

BEYOND THE ANTICIPATED: “MONTELUKAST AND DELIRIUM” – A CASE REPORT**Breezy Ani Sam^{*1}, Nayana Rachel Koshy² and Dr. Sara Kurien K.,³ Dr Jaico Paulose⁴**^{1,2}Pharm D Intern, Nazareth College of Pharmacy, Othara, Thiruvalla.³Assistant Professor, Department of Pharmacology, Believers Church Medical College Hospital, Thiruvalla.⁴Associate Professor Department of Psychiatry, Believers Church Medical College Hospital, Thiruvalla.***Corresponding Author: Breezy Ani Sam**

Pharm D Intern, Nazareth College of Pharmacy, Othara, Thiruvalla.

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ABSTRACT

Montelukast is a leukotriene receptor antagonist (LTRA) that, in contrast to other airway receptors such as prostanoid, cholinergic, or beta-adrenergic receptors, exclusively targets cysteinyl leukotriene receptor type-1 by preventing LTD4 mediated bronchoconstriction with dosages as low as 5 mg. Behavioral alterations with Montelukast administration have been shown in several human trials. Psychotic symptoms, such as hallucinations, insomnia, nightmares, anxiety, aggressiveness and headache are seen in adults and children after taking medicine and stop when Montelukast therapy is withdrawn. We discuss one such instance of Montelukast induced delirium.

KEYWORDS: Montelukast, Leukotriene receptor antagonist, Delirium, Neuropsychiatric adverse effects.**INTRODUCTION**

Asthma patients are treated with anti-inflammatory medications like Montelukast (ML). This substance, a leukotriene receptor antagonist (LTRA), inhibits the human airways cysteinyl leukotriene type 1 (CysLT1) receptors by improving the generation, adhesion, migration, and survival of inflammatory cells like eosinophils, cysteines, which are produced by mast cells and basophils via the metabolism of arachidonic acid and thus exacerbate allergic inflammation. By attaching to CysLT1 receptors and inhibiting the activity of leukotriene D4, which causes smooth muscle contraction, bronchoconstriction, and vasoconstriction and thereby improving clinical parameters, Montelukast reduces allergy and asthmatic symptoms.

There are both drawbacks and benefits to using Montelukast. In addition to being a popular asthma medication, Montelukast also has neuroprotective properties but on the other hand, may cause behavioral abnormalities. The side effects of Montelukast are frequently linked to increased liver enzyme levels, exhaustion, nausea, vomiting, and stomach discomfort. But according to current research, people who take Montelukast may have behavioral abnormalities in children as well as neuropsychiatric symptoms like anxiety, aggression, sleep disturbances, insomnia, irritability, hallucinations, and hyperactivity in adults. The time from exposure to adverse medication responses was shorter than one week in eighty percent of instances. The most frequent adverse medication responses caused

by Montelukast, according to Swedish research, that documented 48 cases, were hallucinations and nightmares.^{[1],[2]}

Delirium is a changed state of consciousness that might last for a few hours or days and is frequently accompanied by bouts of confusion. This illness causes alterations in a person's awareness, including feeling „out of it“, perplexed, nervous, or experiencing unreal things. This may cause anxiety, exhilaration, or terror in addition to cognitive and memory problems. There are several variations of delirium, such as mixed, hyperactive, and hypoactive delirium. Restlessness, agitation, mood fluctuations, hallucinations, and delusional refusal of care are the hallmarks of hyperactive delirium. It is easier to identify than hypoactive delirium, which may cause the patient to slow down and be lethargic.^[8] Although delirium brought on by Montelukast is less common, there have been case reports indicating a connection between the two.^[3] Antihistamines, decongestants, and anticholinergic agents, alone or in combination which are used in the treatment of rhinitis also report side effects like sedation, psychosis, impaired learning and memory, etc.^[4]

CASE REPORT

A 73-year-old male patient who is a known case of diabetes mellitus (DM) and systemic hypertension (HTN) and early on treatment for mood disorders has now presented with complaints of sleep disturbances, and aggressiveness that exacerbated since 1 week and

was admitted in the Psychiatry department. At the time of admission, the patient was drowsy in the morning and sleepless at night, with increased agitation, aggression, and abusive behavior. Control of mood symptoms and sleep normalization were targeted along with control of agitation. Given the manic symptoms, Quetiapine, and Endoxifen were added. Sleep normalization was attempted with Clonidine, Melatonin, and Lemborexant. He was also found to have elevated blood sugars and was put on Metformin + Sitagliptin, Glimepiride, and Inj Mixtard Insulin through which his blood sugar levels were controlled. Since sleep was still an issue, he was started on Hydroxyzine, after which sleep became regularized.

After a week of hospitalization, owing to persisting cough and dyspnea, a Pulmonology consultation was sought, and were advised blood and sputum investigations. Orders were followed and the patient was started on Montelukast (10mg) + Fexofenadine (120mg) combination once daily. After taking the first dose at night, the patient developed a delirious state. Montelukast was further discontinued, and thereafter he maintained the improvement in mood symptoms with normalized sleep and adequate control of blood sugar following which the discharge was planned. Hence a neuropsychiatric syndrome due to Montelukast was suspected. T. Endoxifen was stopped because of further improvement and Syp. Levosalbutamol was added for cough and dyspnea.

DISCUSSION

Montelukast is an antagonist at the leukotriene receptors. It is recommended for adults and pediatric patients over the age of 12 months as a long-term therapy and prophylactic measure for asthma. It can also be used to prevent exercise-induced dyspnea and to treat seasonal allergic rhinitis in individuals older than two years old. It functions by attaching itself to the CysLT type 1 receptor, which inhibits the physiological effects of CysLTs at the receptors, including LTC₄, LTD₄, and LTE₄.^[7]

Disorientation episodes are often associated with delirium, an altered state of consciousness that can linger for several hours or days. While Montelukast-induced delirium was believed to be an uncommon event, case findings, however, point to a possible connection between neuropsychiatric symptoms and Montelukast.^[3] In 125 asthmatic patients, research by Bayer et al. found that 62.4% experienced neuropsychiatric adverse drug responses, which went away after the medicine was stopped.^[5]

Paljarvi et al. performed a propensity score-matched cohort study using electronic health data from 2015 to 2019 in the TriNetX Analytics Network patient database, which included over 51 million patients from 56 healthcare facilities, the majority of which were in the US.^[3] For individuals who received Montelukast, the

odds ratio [OR] for any incidence of neuropsychiatric outcome was 1.11. This study found that individuals with asthma or allergic rhinitis were more likely to have negative neuropsychiatric symptoms after starting Montelukast.^[9]

A thorough study of the metabolism of Montelukast was conducted using in vitro systems, a mouse model, and an embryonic neuron-enriched cell model. The multi-omics method confirmed the disruption caused by Montelukast on glutathione detoxification, neurotransmitter, and neurosteroid pathway change, and mitochondrial activity in neuronal cells. It demonstrated the discovery of eighteen novel MTK metabolites and neuropsychiatric episodes may be brought on by these metabolites.^[6] In the year 2020 FDA specified a boxed warning on significant adverse effects on mental health for Montelukast, suggesting its limited use in asthma and allergic rhinitis. FDA suggested monitoring patients for neuropsychiatric symptoms after prescribing Montelukast.^[11] Vigaccess reports around 30,459 incidents of ADR by Montelukast overall, of which 33.3% involve psychiatric illnesses, including 19 cases of delirium, which were earlier believed to be uncommon. However, the occurrence of Delirium in our patient was deemed "Probable" according to the WHO-UMC causality assessment scales.^[10]

CONCLUSION

For the treatment of asthma and common cold, Montelukast is a preferred choice. Delirium is a temporary altered state of consciousness lasting a few hours or days, often accompanied by periods of disorientation. Here, we discuss a patient with Montelukast-induced delirium. A 73-year-old male patient who developed chronic cough and dyspnea was then prescribed T. Montelukast following which he developed delirium. Once the medication was discontinued, his condition returned to normal.

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CONFLICT OF INTEREST:

NIL.

ABBREVIATIONS

ML : Montelukast
LTRA : Leukotriene receptor antagonist
CysLT1 : Cysteinyl leukotriene type 1
DM : Diabetes mellitus
HTN : Hypertension
LTC₄ : Leukotriene C₄
LTD₄ : Leukotriene D₄
LTE₄ : Leukotriene E₄
OR : Odds ratio

ADR : Adverse drug reactions
FAERS : FDA Adverse Event Reporting System

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