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Urinary cysteinyl leukotriene E4 level and therapeutic response to montelukast in children with mild obstructive sleep apnea

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Abstract

Background: Antileukotriene has been used for alleviating disease severity in children with adenotonsillar hypertrophy (ATH) and mild obstructive sleep apnea (OSA). Previous study showed the relationship between urinary cysteinyl leukotriene E_4 ($uLTE_4$) level and therapeutic response to montelukast in asthmatic adults. However, this relationship has never been investigated in pediatric OSA.

Objectives: To determine the relationship between $uLTE_4$ level and therapeutic response to montelukast in children with ATH and mild OSA.

Population and methods: Children aged 3-15 yrs who had ATH and mild OSA were enrolled. All had quality of life (QoL) (assessed by Thai version OSA-18 QoL questionnaire) and $uLTE_4$ levels measured prior to start a 6-week course of montelukast treatment. Overnight polysomnography (PSG) and QoL reassessment were performed after completing the treatment. Those who demonstrated a large improvement of mean total QoL score or ≥ 50% decrease of obstructive apnea-hypopnea index (OAHI) after the treatment were defined as responders.

Results: Twenty-six children were enrolled (mean age 7.5 ± 2.9 yrs, 38.5% male). After 6-week course of montelukast, nine (34.6%) children showed significant improvement. The mean $uLTE_4$ level from the responders was higher comparing to the non-responders (2,952.56 ± 966.9 vs. 978.6 ± 460.8 pg/mg creatinine; $p < 0.001$). $uLTE_4$ level of ≥ 1,457 pg/mg creatinine had 100% sensitivity and 88.2% specificity in identifying the responders.

Conclusions: We found the association between ULTE4 and therapeutic response to monteleukast. The $uLTE_4$ level of ≥ 1,457 pg/mg creatinine could predict the therapeutic response to montelukast in children who had ATH and mild OSA.

Keywords: obstructive sleep apnea, cysteinyl leukotriene E_4, montelukast, adenotonsillar hypertrophy, children

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Introduction

Obstructive sleep apnea (OSA) is a sleep-disordered breathing not uncommonly found in children. The prevalence varies between 1.2-5.7%.[1] The most common cause of OSA in children is adenotonsillar hypertrophy (ATH). Previous studies demonstrated the abundant expressions of leukotrienes (LTs) and their receptors in adenotonsillar tissues and the positive correlation between urinary cysteinyl leukotrienes (cysLTs) levels and OSA severity in children who had OSA.[2-6] These findings lead to the therapeutic use of leukotriene receptor antagonist such as montelukast in children who have mild OSA secondary to ATH. Several studies reported the significant benefits of montelukast in alleviating OSA severity in this particular population.[7-9] However, it's not all children who responded to the treatment. Previous study showed the relationship between urinary cysteinyl leukotriene E_4 ($uLTE_4$) level and therapeutic response to montelukast in asthmatic

adults.[10] However, this relationship has never been investigated in pediatric OSA. This study was, therefore, aimed to investigate whether $uLTE_4$ level could predict the favorable therapeutic response to montelukast in children who had mild OSA secondary to ATH.

Methods

This study was a cross-sectional study performed at Division of Pulmonolgy, Department of Pediatrics, King Chulalongkorn Memorial Hospital during March 2015 – August 2016. The study population included children aged 3-15 years who had habitual snoring, ATH and mild OSA [diagnosed by the attended overnight polysomnography (PSG)] and were planned for treatment with montelukast according to the Thai Clinical Practice Guideline (CPG) for Diagnosis and Management of Childhood Obstructive Sleep Apnea 2014.[11] Exclusion criteria included those who had neuromuscular diseases, craniofacial anomalies, genetic diseases, chronic lung diseases (including asthma), recent respiratory tract infections within 2 weeks prior to the study, current use of montelukast, antihistamine or intranasal corticosteroid, underlying conditions that could affect the levels of urinary LTE_4 and creatinine (such as urinary tract infection, atopic dermatitis, unstable angina, acute myocardial infarction, coronary artery disease, rheumatoid arthritis, Crohn's disease and malignant astrocytoma), known hypersensitivity to montelukast and poor compliance with PSG. Children whose caregivers could not understand Thai language well were also excluded. The study protocol was approved by the Institutional Review Board for Human Research Study of Chulalongkorn University. Written informed consent and assent (when applicable) were obtained from the participants and their legal guardians before enrolling into the study.

Study protocol

Prior to start treatment with montelukast, all eligible participants had morning urine collected for $uLTE_4$ and creatinine measurements. Their caregivers were asked to complete the Thai-version OSA-18 QoL questionnaire for the assessment of quality of life (QoL). Montelukast (4 mg sachet for participants aged less than 6 years, 5 mg chewable tablet for participants aged 6-15 years, once at bedtime) were prescribed to the participants for six weeks in accordance with the Thai Clinical Practice Guideline (CPG) for Diagnosis and Management of Childhood Obstructive Sleep Apnea 2014.[11] Weekly telephone calls to all participants were made by the investigators to verify their adherence to the treatment and address any potential problems. The participants who forgot to take montelukast even just only for one night were excluded from the study. At the end of 6 weeks, all participants underwent QoL and overnight PSG reassessments to determine the therapeutic response. Those who demonstrated either a large improvement of QoL (decrease of mean total QoL score > 1.5) or ≥ 50% decrease of obstructive apnea-hypopnea index (OAHI) were classified as responders. Clinical factors including the $uLTE_4$ level were compared between the responders and non-responders to determine the association.

Overnight PSG

The attended overnight PSG was undertaken at the Excellence Center for Sleep Disorders, King Chulalongkorn Memorial Hospital using the Sleep System Compumedics™ (Melbourne, Australia) under the supervision of a well-trained sleep technician. The participants presented at the sleep lab at 8.30 P.M. and were discharged at 7 A.M. on the following day. All PSG used standard electroencephalographic monitoring, including frontal leads (F1, F2), central leads (C3, C4), occipital leads (O1, O2), and reference leads at the mastoids (M1, M2); electromyography; and electrooculography methodology. SpO_2 was measured with a finger probe while air flow was measured by two methods including nasal pressure transducer and oro-nasal thermocouple. The thoracic and abdominal respiratory movements were monitored by respiratory inductance plethysmography. The body position was measured by a position sensor attached to the anterior chest wall on the thoracic belt. Carbon dioxide was measured by end-tidal CO_2 monitoring or transcutaneous CO_2 monitoring. Sleep stages were scored in 30-second epochs, according to the American Academy of Sleep Medicine (AASM) standard criteria (AASM 2012).[12] Apnea was defined using oral-nasal thermo-couple excursion, and hypopnea was defined using nasal pressure transducer excursion. Apnea, hypopnea, and respiratory effort-related arousals (RERAs) were scored in accordance to the standard criteria from the AASM Manual 2012.[12] OSA was diagnosed if the participants demonstrated the events of OAHI ≥ 1 episodes/hour of total sleep time (TST). Those who had OAHI 1-5 episodes/hour of TST were categorized as mild OSA.

Quality of life (QoL) assessment

Caregivers who regularly slept with the participants were asked to complete the QoL questionnaire before and after completing a 6-week course of montelukast treatment. The questionnaire used in this study was a Thai-version OSA-18 developed and validated by Kuptanon et al.[13] It was translated from the original English version of Franco's Pediatric OSA instrument (OSA-18) under the permission of the original authors.[14] The questionnaire consisted of 18 items divided into 5 domains (sleep disturbance, physical symptoms, emotional symptoms, daytime functioning and caregiver concerns). The 18 items were scored with a 7-point ordinal scale assessing the frequency of the specific symptoms. The scores on each of the 18 items were summed to produce a total sum score which ranged from 18 to 126. The higher score corresponded to the greater impact of OSA on QOL. The total sum score of QoL was used for grading the impact of OSA on QoL as small (score < 60), moderate (score 60 – 80) and large (score > 80) impact.[14,15] The change of QoL was graded as a large change if the mean total score of QoL (total sum score divided by 18) was altered greater than 1.5.[14,15]

Urinary LTE_4 level measurement

The pretreatment urine specimens were collected, centrifuged and stored at -70°C prior to process for the measurements of creatinine and LTE_4 levels. An immunoassay kit (Cayman Chemical Company; Ann Arbor, MI, USA) was used for the LTE_4 analysis. The $uLTE_4$ levels were expressed in

pg/mg of urine creatinine to adjust for the renal concentrating effect.

Sample size calculation

Since this study was aimed to compare the $uLTE_4$ levels between the responders and non-responders, we referred to the study of Cai, et al[10] and used the following formula for calculating the sample size.

$$n/group = 2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2 / (X_1 - X_2)$$

where $\alpha = 0.05$, $\beta = 0.2$. The calculated sample size was 11 per group.

Data acquisition and analysis

Collected data included demographic data, body weight, height, body mass index (BMI), total sum score and mean total score of QoL, OAHI and $uLTE_4$ levels. Unpaired Student's t-test and Fischer Exact test were used for the comparison between continuous and categorical variables, respectively. Exact logistic regression analysis was used for identifying the independent factors associated with therapeutic response to montelukast. The ROC curve was applied to determine the best cutoff value of $uLTE_4$ level for identifying the responders. Sensitivity, specificity, positive and negative predictive value (PPV, NPV) of $uLTE_4$ level were calculated to assess the validity of this cutoff value in predicting the therapeutic response. A two-tailed *p*-value < 0.05 was considered for statistically significant. The analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA.).

Results

Twenty-six children were eligible to the study. The mean age was 7.5 ± 2.9 years and 38.5% were male. Baseline demographic and clinical data as well as $uLTE_4$ level were showed in **Table 1**. The PSG parameters and the OSA-18 QoL scores before and after a 6-week course of montelukast treatment were showed in **Table 2 and 3**, respectively. After the treatment, there was no significant change in PSG parameters.

Table 1. Baseline demographic and clinical data of the study population

Data	N = 26
Age (yrs)*	7.5 ± 2.9 (3.3 – 12.4)
Male	10 (38.5%)
AR diagnosed by the physicians	14 (53.8%)
BMI (kg/m^2)*	18.6 ± 3.6 (13.5 – 25.9)
BMI z-score ≥ 2	4 (15.4%)
$uLTE_4$ level (pg/mg creatinine)*	1,661,89 ± 1,162.9 (94.9 – 4,998.4)

* Data were present as mean ± SD (range). AR, allergic rhinitis; BMI, body mass index; $uLTE_4$, urinary leukotriene E_4

Table 2. Polysomnographic data before and after 6-week course of montelukast treatment (n = 26)

Parameters	Pre treatment	Post treatment	*p*-value
AHI (episodes/hr)	3.8 ± 1.3 (1.2 – 5)	5.1 ± 4.4 (0.6 – 18.9)	0.15
OAHI (episodes/hr)	3.5 ± 1.2 (1.2 – 5)	4.7 ± 4.5 (0.3 – 18.9)	0.19
Baseline SpO_2 (%)	97.1 ± 1.0 (94 – 99)	97.3 ± 0.9 (94 – 98)	0.57
Nadir SpO_2 (%)	89.8 ± 5.5 (75 – 98)	90.6 ± 4.8 (76 – 96)	0.61
Baseline $P_{ET}CO_2$ tension (mmHg)	37.3 ± 6.1 (21.7 – 49.4)	34.9 ± 2.5 (29.9 – 42)	0.07
Peak $P_{ET}CO_2$ tension (mmHg)	41.3 ± 7.4 (35 – 63)	38.9 ± 3.4 (35 – 47)	0.14
Respiratory-related arousal index (episodes/hr)	11.6 ± 3.1 (5.9 – 17.6)	12.9 ± 4.9 (3.6 – 23.1)	0.27

All data were present as mean ± SD (range). AHI, apnea-hyponea index; OAHI, obstructive apnea-hyponea index; $P_{ET}CO_2$, end-tidal carbon dioxide tension; SpO_2, oxygen saturation measured by pulse oximetry; TST, total sleep time

Table 3. The OSA-18 QoL scores before and after 6-week course of montelukast treatment (n = 26)

OSA-18 QoL score	Pre treatment	Post treatment	*p*-value
Domain 1: sleep disturbance	17.7 ± 3.0 (12.0 – 23.0)	14.4 ± 4.6 (6.0 – 24.0)	0.003
Domain 2: physical suffering	14.5 ± 2.5 (11.0 – 20.0)	12.1 ± 3.0 (7.0 – 18.0)	0.003
Domain 3: emotional distress	12.0 ± 3.5 (3.0 – 18.0)	10.2 ± 3.6 (3.0 – 18.0)	0.07
Domain 4: daytime problems	12.4 ± 2.6 (6.0 – 19.0)	10.7 ± 3.2 (6.0 – 19.0)	0.04
Domain 5: caregiver concerns	19.2 ± 2.4 (16.0 – 24.0)	14.3 ± 4.2 (8.0 – 25.0)	< 0.001
Total sum score of QoL	75.8 ± 9.4 (62.0 – 98.0)	61.7 ± 15.4 (36.0 – 101.0)	< 0.001
Mean total score of QoL	4.2 ± 0.5 (3.4 – 5.4)	3.4 ± 0.8 (2.0 – 5.6)	< 0.001

All data were present as mean ± SD (range). QoL, quality of life

Table 4. Comparison of clinical factors between the responders and non-responders

Clinical factors	Responders (n = 9)	Non- responders (n = 17)	*p*-value
Age (yrs)*	6.4 ± 2.5 (3.9 – 11.8)	8.0 ± 3.1 (3.3 – 12.4)	0.20
Male (%)	3 (33.3%)	7 (41.2%)	1.0
BMI (kg/m^2)*	18.5 ± 3.7 (14.2 – 23.9)	18.6 ± 3.7 (13.5 – 25.9)	0.91
BMI Z-score > 2 (%)	2 (22.2%)	2 (11.8%)	0.59
AR diagnosed by physicians (%)	9 (100%)	5 (29.4%)	< 0.001
uLTE$_4$ level (pg/mg creatinine)*	2,952.56 ± 966.9 (1,571.9 – 4,998.4)	978.6 ± 460.8 (94.9 – 2,012.8)	< 0.001

*Data were presented as mean ± SD (range). AR, allergic rhinitis; BMI, body mass index; uLTE$_4$, urinary leukotriene E$_4$

However, QoL assessment showed significant improvements in all domains of QoL except for domain 3 (emotional distress). Six children (23%) demonstrated ≥ 50% decrease of OAHI while the same number of children demonstrated a large improvement of QoL score after the treatment. There were nine children (34.6%) who demonstrated either a large improvement of QoL score or OAHI and were defined as the responders. The comparison of the clinical data between the responders and non-responders revealed a higher level of uLTE$_4$ in the former group (2,952.56 ± 966.9 vs 978.6 ± 460.8 pg/mg creatinine; p < 0.001) (**Table 4**). Allergic rhinitis (AR) diagnosed by the physician was found in 100 and 29.4% of the responders and non-responders, respectively (**Table 4**). All of them had mild symptoms and had not been on any medications. Among the non-responders, those who had AR had a higher uLTE$_4$ level comparing to those who had no AR (1,451.1 ± 385.6 vs 781.7 ± 333.1 pg/mg creatinine; p 0.002). Among the AR group, those who responded to montelukast treatment had a higher uLTE$_4$ level comparing to those who did not respond to the treatment (2,952.6 ± 966.9 vs 1,451.1 ± 385.6 pg/mg creatinine; p = 0.007).

After adjusting for the confounding factors using the exact logistic regression analysis, uLTE$_4$ level was the independent factor associated with therapeutic response to montelukast treatment (OR 40.56; 95% CI 5.00 - ∞; p < 0.001). The best cutoff value of uLTE$_4$ level for predicting the therapeutic response calculated from the ROC curve was 1,457 pg/mg creatinine with the area under curve of 0.987, 100% sensitivity, 88.2% specificity, 81.8 % positive predictive value and 100% negative predictive value (**Figure 1**).

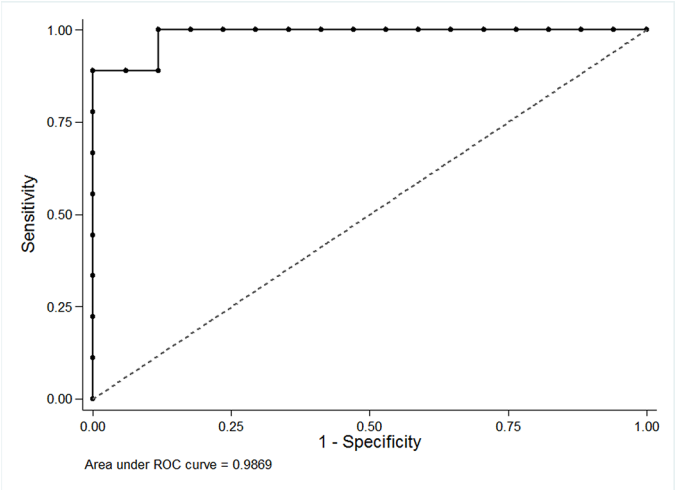

Figure 1. The ROC curve of urinary LTE$_4$ level > 1,457 pg/mg creatinine in predicting therapeutic response to montelukast (100% sensitivity, 88.2% specificity, 81.8% positive predictive value and 100% negative predictive value)

Discussion

In this study, 34.6% of children who had mild OSA secondary to ATH demonstrated a favorable therapeutic response (determined by either a large improvement of QoL or ≥ 50% decrease of OAHI) to a 6-week course of montelukast treatment. We also found a higher level of uLTE$_4$ among the responders comparing to the non-responders. This finding was in accordance with the previous study performed by Cai et al who also reported a positive relationship between uLTE$_4$ level and therapeutic response to montelukast in asthmatic adults.[10]

It has been known that LTs, especially cysLTs play an important role in inducing local inflammation in the upper airway of children who have sleep-disordered breathing. Several studies demonstrated the increased level of cysLTs and expressions of their receptors in adenotonsillar tissues of children with OSA.[2-4,16,17] In vitro study, Dayyat et al reported a dose-dependent pattern of LTD$_4$ in inducing adenotonsillar cell proliferation.[17] This finding supported the findings of in vivo studies which found a positive relationship between urinary LT level and OSA severity.[5,6]

Basing upon the findings of the association among LTs, adenotonsillar tissue proliferation and OSA, antileukotrienes such as montelukast have been increasingly used as an alternative treatment in children who have non-severe OSA. Several studies demonstrated a favorable effect of montelukast in decreasing adenotonsillar size and OSA severity.[7,9] Goldbart et al[7] reported a > 50% decrease of OAHI in 65.2% of children who had mild OSA after having been treated with montelukast for 12 weeks while Kheirandish-Gozal et al reported a reduction in AHI in 71.4% of children who had mild-to-moderate OSA after undertaking montelukast for 16 weeks.[9] Another study performed by Kheirandish-Gozal et al found normalized PSG in 62% children who had mild OSA and having had montelukast plus intranasal steroid for 12 weeks.[8] In our study, with a 6-week course of montelukast treatment, we found a lower response rate (34.6% defined by PSG or QoL criteria,

23% defined by PSG criteria alone) comparing to the previous studies. This could be partly due to the shorter duration of treatment and was in accordance with the in vitro study conducted by Dayyat et al who reported a dose-dependent effect of LT antagonists in decreasing adenotonsillar cellular proliferation rates.[17] Currently, there has been no consensus in regard to the optimal duration of montelukast treatment. The rationale of using 6-week course of montelukast treatment in our study was described in the later part of this section.

Previous studies in pediatric OSA revealed that it's not all children who responded well with montelukast treatment. It still remains unclear, however, which selection criteria should be used for identifying a child who has mild OSA and will benefit with montelukast treatment. Cai et al performed a study in asthmatic adults and found that $uLTE_4$ level > 200 pg/mg creatinine could predict therapeutic response to montelukast in this particular population.[10] Studies of factors associated with therapeutic response to montelukast in pediatric OSA are very scanty. Kheirandish-Gozal et al conducted a large retrospective study in children who had mild OSA and found that children aged < 7 years and non-obese were more likely responsive with montelukast plus intranasal steroid treatment.[8] Our study added new information in regard to the association between high $uLTE_4$ level and therapeutic response to montelukast in children who had mild OSA secondary to ATH. We found $uLTE_4$ level > 1,457 pg/mg creatinine had a very high sensitivity and specificity in predicting the therapeutic response to montelukast. This biomarker is the major urinary metabolite of cysLTs and most reliable analytic parameter for monitoring the endogenous synthesis of cysLTs. We found a variety of $uLTE_4$ levels and various therapeutic responses to montelukast among children who had mild OSA. Variations in genetic background of immunologic pathway involving in leukotriene synthesis and expressions of LT receptors in individuals might play a major role upon the magnitude of cysLT synthesis and subsequently affect various therapeutic responses to montelukast in pediatric OSA even though they have the same disease severity. Another finding in our study that should be noted was a higher prevalence of AR among the responders comparing to the non-responders. This atopic background could contribute to a higher level of $uLTE_4$ and subsequently more favorable response to montelukast treatment among the responders. However, even in the AR group, when we compared $uLTE_4$ between the responders and non-responders, we still found a higher level of $uLTE_4$ among the responders comparing to the non-responders. This implied that montelukast could ameliorate OSA severity in only some AR children and this was related to the $uLTE_4$ level. This implication was confirmed by the exact logistic regression analysis which showed that the high $uLTE_4$ level was the only independent factor associated with therapeutic response to montelukast. Future studies of genetic polymorphisms in leukotriene receptors or immunologic pathways involving in leukotriene synthesis would be beneficial in disclosing the variable inflammatory and therapeutic responses in pediatric OSA especially among those who have associated atopic background.

In this study, there were some limitations that deserved the comments. First, we used either the improvement of OAHI or QoL score to identify the responders. Despite being a subjective index and not well correlated with OSA severity, QoL assessed by OSA-18 questionnaire has been successfully used in many studies for assessing the therapeutic outcomes in pediatric OSA.[18,19] In general clinical practice, most physicians who take care of OSA children perform the clinical assessment by taking the medical history and physical exams instead of using PSG to assess the therapeutic response. In this study, we intended to use either the PSG or QoL criteria for identifying the responders in order to include all kinds of therapeutic responses. The second limitation of our study was a small sample size which led to the inability to categorize the participants into the allergic/non-allergic rhinitis and obese/non-obese groups for the subgroup analyses. Further studies in a larger sample size would reveal a more distinct relationship between $uLTE_4$ level and therapeutic response to montelukast in atopic vs. non-atopic and obese vs. non-obese children. The third limitation of the study was the short duration of montelukast treatment. In this study, the treatment duration (6 weeks) was set accordingly to the Thai CPG for Diagnosis and Management of Childhood Obstructive Sleep Apnea 2014.[11] This guideline has been proposed for the context of a huge number of snoring children but a scarcity of available pediatric sleep specialists and institutes that can provide the sleep studies in Thailand. The Thai CPG recommends a therapeutic trial of 6-week course of montelukast in otherwise normal children who have habitual snoring, ATH and no risk of severe OSA (eg. aged < 3 years, obese, genetic or craniofacial syndromes, neuromuscular diseases and chronic lung diseases). Those who do not respond to medical treatment will be referred to the pediatric sleep specialists for specific evaluations and treatments. The findings of this study would be helpful for selecting a child who will benefit with montelukast treatment.

In conclusions, we reported a positive relationship between high $uLTE_4$ level and therapeutic response to a 6-week course of montelukast in children who had mild OSA secondary to ATH. The $uLTE_4$ level ≥ 1,457 pg/mg creatinine had high sensitivity and specificity in predicting the therapeutic response. This biomarker would be helpful for identifying a child who will benefit with the treatment.

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Conflict of interest

None

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