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Original Articles

Oral Montelukast Versus Inhaled Budesonide in Children with Mild Persistent Asthma: A Pilot Study

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Abstract

Background: Inhaled corticosteroids and montelukast are both recognised as first-line treatment for children with mild persistent asthma. ***Objective:*** The aim of this study was to compare budesonide dry powder, 200 mcg twice a day, with montelukast 5 mg nocte in children with mild persistent asthma. ***Methods:*** Children with mild persistent asthma were recruited from the out-patient department in a non teaching hospital. Double-blinded, double-placebo, randomised, crossover design was used. After a run-in period of two weeks, patients received either montelukast (6 to <=14 years, 5 mg; >14 years, 10 mg) and a placebo dry powder inhaler, 1 puff twice a day or budesonide dry powder, 200 mcg twice a day and a placebo tablet once a day for 8 weeks. After a washout period of two weeks, they were then switched over to receive the alternative treatment for 8 weeks. Outcome measures included change in force expiratory volume in 1 second (FEV-1), symptoms of asthma documented in asthma diary and the time to first exacerbation of asthma. ***Results:*** 19 Children were enrolled (13 boys and 6 girls, mean age 8.58±2.4 years). For the 13 children who received oral montelukast, five dropped out during the washout period. For 15 children who received budesonide Turbuhaler, seven dropped out during washout period. The dropout rates were similar in both treatment groups. (Oral montelukast: 50.0%, budesonide Turbuhaler: 53.8%, p=1.00). Budesonide provided significant greater improvement in FEV-1 compared to montelukast after 4 weeks and 6 weeks of treatment (p=0.031 and p=0.027 respectively). Montelukast group had more asthma exacerbation than the budesonide group (p=0.0419). ***Conclusions:*** The current pilot study suggested that montelukast was less effective than budesonide DPI, 200 mcg twice a day, in preventing asthma exacerbation although the symptom-free days and FEV-1 changes at the end of treatment periods were found to be similar. Budesonide achieves faster improvement of FEV-1 and less asthma exacerbation than montelukast. Multicentre trial enrolling more patients to test this observation is needed.

Key words Asthma; Budesonide; Children; Montelukast; Randomised controlled trial

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Introduction

Airway inflammation is widely recognised to play an important part in the pathogenesis of chronic asthma. Inhaled corticosteroids are the "gold standard" of anti-inflammatory agents in asthma management.[1-5] They have been shown to be effective as preventive medications for adults[6] as well as children.[7,8] Current guidelines[2,9] recommend the use of inhaled corticosteroid as the first-line controller medications. Despite the recognised efficacy of inhaled corticosteroids, many patients still had poorly controlled asthma and poor quality of life.[10] Compliance may be an issue as non-compliance with prescribed inhaled corticosteroids was reported to be associated with exacerbation of asthma.[11] The other concern would be the

safety issue of corticosteroids usage in children especially with regard to the effect on growth, a highly controversial topic.[8,12,13] New therapies that are non-steroidal, effective, easily administered and well tolerated would provide an attractive option.

Leukotrienes are important mediators causing bronchoconstriction, mucous secretion, and increased vascular permeability in asthma.[14] Leukotrienes are produced and released by inflammatory cells including mast cells and eosinophils. Specific leukotriene receptor antagonists are now available and the guideline for diagnosis and management of asthma by the US National Institute of Health Expert Panel[2] included leukotriene modifiers among the long-term control medications for asthma.[2,15] Montelukast, a leukotriene receptor antagonist, was shown to be effective in improving respiratory functions in children and adults.[14,16] Moreover, it was found to protect against exercise induced bronchoconstriction.[17,18] Montelukast was shown to enhance compliance.[19] Previous Cochrane review[20] compared the efficacy of anti-leukotriene agents, i.e. montelukast, pranlukast and zafirlukast, and inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. The results showed that anti-leukotrienes were less effective than inhaled corticosteroids in maintaining asthma control.

As there was no data on the comparison between montelukast and budesonide dry powder inhaler (DPI) or Turbuhaler™ in asthma control in children, a pilot study was undertaken to evaluate montelukast, 5 mg nocte and budesonide DPI, 200 mcg b.i.d. in children with mild persistent asthma.

Methods

This study was a randomised, double-blind, double-placebo, cross-over study to compare the clinical benefits of oral montelukast (5 mg chewable tablet nocte) with inhaled budesonide dry powder inhaler (200 mcg b.i.d.) in 6- to 14-year-old children with mild persistent asthma[21-25] conducted at the paediatric respiratory clinic in Kwong Wah Hospital. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol of this study was approved by the ethics committee and written informed consent by parents was obtained prior to enrollment.

Male and female patients between 6- to 14-year of age with a history of newly diagnosed mild persistent asthma were enrolled in this study. Mild persistent asthma was defined as a forced expiratory volume in 1 second (FEV-1) ≥80% of the predicted value (after withholding β-agonist for ≥6 hours) and to improve by ≥15% after inhaled β-agonist, or if they have symptoms ≥1 time a week but <1 time a day, or if their nighttime symptoms are >2 times a month.[25] Children were eligible for the study only if they demonstrated adequate understanding and competency of using the budesonide DPI as well as the ability to perform reproducible spirometry.

Exclusion criteria included prior use of budesonide DPI, previous intubation for asthma, a history of chronic pulmonary disease other than asthma, upper respiratory tract infection within 3 weeks before the first study visit, or a history of an acute sinus disease requiring antibiotic treatment 1 week before the start of the study, history of taking following medication: astemizole within three months; oral, inhaled or parenteral corticosteroids within one month; cromolyn, nedocromil, oral or long-acting β2-agonist, antimuscarinics, cimetidine, metoclopramide, phenobarbital, phenytoin, terfenadine, loratadine, or anticholinergic agents within two weeks and theophylline within one week before the pre-study visit; patients receiving immunotherapy.

The use of a new or changing doses of concomitant asthma medications by the patient, other than a short-acting, inhaled β2-agonists would result in withdrawal from the study. Short acting β2-agonists could be used as needed. Exacerbation of asthma was defined as one of the following occurrences during the study period: unscheduled visit to general practitioner, accident and emergency department or out-patient clinic due to asthma symptoms, use of systemic corticosteroid due to worsening in asthma or total asthma score equal or larger than 5. Patients with exacerbation of asthma that required additional therapy were treated with oral corticosteroids according to a standard protocol of the authors' department. Patients who had more than two exacerbations of asthma requiring systemic corticosteroid therapy were withdrawn from the study.

The study flow was shown in Figure 1. The study consisted of a 2-week run-in period (period 1) followed by an 8-week, double-blind, double-placebo, active treatment period (period 2). Patients were randomised by the pharmacist, SW, to receive either a chewable tablet of montelukast, 5 mg, and a placebo DPI, or matching placebo of montelukast and budesonide DPI (200 mcg/dose) in accordance to the random number table. Both patients/parents and the attending paediatricians were blinded to medications received. Similar to the trial by van Rensen et

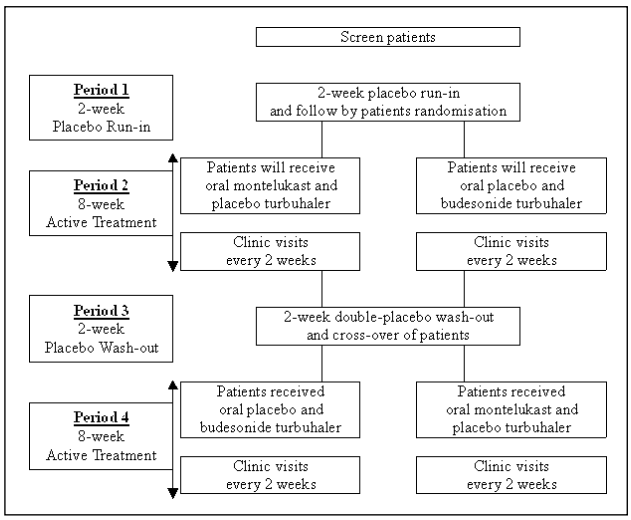

Figure 1 Schedule of study patients.

al,[26] the washout period was selected to be 2 weeks in the current study. After a 2-week washout period, the two groups of patients were switched to the alternative arm (period 4).

Efficacy Evaluation

Primary outcome of this study was the change in FEV-1 from the baseline value that was determined at the end of the run-in period. FEV-1 assessment was repeated at 2nd, 6th and 8th week of treatment. FEV-1 was obtained in accordance to the standard recommended by the American Thoracic Society.[27] Inhaled β-agonists and short-acting antihistamines were withheld for at least 6 and 48 hours respectively prior to spirometry. The largest FEV-1 from a set of three acceptable maneuvers at each clinic visit was recorded as the true value. FEV-1 was presented as percentage of predicted value. Spirometry measurements were collected with the same spirometer (MicroLoop 3535, SPIDA Spirometry software v2.2, MicroMedical Ltd, Kent, UK). The nurses conducting the spirometry were blinded to the study.

Secondary outcome measures included daytime asthma symptoms, nocturnal awakenings and episodes of asthma exacerbation and asthma symptom-free days.

A modified Paediatric Asthma Caregiver Diary (PACD) was used in the study (Appendix 1).[28] Diary questions were read verbatim by care-givers to patients aged 6- to 8-year and their responses recorded; patients aged 9- to 14-year answered the diary questions under adult supervision. Daytime symptoms were recorded in the diary at bedtime and nocturnal symptoms on rising.

Daily symptoms score were calculated by summation of scores from the four questions. Symptom-free day was defined as zero score for the 4 questions. In the diary, the patients also recorded use of oral corticosteroid, unscheduled medical consultation for asthma and hospitalisation due to asthma exacerbation.

Statistical Analysis

All statistical analyses were performed with SPSS version 10.1 (SPSS Inc, Chicago, IL). All continuous variables were described by mean and standard deviation. Baseline values were compared by student's t-test or chi-squared test to ensure no significant difference in these variables between 2 treatment groups. Intention-to-treat analysis was adopted. All missing responses from patients were imputed as the same value to that of the last attendance before dropout. Robustness of intention-to-treat analysis was assessed by repeating the analyses with all missing values discarded. The power of washout period was analysed by comparing values recorded in run-in and washout period in patients who finished crossover by paired student's t-test. Significant difference, if any, between run-in and washout period would indicate that the washout period was not adequate.

For FEV-1, analyses were performed in terms of the changes from baseline. Baseline FEV-1 was defined as FEV-1 of patients determined at the end of run-in or washout period. The changes in FEV-1 throughout the 8 weeks treatment period from baseline were analysed by analysis of variance. Inter-treatment-group comparison of improvement in FEV-1 at different treatment periods were conducted by student's t-test. Symptom-free days were presented as percentage of symptom-free days in the study period. Inter-treatment group comparison of percentage of symptom-free day at each follow-up was compared by Mann-Whitney U test. The time to first exacerbation was analysed using a log-rank test. All statistical tests were 2-tailed, and a p value of 0.05 or less was considered statistically significant.

Results

Nineteen children were enrolled. There were 13 boys and 6 girls. Mean age of all subjects was 8.58±2.4 years (Table 1). The flow of the 19 children was illustrated in Figure 2. For the 13 children who had ever received oral montelukast, five dropped out during the follow up period. For 15 children who had ever received budesonide DPI,

seven dropped out during the follow up period. All dropouts were due to lack of time to attend the clinic every two weeks. The dropout rates were similar in both treatment groups (montelukast: 50%, budesonide DPI: 54%, p=1.00) Altogether, seven children completed the whole study, i.e. 37% of all subjects. Altogether 13 sets of data from montelukast group and 15 sets of data from budesonide DPI were available for analysis.

FEV-1 of patients in two treatment groups were summarised in Table 2. Mean FEV-1 was similar in both treatment groups over the 8-week of treatment. The percentage improvement of FEV-1 from baseline for each patient was computed (Table 2). There were no significant difference between budesonide group and montelukast group at 2 weeks and 8 weeks of treatment period but budesonide group had a significantly greater improvement in FEV-1 than montelukast at 4 weeks and 6 weeks of treatment period. Mean FEV-1 predicted was 99.11%± 13.94 at the end of run-in period and 96.44%±5.43 at the end of washout period and there were no significant difference in FEV-1 between the 2 periods (Paired

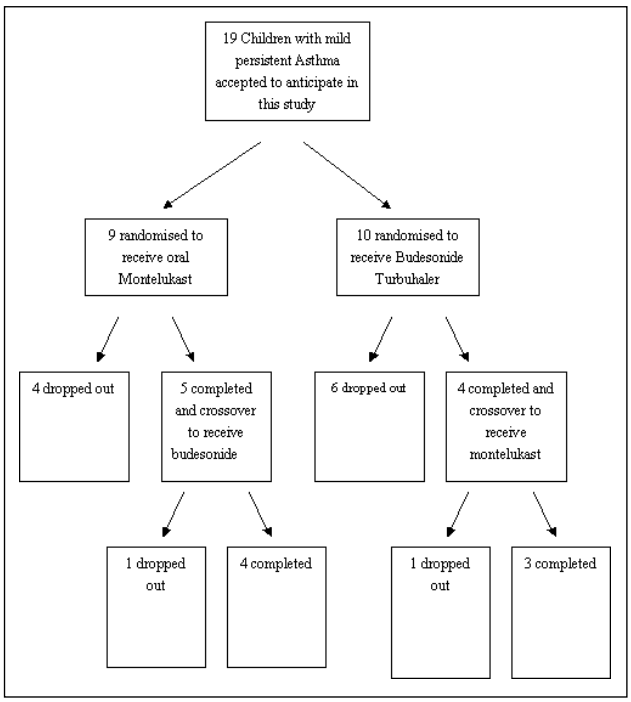

Figure 2 Flow of the 19 enrolled children.

Table 1 Subjects characteristics

	Budesonide N=15	**Montelukast N=13**	**P value**
M : F	8 : 5	9 : 6	1.000
Mean age ± SD	8.385±2.567	8.533±2.167	0.869
Drop-out number (%)	7 (47%)	5 (38%)	0.717

Table 2 Comparison of FEV-1 and percentage improvement between two treatment groups

	Treatment group		
	Budesonide N=15 (Mean ± SD)	**Montelukast N=13 (Mean ± SD)**	**Sig.**
FEV-1 / % predicted			
Baseline	97.87 ± 17.11	100.30 ± 6.13	P=0.612
After 2 weeks of treatment	99.00 ± 11.71	94.92 ± 21.29	P=0.528
After 4 weeks of treatment	104.47 ± 19.08	93.62 ± 13.00	P=0.096
After 6 weeks of treatment	105.00 ± 17.39	93.62 ± 11.53	P=0.055
After 8 weeks of treatment	101.20 ± 19.04	97.62 ± 12.54	P=0.553
ANOVA test*	P=0.710	P=0.681	-
Percentage improvement from baseline†			
After 2 weeks of treatment	2.44 ± 11.07	-4.46 ± 21.98	P=0.294
After 4 weeks of treatment	8.01 ± 18.95	-5.92 ± 11.87	P=0.031‡
After 6 weeks of treatment	9.57 ± 22.04	-5.85 ± 11.06	P=0.027‡
After 8 weeks of treatment	5.20 ± 20.53	-1.90 ± 11.33	P=0.262

* One way analysis of variance comparing the FEV-1 at four different times; † Defined as (FEV-1 at that follow-up / Baseline FEV-1) X 100 ; ‡ statistical significance

t-test, p=0.570). This would suggest that the washout period was long enough to prevent carry-over effect of previous treatment.

No patients in the budesonide group experienced exacerbation of asthma. In the montelukast group, 3 out of 13 patients (23.08%) experienced exacerbation of asthma that rendered unscheduled visit to general practitioners. The probability of patients remaining free from an asthma exacerbation throughout the study was shown in Figure 3 and the budesonide group fared significantly better than the montelukast group.

Summary of symptom-free days was shown in Table 3. No significant difference was found between the two treatment groups. No severe adverse events were reported during the study period. The robustness of intention to treatment analysis was assessed by repeating the analyses when all missing values were discarded. All conclusions were identical.

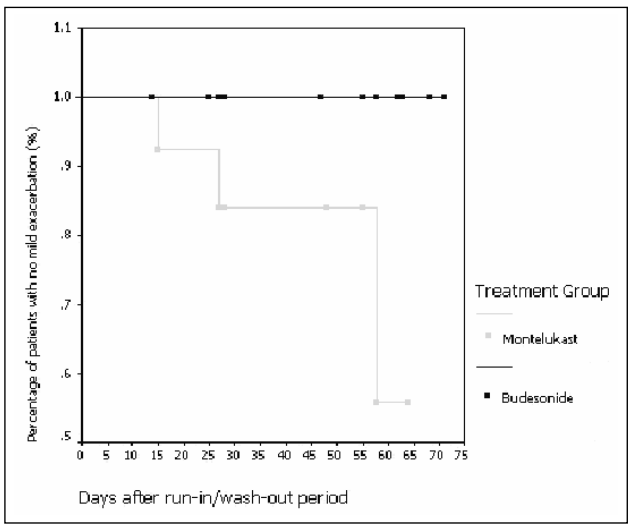

Figure 3 Kaplan-Meier Survival Curves of patients remaining free from an exacerbation during 8 weeks of treatment with oral montelukast, or budesonide DPI.

Discussion

In the Cochrane review on montelukast and inhaled corticosteroids,[20] only three paediatrics trials[29-31] (mean age 10- to 12-year) were included in the review and separate analysis of these 3 trials were undertaken by the authors and no significant difference in asthma control parameters was demonstrated. (Relative risk = 0.78, 95% CI = 0.78 to 1.85). Subsequently, three studies on the same topic were published (Table 4).[32-34] All the data were put together by the authors for meta-analysis of two outcomes, i.e. FEV-1 and symptom-free days (Figures 4 & 5). Both outcomes analysis favoured fluticasone. Similarly, the current study, the first study that compared montelukast with inhaled budesonide DPI for treatment of childhood asthma, demonstrated that an 8-week oral montelukast, 5 mg daily, resulted in less improvement in FEV-1 after 4 weeks and 6 weeks of treatment than that of budesonide. However, the significant difference between these two treatments disappeared after 8 weeks. The 4th and 6th week FEV-1 results were similar to that reported by Malmstrom et al[35] who found FEV-1 to be higher in the beclomethasone group, 200 mcg twice daily, although the current data suggested that the difference disappeared after 8 weeks of treatment. The reasons behind the different results of the current study and that of Malmstrom et al were probably related to the

Table 3 Comparison of percentage of symptom-free day in two treatment groups

	Treatment group		
	Budesonide N=15 Median (IQR)	**Montelukast N=13 Median (IQR)**	**Sig. ‡**
Proportion of symptom-free day* /%			
Baseline	100 (79-100)	100 (100-100)	P=0.427
After 2 weeks of treatment	100 (64-100)	100 (100-100)	P=0.386
After 4 weeks of treatment	100 (71-100)	100 (100-100)	P=0.791
After 6 weeks of treatment	100 (79-100)	100 (100-100)	P=0.762
After 8 weeks of treatment	100 (71-100)	100 (100-100)	P=0.325
Kruskal-Wallis H test †	P=0.848	P=0.915	-

IQR = interquartile range

* Defined by (Number of symptom-free day / Total number of data in that period) x 100; † Kruskal-Wallis H test comparing the proportion of symptom-free day during four different periods of follow-up; ‡ Compared by Mann-Whitney U test

Table 4 Studies that compare inhaled corticosteroids with montelukast in children

First author, year	No. of children	Range of age (years)	Type of inhaled corticosteroids	Duration of treatment
Zeiger et al. 2005[32]	127 with mild-to-moderate persistent asthma	6 to 17	Fluticasone dry powder inhaler	16-week
Ostrom et al. 2005[33]	342 with chronic asthma	6 to 12	Fluticasone dry powder inhaler	12-week
Garcia et al. 2005[34]	994 with mild persistent asthma	6 to 14	Fluticasone metered dose inhaler	12-month
Stelmach et al. 2002[29]	37 with moderate atopic asthma	9 to 14	Triamcinolone metered dose inhaler	8-week
Maspero et al. 2001[30]	124 with asthma	6 to 11	Beclomethasone metered dose inhaler	8-week
Ng et al. (current)	19 with mild persistent asthma	6 to 14	Budesonide dry powder inhaler	8-week

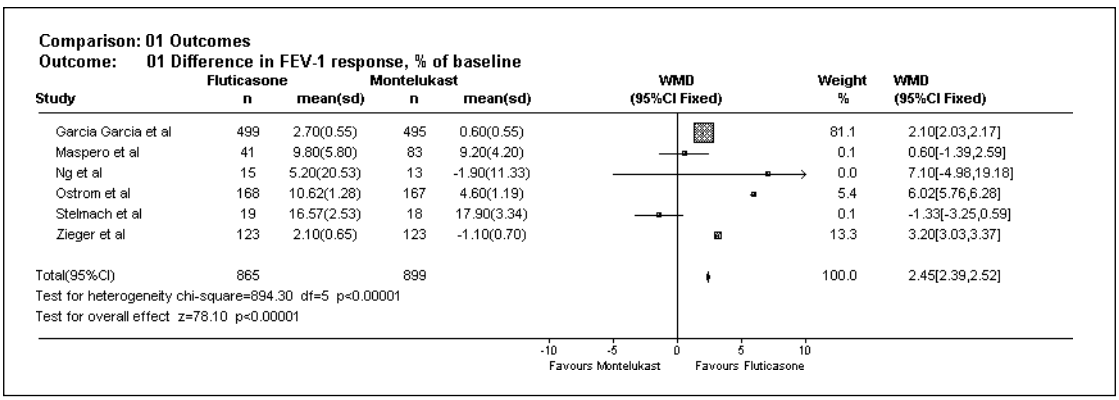

Figure 4 Meta-analysis of FEV-1 response in children between montelukast and fluticasone.

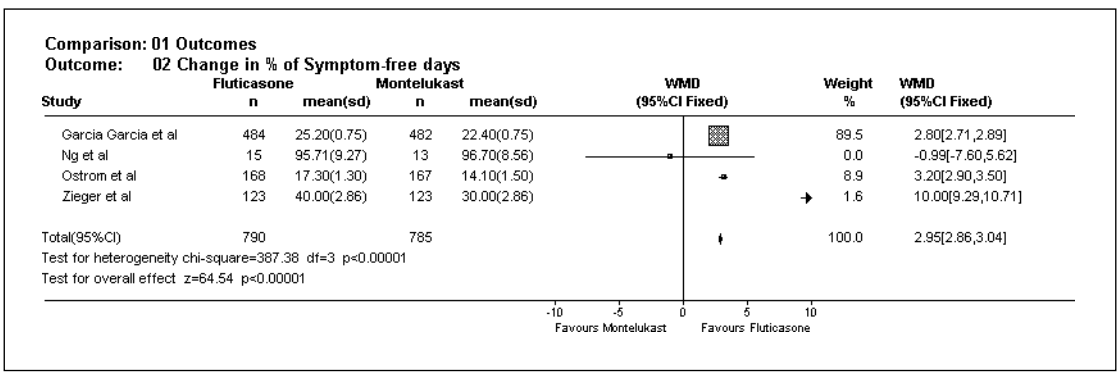

Figure 5 Meta-analysis of symptom-free days between montelukast and fluticasone in children.

differences between the two studies, e.g. adult vs children; beclomethasone vs. budesonide; meter dose inhaler with spacer vs DPI.

The montelukast group was also found to be more likely to have exacerbation of asthma than the budesonide group, 23% vs. 0% (Figure 3). Similarly, Malmstrom et al reported more exacerbation in montelukast group than beclomethasone group, 26% vs. 10%. Despite this higher exacerbation rate in the montelukast group, the symptom-free days were similar between the two groups. This probably reflected the failure of diary to capture the daytime symptoms of mild wheeze or shortness of breath that prompted the children to be brought to medical attention. No difference was found in terms of asthma symptoms documented by asthma diary between the two groups. This was similar to the finding contained in a review done by Wenzel comparing antileukotriene and inhaled corticosteroid.[36]

The current study had three drawbacks. Firstly, the dropout rate was high, 50% to 54% and the rates were similar between the two treatment groups. The main reason for the dropout was the need to attend every two weeks. In future study, the interval between attendances needs to be lengthened. The resulting small sample size decreased the power of the current study. Nevertheless, the current sample size still demonstrated that montelukast group had a significantly higher rate of asthma exacerbation than the budesonide DPI group. The second problem was the short duration of treatment as the standard asthma treatment would be calculated in months not weeks. Thirdly, the current study did not assess patients' preference as oral asthma medication was found to be preferred by patients when compared with inhaled medications.[37] In real life situation, the clinical benefit might well be more in favor of montelukast because of better compliance with montelukast.[38]

Assuming a lower dropout rate at 30% and the inter-group mean difference in percentage improvement of FEV-1 from baseline to be 7%, 123 children will be needed in any future crossover study to allow a power of 0.8 and a type I error rate of 0.05. A longer follow-up period with less frequent follow-up frequency would be needed to confirm the findings of current study.

Conclusion

For paediatric mild persistent asthma, the current pilot study suggests that budesonide dry powder inhaler treated group may possibly be associated with less asthma exacerbation than montelukast treated group for those children with good adherence. Further study that involves more than 100 subjects is required to confirm the finding.

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Appendix 1. Asthma diary

1. How much did your child cough last night after being put to bed for the night until awaking this morning?
   0. Did not cough at all
   1. Coughed very little
   2. Coughed frequently
   3. Coughed almost all night

2. How much did your child's asthma symptoms interfere with your child's sleep last night?
   0. Did not interfere
   1. Awaken 1 times
   2. Awaken more than 1 times
   3. Could not sleep at all

3. How severe was your child's cough today?
   0. No cough
   1. Mild cough
   2. Severe cough
   3. Very severe cough

4. How much did your child's asthma symptoms interfere with your child's activities today, including physical activities such as running, playing, jumping, sports, bike-riding, climbing, or school activities?
   0. No interference
   1. Mild interference
   2. Moderate interference
   3. Severe interference

Has your child had an unscheduled medical consultation for asthma, attendance of Accident and Emergency department or hospitalisation due to worsening of asthma today?
   0. No
   1. Yes

Has your child used additional corticosteroid for treatment of asthma exacerbation today?
   0. No
   1. Yes