Adding Montelukast to Inhaled Corticosteroids in Stepwise Approach for Managing Asthma

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Abstract

Study objectives: Asthma is most effectively controlled with inhaled corticosteroids. If there are difficulties in maintaining control, long acting beta$_2$-agonists or a new alternative: leukotriene receptor antagonists can be added to the therapy. In this study we aimed to investigate the effects of montelukast when added to inhaled corticosteroids (ICS).

Methods: Fourteen stable persistent stable asthmatics receiving ICS and salmeterol for at least three months were enrolled in the study. After baseline assessments, salmeterol was ceased for a two-weeks washout period. Then all subject received 10 mg/daily montelukast added to their ICS therapy. Pulmonary functions, symptom scores and exhaled nitric oxide (eNO) levels were recorded under salmeterol therapy, before and after montelukast therapy in 10 patients who completed the study.

Results: A detoriation occurred in pulmonary functions and symptom scores after ceasing salmeterol. Three months after adding montelukast to ICS, there was a nonsignificant improvement in FEV_1, PEF and eNO, but the improvements in night time symptom scores, bronchodilator consumption and PEF variation were significant ($p<0.01$).

Conclusion: Adding montelukast to ICS was shown to be effective in controlling asthma. When comparing the study parameters under salmeterol and montelukast, there was not a significant difference in pulmonary functions and eNO levels but montelukast was better in controlling night time symptom scores and PEF variation ($p<0.05$).

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Introduction

Asthma is chronic disorder, characterized by exacerbation and remissions, which can be controlled by appropriate management. During the last decade several guidelines have been published for the management of asthma. These guidelines recommend that the best way to manage asthma is to use drugs which demonstrate effects on airway inflammation, since this is the major pathophysiology of asthma.

At present the most effective anti-inflammatory medications recommended in all asthma management guidelines are inhaled corticosteroids (ICS). Despite ICS, in moderate to severe persistent asthmatics who remain inadequately controlled, ICS dose can be increased or an additional medication such as long-acting β-agonists (LABA) can be added to therapy according to stepwise approach to pharmacological therapy

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of asthma in Global Initiative for Asthma (GINA) Workshop Report (1).

With the development of cysteinyl leukotriene receptor antagonists (LTRA), the first new class of antiasthmatic drugs were introduced in the last 25 years. Many studies on these agents showed their effectiveness in asthma treatment (2). They were recommended as an alternative medication to inhaled CS in mild persistent asthmatics (3). There are also reports about the benefits of adding a LTRA to an ICS (4).

The aim of this study was to investigate the effects of montelukast when added to ICS. Furthermore, we compared the lung functions, symptom scores and exhaled nitric oxide (eNO) levels under two treatment modalities: Salmeterol and ICS/Montelukast and ICS.

Methods

Fourteen stable mild to severe persistent stable asthmatics who were taking 800 mg budesonide together with 100 mg salmeterol daily for 3 months were included in the study. The study parameters were Peak Expiratory Flow Rates (PEFR), day and night time symptom scores, bronchodilator consumption, pulmonary function tests and eNO levels.

Study Design

In this open label clinical trial, for a two weeks run-in period, patients recorded their PEFR, day and night time symptom scores and bronchodilator consumption while taking ICS and salmeterol and then they were evaluated with pulmonary function tests and eNO levels.

Inhaled salmeterol was then stopped for a 2-weeks washout period. At the end of two weeks, patients were assessed with the same study parameters again, that was before adding the montelukast therapy.

10 mg/daily montelukast was added to inhaled CS therapy and the patients had 4 more study visits with 3 weeks intervals for measuring the study parameters. In the last visit which was on the 3rd month of montelukast therapy, the effects of montelukast were evaluated.

The study was approved by the Gazi University Medical Faculty's Ethics Committee and all the subjects gave written informed consent.

Pulmonary function tests and nitric oxide measurement

FEV_1 and PEF were measured with Sensor Medics V_{max} 20 spirometer. The best value of three manoeuvres was expressed as a percentage of the predicted value and as absolute value.

eNO was measured on a chemiluminescence analyser (Sievers 280 NOA™, Sievers Instruments, Inc., USA) sensitive to NO from <1 to 500 parts per billion (ppb, by volume). Subjects wore Sievers Accurate NO™ Exhaled Breath Kit that applies resistance to the exhaled breath circuit. This resistance creates positive pressure in the mouth (mean pressure of 10-15 cm H_2O), forces subject's soft plate shut and eliminates nasal NO from the measurement. NO was sampled at a flow rate of 0.05 l/s with tidal breathing method. The zero calibration was performed and ambient air NO was recorded before each test.

Symptoms, maximal diurnal variability, bronchodilator consumption

Diary cards were given to all patients to record β-agonist use, PEFR and asthma symptoms every morning and evening during the study period. The symptom enquiry included assessment of symptoms during the day and night, using four point scale (0=no symptoms; 3=severe symptoms) (5).

Diurnal variability of PEF was calculated as follow (1):

$$\frac{\text{Maximum PEF-Minimum PEF}}{1/2\ (\text{Maximum PEF+Minimum PEF})} \times 100\%$$

Statistical analysis

Values of FEV_1, PEF, eNO, PEF variation, symptom scores and bronchodilator consumption while taking salmeterol, before the beginning of montelukast and after 3 months of montelukast therapy was compared using Wilcoxon test. Results were expressed as the mean ± SEM. A p value of less than 0.05 was considered significant.

Results

Of the 14 patients included in the study, 2 lost follow-up and 2 were excluded from the study because of asthmatic attacks caused by a respiratory tract infection (one on the 3rd week, one in the 6th week of montelukast therapy).

The demographic data of the 10 patients who completed the study are shown in Table 1. Asthma severity was assessed according to GINA guidelines (1).

Table 1. Demographic data of the patients

Number of patients	10
Gender (M/F)	2/8
Age (years)	46.3±3.06
Mean duration of asthma (years)	15.8±5.03
Severity of asthma: Mild persistent	3 (%30)
Moderate persistent	6 (%60)
Severe persistent	1 (%10)
FEV_1 (% predicted)	70.3±5

Table 2. Comparison of pulmonary functions during the study period									
	1*	2**	p	2**	3***	p	1*	3***	p
FEV_1 (l)	1.76±0.12	1.55±0.14	<0.05	1.55±0.14	1.61±0.14	NS	1.76±0.12	1.61±0.14	NS
FEV_1(%)	70.3±0.5	61.1±5.6	<0.05	61.1±5.6	64.2±5.13	NS	70.3±0.5	64.2±5.13	NS
PEF (L/sec)	4.01±0.24	3.44±0.28	<0.05	3.44±0.28	3.81±0.39	NS	4.01±0.24	3.81±0.39	NS
PEF (%)	61.5±2	52.7±3.64	<0.05	52.7±3.64	58±4.43	NS	61.5±2	58±4.43	NS
PEF variation	7.5±2	9.6±2.31	NS	9.6±2.31	0.9±0.64	<0.01	7.5±2	0.9±0.64	<0.05

1*: Under salmeterol therapy
2**: After ceasing salmeterol (Before montelukast therapy)
3***: After montelukast therapy

The outcomes of study parameters were evaluated in three groups:

1. Comparison of parameters while using salmeterol and after the cessation of salmeterol (before montelukast therapy).

2. Comparison of parameters before and after montelukast therapy.

3. Comparison of parameters while using salmeterol and after montelukast therapy.

Pulmonary functions worsened significantly after ceasing salmeterol. They all improved with adding montelukast to the ICS therapy, though the only significant improvements were in PEF variation, night time symptom score and bronchodilator consumption. No significant difference was found when comparing the pulmonary functions under two therapies. However, mean PEF variation was significantly lower with montelukast therapy than salmeterol therapy (Table 2).

Bronchodilator consumption, day and night time symptom scores increased significantly after ceasing salmeterol. After a 3-month montelukast therapy, they all improved and there was a decrease in eNO levels. However, when comparing the study parameters under two treatment modalities, montelukast was better in controlling night time symptom scores and PEF variation (Table 3).

Discussion

In this study, we showed that adding montelukast to ICS is successful in asthma control. Furthermore, we showed that montelukast is as effective as salmeterol in stepwise approach for managing asthma.

Cysteinyl leukotriens, which are important mediators of asthma, have four major roles in asthmatic inflammation: Recruiting inflammatory cells to the bronchial wall, increasing microvascular permeability, stimulating the discharge of mucus secretion and stimulating airway smooth muscle proliferation (6,7).

Leukotrien receptor antagonists (LTRA) block the effects of cysteinyl leukotriens at their receptors on target tissues and inhibition of their activity has been shown to be associated with an improvement in asthma control (8,9). LTRA produce a dual effect within the airways, both as bronchodilators and as inflammation controllers, which has not been demonstrated as clearly in other classes of asthma drugs (2,10,11). Many clinical studies showed their efficacy in improving asthma control and pulmonary functions mainly in mild persistent asthma, exercise and aspirin induced asthma (9,12-19).

LTRA have complementary effects to corticosteroids on inflammation control (9,13,14,20). The results of many studies suggest that antileukotrien drugs in combination with ICS are likely to improve lung functions and asthma

Table 3. Comparison of bronchodilator consumption, symptom scores and eNO during study period.									
	1*	2**	p	2**	3***	p	1*	3***	p
Bronchodilator consumption/day	2.5±0.8	4.9±1.26	<0.01	4.9±1.26	2.2±1.28	=0.05	2.5±0.8	2.2±1.28	NS
Day time symptom score	0.5±0.26	2.2±0.89	<0.05	2.2±0.89	0.1±0.1	NS	0.5±0.26	0.1±0.1	NS
Night time symptom score	0.6±0.22	3±2.12	<0.05	3±2.12	0±0	<0.01	0.6±0.22	0±0	0.05
eNO (ppb)	21.26±5.32	24.58±5.46	NS	24.58±5.46	17.63±7.75	NS	21.26±5.32	17.63±7.75	NS

1*: Under salmeterol therapy
2**: After ceasing salmeterol (Before montelukast therapy)
3***: After montelukast therapy

symptoms more than high doses of ICS without a deterioration in asthma (20,21).

In asthma management guidelines, two approaches are recommended to treat asthmatic patients who continue to experience symptoms on ICS: increase the dose of ICS or add a second therapeutic agent such as LABA, sustained-release theophylline or LTRA. LABA are currently the mostly recommended agents as concomitant therapy as a controller drug for asthma. But in spite of their proven effects in improving asthma symptoms and lung functions when added to ICS (22-25), their chronic usage has been shown to result in developing tolerance to their bronchoprotective effects in some reports (26-28). Their risk of masking airway inflammation was mentioned in some other studies and it was speculated that they can allow an unrecognised asthmatic exacerbation (29).

Adding theophylline to ICS is no longer commonly used as first line therapy primarily because of modest clinical benefit, a narrow therapeutic window, reports of serious adverse events and potential for drug interactions. Recent studies have suggested adding LTRA to ICS as an alternative therapeutic option in these group of patients who continue to experience symptoms on ICS (30,31).

In this study, stopping the salmeterol resulted in significant detoriation of lung functions and symptoms supporting its efficacy in add-on therapy to ICS. We cannot make a comment on how much salmeterol effected the study parameters when added to ICS. This is the disadvantage of this study as we included the patients who were on concomitant therapy with ICS and salmeterol for at least three months.

Montelukast sodium given 1 0mg once daily added to 800 mg budesonide after a two-week washout period resulted in improvement in all study parameters, but only the improvements in PEF variation, night time symptom scores and bronchodilator consumption were significant. Though pulmonary functions did not reached the levels under salmeterol therapy, the other study parameters were higher than the levels with salmeterol therapy. When comparing the study parameters under two treatment modalities, there were no significant differences between pulmonary functions, day time symptom scores and bronchodilator consumption, but night time symptom scores and PEF variation were significantly better with montelukast therapy.

There are limited studies comparing the effects of LABA and LTRA. In the studies of Exercise Study Group and Montelukast/Salmeterol Exercise Study Group, salmeterol and montelukast was compared in exercise induced bronchoconstriction for their bronchoprotective effects. Montelukast has been shown to provide significantly greater effects than salmeterol at 4 and 8 weeks in both studies. The decrease in initial effectiveness of salmeterol was assessed as a tolerance (25,32).

In the first study, comparing the effects of salmeterol and zafirlukast as add-on therapy to ICS, 80% of patients treated with salmeterol provided significantly greater improvement than the patients treated with oral zafirlukast (33). But the study period was only 4 weeks, and these results can be debatable, since tolerance to bronchoprotective effects of salmeterol is usually seen after the 4th week of treatment (28).

Exhaled nitric oxide (eNO) is introduced as a non-invasive marker of airway inflammation in the last decade. eNO has been shown to be elevated in untreated asthmatics or when asthma is out of control (34-38). Although the recent reports are discussing the eNO's place in assessing asthma specific inflammation (39,40,41), it is still advised to take into consideration eNO as a loss-of-control marker or a response marker to anti-inflammatory therapy in asthma (38).

eNO levels have been shown to fall after corticosteroid and nedocromil sodium therapies (36,37,38,42,43), and there are three recent studies about the effects of LTRA on eNO. In the first study that examined eNO levels in children during montelukast therapy, eNO levels decreased significantly (approximately by 33%) and had a trend to increase during the washout phase following montelukast therapy with no significant changes in pulmonary functions (6). It was speculated in that report that, the role of cysteinyl leukotriens in the inflammatory cell recruitment not only ultimately results in cytokine production but also in induction of NO synthase. In the study of Bisgaard et al., two weeks of treatment with 5 mg montelukast in 26 asthmatic children resulted in a decrease in eNO by 20% as compared with placebo (44). Tamoki et al. also showed that addition of pranlukast to the regimen of patients requiring high doses of ICS allowed tapering the dose of ICS by half with no increase in eNO levels, where the patients receiving placebo detoriated with a significant rise in eNO (21).

In our study eNO levels fell on average by approximately 28.2% (from 24.58 ppb to 17.63 ppb) following treatment with montelukast added to ICS on the 12th week of treatment, where the fall began on the 3rd week (Figure 1). The lack of significance in eNO fall may relate to the small number of patients studied. In our patients, the fall in eNO was not accompanied by an improvement in pulmonary functions. This finding agrees with Bratton's findings who showed no change in FEV_1 after montelukast therapy in

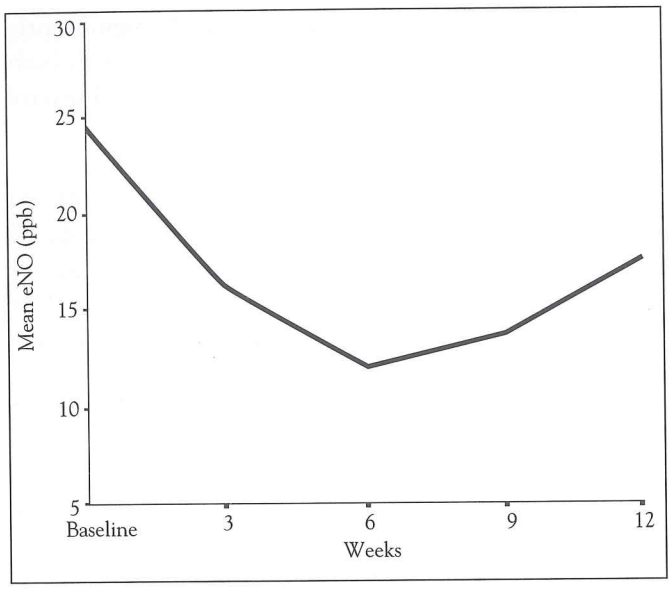

Figure 1. *The fall in eNO with addition of montelukast to ICS*

spite of a significant change in eNO levels (6). This finding was also shown with ICS by Kharitonov (42). It has been agreed that the level of eNO in determining inflammation control is not correlated with pulmonary functions.

The results of this study showed that montelukast can provide a second option in add-on therapy to ICS, as effective as LABA and even more in some disease control parameters. The addition of montelukast to ICS represents a logical option as the combination of these two agents offers different but additive anti-inflammatory effects (30). We will see a better comparison of these agents as add-on therapy to ICS in a larger group of patients in the near future, by the means of asthmatic attacks, quality of life, health care utilisation and safety in a multicentric IMPACT trial, which has began in the beginning of year 2000 with 1200 adults (30).

References

1. Global initiative for asthma (GINA). Global strategy for Asthma management and prevention. NHLBI/WHO workshop report. National Institute of Health. National heart, Lung and Blood institute. Publication No: 95-3659, January 1995.
2. Holgate ST, Bradding P, Sampson AP. Leukotriene antagonists and synthesis inhibitors: New directions in asthma therapy. J Allergy Clin Immunol 1996; 98:1-13.
3. Guidelines For the Diagnosis and Management of Asthma. Expert Panel Report II. National Institutes of Health, National Hearth, Lung and Blood Institute. 1997.
4. Barnes NC. The place of antileukotriene therapy in asthma management guidelines. Eur Respir Rev 1998; 8(60):382-386.
5. Kharitonov SA, Yates DH, Chung KF, Barnes PJ. Changes in the dose of inhaled steroid affect nitric oxide levels in asthmatic patients. Eur Respir J 1996; 9:196-201.
6. Bratton DL, Lanz MJ, Miyazawa N, White CW, Silkoff PE. Exhaled nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: A preliminary study. Pediatr Pulmonol 1999; 28:402-407.
7. Dahlen SE. Leukotriens as common mediators of airway obstruction evoked by many trigger factors in asthma. Eur Respir Rev 1998; 8(60): 369-373.
8. Lane SJ. Leukotriene antagonism in asthma and rhinitis. Respir Med 1998; 92:795-809.
9. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TBl. Montelukast, a Once-Daily Leukotriene Receptor Antagonist, in the Treatment of Chronic Asthma. Arch Intern Med 1998; 158:1213-1220.
10. Calhoun WJ. The impact of antileukotriene therapy on markers of airway inflammation. Eur Respir Rev 1998; 8(60):374-377.
11. Wenzel SE. Antileukotriene Drugs in the Management of Asthma. JAMA 1998; 280:268-269.
12. Altman LC, Munk Z, Seltzer J, Noonan N, Shingo S, Zhang J, Reiss TF. A placebo controlled, dose-ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. J Allergy Clin Immunol 1998; 102:50-56.
13. Reiss TF, Sorkness CA, Stricker W, Botto A, Busse WW, Kundu S, Zhang J. Effects of montelukast (MK-0476), a potent cysteinyl leukotriene receptor antagonist, on bronchodilation in asthmatic subjects treated with or without inhaled corticosteroids. Thorax 1997; 52: 45-48.
14. Reiss TF, Altman LC, Chervinsky P, Bewtra A, Stricker WE, Noonan GP, Kundu S, Zhang J. Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD4) receptor antagonist, in patients with chronic asthma. J Allergy Clin Immunol 1996; 98:528-534.
15. Lipworth BJ. Leukotriene-receptor antagonists. Lancet 1999; 353(9146):57-62.
16. Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, Dockhorn R, Kundu S, Zhang J, Seidenberg BC, Reiss TF. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise induced bronchoconstriction. N Engl J Med 1998; 339:147-52.
17. Reiss TF, Hill JB, Harman E, Zhang J, Tanaka WK, Bronsky E, Guerreriro D, Hendeles L. Increased urinary excretion of LTE4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. Thorax 1997; 52:1030-1035.
18. Dahlen B. Treatment of aspirin-intolerant asthma with antileukotrienes. Am J Respir Crit Care Med 1999; 161:S137-141.
19. Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TR, Seidenberg BC Knorr B. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-aold children with asthma. J Pediatr 1998; 133:424-428.
20. Löfdahl C-G, Reiss TR, Leff JA, Israel E, Noonan MJ, Finn AF, Seidenberg BC, Capizzi T, Kundu S, Godard P. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic children. BMJ 1999; 319:87-90.
21. Tamaoki J, Kondo M, Sakai N, Nakata J, Takemura H, Nagai A, Takizawa T, Konno K. Leukotriene antagonist prevents exacerbation of asthma during reduction of high-dose inhaled corticosteroid. Am j Respir Crit Care Med 1997; 155:269-273.
22. Pauwels RA, Löfdahl C-G, Postma DS, et al. Effect of inhaled formeterol and budesonide on exacerbations of asthma. N Engl J Med 1997; 337:1405-1411.
23. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344:219-224.
24. Woolcock A, Lundback B, Ringdal N, Jacques L. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996; 153:1481-1488.
25. Edelman JM, Turpin JA, Bronsky EA, Grossman J, Kemp JP, Ghannam AF, DeLucca PT, Gormley GJ, Pearlman DS. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. Ann Intern Med 2000; 132:97-104.
26. Bhagat R, Kalra S, Swystun VA, Cockcroft DW. Rapid onset of tolerance to the bronchoprotective effects of salmeterol. Chest 1995; 108: 1235-1239.

27. Cheung D, Timmers MC, Zwindermen AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting beta 2-adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. N Engl J Med 1992; 327:1198-1203.
28. Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. Respir Med 1994; 88:363-368.
29. Mclvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effect of salmeterol on airway inflammation in asthma. Am J Respir Crit Care Med 1998; 158:924-930.
30. Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening A, Haahtela T, Holgate ST, Picado C, Leff JA. Montelukast or salmeterol combined with an inhaled steroid in adult asthma: design and rationale of a randomised, double-blind comparative study (the IMPACT Investigation of Montelukast as a Partner Agent for Complementary Therapy-trial). Respir Med 2000; 94:612-621.
31. Kamada Ak, Szefler SJ. The role of theophylline in the treatment of asthma. Ann Allergy Asthma Immunol 1996; 77:1-3.
32. Villaran C, O'Neill J, Helbling A, Noord JA, Lee TH, Chuchalin AG, Langley SJ, Gunawardena KA, Suskovic S, Laurenzi M, Jasan J, Menten J, Leff JA. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. J Allergy Clin Immunol 1999; 104:547-553.
33. Busse W, Nelson H, Wolfe J, Christopher K, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. J Allergy Clin Immunol 1999; 103:1075-1080.
34. Kharitonov SA, Yates D, Robbins RA, Logan Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. Lancet 1994; 343:133-35.
35. Satouchi M, Maeda H, Yu Y, Yokoyama M. Clinical significance of the increased peak levels of exhaled nitric oxide in patients with bronchial asthma. Internal Medicine 1996; 35:270-75.
36. Barnes PJ, Kharitonov SA. Exhaled nitric oxide: a new lung function test. Thorax 1996; 51:233-37.
37. Massaro AF, Gaston B, Kita D, Fanta C, Stamler JS, Drazen JM. Expired nitric oxide levels during treatment of acute asthma. Am J Respir Crit Care Med 1995; 152:800-803.
38. Kharitonov SA. Exhaled nitric oxide and carbon monoxide in asthma. Eur Respir Rev1999; 9:68:212-18.
39. Lim S, Jatakanon A, M John, Gilbey T, Oconnor BJ, Chung KF, Barnes PJ. Effects of inhaled budesonide on lung function and airway inflammation: assessment by various inflammatory markers in mild asthma. Am J Respir Crit Care Med 1999; 159:22-30.
40. Lim S, Jatakanon A, Meah S Oates T; Chung KF; Barnes PJ. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in mild to moderately severe asthma. Thorax 2000; 55:184-88.
41. Turktas H, Oguzulgen IK, Kokturk N, Memis L. Correlation of exhaled nitric oxide levels and airway inflammation markers in stable asthmatic patients. Eur Respir J 2000; 16(S31):39s.
42. Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 1996; 153:454-57.
43. Türktaş H, Levent E, Oğuzülgen İK, Erbaş D. Effects of Inhaled Budesonid and Nedocromil Sodium on Exhaled Nitric Oxide Levels in Mild Asthmatic Patients. Gazi Medical Journal 1998; 9 (4):167-171.
44. Bisgaard H, Loland L, Anhoj J. No in exhaled air of asthmatic children is reduced by leukotriene receptor antagonist montelukast. Am J Respir Crit Care Med 1999; 160:1227-1231.