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Adverse drug reactions affecting treatment adherence in first-line treatment of asthma: An observational study

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Abstract
Background: Asthma is the most common chronic lung disease among children. International guidelines recommend inhaled corticosteroids (ICS) as the first-line daily controller therapy for children with asthma and leukotriene receptor antagonists (LTRA) as the second alternative therapy. Adherence to treatment is the most significant component to optimize the benefits of therapy in asthma.
Objective: This study aims to investigate the frequency of drug discontinuation due to adverse drug reactions (ADRs) that affect adherence to treatment in children with asthma or asthma and allergic rhinitis using LTRA or ICS as monotherapy.
Methods: The subjects aged 4-18 years with asthma or asthma and allergic rhinitis and using montelukast or ICS as monotherapy were included in the study. They were evaluated in terms of ADRs affecting adherence to treatment in the first and third months of treatment.
Results: A total of 468 cases, 356 of whom received montelukast monotherapy and 112 of whom received ICS treatment, with a mean age of 9.10 ± 3.08 (4-17) years, were included in the study. Males constituted 65.6% of the total cases (n = 307). In the first month of follow-up of the cases, it was observed that 4.8% (n = 17) of the patients in the montelukast group could not continue the treatment due to ADR. It was determined that the drug discontinuation rate in the montelukast group in the first month was significantly higher than in the ICS group (P = 0.016), and the risk of drug discontinuation due to ADR in the montelukast group was 1.333 (95% CI, 1.26-1.40) times higher.
Conclusions: As a result, it was observed that the drug was discontinued due to ADR at a higher rate in children with asthma who received montelukast monotherapy compared to those who received ICS monotherapy.

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Introduction

Asthma is the most common chronic disease of childhood, resulting in significant morbidity and high costs for children and their parents. International guidelines recommend inhaled corticosteroids (ICS) as the first-line daily controller therapy for children with asthma and leukotriene receptor antagonists (LTRAs) as the second alternative therapy.[1] LTRAs are preferred in cases where patients cannot or do not want to use ICS for the treatment of asthma, or who have to discontinue this drug due to side effects of ICS, or who have allergic rhinitis as comorbidity of asthma.[2] In patients whose asthma is not controlled with ICS treatment, adding a second drug rather than increasing the dose of ICS may provide better control of symptoms. In this case, LTRA add-on therapy may be preferred.[2,3] Adherence to treatment is the most significant component to optimize the benefits of therapy in asthma.

ICS provide an effective and safe treatment among children with asthma, at least at low doses. Systemic side effects of ICS such as growth suppression (with a mean reduction of 1 cm in an adult's height) and local side effects, including oropharyngeal candidiasis, are well known. With new studies offering greater adherence to and efficacy of LTRA compared to ICS, the expectation of increased adherence resulting in better asthma control has revived the interest in the use of LTRA as monotherapy or adjunctive therapy.[4]

Montelukast, the only LTRA licensed for use in children younger than 12 years, appears to be generally well tolerated. It has been reported that montelukast-associated adverse drug reactions (ADRs) are primarily limited to mild gastrointestinal disturbances, respiratory symptoms, skin reactions, and headaches. Moreover, the facts that montelukast does not cause growth and adrenal suppression, does not require the correct inhalation technique and spacer use as with ICS, and is taken orally once a day make it more preferred by children with asthma, their parents, and even physicians.[1,4,5]

It has been reported that montelukast can provide similar efficacy, although less effective than ICS, because it has a better possibility of adherence to treatment for all these reasons. The expectation of improved asthma control with increased adherence to montelukast compared to ICS has revived the interest in the use of montelukast as monotherapy or adjunctive therapy. Montelukast, therefore, is often used as an initial control treatment.[1,4-7]

Although it has been reported that montelukast is generally well tolerated, serious neuropsychiatric ADRs have been reported in some clinical trials. Due to the risk of increase in neuropsychiatric ADRs following the use of montelukast and other LTRAs (including aggressive behavior, anxiety, depression, abnormal dreams, excitement, hallucinations, insomnia, irritability, and potential suicidality), the United States Food and Drug Administration (FDA) issued a safety announcement about serious neuropsychiatric ADRs associated with montelukast on March 4, 2020.[8,9] The pharmacological mechanisms that cause neuropsychiatric ADRs remain a mystery.[9]

Anxiety, sleep disturbances, depression, and suicidality are the most significant neuropsychiatric ADRs reported in studies.[5] Sleep disorders among infants and children, depression or anxiety, and psychotic reaction symptoms among adolescents are reported more frequently. It is seen that suicidal behavior and completed suicide have been reported more frequently in practice than previously considered.[10] In conclusion, the incidence of montelukast-associated neuropsychiatric ADRs among children still remains uncertain.[4]

This study aimed to investigate the frequency of drug discontinuation due to ADRs that affect adherence to treatment in children with asthma or asthma and allergic rhinitis using LTRA or ICS as monotherapy.

Method

Study population

In addition to 356 cases, aged 4–18 years with asthma or asthma and allergic rhinitis and receiving montelukast monotherapy, 112 cases in a similar age group and receiving ICS monotherapy were included in the study carried out at the Izmir Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital and Izmir Bakırçay University Çiğli Training and Research Hospital Pediatric Immunology and Allergy Diseases Departments between January 2017 and December 2021. Those who had previously used the mentioned drugs, the cases with additional chronic or psychiatric diseases, and those with a family history of neuropsychiatric disease were not included in the study. The cases that required drug treatment in addition to montelukast or ICS during the first 3 months of follow-up were also excluded from the study. The ICS used in the ICS group were budesonide, fluticasone, and ciclesonide, and they received low and medium doses according to the age group. The correct use of the drugs was explained to the families prior to the treatment.

The groups using montelukast and ICS were evaluated in the first and third months of treatment for ADR affecting the adherence to treatment. They were recommended to apply without waiting for the control date in case of any suspicion of ADR before the date of control. The side effects that were not present before the treatment, but that were observed and noted by the family following the treatment, were taken into consideration. The type of symptoms, the time when they were noted, the number of days it took to recover following the discontinuation of the drug in the cases that applied with ADR were recorded. Except for the cases with hallucinations and that with suicidality, it was observed that the symptoms disappeared with the discontinuation of the treatment (dechallenge), and similar symptoms recurred upon resume of montelukast administration (rechallenge). The cases with hallucinations and their parents did not agree with using the drug again. During the change of the treatment in the follow-up, whether the symptoms recurred or were not monitored. The severe ADR requiring the discontinuation of the drug in the montelukast group and the severe ADR requiring the discontinuation of the drug in the ICS group, as well as the treatment adherence, were compared.

In cases with side effects, the psychiatrist evaluation that was planned in the beginning could not be performed due to not obtaining the consent of the families. The study

was approved by the Ethics Committee (University of Health Sciences, Izmir Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Clinical Researches Ethics Committee, 2014/15) and the Turkish Medicines and Medical Devices Agency, and a written informed consent was obtained from all parents.

Statistical analysis

SPSS (version 22) package program was used for the statistical analysis of the data. The Shapiro–Wilk test was used to evaluate the distribution of the data. While the analysis of categorical data was provided as numbers and percentages, the normally distributed quantitative data were calculated as mean ± standard deviation, and data that were not normally distributed were calculated as median and minimum–maximum. The chi-squared test was used for categorical data in the comparison of groups and to evaluate the odds ratios upon the discontinuation of treatment. A value of $P < 0.05$ was considered statistically significant.

Results

A total of 468 children, 356 of whom received montelukast monotherapy and 112 of who received ICS monotherapy, with a mean age of 9.10 ± 3.08 (4–17) years, were included in the study. Among the cases, 65.6% (n = 307) were males and 34.4% (n = 161) were females, where 51.7% (n = 242) followed with atopic asthma and allergic rhinitis and 48.3% (n = 226) followed with atopic asthma.

In the first month follow-up of these cases, the treatment continuation rate in the montelukast group was 95.5%, while the treatment continuation rate in the ICS group was 100%. It was observed that 4.8% (n = 17) of the patients in the montelukast group could not continue the treatment due to ADR. These ADRs were as follows: hallucinations in 2.0% (n = 7), night fears and sleep disturbances in 1.7% (n = 6), hyperactivity, aggressive offensive behaviors and destructivity in 0.6% (n = 2), night fears and suicidality in 0.3% (n = 1), and nausea and vomiting in 0.3% (n = 1). It was determined that the drug discontinuation rate in the montelukast group in the first month was significantly higher than in the ICS group (P = 0.016), and the risk of drug discontinuation due to ADR in the montelukast group was 1.333 (95% CI, 1.26–1.40) times higher in the first month.

In the third month evaluation of the cases, it was observed that the drug was discontinued in four more cases in the montelukast group due to its side effects. These side effects were 0.6% (n = 2) hyperactivity, aggressive offensive behaviors, and destructivity, and 0.6% (n = 2) night fears and sleep disturbances. On the other hand, 4.4% (n = 15) of the patients stated that they discontinued the drug due to the improvement in symptoms and concerns regarding side effects. In the third month, it was observed that a total of 19 patients (4 patients due to side effects, 15 patients voluntarily) in the montelukast group discontinued the drug treatment. In the ICS group, no patient discontinued the drug due to side effects. However, it was observed that 11.7% (n = 13) of the patients discontinued their drugs due to an improvement in their symptoms and concerns about side effects. In the third month, the rate of drug discontinuation was significantly higher (P = 0.006) in the ICS group due to concerns about side effects or the child being asymptomatic.

At the end of the third month, it was observed that a total of 41 (11.5%) patients in the montelukast group discontinued treatment, 21 (5.9%) of whom discontinued due to ADR and 20 (5.6%) due to an improvement in symptoms or concerns about side effects. In the ICS group, there were no cases of drug discontinuation due to the development of side effects, while it was determined that 13 (11.7%) patients discontinued their treatment due to an improvement in symptoms and concerns about side effects in the third month. In total, the drug discontinuation rate due to side effects was found to be significantly higher in the montelukast group (P = 0.008), and the risk of drug discontinuation due to side effects at the end of the third month was 1.338 times higher than in the ICS group (95% CI, 1.26–1.41).

Montelukast-associated ADRs were observed to improve within a mean of 2.6 ± 1.45 (0–7) days following the discontinuation of the drug, while symptoms improved within 2 days after discontinuation of the drug in seven patients with hallucinations, and within 7 days in the case with suicidality. Except for the cases whose treatment was discontinued due to hallucinations and the case with suicidality, the occurrence of drug side effects was confirmed with rechallenge. The cases with hallucinations and their parents definitely did not agree to use the drug again (Tables 1 and 2).

Table 1 Reasons for drug discontinuation at 3-month follow-up in the montelukast and ICS groups.

	Montelukast		Inhaled corticosteroids			
	1 month	3 months	1 month	3 months	Total (n)	P
Patients, n	356		112		468	
ADR reported by parents, n	17	4	0	0	21	
ADR confirmed by rechallenge*, n	9	4	0	0	13	
Drug discontinuation due to ADR, % (n)	4.8 (17)	1.2 (4)	0 (0)	0 (0)	21	0.008
Drug discontinuation due to non-ADR, % (n)	0 (0)	4.4 (15)	0 (0)	11.7 (13)	28	0.006

ADR, Adverse drug reaction; ICS, inhaled corticosteroids.
*The cases with hallucinations and their parents definitely did not agree to use the drug again. Rechallenge was not performed for these cases.

Table 2 Characteristics of adverse drug reactions (ADRs) with montelukast.

	Montelukast			
	1 month	3 months	Time of emergence	Recovery time
Hallucination, n	7	0	2–3 weeks	1–2 days
Night fears and sleep disturbance, n	6	2	2–3 weeks	3 days
Night fears and suicidality, n	1	0	2–3 weeks	7 days
Hyperactivity, aggressive offensive behavior, and destructivity, n	2	2	2–3 weeks	3 days
Nausea and vomiting, n	1	0	First week	1 day

Discussion

In this study, it was observed that the drug was discontinued due to ADR at a higher rate in children with asthma and who received montelukast monotherapy compared to those who received ICS monotherapy. In the first 3 months of the treatment, the rate of drug discontinuation due to ADR was 5.9% in the montelukast group. While no case of drug discontinuation due to side effects in the ICS group was observed in 3 months, the main reason for drug discontinuation in this group was side effect anxiety and steroid phobia. Almost all of the ADRs in the montelukast group were neuropsychiatric in nature. Adverse effects reported in the montelukast group were hallucinations, night fears and sleep disturbances, suicidality, hyperactivity, aggressive offensive behaviors, destructivity, nausea, and vomiting. In the cases with nausea and vomiting, symptoms appeared in the first week of treatment, while neuropsychiatric ADRs were generally observed after 2–3 weeks of the treatment. Within a mean of 2.6 ± 1.45 (0–7) days following the discontinuation of treatment, it was observed that the symptoms improved within 2 days following the discontinuation of the drug in seven patients with hallucinations, and within 7 days in the patient with suicidality.

In an analysis of adult and pediatric placebo-controlled studies carried out by Philip et al.[11] in 2009, behavior-related ADRs were reported to occur in 2.73% of patients treated with montelukast, and it was reported as 2.27% in the placebo group. However, in a meta-analysis of pediatric randomized controlled studies carried out in 2014, it was stated that montelukast-associated neuropsychiatric ADRs were underreported.[12] In a review of cases published in the same year due to montelukast-associated ADR, psychiatric and nervous system disorders (agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior [suicidality], tremor, dizziness, drowsiness, paresthesia/hypoesthesia, and very rarely seizures) were observed in both adult and pediatric cases. It was reported that the symptoms disappeared following the discontinuation of the drug, but pediatric cases should be followed more carefully in terms of symptoms.[3]

Haarman et al.[13] reviewed all montelukast-associated ADRs among children and adults reported to Netherlands Pharmacovigilance Center Lareb and the WHO Global database, VigiBase®, until 2016. They reported that depression was the most frequently reported ADR among the entire population. Aggression was most frequently reported in children, while nightmares were the frequent neuropsychiatric ADRs recorded in the database in both children and adults. It was emphasized that severe neuropsychiatric ADRs may occur among both adults and children to whom montelukast is prescribed; in particular, nightmares may be seen right after the initiation of montelukast.[13]

Benard et al.[4] retrospectively reviewed the frequency and risk of neuropsychiatric adverse events among children to whom montelukast was prescribed with ICS in a pediatric asthma clinic. Of the 106 cases to whom montelukast was initiated, 16% discontinued using the drug because of neuropsychiatric ADR. These neuropsychiatric ADRs mostly occurred within 2 weeks following the initiation of the drug. The most common ADRs were irritability, aggression, and sleep disturbances. The risk of montelukast-associated neuropsychiatric ADRs was 12 times greater than with ICS. The researchers stated that children with asthma and receiving montelukast treatment had a significantly greater risk of neuropsychiatric ADR leading to discontinuation of the drug than children using ICS.[4] The study was performed prospectively. It was considered that the lower rate in our study may be related to the perception levels of the families.

In a case–control study by Glockler-Lauf et al.,[14] which compared 898 cases and 3497 controls, it was reported that children to whom montelukast was prescribed were twice as more likely to have a neuropsychiatric experience compared to controls. Most of the cases reported in the study applied for anxiety (48.6%) and/or sleep disturbances (26.1%).[14]

Sansing-Foster et al.,[15] using the Sentinel Distributed Database (SDD), compared 457,377 children aged 6 years and older with asthma and using ICS or montelukast in terms of hospitalizations due to depression or self-harm events, and reported that the risk was similar in both groups.[15]

Ekhart et al.[16] analyzed 918 pediatric psychiatric ADRs reported between 2003 and 2016 and reported that the drugs used for the treatment of attention deficit and hyperactivity disorder (methylphenidate and atomoxetine) and those used for asthma treatment (montelukast and fluticasone) were the most frequently reported drugs.[16] Contrary to this study, psychiatric ADR was not reported in our patient group using ICS.

Yılmaz Bayer et al.[17] reported neuropsychiatric ADRs among 62.4% of 125 patients aged 3–18 years using montelukast. Posttreatment temperamental behavior, nightmares, and sleep disorders were significantly more frequent than pretreatment. In this study, the researchers found that the

quality of life of the cases with ADR was more affected than the cases without ADR. They remarked that montelukast-associated neuropsychiatric ADRs are more common than they are reported in the literature and negatively affect the quality of life of children.[17]

In a meta-analysis involving 15 studies, Dixon et al.[18] reported that "anxiety," "sleep disturbances," and "mood disorders" were the most frequently reported ADRs in 7012 cases aged 0–18 years using LTRA. They remarked that the side effects associated with LTRAs are predominantly gastrointestinal and neuropsychiatric disorders.[18]

In the literature, there are few cases of montelukast-associated hallucinations.[19-21] In 2015, Erdem et al.[21] reported 4 hallucinations in 1024 cases. In 2021, hallucinations were reported in 5 of 7012 cases aged 0–18 years in the meta-analysis that also involved the cases mentioned.[18] All of these five reported cases of hallucinations were from Turkey. Özata et al.[20] reported 1 hallucination in 50 cases using montelukast in 2022. It was remarkable to observe hallucinations in 7 out of 356 cases in our patient group. The questions "Could this be a predisposition to some side effects in some ethnic groups? Is it a problem related to the preparations produced in our country?" come to mind.

Psychiatric disorders in patients with asthma constitute the largest component of the enormously increased comorbidity costs. Neuropsychiatric adverse events are particularly important because the psychiatric disorders are responsible for the most significant costs associated with comorbidity in asthma.[9,10,22] In addition to the fact that neuropsychiatric adverse events constitute the most important costs associated with comorbidity in asthma, their negative effects on the quality of life of patients should not be ignored either.[9,17] Although most of the neuropsychiatric disorders and sleep disturbances affecting the pediatric population more frequently improved clinically following the discontinuation of montelukast, their negative effects on the quality of life of patients in the long term are still unknown.[3,4,9] The psychiatric evaluation that we planned in our study could not be performed because the families did not give consent.

In conclusion, while the rate of drug discontinuation due to ADR in the first 3 months of treatment in children with asthma and receiving montelukast monotherapy was 5.9%, there were no cases of drug discontinuation due to ADR in cases receiving ICS monotherapy. Almost all of the ADRs in the montelukast group were neuropsychiatric ADRs. All clinicians who follow up and treat children with asthma should be aware of the relationship between montelukast and neuropsychiatric ADRs. Clinicians should consider the benefits and risks before prescribing montelukast.[14] It is important to comply with the warning "use by considering the possible side effects" issued by the FDA in March 2020, by discussing with the families of the cases in which montelukast will be used.[8] Following up with these neuropsychiatric ADRs should be integrated into the current asthma guidelines. Furthermore, it is important to establish a system where families can report new concerns during treatment. This will enable clinicians to adjust treatment plans earlier and improve adherence in addition to enhancing general patient satisfaction.[4]

More research should be conducted to elucidate the mechanisms that cause ADRs related to LTRAs.[3,9] It would be beneficial to conduct studies that would allow for the identification of individual predictors of montelukast-associated neuropsychiatric adverse events and to identify risk factors for adverse reactions. Although most of the neuropsychiatric ADRs that are frequently observed in the pediatric population improved clinically following the discontinuation of montelukast, studies must be conducted to determine whether they cause long-term psychiatric problems or not and their long-term effects on the quality of life of patients.

Limitations of the Study

1. Comprised a short period of time, that is, the first 3 months of treatment
2. Possibility of parental educational status and perception levels to have affected the results, because the side effects were not present before treatment, but the family observed and noted them after treatment
3. The fact that the psychiatrist evaluation that was planned in the beginning for the cases with side effects could not be performed due to not obtaining consent from the families.

Statement of Ethics

The local Ethics Committee granted the approval for the study (Izmir Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital, Clinical Researches Ethics Committee, 2014/15).

Conflict of Interest

The authors have no conflicts of interest to disclose.

Financial Disclosure

The authors declared that no financial support was received for this study and there no financial relationships relevant to this article to disclose.

Author Contributions

SBE designed the research, followed up with patients, performed data collection, wrote the paper, analyzed results, edited the paper; HTN designed the methodology, analyzed results, edited the paper; DC followed up with patients, performed data collection, edited the paper.

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