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MOOD AND BEHAVIORAL CHANGES ASSOCIATED WITH MONTELUKAST USAGE IN PEDIATRIC CASES

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Abstract

Aim: As leukotriene antagonists are known to be safe in pediatric cases, their side effects should be considered. The purpose of this study is to evaluate the mood and behavioral changes arised with montelukast treatment in pediatric cases.

Patients and Methods: A retrospective study was enrolled with the records of totally 172 patients, 97 of whom were considered as the study group and had the diagnoses of allergic diseases like asthma, allergic rhinitis, etc. and were given montelukast treatments, 75 of whom were considered as the control group and had the diagnoses of allergic and non allergic diseases and were not given montelukast treatments. All patients' demographical datas, mood and behavioral situations of the all allergic and non allergic patients at the beginning of the study, mood and behavioral changes in the allergic study group patients before montelukast treatments (group A), during montelukast treatments (group B) and after montelukast treatments (group C) were evaluated.

Results: Mean of age was 6.11 in the study, 8.12 in the control group (p=0.798). All of the asthmatic patients and all of the non asthmatic patients did not differ from each other in mood and behavioral disorders existed at the beginning of the study (p>0.05). Sleep disturbance (p=0.021), irritation (p=0.000), aggressiveness (p=0.004) and hallucination (p=0.031) were observed more in group B when compared with the patients in group A. Mood and behavioral changes seen in group C did not differ from group A (p>0.05).

Conclusions: Patients who are mentally stable before montelukast treatments may have some disturbances in mood and behaviors during treatments so attention should be paid for such reactions. Clinicians should suspect if the patient has unexpected reactions after montelukast. And further studies are needed to evaluate these datas.

Introduction

Asthma is a chronic inflammatory disorder of the airways and it is the most common (9%) chronic illness of the childhood (1). The follow-up and treatment of asthma is very important in pediatric cases. Many drug studies are made to find the suitable and effective treatments. Cysteinyl leukotrienes, causing bronchoconstriction and inflammation are released in patients with asthma (2). So leukotriene receptor antagonists (LTRAs) are used for the treatments. LTRAs are used in long term control as single or additive therapy for mild and persistant asthma. As their efficacies are known, side effects should be considered. Many studies about their efficacies and safeties have been made in adults and pediatric cases, and generally they have been considered as safe and well tolerated (3,4,5). Also antiviral and anti-inflammatory effects of montelukast were also evaluated in pediatric patients (6).

Although chronic diseases like asthma may cause behavioral and mood disorders in childhood (7,8,9), LTRAs used for asthma treatments may cause these disorders (10,11) .

Studies were made to detect the behavioral and mood changes occured in pediatric patients with asthma. Also studies were made to detect if these changes came up because of asthma itself or because of LTRAs used in its treatment.

So we wanted to show if leukotriene antagonists (montelukast sodium) used for pediatric allergic diseases have any side effects in mood and behavioral situations.

Patients and methods

A retrospective study was conducted between September 2013-November 2013 in Pediatric Allergy and Immunology Outpatient Clinic at Samsun Education and Research Hospital. Totally 172 patients' records (n:97 in study group, n:75 in control group) of demographical datas, diagnoses and their treatments were researched. Patients were evaluated according to their and their parents' answers to the questions during their applications.

Patients were divided into two groups (study and control) according to whether they were given montelukast treatments or not. The study group was (n:97) formed from the patients who had been given montelukast for asthma and other allergic diseases such as atopic dermatitis, allergic rhinitis previously and currently. Patients who had the same allergic diagnoses, also non allergic diseases and did not have montelukast treatments previously and currently were considered as the control group (n:75). Children with the histories of previous and current psychiatric disorders were eliminated from this study.

All patients' complaints at the time of the applications to the hospital and records of the questions asked to the patients and their parents were evaluated. Also patients treated with montelukast were evaluated according to their sleep disturbances, sleep abnormalities, sleepwalking, irritability, anxiety, hallucinations, aggressiveness, and thought disorders observed before montelukast treatments (group A), during montelukast treatments (group B) and after montelukast treatments (group C).

Statistical Analysis

Analyses of demographical data were made with Kolmogrov Smirnov test. Frequencies of datas, between the groups were compared using chisquared tests (McNemar) or Fisher's exact test (two-tailed test). A p value of less than 0.05 was considered statistically significant. Association between mood and behavioral disorders and situation of drug usage were analysed with McNemar test.

Statistical analysis was carried out by using the SPSS 10.0 program. A value of $p< 0.05$ was considered statistically significant.

Results

Totally 172 records of patients were enrolled into the study. Patients were divided into to two groups according to if they were given montelukast treatments or not. 97 of them (56.4%) were diagnosed with allergic diseases such as asthma, allergic rhinitis and were given montelukast treatments. Mean age was 6.11 (age range: 1-16 years, standard dev:3.172, 54 boys/43 girls). Control group consisted of 75 patients (43.6%) and were diagnosed both with allergic and non-allergic diseases. But they did not have the montelukast therapies. The mean of age was 8.12 (age range: 1-18 years, standart dev:5.273, 32 boys/ 41 girls). Patients in the study and control group did not differ statistically according to their mean of ages (Table-1).

There were no statistical differences between all of the allergic (n:107) and all of the non allergic patients' mood and behavioral disorders existed (n:65) at the beginning of the study ($p>0.05$) (Table-2).

According to the mood and behavioral changes observed in group B, sleep disturbance (n:18, $p=0.021$), irritation (n:31, $p=0.000$), aggressiveness (n:34, $p=0.004$), hallucinations (n:7, $p=0.032$) were significantly higher than group A. Other mood and behavioral disorders were not statistically significant in group B when compared with group A ($p>0.05$) (Table-3).

There were no statistical differences in the mood and behavioral changes seen in group C and group A ($p>0.05$) (Table-4).

Discussion

The treatment of asthma is based on the asthma severity and the level of the patients' disease control. The aim to maintain the control of the disease in the patients with stable symptoms is to prevent asthma attacks and to increase the life quality. For this reason leukotriene antagonists are used for the long term therapy for both monotherapy (10) or combination therapies (12,13).

Altough some clinical studies showed that behavioral and development disorders were observed more in the patients with asthma and also this was associated with the severity of it (14). Other studies showed no relationship between behavioral disorders and cysteinyl leukotrienes and their receptors occured in asthma (15). In our study, all allergic patients' mood and behavioral disorders that existed at the beginning of the study with the non-allergic patients' did not have statistical differences ($p>0.05$) so this showed that allergy did not affect patients' mental or emotional situations.

Cytokine expressions elevated with mediators of allergy in the brain by the allergic inflammation cause mood and behavioral changes. As a result montelukast may not be enough to reduce these mediators and this may cause the risk of suicide in allergic patients (16). It was found that risk of suicide increased in the allergic patients who did not have histories of mood disorders before, but had histories of allergy, and this caused an increase for suicide attemption (17). Also allergic sensitizations and allergic rhinitis were found statistically higher (67.5%) in the patients having attention deficit and hyperactivity disorders (18).

We evaluated that allergic patients had more sleep disturbances, irritation, aggressiveness and hallucination during their therapies with montelukast ($p<0.05$) when compared with the patients' mood and behavioral situations existed before their montelukast treatments ($p>0.05$). This might be both due to inadequate decrease of allergic mediators in allergic reactions and might cause these side effects or due to the side effects of montelukast appear during the treatments. But as the mood and behavioral changes did not differ statistically after montelukast usage ($p>0.05$), it was understood that side effects were due to montelukast and they decreased after stopping the drug.

According to the individual case safety report (ICSR) <18 years old patients between 2001-2010, psychiatric adverse reactions who used montelukast were detected in 60 (10%) of 600 patients. Sleep disorders were found in 34 (56.7%) cases who used montelukast (19). So studies and case reports took attention for the psychiatric adverse reactions and sleep disorders occurred after montelukast treatments (20). We also found sleep disturbances 18.6% ($p=0.021$), sleep abnormality 9.3% ($p>0.05$), sleepwalking 2.1% ($p>0.05$) and totally sleep disorders 30% during montelukast usage. Wu WF et al. found no intolerability or adverse reactions after 12 weeks of montelukast usage in patients aged between 2-14 years (21).

Placebo controlled 35 adult (≥15 years) and 11 pediatric (age between 3 months and 14 years) studies were evaluated and behavior related adverse experiences (BRAEs) were found 2.73% in the montelukast, 2.27% in placebo groups. Frequencies of BRAEs were similar between montelukast and placebo groups and suicidality was very rare in montelukast group (22). Reviews of clinical adverse reactions related from 116 studies were reported and suicidality were evaluated. Adverse experience and suicidality related to montelukast were rare and similar between placebo, active control and drug group (23). Also Manalai et al. found no relationship between the suicidality and montelukast (24).

Byrne F et al. reported a young child with neuropsychiatric events several years after the montelukast was started and this case was tought to have an underlying genetic disorder or a predisposing psychological factor (25). Our cases did not have any underlying previous or current psychiatric disorders that might trigger the mood and behavioral changes.

Generally montelukast is well tolerated but some transient and mild side effects (upper respiratory infection, worsening of asthma, pharyngitis, fever, diarrhea, and vomiting) can be seen and this does not change with the duration of drug treatment (26, 27).

Adverse drug reactions associated with montelukast between 1998-2007 were reported in 103 children. 48 patients had psychiatric disorders. Nightmares (n:15), anxiety (n:11), aggression (n:11), sleep disorders (n:10), insomnia (n:3), irritability (n:3), hallucination (n:3), hyperactivity (n:3) and personality disorders were (n:2) observed in some of the patients. The time from exposure to montelukast was less than one week in 80% of cases and 48% of cases (n:23) were ≤ 3 years old. (28).

Hallucination may be an adverse reaction of montelukast. This side effect was showed to be reversible both in previously healthy patients (29) and in patients having psychiatric disorders (30). In our study only one patient (1%) had the complaint of hallucination before montelukast therapy had begun and the ratio of hallucination rised to 7.2% (n:7, p=0.031) during montelukast therapy and decreased to 4.4% (n:3, p=0.500) after stopping the drug. So this showed that montelukast had a significant side effect of hallucination during the treatment and this was reversible and stopped after stopping the drug usage.

Brunlof et al. found that adverse drug reactions were observed in small children especially aged <5 years old. In this study, patients having psychiatric symptoms were more than expected (9). Two pediatric case reports were reported in 2011. Four years old male patient had anxiety and sleep disturbance and his complaints finished two weeks after discontinuation of the drug. Other patient was a 6 years old female and she had anxiety after her montelukast treatment was rised to 5 mg from 4 mg. Her treatment was reduced to 4 mg and she did not have the recurrence of the complaints (31). We observed that all of the side effects during montelukast decreased after stopping the drug and no recurrence established.

Cereza et al. reported the cases that were treated with montelukast according to the adverse reactions seen during their treatments. Twenty four of them (17 children, 7 adults) had nightmares. Fifteen of them were males, nine were females. Fourteen patients had psychiatric symptoms such as insomnia (n:5), nervousness (n:4), hallucinations (n:3), aggressiveness (n:2), irritability (n:2), and anxiety (n:1). Nightmares started on the first day and in the first week of the treatment in 18 patients. In 21 cases nightmares stopped after montelukast discontinuation and nightmares repeated in 3 patients after continuing the drug (32).

These reports may further evaluate the results of montelukast therapies for physicians and give important informations about treatments in pediatric cases having asthma diagnoses.

Asthma and allergic diseases may negatively impact the pediatric patient's life quality and treatment with montelukast by itself may potentiate this. Every unexpected adverse reaction arised with montelukast should be paid attention for follow-up. This study was limited for it was a retrospective study and patients could not be observed individually. Further studies are needed for detailed explanations about montelukast. So patients and health workers should be aware of this situation.

Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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Table-1: Table-1: Demographical distribution of the patients

	Study group	Control group	p
Mean of age	6.11±3.172	8.12±5.273	0.798
Genders (Male)	54 (%55.7)	33 (%44)	0.169
Genders (Female)	43 (%44.3)	42 (%56)	0.169
Total (N)	97 (%56.4)	75 (%43.6)	0.000

Table-2: Comparison of all allergic patients' mood and behavioral changes that existed at the beginning of the study with the non-allergic patients'

	Allergic patients		Non allergic patients		P
	n	%	n	%	
Sleep disturbance	20	18.7	10	15.4	0.579
Sleep abnormality	7	6.5	5	7.7	0.774
Sleepwalking	1	0.9	2	3.1	0.141
Irritation	23	21.5	14	21.5	0.995
Anxiety	15	14	9	13.8	0.975
Hallucination	1	0.9	1	1.5	1
Aggressiveness	27	25.2	10	15.4	0.127
Thought disorders	1	0.9	2	3.1	0.141

Table-3: Comparison of mood and behavioral changes observed in group A and group B in the study group

	Group A		Group B		p
	n	%	n	%	
Sleep disturbance	10	10.3	18	18.6	0.021
Sleep abnormality	3	3.1	9	9.3	0.070
Sleepwalking	1	1	2	2.1	1
Irritation	16	16.5	31	32	0.000
Anxiety	14	14.4	19	19.6	0.125
Hallucination	1	1	7	7.2	0.031
Aggressiveness	21	21.6	33	34	0.004
Thought disorders	1	1	1	1	1

Table-4: Comparison of mood and behavioral changes observed in group A and group C in the study group

	Group A		Group C		p
	n	%	n	%	
Sleep disturbance	5	7.4	8	11.8	0.375
Sleep abnormality	2	2.9	4	5.9	0.625
Sleepwalking	1	1.5	1	1.5	1
Irritation	10	14.7	16	23.5	0.109
Anxiety	10	14.7	12	17.6	0.687
Hallucination	1	1.5	3	4.4	0.500
Aggressiveness	14	20.6	19	27.9	0.227
Thought disorders	1	1.5	0	0	.