Efficacy of treatment with montelukast, fluticasone propionate and budesonide liquid suspension for the prevention of recurrent asthma paroxysms in children with wheezing disorders

BO DING, YANMING LU, YAQIN LI, WENJING ZHOU and FENG QIN

Department of Pediatrics, The Southern Division of Renji Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai 201112, P.R. China

Received July 1, 2019; Accepted August 6, 2019

DOI: 10.3892/etm.2019.7894

Abstract. One-third of the children who suffer from first-time wheezing are estimated to experience recurrences; however, no standard therapeutic strategy with which to prevent these recurrences currently exists. A few studies have compared the three drugs commonly used for the treatment of persistent asthma in children to identify the most effective one for preventing recurrent wheezing. In this study, in an aim to determine the most effective of these drugs, we recruited patients <5 years of age with recurrent wheezing at our hospital, and assigned them randomly to either the oral montelukast [leukotriene receptor antagonist (LTRA)], the inhaled fluticasone propionate (FP), or the inhaled budesonide suspension (BUD) groups for 12-week treatments. We then determined the treatment efficacy (symptomatic improvement) by recording the number of wheezing episodes and emergency visits, the daily treatment cost, the mean accumulated down time and the patient compliance; we then compared the results among the groups. All treatments were found to be equally effective. The daily cost of inhaled FP was lower than that of oral LTRA and inhaled BUD (P<0.00001). The difference in the mean accumulated down time between these groups was not significant (P=0.132). The adherence (patient compliance) to LTRA was significantly higher than the adherence to inhaled corticosteroids (ICS) (P<0.017). On the whole, the findings of this study indicated that all three treatments prevented recurrent wheezing in our pediatric population. FP was found to be more convenient, to require fewer doses, and that it could be easily adjusted. Patient adherence/compliance to treatment was significantly better with LTRA than with ICS.

Correspondence to: Dr Yanming Lu, Department of Pediatrics, The Southern Division of Renji Hospital Affiliated to Shanghai JiaoTong University School of Medicine, 2000 Jiangyue Road, Minhang, Shanghai 201112, P.R. China
E-mail: luyanming1973@aliyun.com

Key words: wheezing, children <5 years of age, montelukast, fluticasone propionate, budesonide suspension liquid

Introduction

Wheezing is one of the most common symptoms of lower respiratory infections among children (1). A bronchiolitis infection is usually the cause of the first wheezing episode. Moreover, recurrent wheezing typically emerges after children have recovered from bronchiolitis, and in some cases, this eventually develops into asthma (2,3). The administration of both oral montelukast [leukotriene receptor antagonist (LTRA)] and inhaled corticosteroids (ICS) are the most common forms of maintenance therapy for children with asthmatic diseases. However, no standard therapy currently exists for the prevention of recurrent wheezing in children following a first episode. Thus, the aim of this study was to compare the efficacy of therapies based on oral montelukast, fluticasone propionate (FP), or budesonide suspension liquid (BUD) in children <5 years of age suffering from wheezing.

Materials and methods

Patients and study design. In this study, we enrolled both out- and in-patients admitted for capillary bronchitis, asthmatic bronchitis, or asthmatic bronchial pneumonia at the Southern Division of Renji Hospital from September, 2009 to November, 2012. We screened 314 continuous patients (210 boys and 104 girls with an average age of 30.1±9.89 months) out of which 239 patients (159 boys and 80 girls) were included based on the guardians' informed written consent. Once in the remission period, we randomly assigned eligible patients to one of the following groups: i) The oral Montelukast group (LTRA; group A, including 54 boys and 26 girls; average age, 29.59±12.04 months); ii) the inhaled FP group (group B; 54 boys and 28 girls; average age, 30.26±7.60 months); and iii) the inhaled BUD group (group C; 51 boys and 26 girls; average age, 30.03±9.34 months). The diagnoses of all the children was based on the criteria in the Zhu Fu-tang Practice of Pediatrics (4). Patients >5 years of age were excluded. In addition, patients with congenital malformations of the respiratory tract, those with a bronchial foreign body and those with bronchial pulmonary dysplasia (BPD) were also excluded. The Ethics Committee of Renji Hospital, Shanghai JiaoTong University School of Medicine approved this study (Approval

no. SHDC12014905), which was conducted following the tenets of the Declaration of Helsinki.

Treatment and patient grouping. All eligible patients were treated with antibiotics, inhaled oxygen and aerosol inhalation during the acute stages. During the remission phase, we administered oral montelukast, 4 mg once daily (Merck Sharp & Dohme, approval no. J20140167) to the patients in group A; inhaled FP 100 μg twice daily (Glaxo Smith Kline, approval no. H20010387) to those in group B; and inhaled budesonide suspension liquid, 500 μg, twice daily (AstraZeneca, approval no. H20140475) to those in group C, and symptomatic therapy as appropriate. All the therapeutic sessions lasted for a period of 12 weeks, and all the children were subsequently followed-up over a 1-year observation period.

Evaluation indicators. We assessed the treatment efficacy (symptomatic relief) and the number of emergency department visits, the daily cost of treatment, the patient compliance, and the mean accumulated down time per group and compared the results among the groups.

Statistical analysis. We used the SPSS 19.0 software (Version 19.0; IBM, Inc.) for statistical analyses. Continuous data are expressed as the means ± standard deviation (SD), and differences among groups were compared using one-way Analysis of Variance (ANOVA) followed by Tukey's honestly significant difference test (HSD). Categorical data were analyzed using the Chi-squared test. P-values <0.05 were considered to indicate statistically significant differences.

Results

General patient information. No statistically significant differences were found in terms of age, sex, or the history of allergies between the 3 groups (P=0.9; Table I).

Comparison of the treatment efficacy between the 3 patient groups. Values for variables of treatment efficacy (symptomatic relief, number of emergency visits) the mean daily cost of treatment, the patient compliance, and the mean accumulated down time for each of the treatment groups were calculated over the period of 1 year and the values were compared (Table II). Groups A, B and C all displayed similar treatment efficacies. The daily cost of treatment for group B was lower than that for the other 2 treatment groups (groups A and C) (P<0.00001). Patients in Group A complied better with the treatment than patients in groups B and C (P=0.017). In addition, no significant differences were found between the 3 groups as regards the accumulated down time (number of days parents missed work).

Discussion

Previous studies have indicated that one-third of infants who develop wheezing for the first time experience recurrences and consequently develop asthma (3,5). Moreover, repeated episodes of wheezing can severely affect children's physical and mental health, increase mental stress, and impose a significant economic burden (6,7). Thus, an appropriate therapeutic agent is important for controlling symptoms, improving pulmonary function and modifying the natural progression of childhood asthma. As a result, the identification of a suitable therapeutic strategy has become a common concern for medical professionals and parents.

The infant respiratory tract exhibits a unique immature structure, incomplete airway function and an abundance of mucosal surfaces (8). Lower respiratory tract infections (viral infections) can lead to small airway epithelium damage, the release of inflammatory mediators, activation in response to cytokines and a Th1/Th2 imbalance, which further induces chronic airway inflammation and leads to recurrent wheezing (3,8-11).

Eosinophils are a major source of cysteinyl leukotrienes (CysLTs). In addition, the synthesis of leukotrienes is significantly increased in response to airway epithelial inflammation or injury (12). CysLTs can attract and activate eosinophils due to the expression of cysteinyl leukotriene receptors (CysLTs1R and CysLTs2R) on eosinophils (13,14). Moreover, CysLTs can induce airway smooth muscle contraction, increase vascular permeability, and stimulate mucus secretion during acute asthmatic attacks. CysLTs have also been shown to be important inflammatory mediators for asthma (12,14). Studies have shown the critical role that CysLTs play causing chronic bronchial inflammation and airway hyperreactivity, as well as inducing airway remodelling by promoting airway smooth muscle hyperplasia and subepithelial fibrosis with collagen deposition (14,15). Highly selective and competitive CycLT receptor antagonists have been shown to alleviate chronic airway inflammation (15). Leukotriene modifiers are another treatment option in cases of persistent asthma (16), they have a good taste, are convenient to use, and are generally well-tolerated with favorable clinical curative effects in children with wheezing. However, leukotriene antagonists can suppress only one inflammatory mediator and result in relatively weak anti-inflammatory activity when compared with ICSs.

ICS display a non-specific anti-inflammatory effect and are considered the first-line treatment for long-term control of persistent asthma in children according to the Global Initiative for Asthma (GINA) guidelines (https://ginasthma.org). Moreover, ICS have a high topical potency and few systemic side-effects (17), as they act directly on the airway mucosa exerting a rapid anti-inflammatory effect (17). In addition, treatment with ICS promotes a local anti-inflammatory effect by increasing lipophilicity and enhancing the affinity for the glucocorticoid receptor in the lungs (18,19). Topical corticosteroids are thought to upregulate membrane β2-adrenoceptors, preventing their downregulation and uncoupling in response to β2-agonists, which can reduce the incidence of drug resistance (17,18). Moreover, corticosteroids can inhibit the production of a number of pro-inflammatory cytokines and the function of phagocytic cells, while modulating the Th1/Th2 imbalance in asthma and inhibiting gland secretion (10,17,20). In addition to improving lung function and reducing airway inflammation, ICS are highly effective for decreasing bronchial responsiveness, asthma symptoms, asthma-related exacerbations, hospitalizations and even death (10,18).

FP and BUD have been associated with effective clinical results and are the most commonly used ICS. A meta-analysis published by Castro-Rodriguez and Rodrigo on the efficacy

Table I. Comparison of the general conditions between the 3 patient groups.

Group	Patients	Age (months, means ± SD)	Allergic constitution	Sex (male:female)
Oral montelukast (Group A)	80	29.59±12.04	30	2.08:1
Inhaled fluticasone propionate (Group B)	82	30.26±7.60	28	1.93:1
Inhaled budesonide (Group C)	77	30.03±9.34	28	1.96:1
Statistical analysis[a]		P=0.9	P=0.9	P=0.9

SD, standard deviation. [a]Analysis by one-way ANOVA (for continuous variables; means ± SD) and the Chi-squared test (for nominal data).

Table II. Comparison of treatment efficacy between the three patient groups.

				Statistical analysis[a]	
Variable/group	Oral montelukast (Group A) (n=80)	Inhaled fluticasone propionate (Group B) (n=82)	Inhaled budesonide (Group C) (n=77)	Overall	Post-hoc test P-value
Duration of breathing (days)	1.66±2.36	0.95±1.87	0.92±1.91	P=0.038 F=3.29	0.074[c] 0.064[d] 0.994[e]
Number of inhalations (time)	0.80±1.07	0.47±0.90	0.45±0.86	P=0.034 F=3.42	0.070[c] 0.056[d] 0.990[e]
Number of emergency visits	0.41±0.83	0.18±0.47	0.18±0.6	P=0.037 F=3.33	0.064[c] 0.070[d] 0.994[e]
Daily cost of treatment (yuan)	2.11±0.53	1.18±0.55	4.24±0.68	P<0.00001 F=559.52	<0.00001[c] <0.00001[d] <0.00001[e]
Patient compliance (percentage, %)	87.9%	73.2%	70.0%		0.017[b]
Accumulated down time (days)	0.91±1.38	0.59±1.35	0.52±1.14	P=0.132 F=2.03	0.260[c] 0.145[d] 0.938[e]

All data, apart from those for patient compliance (which are presented as percentages), are presented as the mean ± standard deviation. [a]Analysis by one-way ANOVA (for continuous variables; means ± SD) followed by Tukey's honestly significant difference test and the [b]Chi-squared test (for nominal data). [c]Group A vs. group B, [d]Group A vs. group C, and [e]Group B vs. group C.

of ICS in preschoolers suffering from wheezing demonstrated that ICS decrease the frequency of acute episodes of asthma (21). The potency of corticosteroids has been measured I in terms of binding affinity to glucocorticoid receptors in lung tissues and the ability to induce cutaneous vasoconstriction (18). FP exhibits marked anti-inflammatory activity, and is currently considered the most potent ICS for the airways (18). FP is twice as potent, in terms of binding affinity and as a cutaneous vasoconstrictor, than budesonide. The percentage of the drug that is systemically available following oral administration has been estimated to be <1% for FP and 11% for BUD (22). Moreover, the use of storage tanks may reduce oropharyngeal irritation. Infants and young children represent a unique subpopulation with significant challenges for drug transportation due to various anatomic, physiological and emotional factors. The infant pharynx is close to the root of the tongue and the epiglottis, which is narrow and collapses easily compared with that of adults. Moreover, infants cry loudly and cannot hold their breath, which leads to substantial reductions in the amount of inhaled medication deposited in the lungs compared to those in individuals who are able to hold their breath (23). BUD is a second-generation corticosteroid that may be easier to administer to infants and toddlers, as it requires no active cooperation; therefore, it is suitable for children of any age. BUD is rapidly-acting (within seconds or minutes), likely due to membrane-bound glucocorticoid receptors and a direct interaction with the airways and vasculature by non-genomic mechanisms (17). Moreover, the addition of a short-acting β2-agonist to a jet-nebulized budesonide suspension can provide rapid relief to patients with symptoms of acute asthma attack (17). However, the cost associated with the use of BUD is high, since it requires administration via

spray inhalation powered by oxygen in hospitals or through an air compressor pump at home. Consistent with the results published in the study by Lan *et al* (24), FP treatment in this study had a lower daily cost than the cost of the inhaled BUD.

Asthma is a chronic inflammatory disease that requires long-term anti-inflammatory treatment to achieve disease control. Although effective therapies are described in GINA, a large proportion of children with asthma do not achieve ideal symptom control (25). Since compliance is the only vital factor associated with the level of asthma control (25), non-adherence to the prescribed daily treatment (parituclarly with ICS) leads to uncontrolled episodes of asthma (26). Such effects are closely related to the inadequate suppression of airway inflammation. Studies have demonstrated that the adherence/compliance to controller therapy ranges between 30 and 80%, and that medication adherence may decrease over time (25,27,28). Multiple factors lead to issues associated with adherence, including the lack of knowledge of the disease, periods of symptom remission, the need to use multiple (often inhaled) medications, forgetting to take medications, and a 'steroid phobia' (29). The findings of this study indicated that the adherence to LTRA was significantly higher than that to ICS.

In reviewing the results of other studies, we found that comparisons between two medications in infants are common (24,30,31); however, to date, at least to the best of our knowledge, there are no studies available comparing three drugs for the treatment of children with persistent asthma. Therefore, in this study, we compared the efficacy of montelukast with that of ICS (inhaled FP or inhaled BUD) in children <5 years of age. We found that all three treatments effectively prevented recurrent wheezing in this pediatric patient group. However, treatment with fluticasone seems to have the advantage of being more convenient. In addition, patient adherence to treatment was significantly better with LTRA than with ICS. These findings highlight the importance of prevention measures and the treatment options available for asthma paroxysms in children who have recovered from wheezing disorders.

However, we are aware of the limitations associated with this study. In particular, the follow-up period was somewhat brief and the sample sizes were relatively small. Therefore, other studies are warranted to examine the association between asthma prevention and treatment after wheezing with longer follow-up times and larger sample sizes. On the whole however, this study demonstrates that all three tested treatments had a similar efficacy, although patient adherence/compliance to treatment was significantly better with LTRA than with ICS.

Acknowledgements

Not applicable.

Funding

The study was supported by the Fund of Shanghai Hospital Development Center (SHDC12014905).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

BD and YLu conceived and designed the study, provided study materials or patients. BD, YLu, YLi, WZ and FQ were responsible for the collection and assembly of the data, data analysis and interpretation. BD was involved in the writing of the manuscript. YLu was involved in the editing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of Renji Hospital, Shanghai Jiaotong University School of Medicine approved this study (approval no. SHDC12014905)

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Brand PLP, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, Henderson J, Kuehni CE, Merkus PJ, Pedersen S, *et al*: Classification and pharmacological treatment of preschool wheezing: Changes since 2008. Eur Respir J 43: 1172-1177, 2014.
2. Ducharme FM, Dell SD, Radhakrishnan D, Grad RM, Watson WT, Yang CL and Zelman M: Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. Can Respir J 22: 135-143, 2015.
3. Beigelman A and Bacharier LB: Infection-induced wheezing in young children. J Allergy Clin Immunol 133: 603-604, 2014.
4. Hu YM, Jiang ZF, Shen K and Shen Y: Zhu Fu-Tang Textbook of Paediatrics. 8th edition. People's Medical Publishing, Beijing, 2012.
5. El-Gamal YM and El-Sayed SS: Wheezing in infancy. World Allergy Organ J 4: 85-90, 2011.
6. Ferrante G and La Grutta S: The Burden of Pediatric Asthma. Front Pediatr 6: 186, 2018.
7. Rodríguez-Martínez CE, Sossa-Briceño MP and Castro-Rodriguez JA: Factors predicting persistence of early wheezing through childhood and adolescence: A systematic review of the literature. J Asthma Allergy 10: 83-98, 2017.
8. Rossi GA and Colin AA: Infantile respiratory syncytial virus and human rhinovirus infections: Respective role in inception and persistence of wheezing. Eur Respir J 45: 774-789, 2015.
9. Wu YF, Su MW, Chiang BL, Yang YH, Tsai CH and Lee YL: A simple prediction tool for inhaled corticosteroid response in asthmatic children. BMC Pulm Med 17: 176, 2017.
10. Ye Q, He XO and D'Urzo A: A Review on the Safety and Efficacy of Inhaled Corticosteroids in the Management of Asthma. Pulm Ther 3: 1-18, 2017.
11. Turunen R, Koistinen A, Vuorinen T, Arku B, Söderlund-Venermo M, Ruuskanen O and Jartti T: The first wheezing episode: Respiratory virus etiology, atopic characteristics, and illness severity. Pediatr Allergy Immunol 25: 796-803, 2014.
12. Piedimonte G, Renzetti G, Auais A, Di Marco A, Tripodi S, Colistro F, Villani A, Di Ciommo V and Cutrera R: Leukotriene synthesis during respiratory syncytial virus bronchiolitis: Influence of age and atopy. Pediatr Pulmonol 40: 285-291, 2005.
13. Wang X, Zhou J, Zhao X and Yi X: Montelukast Treatment of Acute Asthma Exacerbations in Children Aged 2 to 5 Years: A Randomized, Double-Blind, Placebo-Controlled Trial. Pediatr Emerg Care 34: 160-164, 2018.
14. Hosoki K, Kainuma K, Toda M, Harada E, Chelakkot-Govindalayathila AL, Roeen Z, Nagao M, D'Alessandro-Gabazza CN, Fujisawa T and Gabazza EC: Montelukast suppresses epithelial to mesenchymal transition of bronchial epithelial cells induced by eosinophils. Biochem Biophys Res Commun 449: 351-356, 2014.

15. Park JS, Jang AS, Park SW, Lee YM, Uh ST, Kim YH, Cha JY, Park SM and Park CS: Protection of leukotriene receptor antagonist against aspirin-induced bronchospasm in asthmatics. Allergy Asthma Immunol Res 2: 48-54, 2010.
16. Ernst P and Ernst G: Neuropsychiatric adverse effects of montelukast in children. Eur Respir J 50: 50, 2017.
17. Hossny E, Rosario N, Lee BW, Singh M, El-Ghoneimy D, Soh JY and Le Souef P: The use of inhaled corticosteroids in pediatric asthma: Update. World Allergy Organ J 9: 26, 2016.
18. Chung KF, Caramori G and Adcock IM: Inhaled corticosteroids as combination therapy with beta-adrenergic agonists in airways disease: Present and future. Eur J Clin Pharmacol 65: 853-871, 2009.
19. van Aalderen WMC and Sprikkelman AB: Inhaled corticosteroids in childhood asthma: The story continues. Eur J Pediatr 170: 709-718, 2011.
20. Kovesi T, Schuh S, Spier S, Bérubé D, Carr S, Watson W and McIvor RA: Achieving control of asthma in preschoolers. CMAJ 182: E172-E183, 2010.
21. Castro-Rodriguez JA and Rodrigo GJ: Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: A systematic review with meta-analysis. Pediatrics 123: e519-e525, 2009.
22. Pawankar R, Holgate ST and Rosenwasser LJ (eds): Allergy Frontiers: Therapy and Prevention. Springer, Tokyo, 2010.
23. Amirav I, Newhouse MT, Minocchieri S, Castro-Rodriguez JA and Schüepp KG: Factors that affect the efficacy of inhaled corticosteroids for infants and young children. J Allergy Clin Immunol 125: 1206-1211, 2010.
24. Lan WP, Wang J, Dai CL and Pan JH: Efficacy of fluticasone propionate aerosol versus budesonide suspension in treatment of recurrent wheezing caused by bronchiolitis. Zhongguo Dang Dai Er Ke Za Zhi 18: 316-319, 2016 (In Chinese)
25. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MCJM and Verhamme KMC: Prescription patterns, adherence and characteristics of non-adherence in children with asthma in primary care. Pediatr Allergy Immunol 27: 201-208, 2016.
26. Makhinova T, Barner JC, Richards KM and Rascati KL: Asthma Controller Medication Adherence, Risk of Exacerbation, and Use of Rescue Agents Among Texas Medicaid Patients with Persistent Asthma. J Manag Care Spec Pharm 21: 1124-1132, 2015.
27. Wardenier NRA, Klok T, de Groot EP and Brand PLP: Height growth in children with asthma treated with guideline-recommended dosages of fluticasone and electronically assessed adherence. Arch Dis Child 101: 637-639, 2016.
28. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemière C and Ducharme FM: Assessing adherence to inhaled corticosteroids in asthma patients using an integrated measure based on primary and secondary adherence. Eur J Clin Pharmacol 73: 91-97, 2017.
29. Vasbinder EC, Goossens LMA, Rutten-van Mölken MPMH, de Winter BC, van Dijk L, Vulto AG, Blankman EI, Dahhan N, Veenstra-van Schie MT, Versteegh FG, *et al*: e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC): A randomised controlled trial. Eur Respir J 48: 758-767, 2016.
30. Leigh R, Vethanayagam D, Yoshida M, Watson RM, Rerecich T, Inman MD and O'Byrne PM: Effects of montelukast and budesonide on airway responses and airway inflammation in asthma. Am J Respir Crit Care Med 166: 1212-1217, 2002.
31. Stanford RH, Shah M and Chaudhari SL: Clinical and economic outcomes associated with low-dose fluticasone propionate versus montelukast in children with asthma aged 4 to 11 years. Open Respir Med J 6: 37-43, 2012.