Int J Clin Exp Med 2021;14(4):1814-1820
www.ijcem.com /ISSN:1940-5901/IJCEM0125701

Original Article

Effects of montelukast combined with budesonide on lung function and exhaled nitric oxide concentration in children with mild persistent asthma

Zhichao Xie, Mingrong Chai, Weiqiang Gu, Huizhen Yuan

Department of Pediatrics, Affiliated Dongguan People's Hospital, Southern Medical University (Dongguan People's Hospital), Dongguan, Guangdong Province, China

Received November 5, 2020; Accepted November 30, 2020; Epub April 15, 2021; Published April 30, 2021

Abstract: Objective: To investigate the effects of montelukast combined with budesonide on lung function and exhaled nitric oxide concentration in children with mild persistent asthma. Methods: A total of 60 children with mild persistent asthma treated in the pediatric asthma clinic of our hospital were chosen for the study. They were randomly divided into two groups, with 30 cases treated with budesonide as the control group and 30 cases treated with montelukast combined with budesonide as the observation group. After 6 months of treatment, the clinical efficacy, exhaled nitric oxide (FeNO) concentrations, impulse oscillometer lung function (IOS), levels of inflammatory factors, and the incidences of adverse reactions were compared between the two groups before and after treatment. Results: The overall response rate of FeNO in the observation group was higher than that in the control group (93.33% vs. 73.33%, P=0.038); FeNO levels in both groups decreased after treatment compared with that before treatment (P<0.001); the decrease in FeNO level in the observation group was larger than that in the control group (P<0.01). The R5 and R20 indexes of the children in both groups decreased after the treatment compared with those before the treatment (both P<0.05); the degrees of decrease of R5 and R20 indexes of the observation group were greater than tthose of the control group (both P<0.05). After treatment, EOS, and levels of CRP and IL-4 decreased in both groups compared with those before treatment (all P<0.05); the degrees of decrease of EOS, CRP and IL-4 in the observation group were better than those in the control group (both P<0.001); there was no statistically significant difference in the incidence of adverse reactions between the two groups (P>0.05). Conclusion: Montelukast sodium combined with budesonide is effective in the treatment of children with mild persistent asthma, and can effectively reduce the levels of FeNO and inflammatory factors to improve children's lung function, and is relatively safe.

Keywords: Montelukast, budesonide, mild persistent asthma, lung function, exhaled nitric oxide

Introduction

Bronchial asthma is a heterogeneous condition characterized by inflammation and hyperresponsiveness of the airway, and its prevalence rises year by year [1]. With the prolongation of asthma, irreversible narrowing and remodeling of the airway can occur, seriously affecting physical and mental growth and child development [2]. There is no definite pathogenesis of bronchial asthma and there may be a link with the surrounding environment, allergens or immune functions [3]. A child with mild persistent bronchial asthma is characterized as a child with more than 80% of the estimated percentage of the first-second expiratory volume of exertion (FEV1 percent) and with systems lasting more than 12 hours [4]. According to the global guidelines on asthma, low-dose glucocorticoid inhalation is the recommended therapy for patients with mild persistent bronchial asthma [4]. Budesonide is a widely used therapeutic glucocorticoid that can suppress allergic substances and efficiently minimize airway smooth muscle contraction [5]. However, some children with budesonide alone have poor control of asthma symptoms [6]. Some studies have shown that while budesonide can enhance patients' inflammatory response and regulate the disease efficiently, in some patients with

chronic disease, the weak inhibitory action on leukotriene contributes to poor control of the disease [7]. Montelukast sodium can block the leukotriene reaction, and can effectively inhibit airway inflammation and has anti-allergic effects [8]. In recent years, studies have shown that the combined use of budesonide and montelukast sodium in treating mild asthma can enhance the inhibition of inflammation and can effectively control symptoms while reducing the inhaled dose of budesonide. At the same time, there are studies on the increase in the incidences of side effects of long-term use of two drugs [9, 10]. Therefore, there is also debate about the safety and effectiveness of the mixture of the two medications. Based on these contexts, the efficacy and safety of the combination of montelukast and budesonide in children with mild persistent asthma were studied in this study.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of Affiliated Dongguan People's Hospital, Southern Medical University (Dongguan People's Hospital). A total of 60 children with mild persistent asthma who attended the pediatric asthma specialist clinic from July 2018 to June 2019 were divided into two groups randomly. 30 patients in the control group were treated with budesonide and 30 patients in the observation group were treated with montelukast combined with budesonide. Patients included in this study or their family members had signed the informed consent.

Inclusion criteria

1. Patients met the diagnostic criteria for children with mild persistent asthma [11]. Patients were 3-5 years old; 2. Patients could cooperate with IOS and FeNO testing. 3. Patients were able to cooperate with follow-up visits.

Exclusion criteria

1. Individuals with bronchial stenosis or malformation; 2. Patients were unable to cooperate in the completion of IOS and FeNO testing; 3. Patients were taking drugs or foods that affect the results of FeNO testing during testing; 4. Patients with contraindication to budesonide or montelukast sodium.

Methodology

Control group was given Budesonide aerosol nasal spray (5 mL: 20 mg, 200 ug/spray, AstraZeneca Pharmaceuticals Co., Ltd., China) with 1 spray each time, twice daily for 6 months.

The observation group was given montelukast sodium (Merck Ltd., Germany) 4 mg orally on the basis of the control group treatment, once daily, and the treatment effect was evaluated after 6 months of treatment.

Outcome measures

Primary outcome measures

Clinical efficacy is divided into: clinical control, effective and ineffective. The efficacy evaluation criteria were as follows [11]. 1. Clinical control: after treatment, clinical symptoms such as wheezing, dyspnea and other clinical symptoms and pulmonary asthma sound disappeared; 2. Effective: after treatment, clinical symptoms such as wheezing, dyspnea and other clinical symptoms and pulmonary asthma sound were significantly reduced; 3. Ineffective: clinical symptoms did not improve significantly or even worsened.

FeNO concentration was measured in both groups before treatment and at 6 months of treatment. FeNO was measured offline by using the Sunvou-P100 nanocoulomb breath analyzer. The off-line method was used for the determination of FeNO in ppb and eCO in ppm. The FeNO method was in accordance with "the Series of Guidelines for Non-traumatic Inflammatory Markers of Lung Function and Airways in Children (VII): Monitoring of Exhaled Nitric Oxide [12]. The method was explained to the child before the measurement, the test was performed by inhalation through a NO-free air storage bag, and the child was required to inhale by mouth to the total lung volume without breath-holding. The child was told to perform a slow exhalation at a certain expiratory resistance. The exhaled gas entered the storage bag and was collected, after which the gas was connected to the machine for analysis and the results were recorded.

IOS measurement before and 3 months after the treatment: the German Jaeger lung function meter was used, the measurement method of IOS was in accordance with the "Children's Pulmonary Function Series Guide (III): Pulse

Table 1. Comparison of the general information of the two groups of children

Item	Observation group (n=30)	Control group (n=30)	χ^2/t	P
Age (Month)	50.4±8.4	51.4±6.2	1.243	0.202
Sex (M/F)	17/13	16/14	0.067	0.795
Duration of illness (Month)	6.2±1.3	6.3±1.5	0.301	0.765
Height (cm)	122.54±3.21	121.75±2.76	1.022	0.311
Weight (kg)	23.82±2.12	23.63±2.32	0.331	0.742

Table 2. Comparison of the efficacy of the two groups of children

Group	Clinical control	Effective	Ineffective	Total efficiency (%)
Observation group (n=30)	21 (70.00)	7 (23.33)	2 (6.67)	28 (93.33)
Control group (n=30)	12 (40.00)	10 (33.33)	8 (26.67)	22 (73.33)
χ^2		6.584		4.320
P		0.037		0.038

oscillation", the child was told to breathe calmly and tidally, the operator then pressed the cheeks of the child lightly with both hands until the breathing curve on the volumetric time chart was stable [13]. The measurement was taken 3-5 times, and the time for each measurement was not less than 30 seconds. Total respiratory resistance (R5) and central respiratory resistance (R20) were recorded.

Secondary outcome measurement

One tube of venous blood (5 mL) was taken before treatment at the time of admission to the hospital, and 1 tube of venous blood 5 mL was taken 14 days after treatment at 8:00 a.m. The eosinophil (EOS) count, serum C-reactive protein (CRP) level and interleukin-4 (IL-4) level from each patient were examined.

Adverse reactions: the occurrence of adverse reactions during the patient's treatment was recorded, including gastrointestinal reactions, rash, hoarseness, etc.

Statistical methods

SPSS 22.0 statistical software was used, continuous variables were represented as mean ± standard deviation ($\bar{x}$ ± sd), and the Shapiro-Wilk test was used for testing normality. T-test was used for data conforming to normal distribution and homogeneity of variance, and independent samples t-test was used for between-group comparisons. Paired samples t-test was used for comparisons within groups. Enumeration data were tested by Pearson's χ^2 test and expressed as χ^2. P<0.05 was considered statistically significant.

Results

Comparison of the general information of the two groups of children

There was no difference in general information between the two groups of children (P>0.05) as shown in **Table 1**.

Comparison of clinical efficacy between the two groups of children

The total effective rate of FeNO in the observation group was higher than that in the control group (93.33% vs. 73.33%), and the difference was statistically significant (P<0.05), as shown in **Table 2**.

Comparison of FeNO levels in two groups of children before and after treatment

There was no significant difference in FeNO levels between the two groups of children before the treatment (P>0.05). After the treatment, there was a significant decrease in FeNO levels between the two groups of children compared with that before treatment (P<0.001). The degree of decrease of FeNO level in the observation group was better than that in the control group (P<0.01). See **Table 3**.

Comparison of lung function between the two groups of children before and after treatment

There was no significant difference between the R5 and R20 indexes of the two groups of children before treatment (P>0.05), but there was a significant difference between the R5 and R20 indexes of the two groups of children after treatment (P<0.05). The degrees of the decline of R5 and R20 indicators in the observation group was better than those in the control group (P<0.05). See **Table 4**.

Table 3. Comparison of FeNO levels in two groups of children before and after treatment

Item	Observation group	Control group	t	P	Observation group	Control group	t	P
	Before treatment				After treatment			
FeNO (ppb)	19.12±5.34	19.21±5.13	0.067	0.947	8.82±2.43###	11.11±3.65###	2.861	0.006

Note: Compared with before treatment within the same group, ###P<0.001.

Table 4. Comparison of lung function between the two groups of children before and after treatment

Item	Observation group	Control group	t	P	Observation Group	Control group	t	P
	Before treatment				After treatment			
R5	101.95±31.14	100.23±30.23	0.217	0.829	87.03±17.62###	97.23±21.72#	2.010	0.049
R20	91.28±24.26	91.82±24.92	0.085	0.933	74.85±18.75###	83.34±18.78###	2.011	0.049

Note: Compared with before treatment within the same group, #P<0.05; compared with before treatment within the same group, ###P<0.001. R5: Total respiratory resistance; R20: central respiratory resistance.

Table 5. Comparison of inflammatory factors between the two groups of children before and after treatment

Item	Observation group	Control group	t	P	Observation group	Control group	t	P
	Before treatment				After treatment			
EOS (×10^9/L)	0.52±0.16	0.51±0.15	0.250	0.834	0.14±0.09###	0.31±0.13#	5.889	<0.001
CRP (mg/L)	34.23±5.12	35.92±5.76	1.201	0.235	6.23±2.38###	14.34±4.45###	8.802	<0.001
IL-4 (μg/L)	29.34±3.76	30.23±3.99	0.889	0.378	8.53±1.34###	12.76±1.43###	11.821	<0.001

Note: Compared with before treatment within the same group, #P<0.05; compared with before treatment within the same group, ###P<0.001. EOS: eosinophil; CRP: serum C-reactive protein; IL-4: interleukin-4.

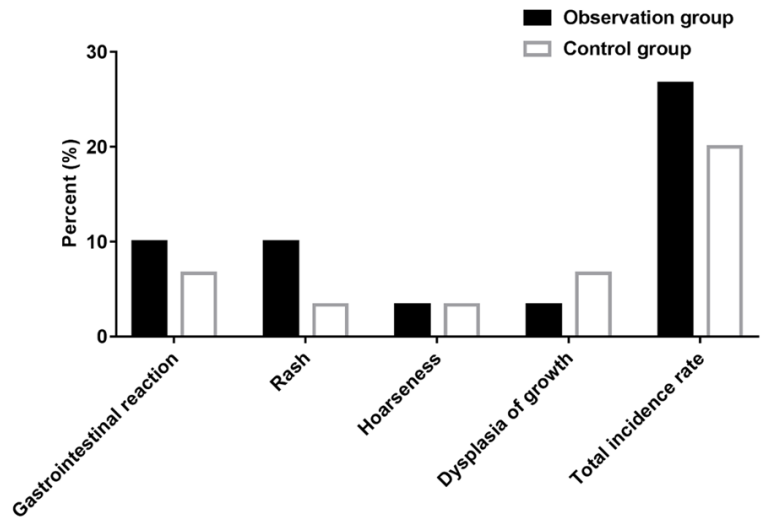

Figure 1. Comparison of the adverse effect of the two groups.

Comparison of inflammatory factors between the two groups of children before and after treatment

There was no significant difference in the indexes of EOS, CRP and IL-4 between the two groups of children before treatment (P>0.05). After treatment, the EOS, CRP and IL-4 of the two groups of children decreased compared with those before treatment (P<0.05). The decrease of EOS, CRP and IL-4 in the observation group is better than that of the control group (P<0.001). See **Table 5**.

Comparison of adverse effects in two groups of children

There was no statistically significant difference between the two groups of children in adverse effects (P>0.05) as shown in **Figure 1**.

Discussion

The worldwide incidence of moderate asthma can hit 50-75 percent [14]. The treatment of mild persistent asthma is largely by inhaled corticosteroids. The clinical application of the glucocorticoid drug budesonide to regulate asthma symptoms is recognized by clinicians and has the characteristics of high affinity, rapid

onset and low side effects. It can inhibit inflammatory mediators and have an anti-inflammatory effect [15]. Angiotensin II expression may be increased and blood vessels may dilate, but some children have been shown to have poor symptom control during the use of budesonide, especially in children with chronic asthma [5]. Studies have shown that leukotriene is a pro-inflammatory factor and plays an important role in the pathogenesis of asthma, while budesonide has a weak inhibitory effect on leukotrienes [5]. Montelukast sodium inhibits the action of leukotrienes. Thus the combined application of budesonide and montelukast sodium has a major impact and can effectively regulate the onset of asthma [16]. This analysis also indicates that in the care of children with moderate chronic asthma, the use of montelukast sodium combined with budesonide is more successful than using budesonide alone, which is consistent with the above research findings.

A previous study found that asthma attacks are directly associated with airway inflammation. Airway epithelial cells are stimulated by inflammatory cells to overexpress inducible nitric oxide synthase (iNOS) when inflammation of the airway occurs, which makes the concentration of nitric oxide in the airway abnormally elevated. A number of inflammatory conditions in the airway can lead to elevated NO but eosinophilic inflammation predominates. A research by some scholars on children with asthma in Vietnam has shown that FeNO can be used as a means to monitor asthma control [17]. Chris et al. have found that FeNO has greater sensitivity and precision than conventional approaches in the detection of asthma in pre-school children [18]. A research conducted by Javier et al. has shown that the abnormality of FeNO is associated with many factors, not only an increase in patients with asthma, but also in patients with allergic diseases such as allergic rhinitis compared to patients without allergic diseases [19]. Studies have also shown that asthmatic children frequently have allergic inflammation of the airways, such as allergic rhinitis, resulting in elevated amounts of FeNO [20]. This research found that in the treatment of moderate chronic asthma, the expression of FeNO in children with montelukast combined with budesonide was lower than that in the budesonide-treated patients alone, indicating that the combined use of the two medications is effective for disease control. FeNO is used to measure inflammation of the airway, while lung function is an important method of measuring the function of the airway and determining illness in children with asthma. One is a microscopic inflammation index and the other is a macroscopic ventilation index. Much interest has been drawn to the interaction between the two. A study by Liu et al. has found that FeNO has greater sensitivity and accuracy in the diagnosis of small airway dysfunction in conjunction with IOS analysis and can better determine the small airway function of the patient [21]. Studies by Zeng and others have shown that FeNO may reflect airway eosinophil inflammatory regulation in children with pre-school asthma, but it can not reflect airway hyperresponsiveness. Therefore, to judge asthma management more correctly, FeNO needs to be paired with IOS testing [22]. This research also indicates that the use of the two medications in children with moderate chronic persistence will successfully enhance lung function. It may be linked to the mixture of the two medications, which may efficiently decrease the inflammation of the airways and improve the inhibitory activity of the proinflammatory factors of leukotriene.

Previous studies have shown that the released and activated EOS can accumulate in the airway, and the activated EOS can secrete a variety of inflammatory mediators, leading to aggravation of the body's inflammatory response, causing bronchial smooth muscle contraction and airway mucosal edema, thus inducing asthma attacks. Serum CRP is an important indicator of clinical response to body inflammation and immune response and has a prompting effect on the severity of the disease. IL-4 is another inflammatory mediator; its high-expression can promote the proliferation of T cells and B cells and the secretion of IgE by B cells. IgE can further induce EOS to secrete basic protein to act on the airway and aggravate airway inflammation [23-25]. In this study, the inflammatory factors EOS, CRP and IL-4 were measured. It also showed that the combined use of the two drugs can effectively improve the inflammation state of the body, which is related to the above-mentioned mechanism.

This research also found that the risks of long-term use of the two drugs did not rise, indicating that the combined use of the two drugs has increased effectiveness and safety. Previous experiments have shown that budesonide can have a degree of inhibitory impact on the height of children [26]. Another study showed that long-term treatment with low-dose or medium-dose budesonide in children with mild persistent asthma was not associated with a decrease in height before puberty [10].

This research still has certain shortcomings. For example, this study is a single-center study. In the future, a multi-center large-sample randomized controlled study can be conducted to verify our results. In this study, the follow-up time is short and the sample size included is small, further studies can increase the sample size and prolong the follow-up time.

In short, montelukast sodium and budesonide in combination are both safe and effective in the care of children with moderate chronic asthma. It can reduce FeNO levels and inflammatory factors effectively, thereby enhancing children's lung function.

Acknowledgements

This work was supported by The Key Projects of Dongguan City Social Science and Technology Development Plan for *Clinical study of exhaled nitric oxide, carbon monoxide and lung function in different periods of childhood asthma* (2018507150011654).

Disclosure of conflict of interest

None.

Address correspondence to: Huizhen Yuan, Department of Pediatrics, Affiliated Dongguan People's Hospital, Southern Medical University (Dongguan People's Hospital), No. 3 South Wandao Road, Xinguyong, Wanjiang District, Dongguan 523059, Guangdong Province, China. Tel: +86-0769-28637205; E-mail: yuanhuizhen54yh@163.com

References

[1] Panettieri RA Jr, Wang M, Braddock M, Bowen K and Colice G. Tralokinumab for the treatment of severe, uncontrolled asthma: the ATMOSPHERE clinical development program. Immunotherapy 2018; 10: 473-490.

[2] Alherbish M, Mobaireek KF and Alangari AA. Admission predictability of children with acute asthma. Ann Thorac Med 2018; 13: 36-41.

[3] Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, Lugogo N, Wenzel S, Chinchilli VM, Mauger DT, Dyer AM, Boushey HA, Fahy JV, Woodruff PG, Bacharier LB, Cabana MD, Cardet JC, Castro M, Chmiel J, Denlinger L, DiMango E, Fitzpatrick AM, Gentile D, Hastie A, Holguin F, Israel E, Jackson D, Kraft M, LaForce C, Lemanske RF Jr, Martinez FD, Moore W, Morgan WJ, Moy JN, Myers R, Peters SP, Phipatanakul W, Pongracic JA, Que L, Ross K, Smith L, Szefler SJ, Wechsler ME and Sorkness CA. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. N Engl J Med 2019; 380: 2009-2019.

[4] Farkowski MM, Maciag A, Zurawska M, Kowalik I, Szwed H and Pytkowski M. Clinical effectiveness and safety of antazoline-based therapy in patients with stable coronary artery disease undergoing pharmacological cardioversion of short-duration atrial fibrillation in the emergency department. Cardiovasc Ther 2018; 36: e12469.

[5] Saito M, Kikuchi Y, Kawarai Lefor A and Hoshina M. High-dose nebulized budesonide is effective for mild asthma exacerbations in children under 3 years of age. Eur Ann Allergy Clin Immunol 2017; 49: 22-27.

[6] Razi CH, Cörüt N and Andıran N. Budesonide reduces hospital admission rates in preschool children with acute wheezing. Pediatr Pulmonol 2017; 52: 720-728.

[7] Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, Fjallbrant H, Jorup C and Martin UJ. Serious asthma events with budesonide plus formoterol vs. budesonide alone. N Engl J Med 2016; 375: 850-860.

[8] O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S and Reddel HK. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018; 378: 1865-1876.

[9] Kim CK, Callaway Z, Park JS, Nishimori H, Ogino T, Nagao M and Fujisawa T. Montelukast reduces serum levels of eosinophil-derived neurotoxin in preschool asthma. Allergy Asthma Immunol Res 2018; 10: 686-697.

[10] Hatziagorou E, Kouroukli E, Avramidou V, Papagianni M, Papanikolaou D, Terzi D, Karailidou M, Kirvassilis F, Panagiotakos D and Tsanakas J. A "Real-Life" study on height in prepubertal asthmatic children receiving inhaled steroids. J Asthma 2018; 55: 437-442.

[11] Jean T, Yang SJ, Crawford WW, Takahashi SH and Sheikh J. Development of a pediatric asthma predictive index for hospitalization. Ann Allergy Asthma Immunol 2019; 122: 283-288.

[12] Editorial Committee of the Chinese Journal of Practical Pediatrics, Pulmonary Function Collaboration Group and Pediatrics Branch of Chinese Medical Association. Guidelines for Children's Pulmonary Function and Airway Non-traumatic Inflammation Index (7): Exhaled Nitric Oxide Monitoring (2017 Edition). Chin J Apply Clin Pediatr 2017; 32: 1622-1627.
[13] Editorial Committee of the Chinese Journal of Practical Pediatrics, Pulmonary Function Collaboration Group, Pediatrics Branch of the Chinese Medical Association. Guidelines for Children's Pulmonary Function (3): Impulse Oscillation (2016 Edition). Chin J Apply Clin Pediatr 2016; 31: 821-825.
[14] Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE and Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008; 31: 143-178.
[15] Podlecka D, Malewska-Kaczmarek K, Jerzyńska J, Stelmach W and Stelmach I. Secondhand smoke exposure increased the need for inhaled corticosteroids in children with asthma. Ann Allergy Asthma Immunol 2018; 121: 119-121.
[16] Trinh HKT, Nguyen TVT, Choi Y, Park HS and Shin YS. The synergistic effects of clopidogrel with montelukast may be beneficial for asthma treatment. J Cell Mol Med 2019; 23: 3441-3450.
[17] Nguyen-Thi-Bich H, Duong-Thi-Ly H, Thom VT, Pham-Thi-Hong N, Dinh LD, Le-Thi-Minh H, Craig TJ and Duong-Quy S. Study of the correlations between fractional exhaled nitric oxide in exhaled breath and atopic status, blood eosinophils, FCER2 mutation, and asthma control in vietnamese children. J Asthma Allergy 2016; 9: 163-170.
[18] Kuo CR, Spears M, Haughney J, Smith A, Miller J, Bradshaw T, Murray L, Williamson P and Lipworth B. Scottish consensus statement on the role of feno in adult asthma. Respir Med 2019; 155: 54-57.
[19] Mallol J, Riquelme C, Aguirre V, Martínez M, Gallardo A, Sánchez C and Córdova P. Value of bronchial reversibility to salbutamol, exhaled nitric oxide and responsiveness to methacholine to corroborate the diagnosis of asthma in children. Allergol Immunopathol (Madr) 2020; 48: 214-222.
[20] Wolthers OD. Budesonide + formoterol fumarate dihydrate for the treatment of asthma. Expert Opin Pharmacother 2016; 17: 1023-1030.
[21] Liu L, Liu W, Liu C, Wang D, Zhao J, Wang J, Wu J, Liu T, Zhang Y, Liu Y, Cao L and Dong L. Study on small airway function in asthmatics with fractional exhaled nitric oxide and impulse oscillometry. Clin Respir J 2018; 12: 483-490.
[22] Zeng J, Hu Q, Zhong SM, Fan WT, Wu XT and Liao W. Study on the correlation between exhaled nitric oxide and airway hyperresponsiveness and asthma control in preschool children. Chongqing Med 2017; 46: 3529-3531.
[23] Rafeeq MM and Murad H. Evaluation of drug utilization pattern for patients of bronchial asthma in a government hospital of saudi arabia. Niger J Clin Pract 2017; 20: 1098-1105.
[24] Swiatkiewicz I and Taub PR. The usefulness of C-reactive protein for the prediction of post-infarct left ventricular systolic dysfunction and heart failure. Kardiol Pol 2018; 76: 821-829.
[25] Kansal P, Nandan D, Agarwal S, Patharia N and Arya N. Correlation of induced sputum eosinophil levels with clinical parameters in mild and moderate persistent asthma in children aged 7-18 years. J Asthma 2018; 55: 385-390.
[26] Maas BM, Wang J, Cooner F, Green D, Yuan Y, Yao L and Burckart GJ. Bone mineral density to assess pediatric bone health in drug development. Ther Innov Regul Sci 2017; 51: 756-760.