EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 12
346-352
Year: 2016

COMPARISON OF EFFICACY OF BUDESONIDE/FORMOTEROL VERSES FLUTICASONE/FORMOTEROL IN THE TREATMENT OF BRONCHIAL ASTHMA

Abin Joseph*[1], Anil Babu[2], Binu Raj C.[3] and Seethadevi B[4].

[1]M. Pharm Student, Department of Pharmacy Practice, National College of Pharmacy Calicut, Kerala.
[2]Associate Professor and HOD, Department of Pharmacy Practice, National College of Pharmacy Calicut, Kerala.
[3]Associate Professor, Department of Pulmoonary Medicine, KMCT Medical College Hospital Calicut, Kerala.
[4]Principal, National College of Pharmacy Calicut, Kerala.

*** Corresponding Author: Abin Joseph**
M. Pharm Student, Department of Pharmacy Practice, National College of Pharmacy Calicut, Kerala.

Article Received on 30/09/2016 **Article Revised on 20/10/2016** **Article Accepted on 09/11/2016**

ABSTRACT

Background and Objectives: The present study was designed to compare fixed combination of budesonide plus formoterol, with the fixed combination fluticasone plus formoterol. Main objective was to find out the combination having more efficiency and least adverse reactions **Methods:** This was a prospective observational study done for 9 months. Total number of patients participated in this study was 85. Out of this 44 patients were treated with budesonide/formoterol (400/6) and 41 patients were treated with fluticasone/formoterol (250/6). Baseline was measured at the time of admission as Forced expiratory volume in 1st second & Peak expiratory flow rate. Review of patients was done after 10 days. **Results & Discussion:** A significant improvement of lung functions from baseline was observed in both groups at all time point. Budesonide/ formoterol showed more improvement in lung function than fluticasone/ formoterol. Budesonide/formoterol showed 2.14L/min increase in peak expiratory flow rate and 1.1% increase in FEV1 than that of fluticasone/ formoterol. Also FEV1 in liter had an increase of 0.04L than fluticasone/ formoterol. **Conclusion:** The combination budesonide/ formoterol had slightly increased efficacy than fluticasone/ formoterol. Tolerability was found to be similar for both combinations. But fluticasone/ formoterol is expensive than budesonide/ formoterol. Thus the budesonide/formoterol is more economical for the patients. It indirectly improves the patient adherence to the medication. Thus budesonide/ formoterol combination was found to be better for an asthma patient in terms of efficacy and cost.

KEYWORDS: Asthma, Budesonide, Formoterol, Fluticasone, Inhaled corticosteroids in asthma.

INTRODUCTION

INHALED CORTICOSTEROIDS (ICS)

This year is the 50th anniversary of the introduction into clinical use of the first modern inhaler for the management of asthma – the pressurized metered-dose inhaler (pMDI). The pMDI was initially used for the administration of the non-selective beta-agonists adrenaline and isoprenaline. However, the epidemic of asthma deaths which occurred in the 1960s led to these drugs being superseded by the selective short-acting beta-agonist salbutamol, and the first inhaled corticosteroid (ICS) beclomethasone. At the same time, sodium cromoglycate was introduced, to be administered via the first dry-powder inhaler, the Spinhaler. But owing to its relatively weak anti-inflammatory action its use is now very limited. Over the last 10 years, the long-acting beta-agonists (LABAs) have become an important add-on therapy for the management of asthma, and they are now often used with ICS in a single ICS/LABA combination inhaler.

LONG ACTING BETA 2 AGONIST

The two long-acting β2-agonists, formoterol and salmeterol, provide long-lasting bronchodilation (12 or more hours) when administered as aerosols. Unlike the more water-soluble short acting β2-agonists, the long-acting agents are lipid-soluble, readily partitioning into the outer phospholipid layer of the cellmembrane. Salmeterol is more β2-selective than albuterol and more bronchoselective by virtue of its property of remaining in the lung tissue cell membrane, which produces its longer duration. However, both formoterol and salmeterol will produce dose-dependent systemic β2-agonist effects.

INHALED CORTICOSTEROID AND BETA 2 AGONIST COMBINATION

Inhaled corticosteroids (ICSs) are the cornerstone of asthma therapy. For patients with persistent or uncontrolled asthma for whom low-to-medium doses of ICSs are insufficiently effective, there may be reluctance to increase the steroid dose because of concerns about

corticosteroid-related adverse events. Instead, patients may be prescribed a combination of an ICS and a long-acting β_2-agonist (LABA). A substantial body of evidence from randomized controlled trials indicates that addition of a LABA to existing ICS therapy is clinically more effective than increasing the dose of ICS monotherapy, even when taking into consideration the heterogeneity observed in patient responses to asthma controller medications. The use of LABAs without concomitant use of an ICS is contraindicated in patients with asthma because LABA monotherapy is less effective than treatment with an ICS and there are concerns regarding its safety.

MATERIAL AND METHOD

Study design
It is a Prospective observational study.

Study duration
Total duration of the study was 9 months.

Study site
The study was conducted at the pulmonary medicine department of a tertiary care teaching hospital.

Ethical approval
Before conducting the study a protocol was prepared for which the permission was obtained from Institutional Ethical Committee (IEC) held on 13th January 2016.

Study population
Sample size for the study was greater than 38 from each treatment group.

Study criteria
The patients who satisfied the inclusion and exclusion criteria were selected randomly.

Inclusion Criteria
- Patient who are willing to participate in the study
- In patients with age greater than or equal to 12 years
- Patients diagnosed with bronchial asthma.
- Patients who are prescribed with budesonide plus formoterol or fluticasone plus formoterol powder inhalation

Exclusion criteria
- Patient using other anti asthmatic drugs
- Pregnancy and lactation

Source of data
Patient Case Records: It included following information:
- Patient Demographics
- Patient history notes
- Drug Treatment charts
- Laboratory investigation report
- Discharge summar

Study materials
- Patient data collection form.
- Informed consent form and patient information sheet

Study procedure
This was a Prospective observational study which was conducted in the pulmonary department of the 500 bed tertiary care teaching hospital. All patients having bronchial asthma using a combination of budesonide + formoterol or fluticasone +formoterol who are willing to participate, after signing informed consent form were included in the study. Selected patients were divided in to two groups such as A and B where.

- A - treated with budesonide + formoterol (400/6) 2 puff BID
- B –treated with fluticasone + formoterol (250/6) 2 puff BID

Outcome was measured in terms of Peak expiratory flow rate (PEFR), forced expiratory volume at first second (FEV1) at the time of admission and follow up was done after 10 days. FEV1 of patients were measured using spirometer and PEFR by peak flow meter.

Other data includes demographic data such as name, age, gender, location, past medical history, patient history, lab values were collected from patient interview, case note and health professionals.

Statistics
Data collected was analyzed using Statistical Package for Social Science version 16 (SPSS). Descriptive statistics were given as mean and SD for continuous data or as percentage for frequency. Before and after treatment was compared with paired t test. Independent variable t test was given as comparison of mean in two populations.

RESULTS AND DISCUSSION
The proposed work entitled **"Comparison of efficacy of budesonide/formoterol verses fluticasone/formoterol in the treatment of bronchial asthma"** was a prospective- study carried out in 500 bedded tertiary care hospital.

Assessment of prevalence of asthma
Total number of patients admitted in pulmonary department were taken for the assessment of prevalence.

Table: Assessment of prevalence of asthma

Category of patients	Total	Males	Females
Number of patient admitted in pulmonary department	3560	1710(48%)	1850(52%)
Number of patient admitted in pulmonary department with asthma	118	50(42.4%)	68(57.6%)

Number of patients received treatment A or B	85	32(37.6%)	53(62.4%)
Prevalence of asthma	3.31%	2.92%	3.67%

Prevalence of asthma in pulmonary department was found to be 3.31%. When this result was categorize by gender, 2.92% and 3.67% for male and female respectively and 70.03% of this asthma patients are using either Budesonide+ formoterol or fluticasone + formoterol combination.

According to the study conducted by **Aggarwal AN et al** prevalence of asthma ranges between 1.33%- 3.55% in different study centres in India and male prevalence ranges from 1.4%- 3.36% and female prevalence ranges 1.23- 3.76%.

Gender distribution

In our study females were more in number than male.

Table: gender distribution

Gender	Number of patients	Percentage
Male	32	38%
Female	53	62%
Total	85	100%

Total number of patients selected from the pulmonary department was 85. Out of that 62% patients belongs to female and 38% belongs to male.

Study shows increased percentage of female patients is due to the increased incidence of females in the department. As we discussed earlier, after puberty females have greater chance for asthma according to **Demarco R et al**.

Treatment groups

Sample size of our study was 76 patients. Data of 85 patients were used in the study.

Table: treatment groups

Treatment group	Number of patients	Males	Female
Budesonide + Formoterol (A group)	44	43.2%(19)	56.8%(25)
Fluticasone + Formoterol (B group)	41	31.7%(13)	68.3%(28)

Total patient participated in the study was 85. Out of that 44 patients were enrolled in group A constitute 19 males and 25 females. 41 patients were enrolled in group B constitute 13 male and 28 females. In both groups female patients are in greater number. The study conducted by **Aggarwal AN et al**. also showed similar result, increased prevalence of asthma in females.

Age classification

In our study 6 age groups were created.

Table: age classification

Age groups (years)	Frequency	Percentage
10 – 19	3	3.5%
20 – 29	1	1.2%
30 – 39	5	5.9%
40 – 49	18	21.2%
50 – 59	15	17.6%
>59	43	50.6%

Asthma was most prevalent in age group greater than 59 having 43 patients and it was about 50.6%. And least prevalent in 20 – 29 group contain only one patient that was 1.2%

Aggarwal AN et al. study also showed similar results that is 59% of patients belongs to the age greater than 60. This concludes chances for exacerbation of asthma increases with age.

The increased percentage of patients in age group greater than 59 is due to the decrease in lungs functions on age. This is due to the decline of lungs function after the age of 30. But, age group 10-19 had greater chance of asthma than 20-29. According to **Huib AM et al**. It was seen that lung function was maximum at the age of 20-35.

Comparison of efficacy of group a and group b

Comparison of efficacy of budesonide/formoterol verses fluticasone/formoterol were done in terms of lung function tests. Two parameters were measured during the

study. They were forced expiratory volume at 1st second and peak expiratory flow rate.

1. Peak expiratory flow rate (pefr)

Table: Peak Expiratory flow Rate (PEFR)

Treatment groups	Base line (L/min)		Review (L/min)		P value	Average increase(L/Min)	
	Mean	SD	Mean	SD		Increase	SD
Group A	155.91	45.35	179.55	48.31	0.000	23.63	5.74
Group B	139.02	48.72	159.76	48.55	0.000	21.46	5.72
						P value = 0.085	

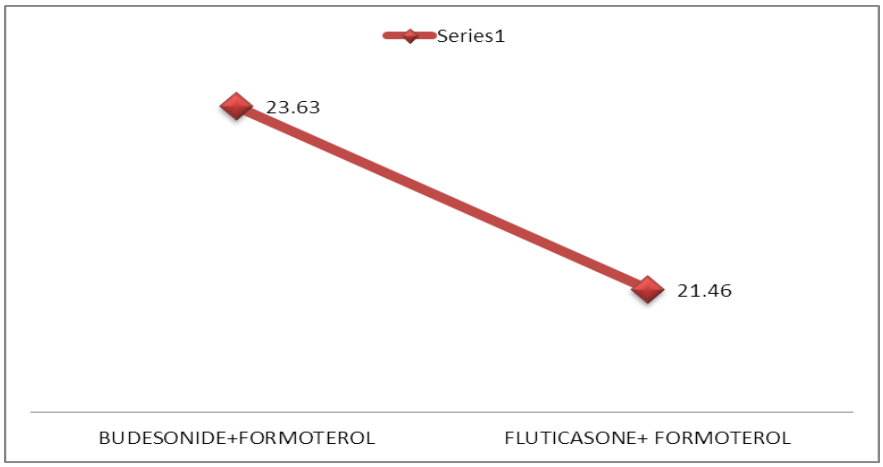

Figure: Improvement of Peak Expiratory Flow Rate from the Baseline

The average increase in PEF Rate on review after 10 days was found to be 23.63 L/min in group A and 21.46 L/min in group B. That means budesonide + formoterol has 2.17L/min increase in PEF Rate than the other group. From the result it was found that budesonide/ formoterol had greater efficacy than fluticasone/formoterol according to Peak Expiratory Flow Rate.

Our study shows similar results to to **Cukier A et al**. also showed greater efficacy for budesonide/formoterol than fluticasone/formoterol to improve peak expiratory flow rate.

2. Improvement of forced expiratory volume at first second (fev1) in (l)

Forced expiratory volume at first second is an important lungs function test to assess the efficacy of asthmatic drug.

Table: Improvement of Forced Expiratory Volume at First Second (FEV1) in (L)

Treatment group	Base line (l)		Review (l)		P value	Increase in fev1		P value
	MEAN	SD	MEAN	SD		INCREASE (L)	SD	
Group A	1.1	0.32	1.29	0.31	0.000	0.19	0.15	0.155
Group B	1.09	0.28	1.24	0.28	0.000	0.15	0.05	

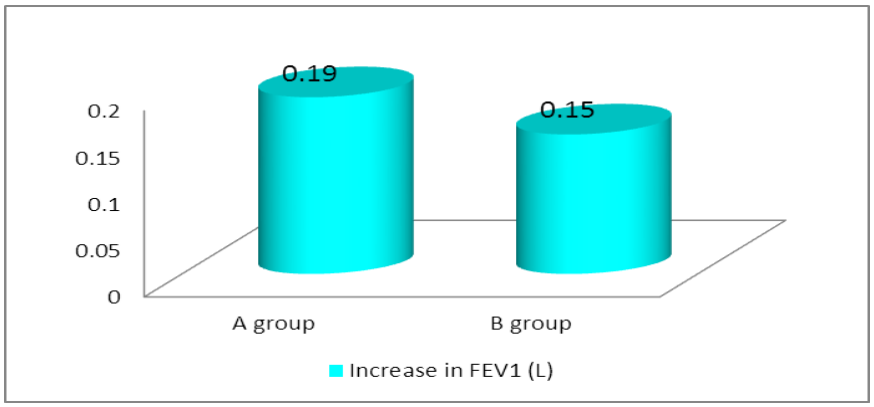

Figure: Improvement of Forced Expiratory Volume at First Second (FEV1) in (L)

From this result it was clear that group A (budesonide + formoterol) showed 0.04L increase in improvement of FEV1 than that of group B (fluticasone + formoterol). Group A showed increased efficacy than that of group B. Greater efficacy of budesonide formoterol was due to the faster onset action of budesonde than the fluticasone. A study conducted by **Day J et al**. also demonstrated the faster onset action for the budesonide than that of fluticasone.

Bodzenta Lukaszyk et al. also showed similar resuts to our study. Their study also showed increased improvement of FEVI in patients treated with budesonide + formoterol combination than that of fluticasone +formoterol. Budesonide/formoterol showed 0.043 L greater improvement than the fluticasone/formoterol.

3. Improvement of forced expiratory volume in first second (fev1) in percentage

Table: Baseline FEV1 and review FEV1 in percentage

Treatment groups	Base line Fev1 in %		Review Fev1 in %		P value	Increase in fev1 in percentage
	Mean	SD	Mean	SD		
Group A	45.38	13.40	54.95	13.12	0.000	9.6
Group B	42.70	10.65	51.21	10.97	0.000	8.5

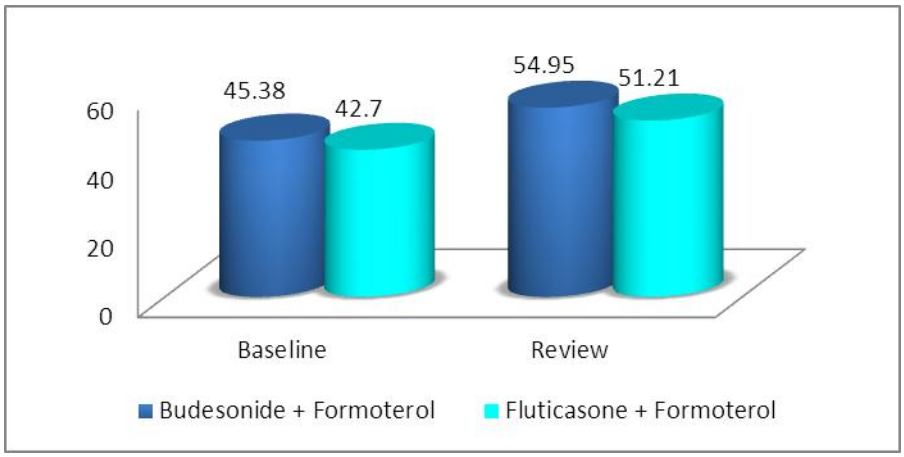

Figure: Baseline FEV1 and review FEV1 in percentage

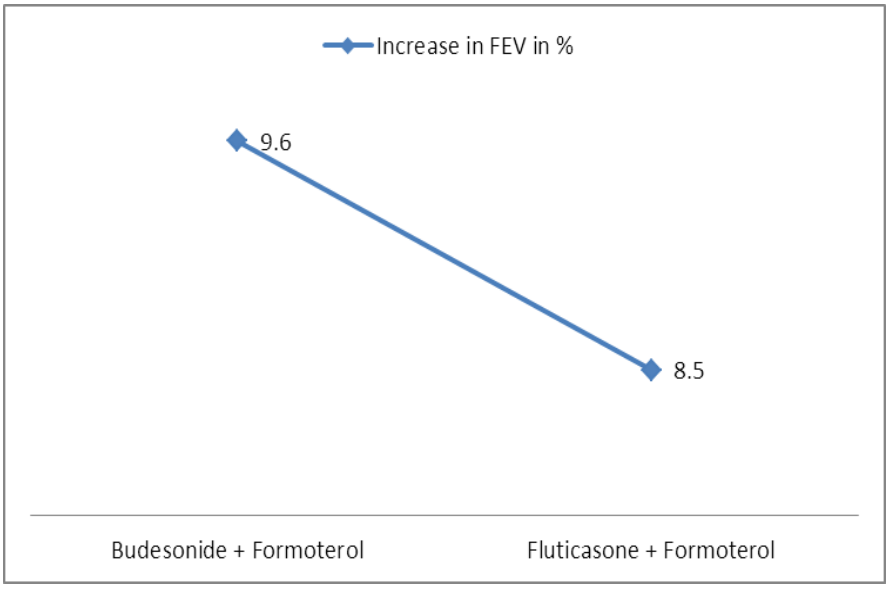

Figure: Improvement of Forced Expiratory volume (FEV1) in Percentage

From this result it was clear that group A (budesonide + formoterol) showed 1.1% increase in improvement of FEV1 than that of group B (fluticasone + formoterol). Group A showed increased efficacy than that of group B. Greater efficacy of budesonide formoterol was due to the faster onset action of budesonde than the fluticasone. A study conducted by **Day J et al**. also demonstrated the faster onset action for the budesonide than that of fluticasone.

Bodzenta L et al. also showed similar resuts to our study. Their study also showed increased improvement of FEVI in patients treated with budesonide + formoterol combination than that of fluticasone +formoterol. In that study, Budesonide/formoterol showed 0.043 L greater imrpovement in FEV1 than the fluticasone/formoterol.

CONCLUSION

This study was performed to compare the efficacy of budesonide/formoterol versus fluticasone/formoterol in bronchial asthma. Both medications were the combination of inhaled corticosteroid with long acting beta 2 agonist. Outcome of the study were measured in terms of forced expiratory volume in first second (FEV1), peak expiratory flow rate (PEFR). Tolerability of these combinations were also assessed. Prevalence of asthma was found to be 3.31%. More prevalence was shown by female population. Both combinations showed significant improvement in FEV1 and PEFR from the baseline. But budesonide/formoterol showed more improvement in FEV1 and PEFR than fluticasone/formoterol. Overall adverse drug reactions were found to be similar in magnitude for both treatment group. Thus both combinations had similar tolerability profile. Budesonide/formoterol is more economical for patient than fluticasone/formoterol. There for this combination is necessary to use in asthmatic patients to reduce the economic burden for purchasing the medication.

ACKNOWLEDGEMENT

First and foremost I would like to thank **God** for blessing us with the opportunity and perseverance to complete this work. This piece of work has been accomplished with the Almighty God, his blessings and his power that work within us and also with the people behind our life for inspiring, guiding and accompanying us through thick and thin.

I express my heartfelt gratitude to each and every one who has helped me to explore the expanses of knowledge.

I would like to gratefully and sincerely thank my guide **Mr. Anil Babu** (HOD**,** Associate professor, Department of pharmacy practice, National College of pharmacy) for his guidance, encouragement, understanding, patience, and support laid by him during this work. His encouragement and valuable suggestions have enabled us to make my work worthy of presentation.

Words are not enough to express my deep gratitude to my esteemed co-guide **Dr. Binuraj C,** Professor, Department of Neurology, KMCT Medical College for his keen interest, timely help and valuable suggestions from very beginning till the completion of the study.

It is an honour to pay my respected and heartfelt thanks to **Dr. B Seethadevi,** our beloved principal and **Prof. R Raju**, Director, National College of Pharmacy, for providing us with all the facilities to move forward with this study.

I extend my special thanks to **Mr. Rajiv P Thomas, Mr. Vinod Thomas, Miss. Anagha R, Miss. Zuhara Mariyam, Mrs. Sebiha Chesmi** and all other **teachers** of National College of pharmacy who shared their knowledge and time with us and for their valuable suggestions during our work.

I express my sincere thanks to **Mr. Rajan**, Librarian, National College of Pharmacy for his sincere co-operation and to **Mr. Durgesh** (Statistician, Department of Community Medicine, KMCT Medical College, Manassery) who helped us to complete the statistical analysis.

I express my gratitude to all the Nursing Staffs and non-clinical staffs of pulmonary department for their co-operation during our study.

I would like to extend my heartfelt thanks to all my **batch mates Ansa, Ameera, Jasmin, Jisha, Sabin, Samily, Soumya, Meghna** for their affection and concern throughout the course of study.

I convey my sincere thanks all my **juniors** in National College of Pharmacy for being so good to us, supporting and helping us in this study.

I wish to thank all **Patients** and their **Caregiver**s who co-operated so willingly with me to complete this study.

I express my sincere thanks to all the **Staff Members** of National College of Pharmacy.

Words have no power to pay regards to my most beloved **Parents, Brother** and **Relatives** for their prayers, love inspiration and encouragement upon me.
Abin Joseph

REFERENCE

1. Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A. Difference between athma exacerbation and poor asthma control. 1999; 353: 364-47.
2. Miller MR, Handkinson J, Brusasco V. Standerdisation of spirometry. Eur Respir J. 2005; 26: 319-38.
3. Quanjer PH, Stanojevic S, Cole TJ. Multi-ethnic reference value for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012; 40: 1324-43.
4. Pellegrino R, Viegi G, Brusasco V. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26: 319-38.
5. Reddel HK, Marks GB, Jenkin CR. Optimal asthma control, starting with high dose of inhaled budesonide. Eur Respir J. 2000; 16: 226-35.

6. Frey U, Brodbeck T. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. Nature. 2005; 438: 667-33
7. Rosi E, Stendardi L, Binazzi B, Scano G. Perception of airway obstruction and airway inflammation in asthma. Lung. 2006; 184: 251-8.
8. Jeremy D, Johnson MD, Welsly M, Theurer D. A stepwise approach to interpretation of pulmpnary function Test. Am fam Physician. 2014; 89(5): 359-366.
9. Kamada AK, Szefler SJ. Issues in the use of inhaled glucocorticoids. Am J Respir Crit Care Med. 1996; 153: 1739.
10. VanAsperen PP, Mellis CM, Sly PD, Robertson C. The roll of corticosteroids in management of childhood asthma. Med J Aus. 2002; 176(4): 168-173.
11. Zollner EW, Lombard CJ, Galal U. Hypothalamic-adrenal-pituitary axis suppression in asthmatic school children .Pediatrics. 2012; 130: 1512-1519.
12. Buhl R. Local oropharyngeal side effects of inhaled corticosteroids in patients with asthma. Allergy. 2006; 61: 518-526.
13. Weatherall M, Clay J, James K. Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. Respirology. 2009; 14: 983-90.
14. Michael T, David H, Richards, Bianca B, Leonardo F. Inhaled corticosteroid and long acting beta2 agonist pharmacological profiles: effective asthma therapy in practice. Respiratory medicine. 2012; 106(1): 9- 19.
15. Wolthers OD. Budesonide + formoterol fumarate dehydrate for the treatment of asthma. Expert Opin Pharmacother. 2016; 17(7): 1023-1030.
16. Bodzenta L, Buhl R, Balint B. Fluticasone/formoterol combination therapy verses budesonide/formoterol for the treatment of asthma. Journal of asthma. 2012; 49(10): 1060-1070.
17. Aggarwal A, Chaudhry K, Chhabra SK, Gupta D, Jindal SK, Katiyar SK et al. Prevalence and risk factor for bronchial asthma in Indian adults: A multicentre study. The Indian Journal of Chest Diseases & Allied Science. 2006; 48: 13-22.
18. Demarco R, Locatelli F, Sunjer J. Difference in incidence of reported asthma related to age in men and women. Am J Respir Crit Care Med. 2000; 162: 68- 74.
19. Huib AM, Bert R, Schouten JP, Dirkje SP. Decline of FEV1 by age and smoking status: facts, figures, fallacies. Thorax. 1997; 52: 820-827.
20. Cukier A, Jacob CMA, N.A. Rosario F, Fiterman J, Vianna EO, Hetzel JL et al. Fluticasone/formoterol dry powder versus budesonide/formoterol in adults and adolescent with uncontrolled or partially controlled asthma. Respiratory medicine. 2013; 107: 1330-1338.
21. Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol. 1998; 102(6): 902-908.