

Efficacy of Fixed dose combination of Formoterol and Fluticasone propionate dry powder inhaler (DPI), in management of “Partly controlled & Uncontrolled” asthma in 5-17 yr group



Medical Science

KEYWORDS :

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ABSTRACT

It has been found that compositions containing formoterol and fluticasone propionate induce an anti-inflammatory activity which is significantly greater than that induced by formoterol or fluticasone propionate alone.

This was an open label, prospective, non-comparative, multicenter study of patients 149, 5-17years old, diagnosed with “Partly controlled & uncontrolled” asthma, treated for 8 weeks with twice daily fixed dose combination of fluticasone and Formoterol DPI capsules (rheocaps), inhaled using DPI device (rheohaler). Asthma control was assessed by changes in FEV₁, FVC, PEFR, validated 5-item Asthma Control test (ACT) & patient/physician global assessments. Spirometry was performed by Easy-on PC Spirometer (made Switzerland) Partly controlled Asthma was defined as daytime symptoms are occurring more than twice a week, sometimes at night and occasionally they limit activity. Quick-relief medicine is needed more than twice a week. Peak flow rate is less than 80 percent of your personal best, and asthma attacks occur at least once a year(GINA Guidelines 2012). Uncontrolled Asthma was defined as uncontrolled if patients have 3 or more of the features of partially controlled asthma at least 3 times a week, and asthma attacks are occurring weekly(GINA Guidelines 2012).

Introduction:

The treatment of asthma has dramatically improved following the increased use of fixed dose inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) combination therapies. The appeal of these combinations is three-fold: Improved patient compliance, Simplified disease management and the certainty of bronchodilator and steroid co-administration. It has been found that compositions containing formoterol and fluticasone propionate induce an anti-inflammatory activity which is significantly greater than that induced by formoterol or fluticasone propionate alone. Keeping this in mind we undertook this study on above combination.

Material and Methods:

It was an open label, non comparative clinical trial Inclusion criteria:

- Institutional Clearance
- Written informed consent
- Male or female subjects, aged 5-17 years.
- Subjects with persistent mild to moderate stable asthma as defined by GINA Guidelines, with
- FEV₁ ≥50 % of that predicted.
- Subjects who have requirement for inhaled steroids and who are treated currently with ≤1000µg of Beclomethasone dipropionate (BDP) suspension or equivalent dose of inhaled steroid, per day for at least 4 weeks prior to screening.
- Able to perform acceptable lung function tests using spirometry.

Exclusion criteria:

- Daily requirement for >1000µg BDP, or equivalent.
- Evidence of active concomitant pulmonary diseases other than asthma.
- Acute upper respiratory tract infection within 2 weeks of the screening visit.
- Acute lower respiratory tract infection within 4 weeks of the screening visit.
- Any change in asthma therapy (other than inhaled short-acting β₂-agonists as rescue medication) or admission to hospital for treatment of asthma within 4 weeks preceding the screening visit
- More than 4 short courses of oral corticosteroids within the six months preceding the screening visit, or any oral corticosteroids in the preceding 4 weeks.

- Concomitant severe decompensated systemic disease (cardiovascular, renal, hepatic, endocrine haematological, neurological or immunological).
- Clinical significant abnormal laboratory values.
- Evidence of alcohol, drug or chemical abuse.
- Treatment with any investigational drug or participation in another clinical study within the 3 months preceding the screening visit.

This was an open label, prospective, non-comparative, multicenter study of patients 149, 5-17years old, diagnosed with “Partly controlled & uncontrolled” asthma, treated for 8 weeks with twice daily fixed dose combination of fluticasone and Formoterol DPI capsules (rheocaps), inhaled using DPI device (rheohaler). Asthma control was assessed by changes in FEV₁, FVC, PEFR, validated 5-item Asthma Control test (ACT) & patient/physician global assessments. Spirometry was performed by Easy-on PC Spirometer (made Switzerland) Partly controlled Asthma was defined as daytime symptoms are occurring more than twice a week, sometimes at night and occasionally they limit activity. Quick-relief medicine is needed more than twice a week. Peak flow rate is less than 80 percent of your personal best, and asthma attacks occur at least once a year(GINA Guidelines 2012).

Uncontrolled Asthma was defined as uncontrolled if patients have 3 or more of the features of partially controlled asthma at least 3 times a week, and asthma attacks are occurring weekly(GINA Guidelines 2012).

Data management:

The data processing was performed by Capturing data into e-Case Report Forms. Data entered was checked by design for completeness and integrity. The primary outcome measures (mean change in FEV₁ & FVC) and secondary outcome measure (mean change in PEFR levels) were described in terms of their descriptive statistics i.e. (i.e. frequency, extreme values (Minimum and Maximum), Mean, Standard Deviation, Median, Standard Error of Mean (SEM), at Baseline (visit 1) and follow up visits 2 & 3. Safety was evaluated by AE monitoring and reported by frequency (incidence rate). Overall efficacy & tolerability data for drug was also reported by means of absolute & relative frequency. Missing values were declared as frequency and percentages where applicable.

Comparison between baseline (visit1) and follow up visits 2 & 3 , were made for efficacy variable and all safety data. The statistical significance $p < .05$ was taken as a level of significance. The 95% confidence Interval (CIs) of change from baseline values was presented along with statistical significance. Paired t –test was performed to assess the statistical significance of the differences between baseline and follow up visits, under each group separately. All analyses were prospectively planned and conducted on an intention-to-treat (ITT) basis. Patient data loss was kept to a minimum by defining ITT eligibility as any patient with at least one baseline and one follow-up visit.

Analysis Of Demographics

1. Total No. Of Patients : 149
 No. Of Males : 79 (53.02%)
 No. Of Females : 32 (21.48%)
 Data Available for 111 patients only

2. Mean Age : 13.71 ± 3.00 yrs. (Between 05 to 17 yrs).
 Range 12 yrs.

Analysis Efficacy Parameters, Age group less than 18 Years

Assessment Of FEV1 - Age Group Less than 18 years Descriptive Statistics Visit 1 to Visit 3:

	N	Minimum	Maximum	Mean	Std. Error	Std. Deviation	Sig. (2-tailed) *
Assessment of FEV1_Visit 1	111	39	418	1.5407	0.0505	0.0379	
Assessment of FEV1_Visit 2	94	73	344	1.7861	0.0762	0.1008	$p < .0001$
Assessment of FEV1_Visit 3	105	88	323	2.1085	0.0573	0.0181	$p < .0001$

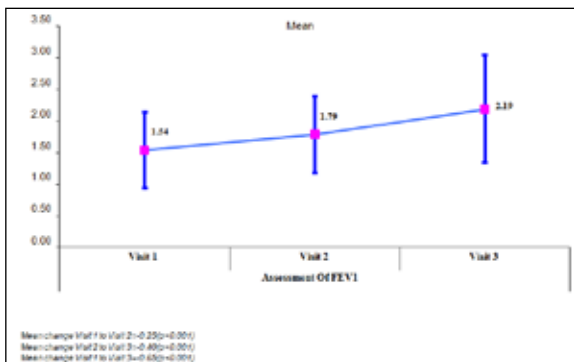


Table & Figure 2 Assessment Of FEV1 - Age Group Less than 18 years Test Of Significance : T-Test

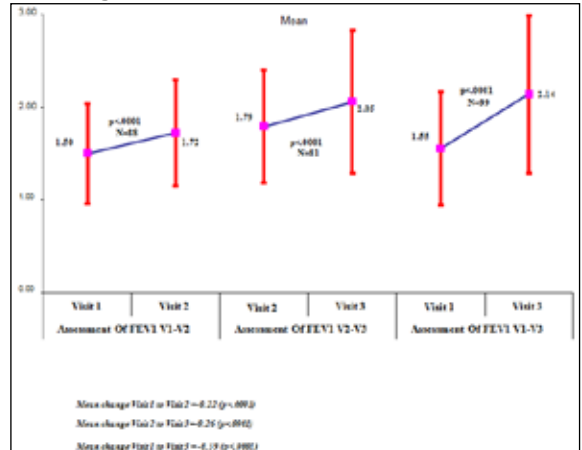
Pair	Assessment of FEV1_Visit 1	Assessment of FEV1_Visit 2	Mean		Std. Deviation	Std. Error Mean
			N	Mean		
Pair 1	Assessment of FEV1_Visit 1	Assessment of FEV1_Visit 2	111	1.5407	0.0379	0.0505
	Assessment of FEV1_Visit 2	Assessment of FEV1_Visit 3	94	1.7861	0.0762	0.1008
Pair 2	Assessment of FEV1_Visit 1	Assessment of FEV1_Visit 3	111	1.5407	0.0379	0.0505
	Assessment of FEV1_Visit 2	Assessment of FEV1_Visit 3	94	1.7861	0.0762	0.1008
Pair 3	Assessment of FEV1_Visit 1	Assessment of FEV1_Visit 3	111	1.5407	0.0379	0.0505
	Assessment of FEV1_Visit 2	Assessment of FEV1_Visit 3	94	1.7861	0.0762	0.1008

Paired Samples Correlations			N	Correlation Sig.
Pair 1	Assessment of FEV1_Visit 1 & Assessment of FEV1_Visit 2		94	.723 .000
Pair 2	Assessment of FEV1_Visit 1 & Assessment of FEV1_Visit 3		91	.807 .000
Pair 3	Assessment of FEV1_Visit 2 & Assessment of FEV1_Visit 3		99	.567 .000

Pair	Assessment of FEV1_Visit 1	Assessment of FEV1_Visit 2	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
						Lower	Upper			
						Pair 1	Assessment of FEV1_Visit 1			
Pair 2	Assessment of FEV1_Visit 1	Assessment of FEV1_Visit 3	-26320	38053	14317	-34924	-17742	-4.180	80	.000
Pair 3	Assessment of FEV1_Visit 2	Assessment of FEV1_Visit 3	-16540	71119	17143	-72738	-44301	-4.191	98	.000

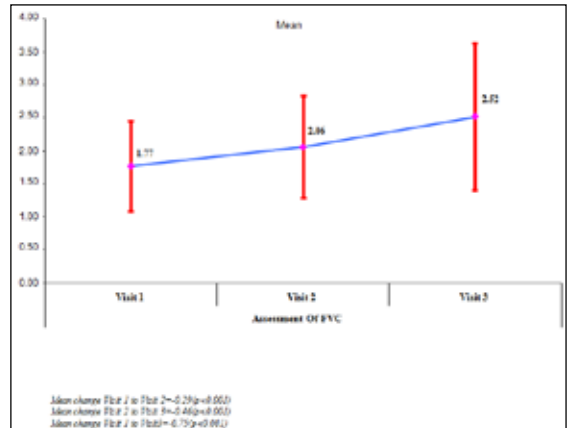
Result show a significant changes in FEV1 levels, from Visit 1 to Visit 2 , Visit 2 to Visit 3 and also from Visit 1 to Visit 3 at ($p < .0001$)

Assessment Of FEV1 - Age Group Less than 18 years. Test Of Significance: T-Test Mean



Assessment Of FVC - Age Group Less than 18 years Descriptive Statistics Visit 1 to Visit 3:

	N	Minimum	Maximum	Mean	Std. Error	Std. Deviation	Sig. (2-tailed) *
Assessment of FVC_Visit 1	94	26	236	1.7084	0.0803	0.6818	
Assessment of FVC_Visit 2	88	75	345	2.0647	0.0902	0.7620	$p < .0001$
Assessment of FVC_Visit 3	125	88	352	2.5274	0.0671	1.1590	$p < .0001$



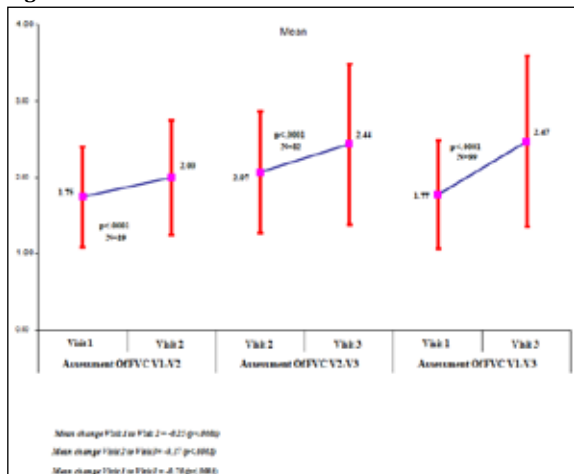
Assessment Of FVC - Age Group Less than 18 years Test Of Significance : T-Test

Pair	Assessment of FVC_Visit 1	Assessment of FVC_Visit 2	Mean		Std. Deviation	Std. Error Mean
			N	Mean		
Pair 1	Assessment of FVC_Visit 1	Assessment of FVC_Visit 2	94	1.7470	0.0803	0.0803
	Assessment of FVC_Visit 2	Assessment of FVC_Visit 3	88	2.0602	0.0902	0.0902
Pair 2	Assessment of FVC_Visit 1	Assessment of FVC_Visit 3	94	1.7470	0.0803	0.0803
	Assessment of FVC_Visit 2	Assessment of FVC_Visit 3	88	2.0602	0.0902	0.0902
Pair 3	Assessment of FVC_Visit 1	Assessment of FVC_Visit 3	94	1.7470	0.0803	0.0803
	Assessment of FVC_Visit 2	Assessment of FVC_Visit 3	88	2.0602	0.0902	0.0902

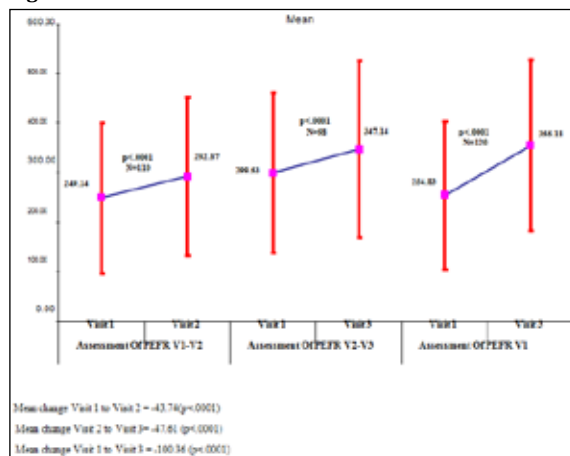
Paired Samples Correlations			N	Correlation Sig.
Pair 1	Assessment of FVC_Visit 1 & Assessment of FVC_Visit 2		88	.799 .000
Pair 2	Assessment of FVC_Visit 1 & Assessment of FVC_Visit 3		82	.822 .000
Pair 3	Assessment of FVC_Visit 2 & Assessment of FVC_Visit 3		99	.722 .000

Pair	Assessment of FVC_Visit 1	Assessment of FVC_Visit 2	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
						Lower	Upper			
						Pair 1	Assessment of FVC_Visit 1			
Pair 2	Assessment of FVC_Visit 1	Assessment of FVC_Visit 3	-35764	55425	94307	-46597	-26990	-7.888	81	.000
Pair 3	Assessment of FVC_Visit 2	Assessment of FVC_Visit 3	-49758	78269	97988	-86189	-64587	-4.873	88	.000

Assessment Of FVC - Age Group Less than 18 years Test Of Significance: T-Test

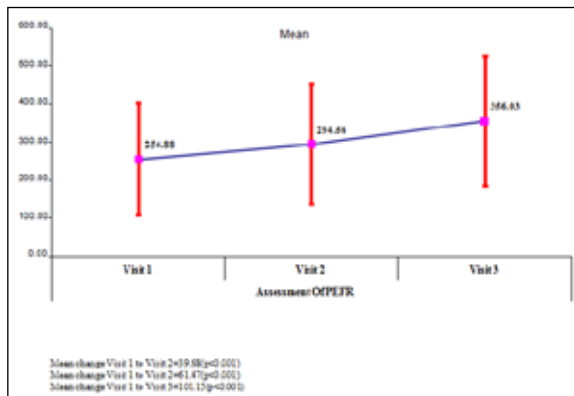


Assessment Of PEFR - Age Group Less than 18 years Test Of Significance : T-Test



Assessment Of PEFR - Age Group Less than 18 years Descriptive Statistics Visit 1 to Visit 3:

	N	Minimum	Maximum	Mean	Std. Error	Std. Deviation	Sig.
Assessment of PEFR_Visit 1	138	86.00	780.00	264.8824	17.84882	147.60704	
Assessment of PEFR_Visit 2	112	106.00	800.00	284.8626	16.02729	158.03263	p<.0001
Assessment of PEFR_Visit 3	121	102.00	800.00	368.0328	14.52328	171.22823	p<.0001



Assessment Of PEFR - Age Group Less than 18 years Test Of Significance : T-Test

Pair	Assessment of PEFR_Visit	Paired Samples Statistics(N)			
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Assessment of PEFR_Visit 1	249.1264	112	162.80214	14.82004
	Assessment of PEFR_Visit 2	292.8727	112	188.80112	18.24997
Pair 2	Assessment of PEFR_Visit 2	289.6306	98	181.34028	18.26783
	Assessment of PEFR_Visit 3	347.1428	98	178.42667	18.02381
Pair 3	Assessment of PEFR_Visit 1	264.8292	120	149.81473	13.80312
	Assessment of PEFR_Visit 3	366.1923	120	172.82665	16.74946

Pair	Assessment of PEFR_Visit 1 & Assessment of PEFR_Visit 2	N	Correlation	Sig.
Pair 1	Assessment of PEFR_Visit 1 & Assessment of PEFR_Visit 2	118	.737	.000
Pair 2	Assessment of PEFR_Visit 2 & Assessment of PEFR_Visit 3	98	.882	.000
Pair 3	Assessment of PEFR_Visit 1 & Assessment of PEFR_Visit 3	120	.713	.000

Pair	Assessment of PEFR_Visit 1 & Assessment of PEFR_Visit 2	Paired Samples Test:					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Assessment of PEFR_Visit 1 & Assessment of PEFR_Visit 2	-43.72636	113.29923	11.20848	-65.19446	-22.25822	-4.047	120	.000
Pair 2	Assessment of PEFR_Visit 2 & Assessment of PEFR_Visit 3	-47.61224	84.94744	8.49007	-64.46288	-30.76160	-5.608	97	.000
Pair 3	Assessment of PEFR_Visit 1 & Assessment of PEFR_Visit 3	-100.36833	123.68812	11.28821	-122.71011	-78.02655	-8.891	119	.000

Discussion:

Very little literature is available in the use of Formoterol and Fluticasone in the management of asthma. However, literature does exist in comparison of formoterol and budesonide combination vs salmeterol and fluticasone in the management of asthma. The pharmacological properties of formoterol, suggests that this drug is an effective symptom reliever, which has been confirmed in clinical studies¹. We do have literature which compared the superiority of formoterol vs salmeterol and fluticasone vs budesonide. In multicentre, randomised, double blind, parallel group study to compare the efficacy and safety of the addition of salmeterol with that of doubling the dose of fluticasone propionate in asthmatic patients not controlled by a low or intermediate dose of inhaled corticosteroids, it was found that addition of salmeterol caused a greater improvement in lung function and symptom control than doubling the dose of fluticasone propionate², hence addition of long acting β2 agonist to inhaled steroids had better control of asthma than to inhaled steroid alone. In a double-blind placebo-controlled crossover study, the bronchodilating properties of formoterol 6, 12 and 24 microg were compared with the effects of salmeterol 50 microg, it was found that Formoterol at all doses had a similar duration of effect to salmeterol 50 microg, as judged from bronchodilation at 12 h after dose administration³. When the relative potency of the two drugs was compared, salmeterol 50 microg was estimated to correspond to formoterol 9 microg (95% confidence interval: 3-19 microg). It was confirmed that formoterol and salmeterol are both long-acting beta2-agonists, but with some differences in effect profile i.e in onset of action of formoterol compared with salmeterol³. Adams NP4 compares the effectiveness of three inhaled steroids, Fluticasone (FP) was compared with either beclomethasone (BDP) or budesonide (BUD) for treating people with chronic asthma⁴. When FP was given to children or adults at approximately half the daily dose of either BDP or BUD, it appeared to be at least as effective as the other two drugs in improving airway opening⁴. There was not enough information available to draw conclusions concerning the effect of these drugs on symptoms, or the risk of an acute asthma exacerbation. When given at the same dose as BDP or BUD, FP treated participants had slightly better lung function, although it did not lead to increased incidences of other side-effects associated with steroids such as oral thrush or sore throat. In a clinical trial of High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. International Study Group, it was double-blind, parallel group study was conducted in 671 patients with severe asthma (already taking between 0.8-2.0 mg of inhaled corticosteroid daily) to compare the safety and efficacy of 6 weeks of treatment with inhaled fluticasone propionate (FP), 1 mg daily, to fluticasone propionate, 2 mg daily, and budesonide (BUD), 1.6 mg daily, delivered via a metered-dose inhaler. Peak expiratory flow (PEF), asthma symptoms, and usage of rescue medication were recorded daily by the patient, it was found that the changes in mean morning PEF from baseline

(weeks 1-6) were: FP 2 mg daily +24 l.min per min; FP 1 mg daily +21 l per min; BUD 1.6 mg daily +13 l.per min⁵. A similar rank order for the three treatments was seen for evening PEF, clinic spirometry, reduction of diurnal PEF variation, symptom scores, and requirement for rescue bronchodilators.

REFERENCE

1. Tattersfield A, Löfdahl C G, Postma D S, Ekström T, Eivindsson A, Schreurs A, Rasidakis A, Karlsson K, Larsson P. On demand treatment: comparison of formoterol Am J Respir Crit Care Med 1999; 159: A636. | 2. J A van Noord, A J M Schreurs, S J M Mol, P G H Mulder, Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. Thorax 1999;54:207-212; doi:10.1136/thx.54.3.207. | 3. M Palmqvist, G Persson, L Lazer, J Rosenborg, P Larsson, and J Lotvall. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency, Eur Respir J 1997; 10: 2484-2489 | 4. Adams NP, Lasserson TJ, Cates CJ, Jones P. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD002310 | 5. JG Ayres, ED Bateman, B Lundback, and TA Harris, High dose fluticasone propionate, 1 mg daily, versus fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. International Study Group; Eur Respir J 1995; 8: 579-586 |