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Original Article

Does short-term montelukast treatment cause sleep problems or psychiatric problems in children? A preliminary study

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Abstract

Aim: Montelukast is one of the treatment choices for symptomatic allergic rhinitis and asthma in children. Various researches emphasized that montelukast use causes neuropsychiatric side effects. The aim of this study was to investigate the effect of short-term montelukast use on children's sleep habits, and whether sleep-related problems and psychiatric problems may occur.

Material and Methods: This prospective study was conducted with 30 children. Psychiatric disorders and symptoms, sleep habits, sleep-related problems were evaluated before the use of montelukast. All of these evaluations were repeated at 4th and 8th week of treatment. Psychiatric assessment was performed with the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version – Turkish. Sleep habits, sleep-related problems were assessed using the Children Sleep Habits Questionnaire Short Form (CSHQ-S) and the Pediatric Sleep Questionnaire (PSQ).

Results: According to the psychiatric assessment, no psychiatric disease or symptom was identified before treatment and at the 4th and 8th week of treatment. The CSHQ-S and PSQ responses were evaluated and there was no significant difference between results obtained before treatment and at the 4th and 8th weeks of treatment.

Conclusion: The results revealed that short-term montelukast use is safe and do not cause changes sleep habits, sleep-related problems or psychiatric problems in children. Long-term follow-up studies with high numbers of participants are needed to test these results and evaluate the possible neuropsychiatric side effects of long-term montelukast use.

Keywords: Montelukast; children; neuropsychiatric; side effect; sleep; psychiatry

INTRODUCTION

Montelukast sodium is a selective leukotriene receptor antagonist that specifically blocks the cysteinyl leukotriene type 1 receptor. Cysteinyl leukotriene type 1 receptors, which are localized in the human respiratory tract, are synthesized by a variety of cells, including mast cells, eosinophils, basophils, and macrophages (1). Cysteinyl leukotriene receptors are thought to play a role in the pathophysiology of asthma and allergic rhinitis (2,3). Montelukast sodium is one of the treatment choices for symptomatic allergic rhinitis and asthma (4,5).

Montelukast is reported to well tolerated and safe for children (6). According to the summary of product characteristics, the most common adverse events in children (1–10% of all users) were headaches, abdominal pain, rashes, thirst, hyperkinesia, asthma, and eczema (7). A warning notice issued by the U.S. Food and Drug Administration in 2009 on the use of antileukotriene agents (montelukast, zafirlukast, and zileuton) noted the risk of neuropsychiatric side effects (7,8). The European Medicines Agency (EMA) accepted a modification and agreed "Pediatric Investigation Plan" for montelukast in October 2009, and national regulatory agencies accepted that neuropsychiatric events were rare adverse reactions in post-marketing experience (9,10). Reported neuropsychiatric side effects were sleep disturbances, insomnia, nightmares, behavioral problems, irritability, aggressiveness, anxiety, depression, agitation/hyperactivity, and suicidality (3). However, according to some studies, neuropsychiatric side effects in montelukast and placebo groups were similar (6,11,12). The information on side effects was obtained from national databases and the WHO Global Individual Case Safety Report database (VigiBase), rather than the clinical studies (10,13-15). Apart from research based on database information,

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there have been a few clinical studies on neuropsychiatric side effects of montelukast. However, these studies were mostly conducted with asthma patients (3,12,16). Many previous studies revealed an association of asthma with neuropsychiatric problems, such as anxiety, depression, and attention deficit hyperactivity disorder (ADHD), and sleep disorders, in patients not treated with Montelukast (17-22). As a result, the effect of asthma on neuropsychiatric problems, independent of the treatment has not been excluded and makes it difficult to assess the independent effect of montelukast treatment on neuropsychiatric side effects.

In the literature, no studies have performed neuropsychiatric assessments before montelukast use and during follow-up for to determine neuropsychiatric side effects. To more clearly determine the possible neuropsychiatric side effects of montelukast, research is needed on individuals other than asthma patients, with evaluations before and after treatment. The aim of this study was to investigate neuropsychiatric effects of montelukast use before and during treatment. The present study investigated sleep habits, sleep problems, and psychiatric problems among children prior to treatment with montelukast for allergic rhinitis and the evaluations were repeated at the 4th and 8th week of treatment. The hypothesis of the study was that short-term montelukast use in children would not cause changes in sleep habits, sleep problems, or psychiatric problems.

MATERIAL and METHODS

This prospective study was conducted at the Otorhinolaryngology and Child and Adolescent Psychiatry Clinics of Malatya Training and Research Hospital. Approval for this cross-sectional study was obtained from Malatya Clinical Trials Ethics Committee (2019/80).

Participants

The study population consisted of 30 children who attended the otorhinolaryngology clinic due to a diagnosis of allergic rhinitis. The inclusion criteria for the study were as follows: aged six years or older, a diagnosis of allergic rhinitis, agreement to montelukast treatment for allergic rhinitis, no disease present apart from allergic rhinitis (active respiratory tract infection, comorbid asthma, nasal polyposis), no use of medications for any reason in the last six months, and no previous use of immunotherapy for allergic rhinitis. The exclusion criteria were as follows: a diagnosis of a psychiatric disorder in the psychiatric evaluation performed prior to montelukast treatment, cessation of montelukast treatment for any reason within the 8-week follow-up, and taking any medication other than montelukast during the follow-up period.

The study was performed in accordance with the principals of the Helsinki Declaration. All the participants and their parents were given detailed information about the study and its goals, and written consent was obtained from the participants and their parents.

Otorhinolaryngological Assessment

Allergic rhinitis was diagnosed by documenting the presence of the following symptoms: sneezing, a runny nose, congestion, and nasal itching. In addition, a clinical assessment and positive skin prick test were used for confirmation of allergic rhinitis. The same specialist otolaryngologist performed all the examinations and tests.

Psychiatric Assessment

In the psychiatric assessment of the participants, the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version – Turkish Version (K-SADS-PL-T) was used. The K-SADS-PL-T is a semi-structured interview, which assesses psychiatric disorders in the pediatric period according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (23). The reliability and validity of the Turkish version of the tool have been demonstrated previously (24). In the current study, a child and adolescent psychiatrist (YED), who was certified and experienced in administering the K-SADS-PL-T, conducted all the interviews. All the participants underwent a psychiatric assessment three times: before montelukast treatment and at the 4th and 8th week of treatment.

Evaluation of Sleep Habits and Sleep-Related Problems

Sleep habits, sleep-related problems and a variety of neuropsychiatric problems were assessed using the Children Sleep Habits Questionnaire Short Form (CSHQ-S) and the Pediatric Sleep Questionnaire (PSQ).

The CSHQ, developed by Owens et al., was designed to research sleep habits and difficulties related to sleep in children (25). An important feature of the CSHQ is that it is based on the International Classification of Sleep Disorders Revised. The CSHQ-short form contains 33 items. The questionnaire defines eight subscales of resistance to bedtime: delay in falling asleep, sleep duration, sleep anxiety, night waking, parasomnia, disrupted respiration in sleep, and daytime drowsiness. The items are rated on a 3-point scale, with 3 points given for “usually” (the stated behavior occurs 5–7 times per week), 2 points given for “sometimes” (2–4 times per week), and 1 point given for rarely (0–1 time per week), with items 1, 2, 3, 10, 11, and 26 given inverse coding (generally 1, sometimes 2, and rarely 3). The 32nd and 33rd items are coded as 0 for not sleepy, 1 for very sleepy, and 2 for falls asleep. A total of 41 points is accepted as the cut-off, and values above this indicate significant sleep problems at the clinical level. The validity and reliability of the Turkish version of the CSHQ-S form have been demonstrated previously (26).

The PSQ is a questionnaire that can be administered to parents of children aged 2–18 years. It is composed of 22 items that question the frequency and severity of snoring during sleep, apnea at night during sleep, breathing difficulties during sleep, daytime sleepiness, attention deficit hyperactivity, nightmares, sleepwalking, bruxism,

and nocturnal enuresis (27). Responses to the items are given as "yes," "no," and "I don't know," which are scored as 1, 0, and missing, respectively. Six items focus on ADHD defined according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (28). The total score of the PSQ is the mean of the scores for all the items, excluding the missing items. Yüksel et al. previously demonstrated the validity and reliability of the Turkish version of the PSQ (29).

Study Design

Children who were admitted to the otorhinolaryngology clinic, diagnosed with allergic rhinitis, and recommended to use montelukast were referred to the child and adolescent psychiatry clinic before starting treatment. In the child and adolescent psychiatry clinic, all the children underwent a psychiatric evaluation using the K-SADS-PL-T. The parents of the children then completed the PSQ and CSHQ-S. After this first assessment, participants began to use montelukast treatment. All the participants were treated with montelukast in oral granule form (5 mg/d chewable tablets, each tablet contained 5.20 mg of montelukast). At the 4th and 8th weeks of treatment, psychiatric evaluation was repeated and parents answered the PSQ and CSHQ-S again. The data obtained were recorded and statistical analysis performed.

Statistical Analysis

The statistical analysis was performed using SPSS (Version 22.0) software. Descriptive statistics for quantitative data are given as the mean ± standard deviation, and the number and percentage (%) are given for qualitative data. The data obtained from the participants pre-treatment and at the 4th and 8th week of treatment were investigated using the Friedman and McNemar tests. Values of $p < 0.05$ were accepted as statistically significant.

RESULTS

The study was completed with 30 children (boys, n = 15; girls, n = 15). The mean age of the participants was 7.6 years (min-max: 6–12, SD: 1.9). Among the participants, 96.7% had no history of psychiatric diseases in the family, and 93.3% had no history of parasomnias in the family. The data related to age, psychiatric diseases, and familial histories of parasomnias are shown in Table 1.

Table 1. Characteristics of the participants

		n	%
Gender	Male	15	50.0
	Female	15	50.0
Family history of psychiatric disorders	No	29	96.7
	Yes	1	3.3
Family history of parasomnias	No	28	93.3
	Yes	2	6.7

According to the psychiatric assessment performed with K-SADS-PL-T, no psychiatric disease or symptom was identified before treatment and at the 4th and 8th week of treatment.

The CSHQ-S scores of the participants before treatment and at the 4th and 8th week of treatment were compared using the Friedman test. The results revealed no statistically significant difference between the CSHQ-S total scores ($p = 0.853$). When the CSHQ-S subscale scores were investigated (resistance to bedtime, delay in falling asleep, sleep duration, sleep anxiety, night waking, parasomnias, disrupted respiration in sleep, and daytime drowsiness), all the subscale scores before treatment and at the 4th and 8th week of treatment were similar. The CSHQ-S data before treatment and at the 4th and 8th week of treatment are shown in Table 2.

Table 2. Comparison of the children sleep habits questionnaire short form (CSHQ-S) scores

	Before treatment		4th week of treatment		8th week of treatment		
	Median (min-max)	25–75th Percentiles	Median (min-max)	25–75th Percentiles	Median (min-max)	25–75th Percentiles	*p*
Total score	44.0 (31-73)	38.0-55.2	41.5 (31-68)	38.7-52.0	42.0 (32-76)	36.0-54.5	0.853
Resistance to bedtime	9.0 (6-18)	6.0-11.2	9.5 (6-15)	7.0-11.0	7.5 (6-18)	6.0-10.0	0.321
Delay in falling asleep	1.0 (1-3)	1.0-1.0	1.0 (1-3)	1.0-1.0	1.0 (1-3)	1.0-1.0	0.834
Sleep duration	3.0 (3-8)	3.0-5.0	3.0 (3-7)	3.0-4.2	3.0 (3-8)	3.0-5.0	0.731
Sleep anxiety	6.0 (4-12)	4.0-8.2	6.0 (4-12)	5.0-9.2	6.0 (4-12)	4.0-7.2	0.572
Night waking	3.5 (3-8)	3.0-6.0	4.0 (3-8)	3.0-5.0	5.0 (3-9)	3.0-5.0	0.075
Parasomnias	9.0 (7-17)	1.7-10.2	8.0 (7-13)	7.0-10.0	8.5 (7-15)	7.0-11.2	0.768
Disrupted respiration in sleep	5.0 (3-9)	3.0-9.0	5.0 (3-9)	3.0-6.0	4.0 (3-9)	3.0-6.2	0.080
Daytime drowsiness	9.5 (6-18)	8.0-13.0	9.5 (6-16)	8.0-12.0	9.5 (6-22)	8.0-11.2	0.717

p value from the Friedman test

The PSQ total scores and "attention deficit hyperactivity" subscale scores of the participants were compared using the Friedman test. The results revealed no statistically significant differences between the PSQ total scores (p = 0.095) and attention deficit hyperactivity (p = 0.305) subscale scores before treatment versus those 4th and 8th week of treatment. As none of the participants reported sleepwalking before or during the treatment period, this item was excluded from the statistical analysis. The responses of the participants to the questions related to snoring during sleep, apnea at night during sleep, breathing difficulties during sleep, daytime sleepiness, nocturnal enuresis, bruxism, and nightmares included on the PSQ before treatment and at the 4th and 8th week of treatment were compared using the McNemar test. The statistical analysis revealed no significant differences between the responses before treatment versus those 4th and 8th week of treatment (Table 3).

Table 3. Comparison of the pediatric sleep questionnaire (PSQ) responses and scores

	Before treatment	4th week of treatment		p	Before treatment	8th week of treatment		p*
		No	Yes			No	Yes	
Snoring during sleep	No	10 (71.4)	4 (28.6)	1.000	No	11 (78.6)	3 (21.4)	1.000
	Yes	5 (31.2)	11 (68.8)		Yes	4 (25.0)	12 (75.0)	
Apnea at night during sleep	No	25 (96.2)	1 (3.8)	1.000	No	25 (96.2)	1 (3.8)	1.000
	Yes	2 (50.0)	2 (50.0)		Yes	2 (50.0)	2 (50.0)	
Breathing difficulty during sleep	No	8 (88.9)	1 (11.1)	0.125	No	5 (55.6)	4 (44.4)	0.267
	Yes	6 (28.6)	15 (71.4)		Yes	9 (42.9)	12 (57.1)	
Daytime sleepiness	No	10 (76.9)	3 (23.1)	0.625	No	11 (84.6)	2 (15.4)	1.000
	Yes	1 (5.9)	16 (94.1)		Yes	1 (5.9)	16 (94.1)	
Nocturnal enuresis	No	22 (95.7)	1 (4.3)	1.000	No	22 (95.7)	1 (4.3)	1.000
	Yes	2 (28.6)	5 (71.4)		Yes	2 (28.6)	5 (71.4)	
Bruxism	No	24 (100.0)	0 (0)	0.500	No	24 (100.0)	0 (0)	0.500
	Yes	2 (33.3)	4 (66.7)		Yes	2 (33.3)	4 (66.7)	
Nightmares	No	23 (95.8)	1 (4.2)	1.000	No	22 (91.7)	2 (8.3)	1.000
		2 (33.3)	4 (44.7)		Yes	2 (33.3)	4 (66.7)	

	Before treatment		4th week of treatment		8th week of treatment		p**
	Median (min-max)	25–75th Percentiles	Median (min-max)	25–75th Percentiles	Median (min-max)	25–75th Percentiles	
Attention deficit hyperactivity subscale score	1.00 (0-4)	0.00-1.00	1.00 (0-4)	0.00-1.00	1.00 (0-4)	0.00-1.00	0.305
PSQ (total score)	0.41 (0.04-1.00)	0.21-0.54	0.31 (0.04-0.86)	0.10-0.46	0.33 (0.04-1.62)	0.10-0.50	0.095

*p** value from the McNemar test. ** *p* value from the Friedman test.

DISCUSSION

In the current study, sleep habits, sleep-related problems, and psychiatric problems among children prior to montelukast treatment for allergic rhinitis and at the 4th and 8th week of treatment were investigated. The results revealed that short-term montelukast use did not cause changes in any of the aforementioned factors.

The majority of previous studies that evaluated neuropsychiatric side effects of montelukast were based on database investigations. Based on data from the Adverse Drug Reaction Swedish database (SWEDISH), researchers reported that montelukast use increased the risk of neuropsychiatric events in children (13,30). "Sleep terrors" and "nightmares" were the most frequently reported adverse neuropsychiatric reactions for montelukast use in the analysis of the SWEDISH database during 2001–2010 (30). Studies using data from national pharmacovigilance databases in France and Spain recorded similar findings (14,15). Apart from national databases, some investigators used data from larger databases, such as VigiBase, which is maintained by the Uppsala Monitoring Centre on behalf of the WHO and includes data from 49 countries. In a study by Perona et al. on adverse drug reactions recorded in VigiBase up to 1 January 2015, the most common side effects reported after montelukast use among those aged younger than 18 years were psychiatric disorders (36%), followed by nervous system disorders (24%). They reported psychiatric disorders comprised personality and behavioral disorders (36%), sleep disorders (36%), mood disorders (36%), anxiety disorders (31%), suicide and self-harming behavior (26%), and depressive disorder (23%) (10). Based on data from the Dutch database of the Netherlands Pharmacovigilance Center Lareb and VigiBase, Haarman et al. reported that depression, aggression, suicidal ideation, abnormal behavior, and nightmares were shown high in children following montelukast treatment (7).

However, data collected from medication side effect reports cannot shed light on the frequency of side effects. In addition, the majority of reports in these databases refer to asthma patients. Many previous studies found that asthma was associated with neuropsychiatric problems, including anxiety, depression, ADHD, suicide, self-harm behavior, and sleep disorders, in the absence of montelukast use (17-22,31). As a result, it is not possible to evaluate the specific neuropsychiatric effects of montelukast use reported in studies based on data obtained from databases.

Clinical investigations assessing the possible neuropsychiatric effects of montelukast are based mainly on case reports and a few retrospective studies (3,12,16,32). In a review, Calapai et al. investigated case reports of side effects linked to montelukast use up to 1 March 2014 (3). In this review, they listed the neuropsychiatric effects considered to be linked to montelukast use as hallucinations, nightmares, sleep disorders (i.e., insomnia, somnolence, night terrors, sleepwalking, and sleep disturbance), behavioral and mood disorders, and suicidal ideation. However, the majority of the case reports included in their review were based on adult asthma patients and patients treated with different combined medications, which may cause neuropsychiatric side effects together with Montelukast (3). In a retrospective cohort study on children aged 1–17 years, children who used montelukast (as monotherapy or adjunct therapy to inhaled corticosteroids) were compared with those who used inhaled corticosteroids as monotherapy (16). The results showed that the cessation rate of medication use linked to neuropsychiatric side effects in the group using inhaled corticosteroids as monotherapy was 1%, whereas this rate was 12 times more in children using montelukast as monotherapy or inhaled corticosteroids, together with montelukast. The same study reported that 75% of neuropsychiatric side effects occurred within 14 days. The most commonly reported neuropsychiatric side effects were irritability, aggression, and sleep problems. Furthermore, these side effects disappeared 3.5 days after medication cessation (16). However, in another retrospective cohort study Ali et al. evaluated 1,920 asthma patients younger than 18 years and did not identify a significant and consistent correlation between montelukast use and neuropsychiatric events (12). In a retrospective analysis of adult and pediatric placebo-controlled trials, Philip et al. showed that behavior-related adverse drug reactions occurred in 2.73% of patients treated with montelukast, and such reactions were not more frequent in the montelukast group than in the placebo group (32).

The current research was a prospective study evaluating neuropsychiatric events before and after montelukast treatment in children with allergic rhinitis. The majority of database investigations and retrospective studies in the literature were conducted with asthma patients. In addition, the majority of case reports are of adults with asthma, and multiple medication use is mentioned. The presence of neuropsychiatric side effects independent of treatment, long durations of treatment, and a high possibility of the use of different treatment choices during the treatment period make it difficult to investigate the independent neuropsychiatric effects of montelukast in asthma patient group. For all these reasons, it is not appropriate to compare the results of the current study with those of database investigation studies and retrospective studies in the literature. However, the results of this study are consistent with the study of Ali et al. and Philip et al. (12,32).

The limitations of this study are its cross-sectional nature, low sample size and the fact that the data on sleep-related problems were obtained from scales completed by the parents. In addition, the data are specific to children treated with a 5 mg/d dose of montelukast for a short period (eight weeks). Thus, it is not possible to generalize these results to patients with long-term use or higher daily doses of montelukast or to adults.

CONCLUSION

This study revealed that short-term montelukast use does not cause changes in children's sleep habits and does not cause sleep disorders and neuropsychiatric side effects. However, it is not possible to generalize the results of this study. Long-term follow-up studies with high numbers of participants are needed to test these results and to assess possible neuropsychiatric effects of long-term montelukast use.

Competing interests: The authors declare that they have no competing interest.

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