improvements in PEF values. In two of these trials the dose of salmeterol used was 100 µg twice daily [10,11] as in the present study (50 µg twice daily).The third trial [12]used the same dose of salmeterol as was used in our study, although the patients may have had milder disease than those in the present study. They included patients receiving doses of 800 µg daily of inhaled steroids compared with 100 µg daily in the present study.

Two previous studies[13,14] have compared different LABA-ICS salmeterol and formoterol treatment in asthmatic patients.The first was a large parallel-group study of 6 months of treatment using the same doses as those used in our study[14]. There was no difference in mean morning PEF, although the evening PEF was better with formoterol at 2, 3, and 4 months.

The second trial[13] also showed improvements in morning and evening PEF values,with two formulations of salmeterol and with formoterol compared with baseline values.These two studies were similar from the present study in two ways. There was no placebo control, both trials were of an open-label design, but the patients who were studied had milder cases of asthma, with higher PEF rates and lower steroid doses.

The present short term study did not investigate exacerbation rates, and a longer trial in this severe patient group, similar to that performed by van der Molen and colleagues[15], would be of interest.

Conclusion:-

We conclude that the long-acting ß2-agonist and inhaled corticosteroid combinations, formoterol 6µg with fluticasone propionate 100 µg and salmeterol 50 µg with fluticasone 100µg propionate as dry powder inhalation, improve morning and evening PEF in patients with persistent asthma but without any significant difference in efficacy between the two combinations.

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