Montelukast and Neuropsychiatric Events in Children: What is the Evidence?

Montelucaste e Eventos Neuropsiquiátricos em Idade Pediátrica: Qual a Evidência?

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RESUMO

A asma é uma doença crónica muito frequente na infância, sendo o montelucaste utilizado no seu tratamento. Este fármaco tem sido associado a alterações neuropsiquiátricas potencialmente letais. O objetivo desta revisão é avaliar a evidência acerca dos seus efeitos neuropsiquiátricos em idade pediátrica. Da pesquisa bibliográfica resultaram 17 artigos e uma norma de orientação clínica, tendo 5 cumprido os critérios de inclusão previamente definidos. Após análise dos artigos considera-se que existe evidência da ocorrência de eventos neuropsiquiátricos em crianças asmáticas medicadas com montelucaste. Os clínicos devem estar informados acerca desta associação, para realizarem prescrições conscientes e estarem alerta durante o seguimento destas crianças. São necessários mais estudos, multicêntricos, com amostras mais robustas, com um período de acompanhamento mais prolongado e com metodologia bem definida, que clarifiquem a associação de montelucaste a eventos neuropsiquiátricos em idade pediátrica.

PALAVRAS-CHAVE: Antiasmáticos/efeitos adversos; Criança; Doenças do Sistema Nervoso/induzidas quimicamente; Montelucaste/efeitos adversos; Perturbações Mentais/induzidas quimicamente

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ABSTRACT

Childhood asthma is a prevalent chronic illness, and the medication montelukast is frequently used as treatment. However, this drug has been linked to neuropsychiatric events that have potentially fatal outcomes. The objective of this review paper was to evaluate the available evidence on this association between montelukast and neuropsychiatric events in children. From an analysis of 17 articles and 1 clinical guidance standard identified by a bibliographic search method, only 5 fulfilled the previously defined inclusion criteria. These selected studies provide support for the existence of possible occurrences of montelukast-induced neuropsychiatric symptoms among asthmatic pediatric patients administered with the medication. Therefore, healthcare providers need to be informed about these risks while making prescribing decisions for young patients who are taking montelukast or undergoing follow-up care subsequently. More multicenter studies are needed, with robust samples, longer follow-up period and well-defined methodology, to clarify the association of montelukast with neuropsychiatric events in children.

KEYWORDS: Anti-Asthmatic Agents/adverse effects; Child; Mental Disorders/chemically induced; Montelukast/adverse effects; Nervous System Diseases/chemically induced

INTRODUCTION

Asthma is the most common chronic disease in childhood, with a prevalence of 6%.[1,2] In Portugal, approximately 7% of the population suffers from this condition according to data gathered by the National Asthma Survey.[3]

Montelukast, an effective antagonist of the leukotriene receptor (LTRA), finds extensive usage as a prophylactic and persistent treatment for asthma. It also provides relief from symptoms caused by allergic rhinitis and is helpful in protecting against exercise-induced bronchoconstriction observed in children and adults.[4-6] The production of leukotrienes occurs because of exposure to environmental allergens alongside viral respiratory infections. Approximately 17% of cases of unresponsive asthma exacerbations are attributed to inflammation due to leukotrienes even after systemic corticosteroid treatment has been administered.[7]

According to the product characteristics summary, children may experience psychiatric disorders as adverse effects. These include abnormal dreaming such as nightmares, insomnia, and sleepwalking; anxiety and agitation that can lead to aggressive behavior or hostility; depression; psychomotor hyperactivity like irritability, restlessness or tremors; changes in attention and memory capabilities; hallucinations and disorientation. Moreover, suicidal ideation along with tendencies towards self-harm are among the reported side effects of this medication for pediatric patients.[8]

The objective of this investigation involves obtaining existing knowledge regarding the safety aspects related to administering specific medication used in routine clinical practice while considering its common neuropsychiatric side effects observed in children.

METHODS

A literature review grounded on clinical guidelines, meta-analyses, evidence-based reviews, and randomized controlled trials carried out from 2013 to April 2023 has been conducted for this writing. The sources utilized in the analysis are predicated upon evidenced-based research practices and standards.

To conduct this study, several scientific search engines such as National Guideline Clearinghouse, NICE, Canadian Medical Association, Cochrane Library and PubMed were utilized. The terms “montelukast”, “neuropsychiatric events” and “children” were used in the search criteria. Inclusion criteria involved articles pertaining to children who underwent intervention via montelukast resulting in neuropsychiatric events (NE). Articles that were duplicate entries or part of systematic reviews and selected meta-analyses along with review articles on the subject matter that deviated from the aim of the review at hand; opinion pieces containing Strength of Recommendation Taxonomy (SORT) C scientific evidence; resources not written in Portuguese, English or Spanish language were exempted from consideration for this academic inquiry.

To determine the levels of evidence (LE) and strength of recommendation (SR), the authors employed the SORT scale from American Family Physician.[9]

The final selection was based on unanimous agreement among all authors, followed by a careful evaluation and rating of quality and level of evidence for each included article via detailed discussion among themselves.

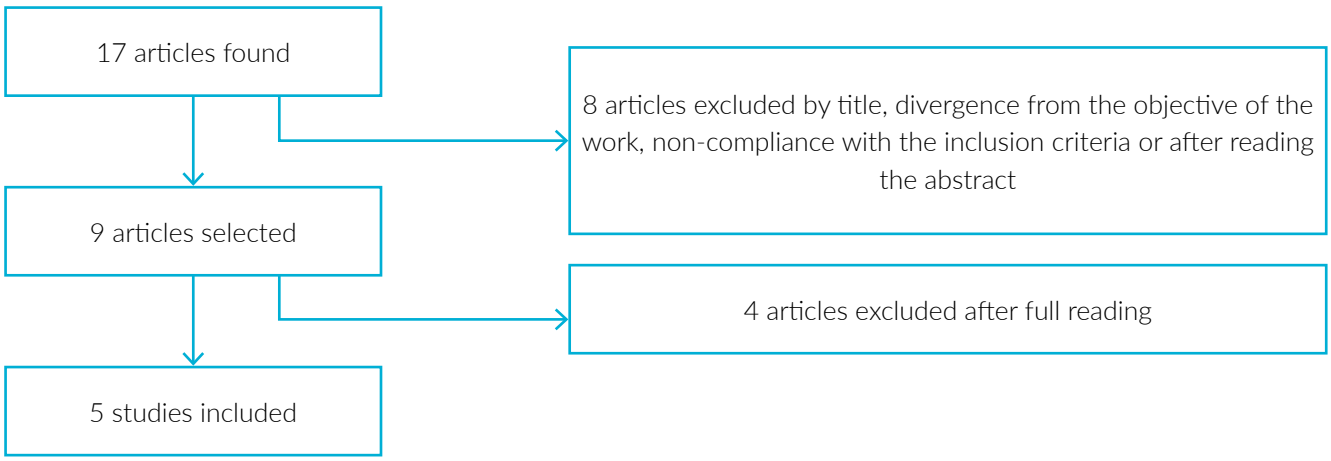

FIGURE 1. Flow diagram PRISMA.

RESULTS

In our search across various databases, we located 17 articles. After assessing their titles and abstracts, only 9 were deemed relevant. Upon reading the full text of these 9 papers, 5 met our criteria for inclusion in this study. To ensure transparency and completeness in reporting our methodology, we utilized the PRISMA guidelines to create a flowchart showing how many articles were found at each stage of screening (Fig. 1).[10] In the study 5 articles were included: 1 systematic review (Table 1) and 4 original articles (Table 2). Of note is that while several other systematic reviews existed on this topic area, only the findings from one review aligned with what was sought by us and thus evaluated exclusively, hereupon leaving out others systematically reviewed works identified earlier.

Dixon and colleagues carried out a systematic review with the objective of determining the frequency of adverse drug reactions (ADRs) associated with LTRA. The study utilized 7 case reports, 7 cohort studies or case-control studies, and 1 randomized control trial; nevertheless, only 3 met the established inclusion criteria outlined by the researchers.[11] A prospective cohort study spanning 24 weeks was designed by Ammari involving montelukast-using asthmatic children aged 2 to 17 years old. The participants were reached via telephone for the reporting of potential NE, which manifested in approximately one-third (32%) of cases. Commonly experienced symptoms included irritability (25%), agitation (18%), aggression (20%), anxiety (12%), nightmares (12%) and insomnia (4%) along with a decline in school performance for about three per cent of those affected. These reported effects surfaced at around two and three-quarter weeks after commencing treatment wherein extreme aggressiveness resulted in discontinuation from the therapy regimen for 2 subjects.[12] In Benard's retrospective cohort study, which involved 168 children who were between the ages of 1 and 17 years old, those who started taking montelukast as either a monotherapy or adjunct therapy to inhaled corticosteroids (ICS) (n=84) were compared with those who began on ICS monotherapy (n=84). The frequency of NE in the group that took montelukast was found to be 16%, characterized by irritability, aggressiveness, and sleep disturbances. Approximately three-quarters of these side effects arose within 2 weeks but vanished after discontinuing medication for only around 3.5 days. Furthermore, stopping treatment due to NE occurred significantly more often with Montelukast than with ICS.[13] A matched, nested case-control study was conducted by Glockler-Lauf, which involved 4395 children aged between 5 and 18 years old. The cases included children who were hospitalized due to a NE or exhibited episodes of urgency. These cases were then paired with up to 4 controls based on their birth year, year of asthma diagnosis and sex. Results indicated that there was a significant statistical difference (p=0.01) in the occurrence of NE among children taking montelukast compared to those who did not take the medication.[14] This review was assigned an evidence level 2.

Ozata *et al* performed a clinical study using a randomized controlled trial method that involved 155 individuals aged from 1.5 to 5 years old, with the subjects being divided into 2 groups: one group consisting of asthmatics (n=95), and the other serving as a control group (n=60). The former included patients

TABLE 1. Systematic Review.

Reference		Type of study	Sample	Intervention	Outcomes	Results	LE
Systematic Review (Dixon EG, Rugg-Gunn CE, Sellick V, Sinha IP, Hawcutt DB, 2021)[11]	**Ammari, 2018**[12]	Prospective cohort study	n=56, age 2-17 years	Telephone contact to question NE	Analyze the frequency of NE in children taking Montelukast	NE were reported in 32% of cases	2
	Benard, 2017[13]	Retrospective cohort study (2011-2016)	n=168, age 1-17 years	Two groups: n=84 ICS monotherapy/ n=84 montelukast. Telephone or personal contact to question NE	Determine the incidence of NE severe enough to lead to the cessation of montelukast	The risk of NE leading to drug cessation was significantly greater with montelukast than ICS (Relative risk 12.0, 95% CI 1.60-90.2)	
	Glocker-Lauf, 2018[14]	Randomized controlled clinical trial (2004-2015)	n=4395, age 5-18 years	Cases: children who were hospitalized due to a NE or exhibited episodes of urgency. Cases were paired with 4 controls	Examine the association between montelukast prescription and NE in children with asthma	Significant differences in NE between montelukast and ICS group. Children who experienced a new-onset NE had nearly 2 times the odds of having been prescribed montelukast (P=0.01)	

ICS - inhaled corticosteroids; LE - level of evidence; NE – neuropsychiatric events

TABLE 2. Original Articles.

Reference	Type of study	Sample	Intervention	Outcomes	Results	LE
Ozata, 2022[15]	Randomized controlled clinical trial, November 2017 - June 2018	n=155, age 1.5-5 years	Asthma group (n=95: ICS n=45, montelukast n=50) and control group (n=60))	Evaluate the CBCL	No statistically significant differences in CBCL between montelucast and ICS (*P*=0.3). Montelukast was discontinued in one asthmatic child due to hallucination	2
Bayer, 2022[16]	Prospective cohort study, september 2013-march 2014	n=125, age 3-18 years	The Neuropsychiatric Complaint Assessment Questionnaire was administered at baseline and 2 weeks after treatment initiation	Reveal the NE in patients taking montelucaste	Significant increase of Montelukast-induced NE compared with pre-treatment ($p<0.001$)	2
Perona, 2016[17]	Retrospective cohort study	All individual case safety reports received (2630) up to 1 January 2015 in which montelukast was used	Analysis of Individual Case Safety Reports up to January 1, 2015 in the World Health Organization database in which montelukast has been associated with NE	Analyse spontaneous reports of NE	2630 NE in people aged < 18 years. The main symptoms reported were sleep disorders, depression/anxiety, and suicidal behaviour	2
Ali, 2015[18]	Randomized controlled clinical trial, 1998-2009	n=30250, age <18 years	Cases: Asthmatics with NE. Cases were paired with 3 controls	Observation of NE and correlation with exposure to montelukast in the last year	No significant differences in NE between montelukast group and control group	2

CBCL - Check Behavior Checklist; ICS - inhaled corticosteroids; LE - level of evidence; NE – neuropsychiatric events

receiving montelukast and ICS treatment. To compare the groups, the Check Behavior Checklist (CBCL) was administered with statistically significant results indicating higher CBCL scores in asthmatics than controls (p=0.001). However, there was no noticeable difference between montelukast and ICS groups regarding CBCL score as p-value equalled 0.3. One participant had to discontinue using Montelukast due to hallucinations. This work was assigned an evidence level 2.[15]

Bayer carried out a prospective cohort study to assess the NE of montelukast in children aged 3-18 years who were taking it for the first time. The Neuropsychiatric Complaint Assessment Questionnaire and Kinder Lebensqualitat Fragebogen (KINDL) Quality of Life scale were administered at baseline and 2 weeks after treatment initiation. Amongst patients, 78 (64%) experienced NE such as temperamental behavior, nightmares and sleep disorders post-treatment (p<0.001). Children aged between 3-7 years showed statistically significant hallucinations compared to pre-treatment levels (p<0.001). These ADRs disappeared within 3 days of discontinuing montelukast therapy. Montelukast was found to cause a decline in quality of life which could be attributed partly due to its association with NE. Upon critical analysis, it has been determined that the level of evidence for this finding is at a 2 on the scale.[16]

Perona conducted a retrospective cohort study to investigate the incidence of NE in individuals under 18 years old taking montelukast. The analysis focused on Individual Case Safety Reports (ICSRs) retrieved from the World Health Organization's database until January 1, 2015, which linked montelukast use with various psychiatric disorders. A total of 2630 cases were reported, with sleep disorders being the main symptom for those below 2 years old while depression/anxiety was common among those between 2 and 11 years old. Suicidal behavior and depression/anxiety were frequently observed among individuals aged 12 to 17 years old. This research is classified as evidence level 2.[17]

Ali *et al* executed a matched nested case-control research involving 30 250 minors to evaluate the association between montelukast and NE. The study aimed to determine whether there was an association between these 2 variables. Each case was paired with 3 controls based on their age, gender, and geographic region. Unlike previous studies, no significant differences were observed in this research regarding group comparison. This work has been classified as evidence level 2 according to academic standards.[18]

DISCUSSION

The inconsistent results found in various studies on the association of montelukast with NE can be attributed to several factors. Firstly, most of the studies had a limited sample size which could have impacted their reliability. Secondly, sometimes treatment with both montelukast and ICS was carried out together making it difficult to ascertain whether all side effects were solely due to montelukastus or from other medications as well. Thirdly, there was no consistent way for evaluating NE across different studies since they employed different scales such as CBCL score and Neuropsychiatric complaint assessment questionnaire among others, leading to difficulties in interpretation and comparison of study outcomes. Also, important information like the number of episodes or period during which these events manifested is missing from most reports. As a result, comparing findings between each report becomes challenging without having an established benchmark evaluation tool that is uniform across all research involved.

The majority of investigations analyzed associate montelukast with NE such as altered behavior patterns, depression, anxiety, aggression, sleep disturbances and nightmares; even suicide in extreme cases was noted. It is important to highlight that although one study did not find any significant discrepancies between montelukast and ICS, it is worth mentioning that there was a recorded incident of discontinuation of the drug due to the occurrence of severe NE such as hallucinations.[15]

One potential reason for the emergence of neuropsychiatric manifestations while using montelukast is associated with its capacity to heighten blood-brain permeability and suppress serotonin as well as noradrenaline production.[4]

Furthermore, an original article found higher rates of behavioral changes amongst asthmatic children than their healthy counterparts suggesting that asthma symptoms themselves can cause depression and negatively impact the quality of life potentially complicating analysis whereby it cannot be concluded if drug administration is solely responsible for all observed neuropsychiatric alterations.[4] Conversely, the alleviation of asthma symptoms through montelukast administration appears to enhance children's energy levels and may be construed as atypical conduct.[19]

To sum up, there is evidence to suggest that asthmatic children receiving montelukast have an elevated likelihood of experiencing neuropsychiatric events

(SR B). It is essential for clinicians to be aware of this association and exercise caution when prescribing the drug while remaining vigilant during follow-up appointments with these patients.

Additionally, families should be encouraged to communicate any effects they observe from the medication as it can aid in adjusting or changing therapy early on leading to increased adherence and maintaining trust in the doctor-patient relationship. More clinical trials encompassing a larger population size along with longer follow-up periods are necessary in order to comprehend the mechanisms responsible for higher occurrences of NE among those taking montelukast.

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